

Case Based approach to Optimal Pharmacotherapy

Best Practices 2022

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Disclosures

- Naushira Pandya is on an advisory board for Sanofi, speaker for Lilly, and Astra Zeneca
- Meenakshi Patel has multiple research grants from several pharmaceutical companies and speaker for TEVA, Lilly, Urovant, Janssen

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Objectives

- Incorporating guideline-based therapy to optimize pharmacotherapy in patients with multi-morbidity
- Simplification of treatment regimens to reduce adverse events
- Improving outcomes through critical review of medications and describing

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Case 1
The problem with hyperkalemia

- A 68 y-old male with a history of type 2 diabetes, CKD (G3a A2), chronic pancreatitis, osteoarthritis, and anemia, began to develop repeated episodes of hyperkalemia over a 3-month period accompanied by weakness
- Current medications:
 - Insulin degludec QD
 - Dulaglutide 3mg SQ weekly
 - Losartan 50 mg QD
 - Amlodipine 10 mg QD
 - Rosuvastatin 20 mg QHS
 - Ibuprofen 400 mg BID PRN
- Laboratory tests: K 5.6 mEq/L, eGFR 47 ml/min/1.73m², BUN 22 mg/dL, Creat 1.2 mg/L, CO₂ 29 mEq/L, A1C 7.9%, U microalb/creat 260 mcg/mg creat

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Question 1

What is the most likely cause of hyperkalemia in this patient?

- A. Excessive intake of potassium rich foods
- B. NSAID use
- C. Chronic kidney disease
- D. Use of an angiotensin receptor blocker

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Question 2

What is the best long-term strategy to manage hyperkalemia in this patient?

- A. Stop losartan
- B. Intermittent doses of sodium polystyrene (Kayexalate)
- C. Low potassium diet
- D. Scheduled doses of sodium-zirconium cyclosilicate (Lokelma)

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Case 1 Management

- Initially he was treated with several doses of 15 g **sodium polystyrene**, but hyperkalemia recurred, and losartan was discontinued
- Subsequently treated with sodium-zirconium cyclosilicate 10 g PO 3 times a day for 48 h, followed by 10 g daily
- The patient decreased the frequency of this to 3 times a week after potassium levels reached 4.5-5 mEq/L
- Losartan was resumed after discussion with his nephrologist and urine microalbumin level dropped to 114 mcg/mg creat

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Differential diagnosis of hyperkalemia by pathogenesis (1of2)

<p>INCREASED INTAKE (URINE K > 20 mEq/L)</p>	<ul style="list-style-type: none"> High K foods with underlying CKD Salt substitutes K supplements routinely with diuretics K-rich parenteral nutrition formulas
<p>DECREASED RENAL EXCRETION (URINE K < 20 mEq/L)</p> <p><u>Mechanisms:</u> Aldosterone downregulation Aldosterone blockade Sodium channel blockade Na-K ATPase blockade</p>	<ul style="list-style-type: none"> K-sparing diuretics (spironolactone) ACEI, ARBs NSAIDs heparin Trimethoprim-sulfamethoxazole Cyclosporine and tacrolimus Chronic kidney disease Type 4 renal tubular acidosis (T2 DM, sickle cell disease, adrenal insufficiency, lower urinary tract obstruction (BPH or neurogenic bladder)

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Differential dx of hyperkalemia by pathogenesis (2of2)

<p>SHIFT OUT OF THE CELLS (URINE K > 20 mEq/L)</p>	<ul style="list-style-type: none"> Metabolic acidosis mostly due to inorganic acids Red cell transfusion β-blockers, methotrexate, digitalis Succinylcholine use in anesthesia Insulin deficiency and hyperglycemia Rhabdomyolysis, tumor lysis syndrome Neuroleptic malignant syndrome following haloperidol
<p>PSEUDOHYPERKALEMIA</p>	<ul style="list-style-type: none"> Prolonged tourniquet or repeated fist clenching Severe leukocytosis and thrombocytosis Traumatic venipuncture Delay in processing the blood sample in lab

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Predictors of the development of hyperkalemia in patients using ACE inhibitors

