Managing Medications in Clinically Complex Elders

"There's Got to Be a Happy Medium"

Michael A. Steinman, MD
Joseph T. Hanlon, PharmD, MS

Multiple medication use is common in older adults and may ameliorate symptoms, improve and extend quality of life, and occasionally cure disease. Unfortunately, multiple medication use is also a major risk factor for prescribing and adherence problems, adverse drug events, and other adverse health outcomes. Using the case of an older patient taking multiple medications, this article summarizes the evidence-based literature about improving medication use and withdrawing specific drugs and drug classes. It also describes a systematic approach for how health professionals can assess and improve medication regimens to benefit patients and their caregivers and families.

JAMA. 2010;304(14):1592-1601 www.jama.com

PATIENT'S STORY

Mr L is an 84-year-old man with dementia and a medical history of atrial fibrillation, diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, gastritis, and gastroesophageal reflux disease. His past surgeries include a transurethral bladder resection for bladder cancer with subsequent urinary incontinence and a lumbar decompression for spinal stenosis in 2008.

Mr L lives with his wife, Mrs L, who also cares for him. He is a retired writer and editor and a lifelong tennis player. On first presentation, his initial concerns were forgetfulness, difficulty walking, and falling. His wife reported that he was "doing almost nothing," maintaining a sedentary lifestyle at home, and following her around. He needed considerable help with bathing and dressing, some assistance with toileting and transferring, and was dependent in most instrumental activities of daily living including shopping, housekeeping, and preparing meals. Mrs L hired a home health aide for several hours a day to help alleviate the substantial burden of caregiving.

At his initial visit, Mr L's blood pressure was approximately 135/60 mm Hg, his heart rate (beats/min) was in the 50s, and his estimated creatinine clearance was 42 mL/min/1.73 m^2. He scored 13 of 29 points on a Folstein Mini-Mental State Examination (MMSE) performed shortly before the visit, consistent with Dr S's clinical impression of moderately severe cognitive impairment. His oral medications were glyburide, 2.5 mg; digoxin, 0.125 mg; warfarin (varying dose); etodolac, 400 mg; docusate sodium, 100 mg; a multivitamin and iron, each taken daily; memantine, 10 mg; metoprolol, 25 mg; and gabapentin, 300 mg; twice daily; essential fatty acids, 3 times daily; and on an as-needed basis, acetaminophen, 650 mg every 6 hours; and lactulose, for a total of 13 medications at 16 scheduled doses per day.

See also p 1606

CME available online at www.jamaarchivescme.com and questions on p 1621.

Mr L's hemoglobin A_{1c} was 5.9% so Dr S discontinued glyburide. Dr S referred him to receive physical therapy and also to social services to discuss options regarding caregiving, social engagement, and long-term care plans. His warfarin dose was managed by nurse practitioners in a nearby hospital's anticoagulation clinic, and his international normalized ratios were maintained in the desired range between 2.0 and 3.0.

Mr L's drug regimen included ongoing use of etodolac and gabapentin after his 2008 lumbar laminectomy, despite no longer reporting pain. Dr S sequentially tapered off both medications, watching for increased reports of pain. Mr L reported no return of pain, his walking improved, and he had no further falls. Dr S also tapered the digoxin, starting by reducing the dose by half for 1 week. His heart rate remained between 50 and 70 beats/min so digoxin was discontinued. He began going to yoga with his wife and then to the gym twice weekly.

Author Affiliations: Division of Geriatrics, University of California, San Francisco, and the San Francisco VA Medical Center, San Francisco, California (Dr Steinman); Division of Geriatric Medicine, Department of Medicine, Department of Epidemiology, and Department of Pharmacy and Therapeutics, University of Pittsburgh; Geriatric Research Education and Clinical Center, and Center for Health Equity Research and Promotion, Veterans Affairs Pittsburgh Healthcare System (Dr Hanlon), Pittsburgh, Pennsylvania.
Corresponding Author: Michael A. Steinman, MD, 4150 Clement St, Box 181G, San Francisco VA Medical Center, San Francisco, CA 94121 (mike.steinman@ucsf.edu).
Care of the Aging Patient: From Evidence to Action is produced and edited at the University of California, San Francisco, by Seth Landefeld, MD, Louise Walter, MD, and C. Bree Johnston, MD; Amy J. Markowitz, JD, is managing editor.
Care of the Aging Patient Section Editor: Margaret A. Winker, MD, Deputy Editor.

Mr L's initial laboratory results had shown a normal hemoglobin level of 13 g/dL, and Dr S discontinued iron; his hemoglobin level subsequently remained stable. Seven months after Mr L's first visit, Dr S asked Mrs L whether memantine was helping her husband's memory (he previously had not tolerated donepezil). She was unsure, and together they decided to try tapering Mr L's use of it. Thereafter, he had greater difficulty with nouns and names so Dr S referred him to speech therapy for cognitive exercises and resumed the memantine at its full dose. He initially showed some improvement, but within 6 months cognitive decline was again apparent.

Mrs L continues to pay for her husband's medication under his Medicare Part D plan. She reports that his activities of daily living have been stable. Socially, he is improved.

Mrs L and Dr S were interviewed by a Care of the Aging Patient editor in December 2009.

Caring for the Patient

Mrs L: *Just looking at [some of his medication] you realized that you could keep taking it, but you don't really have to. . . . It's better to pull it out.*

Use of multiple medications is a common source of concern for patients and clinicians. Nearly 20% of community-dwelling adults aged 65 years and older take 10 or more medications, a figure that can easily be reached by following practice guidelines for a small number of coexisting conditions.[1,2] Multiple medication use is associated with greater use of inappropriate medications and with nonadherence, and imposes substantial cost burdens on older patients even when they have prescription drug insurance.[3-5] In addition, the frequency of adverse drug events increases in proportion to the number of medications used, including drug-specific phenomena as well as nonspecific syndromes including weight loss, falls, and decline in functional and cognitive status.[6-10] Such adverse drug events affect an estimated 5% to 35% of older patients living in the community per year, and are responsible for approximately 10% of hospital admissions in older adults.[11-15]

Despite legitimate concerns regarding multiple medication use, believing that Mr L is taking too many medicines does not help the clinician know which ones to stop. Moreover, such labels can distract from addressing underuse of potentially beneficial medications, which is as prevalent in older adults taking many drugs as in those taking relatively few.[16,17] The task for the clinician is not to determine whether too many or too few medications are being taken, but to determine if the patient is taking the right medications—tailored to the patient's individual circumstances, including his or her constellation of comorbidities, goals of care, preferences, and ability to adhere to medications.

METHODS

We conducted several systematic literature reviews. Our main review evaluated the effect of interventions to improve on suboptimal prescribing across the medication regimen (ie, without focus on a single drug class or disease) for elders in ambulatory settings who were taking multiple medications. Searching PubMed and International Pharmaceutical Abstracts from 1975 through March 2010, the search used a combination of the terms *polypharmacy, multiple medications, polymedicine, suboptimal prescribing, medication misuse, inappropriate prescribing, elderly, geriatric*, and *aged*, and was restricted to randomized clinical trials published in the English language, involving patients aged 65 years and older, and reporting both process measures assessing prescribing and clinical outcome measures. We also reviewed studies of the effects of discontinuing specific types of medications taken by Mr L. Details of the search strategies are available in an eAppendix (available at http://www.jama.com).

