Learning Objectives

1. Summarize common age-related pharmacokinetic and pharmacodynamic changes in older adults.
2. Evaluate the pharmacotherapeutic regimens of older adults to support optimal risk and benefit of medications.
3. Assess inappropriate medication prescribing in older adults using accepted tools.
4. Recommend appropriate pharmacotherapy for patients with dementia.
5. Evaluate the risks and benefits of antipsychotic use in older adults with dementia.
6. Recommend appropriate interventions for patients with behavioral and psychological symptoms related to dementia (BPSD).
7. Differentiate between the types of urinary incontinence and recommend appropriate treatments.
8. Recommend an appropriate benign prostatic hyper trophy (BPH) treatment based on the American Urological Association Symptom Index (AUASI).
9. Recommend appropriate analgesic therapy for older adults with osteoarthritis.
10. Discuss the risks and benefits of medication classes used to treat rheumatoid arthritis and associated comorbidities.

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

Questions 1 and 2 pertain to the following case:
A.R. is an 85-year-old man who presents to the primary care clinic after the death of his spouse 1 month ago. His medical history is significant for hypertension, hyperlipidemia, BPH, and major depressive disorder. His current medications include lisinopril 10 mg daily, atorvastatin 20 mg daily, tamsulosin 0.4 mg daily, diazepam 5 mg at bedtime as needed for sleep, and escitalopram 10 mg daily. His daughter reports that he has been more lethargic and unsteady walking during the past 3 days. The patient reports trouble sleeping and taking diazepam every night this past week. His blood pressure (BP) is 135/72 mm Hg, and his heart rate (HR) is 76 beats/minute. Urinalysis was negative, thyroid-stimulating hormone (TSH) was within the reference range, and Geriatric Depression Scale (GDS) score was 6/15.

1. Which medication is contributing most to this patient’s lethargy and confusion?
   A. Diazepam.
   B. Lisinopril.
   C. Atorvastatin.
   D. Escitalopram.

2. Which age-related change in pharmacokinetics is most likely to underlie this patient’s medication-related problem?
   A. Delayed oral absorption.
   B. Decreased renal excretion.
   C. Slowed metabolism in the liver.
   D. Decreased volume of distribution.

Questions 3–5 pertain to the following case:
P.J., a 76-year-old woman, was recently admitted to a long-term care facility for rehabilitation after multiple falls at home. Her medical history is significant for hypertension, hypothyroidism, Alzheimer disease (AD), hyperlipidemia, and osteoarthritis. She currently takes metoprolol succinate 50 mg daily, levothyroxine 75 mcg daily, atorvastatin 10 mg daily, and donepezil 10 mg daily. Her BP is 126/80 mm Hg and heart rate is 66 beats/minute. Basic metabolic panel results were all within reference ranges; 25-hydroxy vitamin D level was 20 ng/mL, TSH 1.89 mU/L, total cholesterol 180 mg/dL, low-density lipoprotein cholesterol 140 mg/dL, high-density lipoprotein cholesterol 35 mg/dL, and triglycerides 176 mg/dL. Her Mini–Mental State Examination (MMSE) score was 16/30, and her GDS score was 2/15.

3. Which recommendation would be most appropriate to reduce the risk of falls in this patient?
   A. Begin memantine titration.
   B. Initiate vitamin D 1000 units daily.
   C. Decrease metoprolol succinate to 25 mg daily.
   D. Initiate calcium carbonate 500 mg twice daily.

4. Which is the best intervention for reducing the incidence of ischemic stroke in this patient?
   A. Initiate aspirin 81 mg daily.
   B. Increase atorvastatin to 20 mg daily.
C. Initiate hydrochlorothiazide 25 mg daily.
D. Increase metoprolol succinate to 100 mg daily.

5. Which would be most appropriate for complaints of osteoarthritic knee pain?
A. Ibuprofen 200 mg four times daily.
B. Acetaminophen 650 mg three times daily.
C. Tramadol 50 mg three times daily as needed for pain.
D. Hydrocodone/acetaminophen 5/325 mg every 4 hours as needed for pain.

Questions 6–8 pertain to the following case:
T.W. is an 80-year-old woman who presents to your clinic accompanied by her daughter, who no longer feels comfortable leaving her mother alone because of her mother’s “increasing forgetfulness.” T.W.’s medical history is significant for type 2 diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, and osteoarthritis. She is taking the following medications: acetaminophen 650 mg every 6 hours as needed for pain, lisinopril 20 mg daily, furosemide 20 mg daily, potassium chloride 20 mEq daily, carvedilol 12.5 mg twice daily, and glipizide 5 mg daily. Her MMSE score was 18/30. Blood work drawn last week revealed a normal basic metabolic panel, with the exception of a serum glucose reading of 65 mg/dL. Her hemoglobin A1C result was 5.6%. A urinalysis was negative. No nutritional deficiencies were noted. The patient’s BP is 130/80 mm Hg, and her HR is 60 beats/minute. She receives a diagnosis of AD.

6. Which initial intervention would be most appropriate to help with this patient’s cognitive function?
A. Donepezil 10 mg daily.
B. Galantamine ER 24 mg daily.
C. Memantine 10 mg twice daily.
D. Rivastigmine patch 4.6 mg daily.

7. Which intervention would be most appropriate to prevent an adverse drug reaction?
A. Discontinue glipizide.
B. Discontinue lisinopril.
C. Reduce carvedilol to 6.25 mg twice daily.
D. Reduce potassium chloride to 10 mEq daily.

8. One year later, the patient returns to clinic. She has moved in with her daughter. Lately she is wandering around the house continuously. She frequently changes clothes and asks repetitive questions. Her current medication regimen includes donepezil 10 mg daily, which she has been taking for the past 6 months. Which would be most appropriate for this patient’s new behavioral symptoms?
A. Initiate olanzapine 5 mg daily.
B. Initiate risperidone 0.5 mg twice daily.
C. Change donepezil dosage to 23 mg daily.
D. Change acetaminophen to 650 mg every 6 hours around the clock.

Questions 10 and 11 pertain to the following case:
J.P., a 69-year-old man with hypertension and BPH, is admitted after being involved in a motorcycle collision. He sustained serious injuries, resulting in a left leg above-the-knee amputation, and has undergone several surgeries and rehabilitation in the past 2 weeks. His current medications include tamsulosin 0.4 mg daily, atenolol 25 mg daily, amlodipine 10 mg daily, senna/docusate 8.6/50 mg twice daily, oxycodone controlled release 10 mg every 12 hours, and hydromorphone 4 mg every 3 hours as needed for breakthrough pain (uses 1–2 daily). His current BP is 155/88 mm Hg, HR
is 84 beats/minute, and postvoid residual (PVR) volume is 400 mL after voiding 110 mL. His chronic medical conditions are unremarkable except for hypertension, BPH, and gastroesophageal reflux disease (GERD).

10. Which intervention would be most appropriate for this patient?
   A. Increase tamsulosin to 0.8 mg.
   B. Increase atenolol to 50 mg daily.
   C. Change tamsulosin to terazosin 5 mg daily.
   D. Reduce hydromorphone to 2 mg every 3 hours as needed for breakthrough pain.

11. One year later, J.P. complains of osteoarthritis of his right knee. His current medications are amlodipine 10 mg daily, acetaminophen 1000 mg three times daily, omeprazole 40 mg daily, and aspirin 81 mg daily. Which agent would be best to initiate for this patient’s knee pain?
   A. Celecoxib 200 mg daily
   B. Naproxen 500 mg twice daily
   C. Diclofenac 1% gel apply 4 g to knee every 6 hours.
   D. Methylprednisolone 40 mg injected into affected joint.

Questions 12 and 13 pertain to the following case:
D.C., a 72-year-old woman whose medical history is significant for rheumatoid arthritis, type 2 diabetes mellitus, GERD, and hypothyroidism, presents to the clinic with inflammation of the joints of the hands and stiffness lasting 1–2 hours in the morning. She is a smoker, weighs 82 kg, and is 66 inches tall. Her current medications include pantoprazole 40 mg daily, metformin 850 mg twice daily, levothyroxine 100 mcg daily, folic acid 1 mg daily, methotrexate 12.5 mg weekly, naproxen 500 mg twice daily, calcium 600 mg twice daily, and vitamin D 1000 units twice daily. Her blood work reveals a negative rheumatoid factor but positive anti–cyclic citrullinated peptides. The physician determines that this is a flare of moderate disease.

12. Which would be the most appropriate intervention for this patient’s rheumatoid arthritis?
   A. Change naproxen to prednisone 20 mg daily.
   B. Change methotrexate to 25 mg intramuscularly.
   C. Switch methotrexate to leflunomide 20 mg daily.
   D. Add sulfasalazine 500 mg twice daily and hydroxychloroquine 400 mg daily.

13. Three months later she has responded to therapy. A bone mineral density T-score of –2.0 is reported from her latest scan. Her vitamin D level is 40 ng/mL. Which recommendation would be most appropriate to help reduce the risk of major osteoporotic fractures in this patient?
   A. Raloxifene 60 mg daily.
   B. Risedronate 35 mg weekly.
   C. Teriparatide 20 mcg subcutaneously daily.
   D. Increase to calcium 600 mg and vitamin D 2000 mg twice daily.
I. OPTIMIZING PHARMACOTHERAPY IN OLDER ADULTS

A. Aging

1. Aging definition: A normal process whereby the human body declines after peak growth and development. Generally aging results as the body responds to environmental stressors according to the person’s health and lifestyle factors together with genetic makeup. If environmental stressors are severe enough or individual factors have too small of a reserve capacity, aging causes frailty, disability, and increased vulnerability to disease and death.

2. At present, 13.3% (2010 U.S. Census) of Americans are 65 years or older. This figure is projected to rise to 20% by 2050. Older adults are about 13% of the population, but they are responsible for:
   a. 34% of medication costs
   b. 36% of hospital stays
   c. 40% of medication-related hospitalizations
   d. 50% of medication-related deaths

3. At least $30 billion/year is spent on medication-related morbidity.

4. There is large heterogeneity in older people: Diversity is increasing, and incomes have a wide range; some people live independently into their 90s and beyond, whereas others become frail and dependent at a younger age. Measurement of aging with years of life is insensitive to the differences between older people.
   a. If one survives to age 65, it is likely that he or she will live an additional 13–20 years.
   b. If one survives to age 85, it is likely that he or she will live an additional 6–7 years.

B. Pharmacokinetic Changes Associated with Aging

1. Common physiologic changes occur in most older adults, but they are highly variable because of differences in genetics, lifestyle, and environment.

