

Alternative Medications for Medications in the Use of High-Risk Medications in the Elderly and Potentially Harmful Drug–Disease Interactions in the Elderly Quality Measures

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The National Committee for Quality Assurance (NCQA) and the Pharmacy Quality Alliance (PQA) use the American Geriatrics Society (AGS) Beers Criteria to designate the quality measure Use of High-Risk Medications in the Elderly (HRM). The Centers for Medicare and Medicaid Services (CMS) use the HRM measure to monitor and evaluate the quality of care provided to Medicare beneficiaries. NCQA additionally uses the AGS Beers Criteria to designate the quality measure Potentially Harmful Drug–Disease Interactions in the Elderly. Medications included in these measures may be harmful to elderly adults and negatively affect a healthcare plan's quality ratings. Prescribers, pharmacists, patients, and healthcare plans may benefit from evidence-based alternative medication treatments to avoid these problems. Therefore the goal of this work was to develop a list of alternative medications to those included in the two measures. The authors conducted a comprehensive literature review from 2000 to 2015 and a search of their personal files. From the evidence, they prepared a list of drug-therapy alternatives with supporting references. A reference list of nonpharmacological approaches was also provided when appropriate. NCQA, PQA, the 2015 AGS Beers Criteria panel, and the

Executive Committee of the AGS reviewed the drug therapy alternatives and nonpharmacological approaches. Recommendations by these groups were incorporated into the final list of alternatives. The final product of drug-therapy alternatives to medications included in the two quality measures and some nonpharmacological resources will be useful to health professionals, consumers, payers, and health systems that care for older adults. *J Am Geriatr Soc* 2015.

Key words: inappropriate medications; Beers Criteria; medication management

The pharmacopeia of treatment options available to clinicians is vast, and its navigation complicated. A number of factors must be considered when selecting medications for elderly adults, including each individual's parameters that may affect drug pharmacokinetics/pharmacodynamics, formulary choices and related costs, ease of use, and the likelihood the treatment will be safe and effective.¹ The Centers for Medicare and Medicaid Services (CMS) uses the National Committee for Quality Assurance (NCQA) and Pharmacy Quality Alliance (PQA) quality measure Use of High-Risk Medications in the Elderly (HRM) to monitor and evaluate the quality of care provided to Medicare beneficiaries. In addition, NCQA publishes a second quality measure, Potentially Harmful Drug–Disease Interactions in the Elderly.² Both measures, published in 2015, were based on the 2012 American Geriatrics Society (AGS) Beers Criteria and include some medications that elderly adults should avoid, along with drugs that could potentially exacerbate three diseases or conditions (falls, dementia, chronic kidney disease).³ Sometimes these potentially suboptimal medications are appropriate for an individual elderly adult, but these measures can influence a prescriber's choice and result in denial of medication, resulting in treatment delays. In addition,

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prescribing these suboptimal medications may negatively affect a healthcare plan's quality ratings.

Prescribers, pharmacists, patients, and healthcare plans might benefit from having a list of evidence-based alternative medication treatments to avoid these problems, along with some nonpharmacological approaches when appropriate. For this reason, the authors' goals were to develop a list of alternative medications that may be used instead of the potentially high-risk medications included in the two quality measures. This is not meant to diminish the importance of nonpharmacological alternatives for the potentially high-risk medications.

This list of medication alternatives coincides with the publication of the 2015 AGS Beers Criteria. At this time, it is unknown how the quality measures will be revised based on the 2015 AGS Beers Criteria. We anticipate updating the list of medication alternatives based upon the 2015 AGS Beers Criteria and the CMS, NCQA, and PQA quality measures in the future and making it publically available.

METHODS

The list of medications identified as potentially harmful and included in each measure was divided among the three authors based on their areas of expertise and interest. Each author then identified and searched for evidence from the scientific literature supporting alternative medication treatments using common search tools, including PubMed, the Cochrane Library, and Google Scholar for 2000 to 2015. Additional articles identified from the authors' personal files were also considered. Because comparative clinical trials in elderly adults are uncommon, explicit expert panel consensus criteria were also consulted and referenced.⁴⁻⁷ The three authors individually chose drug therapy alternatives along with some nonpharmacological approaches when appropriate and provided supporting articles. All three authors reviewed and critiqued these during a series of conference calls. Preliminary findings were presented at the 2014 AGS annual meeting, and feedback was sought and received from NCQA, PQA, the 2015 AGS Beers Criteria panel, and the Executive Committee of the AGS.

RESULTS

Table 1 shows alternatives for high-risk medications organized into 15 therapeutic classes according to the measure specifications for HRM published in 2015. There are multiple alternatives given for some high-risk medications that can be used for multiple indications (e.g., tricyclic antidepressants). In addition, trimethobenzamide is not included because of recent data showing it to be effective in reducing nausea and vomiting in individuals with Parkinson's disease taking subcutaneous apomorphine, prompting its absence from the 2015 AGS Beers Criteria.⁸ References supporting drug therapy alternatives listed in Table 1 are provided in Appendix 1.

