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Polypharmacy in Older Adults with Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Differentiate the multiple definitions of polypharmacy in order to be able to recognize it in your patient population.
2. Discuss the current data available in evaluating polypharmacy specifically in older adults with cancer and incorporate the data in your evaluation of older patients.
3. Summarize the agents or drug classes that may be deemed inappropriate in older adults to avoid prescribing medications for older patients that may lead to adverse drug events.

ABSTRACT

The definition of "polypharmacy" ranges from the use of a large number of medications; the use of potentially inappropriate medications, which can increase the risk for adverse drug events; medication underuse despite instructions to the contrary; and medication duplication. Older adults are particularly at risk because they often present with several medical conditions requiring pharmacotherapy. Cancer-related therapy adds to this risk in older adults, but few studies have been conducted in this patient population. In this review, we outline the adverse outcomes associated with polypharmacy and present polypharmacy definitions offered by the geriatrics literature. We also examine the strengths and weaknesses of these definitions and explore the relationships among these definitions and what is known about the prevalence and impact of polypharmacy. *The Oncologist* 2010;15:507–522

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Introduction

The term "polypharmacy" can be defined in several ways, including an increased number of medications; the use of potentially inappropriate medications, which can increase the risk for adverse drug events; medication underuse; and medication duplication [1, 2]. Older adults are more likely to experience polypharmacy because they tend to have more medical conditions requiring pharmacotherapy [3–7]. The prevalence of polypharmacy in older adults ranges from 13% to 92% [8–39], depending on the definition of polypharmacy used and the characteristics of the study population evaluated (Table 1). Several adverse outcomes have been linked to polypharmacy, including increases in health care costs and adverse drug events, often leading to increased morbidity [7, 17, 18, 20, 24, 36, 39–62]. However, the evidence for a strong association between polypharmacy and an increased risk of mortality independent of other concomitant risk factors such as comorbidity remains unclear [30, 37, 39, 63–65].

Cancer-related therapy adds to the risk of polypharmacy in older adults, as many new medications may be prescribed, including cancer therapy and supportive medications [66–70], but studies reporting on polypharmacy specifically in older adults with cancer remain sparse [71–74]. This review offers definitions of polypharmacy proposed in the geriatrics literature, examines the strengths and weaknesses of these definitions, and explores the relationship among these definitions and what is known about the prevalence and impact of polypharmacy. In addition, we describe tools for evaluating polypharmacy in daily practice and propose research into how this information can be applied in the geriatric oncology population.

Defining Polypharmacy

Several definitions of polypharmacy have been proposed (Table 2). It was initially defined as the number of medications being used concomitantly [75, 76]. Over time, the definition of polypharmacy shifted to include specific medications or scenarios thought to be more clinically relevant, such as the use of potentially inappropriate medications associated with a high risk of adverse effects in older adults [26, 77]. For example, two patients in their 70s both could be taking five prescription medications, yet their risk for an adverse drug event would be markedly different. The first hypothetical patient with breast cancer, hypertension, and coronary artery disease could be taking aspirin, atorvastatin, metoprolol, lisinopril, and anastrozole. The other could have breast cancer along with depression, atrial fibrillation, and peripheral arterial disease, and be taking amitriptyline, diazepam, warfarin, aspirin, and capecitabine. The second patient could potentially be at increased risk compared with the first patient because of (a) potentially sedating medications (amitriptyline and diazepam); (b) an anticholinergic medication (amitriptyline); and (c) medications that concomitantly augment bleeding risk because of a specific drug-chemotherapy interaction (capecitabine increasing the anticoagulant effects of warfarin) [78].

The clinical significance of distinguishing the "number of medications" from the actual medications taken has not gone unnoticed. A recent review pointed out that many studies use the terms "polypharmacy" and "inappropriate drug use" interchangeably [79]. This confusion is further highlighted in a review that has shown that the definition of polypharmacy in studies can be related either to the number or to the type of medications taken (i.e., medications with a high risk of adverse drug events or unnecessary medications), both of which can lead to an adverse drug event [80]. Table 2 illustrates the multifaceted components of how to define polypharmacy. The inherent difficulties of multiple definitions of polypharmacy become more evident when they are compared [81]. These definitions are described below.

Evaluating Polypharmacy: Current Methods

Number of Medications

Many community-dwelling older adults take multiple prescription medications [1, 2]. The likelihood of older adults receiving prescriptions from multiple providers compounds the risk of polypharmacy [4, 7]. In addition, an increasing number of medications has been associated with a higher frequency of potentially inappropriate medication use [15, 27, 39, 82]. A large number of medications may also place older adults at risk for drug-related complications, seen in a variety of clinical settings [42, 44, 55, 61, 62, 83].

The number of medications is also associated with a higher risk of a more subtle adverse drug event: medication nonadherence [34, 84–86]. This association may be related to the finding that many medication discrepancies (i.e., a discrepancy between what is prescribed and what is actually being taken) are identified in those receiving higher numbers of outpatient prescriptions [87]. As a result, nonadherence is a potential issue for older adults, especially because it has been associated with adverse health-related outcomes, including increased emergency room visits, hospitalization rates, and the potential for increased morbidity and mortality [88].

