Psychiatric Polypharmacy in the Elderly

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Neither Dr. Lee
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have any relevant
disclosures.

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Objectives

- Name three dangers of polypharmacy/prescribing potentially inappropriate medication to the elderly patients with psychiatric concerns
- Be able to identify three common ways in which potentially inappropriate medication prescribing occurs
- Begin to work with cases including a patient story, followed by a medication list. Identify two potentially poor outcomes for each case and two possible steps a prescriber might take to improve the outcome.

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Is there such thing as too many medications in older patients?

Polypharmacy – taking 5 or more prescription medications

- Extremely common in older adults - over 1/3 of adults between 57 and 85 years of age
- Sometimes these medications are safe and necessary - **BUT**
- Sometimes these medications are inappropriate or even harmful

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Why does polypharmacy matter?

- Adherence goes ↓
- Cost goes ↑
- Interactions go ↑
- Overtreatment
- Undertreatment
- Patients can be harmed
- Death

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Most Commonly Prescribed Psychiatric Medications 2018

	Prescriptions	Cost (in dollars)		Prescriptions	Cost (in dollars)
Sertraline	48,999,022	179 million	Quetiapine	20,844,624	273 million
Alprazolam	39, 927,061	105 million	Lamotrigine	15,434,708	731 million
Escitalopram	37,927,061	174 million	Methylphenidate	15,104,867	2.176 billion
Trazodone	34,665,828	115 million	Clonidine	15,058,561	171 million
Bupropion	34,472,232	1.024 billion	Mirtazapine	13,539,039	89 million
D-amphetamine	33,807,381	1.914 billion	Paroxetine	12,874,006	123 million
Fluoxetine	31,190,127	294 million	Amitriptyline	12,843,459	96 million
Citalopram	28,011,615	46 million	Vyvanse	11,569,232	3.594 billion
Duloxetine	26,032,770	378 million	Depakote	11,263,321	363 million
Lorazepam	23,833,390	137 million	Abilify	10,680,324	1.704 billion
Venlafaxine	21,717,245	414 million	Risperidone	10,416,641	485 million

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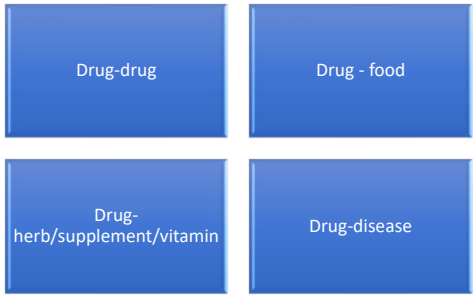
Types of drug interactions



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Types of drug interactions - examples

Drug – drug
- Fluoxetine – Risperidone
  - Fluoxetine can increase blood levels of Risperidone due to inhibition of CYP 2D6

Drug – Food
- Buspirone with grapefruit juice
  - Grapefruit juice inhibits CYP 3A4, which metabolizes Buspirone and can cause serotonin syndrome

Drug – Herb/supplement/vitamin
- St. John's Wort and SSRI's
  - St. John's Wort – an over-the-counter herb used for depression, menopausal symptoms, and other psychiatric illness. Be sure to ask if patients are taking this as the use of both can cause serotonin syndrome

Drug – Disease
- Lithium (renally excreted) with renal disease
  - Poor excretion can lead to toxicity

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Pharmacodynamic vs Pharmacokinetic interaction

Pharmacodynamic
- What a drug does to the body
- Based upon the mechanism of action of a drug
- Can be additive or antagonistic

Pharmacokinetic
- What the body does to the drug
- Another way to think of it: how quickly and by what process the drug enters and leaves the body

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Pharmacodynamics to consider in elderly

Additive effects	Antagonistic effects
• The utilization of two medications lead to a greater response (intended or otherwise) • *Example - quetiapine (with orthostatic hypotension as a side effect) used with another antihypertensive medication*	• Using medications that may result in lesser response by both drugs • *Example - donepezil (cholinergic) with diphenhydramine (anticholinergic)*

