

Refining the Definition of Polypharmacy and Its Link to Disability in Older Adults: Conceptualizing Necessary Polypharmacy, Unnecessary Polypharmacy, and Polypharmacy of Unclear Benefit

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ABSTRACT

The term *polypharmacy* in older adults is generally used in a pejorative context in the medical literature. Because of its link to geriatric syndromes and disability, the avoidance of polypharmacy is usually recommended in older adults as a strategy to optimize functional status. However, there are many polypharmacy regimens based on high-quality trials that clearly reduce the risk of disability in older adults. Other guidelines for older adults recommend the use of additional medications that may or may not be evidence based and that may or may not reduce disability. Therefore, we propose that, in the geriatric literature, polypharmacy now be categorized as “necessary polypharmacy,” “unnecessary polypharmacy,” or “polypharmacy of unclear benefit.” In this article, we discuss the 3 categories of polypharmacy and give examples on each polypharmacy regimen and its potential relationship to disability in older adults.

INTRODUCTION

Older adults, or patients older than 65 years, have diminished reserve capacity, or the physiologic plasticity to adapt, compared with their younger counterparts. Throughout the heterogeneous continuum of geriatric aging (from the robust marathoner to the prefrail patient using a cane to the frail bedbound nursing home resident), older adults have less lean body mass with increased body fat; are more likely to have renal, hepatic, and cardiac insufficiency; take more prescriptions medications on average; and tend to have more medical problems than their younger counterparts. Older adults often experience symptomatic drug toxicity that would not have been felt by their younger counterparts. The more medications an older adult receives, the more susceptible s/he is to these drug-drug, drug-disease, and drug-patient interactions. In older adults, these adverse drug reactions often can be subtle, such as somnolence or restricted activity. Other times they are overt, for example, a fall with hip fracture or symptomatic hypoglycemia. Whether insidious or sudden, drug toxicity leads to substantial morbidity to older adults.

Polypharmacy in patients older than 65 years (ie, “older adults”) is generally defined as taking 5 or more prescription medications.¹ About 4 in 10 older adults are on polypharmacy regimens.² In the geriatric literature, polypharmacy is considered a risk factor for functional decline, leading to dependence on others. Interventions to reduce polypharmacy are considered critical strategies to prevent disability in older adults.³⁻⁵ Classical geriatric teaching emphasizes minimizing the use of prescription medications, especially in older adults at risk of frailty. The addition of 1 prescription

medication—whether the older patient was previously receiving no medications or 4 medications—can lead to substantial adverse drug events that might lead to disability.

Simplistically, major root causes of functional decline in the last year of life in older adults can be divided into at least 4 categories: Disability owing to advanced cancers, primary neurologic disorders, organ failure, and frailty.^{6,7} We will focus on the last 3 mechanisms of disability and their positive or negative relationship with polypharmacy.

We believe that the current definition of polypharmacy, with its negative connotations, is outdated. The definition of polypharmacy should be more nuanced. Recent trials have demonstrated that appropriate polypharmacy regimens can prevent disability in older adults.⁸⁻¹¹ Hence, we believe that polypharmacy should be classified as “necessary polypharmacy” (NP), “unnecessary polypharmacy” (UP), or “polypharmacy of uncertain benefit.”

NP regimens should be considered additional medications that can optimize functional status and prevent disability in older adults. For older patients receiving NP regimens, the benefits outweigh the risks. Initiation and continued adherence are critical in this category. The prescribing of and continued adherence to these regimens indicate high-quality care.

In contrast, UP should be considered additional medications that put older adults at higher risk for the development of disability. For older patients receiving these regimens, the risks outweigh the benefits. Noninitiation of these medication regimens is preferred. Deprescribing is critical in this category.

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Both noninitiation and deprescribing indicate high-quality and thoughtful care.

Polypharmacy of uncertain benefit should be considered additional medications in which the research is unclear on whether the harms balance the benefits. Weighing the potential risks with the possible benefits must be thoughtfully considered, and shared decision making with the patient is critical before finalizing the medication regimen.

NP regimens are generally used in the prevention or treatment of organ failure caused by cardiovascular disease. However, NP regimens have been recommended for the prevention of disability caused by primary neurologic diseases and geriatric syndromes as well.

