Medication optimisation in older adults with cancer

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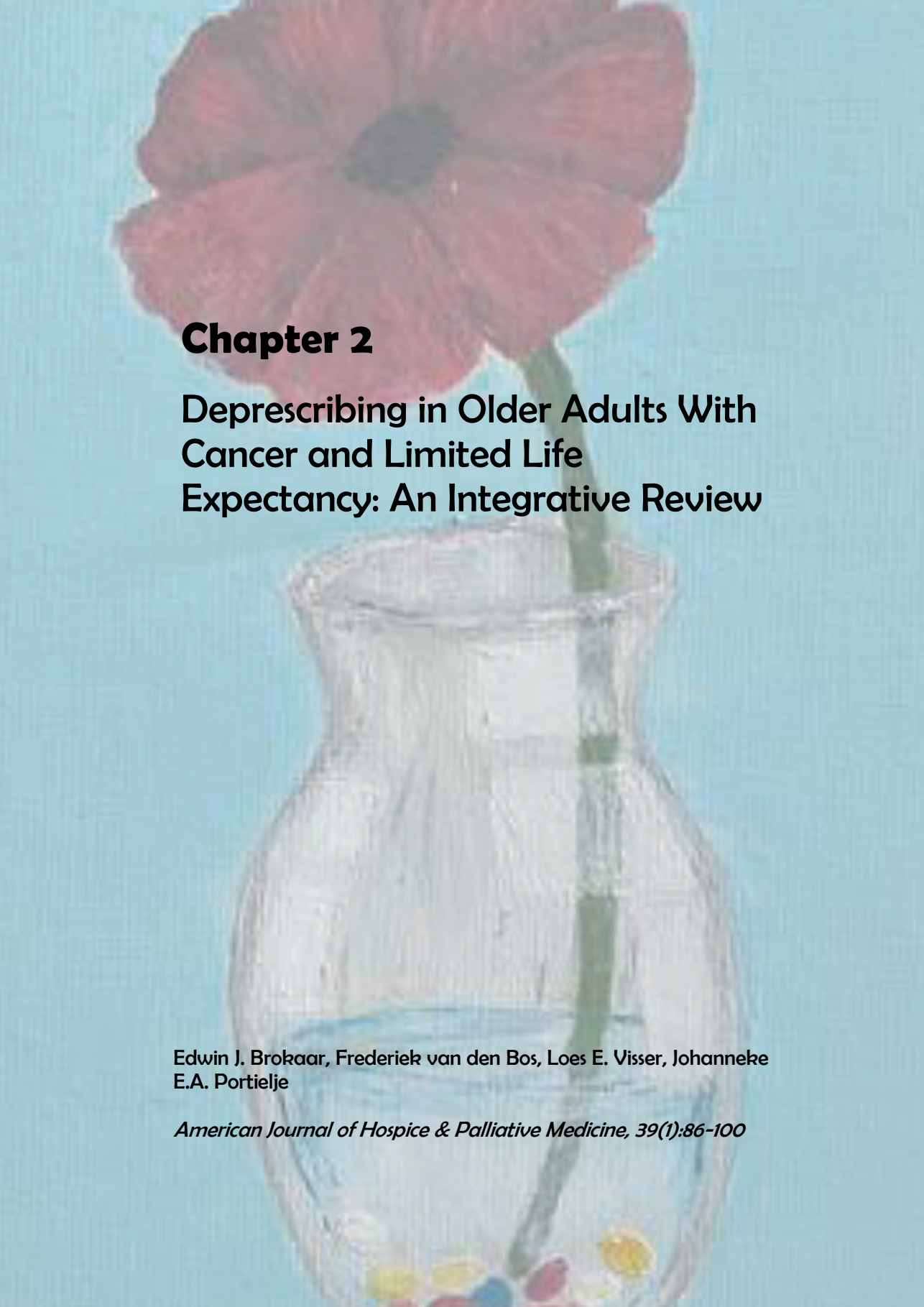

Chapter 2

Deprescribing in Older Adults With Cancer and Limited Life Expectancy: An Integrative Review

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Abstract

Polypharmacy is common in older adults with cancer and deprescribing potentially inappropriate medications becomes very relevant when life expectancy decreases due to metastatic disease. Especially preventive medications may no longer be beneficial, because they may decrease quality of life and reduction in morbidity and mortality may be futile. Although deprescribing of preventive medication is common in the last period of life, it is still unusual during active cancer treatment for advanced disease, although life expectancy is often limited to less than 1 to 2 years in that stage. We performed a systematic search of the literature in Pubmed and Embase on the discontinuation of commonly utilized groups of preventive medication and evaluated the evidence of potential benefits and harms in patients aged 65 years or older with cancer and a limited life expectancy (LLE). From 21 included studies, it can be concluded that deprescribing lipid lowering drugs, antihypertensive drugs, osteoporosis drugs and antihyperglycemic drugs is feasible in a considerable part of patients with a LLE. Discontinuation may be performed safely, without the occurrence of serious adverse events or decrease of survival. The only study that addressed quality of life after deprescribing showed that discontinuation of statins improves quality of life in patients with a LLE. Recurrence of symptoms requiring reintroduction occurred in 0-13% of patients on antihyperglycemic treatment and 8-60% of patients using antihypertensive drugs. In order to reduce pill burden and futile treatment clinicians should discuss deprescribing of preventive medication with older patients with advanced cancer and a LLE.

Introduction

Polypharmacy is increasingly common in older patients with cancer and deprescribing potentially inappropriate or unnecessary drugs is highly relevant when life expectancy decreases due to metastatic disease. Older patients may take multiple medications that may decrease quality of life without benefit in terms of reduced morbidity or mortality [1,2]. Specifically, in frail older patients or patients with limited life expectancy (LLE), the balance between efficacy and safety may become negative due to an increased risk of adverse drug events [3-5]. Deprescribing is common for patients with cancer in the last period of life. However, deprescribing is still unusual for patients with advanced cancer undergoing systemic anticancer treatment, although many of these may have a life expectancy below 1 to 2 years. When life expectancy is reduced, drugs for the prevention of long-term health issues, such as drugs for cardiovascular risk management, prevention of diabetic complications, or prevention of complications of osteoporosis may no longer be appropriate [6-12]. Although these drugs have an anticipated benefit in the future, they may cause adverse drug reactions in the present. In addition, clinically relevant drug-drug interactions with anticancer therapeutics— especially the newer oral anticancer drugs—or co-medication may be prevented by discontinuing possibly inappropriate medications (PIMs) [13-20]. Although PIMs are frequently discontinued in patients in the terminal stage of cancer and in dying patients, it is rare in patients who still undergo an active treatment for cancer. Previous research has shown that despite advanced cancer and a poor prognosis, PIMs are often continued nevertheless [6,7,9-11]. A recent review on 15 tools for deprescribing in frail older patients and individuals with LLE, concluded that most tools are based upon expert opinion or clinical experience [21]. The aim of this study is to review the available scientific evidence of possible harms and benefits of discontinuation of potentially inappropriate preventive medication in patients 65 years with cancer and LLE. We specifically studied deprescribing of lipid lowering drugs, antihypertensive drugs, osteoporosis drugs, and antihyperglycemic drugs.