- Retrospective study of 119 patients in a renal clinic on ACEI
- The mean baseline serum Cr was 2.3 ± 1.2 mg/dl, and the CrCl was 50 ± 27.5 ml/min
- 46 (38.6%) developed hyperkalemia (mean K 5.68 ± 0.3 mEq/l)
- Diabetes and serum creatinine were the main predictors of hyperkalemia (not GFR or serum HCO_3)
- Also common in HF patients on guideline-recommended inhibitors of the renin-angiotensin-aldosterone system (RAAS)
- RAASI therapy is well known to reduce the risk of death and hospitalization in patients with HF and reduced ejection fraction (HF_rEF).
 - ACEI or ARB with a beta-blocker recommended in patients with HF_rEF.
 - Difficult decision of down-titrating or discontinuing RAAS inhibitors

Ahuja TS et al. Am J Nephrol 2000;20:268-272
Kumar R, et al. The Am J Managed care (Feb 2017, 23(2Suppl):527-536)

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Percentage mortality by prior RAAS inhibitor therapy

Epstein et al. AJMC Sept 2015

Humedica database N=205,108 pts
Max RAAS i dose in 19-26%
Submax RAAS i dose in 5-65%
Discontinued in 14-16%

Cardiorenal adverse event/mortality and mortality occurred in 34.3% and 11.0% of patients who discontinued RAAS inhibitors,

Category	Maximum Dose (%)	Submaximum Dose (%)	Discontinued (%)
CKD Stages 3-4	9.8%	20.3%	22.4%
Heart Failure	13.7%	27.7%	20.1%
Diabetes	5.0%	10.1%	13.1%
Total Population	4.1%	9.2%	11.0%

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Case 2 Fracture while on osteoporosis treatment

- An 80 y-old woman with a history of atrial fibrillation, hypothyroidism, hyperlipidemia, vestibular dysfunction, and osteoporosis, developed a transverse fracture of the left femoral shaft in 2021 while getting out of her car.
- She made a good functional recovery after surgical fixation
- Current medications:
 - Clopidogrel 75 mg QD
 - Levothyroxine 100 mcg QD
 - Pravastatin 40 mg QHS
 - Vitamin D3 1000 U QD
 - Calcium 500 mg BID
 - (Alendronate 70 mg Q week discontinued after fracture; had used if for 8-9 y with one drug holiday. She did not wish to consider other treatments for osteoporosis discussed at various visits since 2017)
- Laboratory tests: Ca 9.3 mg/dL, 25 OH Vit D 35 ng/mL, TSH 0.6 mIU/L,

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Question 3

What is the potential cause of this patient's femoral shaft fracture?

- A. Vitamin D insufficiency
- B. Non-adherence with alendronate therapy
- C. Overtreatment with levothyroxine
- D. Long-term use of a bisphosphonate

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Question 4

What is the optimal strategy for treating this patient's osteoporosis?

- A. Continue calcium and vitamin D only
- B. Denosumab every 6 m
- C. Romososumab every m for 1 y
- D. No treatment; reassess bone density in 2 y

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Case 2 Management

- DXA performed in 2019 and 2021 just prior to the femoral fracture, were compared
- She was offered treatment with denosumab or romososumab, but declined it for over 12 m due to concerns of potential adverse events
- She agreed to treatment with denosumab in 2022 after review of her FRAX scores and researching her treatment options
- The dose of levothyroxine was reduced to 88 mcg QD due to low TSH


Year	L1 T score	Fem neck T score	Forearm T score	FRAX 10-yr probability
2019	-2.5	-2.0	-3.0	No FRAX scores
2021	-1.7	-1.8		MOF 36.3%, Hip fx 21.9%

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Atypical femur fractures: rare complication of bisphosphonate therapy

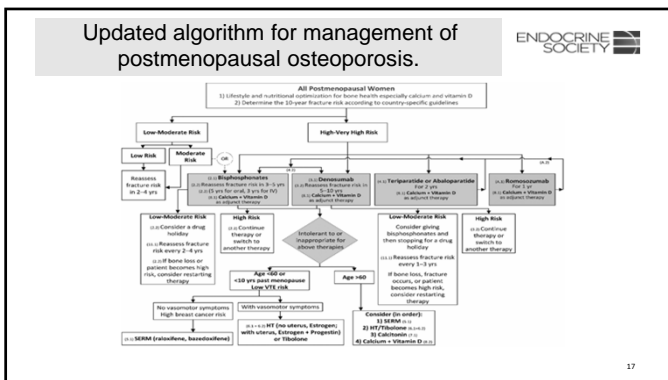
- Usually, median treatment for 7 y
- Treatment with bisphosphonates for up to 5y is typically **not** associated with atypical fractures and is not a reason to defer bisphosphonate therapy in women who are at high risk
- Prolonged therapy can lead to oversuppression of bone turnover ("frozen bone") and increased skeletal fragility causing stress fractures
- In a metaanalysis, the risk of atypical fracture was increased in bisphosphonate users (risk ratio 1.70), low absolute risk (3.2-50 cases/100,000 person years)
- Patients have prodromal symptoms, including dull or aching pain in the groin or thigh