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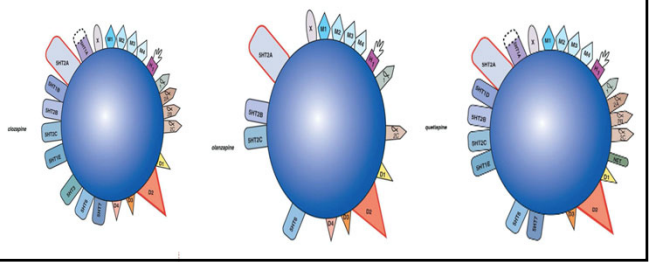
Clozapine, Olanzapine, and Seroquel receptors



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Pharmacokinetics - Cytochrome (CYP) P450 enzymes

Enzymes existing primarily in the liver which increase the water solubility of chemicals to increase their excretion in bile or urine

Main ones to consider for psychiatry include: 1A2, 2B6, 2C9, 2C19, 2D6, 3A4

Different gene expression of these enzymes can make an individual more quickly or slowly excrete them

- Extensive metabolizer (expected drug clearance)
- Ultrarapid metabolizer (fast drug clearance)
- Poor Metabolizer (slow drug clearance)

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Pharmacokinetics continued

Inhibitors	Inducers	Substrate
• When a drug is bound more tightly to a given enzyme than another, making the metabolism of the unbound drug slower • Example strong inhibitors: fluvoxamine, fluoxetine, fluconazole, ketoconazole	• When a drug stimulates the liver to make extra enzyme, expediting the clearance of the affected drug • Example strong inducers: rifampin, phenytoin, phenobarbital, carbamazepine	• A drug that is biologically altered to a metabolite • Example: risperidone to paliperidone (risperidone with a hydroxy group)

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Pharmacokinetic changes in older adults

Absorption	• A decrease in small bowel surface area • slower gastric emptying • higher gastric pH • *can all decrease medication absorption*
Distribution	• Increased total fat and decreased total body water • *Lipophilic drugs will have longer half lives*
Hepatic metabolism	• CYP Enzyme activity decreases with age • First pass metabolism decreases by roughly 1%/year after age 40
Renal Elimination	• After 40 years of age, GFR decreases approximately 8 units/decade

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Clozapine pharmacokinetics and pharmacodynamics

Mainly D2 antagonist, 5-HT2a antagonist, Alpha adrenergic antagonist

1A2 and 3A4 substrate

Via Induction of 1A2, tobacco decreases serum clozapine levels approximately 50%! (from hydrocarbons from smoked plant matter)

- Nicotine replacement products do not induce 1A2 induction (gum, patch, etc.)

Notable 1A2 inhibitors to consider: Ciprofloxacin

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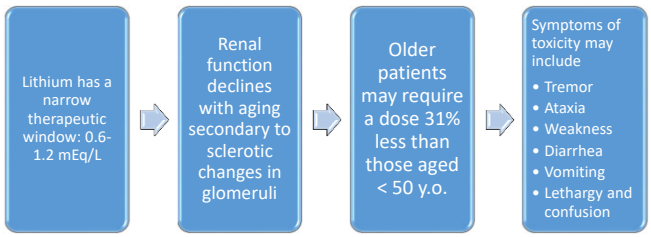
Lithium in geriatric patients



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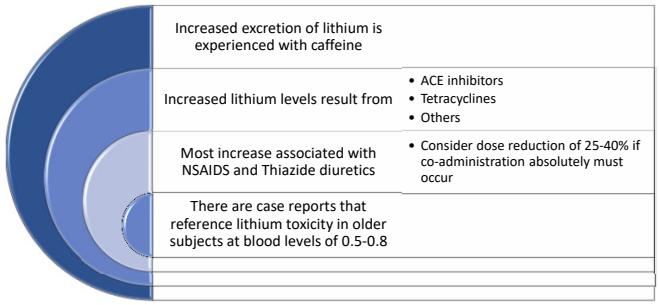
Lithium – drug interactions



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Beers Criteria – American Geriatrics Society

A set of pharmacologic factors for a drug that make certain drugs riskier to use in geriatric patients

- A good tool to reference to find potentially inappropriate medications being used in older adults

Arranged by class with associated quality of evidence, and strength of recommendation

