Choosing Wisely®

An initiative of the ABIM Foundation

American Society of Consultant Pharmacists

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Empowering Pharmacists. Transforming Aging.

Ten Things Physicians and Patients Should Question

1 Don't initiate medications to treat new and emerging symptoms without first ascertaining that the new symptom is not an adverse drug event of an already prescribed medication.

The risk of adverse drug reactions (ADR) and hospital admissions related to ADRs increases with age, polypharmacy and comorbidities. It is prudent for clinicians to be aware of the prescribing cascade to reduce the prescription of potentially unnecessary medications that may cause patient harm. Prescribing cascades are a type of problematic polypharmacy that occur when an adverse drug event (ADE) is misinterpreted as a new medical condition, and a second medication is prescribed to address this emerging ADE. If a suitable alternative is available, discontinuation of the medication thought to be the cause of the ADR would be the best course of action. The decision to prescribe a second medication to counteract an ADR from a first medication should only occur after careful consideration, and where the benefits of continuing therapy with the first medication outweigh the risks of additional adverse reactions from the second medication. Older adults are at an increased risk of experiencing prescribing cascades due to the higher incidence of polypharmacy and multi-comorbidity.

For example, calcium channel blockers (CCBs) are commonly prescribed for hypertension and have the potential to cause peripheral edema. A prescribing cascade occurs when the edema is misinterpreted as a new medical condition and a diuretic is subsequently prescribed to treat the edema. Ideally, the choice of a different antihypertensive may be the best action at this time, in this example. Addressing the prescribing cascade involves focusing on the medication review process and deprescribing initiatives. There are a range of resources to prevent, detect, and reverse prescribing cascades to improve the appropriate use of medications.

2 Don't continue medications at transitions of care without a pharmacist or other qualified health care professional performing a comprehensive medication review to verify accurate and complete medication information in concert with current medical problems.

Transitions of care can contribute to serious medication-related problems when transitioning between different care settings. Older adults with complex health care problems appear to be a group particularly at risk for increased adverse events. To mitigate errors in prescribing and transcribing, routine assessments should include a comprehensive medication review, medication reconciliation, and an accurate medication history with the patient and his or her advocate. A thorough medication history involves following a systematic process of interviewing the patient, family or caregiver and verifying the history with at least one other reliable source of information to determine the complete and correct list of the patient's actual medication use at the time of the transition. Negative outcomes associated with transitions across healthcare settings include increased likelihood of polypharmacy when medications are continued that are no longer indicated, therapeutic drug duplication, heightened risk of adverse drug reactions, and poor adherence related to greater complexity of the medication regimen.

3 Don't recommend highly anticholinergic medications in older adults without first considering safer alternatives or non-drug measures.

Many medications have strong anticholinergic activity including first generation antihistamines (e.g. diphenydramine, doxylamine), tricyclic antidepressants, gastrointestinal antispasmodics, antiemetics, muscle relaxants, medications for urinary incontinence and medications to treat Parkinson disease. Older adults are more sensitive to adverse events associated with anticholinergics including confusion, dry mouth, blurry vision, constipation, urinary retention, decreased perspiration and excess sedation. Anticholinergics have also been associated with increased dementia risk. These medications are especially problematic for people with existing cognitive impairment and bladder anticholinergics should be used judiciously for these patients. It is important to inquire about over-the-counter antihistamine use and help patients select safer alternatives for sleep and seasonal allergies. For example, for seasonal allergies, second generation antihistamines have minimal anticholinergic effects and allergies may be managed with nasal steroids.

Items 1–5 Released May 17, 2021; Items 6–10 Released June 8, 2022

4

Don’t use anticholinergic medications concomitantly with cholinesterase inhibitors in patients with dementia.