Nonprescription medication use, excluding herbal or complementary agents, should also be accounted for when considering the number of medications. Approximately 48% to 63% of older adults take at least one vitamin/min-

Table 1. Representative studies evaluating the prevalence of polypharmacy

Clinical setting/ Reference	Polypharmacy definition	No.	Age of subjects, yr (other characteristics)	Study design	Prevalence, %	Predictors of potentially inappropriate medication use	Polypharmacy-related outcomes
Emergency room							
Hustey et al. [29]	Beers	352	65+	XS	32	—	—
Nixdorff et al. [36]	Beers	124	65+	PC	16	—	26% of those receiving a Beers medication had an adverse drug event
Hospitalized							
Page and Ruscin [38]	Beers	389	75+	RC	27.5	—	Receiving a Beers medication not associated with higher risk of adverse drug event, length of hospital stay, mortality, or discharge to a higher level of care
Berdot et al. [40]	Beers	493,971	65+	RC	49	Higher prevalence in cardiology ward	—
Hajjar et al. [26]	MAI	384	65+ (frail, VA)	XS/PC	75 at admission; 55 at discharge	No. of medications (especially 9+); Hypertension; Multiple providers	—
Hanlon et al. [27]	MAI	397	65+ (frail, VA)	XS/PC	91.9 at admission	Higher Charlson Comorbidity Index; Poor self-rated health scores	—
Ambulatory care/ community-dwelling							
Blalock et al. [12]	Beers	800	65+ (rural setting)	XS	26.6	No. of medications; Hypertension; Low back pain; Low social support ratings; Higher disability scores	—
Cannon et al. [15]	Beers	786	65+ (home health care)	RC	31 (37 if patient taking 9+ prescription medications)	—	—
Maio et al. [33]	Beers	50	65+	RC	25	—	—
Steinman et al. [77]	Beers	196	65+	XS	37	No. of medications	—
Barton et al. [10]	Beers	100	65+ (memory disorders clinic)	XS	25.6[a]	—	—
Buck et al. [14]	Beers	61,251	65+	XS	23	6+ prescription medications; Multiple provider visits; Female sex	—
	Zhan	(Same)	(Same)	(Same)	16–17	(Same)	—
Pugh et al. [109]	Zhan	1,265,434	65+ (VA)	XS	23	No. of medications; Female sex; White race; Psychiatric comorbidity	—
Barnett et al. [8]	Zhan	123,633–156,517	65+ (VA vs. Medicare)	XS	21 (VA); 29 (Medicare)	—	—
Bierman et al. [11]	Zhan	965,756	65+ (VA)	RC	15.6 (male); 18.2 (female)	—	—
Pugh [110]	Zhan	850,154	65+ (VA)	XS	26.2	Less prevalent in geriatrics compared with primary care clinics	—
Pugh et al. [102]	HEDIS DAE	1,096,361	65+ (VA)	XS	19.6	Women had higher prevalence of inappropriate medication use; 10+ medications also associated	
Schmader et al. [115]	MAI	208	65+ (VA)	XS/PC	55	—	Higher MAI scores associated with higher risk of hospitalization and ER visits over a 12-mo period
Steinman et al. [77]	MAI	196	65+	XS	57	—	—
Bregnhøj et al. [13]	MAI	212	65+ (general practice)	XS	94.3	—	—
Tulner et al. [97]	MAI	807	81 (mean) (geriatric outpatient clinic)	PC	25.5	—	—
Long-term care							
Perri et al. [39]	Beers	1,117	65+	RC	46.5	No. of medications; Absence of dementia	Receiving a Beers medication was associated with a higher risk of hospitalization, ER visits, and/or mortality

Representative U.S.-based studies from January 1994 to September 2009.
Abbreviations: ER, emergency room; HEDIS DAE, Healthcare Effectiveness Data and Information Set Drugs to Avoid in the Elderly list; MAI, Medication Appropriateness Index; PC, prospective cohort; RC, retrospective cohort; VA, Veterans Affairs; XS, cross-sectional.
[a]Medications deemed inappropriate for those with underlying cognitive dysfunction.

Table 2. Definitions of polypharmacy

Increased no. of medications
Prescription medications
Nonprescription medications
OTC medication use
Herbal/supplementary agent use
PIM use
Medications of a specific drug type or class that may not be appropriate for a given patient because of age or a concurrent illness/condition
Medication underuse
Medications with a clear benefit for a given illness/condition that a patient is not taking
Medication duplication
Medications of the same or a similar drug class or therapeutic effect concurrently being used that may not beneficial

Abbreviations: OTC, over-the-counter; PIM, potentially inappropriate medication.

eral; 26% to 36% take an herbal, complementary, or alternative medication; and up to 50% take two to four over-the-counter medications on a regular basis [1, 89]. The likelihood of taking such agents increases with age [90]. The use of nonprescription medications increases not only the total number of medications taken but also the risk for drug interactions [90–92]. However, older adults with multiple medical conditions may require this level of pharmacotherapy. As a result, additional definitions of polypharmacy have been developed, including the use of "unnecessary" or potentially inappropriate medication use described below.

