Chapter 9
The Management of Polypharmacy in People with Cancer and Chronic Conditions

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Abstract Polypharmacy has a broad definition, encompassing the use of multiple medications, the use of more medications than necessary, or the use of inappropriate medications. Polypharmacy itself is not necessarily inappropriate, however, it has been associated with negative outcomes in patients with multiple chronic conditions. For people diagnosed with cancer, medications may be prescribed to treat cancer, ameliorate symptoms, improve quality of life and to manage or prevent future complications of chronic diseases. However, the potential benefits of each medication need to be balanced against the potential harms. For example, in studies of older people with cancer, polypharmacy has been associated with greater risk of chemotherapy discontinuation, mortality, grade III-IV toxicity, drug-drug interactions, drug-disease interactions, increased treatment cost and increased use of potentially inappropriate medications (PIMs). Although the possibility confounding by indication cannot be excluded, the results of these studies suggest it is prudent to conduct a comprehensive medication review in patients at risk of adverse drug events. The goal of medication review is not necessarily to reduce a patient's number of medications, but rather to ensure that each medication is appropriate for the patient's goal of care, with an acceptable benefit to risk ratio.

Keywords Polypharmacy · Potentially inappropriate medication · Deprescribing · Drug-drug interactions · Adverse drug events

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Key Points

- Compared to the broader population little is known about polypharmacy in people with chronic conditions and cancer
- The prevalence of polypharmacy in people with cancer ranges from 35 to 50 %. This is higher than the general population. This is potentially due to the additive effect of using medications to treat both cancer and comorbid conditions
- Recent evidence supports defining polypharmacy in older people with cancer as "the use of five or more medications."
- Some chronic conditions (e.g. cardiovascular disease and cerebrovascular disease) are more likely to be associated with polypharmacy than other chronic conditions.
- Drug-drug interactions can occur between medication used to treat cancer and medications used to treat chronic conditions. The higher the number of medications a person uses the higher the likelihood that they will experience a drug-drug interaction. Care should be exercised when prescribing, dispensing or administering any new medication to a person's medication regimen.
- Cancer treatments may lead to the development of chronic conditions (e.g. anthracyclines and cardiovascular disease) or adverse drug events that may be confused with chronic diseases (e.g. coronary spasm with tyrosine kinase inhibitors). Because long term post-marketing safety data are lacking for many newer therapies clinicians and patients should consider new symptoms as potential adverse drug events and investigate accordingly.
- Deprescribing refers to the reduction of medications after consideration of therapeutic goals, benefits, risks and medical ethics.
- Deprescribing should be a patient centered process focusing on the goals of therapy and the risk and benefit for each medication.

9.1 Introduction

As patients accumulate chronic conditions, it stands to reason they will be prescribed medications for symptomatic treatment of their chronic conditions and/or medications used to prevent future complications. These medications are often prescribed in accordance with disease-specific clinical practice guidelines [1], often resulting in positive health outcomes. However, application of disease-specific clinical practice guidelines can result in patients being prescribed a large number of medications [2–4]. For example, application of individual clinical practice guidelines to a hypothetical 79 year old woman with hypertension, diabetes mellitus, osteoporosis, osteoarthritis and COPD would result in 12 separate medications

being recommended, to be administered over five dosing intervals throughout the day [2]. Figures 9.1 and 9.2 (adapted from Barnett et al. [5] and Hovstadius et al. [6]) demonstrate how the number of comorbidities and number of medications used increase with age in a comparable manner.

Polypharmacy is highly prevalent in the general population and increases with age to a point, with recent research demonstrating prevalence of polypharmacy reduces in people aged over 95 years [7, 8]. Over one third of older people in Europe, the United States of America (USA), Australia and New Zealand use ≥ 5 medications each day [3, 9–13]. Polypharmacy has been less extensively investigated for people with cancer, with the reported prevalence ranging from 9 to 86 % [14, 15].

The wide variation in the prevalence of polypharmacy in people with cancer is likely due to a culmination of factors, including younger people having a lower number of comorbidities and the various definitions of polypharmacy that have been used [14]. The difficulties in defining polypharmacy are explored in the following section of this chapter. Despite the wide range of reported prevalence, the majority of studies suggest the prevalence of polypharmacy in people diagnosed with cancer ranges between 35 and 50 % [16–26]. This may be a result of patients being prescribed medications to treat cancer and ameliorate symptoms in addition to medications to manage chronic conditions. A population-based study reported medication use increased in the six months prior to cancer diagnosis [23]. This suggests patients may use medications to treat symptoms relating to their cancer before it is diagnosed.

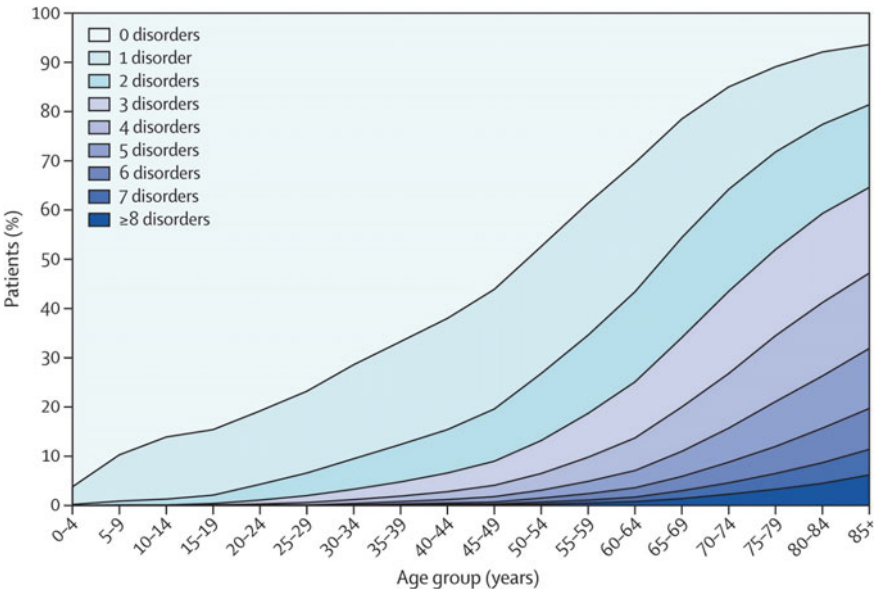

Fig. 9.1 Number of comorbidities with increasing age. Adapted from Barnett et al. [5]

