

Medication-Related Balance Conditions and Falls Risk

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Disclaimers

- I have no conflicts of interest for this topic

Objectives

- Recognize vestibulotoxic drugs by name, uses, and action on the balance system.
- Identify other drugs associated with fall risk by name, uses, and their effect on the body.

Drug Vestibulotoxicity

- These drugs permanently damage the vestibular system
- **Iatrogenic**
 - Adverse effect of medical care
 - Loss of vestibular (or cochlear) function vs. loss of life
- **Therapeutic**
 - A medical strategy
 - E.g. to treat Meniere Disease vestibular symptoms

Aminoglycoside Antibiotics

- Aminoglycoside antibiotics are known to cause permanent vestibulotoxicity and cochleotoxicity at a substantial rate
 - Vestibulotoxicity rate approximately 15%
 - Estimates range widely

Mechanism of Action

- **Protein synthesis inhibitors**
 - Amino acids must be strung together to form proteins
 - The machinery in cells that carries this out is the ribosome
 - Aminoglycosides bind to ribosomes
 - Bind more avidly to bacterial ribosomes than animal cytosolic ribosomes
 - They are different enough despite carrying out same function
 - Inhibit stepping the mRNA through the ribosome
 - An mRNA sequence defining an amino acid sequence cannot be stepped through

Time Course of Aminoglycoside Toxicity

- Various studies show onset range following start of pharmacotherapy
 - Lower end ~week
 - Upper end ~months
 - Onset can be after end of pharmacotherapy
- **Different criteria were used**
 - More sensitive detection would give earlier detection
 - These times would have to be considered rough indication

Aminoglycosides in Use

- amikacin
- gentamicin
- kanamycin
- neomycin
- netilmicin
- paromomycin
- plazomicin
- streptomycin
- tobramycin

Use is Falling

- **Tobramycin is the most prevalent**
 - 376th most prescribed drug in 2020
- **Neomycin is widely used but in a topical combination**
 - e.g. neomycin; polymixin B; Hydrocortisone
 - 315th most prescribed drug in 2020

Uptake Into Hair Cells

- **By unknown mechanisms aminoglycosides enter vestibular perilymph**
 - Systemically administered aminoglycosides enter
 - Transtympanically delivered aminoglycosides enter
- **Enter base of crypt epithelial and dark cells**
- **Unknown if entry into hair cells is from perilymph or endolymph**

Uptake Into Hair Cells

- Entry into hair cells is via the MET channel (mechanoelectrical transduction channel)
- Type I hair cells take up aminoglycosides preferentially over type II hair cells
 - This may be due to the larger number of MET channels on the type I hair cell
 - It is type I hair cells that sustain the damage

Mechanism of Damage

- **Preferential accumulation in hair cells and renal tubular cells**
 - These cells have a common embryological origin
- **Oxidative damage**
 - Potentiated by iron
- **Hair cell death ensues**

Predisposing Factors for Vestibular Toxicity of Aminoglycosides

- **Renal dysfunction**
 - Aminoglycosides cleared by kidney
 - Kidney function affects drug half-life
 - Aminoglycosides also nephrotoxic increasing the likelihood of renal dysfunction in patient taking drug
- **Dehydration**
 - Increases circulating concentration of drug

Predisposing Factors for Vestibular Toxicity of Aminoglycosides

- Loop diuretics
- Anemia
 - Compromises oxygen-carrying ability of blood
 - Hypoxia induces formation of reactive oxygen species

Predisposing Factors for Vestibular Toxicity of Aminoglycosides (cont'd)

- Ototoxicity not associated with dosing schedules or serum drug concentrations
- Danger to fetus when mother takes drug
- Inherited predisposition
 - Drug binding site on mitochondrial ribosome mutated for higher affinity for drug
- Prior history with any ototoxic drug or high noise
 - Damage is cumulative

Prevention Factors for Aminoglycosides

- Patient history to identify family with inherited predisposition
 - Inherited predispositions are relatively rare
 - There are no rapid screening tests commercially available that would yield results in a clinically relevant timeline
- Treating low potassium or low magnesium
- Correcting dehydration
- Minimizing other medications with kidney toxicity