Potentially Inappropriate Medications

Two of the approaches most frequently used to evaluate potentially inappropriate medication use in older adults have been the Beers criteria and the Medication Appropriateness Index (MAI) described below (Table 3).

Beers Criteria and Its Derivations

The Beers criteria consist of a list of medications deemed inappropriate for use in older adults, divided into 2 components: (a) specific drugs or drug classes that are considered inappropriate for use in older adults because they are either ineffective or pose unnecessarily high risk where a safer alternative exists; and (b) drugs that may be inappropriate for use in older adults based on the presence of coexisting diseases or conditions [93]. The Beers criteria have been updated twice since 1991 [93–95]. The most recently updated first and second components of the Beers criteria are outlined below (Tables 4 and 5, respectively). Polypharmacy studies using the most recent Beers criteria have been reported in a variety of clinical settings across several countries [8–10, 12, 14–25, 28–30, 32, 34–39, 46, 77, 96–103].

In addition to the number of medications, older adults receiving medications identified as potentially inappropriate by the Beers criteria have an increased risk for polypharmacy-related adverse outcomes [1, 2, 104], including increased rates of adverse drug reactions [17, 45, 50, 105], hospitalization [30, 39, 45–47, 53, 59, 60], emergency room visits [18, 45, 60], falls [40, 51, 56–58], fractures [52, 58], and lower scores on measures of health-related quality of life [19, 106].

The Beers criteria were further modified by Zhan et al. to develop a streamlined list of potentially inappropriate medications and to delineate medications that carry a higher risk for side effects than others [107]. The drugs listed by the Zhan criteria are compared with the Beers criteria in Table 4. The Zhan criteria identify fewer at-risk medications ultimately deemed inappropriate by expert consensus [81]. Some studies have used both the Zhan and Beers criteria concurrently [25, 81, 99, 108, 109]. The simplicity of the Zhan criteria, however, makes them an easier screening tool in population-based evaluations of polypharmacy [14, 25, 107, 109, 110].

The Beers criteria and their derivations have also been used as potential quality indicators. For example, The Healthcare Effectiveness and Data Information Set (HEDIS) is a program designed by the National Committee for Quality Assurance to identify standards of care for 71 clinical measures across 8 domains; it is used by >90% of health care insurance providers, including Medicare and Medicaid. Recently added to the HEDIS measures in 2007 and revised in 2008 is the list of "Drugs to be Avoided in the Elderly" (DAE) [111]. The DAE lists potentially inappropriate medications for older adult patients, incorporating a curtailed list of high-risk medications similar but not identical to those identified by the Beers criteria (Table 4), and can be found online as well (http://www.ncqa.org/tabid/892/Default.aspx).

In addition to evaluating for potentially inappropriate medications, the potential for clinically significant drug-drug interactions is also being evaluated by insurance plans for older adults. These plans are now incorporating Beers and "Beers-like" indices. As per an initial insurance-based analysis in 2007, almost 25% of approximately 30,000 beneficiaries received at least one prescription for a medication considered inappropriate by the Beers criteria, and up to 6% were reported as having had an adverse drug event [112]. As a result, the HEDIS program has adopted such quality measures to

Table 3. MAI and Beers criteria

Approach	Description	Measures
MAI	Medication appropriateness is determined based on series of 10 items, ranked on scale of 1–3	10 items: Indication, effectiveness, dosage, directions, drug-drug interaction, drug-disease interaction, duplication, duration, comparative cost
Beers	Medication appropriateness based on 2 components and their level of severity (low/high)	2 components: Inappropriate drug class because of risk of toxicity; inappropriate because of potential drug-disease interaction

Abbreviation: MAI, Medication Appropriateness Index.

curtail potentially inappropriate medication use and thus adverse drug events among older adults.

Medication Appropriateness Index

The MAI uses 10 items to assess the degree of appropriateness of a particular medication along a 3-point Likert rating scale (Table 6) [113]. If a medication receives at least one "inappropriate" score on any item, it is deemed inappropriate overall. Several modifications have since been applied to the original MAI. Some studies have incorporated the following modifications: (a) taking into account that some items may be more suitable in particular clinical contexts than others [114, 115]; (b) summating the item scores to create an overall single score of medication appropriateness [60, 115, 116]; and (c) condensing the parameters to just three (indication, efficacy, therapeutic duplication) [26, 116]. The MAI has been applied in several clinical scenarios, including in hospitalized [26, 27, 96, 113, 114, 117] and ambulatory patients [3, 13, 60, 77, 97, 115, 116, 118], as well as used in evaluating medications taken as-needed in addition to regularly scheduled medications [117].

Unlike the Beers criteria, the MAI has not been extensively evaluated in outcomes-based studies. However, higher MAI scores have also been associated with higher rates of hospitalization and emergency room visits as well as a higher risk of adverse drug reactions [97, 116]. Moreover, higher MAI scores are associated with lower self-reported health scores among older adults [27].