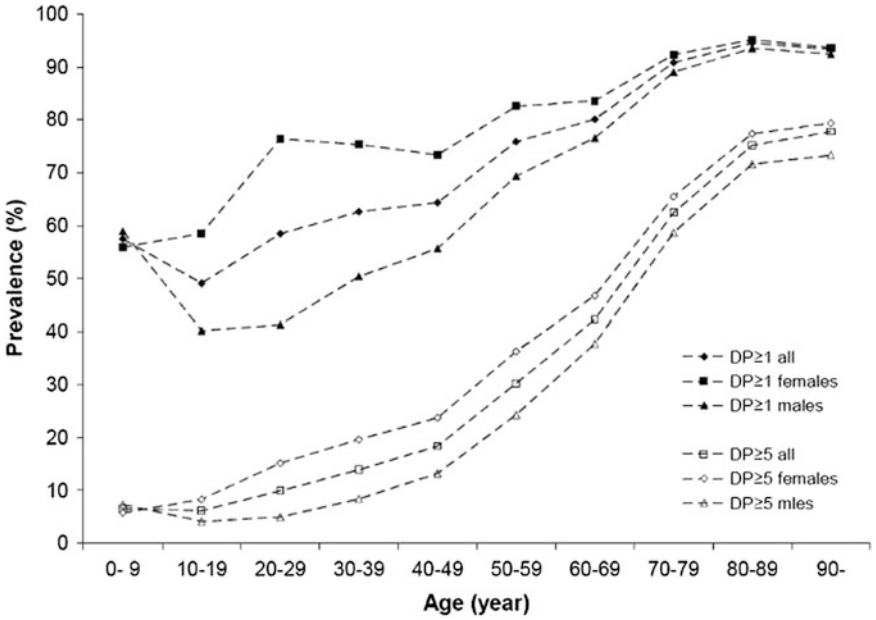

Fig. 9.2 Prevalence of polypharmacy with increasing age. Adapted from Hovstadius et al. [6]. The prevalence of one or more (DPs $\geq$ 1) and five or more (DP $\geq$ 5) dispensed drugs. The prevalence (%) of DP $\geq$ 1 and DP $\geq$ 5 related to sex and age groups in Sweden in 2006. Number of individuals with DP $\geq$ 1 = 6,146,679 (females = 3,466,243 and males = 2,680,436). Number of individuals with DP $\geq$ 5 = 2,227,152 (females = 1,356,934 and males = 870,218)

In the general population, polypharmacy has been associated with a range of adverse outcomes, including adverse drug events (ADEs) [27], hospital admissions [28], and drug-drug interactions [29, 30]. Given that cancer treatments are associated with a range of toxicities and potential drug-drug interactions, these associations are likely to be particularly relevant to people with cancer. This chapter will explore the specific problems polypharmacy poses while caring for patients diagnosed with cancer and chronic conditions. It is imperative to consider a patient's overall medication regimen when considering treatment options for cancer or chronic conditions and when prescribing symptomatic and supportive treatments.

9.2 Defining Polypharmacy

The word polypharmacy is derived from the Greek words "*poly*" meaning more than one, and "*pharmacon*" relating to medications [31]. Inconsistency surrounds the definition of polypharmacy, with the term loosely used to define the use of multiple medications or more medications than is necessary. Most commonly, however,

polypharmacy is more specifically defined using a cut-point number [1]. A range of cut points appear in the general literature, including greater than or equal to two [32], four [33], five [34], six [35], seven [36], eight [37], or nine medications [38]. Recently in response to the high prevalence of ten or more medications, two new terms, excessive polypharmacy and hyperpolypharmacy, have been used [39, 40].

Research investigating polypharmacy within groups of people with cancer has used a narrower range of cut-points. The most common definition has been the use of ≥ 5 or more medications. Other studies have used greater than or equal to three [22], four [21], six [41], eight [42], or nine [19] while others have used ranges of medications, for example 0–3, 4–9 and ≥ 10 [24].

The definition of polypharmacy that is most predictive of various adverse events is likely to depend on the clinical characteristics of the patient sample. Recent research used a novel approach to address the question of how to define the polypharmacy cut point number. An Australian study involving community dwelling older people newly diagnosed with cancer, used receiver operating characteristic (ROC) curves to identify which number of medicines had the best balance between sensitivity and specificity for predicting adverse outcomes due to polypharmacy [43]. ROC curves are a graphical plot displaying the balance between sensitivity and specificity for a given test with a binary (yes/no) outcome (Fig. 9.3). ROC curves were originally designed by radar engineers in World War II to improve the detection of enemy objects. They are now widely used to assess the sensitivity and specificity of tests in many fields from medicine to mining. The Australian study concluded that within the patient cohort studied, the definition of five-or-more medications was reasonable for identifying patients who may be at risk of adverse outcomes including frailty, reduced physical function,

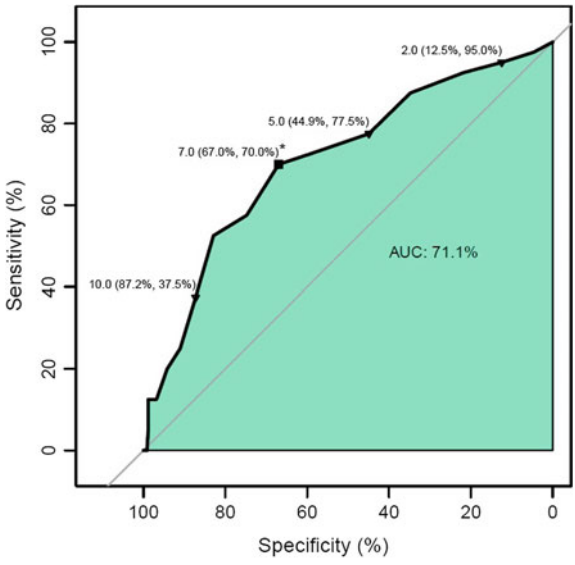

Fig. 9.3 Receiver Operating Characteristic (ROC) curve showing specificity and sensitivity for the association between number of medications and frailty in community dwelling older people with cancer. Adapted from Turner et al. [43] Number of medications (specificity, sensitivity)

falls, exhaustion and reduced performance status (using Karnofsky Performance Scale [KPS] [44]) [43]. The cut-point of five-or-more medications is also supported by research in Japanese and Australian community dwelling older people looking at falls and frailty [45, 46]. To reflect the clinical characteristics of various patient populations, other cut-points may be required. For example, residents of long-term care facilities frequently use nine-or-more medications, thereby in this setting, a higher cut-point may be more useful [47].

