Medication Appropriateness Index

Patient ID# _____ Evaluator _____Date_____

Drug Code _____ Drug_____

To assess the appropriateness of the drug, please answer the following questions and circle the applicable rating:

1. Is there an indication for the drug?	A_____ Indicated	B_____	C_____ Not Indicated	Z DK
Comments:				
2. Is the medication effective for the condition?	A_____ Effective	B_____	C_____ Ineffective	Z DK
Comments:				
3. Is the dosage correct?	A_____ Correct	B_____	C + or C - Incorrect	Z DK
Comments:				
4. Are the directions correct?	A_____ Correct	B_____	C_____ Incorrect	Z DK
Comments:				
5. Are the directions practical?	A_____ Practical	B_____	C_____ Impractical	Z DK
Comments:				
6. Are there clinically significant drug-drug interactions?	A_____ Insignificant	B_____	C_____ Significant	Z DK
Comments:				
7. Are there clinically significant drug-disease/condition interactions?	A_____ Insignificant	B_____	C_____ Significant	Z DK
Comments:				
8. Is there unnecessary duplication with other drug(s)?	A_____ Necessary	B_____	C_____ Unnecessary	Z DK
Comments:				
9. Is the duration of therapy acceptable?	A_____ Acceptable	B_____	C_____ Not acceptable	Z DK
Comments:				
10. Is this drug the least expensive alternative compared to others of equal utility?	A_____ Least expensive	B_____	C_____ Most expensive	Z DK
Comments:				

USE OF THE MEDICATION APPROPRIATENESS INDEX (MAI)

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A. General Instructions[1]

This instrument is intended to assess the appropriateness of medications prescribed by a health care provider and to evaluate patients' self-medication practices. To appropriately apply the MAI, both a list of medical problems and of medications is required. Medication history information obtained from patients may also be helpful. Before evaluating any medications, review the case information and medication profile for each patient. Clinical judgment must always be applied with regard to patient preference and life expectancy. Complete the scale for *each* regularly scheduled, active medication and any "as needed" medications used frequently. Each question in the scale pertains to the individual patient and drug in question. Read each question carefully and circle the score (A, B, C or Z). If you do not understand the question, consult the specific instructions below for clarification. If you do not know the answer to the question, consult a standard medication text or software such as the AHFS Drug Information, Drug Facts and Comparisons, Micromedex®, Clinical Pharmacology (an electronic drug reference), or UpToDate®, unless the specific instructions for the question indicate an alternative source. At times, you may require additional information from the patient's chart to answer a question. In that case, circle Z and specify the necessary information in the comments section. Some regimens contain combination drugs. If the individual components are available and can be used as single entities, then complete the scale for each individual drug. Finally, please note your reasons for any rating of end of life B or C in the comments section.

B. Scoring[2]

For items coded as inappropriate (C), apply the following weights for individual criterion to calculate a summated MAI score *per drug*:

Criterion	Relative Weight Applied to Inappropriate Ratings
Is there an indication for the drug?	3
Is the medication effective for the condition?	3
Is the dosage correct?	2
Are the directions correct?	2
Are there clinically significant drug-drug interactions?	2
Are there clinically significant drug-disease interactions?	2
Are the directions practical?	1
Is this drug the least expensive alternative compared to others of equal utility?	1
Is there unnecessary duplication with other drugs?	1
Is the duration of therapy acceptable?	1

[1] Hanlon JT, et al. J Clin Epidemiol 1992;45:1045 & Hanlon JT, Schmader KE. Drugs Aging 2013;30:893-900.
[2] Samsa G, et al. A summated score for the Medication Appropriateness Index: development and assessment of clinimetric properties including content validity. J Clin Epidemiol 1994;47:891-6.

To calculate a weighted MAI score *per patient*, add MAI scores for *each drug* in the patient's regimen.[3]

C. Other measures that may be used to assess suboptimal prescribing

To implicitly assess *unnecessary use* of medications (i.e., polypharmacy), one may combine MAI ratings for questions 1, 2, and 8.[4] To assess the *underuse* of medications, consider using the implicit Assessment of Underutilization (AOU) of Medication tool.[5] For other measures, please refer to the review articles by Dimitrow,[6] Matanovic,[7] O'Mahony,[8] as well as the 2015 American Geriatrics Society (AGS) Beers Criteria.[9]

D. Specific Instructions For Rating

Question 1: Is there an indication for the drug?

A	B	C	Z
indicated	marginally indicated	not indicated	do not know

Definition: Indication is defined as the sign, symptom, disease, or condition for which the medication is prescribed. The question assesses whether there is sufficient reason to use the drug. Sufficient reason includes not only curative and palliative therapy, but also preventive therapy for a disease, condition or drug effect.

Instructions: A drug is not indicated if no condition exists for its use. Answer the question with the conditions found in the problem list or an alternative standard lisiting (e.g., health conditions checked as "yes" on the Minimum Data Set). If score = C, then questions 9 and 10 are scored C.

Examples: Hydrochlorothiazide (HCTZ) is prescribed and hypertension is recorded on the problem list = A. Olanzapine is prescribed but psychosis, schizophrenia, etc. is not documented = C. Potassium chloride (KCl) for prevention of hypokalemia in the setting of digoxin and diuretic use = A. Isoniazid (INH) and positive PPD plus immunosuppressive condition = A. KCl and diuretics alone without hypokalemia = B.

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[3] Hanlon JT, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. Am J Med 1996;100:428-37 & Schmader KE, et al. Effectiveness of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. Am J Med 2004;116:394-401.

[4] Hajjar ER, et al. Unnecessary drug use in the frail elderly at hospital discharge. J Am Geriatr Soc 2005;53:S178.

[5] Jeffery S, et al. The impact of an interdisciplinary team on suboptimal prescribing in a long term care facility. Consult Pharm. 1999;14:1386-91.

[6] Dimitrow MS, et al. Comparison of prescribing criteria to evaluate the appropriateness of drug treatment in individuals aged 65 and older: a systematic review. J Am Geriatr Soc 2011;59:1521-30.

[7] Matanović SM, Vlahovic-Palcevski V. Potentially inappropriate medications in the elderly: a comprehensive protocol. Eur J Clin Pharmacol 2012;68:1123-38.

[8] O'Mahony D, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Aging 2015;44:213-8.