Table 2 shows 10 therapeutic drug classes that are included in the Potentially Harmful Drug-Disease Interactions in the Elderly measure (a prior history of falls, dementia, chronic kidney disease). Several high-risk medications (e.g., benzodiazepine receptor agonists, tricyclic

antidepressants) can exacerbate more than one disease or condition (e.g., falls, dementia). Similar to Table 1, drugs that can be used for more than one indication may have more than one alternative. References supporting alternatives listed in Table 2 are provided in Appendix 2.

Nonpharmacological alternatives may be appropriate first-line alternatives. Appendix 3 provides resources in which clinicians can find information about nonpharmacological treatment of selected problems and conditions in older adults.

DISCUSSION

This article outlines a list of alternative medications to those included in two quality measures, HRM and Potentially Harmful Drug-Disease Interactions in the Elderly. It is hoped that this list, along with the nonpharmacological approaches identified in Appendix 3, will be helpful to healthcare professionals caring for older adults. By no means is this list of alternatives and resources comprehensive or exhaustive; rather it is a starting point. The strength of these outlined alternatives and resources is that they are based upon information contained in guidelines, metaanalyses, randomized controlled trials, and rigorous observational studies. In addition, in some older adults, the use of a potentially suboptimal medication may be appropriate. Alternatives to some anticholinergic medications, nonsteroidal antiinflammatory drugs (NSAIDs), central nervous system (CNS) medications, and estrogen are elaborated upon below.

Drugs with strong anticholinergic activity are to be avoided because of their potential to be constipating, worsen some forms of lower urinary tract symptoms, dry mucous membranes, and induce delirium or dementia.⁹⁻¹² Older persons who take multiple drugs with anticholinergic activity, be they strong, moderate, or weak in potency, are at greater risk of physical, functional, and cognitive decline.¹¹ Two types of highly anticholinergic drugs (first-generation antihistamines, drugs used for Parkinson's disease) are discussed below.

First-generation antihistamines are notoriously anticholinergic and sedating, often requiring prolonged dosage titration to achieve a therapeutic dose. Their sedating properties, particularly those of diphenhydramine, have been used as the therapeutic effect in many over-the-counter (OTC) sleep aids. Several alternative treatments are available for allergic rhinitis, including first-line options of intranasal saline flushes, a less- or nonsedating oral (second generation) antihistamine, and intranasal corticosteroids. All of these include OTC options. For best results, the latter two options are best started before allergen exposure.

Tremor is an early symptom of Parkinson disease that can be treated with an anticholinergic drug, yet tremor in older adults is often less pronounced, thus shifting the benefit to harm ratio away from the anticholinergic drugs. Evidence-based reviews and guidelines recommend the carbidopa-levodopa combination as first-line treatment for older adults.¹³⁻¹⁷ Dopamine agonists are reserved for later in the disease, given their greater likelihood to cause CNS disturbances.¹³

Table 1. Alternatives for Medications Included in the High-Risk Medications in the Elderly Measure

Therapeutic Class	High-Risk Medications	Alternatives	References (Appendix 1)
Anticholinergic			
First-generation antihistamine	Brompheniramine	Intranasal normal saline	41–46
	Carbinoxamine	Second-generation antihistamine (e.g., cetirizine, fexofenadine, loratadine)	
	Chlorpheniramine	Intranasal steroid (e.g., beclomethasone, fluticasone, over the counter)	
	Clemastine		
	Cyproheptadine		
	Dexbrompheniramine		
	Dexchlorpheniramine		
	Diphenhydramine (oral)		
	Doxylamine		
	Hydroxyzine		
Promethazine			
Triprolidine			
Parkinson disease	Benztpropine (oral) Trihexyphenidyl	Carbidopa/levodopa	14–17
Antiplatelets	Dipyridamole (oral immediate release) Ticlopidine	Antithrombotic therapy for the secondary prevention of noncardioembolic stroke Clopidogrel, aspirin 25 mg with extended-release dipyridamole 200 mg	47
Cardiovascular			
Alpha agonists, central	Guanabenz	Thiazide-type diuretic, ACEI, ARB, long-acting dihydropyridine CCB	48–50
	Guanfacine	In black individuals—thiazide-type diuretic, CCB	
	Methyldopa	For heart failure, diabetes mellitus, chronic kidney disease—ACEI or ARB preferred	
Other	Disopyramide	Atrial fibrillation: For rate control—nondihydropyridine CCB (e.g., diltiazem), beta-blocker	51,52
		For rhythm control—dofetilide, flecainide, propafenone	
	Nifedipine (immediate release)	Long-acting dihydropyridine CCB (e.g., amlodipine)	48–50
Central nervous system			
Tertiary tricyclic antidepressant	Amitriptyline	For depression—SSRI (except paroxetine), SNRI, bupropion (also see Appendix 3)	53–54
	Clomipramine		
	Imipramine	For neuropathic pain—SNRI, gabapentin, capsaicin topical, pregabalin, lidocaine patch	
	Trimipramine		
Barbiturate	Amobarbital	For epilepsy—other anticonvulsants (e.g., lamotrigine, levetiracetam)	26,56–58
	Butabarbital		
	Butalbital		
	Mephobarbital		
	Pentobarbital		
	Phenobarbital		
	Secobarbital		
Vasodilator	Ergot mesylates	Acetylcholinesterase inhibitors, memantine, Vitamin E	59–66
	Isoxsuprine		
Central nervous system, nonbenzodiazepine hypnotics	Eszopiclone	None (see Appendix 3)	67–73
	Zaleplon		
	Zolpidem		
Other	Thioridazine	For schizophrenia—other nonanticholinergic antipsychotic (not chlorpromazine, loxapine, olanzapine, perphenazine, thioridazine, trifluoperazine)	74
	Meprobamate Chloral hydrate (no longer marketed in United States)	For anxiety—buspirone, SSRI, SNRI	75, 76
Endocrine system			
Estrogens with or without progestins (oral or patch)	Conjugated estrogen	Use of vaginal estrogen formulations acceptable for treatment of dyspareunia and vulvovaginitis	32
	Esterified estrogen		
	Estradiol	Vasomotor symptoms—SSRI, SNRI, gabapentin	36, 38, 77–82
	Estropipate		
Sulfonylureas, long-duration	Chlorpropamide	Short-acting sulfonylureas (glipizide, gliclazide), metformin	83
	Glyburide		