Comparison of the Beers Criteria (and Derivations) Versus MAI

Shortcomings of all approaches derived from the Beers criteria include the following: (a) the list is not entirely exhaustive and needs to be updated periodically as new drugs are introduced; (b) it does not assess specific aspects of polypharmacy such as inappropriate dosing, which the MAI assesses; (c) it does not take into account that some "inappropriate" medications may prove beneficial for a particular patient under specific circumstances [1, 2, 77, 119].

Some weaknesses of the MAI include the following: (a) not enough data may be present to apply all 10 of the items; (b) it takes approximately 10 minutes to apply the MAI to each medication; (c) many studies have used more than one evaluator to ensure consistent scoring; and (c) it has been studied primarily in older veterans [26, 27, 60, 113, 116, 120].

Medication Duplication or Underuse

Medication duplicity, which can lead to unnecessary medication use and thus increase the risk of adverse drug events and potential drug interactions, is a criterion evaluated by the MAI, but this component of polypharmacy may still be overlooked. The Unnecessary Drug Use Measure is a modified form of the MAI developed specifically to incorporate these properties in the assessment of polypharmacy [121].

Neither the Beers criteria nor the MAI addresses the full scope for potential drug interactions as well as medication underuse, which refers to the situation in which the addition of a particular agent may actually prove beneficial for a patient with a specific disease [2, 77, 119, 122–128]. Such medication underuse has been associated with adverse effects in older adults and can contribute to drug-related hospitalizations beyond those attributable to adverse drug reactions or nonadherence [129–131]. Separate measures have been developed to address this component specifically [117, 132, 133]. Furthermore, studies have shown discordant results among these different approaches in evaluating the prevalence of polypharmacy. As a result, a combined and/or more comprehensive approach using one or more criteria should be considered [81, 119]. For example, the Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria have recently been formulated to address multiple components of potentially inappropriate medication use/duplicity and medication underuse, respectively [134–136].

Table 4. Comparison of the Beers criteria (first component), Zhan criteria, and HEDIS DAE list

Drug name/class	Beers criteria	Zhan criteria	HEDIS DAE list	Concern (Beers)	Severity rating (high or low) (Beers)
Amiodarone	X			Associated with QT interval problems and risk of provoking torsades de pointes. Lack of efficacy in older adults.	High
Amitriptyline and combination products	X	X	X	Because of its strong anticholinergic and sedation properties, amitriptyline is rarely the antidepressant of choice for elderly patients.	High
Amphetamines/Anorexic agents (except for phenobarbital)	X		X[a]	CNS stimulant adverse effects.	High
Anticholinergics/Antihistamines: chlorpheniramine, diphenhydramine, hydroxyzine, cyproheptadine, promethazine, tripelennamine, dexchlorphenir-amine	X	X[b]	X[b]	All nonprescription and many prescription antihistamines may have potent anticholinergic properties. Nonanticholinergic antihistamines are preferred in elderly patients when treating allergic reactions.	High
Antispasmodics (GI): Belladonna and belladonna-containing products, dicyclomine, hyoscyamine, propantheline, clidinium-chlordiazepoxide	X	X	X	GI antispasmodic drugs are highly anticholinergic and have uncertain effectiveness. These drugs should be avoided (especially for long-term use).	High
Barbiturates (except phenobarbital; except for treating seizures)	X	X[c]	X[c]	Are highly addictive and cause more adverse effects than most sedative or hypnotic drugs in elderly patients	High
Benzodiazepines, long-acting: chlordiazepoxide, chlordiazepoxide-amitriptyline, clidinium-chlordiazepoxide, diazepam, halazepam, chlorazepate	X	X	X	These drugs have a long half-life in elderly patients (often several days), producing prolonged sedation and increasing risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required.	High
Benzodiazepines, short-acting: lorazepam >3 mg; oxazepam >60 mg; alprazolam >2 mg; temazepam and triazolam >0.25 mg	X			Because of increased sensitivity to benzodiazepines in elderly patients, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the suggested maximums.	High
Chlorpropamide	X	X	X	It has a prolonged half-life in elderly patients and could cause prolonged hypoglycemia. It is the only oral hypoglycemic agent that causes SIADH.	High
Cimetidine	X			Adverse CNS effects including confusion.	Low
Clonidine	X	X		Potential for orthostatic hypotension and CNS adverse effects.	Low
Cyclandelate	X		X	Lack of efficacy.	Low
Desiccated thyroid	X		X	Concerns about cardiac effects. Safer alternatives available.	High
Digoxin (not exceeding >0.125 mg/day except when treating arrhythmias)	X			Decreased renal clearance may lead to increased risk of toxic effects.	Low
Diphenhydramine and combination products	X	X	X	May cause confusion and sedation. Should not be used as a hypnotic. When used to treat emergency allergic reactions, it should be used in the smallest possible dose.	High
Dipyridamole, short-acting	X	X	X	May cause orthostatic hypotension.	Low
Disopyramide	X	X		Of all the antiarrhythmic drugs, this is the most potent negative inotrope and therefore may induce heart failure in elderly patients. It is also strongly anticholinergic. Other antiarrhythmics should be used	High
Doxazosin	X			Potential for hypotension, dry mouth, and urinary problems.	Low
Doxepin	X	X		Because of its strong anticholinergic and sedating properties, doxepin is rarely the antidepressant of choice for elderly patients.	High
Estrogens only (oral)	X		X	Evidence of carcinogenic (breast and endometrial) potential and lack of cardioprotective effect in older women.	High
Ethacrynic acid	X			Potential for hypertension and fluid imbalances. Safer alternatives available	Low
Ferrous sulfate >325 mg/day	X			Doses >325 mg/day do not dramatically increase the amount absorbed but greatly increase the incidence of constipation.	Low
Fluoxetine	X			Long half-life of drug and risk of producing excessive CNS stimulation, sleep disturbances, and increasing agitation. Safer alternatives exist.	High
Flurazepam	X	X	X	This benzodiazepine hypnotic has an extremely long half-life in elderly patients (often days), producing prolonged sedation and increasing the incidence of falls and fracture. Medium- or short-acting benzodiazepines are preferable.	High
Guanadrel	X			May cause orthostatic hypotension.	High
Guanethidine	X			May cause orthostatic hypotension. Safer alternatives exist.	High
Indomethacin	X	X		Of all the available NSAIDs, this drugs produces the most CNS adverse effects.	High
Isoxsurpine	X		X	Lack of efficacy.	Low
Ketorolac	X		X	Immediate and long-term use should be avoided in older persons because a significant no. has asymptomatic GI conditions.	High