[9] American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Available at : http://geriatricscareonline.org/toc/american-geriatrics-society-updated-beers-criteria-for-potentially-inappropriate-medication-use-in-older-adults/CL001. Accessed 10/12/2015.

Question 2: Is the medication effective for the condition?

A	B	C	Z
effective	marginally effective	ineffective	do not know

Definition: Effective is defined as producing a beneficial result. The question assesses whether the drug prescribed is capable of being effective for the indication in a ***population*** of patients.
Instructions: Indication and effectiveness are tightly but not perfectly linked items. Physicians may prescribe a drug for a given condition because of theoretical and standard practice reasons (indication) but investigators may demonstrate in clinical trials that the drug is ineffective (e.g., ergot mesylate [Hydergine®] and memory enhancement). Conversely, an indication may not be documented for a drug, yet the drug may work well for the intended effect (e.g., KCl to prevent hypokalemia when using diuretics). In those cases, the reviewer must note the assumed indication in the comments. Also, drugs in which the potential risks outweigh the potential benefits, and thus are incapable of being effective in actual practice, should be rated as ineffective (C). For example, those classified by as high risk drugs by AGS 2015 Beers Criteria should be rated as ineffective (C) **(Appendix I).** The exception would be the use of drugs from this list that are essential medications in palliative care.[10]
Examples: HCTZ for hypertension = A. Histamine type 2 receptor antagonist (H_2RA) prophylaxis in a person with a history of nonsteroidal anti-inflammatory drug (NSAID) induced gastric ulcer = C. Meperidine (Demerol®) for pain = C.

Question 3: Is the dosage correct?

A	B	C	Z
correct	marginally correct	incorrect	do not know

Definition: Dosage is defined as the total amount of medication taken per 24-hour period for regularly scheduled medications.
Instructions: Amounts within the dosage range for initial and maintenance therapy noted in the specified texts are correct. Other sources may specify newer, more appropriate therapeutic class specific ranges (e.g., American College of Chest Physicians [ACCP] consensus conference on antithrombotic therapy) or specific geriatric dosage ranges (e.g., American Pharmacists Association [APhA] Geriatric Drug Dosage Handbook). These ranges should supersede the standard texts as long as the reference is given. Hence, one should also take into account known age-related changes in drug pharmacokinetics and pharmacodynamics. Some patients may have drug labs/levels/vital signs to help assess whether the dosage is appropriate. If dosage is too low then circle C-. If the dosage is too high then circle C+. In summary, a dosage is incorrect if it is outside the accepted geriatrics dose range. If there is no accepted geriatrics dose range, then to be incorrect it must be outside the standard adult range. A dosage may also be incorrect if not adjusted for drug levels and laboratory or vital signs outcomes (**Appendix II**). For dosing of select medications that are primarily renally cleared, see **Appendix III**. For drugs being tapered to discontinuation (e.g., anticonvulsants), low dosage and/or low levels will be considered correct.

[10] De Lima L. International Association for Hospice and Palliative Care list of essential medicines for palliative care. Ann Oncol 2007;18:395-9.

Examples: Glyburide in patient with estimated creatinine clearance of 42ml/min = C (*reason: decreased renal clearance of drug in the elderly*). Captopril 6.25-37.5 mg bid for heart failure (HF) = A. Furosemide 20-40 mg a day for hypertension (HTN) = B. Ranitidine 150 mg bid for peptic ulcer disease (PUD) > 8 weeks = C+ (*reason: maintenance therapy dose is 150 at bedtime*). Atorvastatin at highest end of usual dosage range but cholesterol remains elevated = B (*reason: drug is necessary but additional therapy is warranted*). Patient with chronic cancer pain taking 4 g acetaminophen in divided doses, but who still rates pain as moderate to severe = B (*reason: drug is necessary but additional therapy is warranted*). Warfarin 1 mg daily for mechanical valve with INR of 1.2= C- (*reason: INR not at target goal for this anticoagulation indication*). Alternating warfarin 5mg and 7.5 mg every other day for atrial fibrillation with INR of 2.8 = A (*reason: although lab value is above standard normal range, it is within the therapeutic range of 2.0-3.0 for this anticoagulation indication; therefore, the dosage is correct*).

Question 4: Are the directions correct?

A_____B_____C____ Z
correct marginally correct incorrect do not know

Definition: Directions are defined as the instructions in the use of a medication by a patient. The question assesses the route of administration, relationship to food and liquid, the schedule and time of the day.
Instructions: The directions are incorrect when they specify the wrong route of administration, give wrong or no instructions regarding food and liquid (when specific directions regarding relationship to food or liquid exist), or specify the wrong schedule or the wrong time of day (when specific directions regarding relationship to schedule and time of day exist). See **Appendix IV** for medications with food and fluid requirements, schedule/time of day requirements, and those medications that should not be taken with grapefruit juice.[11] For new drugs, consult the latest edition of the Drugs, Supplements, and Herbal Information.[12] For information regarding meds that should not be crushed and given via enteral tube, refer to the Institute of Safe Medication Practices.[13] When the MAI is used to evaluate patients in institutional care settings, route, food liquid, schedule and time of day requirements do not apply. If the patient transitions from institutional to ambulatory care settings, application may be limited to only medications requiring a specific schedule/time of day for consistency purposes.
Examples: Captopril 25 mg TID = C (*reason: should be taken on an empty stomach*). Glipizide 10 mg daily = C (*reason: should specify "before breakfast"*). Ibuprofen 400mg TID with meals and at bedtime with snack = A. Furosemide 20 mg daily = C (*reason: should specify "in the morning"*). K-Dur® without directions regarding food/liquid = C. Nitropaste® 1" four times daily = C (*reason: must specify nitrate-free interval*). Nifedipine XL 60 mg daily with 8oz of grapefruit at breakfast = C (*reason: should not take with grapefruit juice*).

[11]Bailey DG, et al. Grapefruit-medication interactions: forbidden fruit or avoidable consequences? CMAJ 2013;185:309-16.
[12] www.nlm.nih.gov/medlineplus/druginformation.html
[13] www.ismp.org/tools/donotcrush.pdf

Question 5: Are the directions practical?