Table 1. Common Physiologic Changes with Age That May Change Drug Pharmacokinetics

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Physiologic Change with Aging</th>
<th>Effect on Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>↑ Or no change in stomach pH</td>
<td>↓ Absorption of some drugs and nutrients requiring acid environment</td>
</tr>
<tr>
<td></td>
<td>↓ GI blood flow</td>
<td>Absorption rate may be prolonged</td>
</tr>
<tr>
<td></td>
<td>Slowed gastric emptying</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Slowed GI transit</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Thinning of dermis</td>
<td>↓ Or no change to drug reservoir formation with transdermal formulation</td>
</tr>
<tr>
<td></td>
<td>Loss of subcutaneous fat</td>
<td></td>
</tr>
<tr>
<td>Body composition</td>
<td>↓ Total body water</td>
<td>↑ Volume of distribution and accumulation of lipid-soluble drugs</td>
</tr>
<tr>
<td></td>
<td>↓ Lean body mass</td>
<td>↓ Volume of distribution of water-soluble drugs</td>
</tr>
<tr>
<td></td>
<td>↑ Body fat</td>
<td>↑ Free fraction of highly protein-bound drugs</td>
</tr>
<tr>
<td></td>
<td>↓ Or unchanged serum albumin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ α1-Acid glycoprotein</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>↓ Liver mass</td>
<td>↓ First-pass extraction and metabolism</td>
</tr>
<tr>
<td></td>
<td>↓ Blood flow to the liver</td>
<td>↑ Half-life and ↓ clearance of drugs with a high first-pass extraction and metabolism</td>
</tr>
<tr>
<td></td>
<td>↓ Or no change in CYP enzymes</td>
<td>↓ Or no change in phase I metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No change in phase II drug metabolism</td>
</tr>
<tr>
<td>Renal</td>
<td>↓ Glomerular filtration rate</td>
<td>↓ Renal elimination of many medications</td>
</tr>
<tr>
<td></td>
<td>↓ Renal blood flow</td>
<td>↑ Half-life of renally eliminated drugs and metabolites</td>
</tr>
<tr>
<td></td>
<td>↓ Tubular secretion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Renal mass</td>
<td></td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; GI = gastrointestinal.
2. Absorption
   a. Iron, vitamin B₁₂, antifungals, and calcium are decreased with hypochlorhydria or achlorhydria.
   b. Slower gastric emptying can increase risk of ulceration from aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or potassium chloride tablets.
   c. Most drugs are absorbed by passive diffusion without significant age-related changes.
   d. Transdermal formulations usually require a subcutaneous fat layer to form a drug reservoir for absorption. Use with caution in patients who are thin or cachetic.

3. Distribution
   a. Lipid-soluble benzodiazepines such as diazepam have an increased half-life in older people.
   b. Highly albumin-bound drugs such as phenytoin may have a larger fraction of free (active) drug.
   c. P-glycoprotein, an efflux transporter for several organs including the brain, decreases with aging, which may lead to higher brain concentrations of medications. One example is opioid analgesics.

4. Metabolism
   a. Morphine and propranolol clearance are substantially reduced because of a reduction in first-pass metabolism.
   b. Changes in metabolism through phase I (oxidative) and cytochrome P₄₅₀ (CYP) enzymes are variable and confounded by age, sex, concomitant drugs, and genetics.
   c. Lorazepam, oxazepam, and temazepam are dependent on phase II metabolism and are less affected by age-related changes in metabolism.

5. Elimination
   a. Drugs eliminated through glomerular filtration must be dosed according to individual estimated renal function.
   b. The Cockcroft-Gault equation is a validated method to estimate creatinine clearance (CrCl) for drug dosing in older adults.
   c. The National Kidney Foundation recommends using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation (2009) to estimate glomerular filtration rate. However, this recommendation has not been validated in older adults.

Table 2. Differences in Renal Estimation with Common Formulas

<table>
<thead>
<tr>
<th>Patient: 85-year-old person with an SCr of 1 mg/dL</th>
<th>Cockcroft-Gault Creatinine Clearance (mL/minute)</th>
<th>MDRD Estimated Glomerular Filtration Rate (mL/minute)</th>
<th>CKD-EPI Creatinine Clearance Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>64-inch-tall white woman weighing 60 kg</td>
<td>39</td>
<td>56</td>
<td>51 (stage 3)</td>
</tr>
<tr>
<td>64-inch-tall African American woman weighing 60 kg</td>
<td>39</td>
<td>68</td>
<td>60 (stage 2)</td>
</tr>
<tr>
<td>70-inch-tall white man weighing 75 kg</td>
<td>57</td>
<td>75</td>
<td>68 (stage 2)</td>
</tr>
<tr>
<td>70-inch-tall African American man weighing 75 kg</td>
<td>57</td>
<td>91</td>
<td>79 (stage 2)</td>
</tr>
</tbody>
</table>

Cockcroft-Gault: \[ CrCl = \left(\frac{140 - \text{age}}{72} \times \text{weight in kg}\right) \times \left(\frac{\text{SCr}}{0.85}\right) \] if female

[use actual weight if it is less than ideal body weight]

MDRD: \[ \text{estimated GFR} = 186 \times \text{SCr}^{1.154} \times \text{Age}^{-0.203} \times 1.21 \text{ if black} \times 0.742 \text{ if female} \]

CKD-EPI Creatinine Equation 2009*: \[ \text{CKD-EPI equation expressed as a single equation:} \]
\[ \text{GFR} = 141 \times \left[ \min(\text{SCr}/\kappa, 1)^{\alpha} \times \max(\text{SCr}/\kappa, 1)^{-1.209} \times \text{Age}^{-0.993} \right] \times 1.018 \text{ if female} \times 1.159 \text{ if African American} \]

*SCr is standardized serum creatinine in milligrams per deciliter; \( \kappa \) is 0.7 for women and 0.9 for men, \( \alpha \) is −0.329 for women and −0.411 for men, \( \min \) indicates the minimum of \( \text{SCr}/\kappa \) or 1, and \( \max \) indicates the maximum of \( \text{SCr}/\kappa \) or 1.

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; MDRD = Modified Diet Renal Disease.
Some clinicians round the serum creatinine concentration (SCr) up to 1 mg/dL because older adults have lower muscle mass, which produces less creatinine, and extremely low SCr would overestimate renal function with these formulas. This rounding is not supported by evidence and remains controversial. Also, clinicians may use adjusted weight for obese patients with formulas used for younger adults.

C. Pharmacodynamic Changes Common with Aging

1. Increased sensitivity
   a. Benzodiazepines
   b. Opioids
   c. Antipsychotics, metoclopramide: extrapyramidal effects and tardive dyskinesia
   d. Tricyclic antidepressants, α-blockers, antihypertensives: orthostatic hypotension
   e. Warfarin
   f. NSAIDs: gastrointestinal (GI) bleeding
   g. Anticholinergic agents

2. Decreased sensitivity
   a. β-blockers
   b. β-agonists

3. Impaired homeostasis
   a. Diuretics, angiotensin-converting enzyme inhibitors: sodium and electrolytes
   b. Diuretics: hydration status

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Patient Cases

1. N.H. is an 85-year-old woman who resides at home with her daughter. She weighs 65 kg. Her medical history is significant for type 2 diabetes mellitus and hypertension, and 1 year ago she sustained a right hip fracture after a fall. Her regularly scheduled medications include glyburide 10 mg daily, lisinopril 10 mg daily, metformin 500 mg twice daily, aspirin 81 mg daily, and a multivitamin daily. Her as-needed medications include melatonin 6 mg at bedtime as needed for sleep, meclizine 25 mg ½ tablet three times daily as needed for dizziness, and docusate 100 mg twice daily. Her laboratory results reveal fasting plasma glucose 90 mg/dL, sodium 138 mEq/L, potassium 4.5 mEq/L, chloride 102 mEq/L, CO₂ 25 mEq/L, blood urea nitrogen (BUN) 30 mg/dL, SCr 1.8 mg/dL, and thyroid-stimulating hormone (TSH) 4.0 mU/L. Considering potential for altered pharmacokinetics, which medications are the most likely potential problems for N.H.?
   A. Aspirin and melatonin.
   B. Lisinopril and meclizine.
   C. Lisinopril and metformin.
   D. Glyburide and metformin.

2. Considering potential for increased pharmacodynamic sensitivity, which medications are the most likely potential problems for N.H.?
   A. Aspirin and melatonin.
   B. Lisinopril and meclizine.
   C. Lisinopril and metformin.
   D. Glyburide and metformin.
D. Optimal Pharmacotherapy in Older People
   1. An optimal pharmacotherapeutic regimen is one in which the benefit of the therapy outweighs risk for adverse effects.
   2. To reduce risk, doses of many medications must be adjusted in older people because of age-associated changes in drug pharmacokinetics and pharmacodynamics.
   3. Alternate medications may be more appropriate because of these changes.
   4. Therapeutic window becomes smaller even with dose and drug adjustments.

E. Drug-Related Assessment for Risk in Older Adults
   1. Overuse of medications
      a. Unnecessary drugs: Use of more medications than clinically indicated and unneeded therapeutic duplication
      b. Common unnecessary drugs: GI agents, central nervous system agents, vitamins, minerals
      c. May be caused by
         i. Prescribing cascade: When drug is prescribed for treatment of another drug’s side effects
         ii. Multiple prescribers
         iii. Care transitions
   2. Underuse of medications
      a. Omitted but necessary or indicated drug therapy or inadequate dosing
      b. Commonly underused drugs: anticoagulants, statins, antihypertensives
      c. Medications considered appropriate according to guidelines may be omitted because prescriber or patient is overly wary of adverse drug effects.
   3. Nonadherence
      a. Unintentional nonadherence caused by complex drug regimen
      b. Dementia or other cognitive impairment increases risk.
      c. Cost of medications is another barrier.
      d. Intentional nonadherence because of patient health beliefs or concerns
   4. Withdrawal syndromes
      a. Abrupt discontinuation of medication may cause rebound symptoms or delirium.
      b. Common culprits: antihypertensives, antidepressants, anxiolytics, pain medications
   5. Inappropriate medications
      a. Explicit tools frequently used to identify for quality measure. Best known is the Beers List of Drugs to Avoid in the Elderly, updated in 2012.
         i. Evidence-based list of drugs likely to cause problems
         ii. Adopted by many federal agencies and Part D plans
         iii. Arranged as drugs and drug classes to always avoid, drugs to avoid in certain diseases or conditions, and drugs to be used with caution
         iv. Examples: anticholinergics, long half-life benzodiazepines, sedative-hypnotics, older antipsychotics, certain opiates or pain medications, hypoglycemics, NSAIDs and GI drugs
      b. Implicit tools are patient-centered, take more time to apply. Best studied is the Medication Appropriateness Index.
         i. 10 questions to ask about each medication regarding indication, effect, dosing, directions, interactions, duration, and cost
         ii. Indication, effectiveness, and correct dosage have most weight.
   6. Choosing Wisely Campaign
      a. Two sets of five things to question in older adults
      b. Seven of the 10 items are drug related.
         i. Antipsychotics in patients with dementia should be avoided.
         ii. Target hemoglobin A1C in diabetes management 7.5% or higher
iii. Avoid benzodiazepines and sedative-hypnotics for insomnia, agitation, or delirium.
iv. Do not start antimicrobials to treat bacteriuria without symptoms.
v. Assess benefit and risk of cholinesterase inhibitors.
vi. Appetite stimulants not helpful for anorexia or cachexia
vii. Drug regimen review is necessary with every new prescription.