INFORMATION GATHERING

Assessing Current Medication Use

Before optimizing Mr L's medication regimen, Dr S's first task was to assess what drugs Mr L thought he should be taking, what he actually was taking, and the benefits and harms he was experiencing from his drugs.

A good medication review is essential because discrepancies are common between patients' understanding of what they should be taking, what they actually are taking, and what physicians record on their medication lists.[18,19] There is little direct evidence to support one specific method of medication review over another in ambulatory settings.[20] However, a "brown bag" review in which patients are asked to bring in all of their medicines (including all prescription and over-the-counter medicines, vitamins, supplements, and herbal preparations) can provide a useful snapshot of the patient's current medication use. The clinician can review each medication and inquire about how the patient takes it (eg, by asking "tell me how you take this medication").

Brown bag reviews often present an opportune time to review the effectiveness of medications (eg, control of pain, constipation, or depressed mood) as well as their adverse effects. Patients often do not report drug-related symptoms to their physicians, in part due to limited physician efforts to solicit this information.[21,22] In one major study, such communication gaps were responsible for 37% of remediable adverse drug events.[23] The question "In the past XX months, have you noticed any side effects, unwanted reactions, or other problems with medications you have taken?" has been validated as an effective way to inquire about adverse drug events.[15] Directed questions about common or high-risk symptoms may also be necessary—for example, inquiring about postural symptoms in a patient taking antihypertensive medications.

Assessing Adherence

Mrs L: *I opened his 7-day pill container on a Monday and it was wet. It turned out that he had been taking them out and moving them around and had spilled water in there somehow.*

Table 1. Barriers to Medication Adherence and Targeted Solutions

Barriers	Potential Solutions
Forgetting to take; limited organizational skills	Use pill organizers, medication calendars, blister packs, electronic dispensing devices; simplify regimen and reduce pill burden; encourage active family/caregiver involvement; use Internet-linked or electronic adherence aids and reporting systems
Patient believes drug is not needed, is ineffective, or that too many drugs are being taken	Work collaboratively with patient to address concerns and establish shared goals of care; provide educational (including literacy-appropriate) materials using teach-back approach; assess drug effectiveness; simplify regimen and reduce pill burden
Difficulty taking (eg, opening pill bottles, swallowing)	Substitute with easier-to-use medications (eg, liquid if trouble swallowing; ordering easy-off caps); simplify regimen and reduce pill burden; use pill cutters, oral dosing syringes, insulin syringe magnification, spacer for inhalers
Cost	Substitute with lower-cost medications (eg, generic vs brand name) and reduce unnecessary ones; assess prescription drug insurance and direct patient to apply for low-income subsidy and prescription drug assistance programs

Mr L had several red flags for adherence problems including dementia, a complex medication regimen, and previous adverse drug events.[5,24] Approximately one-half of older patients have problems with adherence to taking at least 1 medication, being evenly split between occasional, frequent, and near-universal omissions of drug doses, although patients nonadherent to taking one of their medications are commonly adherent with others.[24,25]

Patients are often reluctant to admit to nonadherence so a multifaceted approach to evaluating adherence is necessary.[24,26] During medication review, clues about adherence can be deduced from observing medication organization, pill counts, and refill history (using information on the refill date and quantity dispensed printed on the label). Asking patients and their caregivers about their understanding of why they take each medication can also be useful. Although studies have found that age itself does not predict adherence and that older adults understand the purpose of as much as 88% of their medications, lack of understanding increases risk of nonadherence and provides a ready target for intervention.[5,27] More generally, nonadherence can be elicited by nonjudgmental questions such as "I know it must be difficult to take all your medications regularly. How often do you miss taking them?"[24] If nonadherence is identified, the patient should be asked why, with prompting as necessary for common reasons such as those listed in TABLE 1.[5,24] Interventions to improve medication use and adherence are most likely to succeed when they address the reasons underlying these problems.

For many physicians, ideal medication reviews and adherence assessments are an improbable reality given the time pressures of office-based practice.[28] In this setting, focusing on the highest-risk and highest-benefit drugs can yield good return on a limited time investment. Better yet is sharing these responsibilities with other health care professionals. Contacting community pharmacists regarding concerns about patients can help engage their expertise in identifying and crafting solutions to problems with adherence or medication regimens. Where health systems permit, nurses and clinic-based pharmacists should share medication management responsibilities as articulated in the patient-centered medical home model of care.[29] Some medication management programs are available through pharmacy benefit management plans serving Medicare Part D patients (Resources available at http://www.jama.com). Eligibility criteria and scope of these programs are often limited, although more widespread benefits are mandated for implementation by 2013.[30]

Goals of Medication Use

Mrs L: *The family is all guilt-ridden and they tell themselves that they have to keep dear old dad alive . . . . My stake is that he himself has a decent day-to-day life as much as he can.*

Like many older patients in the final chapter of their lives, Mr L and his caregivers are facing choices about using medications that might increase his longevity but negatively affect his quality of life.[31] When getting to know Mr L, one of Dr S's first tasks was to learn what he and his family were trying to achieve through medication use including extension of longevity, reduction in symptoms, and/or minimization of pill burden, medication adverse effects, and costs.[32] Many patients would like to achieve all these goals, but often they come into conflict. The physician's role is thus to understand and clarify the relative prioritization of these values, which usually emerges from multiple conversations about specific medication decisions and general goals of care discussions.

Understanding the life expectancy of patients through application of prognostic tools and clinical judgment can help inform goal-driven decisions about prescribing (Resources).[33] A short life expectancy affords patients limited opportunity to be helped by medications that require several years to achieve a clinical benefit, such as drugs to improve glycemic control in diabetes.[31,32,34] In addition, for patients with advanced dementia, poor prognosis, or both, consensus panels do not recommend (and in some cases advocate against) medications such as statins, bisphosphonates, and cholinesterase inhibitors, although these positions are not universally endorsed.[35-37]

CAN STRUCTURED MEDICATION MANAGEMENT IMPROVE OUTCOMES?

Given Mr L's complex medication regimen and multiple comorbidities, he seems to have been a good candidate for structured medication review and management. The evidence base to guide such approaches is limited. Among 6 studies of medication management that met inclusion criteria in our literature review (see "Methods" section), 3 tested the effect of a clinical pharmacist working with a general practice or

general medicine clinic, 2 examined a comprehensive interdisciplinary medication review in a geriatrics clinic, and 1 examined the effect of expert clinician recommendations through computer-based feedback (TABLE 2).[38-44] Overall, these programs improved markers of pharmaceutical care quality such as reducing medication burden, correcting underuse of medications, and improving a multicomponent score of medication appropriateness. Less evidence is available about the effect of these interventions on clinical outcomes. In the largest study of its type using a multidisciplinary intervention, Schmader et al[43] reduced the rate of serious adverse drug events from 0.6 to 0.4 events per 1000 person-days ($P=.02$). A similar, but nonsignificant ($P=.19$), degree of reduction in all adverse drug reactions was observed in a study of veterans aged 65 years and older by Hanlon et al,[38] with adverse events in 30% of patients receiving medication management vs 40% in patients receiving usual care. There is little conclusive evidence about the effect of comprehensive medication management on other clinical outcomes, including quality of life, health services utilization, and major clinical events; in general, these studies were underpowered for these outcomes.