Anticholinergics (e.g. overactive bladder medications and first-generation antihistamines) competitively inhibit binding of the neurotransmitter acetylcholine, thus reducing the effects of acetylcholine. Cholinesterase inhibitors, used in the treatment of dementia, act by blocking the enzyme acetylcholinesterase thereby inhibiting acetylcholine degradation. Therefore, pharmacologic actions of anticholinergics and cholinesterase inhibitors oppose each other. Concomitant use of anticholinergics with cholinesterase inhibitors reduces the effectiveness of antidementia drugs, the benefits of which are modest at best; concomitant use increases the risk of adverse effects of anticholinergics and may also increase the rate of functional and cognitive decline. Medications with anticholinergic properties are commonly prescribed to treat comorbidities associated with dementia and sometimes the adverse effects of cholinesterase inhibitors. Patients with dementia are sensitive to cognitive impairment induced by medications with anticholinergic properties. In general, it has been recognized that anticholinergics are known to adversely affect cognition in older patients and even more so with concomitant dementia diagnosis.

5

Don’t use two or more medications that are known to increase the risk of bleeding without evaluating the potential risks and benefits. These medications include direct oral anticoagulants (DOACs), warfarin, aspirin, selective serotonin reuptake inhibitors (SSRIs), antiplatelet agents, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids.

Prescribing more than one of these medications concurrently may result in an enhanced risk of bleeding. This heightened bleeding risk may be mediated through complex pharmacokinetic and/or pharmacodynamic mechanisms. It is well established that the combination of anticoagulants and NSAIDs increase bleeding risk. A combination of warfarin with either single or dual antiplatelet therapy significantly increases the risk of major bleeding by 2- to 4-fold, respectively. The most commonly prescribed antidepressant therapeutic class (SSRIs), may decrease platelet serotonin uptake, leading to impaired platelet aggregation, and thereby increased bleeding risk. Specific to gastrointestinal bleeding, SSRIs may also increase gastric acid secretion. Bleeding has been observed in association with other antidepressants in some observational studies, however recent systematic reviews give weight to SSRIs in combination with NSAIDs for increased vigilance for risk of upper gastrointestinal bleeding. In patients where benefits outweigh the risks of the combination, appropriate education of patient and caregivers and appropriate follow-up monitoring for early detection of any signs and symptoms of bleeding is highly recommended.

6

Don’t prescribe or routinely continue medications for older adults with limited life expectancy without due consideration to individual goals of care, presence of comorbidities and time-to-benefit for preventive medications.

Older adults with limited life expectancy (life expectancy less than 24 months) continue to be consumers of health care resources, including preventive medications for chronic diseases that provide questionable benefit. At the end of life, consider shifting from curative to palliative goals of therapy with subsequent modifications in medication use with regards to individual’s goals of care. To identify older adults for whom medications are most likely to benefit (and most likely to harm), a framework that compares an individual’s life expectancy with the time to benefit (TTB) has been proposed. TTB may be defined as the point in time at which patients are expected to derive a benefit from a treatment. TTB is increasingly considered in addition to other measures of medication effectiveness to understand and contextualize the benefits and harms of a therapy for an individual patient. Reducing the use of unnecessary medications may reduce pill burden and adverse drug events, as has the potential to improving quality of life.

Some recent studies have highlighted medications to manage dementia (cholinesterase inhibitors and memantine) and possibly statins as medications of questionable benefit for older adults with advanced dementia.

7

Don’t use three or more CNS-active medications (antidepressants, benzodiazepines, Z-drugs, opioids, gabapentinoids, antipsychotics, antiepileptics), especially in older adults.

There is strong evidence linking the use of multiple CNS-active medications with serious adverse drug events in older adults. Specifically, older adults taking multiple CNS-active medications are at an increased risk for falls and fractures. Furthermore, the combined use of opioids with gabapentinoids increases the risk of opioid-related death. There is high quality of evidence for avoiding combined use of benzodiazepine receptor agonists (benzodiazepines or Z-drugs defined as zopiclone, eszopiclone, zaleplon) and moderate evidence for avoiding combinations of other CNS-active medications. Despite these medications being considered potentially inappropriate in older adults who have a history of falls, many continue to take them after a serious injury.

Benzodiazepines and Z-drugs have minimal effectiveness for sleep and safer alternatives are available (e.g. for anxiety, consider SSRIs; for insomnia, consider treatment of underlying conditions interrupting sleep, and cognitive behavioral therapy). Maintaining patients on the lowest effective dose and evaluating periodically for deprescribing are prudent strategies to mitigate harm from CNS-active medications.