Methods

Search Strategy

We performed a stepwise search as described in detail below on the existing evidence on the discontinuation of drugs for cardiovascular risk management, prevention of complications of osteoporosis, or prevention of diabetic complications in patients 65 years with cancer and LLE. These classes included: lipid lowering drugs, antihypertensive drugs, osteoporosis drugs and antihyperglycemic drugs.

Initially, we searched for evidence supporting the discontinuation in older patients with cancer and LLE, in which LLE is defined as an expected survival of 12 months or less. When we did not find evidence in this specific population, we searched for discontinuation either in (frail) older patients, in patients with cancer, or in patients with LLE.

Data Sources and Searches

The search was performed in Pubmed and Embase from inception until March 2020 with the following search terms and their synonyms: elderly, limited life expectancy, cancer, and potentially inappropriate medication. The search terms for the various drug classes consisted of the MeSH terms for the indication and drug class, pharmacological action, the separate drug classes used for the indication, and the individual drugs, combined with the general

search terms. We limited the search to studies in humans and published in English. Details of the search strategy can be found in Online Appendix A.

Study Selection

Titles and abstracts of all studies retrieved by the search were assessed by 1 investigator (EB) to determine which were eligible for further investigation. All potentially relevant articles were subsequently screened as full text by 2 authors. Disagreements were resolved by consensus. If consensus could not be achieved, the article was discussed with a third reviewer for a final decision.

We included randomized controlled trials and cohort studies, case-control studies, cross-sectional studies, and meta-analyses. Studies were excluded if the primary intervention did not include deprescribing or discontinuing an active treatment, or if the design or outcomes were not applicable in our population. We excluded interim analyzes if the completed study was available. In case only an abstract was available, we attempted to find a final report of the study by searching Medline using the names of first, second and/or final authors as well as keywords from the title. If no full text report was available, these studies were excluded. Finally, citations of included publications were cross-referenced to retrieve any additional relevant studies.

Data Extraction

Two reviewers independently judged the study design and the results of each included study. We extracted study design, study population, mean age, sample size, mean or median survival or life expectancy, and the results of the discontinuation of the drug or drug class. Discontinuation was considered successful if a drug was not restarted during follow-up and there was no recurrence of symptoms or occurrence of serious adverse events. If a study addressed the discontinuation of more than 1 drug class, we extracted the data relevant for the drug class of our interest.

Data Synthesis and Analysis

A meta-analysis was considered unfeasible due to heterogeneity in study designs, and the diversity of patient populations and outcome measures. We described the study populations and quality of the studies and summarized the most relevant study results to describe our main outcomes of interest. If the results of different studies were contradictory, we conferred greater relevance to the studies with a higher match in study population and a with higher quality. Quality assessment was performed using the Study Quality Assessment Tools of the National Heart, Lung, and Blood Institute (NHLBI-SQAT) [22]. NHLBI-SQAT was considered an appropriate tool due to the heterogeneity of the included studies and a meta-analysis was not feasible for each drug class. Studies that met 80% of quality criteria were classified as “Good,” studies that met 60-80% of criteria were classified as “Fair,” and studies that met <60% of criteria were classified as “Poor”.

Results

A total of 21 studies was included in this review. The search strategy and process is outlined in Figure 1. No studies were identified in patients 65 years with cancer and a LLE in accordance with our definition. Two studies were concerned with older adults with a limited life expectancy – in 1 of these studies 49% of the patients had cancer [23] – and the other 19

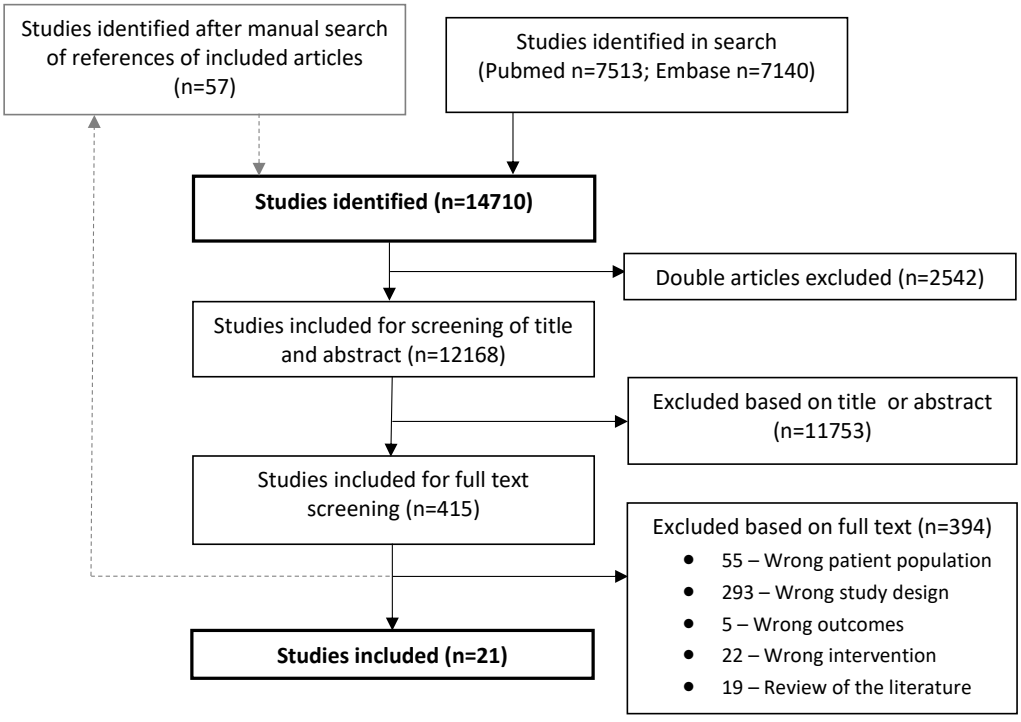
studies were with older adults in general. Twelve out of 21 studies were in community dwelling patients, 5 in a residential aged care facility or nursing home, 2 were in a hospital and/or outpatient clinic, 1 other and for 1 study the setting was not specified. Eighteen studies had a prospective design and 3 had a retrospective design. Four out of 21 studies addressed medication discontinuation in more than 1 drug group of our interest. The mean age of the patients in the studies ranged from 65 to 84 years and the mean follow-up ranged from 78 days to 5 years. The quality of 4 studies was good, 13 were fair and 4 were poor. The 3 most frequently unmet criteria were no blinding of the outcome assessors, no adjustment for possible variation in exposures that can vary and sample size justification or power description. These criteria were not met in 44-88% of the fair and poor studies. Discontinuation attempts were generally labeled successful when drugs were permanently stopped. Reasons specified for unsuccessful discontinuation were unwillingness of physician or patient to discontinue the drug, recurrence of symptoms, or only dose reduction achieved.

Lipid Lowering Drugs

Five studies were identified that addressed deprescribing lipid lowering drugs [2,23-26] (Table 1). One study addressed patients with a LLE, 1 addressed frail older adults and 3 studies addressed patients aged 65 years without further specification of life expectancy or frailty. Three studies were specifically concerned with statins, 2 studies addressed lipid lowering drugs in general.