A challenge for determining whether or not a patient with cancer has polypharmacy is to know which medications should be included in the medication count. Very few studies on polypharmacy in people with cancer have described the inclusion or exclusion of as-needed (PRN) medications [24, 26, 34, 43], complementary and alternative medications [34, 43, 48], non-prescription medications [24, 34, 43] or chemotherapy [49]. To determine polypharmacy, research in oncology settings has utilized medication chart review, medical records review, or comprehensive geriatric assessment, during which a patient's medication use was verified by a health professional. Additionally, most studies report point prevalent medication use. This is where all medications a person is taking on a specific day are counted. When considering patients with cancer and chronic conditions, an appropriate exposure window should be used to take into account medications that may have been administered recently or medications that are given in a cyclical manner during a course of chemotherapy treatment. This will ensure all potential ADEs or drug-drug interactions are considered (see example of trimethoprim/sulfamethoxazole below) [50].

Polypharmacy has been associated with the use of inappropriate medications. Medications can be considered inappropriate when the likely risks outweigh the benefits, especially when safer alternatives exist. As a result of this association, some of the oncology literature has expanded the definition of polypharmacy to include the number of medications a person takes, the use of one or more unnecessary medications, the presence of one or more inappropriate medications, drug-drug interactions or under use of indicated medications [51–55]. This chapter will provide an overview of these two approaches separately, looking at polypharmacy defined by medication count and also looking at inappropriate medication use.

9.3 Are all Chronic Conditions Associated with Polypharmacy?

Both cancer and chronic conditions are associated with aging. Epidemiological studies report that over 60 % of cancer diagnosis and 70 % of cancer mortality in the USA occurs in people aged ≥ 65 years [54]. Furthermore, the number of older people diagnosed with cancer is continuing to rise. Predictions indicate that by 2030 up to one in five people aged ≥ 65 years in the United Kingdom (UK) will be diagnosed with

cancer during their lifetime [56]. This same age group has the highest prevalence of comorbidities and is the highest consumers of medication [57]. Therefore oncologists are likely to encounter patients with multimorbidity and polypharmacy.

The incidence of polypharmacy continues to rise over time [3]. A Swedish population-based study found the prevalence of polypharmacy (defined as ≥ 5 medications) increased by 8 % between 2005 and 2008, with the prevalence of excessive polypharmacy (≥ 10 medications) increasing by 16 % over the same period [7]. Similar observations were made in New Zealand between 2005 and 2013 [3]. This increase in polypharmacy is likely to reflect application of disease-specific clnical practice guidelines to patients with multimorbidity [58]. In 2007, a Scottish population-based study revealed multimorbidity was common in community dwelling people aged ≥ 65 years. Nearly two out of three people (65 %) were diagnosed with multimorbidity, increasing to over four in five (82 %) of those aged ≥ 85 years [5]. One author has described multimorbidity as the most common chronic condition with almost three out of four people in the USA aged ≥ 65 years being diagnosed with three or more chronic conditions [58]. Therefore the number of patients diagnosed with cancer with polypharmacy will continue to rise, making it imperative to balance the goals of treatment for each condition.

However, not all chronic conditions are equally associated with polypharmacy. An Italian hospital based study identified that older people diagnosed with coronary heart disease, cerebrovascular disease and diabetes had greater odds of polypharmacy compared to older people without diabetes and cerebrovascular disease (Odds Ratio [OR] 9.8, 95 % Confidence Interval [95 %CI] 1.3–72.2). This suggested that patients with a diagnosis of coronary heart disease have a higher likelihood of being prescribed polypharmacy [59]. Similar observations have been made in a cross-sectional study investigating community dwelling adults across the USA [60]. The odds of receiving polypharmacy were 68 % greater for people with cardiometabolic and respiratory conditions compared to people with musculoskeletal and respiratory conditions. Therefore when developing treatment plans for patients with cancer and chronic conditions, clinicians should be mindful of which chronic conditions are associated with a greater risk of experiencing polypharmacy.

9.4 Prevalence of Polypharmacy in People with Cancer and Chronic Conditions

A similar range of factors that influence polypharmacy in the general population also impact on the prevalence of polypharmacy in people with cancer. Age had a considerable impact on the prevalence of polypharmacy in a retrospective study of people diagnosed with non-small cell lung cancer. For patients <70 years, only 9 % used ≥ 5 medications, compared to 24 % of patients aged ≥ 70 ($p < 0.001$) [14]. Additionally rates of polypharmacy have been observed to increase at the time of hospital discharge. Research in an acute care hospital ward demonstrated an increase in polypharmacy prevalence (≥ 9 medications) between admission (32 %)

and discharge (38 %). This increase was primarily due to the addition of PRN medications for symptom management [19].

The diagnosis of cancer may also increase the prevalence of polypharmacy compared to patients without cancer. Using the Danish National Health Odense Pharmacoepidemiologic database, Jorgensen et al. [23] compared people with a diagnosis of cancer and matched cases without cancer. People with cancer had a higher prevalence of minor and major polypharmacy (defined as 2–4 and ≥ 5 medications respectively). This suggests that when patients first present to an oncology clinic, a review of the appropriateness of patients medications should be undertaken [34].

9.5 Implications of Polypharmacy in People with Cancer and Chronic Conditions

Most of the time prescribing of medications leads to improved health outcomes [2, 61]. However, despite the benefit that each medication can impart, increased numbers of medications are associated with harms. In community based older people, polypharmacy has been associated with a range of harms including drug-drug interactions, ADEs and hospitalizations. In a cross-sectional study of Canadians aged ≥ 65 years presenting to an emergency department, 31 % of patients using multiple medications had drug-drug interactions [29]. As the number of medications a patient takes increases, the odds of experiencing drug-drug interactions are greater [30, 62]. A different Canadian study investigating polypharmacy in older hospitalized people demonstrated the probability of having ≥ 1 cytochrome-P450 (CYP) mediated drug interaction was 50 % for people using 5–9 medications, 81 % for 10–14 medications, 92 % for 15–19 medications and 100 % for ≥ 20 medications [63]. Across the USA, between 1995 and 2005, patients presenting to hospital using ≥ 5 medications had an 88 % higher risk of experiencing ADEs [27]. Likewise, veterans in the USA using ≥ 5 medications had an almost four-fold increase in unplanned ADE related hospitalisations [28].

