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## Is my older cancer patient on too many medications?

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## ABSTRACT

“Is my older cancer patient on too many medications?” is a question that confronts many physicians. Increasing age is associated with an increase in comorbidity, and consequently an increase in the number of medications prescribed to provide symptomatic relief and prevent disease related sequelae. The use of multiple medications, often termed polypharmacy, is highly prevalent in older people with cancer. Polypharmacy is not necessarily inappropriate but has been associated with drug–drug interactions, use of potentially inappropriate medications and a range of adverse events. Specific medications for which the risks outweigh the benefits are considered inappropriate, particularly when safer alternatives exist. Additionally, the appropriateness of medication therapy for both cancer and non-cancer indications is dependent on a patient’s life expectancy and treatment goals. A range of implicit and explicit tools are available to assist clinicians work as part of a multidisciplinary team to identify inappropriate or unnecessary medications. Inappropriate or unnecessary medications can be targeted for cessation. Deprescribing is the patient-centered process of reducing medications after consideration of treatment goals, benefits and risks, and medical ethics. A six step process for deprescribing in older patients with cancer is presented; 1) determine life expectancy and treatment goals, 2) review medications, 3) evaluate medication appropriateness, 4) identify medications to cease, 5) create a deprescribing plan, and 6) monitor and review. Although further research is required, there is an increasing body of research demonstrating that deprescribing inappropriate or unnecessary medications is feasible, can be done safely, and can improve patient quality of life.

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## Contents

1. Introduction . . . . .	0
1.1. Is Too Many Medications a Problem? . . . . .	0
1.2. Should the Question Be “Too Many Medications” or “Are all the Medications Appropriate”? . . . . .	0
1.3. How Can Medications Be Reduced? . . . . .	0
2. Conclusion . . . . .	0
Disclosures and Conflict of Interest Statements . . . . .	0
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References . . . . .	0

## 1. Introduction

Cancer is often considered a disease of aging with 60% of new cancer diagnoses in the United States of America occurring in patients aged

65 years and over [1]. Increasing age is associated with an increase in non-cancer comorbidities and a corresponding increase in number of prescribed medications [2,3]. When patients first present to their oncologist many are already prescribed a large number of medications for non-cancer related indications [4]. This can lead physicians to question, “is my older cancer patient on too many medications?”

The use of multiple medications, often termed polypharmacy, is highly prevalent among people diagnosed with cancer. The prevalence ranges from 32 to 51% depending on the definition of polypharmacy

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used [5–7], and has been shown to increase six months prior to cancer diagnosis [8]. This suggests that medications may be initiated to treat cancer symptoms prior to cancer being diagnosed [8].

Numerous definitions of polypharmacy have been presented in the geriatrics [9], and oncology literature. Definitions used within the oncology literature include; use of a large number of medications, medication duplication, medications without a clear indication (unnecessary medications), the use of five-or-more medications, use of inappropriate medications and the presence of drug–drug interactions (DDIs) [1,10–14]. Outside of the oncology literature, inappropriate medication use is often defined as that for which the risks outweigh the benefits, particularly when safer alternatives exist [15]. Although the likelihood of DDIs increases with an increasing number of medications, DDIs do not typically define polypharmacy [16].

### 1.1. Is Too Many Medications a Problem?

Polypharmacy is not always inappropriate because there are valid clinical indications for using multiple medications [17]. Polypharmacy may arise due to guideline concordant prescribing for multiple chronic conditions [18]. However, polypharmacy is still an important consideration for older people with cancer. This is because polypharmacy has been associated with harms including impaired physical function [19], grade III–IV toxicity [7,20], frailty [19], falls [21], use of potentially inappropriate medications [22,23], and reduced adherence to oral cancer treatments [24], although the latter is not conclusive [25]. Additionally, increasing numbers of medications places patients at increased risk of drug–drug and drug–disease interactions [16,26].

Drug–drug interactions are of particular concern for older people with cancer. The prevalence of DDIs ranges from 27 to 63% with DDIs reported to result in 4% of cancer deaths in hospitalized patients [27–29]. While the majority of DDIs in older people with cancer involve non-chemotherapeutic medications [30], DDIs may occur between medications used to treat comorbidities and chemotherapy or supportive treatments. The most common DDIs are due to medications metabolized by cytochrome P450 isoenzymes [31]. For example, irinotecan and capecitabine are metabolized by CYP 3A4 and therefore have the potential to interact with non-cancer medications such as amiodarone, diltiazem or fluconazole.