Kutner et al. showed in a randomized trial, that discontinuation of statin therapy did not increase mortality or time to first cardiovascular event compared to continuation of statins in patients with an advanced, life-limiting illness and an estimated life expectancy of less than 1 year and without active cardiovascular disease. Quality of life increased, as measured by the subscales of the McGill Quality of Life Questionnaire that address the physical, psychological, well-being and support domain [23]. The other studies concerning lipid lowering drugs were performed in older patients using medication review or general deprescribing intervention. All these studies mentioned successful discontinuation of lipid lowering medication in 23-83% of patients [2,24-26] In more frail patients or with LLE, lipid lowering drugs were discontinued successfully more frequently than in relatively healthy older adults. In these studies, no serious cardiovascular events or deaths were attributed to the discontinuation of lipid lowering drugs.

Figure 1. Flowchart of studies from search to inclusion



Antihypertensive Drugs

Eleven studies [2,24-33] of discontinuation of antihypertensive medications addressed patients aged 65 years in general (Table 2). Three studies included only patients with hypertension, 8 studies included patients that used drugs with an antihypertensive effect but prescribed for various indications such as heart failure or hypertension. In 4 of these 8 studies, the discontinuation rates were presented for patients with hypertension separately. Four studies were designed to reduce general polypharmacy including discontinuation of antihypertensive drugs.

In these studies, discontinuation of antihypertensive drugs was successful in 32-84% of patients with hypertension with no clear association between frailty or life expectancy and successful discontinuation. Five of these 11 studies specifically describe that no increase in serious cardiovascular events or deaths was observed after discontinuation of antihypertensive drugs and none of the studies indicate an increase in these events. Nelson et al. found a higher success rate in patients that were 65-74 years old compared to older patients (age 75-84 years) [29]. For recurrent hypertension, 8-60% had to restart treatment during the first year. The most frequent reasons (8-76%) to restart antihypertensive medications were cardiac failure and fluid retention, especially for diuretics.

Osteoporosis Drugs

All 8 included studies [26,34-40] identified were in patients aged of 65 years, predominantly postmenopausal women (Table 3). We included 5 studies on the discontinuation of bisphosphonates, 1 on the discontinuation of denosumab, 1 on the discontinuation of calcium and vitamin D supplements, and 1 study in which osteoporosis medication—bisphosphonates and strontium ranelate—was withdrawn as part of a larger medication review. Bisphosphonate treatment can be withdrawn in women aged 65 years without an increased risk of fractures during the 12-18 months after withdrawal [34,36,38-41]. Withdrawal of denosumab, however, is associated with an increased risk of vertebral fractures already after 1 year [37]. One study showed no increase in non-vertebral fractures in the first 2 years following discontinuation of calcium and vitamin D supplementation [35]. Potter et al. deprescribed osteoporosis medication (bisphosphonates and strontium ranelate) in 91% of frail older users and all attempts were successful [26].

Oral Antihyperglycemic Agents

Five studies [2,24,25,42,43] addressed patients aged 65 years, 1 of which was in patients with LLE and/or advanced dementia; 1 study was in frail elderly patients and 1 in nursing home residents. Two studies specifically targeted elderly patients with tight glycemic control (Table 4). In 1 study, only patients with type 2 diabetes were included for discontinuation of antihyperglycemic drugs, the other studies did not mention the type of diabetes specifically. However, the majority of patients in these studies were prescribed antihyperglycemic drugs only indicated for type 2 diabetes.

Sjöblom et al. withdrew antihyperglycemic medications in older nursing home residents with diabetes mellitus type 2 and a HbA1c -6% (42 mmol/mol). Oral antihyperglycemic medications and insulin -20 IU/day were discontinued, insulin dosage was reduced by half if the dose was >20 IU/day. After 3 months, the initial treatment reduction remained successful in 75% of the patients. Mean HbA1c rose from 5.2% (33 mmol/ mol) at baseline to 5.8% (40 mmol/mol) at 6 months [43]. Another study investigated treatment mitigation of nursing home residents with diabetes and with LLE. Treatment de-intensification followed in 45.5% during 90 days of follow-up [42].

Three studies concerned a general medication review and included discontinuation of antihyperglycemic drugs. In 1 of these studies, oral hypoglycemic drugs were discontinued in 60% of frail older adults, as the potential burden or harm outweighed the expected benefit [25]. No deaths or acute hospital admissions were related to the discontinuation, and in 0-12.5% of the patients, antihyperglycemic treatment was restarted. In community-dwelling older adults, sulfonylurea's were discontinued successfully in 83% of the patients, but metformin in 27% [2].

Table 1. Overview of lipid lowering drugs

Study	Type	Patients	Intervention	Sample size (N)	Relevant results	Interpretation	Quality
Kutner et al. (2015)	Randomized controlled trial	Estimated life expectancy 1 month - 1 year. Mean age 74.1±11.6 years; 49% of patients had cancer, 58% had a history of cardiovascular disease.	Discontinuation of statin therapy	381 (189 intervention, 192 control)	Discontinuation of statins did not result in a difference in 60-day mortality or in time to first cardiovascular-related event, but did result in higher McGill QoL. There was no difference between statin use for primary or for secondary prevention.	In older adults with a limited life expectancy, discontinuing statins is safe and associated with improved of QoL.	Good
Potter et al. (2016)	Randomized controlled trial	Older adults living in a residential aged care facility. Mean age 84±7 years.	Deprescribing intervention to reduce polypharmacy, including lipid lowering drugs	95 (47 intervention, 48 control)	Discontinuation of statins was successful in 77% of the users and did not lead to an increase in 12-month mortality.	In frail older adults, discontinuing a range of different medications including statins is safe and feasible.	Fair
Dharmarajan et al. (2020)	Prospective deprescribing feasibility study	Community dwelling older adults and long-term care facility residents Mean age 78.2 years.	Deprescribing intervention to reduce polypharmacy, including lipid lowering drugs	383	Successful deprescription of lipid lowering drugs in 22.9% of the patients encounters without adverse events within 6 months.	Implementation of a deprescribing intervention results in safe deprescription of lipid lowering drugs in a significant proportion of patients	Poor

Table 1 continued

Study	Type	Patients	Intervention	Sample size (N)	Relevant results	Interpretation	Quality
Garfinkel et al. (2010)	Prospective deprescribing feasibility study	Community-dwelling older adults with a life expectancy ≥3 months. Mean age 82.8±6.9 years; 57% was considered frail.	Deprescribing intervention to reduce polypharmacy, including lipid lowering drugs	70	Discontinuation of statins was successful in 50% of the users and did not lead to an increase in 6-month mortality.	Discontinuation of a range of different medications, including statins, was safely achieved with no significant adverse events or deaths related to discontinuation.	Fair
McKean et al. (2016)	Prospective deprescribing feasibility study	Older adults patients with acute hospital admission and ≥8 regular medications. Median age 82.5 (IQR 74-87) years; median Rockwood frailty score 6 (IQR 5-6, indicating high frailty); estimated 3-year mortality 55%	Deprescribing intervention to reduce polypharmacy, including lipid lowering drugs	37/50 included statins	Discontinuation of statins was successful in 57% of the users. During 2.5 months of follow-up, no deaths or acute hospital admissions related to the drug discontinuation were observed.	In frail older adults, discontinuation of a range of different medications, including statins, is safe and feasible.	Fair