(continued)

Table 4. (continued)

Drug name/class	Beers criteria	Zhan criteria	HEDIS DAE list	Concern (Beers)	Severity rating (high or low) (Beers)
Laxatives (stimulant), long-term use	X			May exacerbate bowel dysfunction.	High
Meperidine	X	X	X	Not an effective oral analgesic in doses commonly used. May cause confusion and has many disadvantages compared with other narcotic drugs.	High
Meprobamate	X	X	X	This is a highly addictive and sedating anxiolytic. Those using meprobamate for prolonged periods may become addicted and may need to be withdrawn slowly.	High
Mesoridazine	X		X	CNS and extrapyramidal adverse effects.	High
Methlydopa and combination products	X			May cause bradycardia and exacerbate depression in older adults.	High
Methyltestosterone	X		X	Potential for prostatic hypertrophy and cardiac problems.	High
Mineral oil	X			Potential for aspiration and adverse effects. Safer alternatives available.	High
Muscle relaxants and antispasmodics: methocarbamol, carisoprodol, chlorzoxazone, metaxalone, cyclobenzaprine, oxybutynin (except Ditropan XL)	X	X	X	Most muscle relaxants and antispasmodic drugs are poorly tolerated in elderly patients because they cause anticholinergic adverse effects, sedation, and weakness. In addition, their effectiveness at doses tolerated by elderly patients is questionable.	High
Nifedipine, short-acting	X		X	Potential for hypotension and constipation.	High
Nitrofurantoin	X		X	Potential for renal impairment. Safer alternatives available.	High
NSAIDs (long-term use of full-dosage, longer half-life, non–COX-selective): naproxen, oxaprozin, piroxicam	X			Have the potential to produce GI bleeding, renal failure, high blood pressure, and heart failure.	High
Orphenadrine	X		X	Causes more sedation and anticholinergic adverse effects than safer alternatives.	High
Pentazocine	X	X	X	Narcotic analgesic that causes more CNS adverse effects, including confusion and hallucinations, more commonly than other narcotic drugs. In addition, it is a mixed agonist and antagonist.	High
Propoxyphene and combination products	X	X	X	Offers few analgesic advantages over acetaminophen, yet has the adverse effects of other narcotic drugs.	Low
Reserpine >0.25 mg	X	X		May induce depression, impotence, sedation, and orthostatic hypotension.	Low
Thioridazine	X		X	Greater potential for CNS and extrapyramidal adverse effects.	High
Ticlodipine	X	X		Has been show to be no better than aspirin in preventing clotting and may be considerably more toxic. Safer, more effective alternatives exist.	High
Trimethobenzamide	X	X	X	One of the least effective antiemetic drugs, yet has extrapyramidal effects.	High

[a]The Beers criteria do NOT consider methylphenidate as inappropriate.
[b]Both the Zhan criteria and the HEDIS DAE list consider atropine and combination products as inappropriate in addition to the other anticholinergic agents.
[c]Both the Zhan criteria and the HEDIS DAE list consider phenobarbital as inappropriate.
Abbreviations: CNS, central nervous system; COX, cyclooxygenase; GI, gastrointestinal; HEDIS DAE, Healthcare Effectiveness and Data Information Set Drugs to be Avoided in the Elderly; NSAID, nonsteroidal anti-inflammatory drug; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
Adapted with permission from National Committee for Quality Assurance. HEDIS 2009 National Drug Code (NDC) List. Available online at http://www.ncqa.org/tabid/891/Default.aspx, accessed October 5, 2009; and from Fick DM, Cooper JW, Wade WE et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: Results of a US consensus panel of experts. Arch Intern Med 2003;163:2716–2724, copyright ©2003 American Medical Association. All rights reserved.