The prevalence of dementia is nearly 9% of individuals older than age 65 years.¹² In 2017, the Lancet Commission on dementia care recommended the active treatment of hypertension in adults age 35 years and older as a key intervention to prevent dementia.¹³ Also in 2017, the National Academy of Medicine recommended that the appropriate treatment of hypertension could prevent, delay, or slow clinical Alzheimer-type dementia.¹⁴ Appropriately aggressive polypharmacy with antihypertensive medications in older adults with hypertension is a key component to prevent disability caused by dementia.

Subgroup analysis using Systolic Blood Pressure Intervention Trial (SPRINT) data demonstrated that appropriately aggressive control of blood pressure will reduce disability caused by cardiovascular disease.⁸ Using the automated office blood pressure (AOBP) technique, 2636 patients older than age 75 years (with major exclusion criteria; see Sidebar: Exclusion Criteria for Patients from SPRINT) were randomized to an AOBP systolic pressure target below 140 mmHg (equivalent to a systolic blood pressure of about 150 mmHg using the traditional office-based technique of sphygmomanometry) in the standard treatment group or an AOBP systolic blood pressure of less than 120 mmHg (equivalent to a systolic blood pressure of about 130 mmHg using the traditional blood pressure measurement technique) in the intensive treatment group. On average, older patients needed 2.1 antihypertensive medications to achieve the AOBP systolic blood pressure target of 140 mmHg in the standard treatment group and 2.9 medications to achieve the AOBP systolic blood pressure target of 120 mmHg for the intensive treatment group. The number needed to treat in 3.14 years in the intensive regimen

was 27 to prevent any cardiovascular event (myocardial infarction, cerebrovascular accident, acute coronary syndrome, cardiovascular death) compared with the standard therapy.⁸

Concerns regarding adverse effects of these antihypertensive polypharmacy regimens have been tempered with the results of the SPRINT subgroup analysis, of which more than 30% of study participants were considered frail.⁸ The subgroup analysis showed that there was no absolute increased risk of injurious falls and no statistical difference in orthostatic hypotension in the intensive treatment group compared with the standard treatment group. In addition, there was no difference in gait speed, a proxy of frailty in the geriatric population.

Therefore, given the safety of hypertensive polypharmacy regimens and their proven benefits, we recommend a minimum blood pressure goal of less than 140/90 mmHg using the traditional blood pressure measurement in adults older than age 65 years. For older patients with established cardiovascular disease, chronic kidney disease with an estimated glomerular filtration rate between 20 mL/min/1.73 m² and 59 mL/min/1.73 m², or with a 10-year Framingham Risk Score of greater than 15% (or a 10-year American College of Cardiology/American Heart Association Pooled Cohort Equation Risk Score > 15% or a Kaiser Permanente A Risk Score > 10%), we recommend consideration of a blood pressure goal of less than 130/90 mmHg using traditional blood pressure measurements in noninstitutionalized, ambulatory patients.

NP regimens also have a role in prevention of disability caused by geriatric syndromes. An example might include the use of bisphosphonates, calcium, and vitamin D for the treatment of established osteoporosis. Appropriate use of alendronate has been shown to have a risk reduction of future fractures, including hip fractures, by nearly 50%.¹⁵

Conversely, UP regimens increase the risk of disability because of their strong association with the development of geriatric syndromes.³⁻⁵ Adverse drug reactions from UP regimens lead to unplanned hospitalizations, a risk factor for functional decline in older adults.^{16,17} UP regimens have been linked with the development of primary neurologic disorders.¹⁸ Finally, UP contributes to increased risk of disability by leading to poor medication reconciliation from clinicians and consequently less adherence to NP regimens.

We posit 11 common scenarios of UP regimens in older adults (Table 1¹⁹⁻⁵⁵). They can be considered medication errors that put the patient at higher risk of disability. Unnecessary polypharmacy regimens are a sign of poor prescribing quality.