F. Function with Aging
1. Quality of life, place of residence, social and physical function may become more important than
duration of life.
2. Instrumental activities of daily living (IADLs)
   a. Examples: housekeeping, using phone, managing medications, shopping, cooking, managing
      money
   b. Need to do these to live independently
3. Activities of daily living (ADLs)
   a. Examples: feeding, dressing, bathing, toileting, transferring
   b. Nursing home or home caregivers required if ADLs cannot be performed
4. Cognitive screening: Mini–Mental State Examination (MMSE), Montreal Cognitive Assessment
   (MoCA), St. Louis University Mental Status (SLUMS) Examination
5. Mood: Geriatric Depression Scale
6. Gait and balance: Timed Up and Go, Berg Balance Scale
7. Drugs can alter cognition, mood, and mobility.

G. Geriatric Syndromes
1. Geriatric syndromes follow a concentric model, with multiple risk factors and numerous etiologies
   contributing to a clinical presentation rather than the linear model with one etiology following a defined
   pathogenesis.
2. Falls
   a. Possible etiologies: psychoactive medications, polypharmacy, orthostatic hypotension, hyponatremia,
      myocardial infarction, urinary tract infection
   b. Examples of contributing risk factors: vitamin D deficiency, poor balance, poor vision, environment
3. Delirium
   a. Possible etiologies: psychoactive medications, polypharmacy, hyponatremia, myocardial infarction,
      urinary tract infection
   b. Example of contributing risk factors: dementia, stroke, vitamin B₁₂ deficiency, poor hearing, lack
      of sleep
4. Hazards of hospitalization
   a. Usual aging involves a decline in numerous organ systems, which are further compromised when
      an older patient is admitted to the hospital and expected to remain in bed.
      i. Immobilization leads to deconditioning. Regaining what was lost takes longer in older adults.
      ii. Immobilization and inability to obtain water lead to decreased plasma volume, which can lead
          to syncope, falls, and fractures.
      iii. Sensory deprivation from isolation and lack of glasses or hearing aids can lead to delirium,
          which may be treated with restraints or antipsychotics.
      iv. Immobilization and “tethers” (e.g., intravenous lines, oxygen lines, catheters) necessitate nurs-
          ing assistance to bathroom. Unavoidable delay may lead to incontinence, catheters, infections,
          and pressure sores.
   v. Prescribed diets or nothing-by-mouth status lead to dehydration, malnutrition, insertion of
      feeding tubes, and aspiration pneumonia.
b. Preventable adverse drug events are frequent contributors to increased morbidity and mortality in older hospitalized adults.

c. Functional decline typically follows a hospitalization and is referred to as a cascade to dependency.

d. One study showed subjects that had a loss of ADLs at discharge had a higher mortality rate (40% at 12 months), with only 30% returning to baseline function.

e. Early mobility, adequate nutrition, reduced polypharmacy, and early discharge planning may reduce functional disability and length of stay.

**Patient Cases**

3. N.H. is admitted to the hospital with a broken arm after a fall. While in the hospital she was on bedrest most of the time, lost 2 kg (current weight 63 kg), and had trouble sleeping. She is to be discharged to a rehabilitation facility for 2–3 weeks of therapy. Her medications at discharge are glipizide 5 mg daily, lisinopril 10 mg daily, aspirin 81 mg daily, multivitamin daily, mirtazapine 15 mg at bedtime, calcium 500 mg twice daily, and tramadol 25 mg every 8 hours as needed for pain. When recommending medication changes for this patient, which functional assessment is most important to evaluate?

A. IADLs
B. Depression
C. Pressure sores
D. Gait and balance

4. To maintain and improve function in N.H., which intervention is best to implement?

A. Add simvastatin 10 mg daily.
B. Increase lisinopril to 20 mg daily.
C. Add vitamin D 1000 units twice daily.
D. Change tramadol to naproxen 500 mg twice daily as needed for pain.

**II. DEMENTIA**

A. Epidemiology

1. Affects 4–5 million in the United States
2. Of people 65 years and older, 6% have dementia, increasing to 30–50% of those 85 years and older.

B. Dementia Definition: Cognitive decline in complex attention, executive function, learning and memory, language, perceptual–motor or social cognition AND interferes with work or social functions

1. Delirium should be ruled out first.
   a. Delirium: A disturbance in attention and awareness developing over hours to days with fluctuation over the course of the day
   b. It is a geriatric syndrome, with age, underlying dementia, functional impairment, medical comorbidities as risk factors.
   c. Etiologies include medications such as sedative hypnotics, antidepressants, anticholinergics, opioids, anticonvulsants, and antiparkinson drugs.
2. Mild cognitive impairment (MCI) is a term used for people with some deficits in cognition that do not meet criteria for dementia.
3. Alzheimer disease (AD) is most common type of dementia.
4. Theories of pathogenesis include cholinergic, β-amyloid plaques, tau protein (neurofibrillary tangles), genetics (apolipoprotein E4), and inflammation (cytokines, prion).
5. Multiple other types of dementia exist; few are reversible.

**Table 3. Comparisons of Memory Impairment and Dementias with AD**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Differences from AD</th>
<th>Treatment Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common Irreversible Causes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI</td>
<td>No interference with work or social functions</td>
<td>Eliminate or control risk factors for dementia</td>
</tr>
<tr>
<td></td>
<td>1 in 5 progress to AD</td>
<td>May use CIs, which reduced risk for progression by 40% in 1 study</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>Includes focal neurological signs and symptoms</td>
<td>Control of cardiac and vascular risk factors</td>
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<tr>
<td></td>
<td>Radiologic evidence of stroke</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Onset within 3–6 months of stroke</td>
<td></td>
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<tr>
<td></td>
<td>Abrupt deterioration followed by stepwise progression</td>
<td></td>
</tr>
<tr>
<td>Lewy body dementia</td>
<td>Fluctuating cognition with pronounced variation in attention and alertness</td>
<td>Avoid typical antipsychotics, which may worsen motor symptoms</td>
</tr>
<tr>
<td></td>
<td>Recurrent visual hallucinations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motor features of PD</td>
<td></td>
</tr>
<tr>
<td>Dementia of advanced PD</td>
<td>PD onset predates cognitive impairment</td>
<td>May use CIs or memantine</td>
</tr>
<tr>
<td></td>
<td>Usually at latter stages of PD</td>
<td></td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>Affects personality, behavior, self-care, and language</td>
<td>CIs may worsen behavior and cause agitation</td>
</tr>
<tr>
<td></td>
<td>Onset in ages 45–65 with a 2- to 10-year course</td>
<td></td>
</tr>
<tr>
<td><strong>Reversible Causes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt; deficiency</td>
<td>Progressive memory loss</td>
<td>Replace vitamin B&lt;sub&gt;12&lt;/sub&gt; per standard protocols</td>
</tr>
<tr>
<td></td>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;, serum concentration &lt;300 pg/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be anemic also, but folic acid may disguise the anemia</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Deficient or inadequate replacement of thyroxine</td>
<td>Levothyroxine replacement per standard protocols</td>
</tr>
<tr>
<td>Depression</td>
<td>Trouble concentrating and memory</td>
<td>Treatment of depression per standard protocols</td>
</tr>
<tr>
<td></td>
<td>Apathy and “I don’t care” responses</td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>Triad of progressive memory loss, incontinence, and gait abnormality</td>
<td>Surgical placement of ventricular shunt</td>
</tr>
<tr>
<td></td>
<td>Symptoms improve after lumbar puncture</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- AD = Alzheimer disease
- CI = cholinesterase inhibitor
- MCI = mild cognitive impairment
- NPH = normal pressure hydrocephalus
- PD = Parkinson disease
C. Assessment Tools
   1. Folstein MMSE
      a. 30-point scale; higher is better function.
      b. Untreated AD: Score usually decreases 3–4 points a year.
      c. Heavily relies on verbal and language skills so less accurate if education is poor
   2. SLUMS Examination
      a. 30-point scale; higher number is better function.
      b. Includes adjustment of scores for lower educational status
   3. MoCA
      a. 30-point scale; higher number is better function.
      b. Less reliant on verbal or language skills
   4. Mini-Cog Assessment
      a. 5-point scale; higher number is better function.
      b. Easiest to administer; takes 3 minutes
   5. Research instruments
      a. AD Assessment Scale–Cognitive: (ADAS-Cog): 70-point scale
      b. AD Cooperative Study Activities of Daily Living Inventory: (ADCS-ADL): 54-point scale
      c. Clinician Interview–Based Impression of Change: (CIBIC-Plus): 1–7 points, with 4 points indicating no change
      d. Functional Assessment Staging Test: 7 major stages
      e. Severe Impairment Battery: 100-point scale

D. New Diagnostic Guidelines
   1. Recognizes three phases
      a. Preclinical, asymptomatic phase
      b. Symptomatic, predementia phase (MCI)
      c. Dementia phase
   2. Diagnosis may be identified for research purposes by:
      a. Biomarkers of increased tau or decreased β-amyloid levels in cerebrospinal fluid
      b. Reduced glucose uptake in brain on positron emission tomography scanning using florbetapir F18 or flutemetamol F18
      c. Atrophy of specific brain areas on magnetic resonance imaging
   3. Preclinical and predementia phases are targets for investigational studies to halt progression
   4. For clinicians, usually diagnosis given without these biomarkers or imaging
E. Clinical Presentation and Classification

Table 4. Stages of Alzheimer Disease

<table>
<thead>
<tr>
<th></th>
<th>MMSE (out of 30)</th>
<th>Examples of Cognitive Loss</th>
<th>Examples of Functional Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>20–24</td>
<td>Some short-term memory loss; word-finding problems</td>
<td>Loss of IADLs such as laundry, housekeeping, and managing medications; may get lost in familiar places</td>
</tr>
<tr>
<td>Moderate</td>
<td>10–19</td>
<td>Disorientation to time and place, inability to engage in activities and conversation</td>
<td>Needs assistance with ADLs such as bathing, dressing, and toileting</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;10</td>
<td>Loss of speech and ambulation, incontinence of bowel and bladder</td>
<td>Dependency in basic ADLs such as feeding oneself; often needs around-the-clock care</td>
</tr>
</tbody>
</table>

ADLs = activities of daily living; IADLs = instrumental activities of daily living; MMSE = Mini–Mental State Examination

F. Management

1. Goals are to maintain function and cognition.
   a. Functional management and safety issues
   b. Legal considerations
2. Nonpharmacologic therapy
   a. Education, especially with caregiver
   b. Physical exercise and mental exercise
   c. Management of comorbid conditions
   d. Avoid alcohol and medications that worsen mentation.
3. Medical food: caprylidene triglyceride
   a. Mechanism is to provide ketone bodies for brain to use as energy source when glucose metabolism is impaired.
   b. Not routinely used because study measures became nonsignificant

Patient Case

5. M.B. is an 84-year-old widow living at home alone. She is able to perform ADLs and most IADLs with some assistance from her daughter. Her medications are hydrochlorothiazide 12.5 mg daily for hypertension, tolterodine LA 4 mg daily for incontinence, escitalopram 20 mg daily for depression, acetaminophen 650 mg as needed for arthritis, and calcium/vitamin D for prevention of osteoporosis. Her physician administers the MMSE, and M.B’s score is 23. On physical examination no cogwheel rigidity or tremor is noted.