A	B	C	Z
practical	marginally practical	impractical	do not know

Definition: Practical is defined as capable of being used or put into practice. This question assesses whether the directions for use are practical, so the patient appropriately take or a caregiver may appropriately administer the medication. This reflects the potential for patient adherence without sacrificing efficacy. Additionally, consideration of whether the drug is available on formulary is important when applicable.
Instructions: A drug schedule is considered impractical if the drug can be administered less frequently and still maintain efficacy. Irregular day-to-day schedules that have more regular alternatives are also impractical. In addition, medications specified to be given around the clock on a fixed interval when a more flexible schedule is sufficient is impractical.
Examples: Warfarin 5 mg daily except Tuesday and Sunday 10 mg daily = C (*reason: 6 mg daily is easier*). Glipizide 5 mg bid = C (*reason: 10 mg every morning is equally effective*). Trazodone 75mg at bedtime = A (*reason: dosed once daily and can cue into bedtime routine*). Nifedipine 10mg TID = C (*reason: equally effective alternative, Nifedipine XL 30mg daily, is simpler to administer*). Albuterol metered dose inhaler (MDI) 2 puffs q6h = C (*reason: four times daily is sufficient*).

Question 6: Are there clinically significant drug-drug interactions?

A	B	C	Z
insignificant	marginally insignificant	significant	do not know

Definition: A drug-drug interaction is defined as the effect the administration of one medication has on another drug. Clinical significance connotes a harmful interaction. This question assesses whether the drug in question interacts with another drug in the patient's regimen by affecting its pharmacokinetics (i.e., absorption, distribution, metabolism and excretion) or pharmacodynamics (i.e., the effect that it has on the body).
Instructions: A drug interaction text (e.g., Hansten's *Drug Interactions and Updates*), software program (e.g. Micromedex®, UpToDate®), review articles like Malone (2004)[14] or Hines (2011),[15] the 2015 AGS Beers Criteria (**Appendix V**) may be used as the reference for significant interactions. If no interaction exists, then an insignificant (A) rating is automatic. A marginally significant (B) rating should be given when the reference/program indicates an interaction exists but there is no clinical evidence for toxicity or adverse effects. If the reference/program indicates an interaction exists and sufficient clinical evidence of toxicity or adverse effects (including lack of effect) is available, then the interaction is significant (C). If the reference/program indicates an interaction exists and clinical information is not available, then the interaction may also be considered significant (C). Of note, the drug that *causes* the

[14] Malone DC, et al. Identification of serious drug drug interactions: results of the partnership to prevent drug-drug interactions. J Am Pharm Assoc 2004;44:142-15.
[15] Hines L, Murphy J. Potentially harmful drug–drug interactions in the elderly: a review. Am J Geriatr Pharmacother 2011;9:364-77.

change in pharmacokinetics or pharmacodynamics is the medication that merits the significant (C) rating.
Examples: Cimetidine added to warfarin in a patient with a prolonged PT or signs of bleeding = C (*reason: significant pharmacokinetic interaction*). A tricyclic antidepressant (TCA) or an opioid added to a benzodiazepine = C (*reason: two central nervous system (CNS) drugs can result in a patient having increased falls or confusion* [significant pharmacodynamics interaction]). In the absence of sufficient clinical information, if a patient taking digoxin and is started on verapamil without a concomitant reduction in digoxin dose = C for verapamil. NSAID (e.g., naproxen) for osteoarthritis started on a patient taking warfarin chronically for atrial fibrillation = C for NSAID (*reason: increases bleed risk*).

Question 7: Are there clinically significant drug-disease/condition interactions?

A	B	C	Z
insignificant	marginally insignificant	significant	do not know

Definition: Drug-disease interaction is defined as the effect that the drug has on a pre-existing disease or condition. Clinical significance connotes a harmful interaction. This question assesses whether the drug in question may worsen the patient's disease or condition. A previous history of an idiosyncratic allergic reaction to a drug (e.g., penicillin, sulfa drugs, etc.) is considered a pre-existing condition.
Instructions: Information about drug-disease interactions is listed in the precautions or contraindications sections of the above specified texts/software. If no interaction exists according to the references, then an insignificant (A) rating is automatic. If the drug is contraindicated or highly risky (e.g., "extreme caution" is recommended) for a condition, then the drug-disease is significant (C). **Appendix VI** lists drug-disease interactions to avoid based on a consensus survey of an expert panel of health care professionals. If a drug-disease combination is listed then the drug receives a score of "C;" otherwise, the drug receives an "A." If the drug requires routine caution ("warning, precaution") in the setting of a particular condition, and the patient shows clinical evidence of the disease worsening following the drug is prescribed, then the drug-disease interaction is also significant (C). If the reference indicates an interaction ("warning, precaution") exists but the patient shows no evidence of worsening disease, then the rating is marginal (B).
Examples: Non-aspirin, non-cyclooxygenase-2 (COX-2) NSAIDs in a patient with recent history of PUD and no proton pump inhibitor (PPI) = C. Highly-anticholinergic TCAs (i.e., doxepin, amitriptyline, imipramine) initiated in a patient with lower urinary tract symptoms = C. Dicloxacillin prescribed in a patient with previous history of penicillin rash = C (*reason: clinically significant cross-reaction between dicloxacilin and penicillin*). Codeine prescribed in a patient with a history of gastrointestinal distress = B. Lamotrigine prescribed for new-onset epilepsy in a patient with a history of falls/fractures = B (*reason: although listed in* **Appendix VI**, *treatment is necessary*).

Question 8: Is there unnecessary duplication with other drug(s)?

A_____B_____C_____ Z
necessary marginally necessary unnecessary do not know

Definition: Unnecessary duplication is defined as nonbeneficial or risky overlap of drug(s). Unnecessary duplication exists when two drugs from the same chemical or pharmacological class are prescribed simultaneously.
Instructions: The Veterans Affairs (VA) Medication Classification System is available at the VA Pharmacy Benefits Manager website[16] **(see Appendix VII for exceptions).** The evaluator should look up the generic names of all regularly-scheduled medications in the index to determine the drug class, then refer to **Appendix VII** to see if modifications must be considered. In general, unnecessary duplication occurs when 2 drugs from the same subclass of the major therapeutic classifications are simultaneously prescribed. In some instances, all subclasses (e.g., sedative/hypnotics) should be considered one class. In other cases, subclasses are broken down into discrete categories (e.g., antihypertensives). If at least 2 drugs from the same class are prescribed simultaneously and the order of prescribing is known, then the last drug added is rated "C" and the other drug is rated "B." If the order of prescribing is not known, then a "B" and "C" rating should be randomly assigned.
Examples: Ranitidine added to a regimen that already includes cimetidine = C for ranitidine (*reason: same pharmacologic class*). Flurazepam 15 mg at bedtime and diazepam 5 mg TID = C for one drug, B for the other (*randomly assigned*). Cimetidine and sucralfate prescribed simultaneously for peptic ulcer disease = C for one drug, B for the other (*randomly assigned*).