(Continued)

Table 1 (Contd.)

Therapeutic Class	High-Risk Medications	Alternatives	References (Appendix 1)
Other	Desiccated thyroid Megestrol	Levothyroxine None (see Appendix 3)	84,85
Pain medication			
Skeletal muscle relaxants	Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine	For acute mild or moderate pain—acetaminophen, nonacetylated salicylate (e.g., salsalate), propionic acid derivatives (e.g., ibuprofen, naproxen) if no heart failure or eGFR >30 mL/min and given with PPI for gastroprotection if used for >7 days	18, 86–88
Specific nonsteroidal antiinflammatory drugs	Indomethacin, Ketorolac (oral and parenteral)	For mild or moderate chronic pain—acetaminophen, nonacetylated salicylate (e.g., salsalate), propionic acid derivatives (e.g., ibuprofen, naproxen) if no heart failure or eGFR >30 mL/min and given with PPI for gastroprotection	18, 86–88
Opioids	Meperidine Pentazocine	For acute moderate to severe pain—tramadol, morphine, oxycodone immediate release with acetaminophen For chronic moderate to severe pain—all the above; avoid long-duration, sustained-release dosage forms in opioid-naïve individuals; see neuropathic pain alternatives above under tertiary tricyclic antidepressant alternatives	18, 22, 60, 88 89

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; CCB = calcium channel blocker; PPI = proton pump inhibitor; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor. In all instances including those specified, nonpharmacological approaches should be sought first when appropriate (Appendix 3).

Chronic oral NSAID use increases the risk of gastrointestinal bleeding and acute kidney injury in older adults, particularly in those with common underlying comorbidities of peptic ulcer disease, chronic kidney disease, or congestive heart failure.¹⁸ One potential alternative to chronic oral NSAID therapy for chronic pain is topical therapy. Topical NSAIDs, capsaicin, and lidocaine have the advantage of low risk of adverse events and ease of use, but it is unclear whether all are effective for chronic musculoskeletal pain, such as chronic back or osteoarthritis pain, and neuropathic pain, such as postherpetic neuralgia. Topical NSAID preparations are effective for knee and hand osteoarthritis pain, with the strongest data coming from randomized controlled trials of topical diclofenac.¹⁹ The Food and Drug Administration (FDA) has approved topical diclofenac for this use, although these topical NSAIDs lack evidence of effectiveness for chronic back pain or postherpetic neuralgia, and there can be some systemic absorption. Topical capsaicin in low concentrations (<1%) is effective for osteoarthritis pain, but the data are inconclusive regarding effectiveness in neuropathic pain.²⁰ Topical capsaicin in high concentrations (8% patch) has been shown to be effective for postherpetic neuralgia in randomized controlled trials and is FDA approved for this use but is expensive and best considered when first- and second-line treatments have failed.²¹ Capsaicin products are not effective for chronic low back pain, must be applied carefully, and can cause an unbearable burning sensation. The topical lidocaine patch is effective for postherpetic neuralgia, based on high-quality randomized controlled trials, is FDA approved for this use, and is a first-line therapy for postherpetic neuralgia.²² The effectiveness of topical lidocaine for chronic musculoskeletal pain is unclear because there are no definitive randomized

controlled trials, and therefore it is not FDA approved, but case reports and small trials suggest it may be useful in this situation.