Of note, most studies on improving medication prescribing for elders with multiple medication use evaluated an external intervention such as pharmacist review or referral to a geriatric evaluation and management clinic. Few studies have evaluated clinicians' own attempts to integrate medication management principles into their practice.[46] However, limited data suggest that physicians who are provided structured assessment tools for medication review are able to identify and correct medication problems in a large percent of their patients, although time limitations impede widespread implementation of such reviews.[45-47] For example, one study of a guided approach to optimize prescribing found that the proportion of correct medication decisions in a series of clinical vignettes increased from 35% without the method to 48% with it, with a corresponding decline in the number of potentially harmful decisions from a mean of 3.3 to 2.4 per case.[48]

CHANGING THE MEDICATION REGIMEN

Matching the Medication Regimen to the Patient's Conditions and Goals of Care

Although few data are available about the effect of structured medication management on patient health and well-being, such approaches are endorsed by experts, in part due to clear evidence of beneficial effects on markers of prescribing quality.[49] A simple and effective approach to systematically identify prescribing problems is to match each of the patient's conditions with medications that he or she is taking (TABLE 3). Areas of mismatch can highlight drugs that are being overused (ie, used with no indication), underused (ie, conditions that may benefit from drug therapy that is not currently being offered), and misused (ie, drugs given for an appropriate indication that could be improved by changing the dose, frequency, or substituting another drug with a better profile of benefits, harms, and costs).[50]

Of note, the proper match between clinical conditions and medications is defined not only by guideline recommendations and best practices, but by how medication treatment for a given condition will help the patient attain the goals of care. Thus, the optimized medication regimen for a patient desiring a palliative approach that minimizes medication burden may look quite different than the regimen for a similar patient with the same conditions whose overriding goal is maximizing longevity.

Should Medications Be Discontinued or Substituted? Which Ones?

Dr S: *A lot of the pain complaints that he used to have had disappeared after he had a lumbar surgery in 2008. [His wife] didn't know if he still needed the pain medication, but was too worried to stop them.*

Without knowing anything else about Mr L, the fact that he was taking 13 medications when he first met Dr S suggests a high probability that 1 or more of his medications could or should be stopped.[16,51] Studies of community-based older patients have documented an average of 1 unnecessary drug per patient, including drugs with no identifiable indication or that provide little benefit for the indication for which they are prescribed.[52,53] Perpetuation of unnecessary medications is particularly acute in older adults with multiple prescribers or transitions of care (eg, recent hospital visits).[54-57] In the hospital setting, a large study found that 44% of hospitalized frail older patients were discharged with at least 1 unnecessary medication; common culprits include proton pump inhibitors, central nervous system medications, and vitamin and mineral supplements.[55,58,59]

In addition, drugs given for a useful clinical purpose are often misprescribed. For example, highly anticholinergic antihistamines, tricyclic antidepressants, and other high-risk drugs described in drugs-to-avoid lists for older patients are used by approximately 20% to 30% of adults older than 65 years, whereas in many cases, drugs with better safety and/or efficacy would be a more appropriate choice for the target condition.[60-64] Other common problems with misprescribing include use of inappropriately high or low doses, drug-drug and drug-disease interactions, incorrect directions, and choice of expensive drugs when less expensive alternatives would provide similar benefit at lower cost.[50]

As shown in Table 3, matching Mr L's medications with his conditions shows several drugs for which he lacks a clear current indication, including etodolac, gabapentin, acetaminophen, multivitamins, and iron. These should be among the first drugs considered for discontinuation. Next are drugs for which Mr L has a current indication but that may, given his circumstances, provide limited or no benefit. For Mr L, such drugs include memantine for dementia, glyburide for diabetes, and digoxin for rate control of atrial fibrillation. Finally, certain drugs may have benefits but an unfavor-

able risk profile and should be substituted for others with a more favorable ratio of benefits to harms.

Troublesome symptoms obviously caused by a drug provide a clear signal to consider discontinuation. However, the adverse effects of many drugs are nonspecific and can mimic underlying disease processes, such as Mr L's generalized functional decline. Often, the only way to know whether or not a symptom is an adverse effect is to temporarily stop the drug(s) and see whether the symptoms improve.[65] Although these are individualized clinical decisions, it can be useful to remember the adage that "any symptom in an older patient should be considered a drug side effect until proven otherwise."[66]

With limited exceptions, very few studies address the benefits and harms of discontinuing specific types of medications.[65,67] In the case of Mr L, we could not identify any controlled studies that evaluated outcomes of withdrawing digoxin for rate control in atrial fibrillation, discontinuing hypoglycemic medications in diabetes, or withdrawing memantine in dementia (although we identified 1 randomized trial and 2 poorly controlled trials about withdrawal of cholinesterase inhibitors, which suggested worsening of cognition after stopping the drug).[68-70]

In the absence of high-quality trial data on discontinuing medications, decisions about the cessation of certain drugs should be guided by the epidemiology of prescribing prob-

Table 2. Randomized Controlled Studies to Improve Pharmaceutical Care Quality in Ambulatory Older Adults Using Multiple Medications

Study	Setting and Location	No. of Patients and Inclusion Criteria	Intervention and Duration	Process Measures (Intervention vs Control)	Clinical Outcome Measures (Intervention vs Control)
Pharmacist Interventions					
Hanlon et al,[38] 1996; Cowper et al,[39] 1998	1 VA general medicine clinic; United States	208; Aged ≥65 y taking ≥5 drugs	Pharmacist review, written drug recommendations to primary care physician, and patient counseling at each visit; 12 mo	Decreased MAI score (12.8 vs 16.7; $P<.001$)[a]	No differences in health-related quality of life ($P=.99$), ADEs (30% vs 40%; $P=.19$), and health care costs ($7873 vs $5926; $P>.05$)
Krska et al,[40] 2001	6 general practices; Scotland	332; Aged ≥65 y, taking ≥4 drugs, and ≥2 chronic disease states	Pharmacist review of drugs and related issues; recommendations agreed to by patient's general practitioner; 3 mo	Increased resolution of pharmaceutical care issues (ie, suspected ADEs, monitoring issues, ineffective therapy [83% vs 41%; $P<.001$])	No differences in medication costs, health-related quality of life, clinic visits, and hospitalizations (all $P>.05$)
Lenaghan et al,[41] 2007	1 general practice; Great Britain	136; Aged ≥80 y, taking ≥4 drugs, and ≥1 drug-related risk factor	2 Home visits by community pharmacist; 6 mo	Decreased number of drugs (0.3 fewer vs 0.6 more; $P=.03$)	No difference in hospital admissions ($P=.80$)
Multidisciplinary Team Interventions					
Williams et al,[42] 2004	1 geriatrics clinic; United States	133; Aged ≥65 y taking ≥5 drugs including ≥2 potentially problematic ones	Single multidisciplinary review, contact with primary care physician, and changes implemented; 6 wk	Decreased number of drugs (1.5 vs 0.1 fewer; $P=.001$) and decreased monthly drug costs (savings of $27 vs $1, $P=.006$)	No differences in 9 measures of physical, cognitive, or affective functioning (all $P>.05$)
Schmader et al,[43] 2004	Clinics at 11 VA medical centers; United States	834; aged ≥65 y, frail health status after hospital discharge	Multidisciplinary, protocol-driven geriatric evaluation and management clinic; 12 mo	No difference in number of unnecessary drugs, number of inappropriate drugs, or MAI score[a] ($P>.25$ for each); and decreased number of conditions with omitted drugs (0.2 fewer vs 0.1 more; $P<.001$)	No difference in all ADEs (relative risk, 1.03 [95% CI, 0.86-1.23]; $P=.75$); decreased risk of serious adverse drug events (relative risk, 0.65 [0.45-0.93]; $P=.02$)
Computer Feedback Intervention					
Weber et al,[44] 2008	18 clinic sites; United States	620; Aged ≥70 y taking ≥4 drugs including ≥1 psychoactive	Pharmacist or geriatrician 1-time drug review with message to primary care physician through electronic medical record; 15 mo	Decreased use of psychoactive drugs (effect size, 0.2 drugs per patient; $P=.04$); trend toward decreased number of medications (effect size, 0.5 drugs per patient; $P=.09$)	No difference in risk of falls (odds ratio, 0.86; $P>.05$)