Question 9: Is the duration of therapy acceptable?

A_____B_____C_____ Z
acceptable marginally acceptable unacceptable do not know

Definition: Duration is defined as the length of therapy. This question assesses whether the length of time that the patient has received the drug is acceptable.
Instructions: If the duration of therapy is outside the information source specified range, then the length is unacceptable (C). If it is within the range, or no data exists to make a clear decision, then the length is marginally (B) or fully acceptable (A). Other sources, including the medical record, may specify newer, more acceptable durations of therapy, especially in geriatric conditions. Those sources supersede the specified texts if the reference is available. Generally for a chronic condition, a prolonged duration of therapy will be acceptable. A medication prescribed to a patient with life expectancy less than the time to therapeutic benefit for the medication should be rated as unacceptable (C).[17],[18] (See **Appendix VIII** for Specific Drugs) A If a drug is not indicated (Question 1), then duration is unacceptable (C).
Examples: Haloperidol in a patient with longstanding dementia but no psychotic features = C. Digoxin in a patient with remote history of HF but in normal sinus rhythm = B. INH prophylaxis

[16] Available at: http://www.pbm.va.gov/nationalformulary.asp. Accessed 10/5/2015.
[17] Holmes HM, et al. Integrating palliative medicine into the care of persons with advance dementia: identifying appropriate medication use. J Am Geriatr Soc 2008;56:1306-11.
18. Lavan AH, et al. STOPP-frail criteria:consensus validation.. Age Ageing 2017;46:600–607

for 12 months in recent skin test converter = A. Ampicillin for 10 to 14 days for urinary tract infection (UTI) = A. Nitrofurantoin for 12 months in a patient with indwelling urinary catheter = C. Statin newly prescribed for LDL > 130mg/dl in patient with severe dementia who has 12-month life expectancy = C (*reason: statin time to thereapeutic benefit is 1.5 to 3 years.*[18]).

Question 10: Is this drug the least expensive alternative compared to others of equal utility?

A	B	C	Z
less expensive	equally expensive	more expensive	do not know

Definition: This question assesses how the cost of the drug compares to other agents of equal efficacy and safety.
Instructions: A drug is more expensive if it costs at least 10% more than the average cost/charge of alternatives of equal utility. Alternatives should be considered as medications within the same therapeutic class (see Question 8 for definition). To operationalize, the evaluator can use the local institutional setting prices (e.g., cost per month, per day supply, or per dose) as the standard. If site-specific cost data is not available for assessment, evaluators are encouraged to utilize the Average Wholesale Price (AWP) or the cost index in Drug Facts and Comparisons as their standard. If drug is not indicated (Question 1), then expense is automatically rated "C."
Examples: Ciprofloxacin for an *E. coli* UTI sensitive to ampicillin = C (*reason: ciprofloxacin is more expensive than ampicillin*). Lactulose for constipation before trying psyllium = C (*reason: lactulose is more expensive than psyllium*). Morphine SR in a hospice patient = A (*reason: although may be more expensive than IR form, t is more convenient and may be preferred by patient and therefore demonstrates greater utility*).

[18] Holmes HM, et al. Rationalizing prescribing for older patients with multimorbidity: considering time to benefit. Drugs Aging 2013;30:655-66.

Appendix I. 2015 AGS Beers Do Not Use Criteria[a]

Organ system & Therapetuic Class	***Medication***
Central Nervous System & Psychotropic Drugs	Anticholinergics (e.g., 1st generation antihistamines, benztropine, trihexyphenidyl to treat side effects of neuroleptics) Antipsychotics (1st or 2nd generation) as first-line therapy for behavior problems associated with dementia Benzodiazepine receptor agonists (i.e., benzodiazepines, eszopiclone, zaleplon, zolpidem) Barbiturates
Cardiovascular	Antithrombotics (i.e., dipyridamole ir only) Antiarrhythmics (i.e., digoxin or amiodarone as 1st line therapy for atrial fibrillation, disopyramide, dronaderone) peripheral α_1 blockers for treatment of hypertension Digoxin as first-line therapy for heart failure Nifedipine immediate release for hypertension
Endocrine	Antidiabetic agents (i.e., sliding scale insulin only, long-acting Sulfonylureas [chlorpropamide, glyburide, glimeperide) Desiccated thyroid Hormones (i.e., androgens, esrogens, growth hormone, megestrol)
Musculoskeletal	Meperidine Nonsteroidal anti-inflammatory drugs (e.g., non-cyclogenoxygenase-selective, indomethacin, ketorolac) Skeletal muscle relaxants
Gastrointensional & Genitourinary	Metoclopramide unless for gastroparesis Mineral oil (oral) Proton pump inhibitors for > 8 weeks unless high-risk Desmopressin for nocturia Nitrofurantoin in those with creatinine clearance < 30 mL/min or for long-term suppression of bacteriuria

[a]American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Available at : http://geriatricscareonline.org/toc/american-geriatrics-society-updated-beers-criteria-for-potentially-inappropriate-medication-use-in-older-adults/CL001. Accessed 10/12/2015.

Appendix II. Drug Dosage Rules

Outside of dosage range

High dose + high lab[a]/level[b]/VS = C
High dose + normal lab/level/VS = B
High dose + low lab/level/VS = C

Low dose + high lab[a]/level[b]/VS = C
Low dose + normal lab/level/VS = B
Low dose + low lab/level/VS = C[c]

Within dosage range

Normal dose + high lab[a]/level[b]/VS = C
Normal dose + normal lab/VS = A
Normal dose + low lab/VS = C

[a]Except warfarin or heparin unless PT-INR > 3.5 or 2.5 times control PT, respectively. [b]Unless clinical evidence that patient needs higher levels to control a condition (i.e., digoxin and atrial fibrillation). [c]Unless medication being tapered to be discontinued. VS = vital signs; high VS: systolic blood pressure (BP) > 160 and/or diastolic BP > 90 or pulse > 100. In institutional settings where patients may be clinically unstable, may consider high BP as systolic BP >180 and/or diastolic BP >110. Low VS: systolic BP < 90 or pulse < 40.