Herbal and Complementary/ Alternative Medications

Herbal or complementary/alternative medication (CAM) is becoming increasingly prevalent among adults in the U.S. [89, 137–139]. Studies from the 1990s and early 2000s demonstrated that herbal/CAM use among older adults ranged from 6% to 15% [137, 138]. More recent studies report prevalence rates of 26% to 36% [89, 139]. However, this number may underestimate the true prevalence as demonstrated by a study that reported more than half of older adults do not disclose such use to their physicians [137].

An evaluation of herbal/CAM use is not typically included in standard definitions of polypharmacy described above. However, herbal/CAM use can increase the risk for drug interactions [90, 138]. Many of these interactions pertain to herbal agents such as garlic, ginkgo, and ginseng, which increase the bleeding risk associated with antiplatelet and anticoagulant agents such as aspirin and warfarin [138].

Table 5. The 2002 Beers criteria for potentially inappropriate medication use in older adults: Considering diagnoses or conditions

Disease/condition	Drug name/class	Concern	Severity rating (high or low)
Heart failure	Disopyramide, high-sodium-content drugs	Negative inotropic effect. Potential to promote fluid retention and exacerbation of heart failure.	High
Hypertension	Phenylpropanolamine, pseudoephedrine, diet pills, amphetamines	May produce elevation of blood pressure secondary to sympathomimetic activity.	High
Gastric/duodenal ulcers	NSAIDs, aspirin (>325 mg/day), excluding coxibs	May exacerbate existing ulcers or produce new/additional ulcers.	High
Seizures/epilepsy	Clozapine, chlorpromazine, thiothixene	May lower seizure thresholds.	High
Blood clotting disorders or receiving anticoagulant therapy	Aspirin, NSAIDs, diypyridamole, ticlodipine, clopidogrel	May prolong clotting time and elevate INR values or inhibit platelet aggregation, resulting in an increased potential for bleeding.	High
Bladder outflow obstruction	Anticholinergics, antihistamines, antispasmodics, flavonate, antidepressants, decongestants, tolterodine	May decrease urinary flow, leading to urinary retention.	High
Stress incontinence	Alpha-blockers, anticholinergics, TCAs, long-acting benzodiazepines	May produce polyuria and worsening of incontinence.	High
Arrhythmias	TCAs	Concern because of proarrhythmic effects and ability to produce QT interval changes.	High
Insomnia	Decongestants, theophylline, methylphenidate, MAOIs, amphetamines	Concern because of CNS stimulant effects.	High
Parkinson disease	Metoclopramide, conventional antipsychotics, tacrine	Concern because of antidopaminergic/cholinergic effects.	High
Cognitive impairment	Barbiturates, anticholinergics, antispasmodics, muscle relaxants, CNS stimulants, dextroamphetamine, methylphenidate, methamphetamine, pemolin	Concern because of CNS-altering effects	High
Depression	Long-term benzodiazepines, sympatholytic agents	May produce or exacerbate depression.	High
Anorexia/malnutrition	CNS stimulants, dextroamphetamine, methylphenidate, methamphetamine, pemolin, fluoxetine	Concern because of appetite-suppressing effects.	High
Syncope/falls	Short/intermediate-acting benzodiazepines, TCAs	May produce ataxia, impair psychomotor function, produce syncope, and lead to additional falls.	High
SIADH/hyponatremia	SSRIs	May exacerbate or cause SIADH.	Low
Seizure disorder	Bupropion	May lower seizure threshold.	High
Obesity	Olanzapine	May stimulate appetite and increase weight gain.	Low
COPD	Long-acting benzodiazepines, nonselective beta-blockers	CNS adverse effects. May induce respiratory depression. May exacerbate or cause respiratory depression.	High
Chronic constipation	CCBs, anticholinergics, TCAs	May exacerbate chronic constipation.	Low

Abbreviations: CCB, calcium channel blockers; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SSRI, selective serotonin release inhibitor; TCA, tricyclic antidepressant.

Table 6. Medication Appropriateness Index (MAI)

To assess the appropriateness of the drug, please answer the following questions and circle the applicable score				
1. Is there an indication for the drug?	1 Indicated	2	3 Not indicated	9 DK
2. Is the medication effective for the condition?	1 Effective	2	3 Ineffective	9 DK
3. Is the dosage correct?	1 Correct	2	3 Incorrect	9 DK
4. Are the directions correct?	1 Correct	2	3 Incorrect	9 DK
5. Are the directions practical?	1 Practical	2	3 Impractical	9 DK
6. Are there clinically significant drug-drug interactions?	1 Significant	2	3 Insignificant	9 DK
7. Are there clinically significant drug-disease/ condition interactions?	1 Significant	2	3 Insignificant	9 DK
8. Is there unnecessary duplication with other drug(s)?	1 Necessary	2	3 Unnecessary	9 DK
9. Is the duration of therapy acceptable?	1 Acceptable	2	3 Unacceptable	9 DK
10. Is this drug the least expensive alternative compared with others of equal utility?	1 Least expensive	2	3 Most expensive	9 DK