Includes rationale for recommendations for each class of medication

Not just psychiatric medications are included

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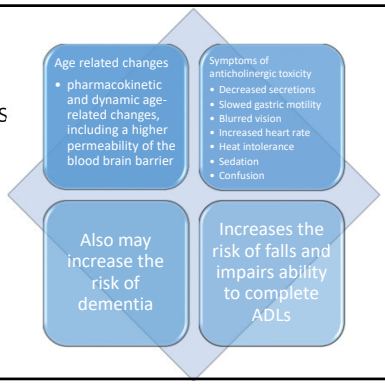
Anticholinergics in the elderly



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What are the anticholinergic meds to watch out for? The Anticholinergic Burden Scale

Antidepressants: paroxetine, tricyclics

SGAs: clozapine and olanzapine

Antihistamines: hydroxyzine, diphenhydramine

Anticholinergic: oxybutynin, benztropine, trihexyphenidyl, scopolamine

Muscle relaxants: orphenadrine, cyclobenzaprine

Categorical Scoring:
- Possible anticholinergics include those listed with a score of 1; Definite anticholinergics include those listed with a score of 2 or 3

Numerical Scoring:
- Add the score contributed to each selected medication in each scoring category
- Add the number of possible or definite Anticholinergic medications

Notes:
- Each definite anticholinergic may increase the risk of cognitive impairment by 46% over 6 years. [3]
- For each on point increase in the ACB total score, a decline in MMSE score of 0.33 points over 2 years has been suggested. [4]
- Additionally, each one point increase in the ACB total score has been correlated with a 26% increase in the risk of death. [4]

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Antihistamines in the elderly

Antihistamines are anticholinergic	Examples
• 2019 Beers Criteria recommends avoidance • Tolerance can develop when used as hypnotics	• Diphenhydramine • Hydroxyzine • Meclizine • Chlorpheniramine • And others… many of which are available over the counter

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Benzodiazepines and Z-drugs in the elderly

2019 Beers criteria recommends avoidance

Geriatric patients are more sensitive to these medications, and increase the risk of falls, delirium, cognitive impairment, motor vehicle accidents

Psychotherapy works BETTER than these drugs for both anxiety and sleep!

Benzodiazepines
- Alprazolam (Xanax)
- Lorazepam (Ativan)
- Temazepam (Restoril)
- Oxazepam (Serax)
- Clonazepam (Klonopin)
- Diazepam (Valium)

Z-Drugs – *nonbenzodiazepine receptor agonist hypnotics*
- Eszopiclone (Lunesta)
- Zaleplon (Sonata)
- Zolpidem (Ambien)

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Delirium

Acute alteration in sensorium, fluctuating in nature, normally worse in the evening (example: sundowning)

- Sensorium: the brain's interpretation, processing, and ability to concentrate on the individual's surroundings

Rate of delirium while hospitalized is as high as 14-56%

- Elderly ICU patients, the rate is as high as 70-87 %
- Many possible causes: including infection, inflammation, medications, etc.
- More common for visual rather than auditory hallucinations to be present
- If as-needed medication must be utilized for agitated/aggressive behavior during this time of altered sensorium, opt for medication with less anticholinergic effects, such as Haldol

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Table 3. Summary of Risk Factors for Delirium

Predisposing factors
Comorbidities
- Alcoholism
- Chronic pain
- History of baseline lung, liver, kidney, heart, or brain disease
- Terminal illness

Demographic factors
- Age older than 65 years
- Male sex

Geriatric syndromes
- Dementia
- Depression
- Elder abuse
- Falls
- History of delirium
- Malnutrition
- Polypharmacy
- Pressure ulcers
- Sensory impairment

Premorbid state
- Inactivity
- Poor functional status
- Social isolation

Precipitating factors
Acute insults
- Dehydration
- Fracture
- Hypoxia
- Infection
- Ischemia (e.g., cerebral, cardiac)
- Medications
- Metabolic derangement
- Poor nutrition
- Severe illness
- Shock
- Surgery
- Uncontrolled pain
- Urinary or stool retention

Environmental exposures
- Intensive care unit setting
- Sleep deprivation
- Tethers