A**ppendix III. Recommendations for Renally Cleared Medications in Older Patients with Chronic Kidney Disease[1-5]**

Medication/Class	*eCrCl (mL/min) using Cockcroft-Gault equation*	*Maximum Dosing Recommendation (mg)*
Acyclovir (*for Zoster*)	10-29	800 every 8 hours
	<10	800 every 12 hours
Amantadine	30-59	100 daily
	15-29	100 every 48 hours
	<15	100 every 7 days
Amiloride	<30	Avoid use
Aminoglycosides (amikacin, gentamicin, tobramycin)	<60	Dose based on drug levels unless 1/kg dose for < 5 days
Apixaban	<25	Avoid use
Chlorpropamide	<50	Avoid use
Cimetidine	<50	400 every 12 hours
Ciprofloxacin	<30	500 every 24 hours
Colchicine	<30	0.3 daily
Colchicine	<10	Avoid use
Cotrimoxazole	15-29	1 DS tablet daily
	<15	Avoid use
Dabigatrin	<30	Avoid use
Digoxin	<60	Dose based on drug levels or ≤ 0.125 mg daily for heart failure
Dofetilide	<20	Avoid use
Duloxetine	<30	Avoid use
Edoxaban	15-50	30 daily
	<15[a]	Avoid use
Enoxaparin (*for prophylaxis*)	<30	30 daily
(*for other indications*)	<30	1/kg daily
Ethambutol (*for treatment*)	<10	15-25/kg every 48 hours
Famciclovir (*for Zoster*)	40-59	500 twice daily
	20-39	500 daily
	<20	250 daily

Medication/Class	*eCrCl (mL/min) using Cockcroft-Gault equation*	*Maximum Dosing Recommendation (mg)*
Famotidine	<50	20 daily
Fluconazole (*for esophageal infection*)	<50	200 daily
Fondaparinux	<30	Avoid use
Gabapentin (*for pain*)	30-59	600 twice daily
	15-29	300 twice daily
	<15	300 daily
Glyburide	<50	Avoid use
Lithium	<60	Dose based on drug levels
Levetiracetam	50-80	500-1000 every 12 hours
	30-49	250-750 every 12 hours
	<30	250-500 every 12 hours
Levofloxacin (*for UTI*)	<20	250 every 48 hours
Memantine	<30	5 twice daily
Metformin	<40	Avoid use
Meperidine	<50	Avoid use
Nizatadine	20-50	150 every other day
	<20	150 every 3 days
NSAIDs	<30	Avoid use
Oseltamivir (*for treatment*)	10-30	75 daily
(*for prevention*)	10-30	75 every other day
Pregabalin	30-60	300
	15-29	150
	<15	75
Probenecid	<30	Avoid use
Procainamide	<60	Dose based on drug level
Ranitidine	<50	150 daily
Rimantadine	<50	100 daily
Rivaroxaban	30-50	15 mg with evening meal
	<15	Avoid use
Spironolactone	<30	Avoid use
Tramadol immediate release	<30	50-100 every 12 hours
Tramadol extended release	<30	Avoid use
Triamterene	<30	Avoid use
Valacyclovir (*for Zoster*)	30-49	1000 every 12 hours
	10-29	1000 every 24 hours
	<10	500 every 24 hours
Vancomycin	<60	Dose based on drug level

Abbreviations: eCrCl = estimated creatinine clearance; UTI = urinary tract infection; NSAID = nonsteroidal anti-inflammatory drug. [a]Use is not recommended for anticoagulation for non-valvular atrial fibrillation if eCrCl > 95 mL/min.

References:
[1] Hanlon JT, et al. Consensus guidelines for oral dosing of primarily renally cleared medications in older adults. J Am Geriatr Soc 2009;57:335–340.
[2] American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Available at : http://geriatricscareonline.org/toc/american-geriatrics-society-updated-beers-criteria-for-potentially-inappropriate-medication-use-in-older-adults/CL001. Accessed 10/12/2015.
[3] Department of Veterans Affairs and Department of Defense. Clinical Practice Guideline for the Management of Chronic Kidney Disease (CKD) in Primary Care. 2014. Available at http://www.healthquality.va.gov/Chronic_Kidney_Disease_Clinical_Practice_Guideline.asp. Accessed October 12, 2015.
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Appendix IV. Medications with specific food, liquid, schedule, and time of day requirements[*†]

Medications That Should Be Taken On An Empty Stomach

Generic Name	*Brand Name*
Ampicillin	
Azithromycin	Zithromax®
Bisphosphonates	
Captopril	Capoten®
Ceftibuten	Cedax®
Deferasirox	Exjade®
Demeclocycline	Declomycin®
Dicloxacillin	
Didanosine (ddI)	Videx®
Diltiazem	Dilacor® XR
Dipyridamole	
Eltrombopag	Promacta®
Erythromycin	
Eszopiclone	Lunesta®
Etidronate disodium	Didronel®
Indinavir	Crixivan®
Isosorbide dinitrate	Isordil®
Lapatinib	Tykerb
Levothyroxine	Levoxyl®/Synthroid®
Liothyronine	Cytomel®
Loratadine	Claritin®
Metoclopramide	Reglan®
Moexipril HCl	Univasc®
Nifedipine	Adalat® CC
Oxymorphone	Opana®
Pazopanib	Votrient®
Penicillin VK	
Quinolones	
Quinapril	Accupril®

Generic Name	*Brand Name*
Ramelteon	Rozerem®
Rifampin	Rifadin®
Sorafenib	Nexavar®
Sucralfate	Carafate®
Nilotinib	Tasigna®
Temozolamide	Temodar®
Tetracycline	Sumycin®
Trospium	Sanctura®
Zafirlukast	Accolate®
Zaleplon	Sonata®
Zolpidem	Ambien®