Abbreviation: DK, Don't know.
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Table 7. Knowledge gaps in evaluating polypharmacy in older adults with cancer

Current practice	Best practice	The resulting gap
Single definitions of polypharmacy in older adults with cancer	Multiple or composite definitions of polypharmacy	Need for consensus on definition of polypharmacy or routine use of multiple approaches in evaluating polypharmacy
Lack of standardization or routine evaluation of potential drug interactions with or without chemotherapy in older adults with cancer at risk for polypharmacy	Use of electronic-based or other methods to evaluate medication lists, including chemotherapy, of older adults with cancer	Lack of understanding of what medications really are taken and how there might be potential for adverse drug events
Lack of implementation of strategies to reduce occurrence of polypharmacy in older adults with cancer and thus potential for adverse drug events	Routine use of pharmacist- or team-driven medication reviews at medical encounters and prior to initiation of chemotherapy	Incorporating such multidisciplinary approaches that have clearly demonstrated reduction in polypharmacy based on prior geriatric studies

As such, herbal/CAM use should be incorporated as part of any assessment of polypharmacy.

Intervention Studies to Decrease Polypharmacy

Most intervention studies have been limited to the implementation of a pharmacist or interdisciplinary team to review medication usage, leading to reduction in the number of medications and/or use of potentially inappropriate medications among older adults in a variety of clinical settings [96, 140–147]. Overall, these studies have shown that these approaches have led to a significant reduction in suboptimal prescribing, and thus potential for adverse drug events in otherwise susceptible older adult patients. However, the impact on such intervention on clinical outcomes may depend upon the particular population. For example, the use of pharmacist-led review of prescription drug appropriateness and subsequent modification translated into less fre-

quent adverse drug events in an outpatient setting but not in those older adults going from hospital discharge to long-term care facilities [144, 145, 147].

However, in many settings, a review of the medication list by a pharmacist or interdisciplinary team may not be available. In these situations, the implementation of electronic drug databases may be useful to help identify at-risk drugs, drug classes, dosages, and schedules [97, 148, 149]. Several electronic drug databases are available to clinicians. One study reviewed several databases and suggested that LexiComp (http://www.lexi.com), Clinical Pharmacology (http://www.clinicalpharmacology.com), and Micromedex (http://www.micromedex.com) had overall high-quality scores based on a composite evaluation of their scope, completeness, and ease-of-use in ability to answer several clinical questions [150]. However, their comparison specifically in a geriatric- or geriatric oncology–based setting has not been reported. Furthermore, the clinical significance and/or relevance of potential drug interactions and thus the "risk" of a certain drug or drug combination require clinician interpretation.

Polypharmacy in Older Adults with Cancer

Prevalence and Clinical Significance

Older adults with cancer are potentially vulnerable to the adverse effects of polypharmacy because cancer treatment often involves exposure to chemotherapy and other adjunctive or supportive medications that may increase the risk of drug interactions. Furthermore, the majority of adults with cancer are ≥65 years, with pre-existing medical conditions requiring pharmacotherapy [151]. A recent workshop sponsored by the National Institute of Aging and the National Cancer Institute reported that the prevalence and impact of medication use in the management of older adults with cancer is an unexplored area that mandates further investigation [152].

Only a few studies have evaluated the prevalence of polypharmacy specifically in geriatric oncology patients. One study reported that 63% in this group had a potential adverse drug interaction, with the majority of such patients receiving at least eight medications on average, and more than half of these interactions classified as moderate-to-severe risk [73]. When applied to outpatients receiving chemotherapy compared with supportive care only, this prevalence decreased to 27% and 31%, respectively [68, 69].

Another study evaluated the number of both prescription and nonprescription medications in older outpatients receiving chemotherapy for a variety of cancer types [74]. These patients were ≥65 years, had three comorbid conditions on average, and were receiving nine medications and at least three chemotherapeutic and/or supportive medications (mainly antiemetics). Several potential chemotherapy-drug interactions were identified; however, the frequency of adverse drug events or chemotherapy toxicity was not reported.

Most recently, the 2003 Beers criteria have been used to evaluate polypharmacy in older adults with cancer, one in an oncology-specific Acute Care for the Elderly unit and another in an outpatient setting [71, 72]. The mean age of patients evaluated was 73.5 and 74 years, respectively. Beers criteria–based prevalence of polypharmacy was 21% and 11%, respectively. Both studies were coupled with pharmacist-based interventions in medication review and subsequent modification, with 53% and 50% of patients, respectively, leading to reduction in the number of at-risk medications.

