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## POLYPHARMACY AND POTENTIALLY INAPPROPRIATE MEDICATION USE IN GERIATRIC ONCOLOGY

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### Abstract

Polypharmacy is a highly prevalent problem in older persons, and is challenging to assess and improve due to variations in definitions of the problem and the heterogeneous methods of medication review and reduction. The purpose of this review is to summarize evidence regarding the prevalence and impact of polypharmacy in geriatric oncology patients and to provide recommendations for assessment and management. Polypharmacy has somewhat variably been incorporated into geriatric assessment studies in geriatric oncology, and polypharmacy has not been consistently evaluated as a predictor of negative outcomes in patients with cancer. Once screened, interventions for polypharmacy are even more uncertain. There is a great need to create standardized interventions to improve polypharmacy in geriatrics, and particularly in geriatric oncology. The process of deprescribing is aimed at reducing medications for which real or potential harm outweighs benefit, and there are numerous methods to determine which

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medications are candidates for deprescribing. However, deprescribing approaches have not been evaluated in older patients with cancer. Ultimately, methods to identify polypharmacy will need to be clearly defined and validated, and interventions to improve medication use will need to be based on clearly defined and standardized methods.

### Keywords

geriatrics; elderly; cancer; polypharmacy; deprescribing; geriatric assessment; geriatric oncology

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## INTRODUCTION

Polypharmacy is often described as a prescribing challenge, particularly in the care of older patients with cancer and multiple comorbid conditions that interact in complex ways. There are various definitions of polypharmacy, making it challenging to understand the scope and impact of the problem. A 2008 review suggested that there are 24 distinct definitions of polypharmacy in general use, encompassing concepts ranging from unnecessary or inappropriate medication use to the use of excessive numbers of medications.<sup>1</sup> The lack of a consistent definition and understanding of polypharmacy creates confusion for clinicians, educators, and researchers.<sup>2</sup>

While the use of many medications may be a good practice for the treatment of many chronic conditions, polypharmacy in the context of care of the older patient generally refers to inappropriate polypharmacy, focusing on the negative aspects of medication use. Taking an increasing number of medications, using medications that are not indicated for existing medical conditions, being exposed to drug-drug interactions, and taking medications that are high risk and/or low benefit (so-called inappropriate medications) are all potential negative aspects of polypharmacy.<sup>3</sup> Among the other negative effects of polypharmacy are increased risk of adverse drug reactions, functional decline and falls, delirium and cognitive impairment, and in some studies, increased risk of hospitalization, healthcare utilization, and mortality, and even underprescribing.<sup>4-7</sup> The more medications a patient is taking, the more likely a patient is to have an adverse drug event, experience a drug-drug interaction, to take a potentially inappropriate medication, or to be nonadherent to one of the medications.<sup>8</sup> However, as demonstrated in recent cohort studies of middle-aged and older adults, polypharmacy may not always be inappropriate or indicative of poor quality care, particularly in chronic conditions in which multiple medications are required to maintain stable disease control, such as cardiovascular disease.<sup>9, 10</sup>

The simplest and most conventional definitions for polypharmacy are those based on the number of medications a patient is taking. When assessing for polypharmacy, a review must include an assessment of non-prescribed medications as well as herbal medicines and supplements. The use of 5 or more medications regularly has been a frequently used definition for polypharmacy. The advantage of such a definition is the replicability in research settings and ease of use in clinical practice when screening patients for polypharmacy.<sup>11</sup> However, the disadvantage of applying such a definition in clinical settings is that simple medication number disregards the harmful or beneficial aspects of each

medication. Using an absolute number of medications to define polypharmacy does not account for a clinician's determination that polypharmacy may be appropriate in some instances, when making individualized prescribing decisions. This is particularly the case for patients with multimorbidity in whom multiple treatments have clear benefits. While some have defined "excessive polypharmacy" as a very high number of medications (such as 10 or more regular medications), this definition may have excellent specificity but inadequate sensitivity to apply as a screening tool for harmful medication use.<sup>12</sup> Taking 5 or more regular medications has been associated with falls, disability, and frailty in general geriatric populations and in geriatric oncology, and thus has some justification as a reasonable cut-point for polypharmacy based on the association with adverse outcomes in older patients.<sup>13, 14</sup> For example, the sensitivity and specificity for 5 or more medications and the risk of falls is 75.7% and 44.5%, respectively; at a cut-point of 10 or more medications, the sensitivity is 24.3% and specificity is 85.5%.<sup>14</sup>