Medications That Should Be Taken With Water/Fluid

Generic Name or Drug Class	*Brand Name*
Alendronate	Fosamax®, Binosto®
Aminophylline	
Chloral Hydrate	
Colestipol	Colestid®
Deferasirox	Exjade®
Everolimus	Afinitor®, Zortress®
Fesoterodine	Toviaz®
Ibandronate	Boniva®
Indinavir	Crixivan®
Lenalidomide	Revlimid®
Lubiprostone	Amitiza®
Nilotinib	Tasigna®
Paliperidone	Invega®
Potassium Chloride	K-Dur®
Psyllium	Metamucil®
Quinolones	Cipro®, Noroxin®
Risedronate	Actonel®
Sapropterin	Kuvan®
Sildosin	Rapaflo®
Sodium Citrate & Citric Acid	Oracit®, Shohl's Solution
Sorafenib	Nexavar®
Tapentadol	Nucynta®
Tiludronate	Skelid®
Varenicline	Chantix®
Vigabatrin	Sabril®
Vorinostat	Zolinza®

Medications That Should Be Taken With Food

Generic Name or Drug Class	*Brand Name*
Alfuzosin	Uroxatral®
Amiloride	Midamor®
Amoxicillin/Clavulanate	Augmentin®
Artemether/Lumefantrine	Coartem®
Atazanavir	Reyataz®
Atovaquone	Mepron®
Bromocriptine	Parlodel®, Cycloset®
Butalbital/codeine	Fiorinal® with codeine
Calcium Acetate	PhosLo®
Calcium Supplements	Os-Cal®
Carbamazepine	Tegretol®
Carvedilol CR	Coreg®
Cefditoren	Spectracef®
Cefpodoxime	Vantin®
Cefuroxime (suspension)	Ceftin®
Celecoxib (doses > 400 mg/day)	Celebrex®
Clarithromycin XL	Biaxin® XL
Clofibrate	Atromid S
Colesevelam	WelChol®
Darunavir	Prezista®
Dronedarone	Multaq®
Fenofibrate	TriCor®
Fluvastatin	Lescol®
Galantamine ER	Razadyne® ER
Griseofulvin	Grifulvin V®, Gris-PEG®
Itraconazole	Sporanox®
Lanthanum carbonate	Fosrenol®
Levodopa/Carbidopa	Sinemet®
Lithium CR	Lithobid®
Lopinovir/Ritonavir	Kaletra®
Lovastatin	Mevacor®
Lubiprostone	Amitiza®
Lurasidone	Latuda®
Meloxicam	Mobic®
Metformin	Glucophage®
Methylprednisolone	Medrol®
Metoprolol	Lopressor®
Mexilitine	
Misoprostol	Cytotec®
Niacin SR	Niaspan®
Nitrofurantoin	Macrobid®, Macrodantin®
Nonsteroidal Anti-Inflammatory Drugs	
Olsalazine	Dipentum®
Oxaprozin	Daypro®

Generic Name or Drug Class	*Brand Name*
Pentoxifylline	
Phenazopyridine	Pyridium®
Posaconazole	Noxafil
Potassium Chloride	Klor-Con®
Prednisone	
Prochlorperazine	Compazine®
Propafenone	Rythmol®
Ritonavir	Norvir®
Rivastigmine	Exelon®
Rufinamide	Banzel®
Sapropterin	Kuvan®
Sevelamer	Renvela®, Renagel®
Sildosin	Rapaflo®
Spironolactone	Aldactone®
Tenofovir	Viread®
Tiagabine	Gabitril®
Ticlopidine	
Trazodone	
Valganciclovir	Valcyte®
Varenicline	Chantix®
Venlafaxine	
Verapamil SR	Calan® SR
Vorinostat	Zolinza®
Ziprasidone	Geodon®

Medications That Should Not Be Taken With Grapefruit Juice

Generic Name or Drug Class	*Brand Name*
*Amiodarone	Cordarone®, Pacerone®
*Apixaban	Eliquis®
*Atorvastatin	Lipitor®
*Buspirone	
Carbamazepine	Carbatrol®, Tegretol®
*Cilostazol	Pletal®
*Clopidogrel	Plavix®
*Crizotinib	Xalkori®
*Cyclosporine	Gengraf®,Neoral®, Sandimmune®
*Dasatinib	Sprycel®
*Dextromethorphan	
*Dronedarone	Multaq®
*Eplerenone	Inspra®
*Ergotamine	
*Erlotinib	Tarceva®
*Erythromycin	
*Everolimus	Afinitor®
*Lapatinib:	Tykerb®

Generic Name or Drug Class	*Brand Name*
*Lovastatin	Mevacor®
*Maraviroc	Selzentry®
Nifedipine	
*Nilotinib	Tasigna®
Nimodipine	Nymalize®
Nisoldipine	Sular®
*Oxycodone	Oxycontin®, Roxicodone®
*Pazopanib	Votrient®
*Primaquine	
*Quetiapine	Seroquel®
*Quinine	
Ranolazine	Ranexa®
Sildenafil	Viagra®
*Simvastatin	Zocor®
*Sirolimus	Rapamune®
*Sunitinib	Sutent®
*Tacrolimus	Prograf®
Tadalafil	Cialis®
*Ticagrelor	Brilinta®
Vardenafil	Levitra®
*Verapamil	Calan®
*Ziprasidone	Geodon®

Medications That Should Be Taken On A Specific Schedule

Medication Name	*Schedule*
Alfuzosin (Uroxatral®)	Immediately following a meal
Artemether/Lumefantrine (Coartem®)	4 tablets at hr 0 and hr 8 on day 1, then 4 tablets twice daily on day 2 and day 3
Atazanavir (Reyataz®)	2 hr before or 1 hr after Videx cheweable tablets
Acarbose (Precose®)	With the first bite of food at each main meal
Capecitabine (Xeloda®)	Within 30 minutes after a meal
Cefpodoxime (Vantin®)	Every 12 hrs
Cilostazol	½ hr before or 2 hr after breakfast and dinner
Disopyramide	Every 6 hrs
Disopyramide SR	Every 8-12 hrs
Entecavir (Baraclude®)	At least 2 hrs before or 2 hrs after a meal
Esomeprazole (Nexium®)	At least 1 hr before meals
Etravirine (Intelence®)	After meals
Exenatide (Byetta®)	Within 60 min of morning and evening meals
Famciclovir (Famvir®)	Every 8 hrs
Gabapentin (Neurontin®)	Three times daily (*doses should not be > 12 hrs apart*)
Gemfibrozil (Lopid®)	½ hr before meals
Heparin (subcutaneous)	Every 8-12 hrs
Indecainide	Every 12 hrs