Polypharmacy may reflect an extensive medical history, and may be indicative of difficulties choosing the optimal treatment strategy [64]. Therefore it is worth considering that the number or severity of comorbidities may be potential confounders when investigating outcomes associated with polypharmacy [65]. It has been postulated that the outcomes associated with polypharmacy are a reflection of underlying multimorbidity, rather than the number of medications patients use [61, 65, 66]. In a study involving analysis of Scottish primary care data for patients aged ≥ 20 years, the relationships between unplanned hospital admissions and both polypharmacy and multimorbidity were considered [65]. Unplanned hospital admissions were strongly associated with number of medications used, although the association decreased as comorbidity count increased. This highlights the need to consider polypharmacy in the context of the patients' chronic comorbidities and treatment goals.

There have been relatively few studies investigating the harms of polypharmacy in people with cancer compared to people in other settings. Polypharmacy has been investigated in relation to recovery from cancer surgery [16, 67], chemotherapy related toxicity [20], drug-drug interactions [48], and survival [18, 41]. Two studies have investigated the association between polypharmacy and cancer related surgical outcomes [16, 67]. Badgwell et al. [16] studied patients undergoing abdominal cancer surgery and found patients using ≥ 5 medications had two times higher odds of having a prolonged hospital admission following surgery. In breast cancer patients aged ≥ 65 years, Rocco et al. found a 16-fold higher rate of post-operative complications for patients using of ≥ 5 medications [67].

The relationship between polypharmacy and chemotherapy toxicity requires further investigation. In a small prospective longitudinal Italian study (n = 16), Iurlo et al. [22] investigated patients aged ≥ 65 years diagnosed with chronic myeloid leukemia. There was an association between polypharmacy (≥ 3 medications) and tyrosine kinase inhibitor dose reduction due to toxicity. It was postulated that CYP-mediated drug interactions may have been responsible for the toxicity and subsequent dose reduction. In a larger prospective cohort study in the Netherlands, Hamaker et al. [20] investigated polypharmacy in a cohort of older people with breast cancer (n = 78). They identified polypharmacy (≥ 5 medications) was the only factor associated with higher treatment related toxicity, with 57 % of patients with polypharmacy experiencing grade III-IV toxicity. Patients using ≥ 5 medications had six times higher odds of experiencing grade III-IV toxicity compared to patients using <5 medications. The largest study (n = 500) to investigate the association between polypharmacy (4–9 medications) and excessive polypharmacy (≥ 10 medications) and toxicity was conducted by Maggiore et al. in outpatient oncology clinics in the USA. In a retrospective cross-sectional study, they concluded that compared to no polypharmacy (0–3 medications) there was no significant association between polypharmacy or excessive polypharmacy and grade III–V chemotherapy related toxicity or unplanned hospitalisations [24]. Reasons for the difference observed may include the range of cancer types and stages, which may influence the treatment regimens included by each study. Iurlo et al. [22] investigated patients with chronic myeloid leukemia, Hamaker et al. [20] studied patients diagnosed with metastatic breast cancer, while Maggiore et al. [24] investigated patients with any type of solid tumor receiving outpatient chemotherapy (excluding nonmelanoma skin cancer). Furthermore, the retrospective analysis conducted my Maggiore et al. was limited to the data that had been previously collected and, therefore, did not allow for assessment of other clinically important outcomes of toxicity including treatment dose reduction, falls or functional decline. These studies highlight the need for further research that is powered to detect any significant associations between polypharmacy and toxicity, considering a range of clinically important adverse outcomes. The association between polypharmacy and chemotherapy discontinuation has been investigated by both Alexa et al. [14] and Huiart et al. [21]. In patients aged ≥ 70 years with non-small cell lung cancer, Alexa et al. [14] found that compared to patients aged <70 years, polypharmacy (≥ 5 medications) was correlated with early cessation of

chemotherapy despite no difference in grade III–IV toxicities. In contrast Huiart et al. [21] found older women with breast cancer who used ≥ 4 medications were 60 % less likely to discontinue their aromatase inhibitor treatment. The difference between these studies lies in the chemotherapy being administered. Alexa et al. investigated the use of platinum based chemotherapy for non-small cell lung cancer, which involves a significant interruption to daily routine, with a high possibility of toxicity, both of which may be seen as harms that outweigh the benefit for older people with polypharmacy due to multimorbidity. Conversely, Huiart et al. investigated daily use of aromatase inhibitors for breast cancer. It is likely that polypharmacy predicted less discontinuation because patients who already have a daily routine for taking multiple medications are unlikely to have a problem adding an aromatase inhibitor to their routine. Conversely, patients not used to taking medications daily may have found adherence difficult.

The association between polypharmacy and mortality in people with cancer is unclear. In a cohort of people undergoing induction therapy for acute myelogenous leukemia, the odds of 30 day mortality increased with each additional medication [18]. For patients receiving ≥ 4 medications compared to ≤ 1, the odds of 30 day mortality were 10 fold higher, with increased overall mortality observed [18]. Freyer et al. [41] also reported reduced overall survival for patients with stage III or IV ovarian cancer using ≥ 6 medications. In contrast to these results Hamaker et al. [20] found no significant association between polypharmacy and mortality in older women with metastatic breast cancer. These studies used similar methodology, adjusting the regression models for variables that were significant in univariate analysis. The difference observed may have been due to small sample sizes or the different cancer types. Alternatively, discontinuation of medications at the end of life setting, would cause an inverse association between polypharmacy and increased mortality. Nevertheless, the variability of results in people with cancer reflects the variability in the broader community [68, 69].

An association between polypharmacy and frailty in older people with cancer has recently been demonstrated. In a recent cross-sectional retrospective analysis of older people newly referred to a senior adult oncology ambulatory center, Nightingale et al. [25] defined frailty as dependence in instrumental activities of daily living (IADLs), significant comorbidities and evidence of geriatric comorbidities. Both polypharmacy (5–9 medications) and excessive polypharmacy (≥ 10) were significantly associated with frailty, more comorbidities and higher Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scores. Similar results were found by Turner et al. [34] who identified polypharmacy was associated with frailty in older community dwelling patients, even after adjusting for age, gender, and Charlson's comorbidity index. In other studies, polypharmacy has been associated with factors that contribute towards frailty. While investigating people newly diagnosed with cancer, Prithviraj et al. [70] collected multiple outcomes assessing functional status, however frailty status was not specifically determined. Despite numerous assessments of functional analysis being performed and investigated, the only significant associations were between polypharmacy and higher ECOG-PS score, higher comorbidity count and greater use of Beers Criteria 2003

medications. While studying the effects of androgen deprivation therapy in older men with prostate cancer, Bylow et al. [17] conducted multiple assessments of functional assessment. The odds of having an abnormal Short Physical Performance Battery score (≤ 9) doubled in patients receiving ≥ 5 medications compared to those receiving <5 medications.