What medication change is indicated at this time?

A. Add donepezil 5 mg daily.
B. Discontinue tolterodine and reassess M.B.
C. Add vitamin B₁₂ 1000-mg injection monthly.
D. Switch hydrochlorothiazide to lisinopril 5 mg daily.
4. Pharmacologic therapy

Table 5. Comparison of Drugs for the Treatment of AD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Maintenance Dose</th>
<th>Dosage Forms</th>
<th>Pharmacologic Properties</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholinesterase Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil</td>
<td>5 mg daily</td>
<td>10 mg daily 10 mg daily May increase to 23 mg/day</td>
<td>Tablets Oral disintegrating tablets</td>
<td>Acetylcholinesterase inhibitor; metabolized in part by CYP2D6 and CYP3A4 Protein binding 96%</td>
<td>Labeled for mild to moderate and moderate to severe AD</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>1.5 mg twice daily 9.5-mg patch daily</td>
<td>3–6 mg twice daily 9.5-mg patch daily; may increase to 13.3-mg patch daily</td>
<td>Capsules Oral solution Transdermal patch</td>
<td>Acetyl- and butyrylcholinesterase inhibitor Nausea, vomiting, and diarrhea seem more intense than with other CIs</td>
<td>Labeled for mild to moderate and moderate to severe AD as well as mild to moderate dementia with Parkinson disease Skin reactions with patch</td>
</tr>
<tr>
<td>Galantamine</td>
<td>4 mg twice daily</td>
<td>8–12 mg twice daily 8–24 mg ER once daily</td>
<td>Tablets Oral solution ER capsules</td>
<td>Selective competitive, reversible acetylcholinesterase inhibitor and nicotine receptor modulator Metabolized in part by CYP2D6 and CYP3A4</td>
<td>Preferable to administer with food Renal dosing adjustment necessary</td>
</tr>
<tr>
<td>Memantine</td>
<td>5 mg once daily 7 mg ER once daily</td>
<td>10 mg twice daily 28 mg ER once daily</td>
<td>Tablets Oral solution ER capsules</td>
<td>N-methyl-d-aspartate receptor antagonist that blocks glutamate transmission</td>
<td>Labeled for moderate to severe AD; may be used in combination with acetylcholinesterase inhibitors.</td>
</tr>
</tbody>
</table>

AD = Alzheimer disease; CI, cholinesterase inhibitor; ER = extended release.

a. Adverse effects of cholinesterase inhibitors (CIs)
   i. GI: nausea, vomiting, diarrhea, elevated risk of GI bleeding
   ii. Central nervous system: headache, insomnia, dizziness
   iii. Cardiac: bradycardia, orthostatic hypotension, syncope (Beers List notes CIs as inappropriate drugs in patients with syncope)
   iv. Genitourinary: incontinence
b. Adverse effects of memantine: agitation, urinary incontinence, insomnia, diarrhea, dizziness, confusion, headache

5. Consensus treatment guidelines in United States, 2001 (partially outdated)
   a. Initiate CI in patients with mild to moderate AD.
   b. No evidence one agent is superior to others
   c. Titrate to recommended maintenance dose as tolerated.
   d. May increase to maximum dose if tolerated and maintenance dose no longer effective
e. In moderate to severe disease may use CI, or memantine, or both CI and memantine
f. Study in 2012 found no benefit with combination therapy.
g. Study in 2011 found no benefit of memantine in mild AD.

6. Controversy over clinically significance responses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Test</th>
<th>Testing Range</th>
<th>Response Difference Compared with Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Cholinesterase inhibitor</td>
<td>AD Assessment Scale—Cognitive</td>
<td>0–70</td>
<td>−2.7</td>
</tr>
<tr>
<td>Memantine</td>
<td>Severe Impairment Battery</td>
<td>0–100</td>
<td>2.97</td>
</tr>
</tbody>
</table>

7. Duration of therapy
   a. Generally need 3–6 months to evaluate for objective benefit with tools
   b. Longest study was for 52 weeks, but many are maintained for years.
   c. Choosing Wisely campaign recommends evaluating at 12 weeks and considering discontinuation if goals of therapy not obtained.
   d. Generally discontinue at advanced stages of disease. Recommend tapering if on high dose.
   e. May see some rebound agitation

8. Herbals and dietary supplements
   a. Vitamin E was not shown effective in large prospective trials.
   b. Gingko biloba was not shown effective in prevention.
   c. Curcumin (turmeric) observational studies support effect.

Patient Cases

6. An 87-year-old man with AD is receiving rivastigmine 6 mg twice daily. His family notes improvement in his functional ability but reports that he is experiencing nausea and vomiting that appear to be related to rivastigmine. Which recommendation is best for this patient at this time?
   A. Advise the patient to take rivastigmine with an antacid.
   B. Change rivastigmine to the patch that delivers 9.5 mg daily.
   C. Discontinue rivastigmine and initiate memantine 5 mg twice daily.
   D. Add prochlorperazine 25 mg by rectal suppository with each rivastigmine dose.

7. A 75-year-old woman with AD who lives at home with her husband has been treated with donepezil 10 mg daily for about 3 years. When she began therapy, her MMSE was 21/30; her present MMSE is 17/30. The patient cannot perform most IADLs but can perform most ADLs with cueing. About 2 months ago, her donepezil was increased to 23 mg, but she could not tolerate it, and it was reduced back to 10 mg daily. Her husband asks about changing her drug treatment to help maintain her function. Which is the next best course of action?
   A. Retry donepezil 23 mg daily.
   B. Initiate memantine 5 mg daily.
   C. Add vitamin E 400 units twice daily.
   D. Switch donepezil to rivastigmine 9.5-mg patch daily.
III. BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA (BPSD)

A. Epidemiology
1. As disease progresses from mild to moderate, BPSD occur. They tend to wane as disease progresses to severe.
2. Up to 90% of patients with dementia have BPSD at some point in disease progression.
3. Associated with high rate of disability, functional decline, poor health outcomes, physical injury, nursing home placement, and emergency services.

Table 7. Symptoms Seen During Disease Progression

<table>
<thead>
<tr>
<th>MMSE Score</th>
<th>Stage</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Mild</td>
<td>Memory loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor drawing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mood swings(^a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild executive function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild personality changes(^a)</td>
</tr>
<tr>
<td>20</td>
<td>Moderate</td>
<td>Unable to learn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aphasia, apraxia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wandering, agitation(^a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aggression, psychosis(^a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Confusion, insomnia(^a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Need ADL assistance</td>
</tr>
<tr>
<td>15</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
<td>Gait changes(^a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incontinence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of ADLs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bed bound</td>
</tr>
<tr>
<td>0</td>
<td>Severe</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Noncognitive symptoms.
ADLs = activities of daily living; MMSE = Mini–Mental State Examination.

B. Assessment Tools: Higher scores indicate more severe symptoms.
1. Neuropsychiatric Inventory
2. Behavioral Pathology in Alzheimer’s Disease (BEHAVE-AD)
3. Cohen-Mansfield Agitation Inventory
4. Scales rarely used in nursing home or clinical practice, but it is important to identify the target behavior, how often it is occurring, and how severe it is in order to assess the response to treatment.
5. Assess for medical reason that may precipitate and treat, if found
   a. Pain is frequent issue that patient cannot communicate.
   b. Treat with scheduled acetaminophen.

C. Nonpharmacologic Treatment: cornerstone of therapy
1. Theory is that behavior is communication of unmet need.
2. Eliminate antecedents and triggers.
3. Person-centered interventions: Consider long-standing habits, values, and beliefs of patient; use distraction, music, aromatherapy.
4. Symptoms likely to respond: wandering, hoarding, hiding objects, repetitive questioning, withdrawal, social inappropriateness, apathy.
D. Pharmacologic Treatment: None of these are U.S. Food and Drug Administration (FDA) labeled indications.

1. Agency for Healthcare Research and Quality has published a summary on the use of atypical antipsychotic agents for off-label indications.
   a. Atypical antipsychotics improve behavioral symptoms of dementia, but effect sizes are small, and adverse effects are significant.
   b. It lists the risk of death at 1 for every 100 patients treated.

**Table 8.** Drug Treatment for BPSD

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Presentation</th>
<th>Treatment Options After Nonpharmacologic Efforts Ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Part of this is caused by the fact that they cannot remember things</td>
<td>Buspirone or SSRI/SNRI or gabapentin Limit benzodiazepines</td>
</tr>
<tr>
<td>Apathy</td>
<td>One of earliest symptoms Nonpharmacologic, tailored to patient’s activities</td>
<td>Cholinesterase inhibitors Methylphenidate, modafinil effective in small, short-term studies</td>
</tr>
<tr>
<td>Depression</td>
<td>Up to 80% of patients with AD have depression</td>
<td>SSRI or mirtazapine</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Sleep/wake cycle is disrupted</td>
<td>Melatonin</td>
</tr>
<tr>
<td>Wandering</td>
<td>Walk so much they begin to lose weight</td>
<td>No drug will stop wandering</td>
</tr>
<tr>
<td>Paranoia</td>
<td>They may think because they cannot find something, you stole it</td>
<td>Risperidone, olanzapine, or quetiapine. Use very low doses. ADEs may offset any benefit.</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Frequently accuse spouse of infidelity</td>
<td></td>
</tr>
<tr>
<td>Sundowning</td>
<td>If psychosis and delusions do not bother anyone, do not use drugs</td>
<td></td>
</tr>
<tr>
<td>Aggression,</td>
<td>Most difficult and best response is to nonpharmacologic treatment</td>
<td>Prazosin is in investigation for agitation</td>
</tr>
<tr>
<td>resistance to care</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADE = adverse drug effect; BPSD = behavioral and psychological symptoms of dementia; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

**Patient Cases**

8. You are evaluating the medication profile of an 87-year-old woman who resides in a secure advanced dementia unit. Her medical history includes dementia (likely AD), Parkinson disease, and osteoarthritis. She needs assistance with all ADLs including total assistance with bathing and dressing and help with feeding. She ambulates with the assistance of a four-wheeled walker. Her medication regimen includes donepezil 10 mg daily, memantine 10 mg twice daily, carbidopa/levodopa 25/100 mg four times daily, oxybutynin extended release 5 mg daily, and a multivitamin supplement daily. The patient’s most recent MMSE score is 5/30. When reviewing the nursing notes, you note several references to the patient’s continuously crying out, “Help me, help me.” She is medically evaluated, and reversible causes of her hypervocalization are ruled out. Which additional assessment tool is most necessary for appropriate assessment of this patient?