Gedmintas L, Solomon DH, Kim SC SO. J Bone Miner Res. 2013;28(8):1729.

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Case 3 Progressive CKD

- A 76 y-old woman with type 2 diabetes complicated by CKD 5, peripheral neuropathy, anemia, HFpEF, HTN, recurrent UTI, and depression, complained of increasing fatigue and somnolence
- She had not been seen in the clinic for 4 m
- She was cheerful, clinically euthyroid, and did not have any decline in muscle strength. There was no evidence of confusion, or de-compensation of heart failure
- Current medications:
 - Hydralazine 50 mg TID, nifedipine ER, labetalol BID
 - Lisinopril 20 mg QD
 - Furosemide 40 mg PRN edema
 - Gabapentin 300 mg TID
 - Novolin 70/30, 52 U in am and 10 U in pm
 - Sertraline 100 mg QD
 - Trimethoprim sulfamethoxazole BID at least every 2 mth for UTI
- Laboratory tests: eGFR 15 ml/min/1.73 m² (was 34, 2 months ago), Hb 10.5 g/dL, K 4.7 mEq/L, TSH 1.9 mIU/L, A1C 6.6%, U microalb/creat 427 mcg/mg creat,

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Question 5

What is the likely cause of her fatigue and somnolence?

- A. Depression
- B. Inappropriate dosing of gabapentin
- C. Hypoglycemia
- D. Decline in renal function

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Case 3 Management

- Metformin was stopped in 2020 after her eGFR dropped to 27 ml/min/1.73 m²
- Freestyle Libre 2 CGM use initiated after a fall
- CGM review showed
 - Episodes of fasting hypoglycemia (50-70 mg/dL) 2-3 times a week
 - Time in Range 52% (BG range 90-200 mg/dL)
 - Hypoglycemia 18%
- Novolin 70/30 doses reduced to 50 U in am and 6U in pm
- Gabapentin dose reduced to 100 mg BID

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Optimizing medication regimen in advanced CKD (4 and 5)

- Gabapentin dose should be reduced
- Trimethoprim sulfamethoxazole dose should be reduced
- Beers Criteria 2019 Table 6

Medication	Cr/CL at which action required	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Trimethoprim-sulfamethoxazole	<30	Increased risk of worsening of renal function and hyperkalemia	Reduce dose if CrCl 15-29 mL/min Avoid if CrCl <15 mL/min	Moderate	Strong
Gabapentin	<60	>95% renally excreted T half 5-7 h Prolonged in CKD	>60 mL/min 30-59: 400-1400 mg/d 15-29: 200-700 mg/d <15: 100-300 mg/d	Moderate	Strong

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Pitfalls in interpretation of A1C: reliability decreased in advanced CKD

<p>A1C can be increased by</p> <ul style="list-style-type: none"> Age (insulin resistance) Race (African American or Hisp) Hypothyroidism Splenectomy Aplastic anemia Polycythemia Hb variants Iron deficiency anemia Metabolic acidosis/uremia <p><small>C. Kim et al. Diabetes Care April 2010 vol. 33 Peacock et al. Kidney International (2008) 7</small></p>	<p>A1C can be decreased by</p> <ul style="list-style-type: none"> Anemia Blood loss, transfusions Abnormal Hb (hemolysis) Hemodialysis and Hct <30% Liver disease Erythropoetin therapy Iron supplements
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Case 4

<ul style="list-style-type: none"> • 86 y.o. female lives alone • 2 recent admissions <ul style="list-style-type: none"> – Exacerbation of CHF – Fall FSBS 69 on admission • ECF admission <ul style="list-style-type: none"> – Strengthening – Prevention of readmissions – Social issues 	<ul style="list-style-type: none"> • 1 story house with basement • 2 children live in town • She is responsible for most meals • SLUMS 25/30 • No other healthcare support
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Medications