CNS medications (antipsychotics, TCAs, SSRIs, antiepileptics, benzodiazepine receptor agonists) increase the risk of falls, especially in individuals with a prior history of falls. Given the literature showing the considerable risk and minimal effectiveness of benzodiazepine receptor agonists for sleep in older adults, new prescriptions for these agents should be avoided.²³ Nonpharmacological options are recommended to treat insomnia initially, including sleep hygiene combined with behavioral interventions (Appendix 3). It is also important to limit the dose and duration of use of antipsychotics to only a few days, especially when used for delirium, for which there is little data suggesting they are helpful.²⁴ Limited duration of antipsychotic use at the lowest dose possible is also important when used to treat behavioral complications of dementia, given the well-known greater risk of mortality.²⁵ There will be times in those older adults with a previous history of falls when it will be necessary to prescribe a new CNS medication (e.g., new-onset epilepsy). In these cases, it is important to choose the most-effective, least-risky antiepileptic. In addition, the use of older hepatic metabolism enzyme-inducing agents (phenobarbital, phenytoin, carbamazepine) that can interact with numerous other medications should be avoided.²⁶ Moreover, there is growing evidence that the use of multiple CNS medications or higher combined doses further increases the risk of falls.^{27–29} When at all possible, decreasing the dosage of currently prescribed CNS medications before initiating a new CNS agent in older adults with a previous history of falls is clinically sensible. It is also clinically sensible, when possible, to discontinue CNS medications such

Table 2. Alternatives to Medications Included in the Potentially Harmful Drug-Disease Interactions in the Elderly*

Diseases and Potentially Harmful Drugs		Alternatives	References (Appendix 2)
Disease	Drugs		
Falls ^a	Anticonvulsants	For new-onset epilepsy—newer agents preferred (e.g., lamotrigine, levetiracetam and calcium/vitamin D ± bisphosphonate) For neuropathic pain—SNRI, gabapentin, pregabalin, topical capsaicin, lidocaine patch	26, 56–58
	Benzodiazepines Nonbenzodiazepine hypnotics (“Z” drugs: eszopiclone, zaleplon, zolpidem)	For anxiety—buspirone, SNRI For sleep—see Appendix 3	75, 76 67–73
	Tricyclic antidepressants (tertiary and secondary) SSRIs	For depression—e.g., SNRI, bupropion For neuropathic pain—SNRI, gabapentin, pregabalin, capsaicin topical, lidocaine patch	53, 54 22, 55
	Antipsychotics	For delirium—short-term use of antipsychotics (e.g., haloperidol, quetiapine) should be restricted to individuals who are distressed or considered a risk to themselves or others and in whom verbal and nonverbal de-escalation techniques are ineffective or inappropriate For schizophrenia—nonanticholinergic agents may be acceptable (not chlorpromazine, loxapine, olanzapine, perphenazine, trifluoperazine, thioridazine) For behavioral complications of dementia—if nonpharmacological approaches have failed and psychosis and danger to self or others, low-dose nonanticholinergic agent (e.g., risperidone, quetiapine) for shortest duration possible may be acceptable	24, 74, 90, 91 74 74, 92
Dementia	Tricyclic antidepressants (tertiary and secondary)	For depression—SSRI, SNRI, bupropion For neuropathic pain—SNRI, capsaicin topical, gabapentin, pregabalin, lidocaine patch	53, 54 22, 55
	Antipsychotics	For behavioral complications of dementia—if nonpharmacological approaches have failed, and psychosis and danger to self or others, low-dose nonanticholinergic agent (e.g., risperidone, quetiapine) for shortest duration possible may be acceptable	74, 92
	H2 blockers	Proton pump inhibitor	93
	Anticholinergics (see table 7 in 2015 AGS Beers criteria for complete list of classes) (e.g., first-generation antihistamines, and anti-Parkinson agents)	For allergy—second-generation antihistamine, nasal steroid For Parkinson disease—levodopa with carbidopa	41–46 14–17
	Benzodiazepines	For anxiety—buspirone, SSRI, SNRI For sleep—see Appendix 3	75, 76 67–73
	Nonbenzodiazepine hypnotics (“Z” drugs)	See Appendix 3	
Chronic kidney disease or chronic renal failure (eGFR <30 mL/min)	All nonaspirin nonsteroidal antiinflammatories (including cyclooxygenase-2 selectives)	For pain—acetaminophen, SNRI, topical capsaicin lidocaine patch	18, 22, 55, 88

eGFR = estimated glomerular filtration rate; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor.

In all instances including those specified, nonpharmacological approaches should be sought first when appropriate (See references 68, 94–123 in Appendix 3).