Delirium-inducing medications
High risk
- Anticholinergics (e.g., antihistamines, muscle relaxa antipsychotics)
- Benzodiazepines
- Dopamine agonists
- Meperidine (Demerol)

Moderate to low risk
- Antibiotics (e.g., quinolones, antimalarials, isoniazid linezolid [Zyvox], macrolides)
- Anticonvulsants
- Antidizziness agents
- Antiemetics
- Antihypertensives (e.g., beta blockers, clonidine [Catapres])
- Antivirals (e.g., acyclovir [Zovirax], interferon)
- Corticosteroids
- Low-potency antihistamines (e.g., histamine H_1 blockers, urinary and gastrointestinal antispasmod
- Metoclopramide (Reglan)
- Narcotics other than meperidine
- Nonsteroidal anti-inflammatory drugs
- Sedatives/hypnotics
- Tricyclic antidepressants

Information from references 2, 15, 18, and 19.

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What approaches can we take to improve medication regimens?

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Perform stepwise	Reasons/examples	Problems/risks to be found	Actions/simplify if possible
1. Medication reconciliation: an accurate medication list	• Know what patient actually takes • Discover unexpected or unfilled prescriptions	• Discontinued medications • Missing medications • Taking incorrectly	• Stop, modify or initiate appropriate therapy • Patient education
2. Adherence assessment: Identify missed doses	Adherence barriers: complex therapy burden: • 3 or 4 times daily doses • missing bottles • duplicate bottles	• Too many doses of medications daily • Unfilled or perpetuated prescriptions • Unaffordability of medications • Presence of side effects	Simplify regimen burden, use cost effective alternatives; eliminate agent(s) with adverse side effects
3. Identify drug–drug interactions using interaction databases	QT prolongation can be additive CYP interactions can lead to dangerous drug levels (either higher or lower than expected)	Monitor the risk, eliminate when risk outweighs benefit	Select noninteracting agents; choose alternatives with lower risk
4. Drug–disease interaction screen	Lithium in chronic kidney disease Clozapine with seizure d/o	High-risk therapy that exacerbates heart failure, hypoglycemia	Select alternate therapy; monitor for high-risk events
5.Overtreatment: accumulating therapy	Identify duplicate or concomitant therapy result in orthostasis, hypoglycemia	Duplicates, medications with additive side effects resulting in toxicity	Adjust doses, taper therapy; monitor results
6.Identify high risk drugs in older adults	**Sedative/hypnotics, opioids, anticholinergics, benzodiazepines, anxiolytics, hypoglycemics**	Monitoring of high-risk therapy is necessary; survey risk before it begins to outweigh benefit	Reduce or eliminate risk; educate patients about OTC anticholinergic avoidance
7. Undertreated indications or missed therapy. START criteria	Overlooked treatment: CAD without a statin, antiplatelet agent after coronary stenting.	In complex regimen, sometimes an indicated medication has fallen unnoticed	Initiate medications that decrease risk for the patient within goals of care
8. Medication monitoring for efficacy and safety	• Lithium without BUN/Cr • Valproate without LFT's • Levothyroxine without TSH	Medication is fulfilling its purpose/indication; safety monitoring for each medication	Routine labs (TSH), drug levels; assess kidney, liver function
9. Evaluate supplements, herbals, vitamins	Supplements often don't do what their advertisers say they do and sometimes can be dangerous.	Except for recommended supplements such as vitamin D, many supplements are noncontributive	Discuss, simplify, educate patients

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Interaction checkers

- Useful tool to double check safety
- Convenient for those unable to quickly reference a textbook
- Expedites the interaction viewing from an entire drug list perspective, rather than having to look up each drug one-by-one
- A way to see if medications in a patient's regimen can interact with one another
- Several interaction checker applications are easily downloadable to phones, computers, or tablets – we like Micromedex and Epocrates but there are others.

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EMR Interaction checkers alone are NOT enough

Physicians override alerts as much as 90% of the time

- Frequent interaction notifications generated the term "Nuisance alert"
- Three categories make up the majority (78%) of "override reasons"
  - "Will monitor or take precautions"
  - "Not clinically significant"
  - "Benefits outweigh the risks"

How often do you take into consideration the effects of discontinuing medications or smoking cessation?