<ul style="list-style-type: none"> • Glimepiride 2 mg daily • Basal Insulin 14 units daily • SSI 2-4 units with meals • Atorvastatin 40 mg daily • ASA 81 mg daily • Colace 100 mg daily • Lisinopril 10 mg daily • Furosemide 40 mg daily • Hydrocodone/APAP 5/325 mg tid • NaCL 1 gm daily • Metoprolol tartrate 25 mg bid 	<p>vs</p> <ul style="list-style-type: none"> – BP 112/68 P70 R 14 O2 92% – Weight 154 Dry weight 138 – 3 + edema on exam – Crackles in lung bases <p>Labs</p> <p>Na 132 K 3.8 Co2 29 Cl 98 BUN 24 Cr 1.3 GFR 56 CXR congestion at bases mild cardiomegaly Echo LVEF 40% no valvular abnormalities</p>
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Question 6

What would you do with the SSI?

- A. Continue it
- B. Stop it in 3 days
- C. Stop it in 5 days
- D. Stop it on admission

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2019 Beers Criteria; Endocrine Society

American Geriatrics Society 2019 Beers Criteria Update Expert Panel

Therapeutic category	Rationale	Recommendation	Quality of evidence	Strength
Insulin, sliding scale	Higher risk of hypoglycemia without improvement in hyperglycemia regardless of care setting; in the absence of basal basal insulin	Avoid (More glucose variability Reactive approach)	Moderate	Strong
Glyburide	Higher risk of severe prolonged hypoglycemia in older adults			

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HYPOGLYCEMIA

Table 6.4—Classification of hypoglycemia

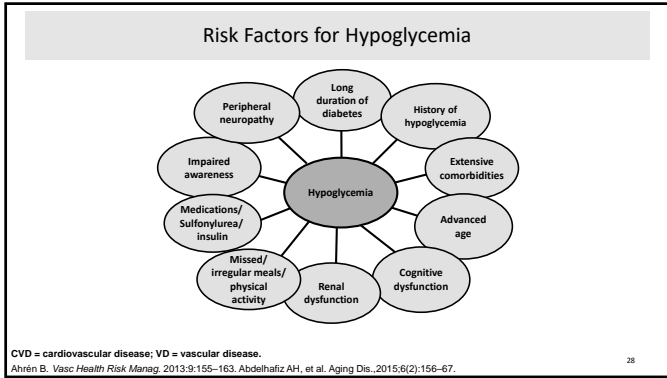
Glycemic criteria/description

Level 1	Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia

Reprinted from Agiostratidou et al. (51).

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Impact of hypoglycemia in the elderly

- Hypoglycemia can worsen neuropathic pain
- Likelihood of falls, dizziness can increase
- Cognitive impairment increases the likelihood of hypoglycemia
- **But** hypoglycemia can worsen cognitive impairment
- Increase in cardiovascular events, hospitalization and total mortality; (HR 2.48 [1.41–4.38]) whether clinically mild or severe hypoglycemia
- Mean cost per hypoglycemia episode: **\$2602**

Ligthelm J *AM Geriatr Soc* 2012 Aug;60(8):1564-70. doi: 10.1111.
Pai-Feng Hsu et al. *Diabetes Care* 2013 Apr; 36(4)

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Question 7

How would you manage her diabetes?

- Keep the regimen the same
- Start metformin
- Stop all current DM meds and start SGLT2 Inhibitor
- Stop all current DM meds and start GLP1 RA
- B C and D

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Major causes of hyponatremia

Disorders in which ADH levels are elevated
Effective circulating volume depletion
True volume depletion
Heart failure
Cirrhosis
Thiazide diuretics
Syndrome of inappropriate ADH secretion, including reset osmostat pattern
Hormonal changes
Adrenal insufficiency
Hypothyroidism
Pregnancy
Disorders in which ADH levels may be appropriately suppressed
Advanced renal failure
Primary polydipsia
Beer drinker's potomania

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Major Causes of Hyponatremia