Finally, polypharmacy of uncertain benefit occurs when risks vs benefits either negate each other or are unclear in relative magnitude. Shared decision making with the patient is paramount in these situations. An example of polypharmacy of uncertain benefit might include the off-label use of gabapentin for the treatment of painful neuropathy. Even if gabapentin improves the quality of life in an older adult by efficaciously reducing painful neuropathy, nearly 1 in 5 will experience dizziness, 1 in 7 will experience somnolence, and 1 in 7 will experience gait disturbances at doses at or above 1200 mg daily in adults of all ages.³² Somnolence and dizziness are the top contributors of restricted activity in older

Exclusion Criteria for Patients from the Systolic Blood Pressure Intervention Trial (SPRINT)

- type 2 diabetes
- history of stroke
- symptomatic heart failure within the past 6 months or reduced (ejection fraction < 35%) left ventricular ejection fraction
- clinical diagnosis or treatment of dementia
- expected survival of less than 3 years
- unintentional weight loss during the preceding 6 months (> 10% of body weight)
- systolic blood pressure of less than 110 mmHg after 1 minute of standing
- resided in a nursing home.

Table 1. Examples and consequences of unnecessary pharmacy		
UP category	UP example	Consequences of UP
Continuation of effective medications when indications have resolved and/or nonpharmacologic approaches would have sufficed	Not initiating medications, by implementing effective nonpharmacologic interventions for medical problems, is preferred in older adults. Examples might include proper diet in patients who have GERD, or weight loss, ice, and physical therapy for the treatment of knee arthritis. However, UP regimens occur when effective medications are continued for an indication that either has resolved or been alleviated so that a nonpharmacologic approach would suffice. Common scenarios might include the continued use of ranitidine for mild GERD owing to poor diet or in a 75-year-old with a history of a hip fracture and the continued use of an SSRI for the treatment of an uncomplicated depression without an attempt to taper the dose for an updated PHQ-9 score (ideally < 10, which generally indicates the patient is no longer in active depression) after 6 mo of pharmacologic treatment.	<ol style="list-style-type: none"> 1. H₂ blockers are associated with disability caused by worsening cognition in patients with dementia.^{19,20} 2. SSRIs are associated with disability caused by an increased risk of falls with fractures.²¹
Continuation of medications when treatment course has been completed	Effective medications are often continued even when the treatment course has been completed. In these clinical scenarios, prolonged medication use contributing to UP can be finite or indefinite. Finite scenarios include overuse with a 10-d, rather than a 5-d, course of levofloxacin for the treatment of an uncomplicated community-acquired pneumonia, ²² or a prolonged 10-d course of corticosteroid treatment, rather than 5 d, for an uncomplicated COPD exacerbation. ²³ Common indefinite scenarios include the continued use of baby aspirin combined with clopidogrel in older adult patients with a stent placed and with coronary artery disease who have a DAPT score ^a < 2, ²⁴ or the indefinite use of omeprazole in an NSAID/aspirin-naïve patient that was initiated during a hospitalization for treatment of a bleeding peptic ulcer.	<ol style="list-style-type: none"> 1. Broad-spectrum antibiotics are associated with disability caused by restricted activity and/or hospitalizations caused by a heightened risk of <i>Clostridium difficile</i> colitis. 2. Corticosteroids are associated with disability caused by an increased risk of delirium²⁵ or increasing future risk of an osteoporotic fracture. 3. DAPT is associated with disability caused by restricted activity and hospitalizations because of a higher risk of stomach ulcers or bleeding 4. PPIs are associated with disability caused by a higher risk of <i>C difficile</i> colitis²⁶ and osteoporotic fractures.²⁷