Frailty is an important consideration for patients with cancer and comorbidities because functional impairment can have significant impact on the treatment they receive. A cross-sectional study observed that frailty can alter chemotherapy choice, with frail patients receiving either reduced dose regimens, alternate less toxic regimens or no chemotherapy at all [71]. Similar results were demonstrated in an Australian cohort of older people with metastatic colorectal cancer. Compared to robust patients, vulnerable and frail patients were less likely to receive doublet therapy and had significantly lower rates of survival at 12 months [72]. These studies highlight the potential for polypharmacy to impact on a range of measures used to determine patient's functional capacity and frailty status. This suggests that each medication prescribed for patients with multiple chronic conditions and cancer should be reviewed regularly to ensure its appropriateness.

9.6 Potentially Inappropriate Medications

In the oncology literature, polypharmacy has also been defined as the presence of potentially inappropriate medications (PIMs). This definition of polypharmacy is somewhat unique to the oncology literature. In the pharmacy and clinical pharmacology literature polypharmacy and PIM use are typically distinct concepts.

PIMs may be prescribed in the treatment of chronic conditions, (e.g. amiodarone for arrhythmia) or prescribed to treat cancer symptoms (e.g. amitriptyline used for neuropathic pain), thereby putting patients with both cancer and chronic conditions at risk of being prescribed PIMs. Many definitions for PIMs exist including the use of one or more medications that do not have an indication, or the use of one or more medications where the risk of harm outweighs the potential for benefit [73–75]. For these definitions to be appropriately used in clinical practice, an understanding of the patient's clinical characteristics and chronic conditions is required. Alternatively, both explicit and implicit tools have been defined to identify potentially inappropriate medications where the benefit may be outweighed by the harms.

Implicit criteria have been developed to take into account an individual patient's clinical situation, including the burden of comorbid disease, and a patient's beliefs, values and treatment goals [76]. However, implicit criteria are time consuming to apply and require good knowledge of the patient and their goals of treatment [76]. Although a range of implicit criteria exist, to date, only the medication appropriateness index (MAI) has been researched for use among patients with cancer [15].

In contrast to implicit criteria, explicit criteria are often dichotomous lists of medications to be avoided [76]. Defining PIMs with explicit criteria allows for quality of prescribing to be measured easily and broadly, however, the individual

patient's circumstances are not considered [77]. Explicit criteria do not consider that preferred treatment alternatives may have been trialed previously without success, with some medications in the Beers Criteria being considered appropriate by some clinicians as second or third line treatment options [76, 78]. While explicit tools do not consider the clinical situation of individual patients, these tools can be useful to prompt clinicians to be alert for possible ADEs or refer for a comprehensive medication review [79].

Explicit criteria measure inappropriateness via multiple approaches. Medications with an unfavorable benefit to harm profile [80], medications that are associated with specific measurable harmful outcomes [81], or medications that once may have been useful, but due to changes in the patients clinical condition, are now classified as unnecessary or 'futile' [82].

In older people with cancer and multimorbidity, the more medications a patient takes, the more likely one or more of the medications in their regimen will be potentially inappropriate. The association between polypharmacy and the use of PIMs has been demonstrated with Beers 2012 Criteria [80], STOPP [83], and HEDIS DAE Criteria [84], which is consistent with results from older people without cancer [85]. Flood et al. [19], identified PIM use defined by Beers 2012 Criteria was associated with polypharmacy, while Nightingale et al. [25] found PIM use defined by Beers 2012 Criteria, STOPP and HEDIS DAE 2011 Criteria was associated with polypharmacy (5–9 medications) and excessive polypharmacy (≥ 10 medications). Likewise, in an American prescription database, Fahlman et al. found PIM use defined by Beers 1997 Criteria was associated with increasing prescription count [86]. Additionally patients with cancer had higher odds of receiving ≥ 2 PIMs compared to patients without cancer.

Not every study has demonstrated associations between use of PIMS and clinically important outcomes. Using Beers 2012 Criteria, Zhan Criteria and the HEDIS DAE 2011 Criteria, Maggiore et al. [24] were unable to detect significant associations between PIM use and chemotherapy toxicity or hospitalization in patients with solid tumors receiving chemotherapy. Likewise, Elliot et al. [18] were unable to find associations between use of Beers 2012 Criteria medication and 30 day mortality, complete remission, ICU admission or increased length of stay in a cohort of patients receiving induction therapy for acute myelogenous leukemia.

While Sect. 4.3 of this text book considers chronic conditions at end of life, it is worth mentioning that some medications may become potentially inappropriate for patients with reduced life expectancy. For example, many medications used in the treatment of chronic conditions are used to prevent future complications. These medications may become inappropriate when the time to benefit exceeds a patients predicted life expectancy [87, 88]. Statins are an example of medications used for primary or secondary prevention of cardiovascular events where the time to benefit may exceed predicted life expectancy [87]. Despite this, approximately 1-in-3 patients with terminal cancer were still using statins at the time of death [89, 90]. An Australian study found that statin use in older people was associated with a four-fold increase in pain for patients aged ≥ 80 years, which is the age group that has no evidence to support statins reducing mortality [91, 92]. Reviewing the

benefit and harms for each medication will help clinicians and patients identify medications that are no longer required. Stopping unnecessary medications reduces polypharmacy, and reduces the potential for ADEs and drug-drug or drug-disease interactions. The process for reducing unnecessary medications is discussed below.

9.7 Drug-Drug Interactions

Polypharmacy increases the risk of drug-drug and drug-disease interactions [48, 49]. The potential for drug-drug interactions increases with each additional medication used [62]. The prevalence of drug-drug interactions in people with cancer ranges from 27–63 % and has been reported to be the cause of 4 % cancer related deaths in hospitalized patients [42, 49, 93]. Drug-drug interactions may occur between medications prescribed to manage chronic conditions and IV or oral chemotherapy or supportive treatments. Likewise, medication prescribed to treat cancer or provide symptomatic and supportive treatment may interact with medications prescribed to treat chronic conditions.