The use of medications and the presence of polypharmacy are on the rise in the general population. In the United States, 90% of adults 65 and older participating in the National Health and Nutrition Examination Survey in 2011-2012 reported taking at least one prescription in the prior 30 days, and 39% reported using 5 or more prescription drugs.<sup>15</sup> Based on population registry data from Tayside, Scotland, 22.1% of all persons used 5 or more drugs, and 24.0% of people 80 years and older were dispensed 10 or more drugs in 2010.<sup>16</sup> An additional contributor to polypharmacy is the use of complementary and alternative medicine, which is highly prevalent in many populations, including older patients with cancer. Such medications contribute to the overall pill burden, cost, nonadherence to conventional medications, and risk of drug-drug and drug-disease interactions.<sup>17</sup>

Older patients with cancer are potentially at a higher risk of polypharmacy. Geriatric oncology patients have a high burden of comorbidity, geriatric conditions, and disability, and are likely to use multiple medications and to be more susceptible to adverse effects of medications.<sup>18</sup> Many may already meet the criteria for polypharmacy prior to the initiation of cancer chemotherapy and supportive care therapies. Cancer-related therapy also adds to the prevalence of polypharmacy because of the increased pill burden and regimen complexity, all of which can lead to compromised cancer management plans, such as treatment delays or premature treatment discontinuation due to toxicity or adverse drug events. Furthermore, in patients with advanced cancer near the end of life, as goals of care change to more palliative treatment, additional medications are added to control symptoms, while few medications for comorbid conditions are stopped.<sup>19</sup> It is uncertain whether the geriatric oncology population is uniquely susceptible to polypharmacy, and whether specific interventions need to be designed for this population. The purpose of this narrative review is to summarize evidence regarding the prevalence and impact of polypharmacy and potentially inappropriate medicine use in geriatric oncology patients and to provide recommendations for assessment and management.

## **POLYPHARMACY AND OUTCOMES IN CANCER**

Several studies have evaluated the prevalence of polypharmacy in older patients with cancer. Depending on the definition of polypharmacy, 11% to 96% of older patients with cancer

were exposed to polypharmacy.<sup>14, 20-26</sup> Nightingale and colleagues found a prevalence of 84% for polypharmacy, which includes 43% of patients who met criteria for excessive polypharmacy, or 10 or more medications.<sup>24</sup> The mean number of medications was 9.23 and this was prior to anticancer therapy initiation for most of the patients in the cohort.<sup>24</sup> Other studies have found that older patients with cancer take a median number of medications of 5 to 9.1.<sup>14, 25</sup> In advanced cancer, patients take more medications, likely because additional drugs are added for supportive care.<sup>27</sup> In one chart review of 100 patients with advanced cancer, 95% had polypharmacy in the week before death.<sup>28</sup> In oncology settings, the presence of polypharmacy has been associated with higher numbers of comorbidities, increased use of inappropriate medications, worse performance status, frailty syndrome, poor physical function and poor survival.<sup>24, 29, 30</sup>

Several studies in geriatric oncology that have looked at multiple risk factors for adverse outcomes have identified the effect of polypharmacy (**Table 1**). As defined by medication number, polypharmacy has been associated with postoperative complications and length of stay.<sup>31, 32</sup> Increased medication number has also been associated with chemotoxicity in some studies, but not consistently.<sup>33, 34</sup> Polypharmacy was not associated with treatment decisions in one study,<sup>35</sup> but was associated with an increased likelihood of receiving non-surgical treatment in another study.<sup>36</sup> In addition, many studies have found an association with polypharmacy and adverse geriatric-specific outcomes. Medication number has been associated with physical function, frailty, and delirium in studies including geriatric oncology patients.<sup>29, 37, 38</sup> A recently published meta-analysis of data from three phase II/III studies in ovarian cancer found that polypharmacy was associated with overall grade III/IV toxicity, hematological and nonhematological toxicities, but not associated with overall survival.<sup>39</sup>

While there are few studies regarding outcomes, the existing evidence suggests that an increased number of medications used in geriatric patients with cancer could increase the risk of complications, chemotoxicity, and increases the risk of functional decline. However, most existing studies have evaluated polypharmacy as a covariate or risk factor as part of a larger exploration of many potential risk factors for adverse outcome. Ultimately, implementing polypharmacy screening and intervention as part of routine practice will require studies specifically designed to examine the impact of polypharmacy on outcomes in older patients with cancer.