^aAlso includes noncancer, nontrauma hip fracture. If agent must be used, consider reducing the use of other central nervous system–active medications that increase the risk of falls and fractures (anticonvulsants, antipsychotics, antidepressants, benzodiazepine receptor agonists).

as antiepileptics (e.g., in individuals who experienced a single seizure around the time of a stroke with no further seizures in these subsequent 2 years and have normal electroencephalograms). It is important, though, that this

class of CNS medications be tapered over a 6- to 12-month period to avoid a withdrawal seizure and only after considering individual and family preferences and current driving status.^{30,31}

Oral and transdermal estrogens are effective treatments for vulvovaginitis, dyspareunia, and vasomotor symptoms, but they increase the risk of ovarian, endometrial, and breast cancers; thromboembolic events; gallbladder disease; and kidney stones. Thus their use should be avoided in women aged 65 and older. Topical alternatives such as water-based vaginal lubricants and silicone-based vaginal moisturizers offer relief from dyspareunia for many women.^{32,33} Vaginal estrogen is another alternative that replenishes the affected tissue with a lower or negligible risk of the serious adverse events of their systemic counterparts.^{32,33} Ospemifene, a specific estrogen receptor modifier, is approved for the treatment of dyspareunia and is another potential alternative,^{34,35} although it shares many of the same warnings as estrogens, and long-term evidence in women aged 65 and older is lacking. The SSRI escitalopram, the SNRI venlafaxine, and gabapentin have all demonstrated efficacy for treating the symptoms of vasomotor instability, most notably hot flashes.^{36–40} Much of this evidence is from trials in women in midlife or with a history of breast cancer. Women with a history of falls should avoid SSRIs and gabapentin.

There are potential limitations to the process that created this list of alternatives. Space limitations prevented alternatives for the other seven drug classes with strong anticholinergic properties from the 2015 AGS Beers Criteria (see table 7) that can exacerbate dementia from being discussed. Suboptimal dose (digoxin, doxepin, reserpine) and duration of use (nitrofurantoin, nonbenzodiazepine hypnotics) criteria were also not addressed. These will be addressed in a future published alternative list based on the response of NCQA, PQA, and CMS to the numerous new suboptimal drugs with these two types of problems included in the 2015 AGS Beers Criteria. The size of the panel that created this list of alternatives was small, although the NCQA, PQA, the 13-member expert panel for the 2015 AGS Beers Criteria panel, and Executive Committee of the AGS also reviewed the list of alternatives that the three-person panel created. A formal evaluation of the quality of evidence or strength of recommendation for each alternative was not provided, but this information is available in some metaanalyses and consensus publications referenced. In addition, the alternatives provided are clinically sensible and are consistent with other expert lists.⁷ Finally, some insurers or individual healthcare systems may provide allowances for coverage of nonpharmacological approaches, such as cognitive behavioral therapy, whereas others may not.

CONCLUSION

A list of drug therapy alternatives to medications included in the Use of High Risk Medications in the Elderly and Potentially Harmful Drug–Disease Interactions in the Elderly quality measures was created from a comprehensive review of the literature and evidence. This list of drug therapy alternatives is intended to be a useful tool for health professionals, consumers, payers, and health systems that care for older adults.

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APPENDIX I REFERENCES FOR ALTERNATIVE MEDICATIONS INCLUDED IN TABLE 1

Anticholinergics, first-generation antihistamines: intranasal normal saline, second-generation antihistamines, intranasal steroid

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42. Cardona V, Guilarte M, Luengo O et al. Allergic diseases in the elderly. *Clin Transl Allergy* 2011;1:1.
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Anticholinergics, for Parkinson's: levodopa/carbidopa

14. Miyasaki JM, Martin W, Suchowesky O et al. Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review. *Neurology* 2002;58:11–15.
15. Scottish Intercollegiate Guideline Network. Diagnosis and pharmacologic management of Parkinson's disease: A national clinical guideline, No. 113, January 2010 [on-line]. Available at <http://www.sign.ac.uk/pdf/sign113.pdf> Accessed April 1, 2015.
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17. Katzenschlager R, Sampaio C, Costa J et al. Anticholinergics for symptomatic management of Parkinson's disease. *Cochrane Database Syst Rev* 2002;(3):CD003735.

Dipyridamide (oral immediate release) and Ticlopidine, Antithrombotic Therapy for the Secondary Prevention of Noncardioembolic Stroke: Clopidogrel or aspirin 25 mg/extended released Dipyridamide 200 mg combination

47. Guyatt G, Akl E, Crowther M et al. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed. *Chest* 2012;141(Suppl):34S.

Cardiovascular, alpha agonists, central: alternative hypertensives

48. Aronow W, Fleg J, Pepine C et al. ACCF/AHA 2011 Expert Consensus Documentation on Hypertension in the Elderly. Executive Summary. *J Am Coll Cardiol* 2011;57:240.
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59. James P, Oparil S, Carter B et al. 2014 Evidence-Based Guideline for the management of high blood pressure in adults (JNC 8). *JAMA* 2014;311:507–520.

Cardiovascular, Disopyramide for atrial fibrillation non-dihydropyridine calcium channel blockers or beta blockers

48. Aronow W, Fleg J, Pepine C et al. ACCF/AHA 2011 Expert Consensus Documentation on Hypertension in the Elderly. Executive Summary. *J Am Coll Cardiol* 2011;57:240.
51. January C, Wann L, Alpert J et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive summary. *Circulation* 2014;130:2054.
52. Stewart S, Ball J, Horowitz D et al. Standard versus atrial fibrillation-specific management strategy (SAFETY) to reduce recurrent admission and prolong survival: Pragmatic, multicentre, randomised controlled. *Lancet* 2015;385:775–784.