Hyponatremia with normal or elevated plasma osmolality
High plasma osmolality (effective osmols)
Hyperglycemia
Mannitol
High plasma osmolality (ineffective osmols)
Renal failure
Alcohol intoxication with an elevated serum alcohol concentration
Normal plasma osmolality
Pseudo hyponatremia (laboratory artifact)
High triglycerides
Cholestatic and obstructive jaundice (lipoprotein-X)
Multiple myeloma
Absorption of irrigant solutions
Glycine
Sorbitol
Mannitol

ADH: antidiuretic hormone. UpToDate® 35

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Evaluation of Hyponatremia

- Good history and physical examination – assess volume status (skin turgor, ocular pressure)
- Medication history (e.g., thiazides, ACEI or ARBs, SSRIs)
- Serum osmolality (measured) to decide tonicity
 - **Effective osmolality = $2Na + 2K + \text{glucose}/18 + \text{BUN}/2.8$ (in millimoles per liter)**
- Urine osmolality (simultaneous)
- Urine sodium (spot sample)-off diuretics for 24h
- Hyperglycemia or renal impairment? (Glucose, BUN, Creat)
- Hypertriglyceridemia or hyperproteinemia? (i.e., rule out pseudo hyponatremia)
- Assess clinically whether patient has evidence of hypothyroidism or adrenal insufficiency

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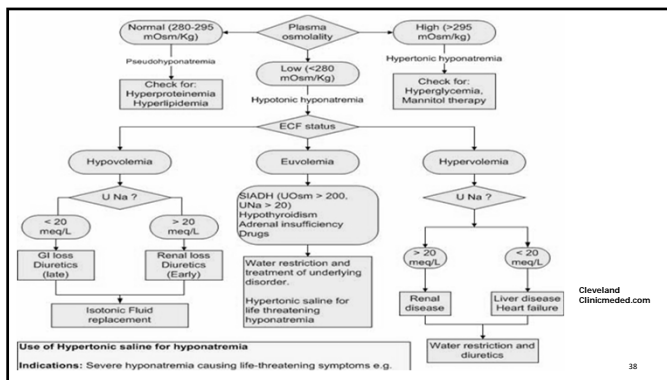
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Evaluation...

- If hyperglycemia is present, the serum Na should be corrected for the effect of glucose to exclude hypertonic hyponatremia
- Evaluated for possible isotonic or hypertonic hyponatremia
 - Patients who have had recent surgery utilizing large volumes of electrolyte-poor irrigation fluid (e.g., prostate or intrauterine procedures)
 - Patients treated with mannitol, glycerol or IVIG
 - Patients with lipemic serum
 - Patients with obstructive jaundice
 - Patients with a known plasma cell dyscrasia

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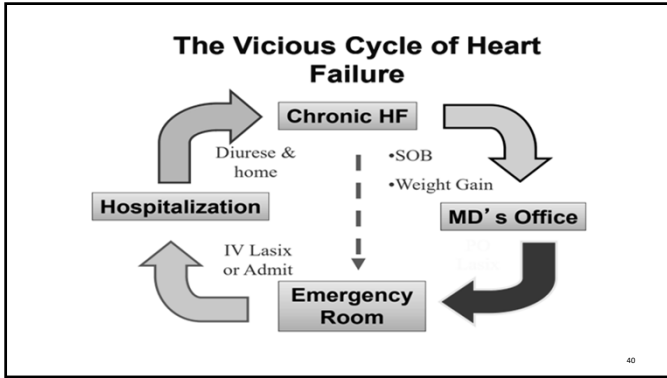
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Question 9

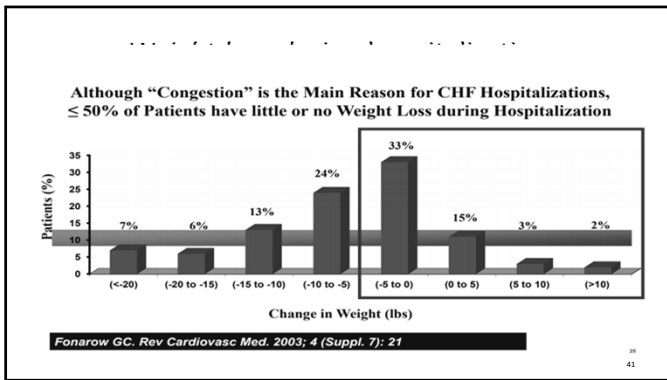
- How would you manage the heart failure?
- Stop the salt tablets
 - Consider switching the ACEi to ARNI
 - Add MRA
 - Add SGLT2i
 - All of the above