## POTENTIALLY INAPPROPRIATE MEDICATION USE

Potentially inappropriate medications (PIMs) are largely referred to as medications lacking evidence-based indications, medications with treatment risks that may outweigh their benefits, medications that are significantly associated with adverse drug reactions, and those that may potentially interact with other medications or other diseases.<sup>40</sup> There have been a few specific criteria developed for identification of PIMs, including the Beers criteria and Screening Tool for Older People's Prescriptions (STOPP). The Beers criteria was originally developed in 1991 as a list of drugs to avoid in older patients residing in nursing homes and has since been updated for older patients 65 and older and revised multiple times by expert panels, most recently in 2015. It is a list of more than 110 potentially problematic

medications to avoid and more than 60 drug-disease combinations to avoid in older people.<sup>41</sup> The STOPP criteria is a list of 80 indicators for appropriate prescribing, including drugs and doses to avoid as well as drug-disease combinations to avoid. STOPP was developed in 2008 and updated in 2015.<sup>42</sup> Another tool to identify inappropriate medication use is the Medication Appropriateness Index (MAI),<sup>43</sup> a list of 10 indicators for prescribing that are applied to each medication on a patient's list. This tool is useful to identify factors like drugs lacking indication, lacking effectiveness, or potentially increasing the risk of harm. The National Comprehensive Cancer Network (NCCN) Older Adult Oncology Guideline refers to the MAI,<sup>44</sup> however, the MAI may be time-consuming to administer, cumbersome for use in clinical settings, must be performed by a skilled clinician with training, and does not address underprescribing.<sup>45</sup> The NCCN guidelines also present a list of specific medications which may be considered of particular concern to the geriatric oncology population including sedatives, first generation anti-histamines and anti-emetic drugs.<sup>44</sup>

In the general geriatric population, 12%-63% are exposed to PIMs, based on either the Beers or STOPP criteria.<sup>46</sup> Most studies evaluating PIMs in patients with cancer have used the Beers criteria.<sup>20, 22, 23, 47-49</sup> To date, one study has evaluated the prevalence of PIMs in patients with cancer using both the Beers and the STOPP criteria in a senior adult oncology ambulatory center in the US.<sup>24</sup> The overall prevalence of PIMs was 51%, and was 38% according to STOPP criteria and 40% according to the 2012 Beers criteria.<sup>24</sup>

## OUTCOMES ASSOCIATED WITH POTENTIALLY INAPPROPRIATE MEDICATION USE

Very few studies have evaluated whether the use of inappropriate medications is associated with adverse outcomes in geriatric oncology. In a study of 414 older patients in the general population, the presence of both PIMs and polypharmacy combined had a statistically significant positive correlation to increased hospital readmissions. PIM use alone, however, was not found to be significantly related to readmissions.<sup>50</sup> In a secondary analysis of a prospective study of factors related to chemotherapy-related adverse events in 7 academic medical centers, there was no association found between either polypharmacy or PIM use and chemotherapy toxicity or hospitalization.<sup>26</sup> Another study evaluating the impact of PIMs on outcomes in patients with breast cancer receiving chemotherapy found no association between PIM use and the composite outcome of emergency room visits, hospitalization or death in 6 months.<sup>51</sup>

Despite the potential harms of PIMs, observational studies of emergency room visits and hospitalizations due to adverse drug reactions (ADRs) have found that most of the medication-related harm in older persons is not due to PIMs, but is in fact due to common classes of medications not considered inappropriate, including anticoagulants, opioids, antiplatelet agents, oral hypoglycemic drugs, insulin, and antiarrhythmic agents.<sup>52</sup> However, in the same secondary analysis of chemotherapy-related adverse events that found no association with PIMs, there was no association between these 6 high risk medication classes and adverse outcomes.<sup>26</sup> There are a few possibilities for the lack of association between PIM use and adverse outcomes in geriatric oncology: 1) there are too few studies to date to show an association, and the studies that have been conducted have included

heterogeneous populations with early stage and advanced cancer patients; 2) it is possible that no association between PIMs and harm exists in geriatric oncology; 3) several medications considered to be PIMs are also necessary supportive oncology drugs, and may actually mitigate harm in older patients. (NCCN) Additionally, PIM criteria may be inapplicable to the end of life oncology population, when preventative medications might be considered inappropriate but PIMs (e.g., benzodiazepines) might be appropriate and recommended.<sup>53</sup>