A. Geriatric Depression Scale.
B. Functional Assessment Staging Test.
C. Neuropsychiatric Inventory.
D. MoCA.
Patient Cases (continued)

9. Which is the best approach to treating her behavioral symptoms?
   A. Begin music therapy with songs patient enjoyed when younger.
   B. Turn the television on to comedy shows.
   C. Add quetiapine 25 mg at 4 p.m. daily.
   D. Add citalopram 10 mg daily.

IV. URINARY INCONTINENCE

A. Epidemiology
   1. Prevalence in community-dwelling elderly women is 38%.
   2. Less common in elderly men: 17%.
   3. Up to 75% of nursing home residents have urinary incontinence (UI).
   4. Transient incontinence can occur due to DRIP:
      D = Drugs, Delirium
      R = Retention, Restricted Mobility
      I = Impaction, Infection, Inflammation
      P = Polyuria, Prostatitis

B. Physiology
   1. During filling, $\beta_3$-adrenergic stimulation relaxes detrusor to increase capacity.
   2. $\alpha$-Adrenergic stimulation tightens the internal bladder sphincter.
   3. Acetylcholine (M$_3$) mediates involuntary and volitional bladder contractions.
   4. Normal bladder emptying occurs with a decrease in urethral resistance and contraction of the bladder muscle.
   5. Aging effects include decreased bladder elasticity and capacity, more frequent voiding, decline in bladder outlet and urethral resistance in women with loss of estrogen, and decrease in flow rate in men with prostatic enlargement.
C. Types of UI

Table 9. Common Types of UI and Drug-Induced Causes

<table>
<thead>
<tr>
<th>Type of Incontinence</th>
<th>Description</th>
<th>Drug-Induced Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urge or overactive bladder</td>
<td>Loss of a moderate amount of urine with an increased need to void. Detrusor instability can be caused by central nervous system damage from a stroke.</td>
<td>Cholinergic agents that stimulate the bladder such as bethanechol and cholinesterase inhibitors.</td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>Loss of small amounts of urine with increased abdominal pressure (e.g., sneezing, coughing). Stress UI is more common in postmenopausal women.</td>
<td>α-Blockers such as prazosin decrease urethral sphincter tone.</td>
</tr>
<tr>
<td>Overflow incontinence</td>
<td>Loss of urine because of excessive bladder volume caused by outlet obstruction or an acontractile detrusor. PVR is often high (&gt;300 mL), indicating incomplete emptying.</td>
<td>Anticholinergic agents, calcium channel blockers, and opioids decrease detrusor muscle contractions.</td>
</tr>
<tr>
<td>Functional incontinence</td>
<td>Inability to reach the toilet because of mobility constraints.</td>
<td>Sedating drugs that cause confusion. Diuretics increase voiding.</td>
</tr>
<tr>
<td>Mixed incontinence</td>
<td>UI that has more than one cause, usually stress and overactive bladder.</td>
<td></td>
</tr>
</tbody>
</table>

PVR = postvoid residual; UI = urinary incontinence.

D. Nonpharmacologic Interventions
1. Pelvic floor exercises (Kegel exercises) are first line for stress, urge, or mixed UI.
2. Exercise and weight loss for patients with BMI >30
3. Bladder training to increase time between voiding in urge incontinence
4. Biofeedback to teach pelvic floor exercises
5. Scheduled and timed voiding may be helpful for patients with dementia.
7. Pessaries, collagen, or other bulking agent injections also help stress incontinence.
8. Prostatectomy in men or self-catheterization for severe overflow incontinence.
### E. Drug Treatment

**Table 10. Recommended Drug Treatment by Type of Incontinence**

<table>
<thead>
<tr>
<th>Type of Incontinence</th>
<th>Drug Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urge or overactive bladder</td>
<td><strong>Antimuscarinic and anticholinergic agents</strong>&lt;br&gt;Oxybutynin, tolterodine, fesoterodine, trosplum, solifenacin, darifenacin</td>
<td>Magnitude of clinical efficacy is modest&lt;br&gt;Differences in adverse reactions exist, but clinical differences in efficacy between these agents have not been shown&lt;br&gt;Longer-acting formulations may be better tolerated</td>
</tr>
<tr>
<td></td>
<td><strong>β3-Agonist</strong>&lt;br&gt;Mirabegron</td>
<td>Recently approved in 2012; appears well tolerated but has not been compared with antimuscarinics</td>
</tr>
<tr>
<td></td>
<td><strong>Botulinum toxin A</strong>&lt;br&gt;intravesical injections</td>
<td>Prevents stimulation of detrusor muscle&lt;br&gt;May cause voiding difficulty</td>
</tr>
<tr>
<td>Stress</td>
<td><strong>α-Adrenergic agonists</strong>&lt;br&gt;Pseudoephedrine, phenylephrine</td>
<td>Efficacy evidence is limited</td>
</tr>
<tr>
<td></td>
<td><strong>Topical estrogens</strong>&lt;br&gt;Conjugated estrogen vaginal cream or estradiol vaginal insert or ring</td>
<td>Use if other symptoms of estrogen deficiency&lt;br&gt;Vaginal estrogens may improve severity of stress incontinence</td>
</tr>
<tr>
<td></td>
<td><strong>Serotonin/norepinephrine reuptake inhibitor</strong>&lt;br&gt;Duloxetine</td>
<td>Not FDA labeled for stress UI; may reduce the severity of incontinence&lt;br&gt;Not significantly different from placebo for symptoms&lt;br&gt;Adverse effects may limit its usefulness</td>
</tr>
<tr>
<td>Overflow</td>
<td><strong>α-Adrenergic antagonists</strong>&lt;br&gt;Alfuzosin, tamsulosin, silodosin, doxazosin, terazosin, prazosin</td>
<td>Adverse effects vary depending on selectivity to receptors in the bladder or prostate (alfuzosin, silodosin, and tamsulosin are more specific)</td>
</tr>
<tr>
<td></td>
<td><strong>5-α-reductase inhibitors</strong>&lt;br&gt;Finasteride, dutasteride</td>
<td>To slow progression</td>
</tr>
<tr>
<td></td>
<td><strong>Cholinomimetics</strong>&lt;br&gt;Bethanechol</td>
<td>Stimulates the detrusor muscle but also systemic cholinomimetic effects</td>
</tr>
<tr>
<td></td>
<td><strong>Phosphodiesterase-5 inhibitors</strong>&lt;br&gt;Tadalafil</td>
<td>5 mg once daily approved for BPH</td>
</tr>
<tr>
<td>Functional</td>
<td>No drug treatments</td>
<td>Consider interventions to remove any potential cause, barriers or obstacles; provide schedules or prompted toileting; assistance may be required to transfer on and off commode</td>
</tr>
<tr>
<td>Mixed</td>
<td>Focus on symptoms that dominate</td>
<td>Consider treatments for individual components (i.e., stress and urge)</td>
</tr>
</tbody>
</table>

BPH = benign prostatic hypertrophy; FDA = U.S. Food and Drug Administration; UI = urinary incontinence.
### Table 11. Comparison of Adverse Effects from Urinary Antimuscarinic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dry Mouth (%)</th>
<th>Constipation (%)</th>
<th>Dizziness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>88</td>
<td>32</td>
<td>38</td>
</tr>
<tr>
<td>Oxybutynin ER/XL</td>
<td>68</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Oxybutynin TDS</td>
<td>10</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Oxybutynin gel</td>
<td>8</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Tolterodine IR, ER</td>
<td>50, 39</td>
<td>10, 10</td>
<td>4, 3</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>99</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Trospium</td>
<td>33</td>
<td>11</td>
<td>?</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>34</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>59</td>
<td>28</td>
<td>0</td>
</tr>
</tbody>
</table>


### Patient Case

10. A 75-year-old woman reports urinary urgency, frequency, and loss of urine when she cannot make it to the bathroom in time. She also wears a pad at night that she changes two or three times because of incontinence. Her medical history is significant for mild cognitive impairment (MMSE = 25), osteoarthritis, and hypothyroidism. A urinalysis is negative. Physical examination is normal, and her postvoid residual (PVR) is normal (less than 100 mL). Which therapy would be best to initiate in this patient at this time?

A. Pelvic floor exercises.
B. Bethanechol.
C. Darifenacin.
D. Tolterodine.

### V. BENIGN PROSTATIC HYPERTROPHY

A. Epidemiology
   1. Benign prostatic hypertrophy (BPH) usually develops after age 40.
   2. By age 60, half of all men have BPH; by age 85, 90% have BPH.

B. Pathophysiology and Clinical Presentation
   1. Type II 5-α-reductase facilitates conversion of testosterone to dihydrotestosterone (DHT), resulting in prostate growth.
   2. Lower urinary tract symptoms (LUTS) are seen in 25% of men.
      a. Voiding (obstructive) symptoms: decreased force, hesitancy, dribbling
      b. Storage (irritative) symptoms: urinary urgency, frequency, nocturia, dysuria
   3. The American Urological Association Symptom Index (AUASI) can help determine severity and appropriate treatment. The index consists of seven questions evaluating the severity of LUTS on a 0–5 scale. Higher numbers indicate more severe symptoms.
C. Evaluation
1. Medical history, digital rectal examination, BUN, serum creatinine, and urinalysis
2. If suspect prostate cancer, plan treatment with 5-α reductase inhibitor, prostate-specific antigen (PSA)
3. If suspect significant urinary retention, need to assess PVR. If PVR is greater than 50 mL, patients have an elevated risk of infection.
4. Assess for medications that may exacerbate BPH symptoms.
   a. α-Adrenergic agonists (decongestants) can stimulate smooth muscle contraction in the prostate and urethra, obstructing urinary flow through the urethra.
   b. Anticholinergic drugs (urinary and GI antispasmodics, antihistamines, tricyclic antidepressants, phenothiazines) can reduce the ability of the bladder detrusor muscle to contract and empty the bladder.
   c. Diuretics can increase urinary frequency and volume.
   d. Testosterone replacement can stimulate prostate growth.
5. If AUASI score is 0–7 (mild), then watchful waiting.
6. Patients with high AUASI scores of 20 and up (severe disease) should be assessed for prostatectomy.
7. Patients with moderate disease (scores 8–19) are candidates for medical treatment.