Cardiovascular, Nifedipine immediate-release for hypertension: long-acting dihydropyridine calcium channel blockers

48. Aronow W, Fleg J, Pepine C et al. ACCF/AHA 2011 Expert Consensus Documentation on Hypertension in the Elderly. Executive Summary. *J Am Coll Cardiol* 2011;57:240.
49. James P, Oparil S, Carter B et al. 2014 Evidence-Based Guideline for the management of high blood pressure in adults (JNC 8). *JAMA* 2014;311:507–520.
50. Weber M, Schiffrin E, White W et al. Clinical Practice Guidelines for the management of hypertension in the community: A statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens* 2014;1:14–26.

Central nervous system, tertiary tricyclic antidepressants: alternatives for depression and neuropathic pain

22. Dworkin RH, O'Connor AB, Backonja M et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 2007;132:237–251.
53. The Management of MDD Working Group. VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. Washington, DC: U.S. Department of Veterans Affairs and Department of Defense, 2009.
54. Gartlehner G, Hansen RA, Kahwati L. Drug class review on second generation antidepressants [on-line]. 2006. Available at <http://www.ohsu.edu/drugeffectiveness/reports/final.cfm> Accessed April 1, 2015.
55. Moulin DE, Clark AJ, Gilron I et al. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage* 2007;12:13–21.

Central nervous system, barbiturates: epilepsy—other anti-convulsants

26. Pugh MJ, Berlowitz DR, Rao JK et al. The quality of care for adults with epilepsy: An initial glimpse using the QUIET measure. *BMC Health Serv Res* 2011;11:1.
56. Rowan AJ, Ramsay E, Collins JF et al. New onset geriatric epilepsy: A randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology* 2005;64:1868–1873.
57. Correll CM, Bazil CW. Management of seizures in the elderly. *Curr Geriatr Rep* 2014;3:73–82.
58. Werhahn KJ, Trinka E, Dobesberger J et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. *Epilepsia* 2015;56:450–459.

Central nervous system, vasodilators: acetylcholinesterase inhibitors and memantine, Vitamin E

59. Practice Guideline for the treatment of patients with Alzheimer's disease and other dementias, 2nd Ed. From the American Psychiatric Association's Workgroup on Alzheimer's Disease and Other Dementias and Steering Committee on Practice Guidelines. Available at: http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/alzheimers.pdf Accessed April 1, 2015.
60. Fillit HM, Doody RS, Binaso K et al. Recommendations for best practices in the treatment of Alzheimer's disease in managed care. *Am J Geriatr Pharmacother* 2006;4(Suppl A):S9–S24.
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63. National Institute for Health and Clinical Excellence (NICE). Alzheimer's disease—donepezil, galantamine, rivastigmine (Review) and memantine (amended) [on-line]. Available at www.nice.org.uk/TA111 Accessed January 20, 2014.
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Central nervous system, nonbenzodiazepine hypnotics: none

67. Leshner A, Baghdoyan H, Bennett S et al. NIH statement regarding the treatment of insomnia. Manifestations and Management of Chronic Insomnia in Adults June 13–15, 2005. *Sleep* 2005;28:1049–1057.
68. Morin C. Efficacy of behavioral and psychological treatments of chronic insomnia. *J Clin Sleep Med* 2005;1:e482–e483.
69. Cluydts R, Peeters K, DeBouyalsky I et al. Comparison of continuous vs. intermittent administration of zolpidem in chronic insomniacs: A double-blind, randomized, pilot study. *J Int Med Res* 1998;26:13–24.
70. Hajak G, Cluydts R, Declerck A et al. Continuous versus non-nightly use of zolpidem in chronic insomnia: Results of a large-scale, double-blind, randomized, outpatient study. *Int Clin Psychopharmacol* 2002;17:9–17. Erratum in: *Int Clin Psychopharmacol* 2002;17:206.
71. Perlis ML, McCall WV, Krystal AD et al. Long-term, non-nightly administration of zolpidem in the treatment of patients with primary insomnia. *J Clin Psychiatry* 2004;65:1128–1137.
72. Solvetsen B, Omvik S, Pallesen S et al. Cognitive behavioral therapy or zopiclone for treatment of chronic primary insomnia. *JAMA* 2006;295:2851–2858.
73. Walsh JK, Roth T, Randazzo A et al. Eight weeks of non-nightly use of zolpidem for primary insomnia. *Sleep* 2000;23:1087–1096.