Abbreviations: ADE, adverse drug events; MAI, Medication Appropriateness Index; VA, Veterans Affairs.
[a]Lower score indicates a better process measure with MAI.

lems and by common sense. In assessing harms, particular attention should be paid to drugs that carry a high risk of serious adverse effects, including warfarin, hypoglycemic medications, and digoxin (TABLE 4), which account for one-third of all emergency department visits in older patients due to adverse drug events.[76] In the case of Mr L, this provides extra reason to critically evaluate Mr L's diabetes regimen and digoxin. Mr L likely did not need medications for

Table 3. Matching Mr L's Conditions and Medications[a]

Condition	Drug Given for Condition	Potential Problem[a]	Notes
Dementia	Memantine 10 mg twice daily	Potentially unnecessary	Withdrawal trial later attempted, which suggested that memantine provided benefit, so restarted
Atrial fibrillation	Digoxin 125 µg daily	Probably unnecessary, potentially harmful	Likely not needed for rate control while also taking a β-blocker and may be contributing to falls and cognitive and functional decline (drug-disease interaction)
	Metoprolol 25 mg twice daily		Will help manage hypertension
	Warfarin (varying dose)		Prothrombin time international normalized ratio is well-controlled with help of anticoagulation clinic; given this, reduction in risk of stroke exceeds risk of serious bleeding complications
Diabetes mellitus	Glyburide 2.5 mg daily	Probably unnecessary, potentially harmful	Likely not needed due to good control of hemoglobin A_{1c} (guidelines recommend goal A_{1c} level of 7%-8% in older patients; overly aggressive control yields more harm than benefits); any dosage of glyburide inappropriate given risk of hypoglycemia in patients with chronic kidney disease
Hypertension	Metoprolol 25 mg twice daily		Also used for atrial fibrillation
Hyperlipidemia	Essential fatty acids 3 times daily	Potential underuse of statin therapy	Statin therapy reduces cardiovascular events in high-risk populations, may slow progression of vascular dementia; however, is controversial in patients with limited life expectancy and may be inappropriate if goals of care are focused on palliating current symptoms
Chronic kidney disease			Angiotensin-converting enzyme inhibitor may be considered but not strongly indicated in absence of proteinuria; ensure that drugs are dosed for renal function
Gastritis, gastroesophageal reflux disease		Potential underuse	If symptomatic and refractory to lifestyle modification, consider proton pump inhibitor or H_2 blocker
Incontinence following bladder cancer surgery			Likely not amenable to medication therapy; bladder antispasmodics (eg, oxybutynin) may worsen cognition
Falls and gait instability		Potential underuse	Consider adding vitamin D, calcium, and bisphosphonate for fracture prophylaxis; however, oral bisphosphonates may pose problem in patients with swallowing difficulty or difficulty staying upright after dosing and may be inconsistent with goals of care; some of patient's drugs may worsen gait and increase fall risk—particularly digoxin and possibly gabapentin (drug-disease interactions)
Functional/cognitive decline			Same drugs that may precipitate falls (eg, digoxin) may worsen cognition and functional status
Constipation, hemorrhoids	Docusate 100 mg daily	Ineffective	Limited effectiveness for constipation
	Lactulose as needed	Suboptimal choice	Long latency period before action and may not be best choice for as-needed medication; dietary modification (increased fiber and water) may provide effective nondrug alternative
Past history of pain from spinal stenosis that was surgically repaired	Etodolac 400 mg daily	No current indication, potentially harmful	No longer needs pain medication (pain resolved after spinal stenosis surgically corrected); etodolac may worsen kidney function and hypertension and increase risk of gastrointestinal bleed (particularly in combination with warfarin [drug-drug and drug-disease interactions])
	Gabapentin 300 mg twice daily	No current indication, potentially harmful	Not needed; may worsen falls and cognition (drug-disease interaction)
	Acetaminophen 650 mg every 6 hours as needed for pain	No current indication, adherence	Not needed; difficult to use 4-times-daily–medication regularly
Past history of anemia	Iron	No current indication, potentially harmful	No current evidence of anemia; can worsen constipation (drug-disease interaction)
Drugs being given for no readily identifiable reason	Multivitamin daily	No indication	Little evidence that multivitamins improve outcomes in unselected populations; vitamin D can be useful for fall and fracture prevention but standard multivitamins contain insufficient quantity

[a] At the time that Mr L first met Dr S.

Table 4. Selected High-Risk Drugs

Drug	Potential Harm	Comment
Insulin and sulfonylureas	Hypoglycemia	May often be appropriate; however, aggressive glycemic control may often yield greater harms than benefits in older adults[34,71,72]
Warfarin	Gastrointestinal, intracranial bleeding	Although a high-risk drug, benefits of warfarin therapy often outweigh harms; maintenance of prothrombin time international normalized ratio in therapeutic range tightly linked to risk/benefit ratio[73]
Digoxin	Impairment of cognition, heart block	May have a third-line role in management of systolic heart failure; suboptimal choice for rate control in atrial fibrillation
Benzodiazepines	Falls	Associated with as much as a 60% increase in fall risk[74]
Diphenhydramine, other first-generation antihistamines	Impaired cognition, urinary retention in men	Poor choice as sleep aid due to anticholinergic effects, next-day sedation, impact on performance including driving; close medication reconciliation important because patients may also obtain over-the-counter drugs
Antipsychotics	Death, pneumonia	Elevated risk of death when used to treat behavioral complications of dementia, although in selected cases, benefits may exceed risks if consistent with patient goals of care[75]

his diabetes, on the basis of guidelines and evidence suggesting that tight glycemic control in the setting of advanced age or multiple comorbidities can result in greater harms than benefits.[34,71] Even if Mr L did require medication for glycemic control, glyburide would be a poor choice because this agent is relatively contraindicated for patients with creatinine clearance less than 50 mL/min/1.73 m^2 and carries a higher risk of severe hypoglycemia than other sulfonylureas.[77-79] Nonetheless, the presence of a high-risk drug should not automatically mandate a medication change without further exploration of context.[52] For example, tricyclic antidepressants are often problematic in elders due to a high frequency of anticholinergic adverse effects. However, if an older patient is already taking a tricyclic antidepressant for a valid indication and reports excellent symptom control, has no anticholinergic symptoms, and is reluctant to switch medications, it may be reasonable to continue the medication while educating the patient to be vigilant for potential future adverse effects.

