Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Anticholinergics ^b				
First-generation antihistamines Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Dimenhydrinate Diphenhydramine (oral) Doxylamine Hydroxyzine Meclizine Promethazine Pyrilamine Triprolidine	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate.	Avoid	Moderate	Strong
Antiparkinsonian agents Benztropine (oral) Trihexyphenidyl	Not recommended for prevention or treatment of extrapyramidal symptoms with antipsychotics; more effective agents available for treatment of Parkinson disease	Avoid	Moderate	Strong
Antispasmodics Atropine (excludes ophthalmic) Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Homatropine (excludes opthalmic) Hyoscyamine Methscopolamine Propantheline Scopolamine	Highly anticholinergic, uncertain effectiveness	Avoid	Moderate	Strong
Antithrombotics Dipyridamole, oral short acting (does not apply to the extended-release combination with aspirin) Anti-infective	May cause orthostatic hypotension; more effective alternatives available; IV form acceptable for use in cardiac stress testing	Avoid	Moderate	Strong
Nitrofurantoin	Potential for pulmonary toxicity, hepatoxicity, and peripheral neuropathy, especially with long-term use; safer alternatives available	Avoid in individuals with creatinine clearance <30 mL/min or for long-term suppression	Low	Strong
Cardiovascular				
Peripheral alpha-1 blockers for treatment of hypertension Doxazosin Prazosin Terazosin	High risk of orthostatic hypotension and associated harms, especially in older adults; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile	Avoid use as an antihypertensive	Moderate	Strong
Central alpha-agonists		Avoid as first-line antihypertensive	Low	Strong

Table 2 (Contd.)

organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Clonidine for first-line treatment of hypertension Other CNS alpha-agonists Guanabenz Guanfacine Methyldopa Reserpine (>0.1 mg/day)	High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension		Low	Strong
Disopyramide	May induce heart failure in older adults because of potent negative inotropic action; strongly anticholinergic; other antiarrhythmic drugs preferred	Avoid	Low	Strong
Dronedarone	Worse outcomes have been reported in patients taking dronedarone who have permanent atrial fibrillation or severe or recently decompensated heart failure.	Avoid in individuals with permanent atrial fibrillation or severe or recently decompensated heart failure	High	Strong
Digoxin for first-line treatment of atrial fibrillation or of heart failure	Use in atrial fibrillation: should not be used as a first-line agent in atrial fibrillation, because there are safer and more effective alternatives for rate control supported by high-quality evidence. Use in heart failure: evidence for benefits and harms of digoxin is conflicting and of lower quality; most but not all	Avoid this rate control agent as first- line therapy for atrial fibrillation	Atrial fibrillation: low	Atrial fibrillation: strong
		Avoid as first-line therapy for heart failure	Heart failure: low	Heart failure: strong
		If used for atrial fibrillation or heart failure, avoid dosages >0.125 mg/day	Dosage >0.125 mg/day: moderate	Dosage >0.125 mg/day: strong
Nifedipine, immediate release	Potential for hypotension; risk of precipitating myocardial ischemia	Avoid	High	Strong
Amiodarone	Effective for maintaining sinus rhythm but has greater toxicities than other antiarrhythmics used in atrial fibrillation; may be reasonable first-line therapy in patients with concomitant heart failure or substantial left ventricular hypertrophy if rhythm control is preferred over rate control	Avoid as first-line therapy for atrial fibrillation unless patient has heart failure or substantial left ventricular hypertrophy	High	Strong
entral nervous system				
Antidepressants, alone or in combination Amitriptyline Amoxapine Clomipramine Desipramine Doxepin >6 mg/day Imipramine	Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≤6 mg/day) comparable to that of placebo	Avoid	High	Strong

(Continued)

Table 2 (Contd.)