Central nervous system, other: alternatives for schizophrenia and anxiety

74. Maher AR, Maglione M, Bagley S et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: A systematic review and meta-analysis. *JAMA* 2011;306:1359–1369.
75. Baldwin D, Woods R, Lawson R et al. Efficacy of drug treatments for generalised anxiety disorder: Systematic review and meta-analysis. *BMJ* 2011;342:d1199.
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Endocrine system, estrogens with or without progestins: short-term use of vaginal dosage form acceptable for treatment of dyspareunia; vasomotor symptoms—selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, gabapentin

32. The North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. *Menopause* 2013;20:888–902.
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Endocrine system, sulfonyleureas, long-duration: short-acting sulfonyleureas or metformin

83. American Geriatrics Society Expert Panel on the Care of Older Adults with Diabetes Mellitus. Guidelines Abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 Update. *J Am Geriatr Soc* 2013;61:2020–2026.

Endocrine system, other: levothyroxine

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Pain medications, skeletal muscle relaxants: acute mild to moderate pain

18. AGS Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc* 2009;57:1331–1346.
86. Graham DY, Agrawal NM, Campbell DR et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: Results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. *Arch Intern Med* 2002;162:169.
87. Lin KJ, Hernández-Díaz S, García Rodríguez LA. Acid suppressants reduce risk of gastrointestinal bleeding in patients on antithrombotic or anti-inflammatory therapy. *Gastroenterology* 2011;141:71–79.
88. Abdulla A, Adams N, Bone M et al. Guidance on the management of pain in older people. *Age Ageing* 2013;42(Suppl 1):i1–i57.

Pain medications, specific nonsteroidal antiinflammatory drugs: mild to moderate chronic pain—acetaminophen, nonacetylated salicylate or propionic acid derivatives if no heart failure or estimate glomerular filtration rate >30 mL/min and given with proton pump inhibitor for gastroprotection

18. AGS Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc* 2009;57:1331–1346.
86. Graham DY, Agrawal NM, Campbell DR et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: Results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. *Arch Intern Med* 2002;162:169.
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Pain medications, opioids: alternatives for acute and chronic moderate to severe pain

18. AGS Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc* 2009;57:1331–1346.
22. Dworkin RH, O'Connor AB, Backonja M et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 2007;132:237–251.
55. Moulin DE, Clark AJ, Gilron I et al. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage* 2007;12:13–21.
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APPENDIX II REFERENCES FOR ALTERNATIVE MEDICATIONS INCLUDED IN TABLE 2

Falls, anticonvulsants

22. Dworkin RH, O'Connor AB, Backonja M et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 2007;132:237–251.
26. Pugh MJ, Berlowitz DR, Rao JK et al. The quality of care for adults with epilepsy: An initial glimpse using the QUIET measure. *BMC Health Serv Res* 2011;11:1.
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57. Correll CM, Bazil CW. Management of seizures in the elderly. *Curr Geriatr Rep* 2014;3:73–82.
58. Werhahn KJ, Trinka E, Dobsberger J et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. *Epilepsia* 2015;56:450–459.

Falls, benzodiazepines and nonbenzodiazepine hypnotics

67. Leshner A, Baghdoyan H, Bennett S et al. NIH statement regarding the treatment of insomnia. Manifestations and Management of Chronic Insomnia in Adults June 13–15, 2005. *Sleep* 2005;28:1049–1057.
68. Morin C. Efficacy of behavioral and psychological treatments of chronic insomnia. *J Clin Sleep Med* 2005;1:e482–e483.
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76. Stewart RE, Chambless DL. Cognitive-behavioral therapy for adult anxiety disorders in clinical practice: A meta-analysis of effectiveness studies. *J Consult Clin Psychol* 2009;77:595–606.

Falls, tricyclic antidepressants and selective serotonin reuptake inhibitors

22. Dworkin RH, O'Connor AB, Backonja M et al. Pharmacologic management of neuropathic pain: Evidence based recommendations. *Pain* 2007;132:237–251.
53. US Department of Veterans Affairs and Department of Defense. VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. Washington, DC: US Department of Veterans Affairs and Department of Defense, 2009.
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55. Moulin DE, Clark AJ, Gilron I et al. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage* 2007;12:13–21.

Falls, antipsychotics, delirium and dementia

24. Inouye SK, Marcantonio ER, Metzger ED. Doing damage in delirium: The hazards of antipsychotic treatment in elderly people. *Lancet Psychiatry* 2014;1:312–315.

74. Maher AR, Maglione M, Bagley S et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: A systematic review and meta-analysis. *JAMA* 2011;306:1359–1369.
90. Leentjens AF, Molag ML, Van Munster BC et al. Changing perspectives on delirium care: The new Dutch guideline on delirium. *J Psychosom Res* 2014;77:240–241.
91. The American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. Postoperative delirium in older adults: Best practice statement from the American Geriatrics Society. *J Am Coll Surg* 2015;220:136–148.
92. Pietro G, DeFazio P, Manfredi VGL et al. Use and safety of antipsychotics in behavioral disorders in elderly people with dementia. *J Clin Psychopharmacol* 2014;34:109–123.