Underuse of Potentially Beneficial Medications

Although use of ineffective or harmful medications is common in older adults, the same patients often are not prescribed potentially beneficial medications, for example warfarin for atrial fibrillation, antidepressants for major depression, pain medications, and laxatives.[16,50,80] Mr L has some conditions that might benefit from additional drug therapy beyond what he is receiving (Table 3). In patients in their final years of life, preference usually should be given to ensuring that troublesome symptoms such as pain and depressed mood are adequately treated. However, some forms of primary prevention can be appropriate if consistent with goals of care. For example, vitamin D deficiency is common in older patients and has been implicated in falls and fracture risk (along with an emerging variety of other conditions), and repletion can reduce risk of these outcomes.[81,82] Thus, vitamin D supplementation (≥800 IU/d) should be considered for Mr L, particularly if his serum 1,25-dihydroxyvitamin D level is low.[82] For many conditions, the relative paucity of drug trials that include old-old adults or those with extensive comorbidities limits the evidence basis for treating patients such as Mr L. However, in many cases, it appears likely that the relative risk reduction observed in middle-aged and young-old adults is not radically different in the old-old.[83]

Discontinuing Medications

Dr S: *I very rarely stop things cold—especially something such as a pain medicine, which could very well be helping the patient; that might be the reason he's not complaining of pain.*

When starting drugs in older adults, geriatricians often begin drugs one at a time and follow the dosing mantra of "start low and go slow." Limited evidence is available about the best ways to stop medications in older people, although in clinical practice many follow a similarly sequential, step-wise approach to discontinuing drugs.[65] In certain circumstances, an all-at-once approach may be warranted when dangerous signs or symptoms are thought likely to be due to drugs but the exact culprit cannot be identified, or when tendencies toward clinical inertia in a patient or practice environment suggest that future opportunities for medication modification will be limited.

Medications can typically be effectively withdrawn once the decision has been made to do so, although unwanted reactions in the period after withdrawal are common.[84,85] In one of the only broad-based studies of the topic in ambulatory older patients, 26% of drug discontinuations were accompanied by worsening of the underlying disease (eg, recurrence of angina or high blood pressure) and 4% were accompanied by physiologic withdrawal reactions (mostly to β-blockers and benzodiazepines).[86] For many drugs, risk of adverse withdrawal events can be minimized by slow, careful tapering of drug dose. This is particularly true for drugs to which the body adapts over time, for example through up- or down-regulation of end-organ receptors, which produce a physiologic withdrawal reaction if the drug is withdrawn abruptly.[65] Although the scientific basis for how to withdraw specific drugs is scant, a rule of thumb is that drugs can usually be tapered down at the same rate at which they are titrated up at the initiation of drug therapy. Common drugs that require tapering include opioids, β-blockers, clonidine, gabapentin, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricy-

clic antidepressants.[65] Regardless of the speed of the taper, patients should be monitored for adverse withdrawal events, including educating and activating patients to recognize and report concerning symptoms.[13,29] Communication with other health care professionals involved in prescribing for the patient is critical when stopping related drugs. For example, Mr L's warfarin dosing might have been affected by discontinuing other drugs and the anticoagulation clinic should have been alerted to the change.

Sometimes drugs are stopped on a trial basis to determine if potential adverse drug effects resolve or symptoms of the underlying disease worsen. Such assessments can be complicated by fluctuations of symptoms and biomarkers in an individual patient; for example, it may be difficult to ascertain whether improvement in symptoms after withdrawing a drug was the result of stopping the drug or natural fluctuations in the disease course. In this case, a formal rechallenge with the drug (ie, as part of an n-of-1 trial) may help to establish causality.[87]

IMPROVING ADHERENCE TO THE NEW REGIMEN

Mrs L: *We looked and saw how confused he was so I told him I was going to take over all of his medicines.*

The benefits of changing the medication regimen are contingent on the patient adhering to the revised plan of care. Improving adherence requires diagnosing barriers to proper medication use and devising strategies to overcome those barriers (Table 1).

Randomized controlled trials of strategies to improve adherence to chronic medications have yielded mixed results, and often have studied multifaceted interventions in a manner that makes it difficult to unpack the contribution of each component to improving adherence.[88-90] However, several lessons emerge from the data. First, education through oral counseling or written instruction is important, but often insufficient unto itself. Most randomized trials of intensive educational interventions have yielded minimal to moderate impacts on adherence and little effect on clinical outcomes.[88,89] Nonetheless, common sense suggests it is useful to briefly discuss and write out instructions for taking a medication that is being newly prescribed or modified. A teach-back approach, in which the patient or caregiver is asked to describe the purpose of the drug, instructions for its use, and adverse effects to be aware of can help to ensure comprehension.

In contrast to a focus on education, a potent intervention to improve adherence is simplifying medication dosing schedules. Observational studies have found that adherence drops steeply with increasing number of doses per day, with average adherence falling from roughly 80% in patients taking once-daily regimens to 50% in those taking 4-times-per-day regimens.[91] Randomized controlled trials have found large differences in adherence in patients randomized to medications requiring different numbers of doses per day, although effects on downstream clinical outcomes were mixed.[88] Thus, whenever possible, clinicians should minimize dosing frequency by prescribing longer-acting medications and dosing different drugs at the same time. In addition, pill burden can be reduced by using medications that can treat 2 or 3 conditions simultaneously (for example, β-blockers in a patient with hypertension, heart failure, and atrial fibrillation with rapid ventricular response). Attempts to reduce dosing frequency may be particularly potent for patients with cognitive difficulties, but are also helpful for cognitively intact patients or caregivers (such as Mr L's wife), who can also frequently forget to take or administer medicines and may resist the pill burden and lifestyle impacts that come with multiple dosings.[24]

Other approaches can help address common barriers to adherence, including behavioral interventions (eg, cues, medication organizers, packaging), involvement of family and friends (eg, support, monitoring, and administering medications, as was done for Mr L), and by having patients demonstrate ability to self-medicate in a controlled environment (eg, in the hospital or long-term care facility) before discharge to home without support.[88-90] In addition, addressing medication costs, for example, by prescribing lower-cost generic alternatives instead of brand-name drugs, can reduce cost-related nonadherence as well as negative effects on other aspects of the patient's financial well-being.[92] Many patients will need a combination of approaches, and pharmacists can be helpful partners in devising and following strategies to improve adherence.

MONITORING AND FOLLOW-UP

Ongoing monitoring for the toxicity and effectiveness of drug therapy is critical to providing quality care and improving outcomes, but current practices often fall short.[93,94] Approximately one-third to two-thirds of patients taking angiotensin-converting enzyme inhibitors, digoxin, carbamazepine, and other drugs that require laboratory-based safety monitoring fail to receive minimum standards for monitoring.[49,95,96] If suboptimal monitoring or frequent deviations from target levels have been present, barriers to monitoring and safe drug dosing should be assessed. If such barriers cannot readily be remediated, the clinician should consider discontinuing the drug.

Finally, systematic review of a patient's medication list (eg, using the brown bag framework suggested in this article) is a form of monitoring that should be done periodically. Although the frequency of such reviews should be tailored to patient circumstances, good starting points include recommendations by the National Committee for Quality Assurance and the Assessing Care of Vulnerable Elders (ACOVE) project, which consider medication review at least once per year to be an important measure of care quality in older adults.[97,98] Declines in function and the onset or worsening of geriatric syndromes such as cognitive decline or falls may represent adverse drug effects or signal a change in goals of care and should also precipitate medication review.