rgan System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Nortriptyline Paroxetine Protriptyline Trimipramine				
Antipsychotics, first (conventional) and second (atypical) generation	Increased risk of cerebrovascular accident (stroke) and greater rate of cognitive decline and mortality in persons with dementia Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible <i>and</i> the older adult is threatening substantial harm to self or others	Avoid, except in schizophrenia or bipolar disorder, or for short-term use as antiemetic during chemotherapy	Moderate	Strong
Barbiturates Amobarbital Butabarbital Butalbital Mephobarbital Pentobarbital Phenobarbital Secobarbital	High rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages	Avoid	High	Strong
Benzodiazepines Short and intermediate acting: Alprazolam Estazolam Lorazepam Oxazepam Temazepam Triazolam Long acting: Chlordiazepoxide (alone or in combination with amitriptyline or clidinium) Clonazepam Clorazepate Diazepam Flurazepam Quazepam	Older adults have increased sensitivity to benzodiazepines and decreased metabolism of longacting agents; in general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults May be appropriate for seizure disorders, rapid eye movement sleep behavior disorder, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, and periprocedural anesthesia	Avoid	Moderate	Strong
Meprobamate Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, "Z-drugs") Eszopiclone Zaleplon Zolpidem	High rate of physical dependence; sedating Nonbenzodiazepine benzodiazepine receptor agonist hypnotics (ie, Z drugs) have adverse events similar to those of benzodiazepines in older adults (eg, delirium, falls, fractures); increased emergency room visits/ hospitalizations; motor vehicle crashes; minimal improvement in sleep latency and duration	Avoid Avoid	Moderate Moderate	Strong Strong
Ergoloid mesylates (dehydrogenated ergot alkaloids) Isoxsuprine	Lack of efficacy	Avoid	High	Strong

Table 2 (Contd.)

Rationale	Recommendation	Evidence	Strength of Recommendation
Potential for cardiac problems; contraindicated in men with prostate cancer	Avoid unless indicated for confirmed hypogonadism with clinical symptoms	Moderate	Weak
Concerns about cardiac effects; safer alternatives available	Avoid	Low	Strong
Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women	Avoid systemic estrogen (eg, oral and topical patch)	Oral and patch: high	Oral and patch strong
Evidence indicates that vaginal estrogens for the treatment of vaginal dryness are safe and effective; women with a history of breast cancer who do not respond to nonhormonal therapies are advised to discuss the risks and benefits of low-dose vaginal estrogen (dosages of estradiol	urinary tract infections, and other	Vaginal cream or vaginal tablets: moderate	Topical vagina cream or tablet weak
Impact on body composition is small and associated with		High	Strong
Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting. Avoid insulin regimens that include only short- or rapidacting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin. This recommendation does not apply to regimens that contain basal insulin or long-acting insulin.	Avoid	Moderate	Strong
Minimal effect on weight; increases risk of thrombotic	Avoid	Moderate	Strong
Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes SIADH Glimepiride and glyburide: higher risk of severe prolonged hypoglycemia in older adults	Avoid	High	Strong
Can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults and with prolonged exposure	Avoid, unless for gastroparesis with duration of use not to exceed 12 weeks except in rare cases	Moderate	Strong
Potential for aspiration and adverse effects; safer	Avoid	Moderate	Strong
Risk of Clostridium difficile infection and bone loss and fractures	Avoid scheduled use for >8 weeks unless for high-risk patients (eg, oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment (eg, because of failure of drug discontinuation trial or H2-receptor antagonists)	High	Strong
	Concerns about cardiac effects; safer alternatives available Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women Evidence indicates that vaginal estrogens for the treatment of vaginal dryness are safe and effective; women with a history of breast cancer who do not respond to nonhormonal therapies are advised to discuss the risks and benefits of low-dose vaginal estrogen (dosages of estradiol <25 µg twice weekly) with their healthcare provider Impact on body composition is small and associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia, impaired fasting glucose Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting. Avoid insulin regimens that include only short- or rapidacting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin. This recommendation does not apply to regimens that contain basal insulin or long-acting insulin. Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes SIADH Glimepiride and glyburide: higher risk of severe prolonged hypoglycemia in older adults Can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults and with prolonged exposure Potential for aspiration and adverse effects; safer alternatives available Risk of Clostridium difficile infection and bone loss and	Concerns about cardiac effects; safer alternatives available Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women Evidence indicates that vaginal estrogens for the treatment of vaginal dryness are safe and effective; women with a history of breast cancer who do not respond to nonhormonal therapies are advised to discuss the risks and benefits of low-dose vaginal estrogen (dosages of estradiol <25 µg twice weekly) with their healthcare provider Impact on body composition is small and associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia, impaired fasting glucose Higher risk of hypoglycemia management regardless of care setting. 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Avoid insulin regimens that include only short- or rapidacting insulin. This recommendation does not apply to regimens that contain basal insulin or long-acting insulin. Minimal effect on weight, increases risk of thrombotic events and possibly death in older adults Can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults; can cause prolonged hypoglycemia causes SIADH Glimepiride and glyburide: higher risk of severe prolonged exposure Potential for aspiration and adverse effects; safer alternatives available Risk of Clostridium difficile infection and bone loss and fractures Avoid vide systemic estrogen (eg, oral and topical patch) Vaginal cream or vaginal tablets: acceptable to use low-dose intravaginal estrogen for management of vaginal tablets: moderate vaginal symptoms. Avoid entrections, and other vaginal symptoms. Vaginal cream or vaginal tablets: acceptable to use low-dose intravaginal estrogen for management of dyspareunia, recurrent lower urinary tract infections, and other vaginal symptoms. Avoid entrections, and other vaginal symptoms. High whore the defective with topical patch in topical patch is defended in the topical patch in dits defended in the patch is defended in the patch is defended in