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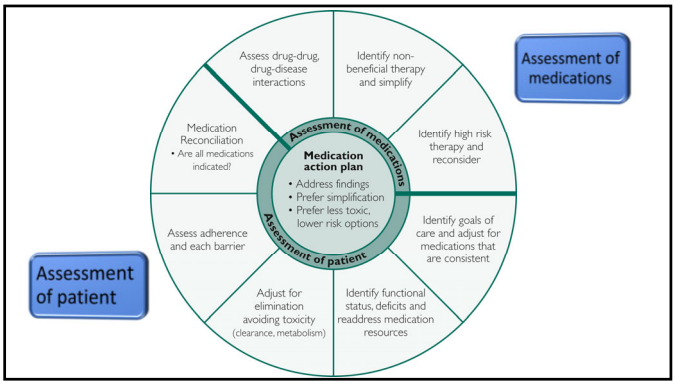

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The SAIL Protocol for Appropriate Prescribing

Simple	• The drug regimen must be as simple as possible • Aim for once-daily regimens
Adverse	• Possible adverse effects of each drug must be clearly understood • Drugs must have a wide therapeutic window unless there is no alternative (Lithium) • Drugs must not interact with other drugs in the regimen
Indication	• The indication for each drug must be clear • Each drug must have a clearly defined therapeutic goal • Each drug must achieve the desired therapeutic goal
List	• The list of drugs must be accurate • The list of drugs must include prescriptions, over-the-counter medications, and herbs or alternative medications • The patient's list must correspond to the physician's list

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Deprescribing – prime candidates

- Benzodiazepines, Z-drugs
- Anticholinergic medications
- Antihistamines
- Multiple meds in the same class (sometimes)
  - Attempt to understand the justification for the original decision to prescribe
- Antipsychotics (sometimes)
  - Be careful of being too quick to remove these
- Herbs/vitamins/supplements (minus vitamin D)
- Medications for primary care examination
  - NSAIDs
  - Hypoglycemics
  - Antihypertensives
  - Statins
  - Opiods

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Tips for discontinuing benzodiazepines and z-drugs

- Explain the benefits and risks of these drugs the first time you discuss them with the patient
  - Risk of fall/broken bones increases in elderly patients
  - Risk of cognitive impairment is significant in elderly patients
  - Daily use of these drugs is associated with tolerance which can be mistaken for a "need" for the drug when anxiety/insomnia happen when a dose is skipped
- Express confidence that with a slow, steady pace, successful d/c of these meds is both desirable and possible
- Daily dose can be cut in half without danger of w/d seizure BUT you can go more slowly in most cases and patient will be more comfortable – reductions of 10-25% of the total dose can be made monthly without difficulty most of the time
- Don't be afraid to increase frequency of prescriptions for patients who are running out of their meds early – every 2 or every 1 week scripts are needed in some patients to keep them on track

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Vignette from geriatric experience – Mrs. A

A 72-year-old female arrives to the emergency department via ambulance from her nursing home due to aggressive behaviors including pushing and striking other residents and staff. She has a diagnosis of major neurocognitive disorder and is confused during the entirety of the evaluation. Staff had noted she was refusing medications the past 5 days which included Depakote and escitalopram. The ED provider calls for admission to the unit with the valproic acid level collected in the ED being 14 (normal range 50-100).

Given that the patient had refused medications, likely making the VPA level low, is other laboratory testing necessary?

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Vignette from geriatric experience – Mr. B

A 65-year-old male is admitted with with prodromal Lewey body dementia and worsening anxiety over the past 2 years secondary to increasing worry about his deterioration from the standpoint of his health/mind as well as about his relationships with family, and his finances. His outpatient provider had given him alprazolam as a prn over this time for which he uses approximately once or twice per day for his anxiety, and he mentions he has not tried other medications to treat his anxiety.

Is there anything that you would like to switch to or add to his medication regimen?