CONCLUSIONS

Prescribing for older patients is an extraordinarily complex endeavor. However, as illustrated by Dr S, Mr L, and his caregiver Mrs L, a thoughtful, systematic approach to addressing the medication regimen can bring order to complexity and make a meaningful difference in patient outcomes. The success of Dr S's care of Mr L was not in knowing the "right" answer for her patient from the beginning, but rather from using a careful, stepwise process that merged key principles of pharmacologic care with the clinical reality, social situation, and goals of care of the patient.

Financial Disclosures: None reported.
Funding/Support: Dr Steinman was supported by the National Institute on Aging and the American Federation for Aging Research (K23 AG030999) and by the Department of Veterans Affairs (IIR 06-080). Dr Hanlon was supported by grants from the National Institute of Aging (R01AG027017, P30AG024827, T32 AG021885, K07AG033174, and R01AG034056), the National Institute of Mental Health (R34 MH082682), the National Institute of Nursing Research (R01 NR010135), the Agency for Healthcare Research and Quality (HS017695 and HS018721), and a Veterans Administration Health Services research grant (IIR-06-062). The Care of the Aging Patient series is made possible by funding from The SCAN Foundation.
Role of the Sponsor: The funders had no input in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
Online-Only Material: A list of relevant Web sites and eAppendix are available at http://www.jama.com.
Additional Contributions: We thank Lars Osterberg, MD, and Rabbi Dorothy Richman for their helpful suggestions about the structure and content of this article. We thank the patient, the patient's wife, and the physician for sharing their stories and providing permission to publish them.

REFERENCES

1. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases. *JAMA*. 2005;294(6):716-724.
2. Slone Epidemiololgy Center at Boston University. Patterns of medication use in the United States, 2006. http://www.bu.edu/slone/SloneSurvey/AnnualRpt/SloneSurveyWebReport2006.pdf. Accessed June 2, 2010.
3. Madden JM, Graves AJ, Zhang F, et al. Cost-related medication nonadherence and spending on basic needs following implementation of Medicare Part D. *JAMA*. 2008;299(16):1922-1928.
4. Steinman MA, Landefeld CS, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc*. 2006; 54(10):1516-1523.
5. Vik SA, Maxwell CJ, Hogan DB. Measurement, correlates, and health outcomes of medication adherence among seniors. *Ann Pharmacother*. 2004; 38(2):303-312.
6. Chrischilles E, Rubenstein L, Van Gilder R, Voelker M, Wright K, Wallace R. Risk factors for adverse drug events in older adults with mobility limitations in the community setting. *J Am Geriatr Soc*. 2007;55(1):29-34.
7. Field TS, Gurwitz JH, Harrold LR, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. *J Am Geriatr Soc*. 2004;52(8):1349-1354.
8. Agostini JV, Han L, Tinetti ME. The relationship between number of medications and weight loss or impaired balance in older adults. *J Am Geriatr Soc*. 2004; 52(10):1719-1723.
9. Magaziner J, Cadigan DA, Fedder DO, Hebel JR. Medication use and functional decline among community dwelling older women. *J Aging Health*. 1989; 1:470-484 doi:10.1177/089826438900100404.
10. Larson EB, Kukull WA, Buchner D, Reifler BV. Adverse drug reactions associated with global cognitive impairment in elderly persons. *Ann Intern Med*. 1987; 107(2):169-173.
11. Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions. *Ann Pharmacother*. 2008;42(7):1017-1025.
12. Hanlon JT, Pieper CF, Hajjar ER, et al. Incidence and predictors of all and preventable adverse drug reactions in frail elderly persons after hospital stay. *J Gerontol A Biol Sci Med Sci*. 2006;61(5):511-515.
13. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*. 2003; 289(9):1107-1116.
14. Hanlon JT, Schmader KE, Koronkowski MJ, et al. Adverse drug events in high risk older outpatients. *J Am Geriatr Soc*. 1997;45(8):945-948.
15. Chrischilles EA, Segar ET, Wallace RB. Self-reported adverse drug reactions and related resource use. *Ann Intern Med*. 1992;117(8):634-640.
16. Steinman MA. Polypharmacy and the balance of medication benefits and risks. *Am J Geriatr Pharmacother*. 2007;5(4):314-316.
17. Gurwitz JH. Polypharmacy. *Arch Intern Med*. 2004;164(18):1957-1959.
18. Kaboli PJ, McClimon BJ, Hoth AB, Barnett MJ. Assessing the accuracy of computerized medication histories. *Am J Manag Care*. 2004;10(11 pt 2):872-877.
19. Bedell SE, Jabbour S, Goldberg R, et al. Discrepancies in the use of medications. *Arch Intern Med*. 2000;160(14):2129-2134.
20. Bayoumi I, Howard M, Holbrook AM, Schabort I. Interventions to improve medication reconciliation in primary care. *Ann Pharmacother*. 2009;43(10): 1667-1675.
21. Weingart SN, Gandhi TK, Seger AC, et al. Patient-reported medication symptoms in primary care. *Arch Intern Med*. 2005;165(2):234-240.
22. Richard C, Lussier MT. Nature and frequency of exchanges on medications during primary care encounters. *Patient Educ Couns*. 2006;64(1-3):207-216.
23. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med*. 2003;348(16):1556-1564.
24. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005; 353(5):487-497.
25. Gray SL, Mahoney JE, Blough DK. Medication adherence in elderly patients receiving home health services following hospital discharge. *Ann Pharmacother*. 2001;35(5):539-545.
26. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*. 1986;24(1):67-74.
27. Wallsten SM, Sullivan RJ Jr, Hanlon JT, Blazer DG, Tyrey MJ, Westlund R. Medication taking behaviors in the high- and low-functioning elderly. *Ann Pharmacother*. 1995;29(4):359-364.
28. Cutler DM, Everett W. Thinking outside the pillbox–medication adherence as a priority for health care reform. *N Engl J Med*. 2010;362(17):1553-1555.
29. Feldstein AC, Smith DH, Perrin N, et al. Improved therapeutic monitoring with several interventions. *Arch Intern Med*. 2006;166(17):1848-1854.
30. Thompson CA. New health care laws will bring changes for pharmacists. *Am J Health Syst Pharm*. 2010;67(9):690-695.
31. Walter LC, Covinsky KE. Cancer screening in elderly patients. *JAMA*. 2001; 285(21):2750-2756.
32. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. *Arch Intern Med*. 2006;166(6): 605-609.
33. Reuben DB. Medical care for the final years of life. *JAMA*. 2009;302(24): 2686-2694.
34. Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. *J Am Geriatr Soc*. 2003;51(5 suppl guidelines):S265-S280.
35. Holmes HM, Sachs GA, Shega JW, Hougham GW, Cox Hayley D, Dale W. Integrating palliative medicine into the care of persons with advanced dementia. *J Am Geriatr Soc*. 2008;56(7):1306-1311.
36. Parsons C, Hughes CM, Passmore AP, Lapane KL. Withholding, discontinuing and withdrawing medications in dementia patients at the end of life. *Drugs Aging*. 2010;27(6):435-449.
37. Wenger NS, Solomon DH, Amin A, et al; ACOVE-3 Clinical Committee. Application of assessing care of vulnerable elders-3 quality indicators to patients with advanced dementia and poor prognosis. *J Am Geriatr Soc*. 2007;55(suppl 2): S457-S463.
38. Hanlon JT, Weinberger M, Samsa GP, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. *Am J Med*. 1996;100(4):428-437.
39. Cowper PA, Weinberger M, Hanlon JT, et al. The cost-effectiveness of a clinical pharmacist intervention among elderly outpatients. *Pharmacotherapy*. 1998; 18(2):327-332.
40. Krska J, Cromarty JA, Arris F, et al. Pharmacist-led medication review in patients over 65. *Age Ageing*. 2001;30(3):205-211.
41. Lenaghan E, Holland R, Brooks A. Home-based medication review in a high risk elderly population in primary care—the POLYMED randomised controlled trial. *Age Ageing*. 2007;36(3):292-297.
42. Williams ME, Pulliam CC, Hunter R, et al. The short-term effect of interdisciplinary medication review on function and cost in ambulatory elderly people. *J Am Geriatr Soc*. 2004;52(1):93-98.
43. Schmader KE, Hanlon JT, Pieper CF, et al. Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. *Am J Med*. 2004;116(6):394-401.
44. Weber V, White A, McIlvried R. An electronic medical record (EMR)-based