Dementia Tricyclic antidepressants (tertiary and secondary)

22. Dworkin RH, O'Connor AB, Backonja M et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 2007;132:237–251.
53. The Management of MDD Working Group. VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. Washington, DC: U.S. Department of Veterans Affairs and Department of Defense, 2009.
54. Gartlehner G, Hansen RA, Kahwati L. Drug class review on second generation antidepressants [on-line]. 2006. Available at <http://www.ohsu.edu/drugeffectiveness/reports/final.cfm> Accessed April 1, 2015.
55. Moulin DE, Clark AJ, Gilron I et al. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage* 2007;12:13–21.

Dementia, antipsychotics

74. Maher AR, Maglione M, Bagley S et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: A systematic review and meta-analysis. *JAMA* 2011;306:1359–1369.
92. Pietro G, DeFazio P, Manfredi VGL et al. Use and safety of antipsychotics in behavioral disorders in elderly people with dementia. *J Clin Psychopharmacol* 2014;34:109–123.

Dementia, histamine blockers

93. Achem SR, DeVault KR. Gastroesophageal reflux disease and the elderly. *Gastroenterol Clin North Am* 2014;43:147–160.

Dementia, anticholinergics

14. Miyasaki JM. Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review. *Neurology* 2002;58:11–17.
15. Scottish Intercollegiate Guideline Network. Diagnosis and pharmacologic management of Parkinson's disease: A national clinical guideline, No. 113, January 2010 [on-line]. Available at <http://www.sign.ac.uk/pdf/sign113.pdf> Accessed April 1, 2015
16. Ferreria JJ, Katzenschlager R, Bloem BR et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management. *Eur J Neurol* 2013;20:5–15.
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Dementia, benzodiazepines

67. Leshner A, Baghdoyan H, Bennett S et al. NIH statement regarding the treatment of insomnia. Manifestations and Management of Chronic Insomnia in Adults June 13–15, 2005. *Sleep* 2005;28:1049–1057.
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71. Perlis ML, McCall WV, Krystal AD et al. Long-term, non-nightly administration of zolpidem in the treatment of patients with primary insomnia. *J Clin Psychiatry* 2004;65:1128–1137.
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73. Walsh JK, Roth T, Randazzo A et al. Eight weeks of non-nightly use of zolpidem for primary insomnia. *Sleep* 2000;23:1087–1096.
75. Baldwin D, Woods R, Lawson R et al. Efficacy of drug treatments for generalised anxiety disorder: Systematic review and meta-analysis. *BMJ* 2011;342:d1199.
76. Stewart RE, Chambless DL. Cognitive-behavioral therapy for adult anxiety disorders in clinical practice: A meta-analysis of effectiveness studies. *J Consult Clin Psychol* 2009;77:595–606.

Dementia, nonbenzodiazepine hypnotics

67. Leshner A, Baghdoyan H, Bennett S et al. NIH statement regarding the treatment of insomnia. Manifestations and Management of Chronic Insomnia in Adults June 13–15, 2005. *Sleep* 2005;28:1049–1057.
68. Morin C. Efficacy of behavioral and psychological treatments of chronic insomnia. *J Clin Sleep Med* 2005;1:e482–e483.
69. Cluydts R, Peeters K, DeBouyalsky I et al. Comparison of continuous vs. intermittent administration of zolpidem in chronic insomniacs: A double-blind, randomized, pilot study. *J Int Med Res* 1998;26:13–24.
70. Hajak G, Cluydts R, Declerck A et al. Continuous versus non-nightly use of zolpidem in chronic insomnia: Results of a large-scale, double-blind, randomized, outpatient study. *Int Clin Psychopharmacol* 2002;17:9–17. Erratum in: *Int Clin Psychopharmacol* 2002;17:206.
71. Perlis ML, McCall WV, Krystal AD et al. Long-term, non-nightly administration of zolpidem in the treatment of patients with primary insomnia. *J Clin Psychiatry* 2004;65:1128–1137.
72. Solvetsen B, Omvik S, Pallesen S et al. Cognitive behavioral therapy or zopiclone for treatment of chronic primary insomnia. *JAMA* 2006;295:2851–2858.
73. Walsh JK, Roth T, Randazzo A et al. Eight weeks of non-nightly use of zolpidem for primary insomnia. *Sleep* 2000;23:1087–1096.

Chronic kidney disease or chronic renal failure (estimate glomerular filtration rate <30 mL/min), nonsteroidal anti-inflammatory drugs

18. AGS Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological Management of Persistent Pain in Older Persons. *J Am Geriatr Soc* 2009;57:1331–1346.
22. Dworkin RH, O'Connor AB, Backonja M et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 2007;132:237–251.
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APPENDIX III RESOURCES FOR NONPHARMACOLOGICAL ALTERNATIVES TO MEDICATIONS INCLUDED IN THE USE OF HIGH-RISK MEDICATIONS IN THE ELDERLY AND POTENTIALLY HARMFUL DRUG–DISEASE INTERACTIONS IN THE ELDERLY QUALITY MEASURES

General

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