Abbreviations: QoL – quality of life, IQR – interquartile range

Table 2. Overview of antihypertensive drugs

Study	Type	Patients	Intervention	Sample size (N)	Relevant results	Interpretation	Quality
Gulla et al. (2018)	Randomized controlled trial	Nursing home residents. Mean age 87 years (range 66-104)	Multimodality intervention including medication review aimed to reduce polypharmacy including antihypertensive treatment versus usual care	295 (164 intervention, 131 control)	Antihypertensive medication was discontinued in 32% of 164 users and had to be restarted in 3. Subsequent blood pressure increase was usually temporarily. Hospitalization decreased following discontinuation, and mortality did not increase.	Medication review can be used to safely discontinue antihypertensive drugs.	Fair
Walma et al. (1997)	Randomized controlled trial	Community dwelling older adults receiving diuretic therapy for ≥6 months. Indication for diuretics: hypertension (44%), heart failure (42%), oedema (14%, other/unknown (1%) Mean age 76 years.	Discontinuation of diuretics versus control	202 (102 intervention, 100 control)	Diuretics could be discontinued in 51% of older adults, without adverse events. Restarting diuretics was necessary in 49%, most often for symptoms of heart failure (25%) and for recurrent hypertension (9%). In patients with hypertension as indication, discontinuation was successful in 62%. Discontinuation did not lead to hospitalizations or deaths for six months.	Discontinuing diuretics of feasible and safe in the majority of older adults when prescribed for hypertension, but not when prescribed for heart failure.	Good

Table 2 continued

Study	Type	Patients	Intervention	Sample size (N)	Relevant results	Interpretation	Quality
Ekbom et al. (1994)	Prospective observational cohort study	Community dwelling older adults with hypertension. Mean age 75.2±3.8 years.	Discontinuation of antihypertensive drugs	333	During the first year following discontinuation, 40% of the patients did not restart antihypertensive medication; 20% restarted active treatment within 5 years. There was no increase in all-cause mortality following discontinuation, independent of the need for a restart.	In older adults, discontinuation of antihypertensive medication can be attempted safely.	Fair
Nelson et al. (2002)	Prospective observational cohort study	Community dwelling older adults. Median age 71 years (range 65-84)	Discontinuation of antihypertensive therapy	503	During the first year following discontinuation, 37% of the patients remained normotensive and did not restart antihypertensive medication. Half of the patients that returned to hypertension did so during the first 70 days.	Withdrawal of antihypertensive medication is feasible in over one third of healthy older adults.	Fair

Table 2 continued

Study	Type	Patients	Intervention	Sample size (N)	Relevant results	Interpretation	Quality
Straand et al. (1993)	Prospective observational cohort study	Community dwelling older adults Mean age 82 years (range 75-95)	Discontinuation of long-term diuretic therapy	33	Discontinuation of diuretic medication was successful in 55% after 6 months of follow-up. In 6 patients in whom discontinuation failed, the following serious event was labelled as probably or possibly being related to the discontinuation.	More than half of the patients could discontinue diuretic therapy successfully. Monitoring for adverse events is mandatory.	Fair
Van Kraaij et al. (1997)	Retrospective observational cohort study	Patients aged ≥75 years admitted to a geriatric hospital ward or outpatient clinic. Median age 82 years (range 75-102).	Discontinuation of diuretic therapy	218	Diuretics were discontinued in 218/593 (37%) patients. During the first year, 66 (31%) restarted diuretics. Patients with hypertension as indication were twice as likely to remain off diuretics than patients with heart failure.	Diuretics for hypertension can be withdrawn in a significant proportion of older adults.	Fair
Van Kraaij et al. (1998)	Retrospective observational cohort study	Older adults aged ≥75 years admitted for the first time to a nursing home facility. Mean age 82.8±5.4 years	Discontinuation of diuretic therapy	82	Diuretics were discontinued in 82/220 (37%), with permanent withdrawal in 48 (21%). Discontinuation was less successful when diuretics had been prescribed for heart failure or ankle edema. No life-threatening cardiovascular events or increased mortality due to diuretic withdrawal were reported.	Diuretics can be withdrawn safely in a significant proportion of older adults.	Fair

Table 2 continued

Study	Type	Patients	Intervention	Sample size (N)	Relevant results	Interpretation	Quality
Potter et al. (2016)	Randomized controlled trial	Older adults living in a residential aged care facility. Mean age 84±7 years	Deprescribing intervention to reduce polypharmacy, including antihypertensive drugs	95 (47 intervention, 48 control)	Discontinuation was successful in 70% of users of antihypertensive drugs and did not lead to an increase in 12-month mortality. ACE-inhibitors and AT2-antagonists were discontinued successfully in 93% of attempts; calcium channel blockers in 67% of attempts; betablocking agents in 100% of attempts.	In frail older adults, discontinuing a range of different medications including antihypertensive drugs is safe and feasible.	Fair
Garfinkel et al. (2010)	Prospective deprescribing feasibility study	Community-dwelling older adults with a life expectancy ≥3 months. Mean age 82.8± 6.9 years ; 57% was considered frail.	Deprescribing intervention to reduce polypharmacy, including antihypertensive drugs	70	Discontinuation was successful in 50/95 (53%) of antihypertensive drugs and no deaths were considered to be related to drug discontinuation.	Discontinuation of a range of different medications, including antihypertensive drugs, was safely achieved with no significant adverse events or deaths related to discontinuation.	Fair

Table 2 continued

Study	Type	Patients	Intervention	Sample size (N)	Relevant results	Interpretation	Quality
Dharmarajan et al. (2020)	Prospective deprescribing feasibility study	Community dwelling elderly and long-term care facility residents. Mean age 78.2 years	Deprescribing intervention to reduce polypharmacy, including antihypertensive drugs	383	Successful deprescription in 20.8% of encounters with antihypertensive drugs and in 9.2% of encounters with diuretics	Implementation of a deprescribing intervention results in safe deprescription of antihypertensive drugs in a significant proportion of patients	Poor
McKean et al. (2016)	Prospective deprescribing feasibility study	Older adults admitted acutely to hospital with ≥8 regular medications. Median age 82.5 (IQR 74-87) years; median Rockwood frailty score 6 (IQR 5-6, indicating high frailty); projected 3-year mortality 55%	Deprescribing intervention to reduce polypharmacy, including antihypertensive drugs	50	Discontinuation was successful in 37/71 (52%) of antihypertensive drugs. Successful discontinuation was achieved for the following drug classes: ACE-inhibitors – 48%; diuretics – 52%; other antihypertensive drugs – 59%. No deaths or acute hospital admissions related to the drug discontinuation for 2.5 months.	In frail older adults, discontinuation of a range of different medications, including antihypertensive drugs, is safe and feasible.	Fair

Abbreviations: QoL – quality of life, ACE – angiotensin converting enzyme, AT2 – angiotensin 2, IQR – interquartile range

Table 3. Overview of osteoporosis drugs

Study	Type	Patients	Intervention	Sample size (N)	Relevant results	Interpretation	Quality
Black et al, (2006)	Randomized controlled trial	Community-dwelling, postmenopausal women with low FN-BMD. Mean age 73±6 years	Discontinuation of alendronate treatment after ≥3 (mean 5) years with continuation of calcium and vitamin D supplementation.	437	Discontinuing alendronate resulted after five years in: TH-BMD decreased to pre-treatment values in five years; FN- and trochanter BMD decreased, but remained above pre-treatment levels; LS-BMD increased slightly. No significant increase in all clinical fractures, X-ray detected vertebral fractures or non-vertebral fractures between groups; increase in clinical vertebral fractures compared to patients continuing alendronate ($RR_{alendronate}$ 0.45 (95-CI 0.24-0.85)).	Discontinuation of alendronate after ≥3 years of therapy does not significantly increase fracture risk for up to five years.	Good
Michalska et al. (2006)	Randomized controlled trial	Community-dwelling women with postmenopausal osteoporosis Mean age in placebo group 65±6 years	Discontinuation of alendronate treatment after ≥3 (mean 3.5) years with continuation of calcium and vitamin D supplementation.	33	Discontinuing alendronate resulted after 12 months in decrease of LS-BMD. TF- and FN-BMD did not change significantly.	This small study revealed no significant increase in fractures following discontinuation of alendronate treatment for 3.5 years.	Fair