Continuation of medications after a period that is no longer considered safe	Medications are continued for periods that are not considered safe. For example, metoclopramide is often prescribed for treatment of gastroparesis in older adults. Long-term use of metoclopramide leads to heightened risk of tardive dyskinesia. ²⁸ Long-term alendronate use has been associated with atypical femoral fractures (AFF), fractures that occur with no trauma. Continuous use of alendronate for more than 10 years increases the risk of AFF without additional fracture reduction. ^{29,30}	<ol style="list-style-type: none"> 1. Metoclopramide is associated with an increased risk of disability caused by restricted activity. 2. Long-term bisphosphonate use is associated with AFF. In turn, AFF leads to restricted activity and increased risk of delirium owing to hospitalization for AFF repair.
Continuation of medications that were never efficacious in alleviating the symptoms	Medications may help the symptoms of some older adults, but not others. Ineffective medications are often initiated and continued in older patients, contributing to UP. Common scenarios include the continuation of risperidone for the intended treatment of behavioral disturbances in patients with dementia or the continuation of gabapentin for the intended treatment of neuropathy. In both clinical scenarios, the likelihood of the medication being effective for its intended indication is low. For example, risperidone was not shown to demonstrate statistical improvements in the Clinical Global Impression of Change Scale in patients with dementia with behavioral disturbances compared with placebo. ³¹ A Cochrane Review states that more than half of the patients receiving high-dose gabapentin will not have worthwhile pain relief in patients (of all ages) with postherpetic or diabetic neuropathy. ³²	<ol style="list-style-type: none"> 1. Antipsychotic use is associated with disability owing to an increased risk of stroke, hospitalization caused by pneumonia, and restricted activity owing to fractures.^{33,35} 2. Gabapentinoids are associated with disability owing to the increased risk of falls with fractures.³⁶
Continuation of previously effective medications that are no longer effective because of tolerance	Older adults often continue the use of previously effective medications that lose their efficacy because of tolerance. Examples include the long-term use of lorazepam for anxiety treatment or the continued use of hydrocodone/acetaminophen for treatment of osteoarthritis. Neither class has been shown to be effective for its indications after long-term daily use. ^{37,38}	<ol style="list-style-type: none"> 1. Benzodiazepines are associated with disability caused by an increased risk of delirium³ and falls.⁴ 2. Opioids are associated with disability owing to an increased risk of sedation and falls.³⁹
Duplication of medications within the same class	Older adults may use different medications in the same class. This may be unintentional because they have multiple prescribers who use different health care records or who do not inquire about over-the-counter medication use, or it may be the result of low health care literacy in an older patient. Using medications in the same class may lead to increased adverse-effect potential without change in efficacy. Examples include the use of lorazepam and clonazepam for anxiety-related issues, or the use of over-the-counter ibuprofen (unknown to the prescribing physician) along with prescription meloxicam.	<ol style="list-style-type: none"> 1. Benzodiazepines are associated with an increased risk of delirium and falls^{3,4} 2. NSAIDs increase risk of disability because of restricted activity and hospitalizations for treatment of acute renal insufficiency and peptic ulcers.