Medication Name	*Schedule*
Insulin	½ hr before meals and at bedtime
Isosorbide mononitrate	Twice daily (*7 hrs apart*)
Lansoprazole (Prevacid®)	Before meals
Levofloxacin (Levaquin®) oral solution	1 hr before or 2 hrs after eating
Methscopolamine (Pamine®)	½ hr before meals and at bedtime
Methylphenidate (Ritalin®)	30-45 min before meals
Metoclopramide (Reglan®)	30 minutes after meals and at bedtime
Metronidazole ER (Flagyl®)	1 hr before or 2 hrs after meals
Miglitol (Glyset®)	With the first bite of food at each main meal
Moricizine	Every 8 hrs (*occasionally every 12 hrs*)
Nateglinide (Starlix®)	1-30 min before meals
Nitrates (Isordil®, NTP)	Specify nitrate free-interval
Nitroglycerin Patch	Specify nitrate free-interval
Norfloxacin (Noroxin ®)	1 hr before or ≥ 2 hrs after a meal and dairy products
Omeprazole (Prilosec®)	½ hr before meals
Pramlintide (Symlin®)	Immediately prior to major meals *(≥250 kcal or > 30g carbs*)
Procainamide	Every 4-6 hrs
Procainamide SR	Every 6-8 hrs
Promethazine	Before meals and/or prior to bedtime
Propafenone	Every 8 hrs
Propranolol (Inderal®)	Before meals and at bedtime
Quinidine gluconate	Every 8-12 hrs
Quinidine sulfate	Every 6 hrs
Quinidine sulfate SR (Quinidex®)	Every 8-12 hrs
Ramelteon (Rozerem®)	Within 30 min of bedtime (*avoid taking with high-fat meals*)
Repaglinide (Prandin®)	15-30 min before the start of a meal
Salmeterol (Serevent®)	Every 12 hrs
Saquinavir (Invirase®)	Three times daily within 2 hrs of full meals
Selegiline	With breakfast and lunch
Stavudine (Zerit®)	Every 12 hrs
Sucralfate	After meals and at bedtime
Tamsulosin (Flomax®)	½ hour before meal
Tacrolimus (Prograf®)	Every 12 hrs
Theophylline	Every 6 hrs
Theophylline SR	Every 8-12 hrs
Tiludronate (Skelid®)	2 hrs before or 2 hrs after meals
Voriconazole (Vfend®)	Every 12 hrs and 1 hr before or after meal
Zilueton CR (Zyflo CR®)	Within 1 hr after morning or evening meals

Medications That Should Be Taken At A Specific Time Of Day

Medication Name/Class	*Time of day*
Antidepressants (except SSRIs, bupropion)	Bedtime
Chloral Hydrate	Bedtime
Cimetidine	Bedtime (*if twice daily, give 2nd dose in the morning*)
Clomipramine	Bedtime
Corticosteroids (oral)	Morning (*between 6-10 AM*)
Diuretics	Morning (*if twice daily, give 2nd dose before 4 pm*)
Donepezil (Aricept®)	Bedtime
Doxazosin XL (Cardura XL®)	Morning
Flurazepam	Bedtime
Fluvastatin IR, lovastatin IR, simvastatin	Evening
Lisdexamfetamine (Vyvanse®)	Morning
Mirtazapine (Remeron®)	Bedtime
Niacin/Lovastatin, ER (Advicor®)	Bedtime
Oral Hypoglycemics bid	Before breakfast (*if twice daily, give 2nd dose before evening meal*)
Paliperidone (Invega®)	Morning
Phenobarbital (Luminal®)	Bedtime
Phenytoin (Dilantin®)	Bedtime
Proton Pump Inhibitors	After meals in the morning
Quinine	Bedtime
Ranitidine	Bedtime (*if twice daily, give 2nd dose in the morning*)
Ramelteon (Rozerem®)	Within 30 minutes of bedtime
Rasagiline (Azilect®)	Early in the day
Simvastatin (Zocor®)	Bedtime
Terazosin	Bedtime
Triazolam	Bedtime (on an empty stomach)
Zaleplon (Sonata®)	Bedtime
Zolpidem, CR (Ambien®, Ambien CR®)	Bedtime (should not be taken with or immediately after a meal)

*High risk medication. †For drugs marketed in the United States after 2010 or for drugs not available in United States but available in other countries, consult current pharmacotherapy reference.

Appendix V. Clinically Important Drug-Drug Interactions[1-3]

Drug Affected	Precipitant Drug (s)
ACEI/ARB	K supplements, K sparing diuretics (amiloride, triamterene), aliskiren
α blockers, peripheral	Loop diuretics
Anticholinergic	Anticholinergic
Antiplatelet[a]	NSAIDs (unless patient also prescribed PPI)
Carbamazepine	Erythromycin, clarithromycin, fluoxetine, dilitazem, verapamil, rifampin
CNS med[b]	≥2 other CNS meds
Corticosteroid	NSAIDs
Cyclosporine	Rifampin
Dextromethorphan	MAOI
Disopyramide	Cimetidine
Digoxin	Amiodarone, clarithromycin, propafenone, quinidine, verapamil
Ergots for migraine	Macrolide antibiotics (clarithromycin, erythromycin)
Estrogen/progestin OC	Rifampin
Ganciclovir	Zidovudine
Lithium	ACEI, loop diuretics
MAOI	Buspirone, Opioids (fentanyl, meperidine, tramadol, tapentadol), SSRIs, SNRIs, sypathomimetics
Methotrexate	Trimethoprim
Opioid	BZD RA, Gabapentinoid
Pimozide	Macrolides (clarithromycin, erythromycin), azoles (fluconazole, itraconazole, ketoconazole)
Phenytoin	Amiodarone, imidazoles, TMP/SMX
Procainamide	Amiodarone, cimetidine, ranitidine, TMP/SMX
Quinidine	Cimetidine
SSRI	St John's wort, tramadol
Statins	Cyclosporine, gemfibrozil
Statins (CYP3A4-Ator-, lo-, sim-,vastatin)	Diltiazem. imidazoles, macrolides, nefazadone, verapamil[c],
Sulfonylureas	Imidazoles
Theophylline	Barbiturates, cimetidine, fluvoxamine, imidazoles, Mexilitene, quinolones (ciprofloxacin),
Ttizanidine	Ciprofloxacin
Triazolam	imidazoles, macrolides, nefazadone
Thiopurines	Allopurinol, febuxostat
Warfarin	Amiodarone, barbiturates, imidazoles, macrolides, NSAIDs, quinolones (ciprofloxacin), TMP/SMX