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Table 2 (Contd.)

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Pain medications				
Meperidine	Oral analgesic not effective in dosages commonly used; may have higher risk of neurotoxicity, including delirium, than other opioids; safer alternatives available	Avoid	Moderate	Strong
Non-cyclooxygenase-selective NSAIDs, oral: Aspirin >325 mg/day Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin	Increased risk of gastrointestinal bleeding or peptic ulcer disease in high-risk groups, including those >75 years or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents; use of proton-pump inhibitor or misoprostol reduces but does not eliminate risk. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in ~1% of patients treated for 3-6 months and in ~2%-4% of patients treated for 1 year; these trends continue with longer duration of use. Also can increase blood pressure and induce kidney injury. Risks are dose related.	Avoid chronic use, unless other alternatives are not effective and patient can take gastroprotective agent (proton-pump inhibitor or misoprostol)	Moderate	Strong
Indomethacin Ketorolac, includes parenteral	Increased risk of gastrointestinal bleeding/peptic ulcer disease and acute kidney injury in older adults Indomethacin is more likely than other NSAIDs to have adverse CNS effects. Of all the NSAIDs, indomethacin has the most adverse effects.	Avoid	Moderate	Strong
Skeletal muscle relaxants Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine Genitourinary	Most muscle relaxants poorly tolerated by older adults because some have anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults questionable	Avoid	Moderate	Strong
Desmopressin	High risk of hyponatremia; safer alternative treatments	Avoid for treatment of nocturia or nocturnal polyuria	Moderate	Strong

Abbreviations: CNS, central nervous system; HFrEF, heart failure with reduced ejection fraction; NSAID, nonsteroidal anti-inflammatory drug; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

a The primary target audience is the practicing clinician. The intentions of the criteria include (1) improving the selection of prescription drugs by clinicians and patients; (2) evaluating patterns of drug use within populations; (3) educating clinicians and patients on proper drug usage; and (4) evaluating health-outcome, quality-of-care, cost, and utilization data.

^bSee also criterion on highly anticholinergic antidepressants.