## ADDRESSING POLYPHARMACY AS PART OF GERIATRIC ASSESSMENT

A strategy to provide more appropriate, safe medication use in older patients with cancer may need to go beyond simple medication number, PIMs, and high risk medications to include a comprehensive evaluation of medication use and risk factors for ADRs. The medication use process comprises a series of stages including prescribing, communicating medication orders, dispensing, administering and monitoring. Because of this multi-stage process, adequate patient-provider consultation time is needed to conduct comprehensive medication assessments in order to identify all medication related problems. This comprehensive medication assessment should be done periodically, especially with the initiation or modification of the patient's oncologic management or when there are changes in disease management, changes in clinical condition and/or during transitions of care. During the visit, the provider should confirm medication indication (e.g. medication-condition matching), dosage (e.g. dosages appropriate for renal and/or liver function), duration, assess for drug duplication, drug-drug-, drug-disease interactions and adverse effects; in addition, the patient's ability to read medication label directions and to manage medications in an organized manner should be assessed. The provider should not only consider the pharmacological properties of the medications, but should also consider the patient's comorbidities, cancer prognosis, cognitive and functional status as well as social, cultural and economic factors. In this way, the prescribing process encompasses the patient's goals of care coupled with maintaining quality of life. A comprehensive medication review is considered to be an integral part of the geriatric oncology assessment based on the NCCN Older Adult Oncology guidelines.<sup>44</sup> The guidelines recommend a comprehensive medication assessment, which includes a thorough review of patients' medications with subsequent discontinuation of any nonessential medications and evaluation for drug interactions, adverse effects, and patient adherence. Geriatric assessment (GA) is a compilation of various validated tools to assess multiple domains in older adults and has been shown in prior studies to influence decision-making and predict outcomes such as hospitalization and treatment complications in older patients with cancer.<sup>35, 54</sup> While the domains of GA include a comprehensive assessment of functional status, nutrition, comorbidities, cognition, mental health, and social supports, a clear method for the assessment of polypharmacy has not been established.

In recent years, an increasing number of studies have incorporated the use of GA in older adults with cancer.<sup>35, 36, 55</sup> However, polypharmacy was not consistently included as part of the GA, which may be due to studies showing mixed results in the correlation between polypharmacy and various clinical outcomes, compared to strong correlations noted in other GA domains such as comorbidities, functional and nutritional status.<sup>33, 56-59</sup> For studies that



did include medication assessment, the data was often analyzed and presented as number of medications. For example, Joly et al. identified that 43% of older patients aged 65 or above with normal Karnofsky performance status (80%-100%) reported taking 9 or more medications.<sup>60</sup> Some studies further characterized polypharmacy but the definition varies, with the most common definition being the concurrent use of 5 medications.<sup>35, 36, 55</sup>

When polypharmacy is detected from GA, it is unclear whether interventions aimed at reducing medication number are of benefit. Further, many recommended interventions made through GA may not have adequate uptake by oncologists. Selected studies published since 2010 assessing polypharmacy and associated interventions are shown in **Table 2**. In the ELCAPA study, geriatricians proposed to have the prescribed medication changed in 31% of patients based on GA results but the percentage of uptake from the proposed medication intervention as well as the benefits of the intervention were not reported.<sup>35</sup> In a study by Kalsi et al, GA interventions were shown to improve chemotherapy tolerance in older patients aged 70 or above undergoing chemotherapy.<sup>61</sup> In this population, 19% received intervention to reduce unnecessary medications such as adjustment of anti-hypertensive medications in over or undertreated patients. These interventions, however, vary across the various studies and were not clearly defined. In addition, while different definitions of polypharmacy account for variation in different studies, differences in the way medication use is actually assessed may lead to significant variation in prevalence and impact on outcomes.