Table 3 continued

Study	Type	Patients	Intervention	Sample size (N)	Relevant results	Interpretation	Quality
Dawson-Hughes et al. (2000)	Prospective observational cohort study	Healthy, community-dwelling men and women. Mean age 73±4 years.	Discontinuation of calcium and vitamin D supplements after 3 years of use	147	All BMD-gain was lost 2 years after discontinuation, except for TB-BMD in men.	This small study had insufficient power to reveal a significant increase in fractures during two years after discontinuation of calcium and vitamin D supplementation for 3 years.	Good
Deane et al. (2007)	Prospective observational cohort study	Postmenopausal community-dwelling women Mean age 66.7±2.1 years	Discontinuation of long-term (>5 years) bisphosphonate (etidronate or alendronate) use with continuation of calcium and vitamin D supplementation	35	Discontinuing long-term bisphosphonate treatment did not result in change in LS-BMD or TH-BMD after 12-18 months; FN-BMD gradually decreased, but remained above pre-treatment levels. No new symptomatic fractures occurred.	Discontinuation of bisphosphonate treatment for >5 years does not lead to an increased fracture rate in the first 12-18 months.	Poor
McClung et al. (2017)	Prospective observational cohort study	Community-dwelling, postmenopausal women Mean age 68.9±6.4 years	Discontinuation of denosumab of treatment after 4 to 8 years of use without subsequent osteoporosis treatment	65	Discontinuing long-term denosumab treatment resulted in a decrease in LS- and TH-BMD with 7.4% and 7.8% respectively and fracture rate increased from 4.9% to 9.8% after 12 months. Subsequent treatment with osteoporosis medication prevented BMD decrease and reduced fracture rate.	Discontinuing long-term denosumab treatment induces an increased risk of osteoporotic fractures during the first twelve months.	Poor

Table 3 continued

Study	Type	Patients	Intervention	Sample size (N)	Relevant results	Interpretation	Quality
Silva et al. (2011)	Prospective observational cohort study	Community-dwelling, postmenopausal women Mean age 71.0±6.7 years.	Discontinuation after ≥5 years alendronate treatment with continuation of appropriate calcium and vitamin D supplementation.	40	Discontinuing long-term alendronate treatment resulted in clinically significant BMD loss in spine and/or in femoral neck in 20-40% of the patients after 12 months. No elevated risk of fractures was observed.	Discontinuation after ≥5 years of alendronate treatment does not lead to an increased fracture rate in the first 12 months.	Poor
Watts et al. (2008)	Prospective observational cohort study	Community-dwelling, postmenopausal women with osteoporosis. Mean age and 72.0±7.5 years	Discontinuation after 3 years risedronate treatment with continuation of appropriate calcium and vitamin D supplementation.	398	Discontinuing alendronate treatment after 3 years resulted in a decrease in BMD after 12 months, but BMD remained above pretreatment levels. The risk of vertebral fractures remained below never users (RR 0.54; 95-CI 0.34-0.86, p=0.009).	Discontinuation after 3 years of risedronate treatment for does not result in increased fracture rate in the first 12 months.	Fair
Potter et al. (2016)	Randomized controlled trial	Older patients living in a residential aged care facility Mean age 84 ± 7 years	Deprescribing intervention to reduce polypharmacy, including osteoporosis drugs	95 (47 intervention, 48 control) 11	Osteoporosis medication was discontinued in 91% without a significant effect on adverse events or 12-month mortality	Discontinuing osteoporosis medication is safe and feasible.	Fair

Abbreviations: FN – femoral neck, BMD – bone mineral density, TH – total hip, LS – lumbar spine, TF – total femur, TB – total body, RR – relative risk, CI – confidence interval

Table 4. Overview of antihyperglycemic drugs

Study	Type	Patients	Intervention	Sample size (N)	Relevant results	Interpretation	Quality
Sjöblom et al. (2008)	Prospective observational cohort study	Older NH-residents with type 2 diabetes. Mean age 84.1±8.8 years	Discontinuation of antihyperglycaemic drugs in patients with DM2 and HbA1c ≤6.0% (42 mmol/mol)	32	Discontinuation of antihyperglycaemic drugs was successful in 75%; four patients (12.5%) developed hyperglycemia and antihyperglycaemic therapy was reintroduced. Mortality was not increased.	Oral antihyperglycaemic agents can be discontinued completely and insulin use can be reduced safely in the majority of older adults with DM2 and tight glycaemic control.	Fair
Niznik et al. (2020)	Retrospective observational cohort study	Patients ≥65 years with diabetes and a limited life expectancy and/or advanced dementia admitted to a nursing home. >50% likelihood of death within 6 months (based on Mortality Risk Index-Revised or admission assessment) and/or advanced dementia	Treatment de-intensification in patients with HbA1c ≤7.5% and ≥1 antihyperglycaemic drug	3056	Potential overtreatment of diabetes was observed in 43.9% on admission. Cumulative incidence of treatment de-intensification within 90 days was 45.5%	A substantial proportion of older NH residents may be overtreated for diabetes, despite LLE and/or advanced dementia.	Fair
Dharmarajan et al. (2020)	Prospective deprescribing feasibility study	Community dwelling older adults and long-term care facility residents. Mean age 78.2 years	Deprescribing intervention to reduce polypharmacy, including antihyperglycaemic drugs	383	Successful deprescription of oral antihyperglycaemic drugs in 15.5% and of insulin in 13.3% of patients encounters without adverse events within 6 months.	Implementation of a deprescribing intervention results in safe deprescription of antihyperglycaemic drugs in a significant proportion of patients.	Poor

Table 4 continued

Study	Type	Patients	Intervention	Sample size (N)	Relevant results	Interpretation	Quality
Garfinkel et al. (2010)	Prospective deprescribing feasibility study	Community-dwelling older adults with a life expectancy ≥3 months. Mean age 82.8±6.9 years; 57% was considered frail	Deprescribing intervention to reduce polypharmacy, including antihyperglycaemic drugs	70	Discontinuation of sulfonylureas was successful in 83% and of metformin in 27%. No deaths were considered to be related to drug discontinuation.	Discontinuation of a range of different medications, including oral antihyperglycaemic drugs, was safely achieved with no significant adverse events or deaths related to discontinuation.	Fair
McKean et al. (2016)	Prospective deprescribing feasibility study	Older adults admitted acutely to hospital with ≥8 regular medications. Median age 82.5 (IQR 74-87) years; median Rockwood frailty score 6 (IQR 5-6, indicating high frailty); projected 3-year mortality 55%	Deprescribing intervention to reduce polypharmacy, including oral antihyperglycaemic drugs	15/50 included oral antihyperglycaemic drugs	Discontinuation of oral hypoglycaemic agents was successful in 60%. No deaths or acute hospital admissions related to the drug discontinuation for 2.5 months.	In frail older adults, discontinuation of a range of different medications, including oral antihyperglycaemic drugs, is safe and feasible.	Fair