8

Don't combine opioids with benzodiazepines or gabapentinoids to treat pain in older adults and re-evaluate routinely for deprescribing during chronic use.

Co-prescribing of benzodiazepines or gabapentinoids (gabapentin, pregabalin) with opioids is increasingly utilized in the multimodal treatment of acute and chronic pain despite limited evidence to support the effectiveness of this practice. Population studies have demonstrated that these combinations are associated with increased risk of serious adverse outcomes such as excessive sedation, overdose events, and death. In 2019, The FDA required new warnings about the risk of serious breathing difficulties that can lead to death in patients who use gabapentanoids with opioid pain medicines or other drugs that depress the central nervous system, or those who have underlying respiratory impairment, such as patients with chronic obstructive pulmonary disease, or the elderly.

Older adults may be particularly vulnerable due to age-related changes in pharmacokinetics, pharmacodynamics, and medical comorbidity. Initiation of combination therapy should be avoided whenever possible; older patients who require chronic concurrent use of these medication classes should be closely monitored and periodically evaluated for deprescribing.

Choosing Wisely Canada (Canadian Pharmacists Association) spells out an important consideration for prescribing benzodiazepines that includes discontinuation strategies, except for patients with valid indications requiring long-term use of these medications.

9

Don't prescribe tramadol for older adults without due consideration of the potential risks and harms related to serotonergic excess, seizures, falls and drug-drug interactions.

The utilization of tramadol, a weak and mixed centrally acting opioid analgesic, has increased steadily over the past decade, a trend influenced by perceived safety advantages over opioid medications like morphine, oxycodone, and hydrocodone. However, a recent national study reported that older adults account for 33% of tramadol-associated emergency department visits and half of subsequent hospitalizations, suggesting that greater scrutiny of tramadol's safety in this population is warranted.

Tramadol's adverse effects such as sedation, and the potential for serotonin syndrome and hyponatremia are well recognized by clinicians, however tramadol-induced seizures and hypoglycemia are particularly harmful for older adults and may further elevate risk of falls and fractures.

The risk of tramadol's clinically relevant adverse effects is heightened among patients with decreased renal function.

By way of brief review, the opioid receptor-mediated analgesic effects are mainly attributed to the active metabolite M1 (O-desmethyltramadol), whereas the inhibition of the neurotransmitter reuptake is caused by the parent drug. The metabolic conversion to the M1 metabolite is mediated primarily through CYP2D6 enzyme, which exhibits substantial genetic variability, consequently the pharmacological effect of tramadol is affected by drug-drug and drug-gene interactions.

Knowledge of this genetic variability to tramadol's analgesic response and potential for drug-drug interactions may help optimize pain control and prevent emergence of adverse effects.

10

Don't use strong CYP3A4 and P-glycoprotein inhibitors or inducers with Direct Oral Anticoagulants (DOACs) and periodically assess the medication regimen for such drug-drug interactions.

Direct Oral Anticoagulants (DOACs) such as dabigatran, rivaroxaban, and apixaban have significantly fewer drug-drug interactions (DDIs) as compared to warfarin. However, there are notable DDIs with strong CYP3A4 and P-glycoprotein (p-gp) inhibitors with DOACs, which clinicians need to consider necessitating dosage adjustments and monitoring for their older patients.

As a general principle, drugs that are inhibitors block the metabolic activity of one or more CYP450 enzymes and their effects usually occur immediately. Inducers, on the other hand increase CYP450 enzyme activity by increasing enzyme synthesis thereby causing a delay before this increased enzymatic activity has an impact on metabolism.

Each of the DOACs is a substrate for p-glycoprotein (p-gp), an efflux transporter located in the gut mucosa, and therefore, all DOACs are susceptible to drugs that induce or inhibit p-gp. Dabigatran requires efflux transportation by the p-gp, however it is independent of the CYP450 enzyme system. Apixaban and rivaroxaban, on the other hand undergo minor hepatic metabolism by CYP enzymes. Moreover, alterations in varying rates of renal elimination of DOACs should be equally considered as possibly additive to the metabolic effects affecting outcome from DDIs.