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Vignette from geriatric experience – Mr. C

A 69-year-old male is seen on the inpatient geriatric psychiatry unit. He has a working diagnosis of schizoaffective disorder, depressed type, and his med list when he arrives consists of

- lamotrigine 100mg twice daily
- trazodone 50mg nightly
- mirtazapine 7.5mg nightly
- quetiapine 200 mg daily
- haloperidol 5mg nightly
- vilazodone 40mg daily
- buspirone 10mg three times daily

He is calm, cooperative, and oriented, but with ongoing depressive symptoms, hallucinations, and mentions trouble sleeping during your interview.

What changes could you consider making to his medication regimen?

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Vignette from geriatric experience – Mr. D

A 64-year-old bipolar male is brought to the emergency department by his wife after umpiring a little league game on a hot day this summer. He arrives with in his uniform with chest plate and long pants and socks still on. He is confused, lethargic, tremulous, and drenched in sweat. His wife does not know the medication he takes to manage his bipolar disorder but knows that he has been on it for years, and that the family believes in being "all natural" whenever possible and states this is reflected in the very few medications they take.

What lab do you suspect to be abnormal?

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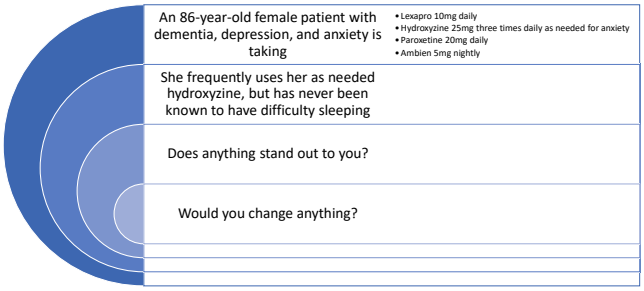
Medication list example – Ms. E



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Question 1

A 75 year old woman, new onset of major depression 3 months ago. Two months ago, she was started on sertraline 50mg qday. At her follow up visit one month ago, the patient states she is somewhat improved but still is experiencing significant symptoms of depression. She does not have side effects. Which of the following is the best course of action?

a. Add escitalopram 5mg qday to the sertraline
b. Add aripiprazole 2mg qday to the sertraline
c. Increase the sertraline to 100mg qday
d. Make no changes and see the patient again in 8 weeks

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Question 2

An 86 y.o. man with schizophrenia diagnosed 60 years ago is increasingly agitated and paranoid despite treatment with Risperdal 4mg qhs that worked well until about 3 months ago. Which of the following is the best course of action?

A. Add quetiapine 50mg TID PRN for agitation
B. obtain basic lab testing UA/CBC/CMP for potential causes of delirium and if negative, add fluoxetine 10 mg qday
C. Add lorazepam 1mg QID PRN for agitation
D. Obtain basic lab testing UA/CBC/CMP for potential causes of delirium and if negative, increase Risperdal to 6mg qhs

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Question 3

You are treating a 67 y.o. woman with obsessive compulsive disorder who is stable on fluvoxamine 150 mg qday. She is in what was reported as a low-speed car accident and started on tizanidine 2mg q 6 hours PRN in the ED for neck pain. Her son calls you later and says her mother is sleeping all day and seems confused when she wakes. She has not been eating or drinking. What could be going on?

A. The patient has a head injury that was not diagnosed in the ED

B. the patient's tizanidine (Zaniflex) level is increased 10 fold secondary to interaction with fluvoxamine

C. The patient has undiagnosed blood loss from an internal injury that was not diagnosed in the ED

D. a, b, or c are all possible

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Question 4

A 75 y.o. male on clozapine 400 mg qhs is admitted to the ICU with pneumonia for a stay that has lasted 5 days. The ICU team is puzzled because the patient seems less awake and alert now than he did when he arrived on the unit. When you speak with his daughter, you find out that the patient was smoking 1.5 packs of cigarettes/day prior to his hospital stay. What is the reasonable course of action?

A. decrease his clozapine dose to 300 mg qhs while he is in the hospital and not smoking

B. Change the clozapine to olanzapine as the clozapine is causing the patient to be obtunded and is thus the unsafe choice

C. Discontinue the clozapine, as it is not needed when the patient is sleepy

D. Add methylphenidate 20mg qday to wake the patient up

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