Abbreviations: DM2 – diabetes mellitus type 2, NH – nursing home, CGA – comprehensive geriatric assessment, IQR – interquartile range

Discussion

In conclusion, although harms and benefits of discontinuation of preventive medication in older patients with cancer and a limited life expectancy have thus far not been specifically studied, a number of studies has addressed this subject in other populations with a limited life expectancy. Good quality studies provide evidence that statins, bisphosphonates and calcium and vitamin D may be discontinued without adverse events in older patients with LLE. Discontinuation of statins in this population has in addition been shown to improve quality of life. Also, anti-hypertensive medication can be discontinued in patients with a LLE, provided the indication for prescription is not an alternative diagnosis such as heart failure. Although discontinuing antihyperglyaemic drugs in older patients with a LLE has only been evaluated in observational studies, the general view was that deprescription was often feasible and safe. Only discontinuation of denosumab may not be safe as it is associated with an increased fracture incidence. These findings supports the concept of deprescribing of drugs that are expected not to contribute to health benefits given a patient's condition and life expectancy and on the other hand may be associated with side effects.

The studies included in this review were in hospitalized patients and nursing home residents, but also in community dwelling elderly. In general, most of the nursing home residents and—to a lesser extend—hospitalized patients will have a life expectancy below average, so we expect that the results of these studies are exchangeable with our target population of older patients with cancer. Furthermore, if discontinuing drugs is safe and feasible in relatively healthy community dwelling older adults, we expect that safely discontinuing these drugs in older adults with cancer and a LLE is possible as well. Deprescribing is generally shown to be feasible and safe, patient preferences should play a central role in deprescribing, particularly in patients with LLE where the uncertainties about the benefits and harms of medications increase.

Of course, deprescribing is guided, at best, by evidence from randomized controlled trials, in which the older patient with cancer and LLE are not easily included. So while randomized controlled trials are the gold standard of evidence, alternative research designs, including observational designs, cohort studies and mixed-methods research integrating qualitative approaches are needed in this area of research as they are more feasible and reflect real life data. The majority of the studies included in this review are observational studies and these do show that deprescribing of preventive medications including antihypertensive drugs, osteoporosis drugs, and antihyperglycemic drugs, frequently is feasible in a substantial part of the patients and does not lead to serious adverse events, acute hospital admissions or death. Our review shows that a large proportion of patients with a limited life expectancy is willing to discontinue preventive medications in consultation with their physician.

Lipid lowering Drugs

In this review we found evidence that discontinuation of statins is safe in both primary and secondary prevention when the remaining life expectancy is limited. This is also supported by the fact that time until benefit (TUB) in older adults is 1.9 years [44,45]. Quality of life was shown to improve after discontinuation of statins. This may be explained by the fact that, statins are known to cause myopathies or statin-associated muscle symptoms in 0.3-33% of the users [46] and even more in the older population [47]. At the same time the vast majority of these patients are willing to have their statin deprescribed [48]. Therefore, we propose to discuss discontinuation of statins with all older patients with cancer and a LLE. The exception

may be for patients with active cardiovascular disease or a recent cardiovascular event in whom continuation of statins is required.

Antihypertensive Drugs

The purpose of antihypertensive treatment among others is reducing cerebrovascular incidents, an effect that does not occur immediately. This is apparent by the TUB of antihypertensive medication, which is between 2 to 4 years for mortality and any cardiovascular event [49,50]. Strict regulation of hypertension may provide little short-term benefit or may even worsen symptoms in older patients patient with LLE and the reviewed studies show that discontinuation of antihypertensive medication often is feasible and safe. Older patients are more prone to side effects, in particular postural hypotension [51]. Furthermore, antihypertensive drugs are associated with cognitive decline, falling, and electrolyte disturbances [52], which may become even more pronounced in patients with cancer and a LLE due to progression of the cancer. Therefore discontinuing antihypertensive medication should be considered in older adults with cancer and LLE. If the indication of the antihypertensive medication, however, is heart failure or fluid retention, symptoms frequently recur and discontinuation is not recommendable.

Osteoporosis Drugs

The treatment goal of osteoporosis medication is to reduce the occurrence of fractures. Strengthening bone tissue with pharmacotherapeutic agents is a slow process. The TUB for bisphosphonates is 6 months to 3 years, varying with the type of fracture [53-56]. As bisphosphonates are incorporated in bone tissue, their effect remains evident for at least 1 year after discontinuation. The major adverse drug reactions of oral bisphosphonates are gastro-intestinal symptoms and the required dietary and postural measures could impact the quality of life negatively [57]. We propose to discuss discontinuation of bisphosphonates, calcium and vitamin D, for treatment or prevention of osteoporosis with cancer patients and a LLE. When these drugs are prescribed for bone metastases and related pain, they should definitely not be discontinued.

Discontinuation of denosumab, on the contrary, was shown to increase fracture risk in the subsequent year. Importantly, denosumab for osteoporosis generally causes only minor side effects, comparable to placebo [58,59]. Therefore, discontinuation of denosumab cannot be recommended.

Antihyperglycemic Drugs

The treatment of diabetes has 2 main goals: short term prevention of (symptomatic) hypo- and hyperglycemia and long term prevention of micro- and macrovascular complications. The TUB of antihyperglycemic therapies for these long term complications is 7 to 10 years [60,61]. The short term complications, on the contrary, are acute and require immediate action. Especially in older adults with advanced cancer, dietary intake may be reduced due to the disease or chemotherapy [62] increasing the risk of hypoglycemia. The consensus based guidelines advise a higher target HbA1c for frail older adults and Diabetes UK issued a strategy document for handling diabetes at the end of life and proposes a fasting glucose level of 6-9 mmol/l (108-162 mg/dl), or even up to 15 mmol/l (270 mg/dl) when glucose monitoring is considered less worthwhile [63,64]. The adverse drug reactions with the most impact on the quality of life in older adults are hypoglycemic episodes [65-67]. We propose to decrease the intensity of the treatment regimen for diabetes stepwise in older adults with advanced cancer

and LLE. In patients with type 1 diabetes, insulin should not be discontinued, but the dosage may need to be adjusted to match changes in physical activity and dietary intake. Of note, in patients with cancer, treatment with corticosteroid such as prednisone or dexamethasone may evoke hyperglycemia that requires treatment with insulins.