Since drug product labeling does provide specific guidance for management of inhibitor interactions, it is highly recommended to consult this information before prescribing decisions are made. It is prudent for clinicians to exercise caution when co-prescribing a DOAC and a strong CYP3A4 and/or p-gp inhibitor to minimize bleeding or conversely in the case of a strong inducer (rifampin) to prevent the risk of thrombotic events. Pharmacokinetic DOAC drug-drug interactions are clinically important because patient harm may go unnoticed due to no INR-equivalent testing and monitoring for DOACs as compared to warfarin.

In a recent review, the most significant interacting drugs to cause bleeding events with DOACs were amiodarone and ritonavir via inhibition of p-gp and CYP3A4. Conversely, a reduction in DOAC levels has been observed in some case reports and pharmacokinetic studies when used concomitantly with enzyme inducers (rifampin, carbamazepine) potentially resulting in therapeutic failure.

It is advisable for all clinicians to periodically assess the patient's medication regimen for DDIs when DOACs are prescribed. Advanced age, low body weight, renal impairment, or concomitant antiplatelet medications are additional factors that may impact the severity and outcome of DOAC drug-drug interactions.

How This List Was Created (1–5)

A deprescribing task force led by chair (Manju T. Beier, Pharm D, BCGP, FASCP) was created by ASCP in November 2018. Members comprised of pharmacists practicing in academia, community and long-term care settings. The chair also invited pharmacists from international countries (Canada and Australia) where deprescribing initiatives have a strong focus and literature base. The collective experience and knowledge represent a focus on medication management, medication selection and reconciliation, and monitoring for drug-drug interactions (DDIs). The emphasis is on older adults no matter where they reside in step with ASCP's mission.

Definition wise, deprescribing is a stepwise reduction of unnecessary or potentially inappropriate medications in concert with patient and family goals and wishes. We recognize that even with the best of intentions, many older adults are left on unnecessary and potentially dangerous or duplicative medications that might precipitate adverse events and other negative outcomes.

The task force prioritized formulation of the Choosing Wisely (CW) List, since the goals of CW intersect and overlap with deprescribing initiatives. The list was created to address general medication regimen review statements, and more importantly to address the paucity of statements that address DDIs with several incriminating medication therapeutic classes prescribed for older adults. After a review of published CW statements on www.choosingwisely.org and also a review of CW statements published by international countries, it was decided by consensus to have a strong emphasis on DDIs.

After several virtual meetings, the CW workgroup was divided into subgroups to formulate DDIs that have a strong evidence base in the literature and those that focus on CNS therapeutic classes, anticholinergic burden, heightened bleeding risk, and other pivotal pharmacokinetic and pharmacodynamic DDIs. For each statement the group formulated a rationale that was evidence-based accompanied with several recent, pertinent references. The compiled list (after several virtual meetings and email discussion) was further reduced to top ten statements with the strongest evidence base and practice trends on medication management in older adults.

The top five list was selected by consensus for initial submission.

Attached is a recently published guest editorial in ASCP's journal that highlights the emphasis on DDIs.
Beier MT. Vigilance of Drug-Drug Interactions to Mitigate ADRs: Front and Center for Pharmacists (Guest Editorial). *Sr Care Pharm* 2020; 35:336-7.

How This List Was Created (6–10)

A deprescribing task force led by chair (Manju T. Beier, Pharm D, BCGP, FASCP) was created by ASCP in November 2018. Members comprised of pharmacists practicing in academia, community and long-term care settings. The chair also invited pharmacists from international countries (Canada and Australia) where deprescribing initiatives have a strong focus and literature base. The collective experience and knowledge represent a focus on medication management, medication selection and reconciliation, and monitoring for drug-drug interactions (DDIs). The emphasis for all our statements is on older adults no matter where they reside in step with ASCP's mission. Our first 5 CW statements were published in May 2021.

As previously addressed, the rationale for the new 2022 list (statements 6–10) includes one medication review statement in older adults with limited life expectancy, and three statements emphasizing the adverse combination of CNS medications that have a strong evidence base in the literature including tramadol's potential for greater harm than benefit for pain relief, especially in older adults. We had previously highlighted pharmacodynamic DDIs for heightened bleeding risk, and this time our statement addresses the complexity of pharmacokinetic DDIs with Direct Oral Anticoagulants (DOACs).

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