### 1.2. Should the Question Be “Too Many Medications” or “Are all the Medications Appropriate”?

“Is my patient on too many medications?” may not always be the right question. Although polypharmacy is often viewed as being synonymous with overtreatment, ironically polypharmacy may also be associated with under treatment. This may be because physicians are reluctant to prescribe an additional medication to an already long list of medications, even if the additional medication is recommended in clinical practice guidelines [32–34]. Therefore, optimizing medication therapy requires the clinician to not only focus on the number of medications, but also on whether each medication is appropriate in relation to a patient's goals and life expectancy. Assessing medication appropriateness requires an individualized assessment of the risk and harms of treatment.

When considering a medications appropriateness, there are several factors to contemplate. Firstly, because of age-related pharmacokinetic and pharmacodynamic changes, older people may be at increased risk of adverse drug events and treatment toxicity [35–37]. These changes may be exacerbated in older people with cancer as a result of volume of distribution changes from oedema or anemia [35]. Secondly, changes in frailty status may also confer greater susceptibility to adverse drug events and treatment toxicity [38,39]. Thirdly, reduced life expectancy may be a factor in patients choosing to focus on treatment of symptoms rather than preventative management of chronic conditions.

Assessing whether a medication is unnecessary or inappropriate requires a comprehensive understanding of the patient's clinical situation,

their treatment goals and the indication for each medication. To elucidate this understanding, several studies have used multidisciplinary geriatric oncology teams consisting of oncologists, geriatricians, nurses, pharmacists and allied health workers [22,40,41]. Goals of the team include reviewing a patient's life expectancy, frailty status, treatment goals and identifying inappropriate or unnecessary medications. To determine if a medication is unnecessary requires knowledge of the indication it is being used to treat. For example, ACE inhibitors can be prescribed as a preventative medication, or to provide symptomatic relief. Used in the treatment of congestive heart failure, ACE inhibitors reduce symptoms which may be clinically relevant for patients. Conversely, used as an antihypertensive, ACE Inhibitors may prevent future complications, which may not be a treatment goal for a patient in the terminal phase. Determining if an ACE inhibitor is prescribed for symptomatic relief, or as preventative therapy, can guide physicians in determining if it is necessary, or if it can be deprescribed.

A range of implicit and explicit tools have been developed to assist clinicians identify potentially inappropriate medications. Explicit tools include Beers Criteria and STOPP [15,42]. When applying these tools, the prevalence of PIMs in older people with cancer ranges from 11% to 41% or 32% to 38% respectively [22,43]. The use of PIMs has been associated with polypharmacy, and with being frail as opposed to fit [40]. A number of studies have used clinical pharmacists within a multidisciplinary team to identify PIMs. A recent study demonstrated that pharmacist review was associated with a decline in the prevalence of PIM use from 32% at hospital admission to 16% at hospital discharge [43]. However, prospective trials are required to determine if medication review leads to improved clinical outcomes. In a study of community dwelling older people, STOP&START criteria identified only 19% of all drug related problems [44]. Therefore, clinical judgment is needed to determine whether the benefit of a specific medication outweighs the risk in older people with cancer [40].

Life expectancy can play an important role in determining a medications appropriateness. Many non-cancer medications may be deemed inappropriate, unnecessary or futile in patients with limited life expectancy [45]. For example, medications that provide symptom relief, yet increase the risk of harm, may be inappropriate, and are candidates for deprescribing under supervision. Additionally, medications used to prevent future complications from comorbidities may become unnecessary, or futile, if the time to benefit that is longer than the patient's life expectancy [45,46]. Statins need to be used for many years before demonstrating a reduction in cardiovascular events. Despite this, studies investigating statin use in patients with terminal cancer reveal that approximately one third of patients with cancer use statins at the time of death [47,48]. In addition to having limited benefit, statins may also increase the risk of harm. A study of community dwelling older people with cancer found that the odds of statin users aged  $\geq 80$  years experiencing moderate to severe pain were four-fold greater compared to those who did not use statins [31]. There is no direct evidence that statins reduce mortality in patients aged  $\geq 80$  years [32]. Statins, along with other preventative medications, may be classed as futile and therefore considered as candidates for deprescribing [45].

There is an increasing body of evidence to support deprescribing inappropriate and unnecessary medications in older people. A study enrolling patients with limited life expectancy investigated outcomes from deprescribing statins. There was no increase in cardiovascular events or mortality [49]. Additionally, patients who had their statins deprescribed reported a significant increase in quality of life. This supports previous studies in frail older people with multimorbidity, where deprescribing inappropriate and unnecessary medications reduced hospital admissions and improved patient perceived health related quality of life [50,51].

### 1.3. How Can Medications Be Reduced?

Medications identified as inappropriate or unnecessary are potential candidates for deprescribing. Deprescribing is defined as the process of

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