Despite the need to re-evaluate therapies for older patients with cancer and LLE, there are no guidelines available for these specific patients. Studies that explored the feasibility of discontinuing medication almost invariably utilize a decision support tool like the Medication Appropriateness Index (MAI) [6]. Two tools may be of special interest in older adults with cancer and LLE. The Oncpal guideline is made for deprescribing inappropriate medications in palliative patients with cancer. The median age of the validation cohort was 66 years (range 23-93) with a median of 10 (range 4-21) medications per patient [68]. The STOPPFrail guideline is developed for frail older adults (e.g. end stage irreversible disease, poor 1 year survival prognosis, severe functional impairment, goal of symptom control) [3]. Both guidelines are developed using Delphi methodology and criteria are only partly evidence-based.
This review adds additional information to aid the clinician in assessing possible benefits and harms of discontinuing several groups of preventive medications in older adults with cancer and a LLE. To our knowledge there has been no attempt in the literature to define the decision-making process for physicians in determining which preventive medications should be discontinued in older patients with cancer and LLE that quantifies the expected success rates and complication rate per medication group.
A strength is that we found several studies that addressed the discontinuation of a range of preventive medications in relatively frail older adults. These studies reveal that approximately 50% or more of the preventive medications in use can be discontinued without serious adverse events. Therefore, despite the lack of direct evidence from discontinuation studies, discontinuing preventive drugs does seem safe and feasible in a substantial proportion of the older adults as we argue based on TUB and possible harmful effects of the medication classes.
The first limitation of this review is that the majority of the studies we found, were in older, non-frail adults without cancer and without a LLE. This may limit the possibility to draw solid conclusions about the safety of discontinuing preventive medication in the population we are interested in. However, if discontinuing medication is safe and feasible in these patients, these results seem applicable for older adults with cancer and LLE. Another limitation is the small number of suitable studies we found in our primary search. Despite an extended syntax, almost half of the studies were identified using cross-referencing. We learned that these articles missed in our initial search could have been identified by using “withdrawal” and “discontinuation” instead of “medication withdrawal” and “medication discontinuation” in our search strategy. Adjusting the search strategy in this yielded over 45,000 titles, prohibiting feasible review. More than half of the included studies were of fair quality. This was often due to lack of blinding of the outcome assessors, which is understandably difficult in this type of studies.
The evidence of the effects of deprescribing on QoL in older adults with cancer and a LLE is very limited. Future research should not only address the safety and feasibility of deprescribing, but the impact on QoL as well. Future research should also include the effect of treatment duration prior to deprescribing, as effects and side effects of a preventive drug may last for some time after discontinuation.

Conclusion

The recognition of reduced remaining life expectancy in older patients with cancer presents an opportunity to re-examine once-appropriate therapies and to reconsider their use. This review adds evidence that can be used in the decision making process of prescribing of preventive medication. The discontinuation of lipid lowering drugs, antihypertensive drugs and osteoporosis drugs appears to be safe and feasible. The few studies that have addressed discontinuation of antihyperglycemic drugs, indicate that discontinuation is often feasible in type 2 diabetes. Clinicians should be alert on the possibility of—and need for—discontinuing preventive medication when treating older adults with cancer and a LLE. Further research is needed to better inform the process of prescribing in these patients. The benefits of therapy should be better quantified and goals of therapy must be understood in the context of a LLE. Evidence regarding quality of life after deprescribing and patients' preferences are needed to develop shared decision-making models that are useful to clinicians and patients so that clinicians can confidently discontinue unnecessary medications, thereby reducing the pill-burden and possible adverse drug reactions.

References

1. Frazier SC. Health outcomes and polypharmacy in elderly individuals: an integrated literature review. J Gerontol Nurs. 2005; 31(9):4-11.
2. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. Arch Intern Med. 2010; 170(18):1648-1654.
3. Lavan AH, Gallagher P, Parsons C, O'Mahony D. STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. Age Ageing. 2017;46(4):600-607.
4. Scott IA, Anderson K, Freeman CR, Stowasser DA. First do no harm: a real need to deprescribe in older patients. Med J Aust. 2014;201(7):390-392.
5. Scott IA, Hilmer SN, Le Couteur DG. Going beyond the guidelines in individualising the use of antihypertensive drugs in older patients. Drugs Aging. 2019;36(8):675-685.
6. 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(7):643-651.
7. Oliveira L, Ferreira MO, Rola A, Magalhaes M, Ferraz Goncalves J. Deprescription in advanced cancer patients referred to palliative care. J Pain Palliat Care Pharmacother. 2016;30(3):201-205.
8. Poudel A, Yates P, Rowett D, Nissen LM. Use of preventive medication in patients with limited life expectancy: a systematic review. J Pain Symptom Manage. 2017;53(6):1097-110.e1.
9. Raijmakers NJ, van Zuylen L, Furst CJ, et al. Variation in medication use in cancer patients at the end of life: a cross-sectional analysis. Support Care Cancer. 2013;21(4):1003-1011.
10. Riechelmann RP, Krzyzanowska MK, Zimmermann C. Futile medication use in terminally ill cancer patients. Support Care Cancer. 2009;17(6):745-748.
11. Silveira MJ, Kazanis AS, Shevrin MP. Statins in the last six months of life: a recognizable, life-limiting condition does not decrease their use. J Palliat Med. 2008;11(5):685-693.
12. Turner JP, Shakib S, Singhal N, et al. Statin use and pain in older people with cancer: a cross-sectional study. J Am Geriatr Soc. 2014;62(10):1900-1905.
13. Alkan A, Yasar A, Karci E, et al. Severe drug interactions and potentially inappropriate medication usage in elderly cancer patients. Support Care Cancer. 2017;25(1):229-236.
14. Balducci L, Goetz-Parten D, Steinman MA. Polypharmacy and the management of the older cancer patient. Ann Oncol. 2013; 24(Suppl 7):vii36-40.
15. Pape E, Michel D, Scala-Bertola J, et al. Effect of esomeprazole on the oral absorption of dasatinib in a patient with Philadelphiapositive acute lymphoblastic leukemia. Br J Clin Pharmacol. 2016;81(6):1195-1196.
16. Popa MA, Wallace KJ, Brunello A, Extermann M, Balducci L. Potential drug interactions and chemotoxicity in older patients with cancer receiving chemotherapy. J Geriatr Oncol. 2014; 5(3):307-314.
17. Riechelmann RP, Tannock IF, Wang L, Saad ED, Taback NA, Krzyzanowska MK. Potential drug interactions and duplicate prescriptions among cancer patients. J Natl Cancer Inst. 2007;99(8): 592-600.
18. van Leeuwen RW, Brundel DH, Neef C, et al. Prevalence of potential drug-drug interactions in cancer patients treated with oral anticancer drugs. Br J Cancer. 2013;108(5):1071-1078.