Abbreviations: ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; K = potassium; NSAIDs = nonsteroidal anti-inflammatory drugs; PPI = proton pump inhibitor; CNS = central nervous system medications; MAOI = monoamine oxidase inhibitors; OC = oral contraceptive; SSRI = selective serotonin reuptake inhibitor; [a]Includes aspirin. [b]CNS medications include: opioid, anticonvulsants, antipsychotics, benzodiazepine receptor agonists (i.e., benzodiazepines, zolpidem, zaleplon, eszopiclone), tricyclic antidepressants, selective serotonin reuptake inhibitors. [c]Only atorvastatin, lovastatin, and simvastatin

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Appendix VI. Clincally significant drug-disease interactions

CKD (stages III-IV) NSAID, all
Chronic constipation Anticholinergics Diltiazem Opioid receptor agonists (without concomitant stimulant laxative) Verapamil
Delirium Anticholinergics Benzodiazepine receptor agonists[a] Chlorpromazine Corticosteroids Histamine type 2 receptor antagonists Meperidine Thioridazine Tricyclic antidepressants
Dementia and Cognitive Impairment Antihistamines, 1st generation Antipsychotics (chronic and as-needed use) Benzodiazepine receptor agonists[a] Bladder antimuscarinic drugs Gastrointenstinal antispasmodics (e.g., dicyclomine, hyoscyamine) Histamine type 2 receptor antagonists Skeletal muscle relaxants (orphenadrine, cyclobenzaprine) Tricyclic antidepressants
Heart Failure Nondihydropyridine calcium channel blockers (diltiazem, verapamil) *in* ***systolic*** *HF only* Cilostazol Dronaderone NSAID Thiazolidinediones (pioglitazone, rosiglitazone)
History of Falls/Fractures Anticonvulsants Antipsychotics Benzodiazepines receptor agonists Opioid receptor agonists Selective serotonin reuptake inhibitors

Selective norepineprhine reuptake inhibitors Tricyclic antidepressants
History of Peptic Ulcer Disease Aspirin > 325mg/day without gastroprotection NSAID, non-COX-2-selective, without gastroprotection
Insomnia Decongestants, oral (i.e., pseudoephedrine, phenylephrine) Stimulants (e.g., amphetamine, methylphenidate, pemoline) Theobromines (i.e., theophylline, caffeine)
Lower Urinary Tract Symptoms Anticholinergics
Parkinsons's Disease Antipsychotics, all (except for clozapine or pimavanserin) Metoclopramide Prochlorperazine Promethazine
Seizures Antipsychotics, atypical (i.e., clozapine, olanzapine) Antipyschotics, conventional (e.g., chlorpromazine, thioridazine, thiothixene) Bupropion Maprotiline Tramadol
Syncope Acetylcholinesterase inhibitors α blockers, peripheral (i.e., doxazosin, prazosin, terazosin) Antipsychotics (i.e., chlorpromazine, olanzapine thioridazine) Tricyclic antidepressants, all
Urinary Incontinence α blockers (avoid in women) Estrogen oral and transdermal dosage forms only (applies to women)

[a]Refers to benzodiazepines, eszopiclone, zaleplon, and zolpidem.

Appendix VII. Modifications of Veterans Affairs Medication Classification System

Code	Class	Comments
AH100	Antihistamines	Consider all subclasses as one
CN300	Sedative/Hypnotics	Consider all subclasses as one
CN400	Anticonvulsants	Exclude - therapeutic category
CN500	Antiparkinson	Exclude - therapeutic category
CN600	Antidepressants	Combine CN601, CN603, CN609 into one
CN700	Antipsychotics	Combine CN701, CN709 into one
CV250	Antianginals	Consider as nitrates (*only ones starred*)
CV300	Antiarrhythmics	Exclude consideration as therapeutic category as combination therapy can be appropriate
CV359	Antilipemics Agents, Other	Split into discrete categories as indicated (*Bile Acid Sequestrants, Others*)
	Bile Acid Sequestrants	Colestipol, cholestyramine
	Others	Examples: niacin, gemfibrozil, probucol
CV409	Antihypertensives	Split into discrete categories as indicated (*Central/peripheral α blockers, Vasodilators*)
	Central/Peripheral α Blockers	Examples: clonidine, methyldopa, reserpine
	Vasodilators	Minoxidil (*count as CV402*)
GA300	Antiulcer agents	Combine GA301, GA302 & GA304, into one
MS400	Antigout agents	Exclude - therapeutic category
RE000	Respiratory	Combine RE120 and RE125 into one
RE120	Respiratory	No therapeutic duplication between long- and short-acting ß2 agonists
BL117	Platelet Aggregation Inhibitors	Aspirin indicated for antiplatelet effects
CN103	Non-opioid Analgesics	Aspirin indicated for minor pain
CN104	Non-steroidal Anti-inflammatories	Aspirin indicated for anti-inflammatory

Appendix VIII Drugs to Consider Duration of Use "Unacceptable" For Those At EOL

Anti-dementia agents
Anti-platelet agents (not asa)
Cytotoxic chemotherapy
Hormone antagonists
Immunomodulators (e.g., etanercept)
Leukotriene receptor antagonists
Lipid-lowering agents (e.g., statins)
?Others- ACEI/ARB, Allopurinol, Alpha blockers (for BpH), Anticoagulants, Antidepressants, antiinfectives, antipsychotics, antivertigo, ARB, ASA, Bisphosphonates, BP meds, BZDRA, CCB, Calcium/Vit. D, CNS stimulants, DM drugs, Estrogen, , expectorants, GU antispasmodics, H2 RA, Iron, MVIs, Minerals, NSAIDs, PPIs, Rubefacients, SERMs, Theophylline, Vitamins?

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