## DEPRESCRIBING AS A POTENTIAL INTERVENTION FOR POLYPHARMACY

Deprescribing is defined as the “systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences.”<sup>62</sup> While few studies have evaluated the positive outcomes of deprescribing, several trials have evaluated the potential negative consequences of stopping medications, including exacerbation of the underlying disease as well as drug withdrawal syndromes.<sup>63</sup> A systematic review of drug withdrawal trials found that the vast majority of medications could be safely stopped without adverse events, with careful attention to slower withdrawal and close monitoring when stopping cardiovascular drugs and psychotropic agents.<sup>63</sup> Studies evaluating the positive effects of deprescribing have shown a reduction in overall medication number, reduction in the number of inappropriate medications, reduction in hospital length of stay, association with global improvements in health, and improvements or slower declines in quality of life.<sup>62</sup> No studies have been specific to geriatric oncology patients, and thus, the benefits and harms of deprescribing in geriatric oncology are unknown.

Patients who are prescribed multiple drugs, who take potentially inappropriate medications (PIMs), and who have changing goals of care are among the candidates for careful medication review with a consideration of deprescribing where appropriate. The process of deprescribing has been described in five steps (see **Box**).<sup>62</sup> Some of the steps may seem more straightforward and feasible in geriatric oncology. The ability to identify those drugs that are high risk/low benefit and to prioritize their discontinuation remains an area in which

further research is greatly needed, both in geriatric oncology and in general geriatric populations.

Although deprescribing is a possible intervention for older patients with cancer who have polypharmacy, the question remains who should lead this intervention among a team that may consist of a geriatrician, oncologist, pharmacist, and primary care provider. Barriers to accomplishing a deprescribing intervention include the oncologists' familiarity and comfort with making changes to non-cancer medications, the need for communication and coordination with other providers, the patient or family member's reluctance to change medication, and, of course, the lack of evidence of benefit or harm of deprescribing in this population.

One approach to optimizing the prescribing and de-prescribing process is through utilization of pharmacists as part of the healthcare delivery model for inter-professional, team-based care.<sup>41</sup> The Institute of Medicine recognizes the significant role played by pharmacists in the areas of medication therapy management and medication safety, as well as the value of pharmacist–physician collaboration in patient care.<sup>64-66</sup> Pharmacists have the professional education, training, skills, and medication use expertise to employ evidence-based medicine which is crucial for this complex population that takes multiple medications. Teams led by pharmacists to identify, prevent, and resolve medication related problems and promote the correct use of medications may improve the likelihood that patients receive appropriate pharmaceutical care.<sup>7</sup> Thus, there is potential for pharmacists to play an important role as a member of the inter-professional team.

## CONCLUSIONS

In summary, there is a need for validated methods to define polypharmacy and to incorporate assessment and evaluation as a standard part of GA for older adults with cancer. While there are many acceptable definitions of polypharmacy, GA that includes screening for harmful medication use may require a simplified approach, to be able to consistently define the prevalence and impact of the problem and to design interventions. An increased number of medications that a patient is regularly taking is the most significant independent predictor of harm,<sup>62</sup> both in general geriatric and in geriatric oncology populations. Once polypharmacy has been screened, the next step is to use a combination of tools designed to identify harmful medication use, such as the Beers and STOPP criteria, the MAI, as well as a review for high risk drugs. The Beers, STOPP, and MAI are considered viable options for use in clinical practice and may complement each other in their ability to identify harmful medications. Once harmful medication use has been identified, deprescribing interventions need to be initiated. Ultimately, to incorporate the assessment of polypharmacy into GA studies and interventions, a clear, simple definition of polypharmacy would be beneficial, and the methods of medication review and intervention need to be clearly described and developed within the field to improve replicability of such studies.

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**Box. Steps to Deprescribe<sup>62</sup>**

- 1) Reconcile all medications and consider their indications.
- 2) Consider overall risk of harm when considering the intensity of deprescribing intervention.
- 3) Assess each drug in terms of current or future benefit in relation to current or future harm.
- 4) Prioritize drugs for deprescribing, giving preference to those that have the most unfavorable risk/benefit ratio and least likelihood of withdrawal symptoms.
- 5) Implement a discontinuation plan and monitor for improvement or adverse effects as the result of deprescribing.