D. Drug Treatment
1. α-Adrenergic blockers: Relieve LUTS in men with moderate or severe AUASI scores by reducing smooth muscle contractions in the urethra and surrounding tissues
   a. Nonspecific α-adrenergic blockers such as doxazosin and terazosin also lower BP significantly.
   b. Newer agents are uroselective antagonists of α1-adrenergic receptors (tamsulosin, silodosin) and selective antagonists of postsynaptic α1-adrenergic receptors (alfuzosin) in the prostate and bladder. They may have less associated hypotension.
   c. All α-blockers can cause hypotension.
   d. Compared with placebo, the α-blockers lower the AUASI by 4 to 6 points in patients with LUTS and BPH.
   e. All α-blockers are metabolized through the CYP3A4 pathway and have drug interactions with strong CYP3A4 inhibitors and inducers.
   f. Intraoperative floppy iris syndrome is a concern with α-blockers, especially tamsulosin. Men with LUTS being offered α-blockers should be asked about planned cataract surgery. Men with planned cataract surgery should avoid the initiation of α-blockers until their cataract surgery is completed.
2. α-Reductase inhibitors
   a. These agents prevent the conversion of testosterone to DHT, modify the disease course, and may reduce the risk of urinary retention and surgical interventions.
      i. Finasteride competitively inhibits type II 5-α-reductase and lowers prostatic DHT by 80%–90%.
      ii. Dutasteride is a nonselective inhibitor of both type I and II 5-α-reductase. Prostatic DHT production is quickly suppressed with this agent.
      iii. Despite these pharmacologic differences, no differences between these two agents were observed in trials; both reduce prostate size.
   b. α-Reductase inhibitors do not immediately reduce LUTS and should be reserved for use in men with large prostate volume (more than 40 g). At least 6 months of therapy is usually needed to achieve clinical benefit. Prostate size may be reduced by about 25% during this interval.
   c. PSA concentrations are used to monitor for prostate cancer. Because these agents lower PSA concentrations, a baseline PSA test is recommended before initiating treatment with α-reductase inhibitors.
   d. Long-term therapy with an α-reductase inhibitor can increase the risk of high-grade tumors of the prostate in healthy men without a history of prostate cancer.
3. Phosphodiesterase type-5 inhibitors
   a. Tadalafil 5 mg once daily is approved for use in BPH.
   b. Mechanism is thought to be caused by phosphodiesterase-induced smooth muscle relaxation in the bladder, urethra, and prostate.
   c. Studied as monotherapy; the FDA does not recommend in combination with α-blockers because the combination has not been adequately studied for the treatment of BPH, and there is a risk of lowering BP. May be used in practice to treat both BPH and erectile dysfunction with a 4-hour separation of doses.

4. Combination therapy
   a. May be needed in men with LUTS, a larger prostate size, and an elevated PSA
   b. Finasteride and doxazosin most studied; dutasteride is FDA label approved for use with tamsulosin in symptomatic men having an enlarged prostate.
   c. Two large clinical trials [Medical Therapy of Prostatic Symptoms (MTOPS) and the Combination of Avodart and Tamsulosin studies (CombAT)] evaluated monotherapy versus combination therapy and concluded that in men with LUTS and an enlarged prostate, further benefit can be achieved by using the two drugs in combination.

5. Supplements
   a. Saw palmetto plant extract (*Serenoa repens*)
   b. Conflicting evidence about the efficacy of saw palmetto in relieving LUTS; two recent trials suggested no benefit over placebo.
   c. Use of this agent with 5-α-reductase inhibitors may reduce the efficacy of the reductase inhibitors.

6. Surgery is preferred in men with severe symptoms and in those with moderate symptoms who have not adequately responded to medical options.

7. Anticholinergic agents can be appropriate and effective treatment alternatives in men without an elevated PVR when LUTS are predominantly storage (irritative) symptoms.

### Table 12. Comparison of Drugs for the Treatment of Benign Prostatic Hypertrophy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose Range</th>
<th>Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terazosin</td>
<td>1–10 mg daily</td>
<td>Orthostatic hypotension</td>
<td>Initiate at low dose; can titrate up every 2–7 days</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>1–8 mg daily</td>
<td></td>
<td>Start at bedtime</td>
</tr>
<tr>
<td>Alfuzosin ER</td>
<td>10 mg daily</td>
<td>Orthostatic hypotension</td>
<td>No need to titrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Take after a meal</td>
</tr>
<tr>
<td>Tamsulosin modified release</td>
<td>0.4–0.8 mg daily</td>
<td>May cause less orthostasis</td>
<td>Start at bedtime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Causes ejaculatory dysfunction</td>
<td></td>
</tr>
<tr>
<td>Silodosin</td>
<td>8 mg daily</td>
<td>Causes ejaculatory dysfunction</td>
<td>Contraindicated if CrCl &lt; 30 mL/minute</td>
</tr>
<tr>
<td></td>
<td>4 mg daily if CrCl 30–50 mL/minute</td>
<td>appears less sedating</td>
<td>Take with food</td>
</tr>
<tr>
<td>Finasteride</td>
<td>5 mg daily</td>
<td>Decreased libido</td>
<td>Onset of action is usually 6 months</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>0.5 mg daily</td>
<td>Pregnancy category X</td>
<td>Monitor PSA</td>
</tr>
<tr>
<td>Dutasteride/tamsulosin</td>
<td>0.5/0.4 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tadalafil</td>
<td>5 mg daily</td>
<td>Orthostatic hypotension</td>
<td>Avoid use with α-blockers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No data in combination or with long-term use</td>
</tr>
</tbody>
</table>

CrCl = creatinine clearance; ER = extended release; PSA = prostate-specific antigen.
Patient Case
11. An 85-year-old man with LUTS visits his physician, who determines his AUASI score is 15. His BP is 118/70 mm Hg sitting. A digital rectal examination confirms the diagnosis of BPH, and the physician schedules a further workup including a prostate ultrasound, which shows a prostate volume of 31 g. Which therapy is best at this time?
   A. Terazosin.
   B. Finasteride plus saw palmetto.
   C. Tamsulosin.
   D. Finasteride plus tamsulosin.

VI. OSTEOARTHRITIS

A. Epidemiology
   1. Osteoarthritis (OA) is the most prevalent form of arthritis, affecting more than 46 million Americans.
   2. Highly associated with aging
   3. Women are afflicted more often than men.
   4. Large weight-bearing joints (e.g., hip and knee) are commonly affected.

B. Etiology and Pathophysiology
   1. Risk factors include age, female sex, obesity, genetics, sports activities, occupation, previous injury, acromegaly
   2. Loss of cartilage occurs in the joint as the balance of chondrocyte function shifts from formation to destruction. Secondary inflammation and production of cytokines play a role.
   3. Subchondral bone and the synovium are damaged, and the joint space narrows.
   4. Single injuries or repeated micro-injuries may initiate or accelerate process.
   5. Symptoms of pain result from activation of nociceptive nerve endings in the damaged joint.
   6. Therapy goals: To relieve pain and swelling, maintain or improve joint function, prevent loss of function, and maintain or improve quality of life

C. Nonpharmacologic Treatment
   1. Patient education: lifestyle, expectations, when to seek care
   2. Weight loss decreases the biomechanical load on large weight-bearing joints; even a small amount of weight loss helps decrease pain and disability.
   3. Exercise
   4. Physical and occupational therapy
   5. Surgery

D. Drug Therapy
   1. Acetaminophen is first line, with as-needed doses followed by scheduled dosing to maximum of 4 g daily in divided doses.
      a. 1000 mg every 6 hours for three times daily or 650 mg every 6 hours
      b. Ensure that patient knows to watch for “hidden” acetaminophen in other products.
      c. Monitor for hepatotoxicity in patients with elevated risk of liver disease (previous liver problems, heavy alcohol consumption) with periodic liver function tests.
2. NSAIDs are used if acetaminophen response inadequate in select patients.
   a. Avoid chronic use or, if necessary, use a COX-2 selective NSAID, or add a proton pump inhibitor to reduce the risk of GI bleeding.
   b. If one NSAID is not effective, switch to others.
   c. Monitor for adverse effects: rash, abdominal pain, GI bleeding, renal impairment, hypertension, heart failure, and drug-drug interactions.
   d. For patients taking aspirin (for cardiac disease), a proton pump inhibitor may be recommended for gastric protection. Patients should be educated to take aspirin at least 30 minutes before their first daily dose of NSAID in the morning to avoid any interactions or reductions in aspirin efficacy. Naproxen appears to be safest with respect to cardiac risk.
   e. Monitor in chronic users: complete blood cell count, BUN, serum creatinine, and aspartate aminotransferase at least annually

3. Topical agents: Helpful for knees or smaller joints near surface of skin. Limited efficacy for widespread joint pain.
   a. Capsaicin difficult to administer: Wear gloves, avoid contact with eyes, and do not skip doses. Local irritation occurs in 40%.
   b. Diclofenac 1% gel (or patch is FDA labeled for minor trauma): Four short-term trials showed a 50% reduction in pain in 40% of subjects (number needed to treat = 5); longer-term trials had number needed to treat = 10. Comparative trials with oral administration showed no difference in proportion who received pain relief.

4. Intra-articular glucocorticoid injections
   a. Methylprednisolone or triamcinolone 10- to 40-mg injection depending on size of joint; may be repeated every 3 months
   b. Primary adverse effects are risk for septic arthritis, synovitis.

5. Intra-articular hyaluronans may be used if glucocorticoid injections are ineffective.
   a. Meta-analysis indicates effects last up to 30 weeks.
   b. Frequency of injection undetermined: annual or more often?

6. Alternative dietary supplements: Glucosamine sulfate, 400–500 mg taken three times daily, with or without chondroitin, may be considered for chronic therapy to prevent joint degradation and relieve pain.
   a. Evidence to support treatment is contradictory. Sulfate vs. HCl salt
   b. The adverse effect profile of glucosamine is similar to that of placebo and includes GI complaints

7. Opioids
   a. Patients with persistent, moderate to severe pain from OA who do not respond to more conservative strategies are candidates for treatment with opioids. The American Geriatrics Society recommends treatment with opioids for OA when older patients do not respond to initial acetaminophen therapy rather than chronic use of NSAIDs.
   b. Hydrocodone/acetaminophen combination now Schedule II.
   c. Tramadol alone or in combination with acetaminophen is an alternative when NSAIDs are ineffective or contraindicated.
   d. Stronger opioids can be more effective but can incur more significant adverse effects.
   e. Monitor and anticipate opioid adverse effects and treat accordingly.
Patient Case
12. An 85-year-old man presents with pain from hip OA. He has hypertension, coronary artery disease, and BPH. For his OA, he has been taking acetaminophen 650 mg three times daily. He reports that acetaminophen helps but that the pain persists and limits his ability to walk. Which is the best next step for this patient?
   A. Change acetaminophen to celecoxib.
   B. Add hydrocodone.
   C. Change acetaminophen to ibuprofen.
   D. Add glucosamine.