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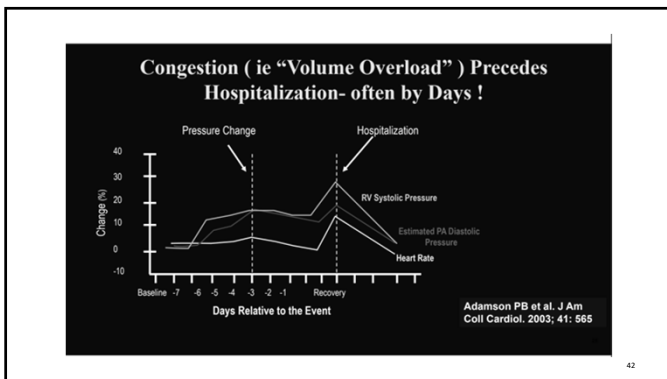
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Case 5

- 78-year-old female with history of hypertension, CAD, hyperlipidemia, multiple strokes and advanced osteoarthritis. In addition, she has hypothyroidism, anxiety and bipolar disorder. She has a history of hallucinations, and lives by herself. Her daughter is supportive.
- She was admitted to your facility following a right total knee arthroplasty for rehabilitation
- She is a non-smoker and consumes alcohol rarely.
- Vital signs: Blood pressure 117/67 respirations 18/min, temperature 97.9, pulse 97/min, pulse ox 96%
- Labs: Electrolytes normal GFR 110 WBC 8.5 hemoglobin 11.5 hematocrit 34.5 platelets 251

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Medication list

- | | |
|--|--|
| • Cyanocobalamin 1000 mcg daily | • Hyoscyamine sulfate extended release 0.375 mg every 12 hours |
| • Ondansetron 4 mg every 4 hours as needed | • Oxycodone 5 mg every 4 hours as needed |
| • Potassium chloride 40 mEq daily | • Buspirone 10 mg 3 times a day |
| • Calcium 500 mg twice a day | • Fluoxetine 60 mg daily |
| • Levothyroxine 137 mcg daily | • Trazodone 100 mg daily |
| • Omeprazole 20 mg daily | • Olanzapine 7.5 mg daily |
| • Aspirin 81 mg daily | • Tizanidine 4 mg 4 times a day |
| • Pravastatin 20 mg daily | • Atomoxetine 100 mg daily |
| | • Alprazolam 0.5 mg every 8 hours as needed |

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Question 10

- Which of the medications cause concern?
- The combination of a benzodiazepine, a muscle relaxant and an opioid
 - The combination of two activating agents, fluoxetine and atomoxetine and sedating agents, trazodone and alprazolam
 - Antipsychotic in the setting of history of strokes
 - Fluoxetine 60 mg and buspirone 10 mg tid
 - All of the above

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Case 6

- 68-year-old female presented to the hospital with a fall. She sustained right-sided rib fractures. She had a chest tube placed for subcutaneous emphysema.
- She was diagnosed with a urinary tract infection. She had no abdominal pain dysuria or hematuria. She has no fever or chills. Her urine culture grew 10-50,000 E. coli, 10-50,000 Proteus mirabilis and urethral flora. She was treated with cephalexin 500 mg twice a day for 5 days.
- She has a history of constipation, lumbar spondylosis, and is weak on her right side.
- Vital signs are stable
- Labs are stable normal GFR

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Medications

- | | |
|--|--|
| • Ceftin 500 twice a day for 3 more days | • Gabapentin 300 mg 3 times a day |
| • Acetaminophen 650 mg 3 times a day | • Ibuprofen 600 mg 3 times a day |
| • Bisacodyl 5 mg enteric-coated daily | • Lidocaine 4% patch to the rib area daily |
| • Calcium carbonate 500 mg twice a day | • Liothyronine 25 mcg daily. |
| • Citalopram 10 mg daily | • Lisinopril 10 mg daily |
| • Docusate 100 mg daily | • Methocarbamol 500 mg 3 times a day |
| • Polyethylene glycol 17 g daily | • Tramadol 50 mg every 4 hours |
| | • Oxycodone 5 mg every 4 hours as needed |

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Question 11

Did she have a urinary tract infection that needed to be treated with an antibiotic?