19. van Leeuwen RW, Jansman FG, van den Bemt PM, et al. Drug-drug interactions in patients treated for cancer: a prospective study on clinical interventions. Ann Oncol. 2015;26(5):992-997.
20. van Leeuwen RW, Swart EL, Boom FA, Schuitenmaker MS, Hugtenburg JG. Potential drug interactions and duplicate prescriptions among ambulatory cancer patients: a prevalence study using an advanced screening method. BMC Cancer. 2010;10:679.
21. Thompson W, Lundby C, Graabaek T, et al. Tools for deprescribing in frail older persons and those with limited life expectancy: a systematic review. J Am Geriatr Soc. 2019;67(1):172-180.
22. National Heart Lung, and Blood Institute. Study quality assessment tools. Accessed April 2020. https://www.nhlbi.nih.gov/ health-topics/study-quality-assessment-tools
23. Kutner JS, Blatchford PJ, Taylor DH Jr., et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. JAMA Intern Med. 2015;175(5):691-700.
24. Dharmarajan TS, Choi H, Hossain N, et al. Deprescribing as a clinical improvement Focus. J Am Med Dir Assoc. 2020;21(3): 355-360.
25. McKean M, Pillans P, Scott IA. A medication review and deprescribing method for hospitalised older patients receiving multiple medications. Intern Med J. 2016;46(1):35-42.
26. Potter K, Flicker L, Page A, Etherton-Beer C. Deprescribing in frail older people: a randomised controlled trial. PLoS One. 2016; 11(3):e0149984.
27. Ekbom T, Lindholm LH, Oden A, et al. A 5-year prospective, observational study of the withdrawal of antihypertensive treatment in elderly people. J Intern Med. 1994;235(6):581-588.
28. Gulla C, Flo E, Kjome RL, Husebo BS. Deprescribing antihypertensive treatment in nursing home patients and the effect on blood pressure. J Geriatr Cardiol. 2018;15(4):275-283.
29. Nelson MR, Reid CM, Krum H, Muir T, Ryan P, McNeil JJ. Predictors of normotension on withdrawal of antihypertensive drugs in elderly patients: prospective study in second Australian National Blood Pressure Study Cohort. BMJ. 2002;325(7368): 815.
30. Straand J, Fugelli P, Laake K. Withdrawing long-term diuretic treatment among elderly patients in general practice. Fam Pract. 1993;10(1):38-42.
31. van Kraaij DJ, Jansen RW, Bruijns E, Gribnau FW, Hoefnagels WH. Diuretic usage and withdrawal patterns in a Dutch geriatric patient population. J Am Geriatr Soc. 1997;45(8):918-922.
32. van Kraaij DJ, Jansen RW, Gribnau FW, Hoefnagels WH. Use of diuretics and opportunities for withdrawal in a Dutch nursing home population. Neth J Med. 1998;53(1):20-26.
33. Walma EP, Hoes AW, van Dooren C, Prins A, van der Does E. Withdrawal of long-term diuretic medication in elderly patients: a double blind randomised trial. BMJ. 1997;315(7106):464-468.
34. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA. 2006;296(24):2927-2938.
35. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of withdrawal of calcium and vitamin D supplements on bone mass in elderly men and women. Am J Clin Nutr. 2000;72(3):745-750.
36. Deane A, Constancio L, Fogelman I, Hampson G. The impact of vitamin D status on changes in bone mineral density during treatment with bisphosphonates and after discontinuation

following long-term use in post-menopausal osteoporosis. BMC Musculoskelet Disord. 2007;8:3.
37. McClung MR, Wagman RB, Miller PD, Wang A, Lewiecki EM. Observations following discontinuation of long-term denosumab therapy. Osteoporos Int. 2017;28(5):1723-1732.
38. Michalska D, Stepan JJ, Basson BR, Pavo I. The effect of raloxifene after discontinuation of long-term alendronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab. 2006; 91(3):870-877.
39. Silva AG, Vieira JG, Kunii IS, Lana JM, Lazaretti-Castro M. The effects of discontinuing long term alendronate therapy in a clinical practice setting.Arq Bras EndocrinolMetabol. 2011;55(4):272-278. 40. Watts NB, Chines A, Olszynski WP, et al. Fracture risk remains reduced one year after discontinuation of risedronate. Osteoporos Int. 2008;19(3):365-372.
40. Curtis JR, Westfall AO, Cheng H, Delzell E, Saag KG. Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday. Osteoporos Int. 2008;19(11):1613-1620.
41. Niznik JD, Hunnicutt JN, Zhao X, et al. Deintensification of diabetes medications among veterans at the end of life in VA nursing homes. J Am Geriatr Soc. 2020;68(4):736-745.
42. Sjoblom P, Tengblad A, Lofgren UB, et al. Can diabetes medication be reduced in elderly patients? An observational study of diabetes drug withdrawal in nursing home patients with tight glycaemic control. Diabetes Res Clin Pract. 2008;82(2): 197-202.
43. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-2207.
44. Ridker PM, Lonn E, Paynter NP, Glynn R, Yusuf S. Primary prevention with statin therapy in the elderly: new meta-analyses from the contemporary JUPITER and HOPE-3 randomized trials. Circulation. 2017;135(20):1979-1981.
45. Magni P, Macchi C, Morlotti B, Sirtori CR, Ruscica M. Risk identification and possible countermeasures for muscle adverse effects during statin therapy. Eur J Intern Med. 2015;26(2):82-88.
46. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/ACVPR/AAPA/ABC/ACPM/ADA/AGS/
47. APhA/ASPC/NLA/ PCNA guideline on the management of blood cholesterol: executive summary. Circulation. 2019;139(25):e1046-e1081.
48. Qi K, Reeve E, Hilmer SN, Pearson SA, Matthews S, Gnjidic D. Older peoples' attitudes regarding polypharmacy, statin use and willingness to have statins deprescribed in Australia. Int J Clin Pharm. 2015;37(5):949-957.
49. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008; 358(18):1887-1898.
50. Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. Cochrane Database Syst Rev. 2009;(4):CD000028.
51. Lim KK, Sivasampu S, Khoo EM. Antihypertensive drugs for elderly patients: a cross-sectional study. Singapore Med J. 2015;56(5):291-297.
52. Dickerson LM, Gibson MV. Management of hypertension in older persons. Am Fam Physician. 2005;71(3):469-476.
53. Inderjeeth CA, Chan K, Kwan K, Lai M. Time to onset of efficacy in fracture reduction with current anti-osteoporosis treatments. J Bone Miner Metab. 2012;30(5):493-503.

54. van de Glind EM, Willems HC, Eslami S, et al. Estimating the time to benefit for preventive drugs with the statistical process control method: an example with alendronate. Drugs Aging. 2016; 33(5):347-353.
55. Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008a;(1):CD004523.
56. Wells GA, Cranney A, Peterson J, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008b; (1):CD001155.
57. Zhou M, Zheng Y, Li J, et al. Upper gastrointestinal safety and tolerability of oral alendronate: a meta-analysis. Exp Ther Med. 2016;11(1):289-296.
58. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-765.
59. Zhou Z, Chen C, Zhang J, et al. Safety of denosumab in postmenopausal women with osteoporosis or low bone mineral density: a meta-analysis. Int J Clin Exp Pathol. 2014;7(5):2113-2122.
60. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003;63(1):225-232.
61. Beckman JA, Creager MA. Vascular complications of diabetes. Circ Res. 2016;118(11):1771-1785.
62. Poulson J. The management of diabetes in patients with advanced cancer. J Pain Symptom Manage. 1997;13(6):339-346.
63. Diabetes UK. End of Life Diabetes Care: Full Strategy Document, 2nd ed. 2013.
64. End of Life Diabetes Care—Clinical Care Recommendations. 3rd Edition March 2018. Accessed April 19, 2019. https://www. diabetes.org.uk/resources-s3/2018-03/EoL_Guidance_2018_ Final.pdf
65. Lipska KJ, Krumholz H, Soones T, Lee SJ. Polypharmacy in the aging patient: a review of glycemic control in older adults with type 2 diabetes. JAMA. 2016;315(10):1034-1045.
66. Muller N, Khunti K, Kuss O, et al. Is there evidence of potential overtreatment of glycaemia in elderly people with type 2 diabetes? Data from the GUIDANCE study. Acta Diabetol. 2017; 54(2):209-214.
67. Nicolucci A, Pintaudi B, Rossi MC, et al. The social burden of hypoglycemia in the elderly. Acta Diabetol. 2015;52(4):677-685.
68. 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(1):71-78.