(Adapted from Scott IA, Hilmer SN, Reeve E, Potter K, Le Couteur D, Rigby D, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med.* 2015;175(5):827-34.)

**Table 1**

## Polypharmacy and Association with Outcomes in Geriatric Oncology

Study	Population	Definition of Polypharmacy	Patients Meeting Polypharmacy Criteria		Outcomes
			N	%	
Caillet et al. 2011 <sup>35</sup>	375 patients >70 years with solid tumors in a GA intervention; 54.6% had metastatic disease	5 oral medications daily	242	67%	Not associated with a change in cancer treatment plan
Parks et al. 2015 <sup>36</sup>	47 women >70 years with early stage, operable breast cancer	4 daily medications	27	59%	Associated with non-surgical treatment of cancer (p=0.002)
de Glas et al. 2013 <sup>31</sup>	3179 women >65 years who underwent surgery for breast cancer (all stages)	5 different types of medication	428	14%	Associated with the risk of postoperative complications OR 1.84, 95% confidence interval (CI) 1.46-2.32
Badgwell et al. 2013 <sup>32</sup>	111 patients >65 years undergoing abdominal surgery for types of cancer, primarily GI	Use of >5 medications	53	48%	Increased length of stay OR 2.45, 95% CI 1.09-5.49
Hamaker et al. 2014 <sup>33</sup>	73 women >65 years with metastatic breast cancer receiving first-line single-agent palliative chemotherapy	Use of >5 medications	37	51%	Associated with grade 3-4 chemotherapy-related toxicity Unadjusted OR 6.38, 95% CI 1.99-23.47
Freyer et al. 2005 <sup>37</sup>	83 women >70 years with Stage III/IV ovarian cancer	6 daily medications	7	8%	Lower overall survival (p=0.04) for those with polypharmacy
Kim et al. 2014 <sup>34</sup>	98 patients >65 years receiving palliative chemotherapy (multiple cancer sites included)	>6 medications	39	40%	No association with early discontinuation of palliative chemotherapy
Turner et al. 2014 <sup>29</sup>	385 patients >70 years seen in an outpatient oncology clinic (multiple cancer sites included)	Use of >5 regular medications	221	57%	Associated with impaired physical function (OR 1.13, 95% CI 1.06-1.20) and being frail (OR 4.48, 95% CI 1.90-10.54) and pre-frail (OR 2.35, 95% CI 1.43-3.86)
Senel et al. 2015 <sup>38</sup>	213 patients, mean age 60.3 years, in an inpatient palliative care unit (multiple cancer sites included)	Use of >3 medications	111	52%	Associated with incident delirium in univariate analysis (p<0.05)
Elliot et al. 2014 <sup>30</sup>	150 patients >60 years of age, with acute myelogenous leukemia (AML)	Use of >4 medications	78	52%	Associated with 30-day mortality in adjusted analysis (OR 9.98, 95% CI 1.18-84.13). Lower odds of achieving remission (OR 0.20, 95% CL 0.06-0.65)



**Table 2**

## Interventions for Polypharmacy in Geriatric Assessment Studies

Study	Definition of Polypharmacy	Interventions	Outcome
Aparicio et al. 2010 <sup>67</sup>	1 anticoagulant or 2 cardiovascular or 2 psychotropic medications or 10 medications	Geriatricians proposed non-oncological treatment adaptation	CGA led to an adaptation of the non-oncological treatment in 15 (72%) and of the social care in 8 (38%) patients, but never modified the oncological strategy
Caillet et al. 2011 <sup>35</sup>	Concurrent use of $\geq 5$ medications	Geriatricians proposed change in prescribed medication	Functional status assessed by the ADL score and malnutrition were independently associated with changes in cancer treatment
Horgan et al. 2012 <sup>68</sup>	--	Geriatric oncology service made recommendations on medication change	Previously unidentified medical problems were identified in 70% of patients
Kalsi et al. 2015 <sup>61</sup>	Concurrent use of $\geq 5$ medications	Intervention to reduce unnecessary medications such as adjustment of antihypertensive medications in over or undertreated patients	Geriatrician-led CGA interventions were associated with improved chemotherapy tolerance

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