- A. Yes
- B. No

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Question 12

How would you treat her constipation?

- A. Continue current regimen
- B. Discontinue docusate and bisacodyl
- C. Increased dose of polyethylene glycol if needed
- D. Discontinue all drugs and replaced with linaclotide
- E. Minimize use of narcotics
- F. All except A

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Ten Medications Older Adults should Avoid or Use with Caution

AGS Health in Aging Foundation

- Non-steroidal anti-inflammatory drugs (caution)
- Digoxin (caution)
- Diabetes drugs: glyburide, chlorpropamide (avoid)
- Muscle relaxants: methocarbamol, cyclobenzaprine (avoid)
- Drugs for insomnia, anxiety: benzos, zolpidem (avoid)
- Anticholinergics: amitriptyline, dicyclomine, etc. (avoid)
- Pain reliever : analgesic meperidine (avoid)
- OTC: diphenhydramine, chlorpheniramine (avoid)
- Antipsychotics, if no psychosis: haloperidol (caution)
- Estrogen pills and patches (avoid)

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The Need to Prescribe Appropriately!

Inappropriate or Over-prescribed	Under-prescribed
Anti-infective agents	ACE inhibitors (diabetes, CKD)
Anticholinergic agents	ACE inhibitors for HF
Benzodiazepines	Angiotensin receptor blockers
H2 receptor antagonists, PPIs	Anticoagulants
Laxatives and stool softeners	Antihypertensives
NSAIDs	Diuretics for hypertension
Sedating antihistamines	β blockers for MI or heart failure
Tricyclic antidepressants for pain	Bronchodilators
Vitamins and minerals	PPIs or misoprostol with NSAIDs
GI antispasmodics	Statins
Sliding Scale insulin	Vitamin D

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Appropriate prescribing in the elderly

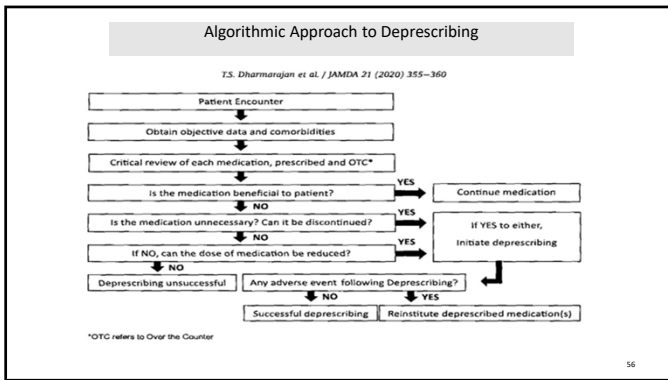
1. Is there an indication for the drug?
2. Is the medication effective for the condition?
3. Is the dosage correct?
4. Are the directions correct?
5. Are the directions practical?
6. Are there clinically significant drug-drug interactions?
7. Are there clinically significant drug-disease/condition interactions?
8. Is there unnecessary duplication with other drugs?
9. Is the duration of therapy acceptable?
10. Is this drug the least expensive alternative compared with others of equal usefulness?

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Deprescribing: Success Can Vary with Drugs

Dharmarajan TS et al. JAMDA. 2020; 21:355-360

Higher Success	Lower Success
Lipid lowering drugs	Antipsychotic agents
Multivitamin –minerals, and iron	Antidepressants
Proton pump inhibitors	Laxatives and stool softeners
Antihistamines	Thyroid hormones
Analgesics	Anxiolytics and hypnotics

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Choosing Wisely
CELEBRATING 10 YEARS
An initiative of the ABIM Foundation

Choosing Wisely:
Some Things Clinicians Should Question

- Do not use antipsychotics as first choice to treat behavioral and psychological symptoms of dementia (AGS)
- Don't use benzodiazepines or other sedative-hypnotics in the old as first choice for insomnia, agitation, delirium (AGS)
- Don't maintain long-term PPI therapy for GI symptoms without an attempt to stop / reduce the PPI at least once per year in most patients (exemption: GI bleeding and Barrett esophagitis) (Canadian Guidelines, 2019)
- Don't prescribe or routinely continue medications for older adults with limited life expectancy without due consideration to individual goals of care, comorbidities, and time-to-benefit for preventive medications (ASCP)

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DISCUSSION

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