Herbal/CAM Use in Older Adults with Cancer

Herbal/CAM use can pose a significant risk in older adults with cancer. Its use in adults with cancer in the U.S. has been evaluated in several studies, with a prevalence ranging from 25% to 91%, depending on the study population and the definition of CAM used [153–189]. Only one study focused on older cancer patients, reporting a CAM prevalence of 33%, but limited the cancer type to breast, colorectal, prostate, and lung [189]. Predictors for herbal/CAM use have included the following: (a) female sex [153, 155–157, 160, 161, 164, 167, 169, 172, 181, 189]; (b) younger age [154, 156, 159, 160, 162, 172, 175, 176, 185, 186, 189]; (c) higher education levels [153, 158, 162–165, 169, 172, 176, 177, 185–187]; (d) higher income levels [165, 177, 179, 186]; (e) higher scores on measures of cancer-related physical and/or mental symptoms [153–155, 167, 170, 175, 184, 189]; and (f) advanced disease [155, 157, 162, 165]. However, none of these studies focused on herbal/CAM use in the context of polypharmacy in older adults with all cancer types or associated herbal/CAM use with outcomes.

A study evaluating outpatients undergoing chemotherapy demonstrated that almost a quarter to a half reported taking an herbal supplement or vitamin, respectively [182]. In evaluating all supplements, the 5 most frequently used supplementary agents were vitamin C (47%), a multivitamin (46%), vitamin E (42%), coenzyme Q10 (23%), and selenium (22%). When excluding vitamins, the 5 most commonly used supplementary agents were coenzyme Q10 (23%), selenium (22%), eicosapentaenoic acid (fish oil) (20%), garlic (18%), and zinc (17%).

The potential interactions of such herbal agents with

chemotherapy have been reviewed [190]. For example, irinotecan has augmented gastrointestinal toxicity in patients concomitantly taking St. John's wort [191]. Those agents deemed a higher risk are those with competing cytochrome P450 and/or P-glycoprotein interactions such as garlic, ginseng, Echinacea, St. John's wort, ginkgo, and kava. This finding is of concern because garlic, ginseng, and gingko remain in the top 10 of the most frequently used herbal agents among adults nationally as of 2006 [89]. Although the prevalence of herbal/CAM use has not been fully elucidated specifically in older adults with cancer, the importance of evaluating herbal/CAM use has led some centers to provide resources for both cancer patients and their providers to evaluate an individual agent's potential benefits as well as toxicities [192].

Knowledge Gaps

Several gaps remain in our knowledge of polypharmacy in the geriatric oncology population (Table 7). First, to our knowledge, no prospective, longitudinal studies have reported the association of polypharmacy with cancer therapy toxicity or other adverse drug events. Second, the risk of drug-chemotherapy and drug-drug interactions in this target population needs to be further explored. Third, prior studies have used only single methods in identifying and/or measuring polypharmacy, such as number of medications or the Beers criteria; however, multiple methods of evaluating polypharmacy may provide greater insight into the associated risk of adverse drug events and determine which approaches are more closely linked to that risk. Specific attention to over-the-counter medication or herbal/CAM use in these evaluations of polypharmacy in older adults with cancer is also needed.

Future Directions

Polypharmacy in its various guises is a common problem facing older adults. In this article, we describe several common definitions of polypharmacy in the geriatric population, but, regardless of definition, polypharmacy has been clearly linked with several adverse outcomes, including increased risk of adverse drug reactions [17, 45, 50, 97, 105]; medication nonadherence [34, 84–86]; hospitalization [30, 39, 45–47, 53, 59, 60]; emergency room visits [18, 45, 60, 97, 116]; falls and/or fractures [40, 51, 56–60]; and lower self-reported health scores [19, 27, 106].

Given the added degree of pharmacologic complexity that chemotherapy and cancer-specific supportive care may engender, older adults with cancer are more vulnerable to the risks associated with polypharmacy. Studies directed toward prevalence and associated outcomes in this unique group of older adults are under way (ClinicalTrials.gov Identifier: NCT00477958). These studies will allow better evaluation of potential drug interactions, herbal/CAM use, and predictors of polypharmacy in addition to chemotherapy toxicity in this vulnerable patient population.

Meanwhile, based on what we already know about polypharmacy in older adults with cancer, we would recommend these steps to hematologists and oncologists treating these vulnerable patients:

(a) Perform a careful review of the patient's list of medications, including indications and dosages.

(b) Directly inquire about over-the-counter and herbal/complementary agents.

(c) Evaluate in advance the potential interactions between the chemotherapy regimen and other medications to minimize drug interactions and subsequent toxicity; discuss with pharmacy staff where appropriate.

(d) Consider use of electronic drug databases that may help identify at-risk drugs, drug classes, dosages, and schedules, bearing in mind the limitations of such tools, especially if pharmacy-based support is not readily available or accessible.

(e) Maintain an open and active line of communication with the patient's other medical providers regarding changes or additions to medication lists.

(f) Continue to perform routine medication reconciliation at every clinical visit in conjunction with pharmacy and/or nursing staff where appropriate.

The knowledge that we have gained thus far from the geriatrics literature can facilitate oncologists in developing more effective strategies to assess, monitor, and ultimately prevent polypharmacy in older adults with cancer.

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