VII. RHEUMATOID ARTHRITIS

A. Epidemiology
   1. A systemic disease characterized by a bilateral inflammatory arthritis that usually affects the small joints of the hands, wrists, and feet
   2. The prevalence is estimated to be between 1% and 2%, with women predominating until after age 60, when it becomes equal.
   3. Rheumatoid arthritis (RA) can occur at any age but has an increasing prevalence up to age 70.
   4. RA is an autoimmune disease with a strong genetic predisposition.

B. Pathophysiology and Clinical Presentation
   1. Chronic inflammation of the synovium leads to proliferation and development of a pannus.
   2. The pannus invades joint cartilage and eventually causes erosion of the bone and joint destruction.
   3. The cause of the initial inflammatory activation is unknown, but once activated, the immune system produces antibodies and cytokines that accelerate cartilage and joint destruction.
   4. Patients present with joint pain and stiffness, fatigue, and other inflammatory symptoms. Symptoms also include warmth, redness, and swelling of the joints, usually with symmetrical distribution.
   5. Laboratory tests often reveal a positive rheumatoid factor (RF), elevated sedimentation rate, C-reactive protein, anti–cyclic citrullinated peptide antibodies, and normochromic normocytic anemia.
   6. RA can also affect other organs, causing pulmonary fibrosis, vasculitis, and dry eyes.

C. Treatment
   1. The treatment goal is to control the inflammatory process so that disease remission occurs. This should lead to relief of pain, maintenance of function, and improved quality of life. Treatment response can be measured by:
      a. Reduction in the number of affected joints and in joint tenderness and swelling
      b. Improvement in pain
      c. Decreased amount of morning stiffness
      d. Reduction in serologic markers such as RF
      e. Improvement in quality-of-life scales
   2. Nonpharmacologic treatment: concurrent with pharmacologic treatment
      a. Rest during periods of disease exacerbation
      b. Occupational and physical therapy to support mobility and maintain function
      c. Maintenance of a normal weight (avoid overweight and obesity) to reduce biomechanical stress on joints
      d. Assistive devices if needed
      e. Surgery for tendons or joints
3. Disease-modifying antirheumatic drugs (DMARDs)
   a. Start DMARD within 3 months of diagnosis.
   b. Step-down approach: Start with DMARD (1 or more depending on disease severity) along with anti-inflammatory drug (NSAID, steroid). As pain is controlled, reduce anti-inflammatory agent. As joint damage is controlled, reduce DMARD.
   c. Nonbiologic DMARDs are first line.
      i. Methotrexate has most long-term data and better outcomes.
      ii. Hydroxychloroquine has slow onset of action.
      iii. Sulfasalazine is drug of choice in pregnancy but has slow onset too.
      iv. Leflunomide
      v. Some patients with poor prognostic indicators such as functional limitation, extra-articular disease, positive RF, anti–cyclic citrullinated peptide antibodies, or bony erosions on radiography may be candidates for combination DMARD therapy.
   d. Biologic DMARDs are used in combination for severe disease or as alternatives if nonbiologic DMARDs are ineffective or contraindicated. Etanercept, infliximab, abatacept, or rituximab are most often used.
4. NSAIDs, glucocorticosteroids, or both can be used to provide immediate treatment of pain and inflammation.
   a. NSAIDs do not affect disease progression in RA; their anti-inflammatory effect occurs within 1–2 weeks of daily dosing, whereas the analgesic effect begins within several hours of administration.
   b. Glucocorticosteroids (dosed at 10 mg daily or less) are not recommended for long-term use because of their many adverse effects and long-term complications. They are often used as bridge therapy to provide anti-inflammatory effects while waiting for the DMARDs to take effect.

### Table 13. Selected DMARDs for Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Customary Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonbiologic DMARDs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>7.5–15 mg every week</td>
<td>Probably first-line DMARD; monitor for myelosuppression, liver dysfunction, and pulmonary fibrosis; a teratogen</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>(Arava) 10–20 mg/day</td>
<td>Similar to methotrexate; an initial loading dose may give therapeutic response within the first month</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>200–300 mg twice daily</td>
<td>Must routinely monitor for ocular toxicity; however, this agent has a better adverse effect profile overall</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>500–1000 mg twice daily</td>
<td>GI adverse effects often limit the use of this agent</td>
</tr>
<tr>
<td><strong>Biologic DMARDs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>(Enbrel) 50 mg SC weekly</td>
<td>Binds to TNF, inactivating this cytokine; generally well tolerated; usually used in those whose methotrexate therapy fails; monitor for infection; check baseline PPD</td>
</tr>
<tr>
<td>Infliximab</td>
<td>(Remicade) 3 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks thereafter</td>
<td>A mouse/human chimeric antibody to TNF; used in combination with methotrexate to prevent formation of antibodies to this protein; monitor for infection; check baseline PPD</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>(Humira) 40 mg SC every 2 weeks</td>
<td>Human antibody to TNF; less antigenic than other TNF antibodies; monitor for infection; check baseline PPD</td>
</tr>
</tbody>
</table>
Table 13. Selected DMARDs for Rheumatoid Arthritis (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Customary Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anakinra (Kineret)</td>
<td>100 mg SC daily</td>
<td>IL-1 receptor antagonist; avoid combination therapy with TNF agents because of elevated risk of infection</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Two infusions of 1000 mg given 2 weeks apart</td>
<td>Chimeric antibody to CD20 protein on B lymphocytes; corticosteroid infusions help reduce infusion reactions; used in combination with methotrexate to improve response</td>
</tr>
<tr>
<td>Abatacept (Orencia)</td>
<td>Weight-based dose every 2 weeks for 2 doses and then monthly (i.e., 750 mg for those weighing 60–100 kg)</td>
<td>Inhibits interactions between antigens and T cells; may be useful in those who do not respond to TNF inhibitors; monitor for infusion reactions</td>
</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>50 mg SC every month</td>
<td>Monoclonal antibody against TNF Intended for use in combination with methotrexate Monitor for infections</td>
</tr>
<tr>
<td>Certolizumab pegol (Cimzia)</td>
<td>400 mg SC at 0, 2, and 4 weeks, then 200 mg every other week</td>
<td>Monoclonal antibody against TNF; may have best response when used in combination with methotrexate Monitor for infections</td>
</tr>
<tr>
<td>Tocilizumab (Actemra)</td>
<td>4 mg/kg IV infusion every 4 weeks; can increase to 8 mg/kg on the basis of clinical response</td>
<td>Anti–human IL-6 receptor monoclonal antibody; indicated for patients who have not responded to TNF inhibitors Monitor for infections</td>
</tr>
<tr>
<td>Tofacitinib (Xeljanz)</td>
<td>5 mg twice daily</td>
<td>Oral Janus kinase inhibitor; intended as second-line therapy Can be used as monotherapy or in combination with methotrexate</td>
</tr>
</tbody>
</table>

DMARD = disease-modifying antirheumatic drug; GI = gastrointestinal; IL = interleukin; IV = intravenous(ly); NSAID = nonsteroidal anti-inflammatory drug; PPD = purified protein derivative; SC = subcutaneously; SSRI = selective serotonin reuptake inhibitor; TNF = tumor necrosis factor.

D. Comorbid Conditions

1. Patients with RA are more likely to develop other chronic diseases either from the effects of RA or from medications used to treat RA.
2. Cardiovascular disease (myocarditis and heart failure) causes 40% of all deaths in patients with RA. Low-dose aspirin, omega-3 fatty acids, statins, or combination therapy should be considered.
   a. Follow standard guidelines to lower cardiovascular risk factors.
   b. European guidelines recommend multiplying risk score by 1.5 for patients with RA who have disease of 10 years or more, are positive for RF or anti–cyclic citrullinated peptide, or have severe extra-articular disease manifestations (two of the three should be present).
3. Infection risk is elevated, particularly pulmonary infections and sepsis. A history of tuberculosis or hepatitis B calls for extra vigilance. Tuberculosis screening is required for patients who are considered for therapy with biologic DMARDs.
4. Malignancy is more common, particularly GI cancers and lymphoproliferative disorders. Also, melanoma and lung cancer rates were elevated in one cohort study.
5. Osteoporosis is more common in patients with RA. Calcium and vitamin D are recommended. In addition, bisphosphonates should be considered for prevention if prednisone 5 mg or more daily is prescribed.
Patient Case

13. A 65-year-old woman received a diagnosis of RA 1 year ago. At the time of her diagnosis, her RF titer was 1:64; she presented with joint inflammation in both hands and about 45 minutes of morning stiffness. She began therapy with oral methotrexate and currently receives 15 mg weekly, folic acid 2 mg daily, ibuprofen 800 mg three times daily, and omeprazole 20 mg daily. At today’s clinic visit, the patient reports the recurrence of her symptoms. Radiographic evaluation of her hand joints shows progression of joint space narrowing and bone erosion. Which is the next best step for this patient?

A. Administer etanercept.
B. Change to leflunomide.
C. Add prednisone bridge therapy.
D. Switch to hydroxychloroquine.

Acknowledgment: The contributions of the previous authors, Drs. Norma Owens, Jennifer Dugan, and Dominick Trombetta, are acknowledged.
REFERENCES

Principles to Promote Optimal Medication Use in Older People


Dementia


Behavioral Symptoms of Dementia


Urinary Incontinence and Benign Prostatic Hypertrophy


Osteoarthritis and Rheumatoid Arthritis


ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: D**
Renal elimination is usually the most significantly changed pharmacokinetic value in older people. In this patient, her advanced age and diseases will add to her loss of renal function. Using the Cockcroft-Gault equation, this patient's estimated CrCl is 24 mL/minute.

Creatinine clearance = \[\frac{(140 - 85)65}{(72 \times 1.8)}\] \times 0.85.

At this level of function, glyburide elimination would be prolonged, and metformin use is contraindicated.

2. **Answer B**
Common pharmacodynamic changes associated with aging include impaired homeostasis for electrolytes with angiotensin-converting enzyme inhibitors such as lisinopril and increased sensitivity to anticholinergic side effects from drugs such as meclizine.

3. **Answer: D**
This patient experienced a geriatric syndrome (a fall) and hazards of hospitalization (decline in organ systems and function) seen with many elderly patients. At this time, she has several risk factors for another fall, including a history of falls, diseases such as diabetes and hypertension, dizziness, and use of several drugs. An assessment of gait and balance would help determine the severity of her risk.

4. **Answer: C**
Efforts to maintain bone and muscle strength are more important for this patient than primary prevention of cardiovascular disease with simvastatin or lisinopril. Most older people do not consume a diet rich in vitamin D, have less sun exposure, and are more likely to be deficient in vitamin D, which is a risk factor for falls and reduced muscle strength. Furthermore, naproxen is not a good alternative for N.H. because of her poor renal function.