intervention to reduce polypharmacy and falls in an ambulatory rural elderly population. *J Gen Intern Med*. 2008;23(4):399-404.
45. Pit SW, Byles JE, Cockburn J. Medication review. *J Am Geriatr Soc*. 2007; 55(6):927-934.
46. Krska J, Gill D, Hansford D. Pharmacist-supported medication review training for general practitioners. *Med Educ*. 2006;40(12):1217-1225.
47. Drenth-van Maanen AC, van Marum RJ, Knol W, van der Linden CM, Jansen PA. Prescribing optimization method for improving prescribing in elderly patients receiving polypharmacy. *Drugs Aging*. 2009;26(8):687-701.
48. Drenth-van Maanen AC, van Marum RJ, Knol W, et al. Prescribing optimization method for improving prescribing in elderly patients receiving polypharmacy. *Drugs Aging*. 2009;26(8):687-701.
49. Higashi T, Shekelle PG, Solomon DH, et al. The quality of pharmacologic care for vulnerable older patients. *Ann Intern Med*. 2004;140(9):714-720.
50. Hanlon JT, Schmader KE, Ruby CM, Weinberger M. Suboptimal prescribing in older inpatients and outpatients. *J Am Geriatr Soc*. 2001;49(2):200-209.
51. Goulding MR. Inappropriate medication prescribing for elderly ambulatory care patients. *Arch Intern Med*. 2004;164(3):305-312.
52. Steinman MA, Rosenthal GE, Landefeld CS, Bertenthal D, Kaboli PJ. Agreement between drugs-to-avoid criteria and expert assessments of problematic prescribing. *Arch Intern Med*. 2009;169(14):1326-1332.
53. Doucette WR, McDonough RP, Klepser D, McCarthy R. Comprehensive medication therapy management. *Clin Ther*. 2005;27(7):1104-1111.
54. Boockvar KS, Liu S, Goldstein N, Nebeker J, Siu A, Fried T. Prescribing discrepancies likely to cause adverse drug events after patient transfer. *Qual Saf Health Care*. 2009;18(1):32-36.
55. Hajjar ER, Hanlon JT, Sloane RJ, et al. Unnecessary drug use in frail older people at hospital discharge. *J Am Geriatr Soc*. 2005;53(9):1518-1523.
56. Hajjar ER, Hanlon JT, Artz MB, et al. Adverse drug reaction risk factors in older outpatients. *Am J Geriatr Pharmacother*. 2003;1(2):82-89.
57. Green JL, Hawley JN, Rask KJ. Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? *Am J Geriatr Pharmacother*. 2007;5(1):31-39.
58. Grant K, Al-Adhami N, Tordoff J, Livesey J, Barbezat G, Reith D. Continuation of proton pump inhibitors from hospital to community. *Pharm World Sci*. 2006; 28(4):189-193.
59. Thomas L, Culley EJ, Gladowski P, Goff V, Fong J, Marche SM. Longitudinal analysis of the costs associated with inpatient initiation and subsequent outpatient continuation of proton pump inhibitor therapy for stress ulcer prophylaxis in a large managed care organization. *J Manag Care Pharm*. 2010;16(2):122-129.
60. Simon SR, Chan KA, Soumerai SB, et al. Potentially inappropriate medication use by elderly persons in US health maintenance organizations, 2000-2001. *J Am Geriatr Soc*. 2005;53(2):227-232.
61. Pugh MJ, Hanlon JT, Zeber JE, Bierman A, Cornell J, Berlowitz DR. Assessing potentially inappropriate prescribing in the elderly Veterans Affairs population using the HEDIS 2006 quality measure. *J Manag Care Pharm*. 2006;12(7):537-545.
62. Zhan C, Sangl J, Bierman AS, et al. Potentially inappropriate medication use in the community-dwelling elderly. *JAMA*. 2001;286(22):2823-2829.
63. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults. *Arch Intern Med*. 2003;163(22):2716-2724.
64. Ryan C, O'Mahony D, Kennedy J, Weedle P, Byrne S. Potentially inappropriate prescribing in an Irish elderly population in primary care. *Br J Clin Pharmacol*. 2009;68(6):936-947.
65. Bain KT, Holmes HM, Beers MH, Maio V, Handler SM, Pauker SG. Discontinuing medications. *J Am Geriatr Soc*. 2008;56(10):1946-1952.
66. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people. *BMJ*. 1997;315(7115):1096-1099.
67. Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG. Medication withdrawal trials in people aged 65 years and older. *Drugs Aging*. 2008;25(12): 1021-1031.
68. Holmes C, Wilkinson D, Dean C, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology*. 2004; 63(2):214-219.
69. Minett TS, Thomas A, Wilkinson LM, et al. What happens when donepezil is suddenly withdrawn? *Int J Geriatr Psychiatry*. 2003;18(11):988-993.
70. Farlow M, Potkin S, Koumaras B, Veach J, Mirski D. Analysis of outcome in retrieved dropout patients in a rivastigmine vs placebo, 26-week, Alzheimer disease trial. *Arch Neurol*. 2003;60(6):843-848.
71. Greenfield S, Billimek J, Pellegrini F, et al. Comorbidity affects the relationship between glycemic control and cardiovascular outcomes in diabetes. *Ann Intern Med*. 2009;151(12):854-860.
72. Gerstein HC, Miller ME, Byington RP, et al; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-2559.
73. Mant J, Hobbs FD, Fletcher K, et al; BAFTA Investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA). *Lancet*. 2007;370(9586):493-503.
74. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med*. 2009;169 (21):1952-1960.
75. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia. *JAMA*. 2005;294(15):1934-1943.
76. Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. *Ann Intern Med*. 2007;147(11):755-765.
77. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med*. 1997;157(15):1681-1686.
78. Charpentier G, Riveline JP, Varroud-Vial M. Management of drugs affecting blood glucose in diabetic patients with renal failure. *Diabetes Metab*. 2000; 26(suppl 4):73-85.
79. Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM. A systematic review and meta-analysis of hypoglycemia and cardiovascular events. *Diabetes Care*. 2007;30(2):389-394.
80. Lipton HL, Bero LA, Bird JA, McPhee SJ. The impact of clinical pharmacists' consultations on physicians' geriatric drug prescribing. *Med Care*. 1992;30 (7):646-658.
81. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls. *JAMA*. 2004;291(16):1999-2006.
82. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency. *Arch Intern Med*. 2009; 169(6):551-561.
83. Scott IA, Guyatt GH. Cautionary tales in the interpretation of clinical studies involving older persons. *Arch Intern Med*. 2010;170(7):587-595.
84. Gerety MB, Cornell JE, Plichta DT, Eimer M. Adverse events related to drugs and drug withdrawal in nursing home residents. *J Am Geriatr Soc*. 1993;41 (12):1326-1332.
85. Garfinkel D, Zur-Gil S, Ben-Israel J. The war against polypharmacy. *Isr Med Assoc J*. 2007;9(6):430-434.
86. Graves T, Hanlon JT, Schmader KE, et al. Adverse events after discontinuing medications in elderly outpatients. *Arch Intern Med*. 1997;157(19):2205-2210.
87. Scuffham PA, Nikles J, Mitchell GK, et al. Using n-of-1 trials to improve patient management and save costs. *J Gen Intern Med*. 2010;25(9):906-913.
88. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions. *Arch Intern Med*. 2007;167(6):540-550.
89. Conn VS, Hafdahl AR, Cooper PS, Ruppar TM, Mehr DR, Russell CL. Interventions to improve medication adherence among older adults. *Gerontologist*. 2009; 49(4):447-462.
90. Russell CL, Conn VS, Jantarakupt P. Older adult medication compliance. *Am J Health Behav*. 2006;30(6):636-650.
91. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001;23(8):1296-1310.
92. Hsu J, Fung V, Price M, et al. Medicare beneficiaries' knowledge of Part D prescription drug program benefits and responses to drug costs. *JAMA*. 2008; 299(16):1929-1936.
93. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA*. 2006;296(15):1858-1866.
94. Raebel MA, Ross C, Xu S, et al. Diabetes and drug-associated hyperkalemia: effect of potassium monitoring. *J Gen Intern Med*. 2010;25(4):326-333.
95. Hurley JS, Roberts M, Solberg LI, et al. Laboratory safety monitoring of chronic medications in ambulatory care settings. *J Gen Intern Med*. 2005;20(4):331-333.
96. Raebel MA, McClure DL, Simon SR, et al. Laboratory monitoring of potassium and creatinine in ambulatory patients receiving angiotensin converting enzyme inhibitors and angiotensin receptor blockers. *Pharmacoepidemiol Drug Saf*. 2007;16(1):55-64.
97. National Committee for Quality Assurance. HEDIS 2010 . http://www.ncqa.org/tabid/1044/Default.aspx. Accessed May 4, 2010.
98. Shrank WH, Polinski JM, Avorn J. Quality indicators for medication use in vulnerable elders. *J Am Geriatr Soc*. 2007;55(suppl 2):S373-S382.