Oral cancer treatments are becoming increasingly common because they can provide patients with improved convenience and quality of life. However, the potential for drug-drug interactions, resulting in treatment toxicity or treatment failure is important to consider. For example, capecitabine is metabolized by cytochrome P450 3A4 (CYP3A4). Medications prescribed for the management of cardiovascular disease, including atorvastatin and diltiazem, are also metabolized by CYP3A4. When administered together, there is competition for the CYP3A4 enzyme, which can lead to irinotecan or capecitabine having reduced metabolism, leading to toxicity [94]. The reverse has also been demonstrated with the reduced efficacy of tamoxifen when co-administered with the CYP 2D6 inhibitor paroxetine. In one study, patients who used paroxetine for at least 75 % of the time they were being treated with tamoxifen had nearly an increase in the odds of death by almost 50 % compared to patients who did not use paroxetine (HR 1.46, 95 % CI 1.15–1.84) [95]. Drug-drug interactions are not limited to cytochrome mediated interactions. Erlotinib, dasatinib, gefitinib, nilotinib and ponatinib all require a low pH to be absorbed [96]. Therefore, when taken together with proton pump inhibitors, their absorption and efficacy is reduced. This clinical scenario can be quite common, with Todd et al. [97] identifying 55 % of patients prescribed erlotinib for the treatment of advanced non-small cell cancer were also prescribed proton-pump inhibitors.

Clinicians also need to be aware of medications that are prescribed as supportive therapy, particularly when prescribed as short term or cyclical use. For example anti-infective agents including trimethoprim/sulfamethoxazole, ciprofloxacin, clarithromycin and fluconazole may be commonly prescribed to patients with prolonged neutropenia to prevent Pneumocystis pneumonia [98]. Each of these anti-infective agents can interact with medications used in the management of diabetes (glipizide and glyburide), increasing the odds of hypoglycemia [99].

Intravenously administered chemotherapy is not susceptible to the pharmacodynamic drug absorption interactions that oral chemotherapy is susceptible to. However, as with oral chemotherapy, cytochrome mediated interactions are possible for injectable chemotherapy. Irinotecan is also metabolized by CYP3A4, and therefore can cause toxicity when co-administered with CYP3A4 inhibitors. Both doxorubicin and vinblastine are metabolized by CYP2D6 and, therefore, may interact with antidepressants including fluoxetine and paroxetine which are potent inhibitors of CYP2D6. Alternatively, interactions could occur via renal elimination. For example, methotrexate is predominantly renally cleared. Patients with cardiovascular disease may be prescribed angiotensin converting enzyme (ACE) inhibitors and diuretics, which can reduce renal function, causing methotrexate to accumulate. Likewise, nonsteroidal anti-inflammatory drugs (NSAIDs) can cause a rapid deterioration in renal function which has been observed to cause a lethal accumulation of both methotrexate and cisplatin when co-administered. Patients with chronic conditions such as rheumatoid arthritis may take NSAIDs on a regular or PRN basis, and therefore clinicians should take measures to prevent the co-administration of medications that reduce renal function for patients receiving renally cleared chemotherapy.

Unfortunately drug-drug interactions are common in people with cancer and chronic conditions and are associated with polypharmacy. On an inpatient hematology ward, Tavakoli-Ardakani et al. [100] reported 38 % of patients had potential drug-drug interactions with a significant correlation existing between the number of medications ordered and the number of potential drug-drug interactions identified. In 2005, Riechelmann et al. [42] identified 63 % of their cohort of inpatients diagnosed with cancer experienced drug-drug interactions, which was associated with an increased length of stay. Patients using ≥ 8 medications were at nearly 10 times higher odds of experiencing drug-drug interactions compared to those using <8 medications [42]. Riechelmann et al. also investigated outpatients with cancer in 2007 [49] and a palliative care setting in 2008 [48] and demonstrated that for each additional medication used the odds of drug-drug interactions rose by 40 and 30 % respectively. In the outpatient setting, they demonstrated that drug-drug interactions were associated with medications used to treat comorbid disease states, rather than supportive symptomatic treatment [49]. Therefore clinicians need to be mindful of all medications a patient is taking for their chronic diseases when choosing a cancer treatment regimen. Oncologists should also be vigilant in checking for new additions to the medication regimen by other prescribers, as specialists in other fields may be unaware of the potential for medications they prescribe to interact with cancer treatments.

While potential drug-drug interactions are common, not all interactions are clinically significant. Therefore, it can be difficult to determine which interactions should be avoided, and which interactions should be monitored. In a palliative care setting in the UK, 267 potential drug-drug interactions were observed in 132 patients. Over 40 % (n = 112) of the interactions were deemed clinically significant, with nearly a third of them (n = 31) deemed preventable by stopping medications that were no longer appropriate [101]. Where possible, clinicians can avoid

drug-drug interactions by changing one of the interacting medications to an alternative that does not interact, for example, changing from atorvastatin to pravastatin if a statin is deemed to be necessary. If the statin is no longer required, ceasing statin treatment will also avoid the interaction and reduce polypharmacy.

9.8 Polypharmacy and Chronic Conditions as a Result of Cancer Treatment

The association between cancer treatments and the development of comorbidities is important to consider when caring for patients who are currently receiving, or have previously received, treatment for cancer. Thus far, this chapter has discussed polypharmacy due to patient's comorbidities, or as a result of symptomatic and supportive treatments. However, clinicians should be mindful of polypharmacy that may result from treating cancer, especially when treating younger patients. Older chemotherapies have well established associations with chronic diseases. For example, anthracyclines can damage myocardial tissue and, therefore, have detrimental effects on the cardiovascular system, with many guidelines recommending a lifetime limit on doxorubicin due to the potential to cause cardiotoxicity. Likewise alkylating agents, 5-fluorouracil and paclitaxel are associated with cardiotoxicity [102]. Therefore, treatment of younger patients may increase the prevalence of chronic conditions in later years, which will increase the likelihood of polypharmacy in the treatment of these chronic conditions [103]. It is important for clinicians to discuss these issues with younger patients before commencing and completing treatment.