5. **Answer: B**
This patient has a positive screen for mild dementia. However, when evaluating her cognitive loss, it is important to limit the use of any drug that could contribute to confusion. Anticholinergics such as tolterodine can cause confusion, so it would be best to discontinue this agent and reassess cognition before beginning treatment for AD. Also, before beginning vitamin B12 injections, the patient should first have laboratory evidence of deficiency. There is no reason to anticipate that hydrochlorothiazide would cause her cognitive decline, so a switch to lisinopril is not indicated at this time.

6. **Answer: B**
Rivastigmine is a potent inhibitor of acetyl and butyryl cholinesterase, leading to significant cholinergic adverse effects such as nausea, vomiting, and diarrhea. However, use of the transdermal delivery system generates even plasma concentrations and lessens the incidence of cholinergic adverse effects. Because the maintenance dose has been achieved with rivastigmine 12 mg, this man can switch to the patch that delivers 9.5 mg/day.

7. **Answer: B**
Over 3 years, this patient has declined only 4 points on her MMSE, which suggests a treatment response to donepezil. Furthermore, the patient is still able to live at home with her husband, and she has maintained some function in her basic ADLs. However, she has failed a higher donepezil dose, and there is no evidence that retrying it later is useful. Switching from one cholinesterase inhibitor to another has not been shown effective. Because she has benefited from donepezil use, she should not abruptly discontinue it. Some, but not all, clinical trials with memantine show an additional treatment response when memantine is added to donepezil therapy. When the benefits, risks, and costs have been openly discussed and family preferences are to consent to therapy, a time-based trial is reasonable. Memantine should be initiated at 5 mg daily. Donepezil can be evaluated for tapering after memantine titration is achieved. Vitamin E has shown no effect in large prospective trials of AD and should not be initiated.

8. **Answer: C**
Patients in the late stages of dementia (as evidenced by an MMSE of 5/30) would be unable to cooperate for administration of the Geriatric Depression Scale. The Functional Assessment Staging Test may help identify prognosis but would not benefit her in the management of her BPSD. The MoCA might validate the findings of the MMSE but would not help in management of BPSD. The Neuropsychiatric Inventory would provide
an objective baseline of BPSD so that interventions implemented could be assessed for effectiveness with a reevaluation.

9. Answer: A
Adding quetiapine would probably result in sedation and increase her risk of mortality. Although the behavior might decrease during periods of sedation, a chemical restraint is inappropriate for behavior not likely to harm the patient or others, and the behavior often returns when the patient adjusts to or develops a tolerance for the sedative properties. Citalopram does not have much evidence of effectiveness in the literature for symptoms besides depression. Television shows often confuse patients with severe AD because they cannot follow the activities or the plot and become frustrated. A behavioral approach with music therapy is the best method to try in this patient.

10. Answer: C
This patient shows symptoms of urge incontinence. There is some evidence that darifenacin, a selective muscarinic blocker, does not worsen cognition, and it would be preferred to tolterodine in this patient with MCI. Bethanechol is an option for overflow incontinence and could worsen her urge symptoms. Pelvic floor exercises are best used in stress incontinence.

11. Answer: C
Pharmacologic therapy targeted at reducing urethral sphincter pressure has proved effective in reducing BPH symptoms. Tamsulosin is an α-adrenergic blocker with more specific activity for the genitourinary system. Given that the patient already has low normal blood pressure, tamsulosin would be preferred to terazosin. Orthostatic hypotension can still occur with all α-adrenergic blockers, so patients should be monitored when therapy is initiated. Finasteride, an α-reductase inhibitor, and combination therapy with these agents are recommended when there is evidence of large prostate size. Saw palmetto is not recommended in combination with 5-α-reductase inhibitors because it may reduce the efficacy of the reductase inhibitors.

12. Answer: B
The American Geriatrics Society recommends treatment with opioids for OA when older patients do not respond to initial therapy with acetaminophen. The NSAIDs and COX-2 inhibitors are seldom considered when a thorough assessment of the patient shows that the risk of treatment (GI bleeding and renal disease) does not outweigh the potential benefit. Glucosamine can be added to this patient’s medication regimen; however, even if effective, it will not provide immediate pain relief.

13. Answer: A
This woman has indicators of a poor prognosis with rheumatoid arthritis (positive RF, many symptoms) and has not responded to methotrexate therapy. Although the next treatment step is not entirely clear, her best choices are between double or triple combination DMARD therapy and a biologic agent. Leflunomide or hydroxychloroquine would not be recommended as monotherapy for someone who has not responded to methotrexate. Etanercept has a response in 60%-75% of patients whose therapy with methotrexate has failed. Glucocorticosteroids are used as adjunctive therapy for the first several months of treatment with a disease-modifying agent and would not be adequate treatment at this time.
1. Answer: A
Diazepam is a long-acting benzodiazepine that can accumulate in older patients, resulting in excessive lethargy, sedation, and unsteady gait, and the patient admits taking it every night over the past week. A worsening of the patient’s depression is evident with the recent bereavement; however, that would not explain the unsteady gait. Lisinopril is not likely to cause this problem with his blood pressure at target.

2. Answer: C
In older patients, the volume of distribution of lipidsoluble drugs such as diazepam is increased, not decreased. In addition, changes in metabolism through phase I (oxidation) are diminished. Diazepam tends to accumulate with reduced capacity for elimination, resulting in excessive sedation and an increased risk of falls in older patients.

3. Answer: B
The patient is not experiencing any symptoms of hypotension; therefore, no changes in her metoprolol therapy are warranted. Insufficient information is provided to determine the need to add memantine at this time. Adding vitamin D to this resident's regimen, given her deficient serum levels, may help reduce falls. Adding calcium carbonate may be helpful but will not reduce fall risk.

4. Answer: A
The U.S. Preventive Services Task Force recommends aspirin use in women 55–79 years of age to prevent ischemic strokes in women with a low risk of GI bleeding. This patient has no history of GI bleeding and would probably benefit from low-dose aspirin. Increasing the dose of metoprolol or adding hydrochlorothiazide might increase the risk of falls without providing additional risk reduction at her current BP. Similarly, increasing her atorvastatin dose might marginally improve her low-density lipoprotein cholesterol but would not significantly change her risk of ischemic stroke. Furthermore, given this patient’s age over 75, the newest guidelines for prevention of cardiovascular disease do not recommend titration above moderate intensity statin therapy.

5. Answer: B
An initial trial of acetaminophen at doses less than 3 g/day is a reasonable option for frail patients with OA pain. Ibuprofen and tramadol would be alternatives when more conservative medications have failed a trial of 1–2 weeks. As-needed hydrocodone/acetaminophen should be used cautiously in older patients who have significant osteoarthritic pain and are unable to tolerate other drugs.

6. Answer: D
All cholinesterase inhibitors have similar efficacy. The rivastigmine transdermal patch is better tolerated than the oral dosage formulation. Donepezil tends to be better tolerated than the other oral cholinesterase inhibitors. Doses of cholinesterase medications should be titrated slowly to prevent GI upset. The initial dose of donepezil is 5 mg daily at bedtime, and for galantamine ER, the dose is 8 mg once daily. The rivastigmine patch 4.6 mg is the appropriate initial starting dose. Memantine has not shown any beneficial effect in maintaining cognitive function as measured by MMSE scores.

7. Answer: A
This patient’s current fasting blood glucose of 65 mg/dL and A1C value of 5.6% should prompt the pharmacist to request glipizide discontinuation. The recommendation for A1C goal for older patients with several comorbid conditions is to keep it above 7.5%. The goals of therapy are to prevent hypoglycemia in older patients at greatest risk of this adverse drug reaction. There is no rationale for reducing the dose of carvedilol, and given a normal basic metabolic panel and her blood pressure, reducing potassium chloride or discontinuing lisinopril is not indicated at this time.

8. Answer: D
There is no evidence at this time that would support increasing the dose of donepezil to 23 mg to manage behavioral symptoms of dementia. The off-label use of atypical antipsychotic medications in patients with behavioral symptoms of dementia should be reserved for patients who pose a danger to themselves or others or experience hallucinations or delusions that are stressful to them. Adding acetaminophen to treat possible pain
that could be causing T.W.’s behavior should be tried before more aggressive strategies.

9. Answer: A
Any new symptom of UI in an older adult should be thoroughly evaluated to determine whether there is a reversible cause. Infection, or the “I” in the mnemonic DRIP, may be the cause of the new symptoms in this patient. Urinalysis would be the most appropriate intervention to treat this reversible cause of incontinence. Tolterodine is used in urge incontinence that does not respond to an adequate pelvic floor muscle trial. Duloxetine has been used off-label for stress incontinence. Pelvic floor muscle exercises or Kegel exercises should be first-line therapy for stress, urge, or mixed incontinence in women.

10. Answer: C
In this patient with comorbid conditions of hypertension and BPH, the choice of α-blockers is based on the adverse effect profiles. This patient has an elevated PVR volume, so changing tamsulosin to terazosin might achieve a reduction in both BP and urinary retention. Increasing the atenolol dose would address just the increased BP, with no effect on the current problem of acute urinary retention. The patient is receiving moderate doses of controlled-release opioid, so reducing the hydromorphone dose for breakthrough pain is unlikely to help reduce the obstruction that may be worsened by the narcotics.

11. Answer: C
This patient is currently receiving 3 g of acetaminophen daily without adequate response, so a change in treatment is indicated. Diclofenac gel may provide adequate relief without systemic side effects. He has a history of GERD and is on aspirin, so naproxen is not preferred. Evidence indicates that initially GI bleeding is reduced with celecoxib, but this is not maintained with chronic use. Methylprednisolone injection is more aggressive treatment and may be considered if topical diclofenac is ineffective.

12. Answer: D
In patients with recurring rheumatoid arthritis symptoms, moderate disease activity, and presence of a poor prognostic factor (anti–cyclic citrullinated peptides), adding sulfasalazine and hydroxychloroquine to methotrexate follows guidelines from the 2012 American College of Rheumatology recommendations update for the treatment of rheumatoid arthritis. Specifically, they recommend either double or triple combination DMARD therapy for patients with an inadequate response to methotrexate. Prednisone may be used as bridge therapy, but continued therapy may not be supported by a risk-benefit analysis. Changing the administration of methotrexate from the oral route to the intramuscular route would not confer any significant advantage in this case. Similarly, changing methotrexate to monotherapy with leflunomide would not provide any significant benefits.

13. Answer: B
Patients with a low bone mass and a T-score of –2.5 or less at the femoral neck, total hip, or lumbar spine, with a 10-year probability of having a major osteoporosis-related fracture of 20% or greater on the basis of the World Health Organization Fracture Risk Assessment Tool would benefit from an osteoporosis medication. This patient’s risk fits that category, and she is already on adequate calcium and vitamin D. Adding a bisphosphonate is the most appropriate intervention at this time. Adding raloxifene or teriparatide is inappropriate for the treatment of this patient right now but might be appropriate care in a different scenario.