Resources for Clinicians on Medication Adherence, Management, Cost Reduction, and Problems

ADHERENCE

Osterberg L et al. Adherence to medication. *N Engl J Med*. 2005;353:487-497. http://www.ncbi.nlm.nih.gov/pubmed/16079372

World Health Organization

Adherence to long-term therapies: evidence for action [report]. World Health Organization: Geneva, 2003. http://www.who.int/chp/knowledge/publications/adherence_report/en/

US Department of Veterans Affairs

http://www.hiv.va.gov/vahiv?page=ptli-04-01

National Council on Patient Information and Education (NCPIE) Medication Use Safety Training (MUST) Program

http://www.mustforseniors.org

Center for Connected Health

http://www.connected-health.org/programs/medication-adherence.aspx

MEDICATION MANAGEMENT

American Society of Consultant Pharmacists

http://www.ascp.com

American Pharmacists Association

http://www.pharmacist.com/MTM

REDUCING DRUG COSTS

Medicare

https://www.medicare.gov/find-a-plan/questions/home.aspx or 1-800-MEDICARE

State Pharmaceutical Assistance Programs

http://www.medicare.gov/navigation/medicare-basics/medical-and-drug-costs.aspx

Industry and Other Assistance Programs

http://www.needymeds.org
http://www.rxassist.org
https://www.pparx.org/

IDENTIFYING POTENTIALLY INAPPROPRIATE MEDICATIONS

Fick DM 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;163:2716-24. http://archinte.ama-assn.org/cgi/reprint/163/22/2716

Gallagher P. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther*. 2008;46:72-83. http://www.ncbi.nlm.nih.gov/pubmed/18218287

Hanlon JT et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol*. 1992;45:1045-51. http://www.ncbi.nlm.nih.gov/pubmed/1474400

Geriatrics at Your Fingertips

http://www.geriatricsatyourfingertips.org/

IDENTIFYING MEDICATION UNDERUSE

Barry PJ et al. START (Screening Tool to Alert Doctors to the Right Treatment)—an evidence-based screening tool to detect prescribing omissions in elderly patients. *Age Aging*. 2007;36:632-638. http://ageing.oxfordjournals.org/cgi/reprint/36/6/632

Shrank WH et al. Quality Indicators for Medication Use in Vulnerable Elders. *J Amer Geriatr Soc*. 2007;55:s373-382. http://www.ncbi.nlm.nih.gov/pubmed/17910560

RENAL DOSING FOR COMMON DRUGS

Hanlon JT et al. Consensus guidelines for oral dosing of primarily renally cleared medications in older adults. J Amer Geriatr Soc. 2009;57:335-340 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2640432/

Olyaei AJ et al. Drug dosing in the elderly patients with chronic kidney disease. Clin Geriatr Med. 2009;25:459-527 http://www.ncbi.nlm.nih.gov/pubmed/19765493

Creatinine Clearance Online Calculator

http://www.globalrph.com/multiple_crcl.htm

American College of Physicians Drug Prescribing in Renal Failure

http://www.acponline.org/running_practice/technology/mobile_computing/clinical_references/

IDENTIFYING CLINICALLY SIGNIFICANT DRUG-DISEASE INTERACTIONS

Lindblad CI et al. Clinically important drug-disease interactions and their prevalence in older adults. *Clin Ther*. 2006;28:1133-1143. http://www.ncbi.nlm.nih.gov/pubmed/16982290

IDENTIFYING CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTIONS

Malone DC et al. Identification of serious drug-drug interactions: results of the partnership to prevent drug-drug interactions. *J Amer Pharm Assoc*. 2004;44:142-151. http://www.ncbi.nlm.nih.gov/pubmed/15098848

Hansten PD, Horn JR. Drug Interactions Analysis and Management. Wolters Kluwer Health: St Louis, MO; 2010. (book—no online link)

ONLINE AND PDA-BASED DRUG INFORMATION AND INTERACTION CHECKS

Free

http://www.epocrates.com

Subscription

http://www.lexi.com
http://www.factsandcomparisons.com
http://www.micromedex.com

Common, Clinically Important Drug-Drug Interactions in Hepatic Metabolism

http://medicine.iupui.edu/clinpharm/DDIs/