In addition to the well-defined short-term ADEs and well-known long term ADEs from certain older chemotherapies, clinicians need to consider the less well known and less certain long-term ADEs of newer targeted therapies. Small molecule targeted therapies have only been used in clinical practice since the early 2000s. While they have dramatically changed the treatment course and survival outcomes of certain cancers, the long-term effects of these medications are largely unknown. Clinical trials with long term follow up for tyrosine kinase inhibitors have generally excluded patients with cardiovascular disease, thereby limiting the external generalizability of the results. Additionally, clinical trials of the second and third line tyrosine kinase inhibitors have had limited long-term follow up, generally confined to five years or less [104]. Larger, pharmacoepidemiological studies are required to adequately address the range of long term side effects associated with the wide use of these newer treatments. Despite the limited long-term follow up for many of the newer treatments, there is evidence to suggest that they are associated with the development of toxicities that include chronic conditions, such as congestive heart failure, cardiac arrhythmias, vascular events and pulmonary toxicity [104].

While there are well known and well established links between chronic diseases and some older therapies, these associations may be less obvious for newer therapies. For example, in a younger male who presents with symptoms of angina, it is difficult to distinguish between new development of cardiovascular disease, versus the presentation of ADEs such as coronary spasm, thrombus or vascular deficiency due to targeted therapy. Failure to differentiate symptoms of angina as an ADE as opposed to development of a chronic disease may lead to prescribing of guideline driven polypharmacy, rather than reassessment of the targeted treatment. Many doctors who are not familiar with cancer medications may be unaware of these potential ADEs, which highlights the importance of good communication and follow up with patients receiving long term oral therapies.

9.9 Methods to Address Polypharmacy

Addressing polypharmacy in patients with cancer and chronic conditions can be difficult, especially when one or more of the medications is a cancer treatment. This may cause a problem as prescribers who do not specialize in treating cancer may lack specialist knowledge relating to cancer medication, while clinicians who specialize in treating cancer may lack knowledge relating to the medications used in the treatment of chronic conditions [105]. Qualitative research has identified that prescribers often report reluctance to discontinue a medication initiated by another prescriber [105, 106]. Therefore without good communication between all clinicians, medications often accumulate.

Deprescribing refers to the reduction of medications after consideration of therapeutic goals, benefits and risks, and medical ethics [105]. While reducing inappropriate or unnecessary medication may provide benefits, it must be done with clear communication, to ensure the patient and their care-givers and families understand the reason. Often, in an effort to encourage compliance, patients are instructed that a medication for their chronic condition should be used "for life." Deprescribing such a medication can cause undue concern for patients including making them feel like they are not worthy of treatment, feeling like they have been abandoned by the health system, feeling concerned they are imminently about to die, or feeling confused with which prescriber they should believe [107]. For example, while statins may be inappropriate because they have a long time to benefit and their lack of mortality benefit in primary prevention for patients aged ≥ 80 years, stopping a statin may cause undue concern without good prescriber-patient communication.

Only one prospective study has investigated the outcomes of deprescribing medications in people with cancer and chronic diseases [108]. Unfortunately, this study might not be generalizable to the majority of people with cancer and comorbidities, as it was conducted in a palliative care setting. Patients with a life expectancy between 1 and 12 months were randomized to deprescribing their statin or control. No significant difference was observed in either survival rate at 60 days or new cardiovascular events, suggesting there is no immediate harm from

deprescribing statins. Interestingly, patients who stopped their statins reported significantly higher quality of life scores which is an important outcome for patients with a limited life expectancy [108].

The process for deprescribing medications in people with cancer and chronic conditions should be patient focused and appreciate that a patient's health status is dynamic, thereby benefits and harms for each medication may change over time [109]. Various methodologies have been developed to guide clinicians in reducing inappropriate polypharmacy [88, 110, 111]. Figure 9.4 summarizes the steps required for patient focused deprescribing in patients with cancer and chronic conditions.

Firstly, clinicians should discuss with patients and their families and care-givers about the goals of treatment. Patients have dynamic health status, which may shift between states of being robust, vulnerable and frail. Additionally, as a patient's health status deteriorates, they may have a higher focus on quality of life, rather than on life extension. As these goals change, the appropriateness of each medication should be reviewed. One way to review the appropriateness is to consider the benefit-to-harm ratio of each medication [113]. If the harms from a medication (including exposure to ADEs or drug-drug and drug-disease interactions) are greater than the benefit provided by the medication, it should be considered for deprescribing. When considering the benefit of each medication, the time to benefit should also be taken into account. Some preventative medications require years of continuous use before a mortality benefit becomes apparent. A useful way for discussing the benefit-to-harms ratio with patients and their families and care-givers is through the use of number needed to treat (NNT) and number needed to harm (NNH) [111].

The second step requires a thorough review of each medication a patient is using including regular and when required medications. This requires clinicians to specifically enquire about oral and intravenous chemotherapy, cyclical medications used to provide supportive and symptomatic relief, prescription medications used in the management of chronic conditions, over-the-counter medications and complementary and alternative therapies. Adherence should also be checked at this time, to identify medications that remain on the medication list despite no longer being used by the patient.

Once a complete medication history has been obtained, each medication should be checked to ensure it aligns with the patients current goals of care. Medications which have no clinical indication, have a time-to-benefit longer than the patients' predicted life expectancy, or medications that no longer meet the patients' goals of care can be identified for deprescribing. Likewise, medications causing ADEs or drug-drug interactions should be considered for deprescribing. In addition, for patients aged 65 years and over, the medication list should be assessed to ensure it does not contain any potentially inappropriate medications. Lists such as Beers criteria and STOPP/START criteria are the most commonly used tools for evaluating medication appropriateness in older people with cancer [73, 83].