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<p>Use of medications with opposing mechanisms of action</p>	<p>Older adults may take different medications that have opposing mechanisms of action. This leads to an increase in the adverse effect profile with the blunting or cancellation of the intended benefit. Use of the highly anticholinergic medication oxybutynin and the anticholinesterase donepezil is not an uncommon regimen in nursing home patients with incontinence and dementia.⁴⁰ Other scenarios might include the use of modafinil and zolpidem for older patients with somnolence and insomnia. (Conversely, the coprescribing of medications of opposing mechanisms can be considered high-quality prescribing in the scenarios that include glucagon in older patients receiving high-dose insulin,⁴¹ or naloxone for patients receiving high-dose opioids.³⁷ Glucagon would be administered by the family for patients with diabetes with symptomatic hypoglycemia, and naloxone would be administered by the family for patients with evidence of opioid overdose.)</p>	<p>1. Anticholinergics and sedative-hypnotics are associated with disability owing to an increased risk of falls and delirium.^{3,5}</p>
<p>Continued use of medications in patients with limited life expectancy</p>	<p>The time of accrual for net clinical benefit from medications must be greater than the anticipated life expectancy of an older adult. For example, UP regimens occur when additional diabetic medications are added to attain an HbA_{1c} of < 7.0% in frail older adults.⁴¹ The UKPDS showed that time for macrovascular benefits with tight glycemic control in younger adults was 10 to 19 years.⁴² Tight glycemic control may lead to hypoglycemia with substantial morbidity. HMG-CoA reductase inhibitors (statins) are used for preventive (primary and secondary) indications and should be considered part of a NP regimen in most older patients with established atherosclerotic disease. However, statin regimens are often continued in patients with limited life expectancy. The deprescribing of statins has been shown to be safe and can improve quality of life in patients with an anticipated life expectancy of < 1 year (absent a recent cardiovascular event).⁴³</p>	<p>1. Insulin and/or oral sulfonylureas can lead to hospitalization for hypoglycemia treatment. Hospitalizations are associated with disability owing to restricted activity.¹⁶ 2. Statins are associated with disability owing to restricted activity resulting from myalgias.</p>
<p>Pharmacologic overtreatment of a disease</p>	<p>Overtreatment of diseases with medications is common in older adults. Common scenarios are the continued use of hypoglycemic medications in older adults with an HbA_{1c} < 7.0% or the continued use of antihypertensive medications with an SBP < 110 mmHg (using the traditional BP technique) without a history of cardiomyopathy.⁴⁴ Dose deintensification when appropriate is equally important to reduce the risk of adverse effects. Examples include avoiding the use of high-dose digoxin (defined as > 0.125 mg daily⁴⁵) to reduce risk of hospitalization caused by digoxin toxicity⁴⁶ and avoiding the long-term use of inappropriate use of aspirin, 325 mg daily, for primary or secondary prevention of CVD.</p>	<p>1. Pharmacologic overtreatment of diabetes can result in an increased risk of disability owing to hospitalizations and an increased risk of cognitive impairment.^{46,47} 2. Pharmacologic overtreatment of antihypertensive medications may be associated with disability owing to an increased risk of falls and syncope. 3. High-dose digoxin may be associated with disability owing to restricted activity and/or hospitalization caused by an adverse drug reaction. 4. Aspirin, 325 mg daily, likely puts older patients at higher risk of peptic ulcers without additional benefit compared with doses of aspirin 75 mg to 162 mg daily.^{48,49}</p>
<p>Use of potentially harmful medications</p>	<p>Potentially harmful medications are medications that should almost always be avoided in adults older than age 65 years and cataloged by the Beers Criteria.³⁶ The 2 most common classes of potentially harmful medications prescribed are highly anticholinergic medications and sedative-hypnotics. Examples of commonly used highly anticholinergic medications include the use of paroxetine for the treatment of depression or the use of nortriptyline for the treatment of peripheral neuropathy. Examples of commonly used sedative-hypnotics are daily use of zolpidem for the treatment of insomnia or lorazepam for the treatment of anxiety.</p>	<p>1. Anticholinergics have been associated with a higher risk of injury and dementia.⁵⁰⁻⁵² 2. Sedative-hypnotics are considered a potentially harmful medication because of their association with a heightened risk of pneumonia, falls with fractures, delirium, and dementia.^{3,4,53-55}</p>
<p>Duplication of medications that have the same adverse-effect profile</p>	<p>Use of different medications with the same adverse-effect profile is a UP regimen that puts an older adult at high risk of disability. The concurrent use of multiple highly anticholinergic medications (eg, paroxetine for depression, nortriptyline for peripheral neuropathy, and oxybutynin for urinary incontinence) increases the cumulative anticholinergic burden, putting an older adult patient at increased risk of deleterious adverse effects. Another common UP regimen that occurs in older adults is concurrent, multiple psychoactive medications.</p>	<p>1. Anticholinergics have been associated with a higher risk of injury and dementia.⁵⁰⁻⁵² 2. Sedative-hypnotics, opioids, antipsychotics, and SSRIs increase the risk of disability by increasing the risk of delirium and falls.^{3,4}</p>

^a In a patient without an ischemic or bleeding event after the initiation of dual antiplatelet therapy (ie, aspirin combined with a thienopyridine such as clopidogrel) for the indication of coronary artery stent placement, the "DAPT score" gives guidance on whether continuation or cessation of dual antiplatelet therapy past 12 mo places the patient at higher risk for bleeding (with the continuation of dual antiplatelet therapy) or an ischemic event (with the cessation of thienopyridine). Risk factors for an increased risk for bleeding with continuation of dual antiplatelet therapy after 12 mo include age older than 65 y (-1 point for age 65 to 74 y and -2 points for age 75 y and older). Risk factors for an increased risk for ischemic events with cessation of dual therapy after 12 mo of use include smoking, diabetes mellitus, prior myocardial infarction or percutaneous coronary intervention, myocardial infarction at presentation, ejection fraction < 30%, vein graft percutaneous coronary intervention, paclitaxel stent, or stent diameter < 3 mm (+1 point for each of these risk factors). Using this DAPT score, patients with less than 2 points would favor cessation of the thienopyridine at 12 mo. Patients with a DAPT score of 2 points or greater would favor continuation of dual antiplatelet therapy past 12 mo.

BP = blood pressure; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DAPT = dual-antiplatelet therapy; GERD = gastroesophageal reflux disease; H₂ = histamine 2; HbA_{1c} = hemoglobin A1C; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; NP = necessary polypharmacy; NSAID = nonsteroidal anti-inflammatory drug; PHQ = Patient Health Questionnaire; PPI = proton pump inhibitor; SBP = systolic blood pressure; SSRI = selective serotonin reuptake inhibitor; UKPDS = UK Prospective Diabetes Study; UP = unnecessary polypharmacy.

adults,⁵⁶ a risk factor for future disability.¹⁷ Gait impairment is a risk factor for falls.⁴

Another example includes the use of proton pump inhibitors (PPIs) in older adults receiving aspirin and clopidogrel (and with no history of peptic ulcer and/or not receiving concurrent corticosteroids, anticoagulants, or nonsteroidal anti-inflammatory drugs). The American College of Cardiology and the American Heart Association state that it is “reasonable” to use PPIs for these patients of “advanced age” who are receiving aspirin and clopidogrel therapy.²⁴ Whether the reduction in peptic ulcer risk with the use of PPIs in this setting balances the increased risk of infections²⁶ and osteoporotic fractures²⁷ is not established.

We recognize that guidelines have been created for medication appropriateness by expert groups from all medical specialties that influence how physicians prescribe to older adults (see Sidebar: Consensus Statement on Polypharmacy). Controversy has shrouded guidelines because of the diversity of function in adults older than age 65 years and because of publication biases. Although we recognize that the theme of 1 size fits all will never apply to all patients older than age 65 years, exceptions should be minimized. Initiating UP or not initiating NP as well as refilling UP and not deprescribing UP can have monumental consequences for risk of future disability. Shared decision making should always occur in discussions with older patients with a focus on the risk/benefit ratio of NP, UP, and polypharmacy of uncertain benefit.

Consensus Statement on Polypharmacy

Properly addressing polypharmacy has been an area of focus for many years by Michael Kanter, MD, previously Chief Quality Officer for The Permanente Federation and currently Professor and Chair of Clinical Sciences at the Kaiser Permanente (KP) School of Medicine. However, the implications of polypharmacy and its role in the preservation of functional status in older adults can be vastly different to different physicians.

This article is a culmination of years of communications to better understand and reconcile the meaning of polypharmacy that have included Eric Lee, MD (Chief of General Internal Medicine, KP West Los Angeles Medical Center and Co-Chair of the High Risk Drugs in the Elderly Committee, KP Southern California [KPSC]); Jeffrey Brettler, MD (Hypertension Physician Lead, KPSC); Steven Steinberg, MD (Regional Chief of Family Medicine, KPSC); Peter Khang, MD (Regional Chief of Geriatrics, Palliative Medicine and Continuing Care, KPSC); Christopher Distasio, MD (Regional Chief of Neurology, KPSC); John Martin, MD (Co-Chair of Diabetes Care, KPSC); Mark Dreskin, MD (Chair of Integrated Behavioral Health, KPSC); Nolan Thompson, MD (Regional Chief of Psychiatry, KPSC); Timothy Cotter, MD (Regional Chief of Cardiology, KPSC); Kim Thai, MD (Regional Chief of Physical Medicine, KPSC); Lyn Yasumura, MD (Regional Chief of OB/GYN, KPSC); and Nancy Gibbs, MD (formerly Regional Chief of Geriatrics and Continuing Care and Co-Chair, High Risk Drugs in the Elderly Committee, KPSC).

This is a consensus statement that we hope all physicians consider when addressing the initiation, refilling, or deprescribing of medications in patients age 65 years and older.

Language shapes how we think and act. Among geriatricians, the term *polypharmacy* has a negative connotation and suggests needlessly putting older adults at higher risk of harm. We must update this antiquated definition of polypharmacy by refining the term as *NP*, *UP*, or *polypharmacy of uncertain benefit*. Not all polypharmacy should be avoided, and in many circumstances, polypharmacy should be recommended. In older adults, superior prescribing performance reflects the appropriate noninitiation and deprescribing of UP, the appropriate initiation and continuation of NP, and thoughtful consideration of polypharmacy of uncertain benefit. ❖

Disclosure Statement

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