Deprescribing medications is best done one at a time when possible, to allow monitoring for return of symptoms or withdrawal effects [114, 115]. Once a list of medications to be deprescribed has been compiled, the order in which they should

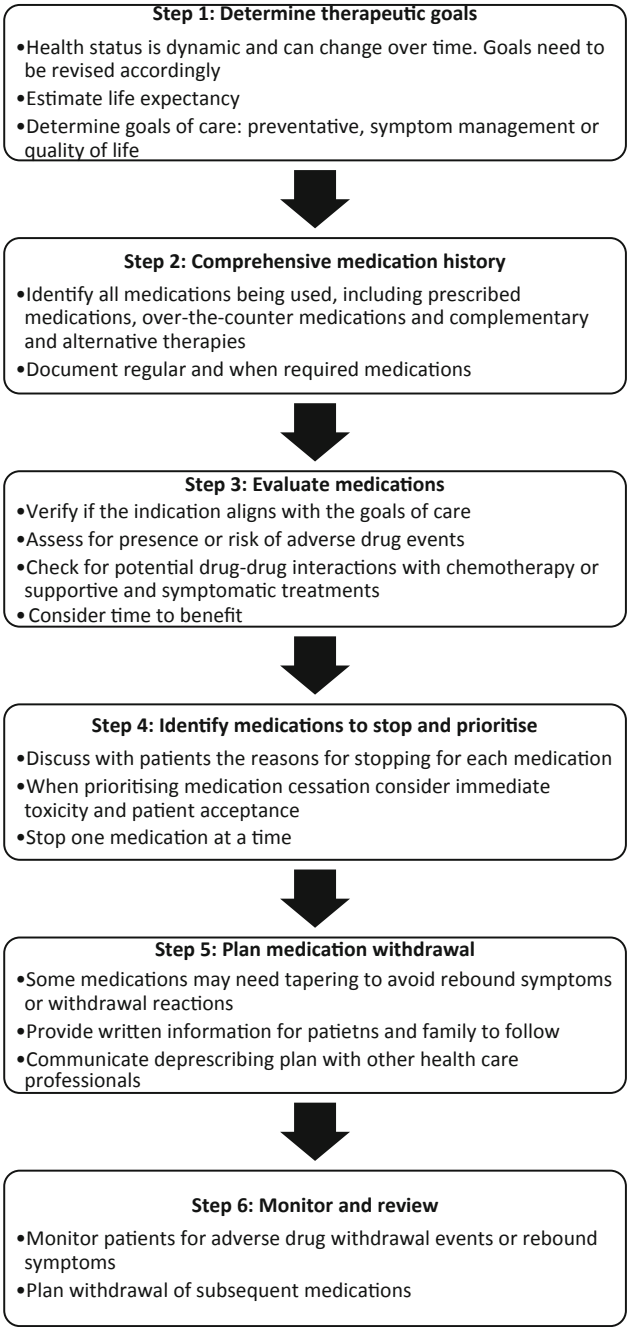

Fig. 9.4 Patient centered process for deprescribing. Adapted from Reeve et al. [112]

be discontinued needs to be determined. There are several factors to be considered when determining the order of deprescribing [88]. Firstly, deprescribing medications that are suspected of causing toxicity or serious drug-drug interactions may be a priority. Alternatively, deprescribing medications that patients prioritize for stopping may result in higher patient acceptance. Additionally, some clinicians choose to deprescribe medications that may potentially cause adverse drug withdrawal events last, as these may take longer to deprescribe, requiring a gradual tapering protocol.

The final steps in a patient focused deprescribing process involve patient monitoring and follow up. Depending on the patients' cancer treatments, they may have frequent appointments with their oncologist, making the oncologist an obvious choice for monitoring for withdrawal or rebound symptoms. However, if a patient is receiving outpatient therapy or oral chemotherapy and is not requiring regular visits with their oncologist, the role of follow up and monitoring might be performed more appropriately by another health care professional such as their family physician so long as each physician understands their role in the deprescribing process [116]. Regardless of who the follow up clinician is, the patient, their family, their caregiver and the whole health care team should be provided with documentation clearly stating what is occurring within the deprescribing process, and who the contact person is for follow up.

9.10 Future Directions for Research and Practice

Additional research is required into problems that can occur when treating people with chronic conditions and cancer. Firstly, longitudinal research is required to quantify the possible long-term ADEs associated with newer targeted therapies. This will be important to guide practice when choosing therapies for people with chronic conditions. For example, if a patient presents with cardiovascular disease, a physician may choose not to prescribe a targeted therapy that has been found to be associated with causing cardiovascular events. Similarly, research is required to understand the mechanism behind the possible long term ADEs of newer therapies, and to determine if switching medications can reverse the effects. This would inform practice and allow physicians to differentiate between symptoms being irreversible ADEs, reversible ADEs or development of chronic conditions. Being able to differentiate between the causes of symptoms will dramatically alter the way they are treated.

Further research is also required to determine the most effective ways to deprescribe for patients with chronic conditions and cancer. Discussing deprescribing of medications can cause undue concern for patients, as they may feel that they are being abandoned by their health care team, they are no longer deserving of treatment, their death is imminent, or they may lose hope [107, 117]. While qualitative research has been conducted in community dwelling people with chronic conditions and in long term care facilities to identify the barriers and enablers of deprescribing, there is a paucity of research investigating deprescribing on people

with cancer and chronic conditions [105, 117, 118]. Future research needs to consider the barriers and enablers to deprescribing in people with cancer and chronic conditions because there is likely to be a number of important differences. Firstly, patients may be offered chemotherapy, along with supportive symptomatic treatments, each of which increases the medication burden, and increases the potential for ADEs, drug-drug interactions and drug-disease interactions, making the benefits of deprescribing greater [22, 42, 100, 101]. Additionally, the diagnosis of cancer is a sentinel event that may change the goals of care for people with chronic conditions. This may reduce the focus on preventative medications, to focusing on quality of life [107, 109]. Finally, access to specialist physicians and family physicians may be limited for residents of long term care facilities therefore making it difficult to discuss medication use and deprescribing [105]. This is in contrast to people with cancer and chronic conditions, who may visit doctors, and therefore need to actively manage the potential communication barriers between primary care and tertiary care [90, 94].

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Further Reading—Further information on de-prescribing medications can be found at:

119. Best Practice New Zealand "Stopping medicines" guide http://www.bpac.org.nz/BPJ/2010/April/docs/bpj_27_stop_guide_pages_10-23.pdf
120. Medstopper is an academic site for clinicians that provides an overview of number needed to treat and number needed to harm in elderly patients with comorbidities (not specific to cancer patients) medstopper.com
121. Deprescribing.org is a collaboration between clinicians, academics, researchers and patients, dedicated to the reduction of unnecessary and harmful medications in seniors (not specific to cancer patients) deprescribing.org
122. A summary of adverse drug withdrawal reactions can be found at: Bain KT, Holmes HM, Beers MH, Maio V, Handler SM, Pauker SG (2008) Discontinuing medications: a novel approach for revising the prescribing stage of the medication-use process. J Am Geriatr Soc 56:1946–1952

Further Reading—Further information on the definition of polypharmacy in people with cancer and chronic conditions:

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