Prevention Factors for Aminoglycosides

- Mechanism of vestibular damage is oxidative stress
- Two studies claimed protection from gentamicin by the antioxidant aspirin
 - Sha *et al.* (2006) and Behnood *et al.* (2009)
 - This potential has not found its way into clinical practice

Prevention Factors for Aminoglycosides

- Two studies claimed protection using the antioxidant N-acetylcysteine
 - During gentamicin therapy Feldman *et al.* (2007)
 - During amikacin therapy Tokgoz *et al.* (2011)
 - This potential has not found its way into clinical practice

Prevention Factors for Aminoglycosides

- Two studies claimed protection from platin drugs using the antioxidant sodium thiosulphate
 - During cisplatin therapy Freyer *et al.* (2017)
 - Incidentally the trial showed decreased overall survival
 - During cisplatin therapy Brock *et al.* (2018)
 - This potential has not found its way into clinical practice
 - During gentamicin in rats Hochman *et al.* (2006)
 - Showed no protection for sodium thiosulphate
 - No human data showing aminoglycoside protection by sodium thiosulphate

Antimalarial Vestibulotoxicity

- **Quinine**
 - Used in treatment of malaria and babesiosis
 - Mechanism by which it acts against parasite is unknown
 - Speculated that it impairs the function of intracellular vesicles
 - Affects muscle contractile activity
 - Documented adverse effects include dizziness (>10%) and vertigo (>10%)

Antimalarial Vestibulotoxicity

- **Quinine**
 - Also a content of tonic water
 - Dizziness and vertigo are two of a constellation of adverse effects known as cinchonism
 - Cinchonism symptoms typically cease with discontinuation
 - Use for leg cramps has been disproven

Antimalarial Vestibulotoxicity

- **Quinidine;dextromethorphan (Nuedexta)**
 - For treatment of behavioral symptoms of dementia
 - Pseudobulbar affect
 - Associated with fall risk

Antimalarial Vestibulotoxicity

- **Hydroxychloroquine**
 - Used in treatment of
 - Malaria
 - and prophylactically
 - Rheumatoid arthritis
 - Systemic lupus erythematosus
 - Discoid lupus erythematosus
 - Lupus nephritis

Antimalarial Vestibulotoxicity

- **Hydroxychloroquine**
 - Mechanism by which it acts against parasite is unknown
 - Speculated that it binds to DNA and inhibits DNA replication
 - Speculated that it impairs the function of intracellular vesicles
 - Mechanism by which it acts as antiinflammatory and immunomodulator is unknown
 - Speculated that it reduces cytokines
 - Speculated that it impairs immune effector cells
 - Speculated that it impairs the function of intracellular lysosomes

Antimalarial Vestibulotoxicity

- **Hydroxychloroquine**
 - Documented adverse effects include dizziness, nystagmus, and vertigo
 - These effects can last for months after drug is discontinued
 - Has a long half-life of 40 days

Antimalarial Vestibulotoxicity

- **Mefloquine**
 - Used in malaria prophylaxis and treatment
 - Mechanism by which it acts against parasite is unknown
 - Speculated that it binds to DNA and inhibits DNA replication
 - Speculated that it impairs the function of intracellular vesicles
 - Documented adverse effects include dizziness, vertigo, and loss of balance
 - These effects can last for months after drug is discontinued
 - Pharmacological doses in rats caused vestibular hair cell loss

Industrial Chemical Vestibulotoxicity

- Ethyl benzene
 - For making styrene, also component of gasoline
- Styrene
 - For manufacture of plastics and rubbers
- Toluene
 - For making paints, lacquers, and adhesives
- Trichloroethylene
 - For degreasing
- Xylene
 - A solvent

Platin Vestibulotoxicity

- **Despite the enormous toll platin drugs take on hearing**
 - There exist sparse and inconsistent reports of vestibular damage
 - Endocochlear potential is as high as +80-100 mV
 - Endovestibular potential is only up to +10 mV
 - These differences are thought to be responsible for efficient mobility of platin drugs in the cochlea and inefficient mobility in the vestibule

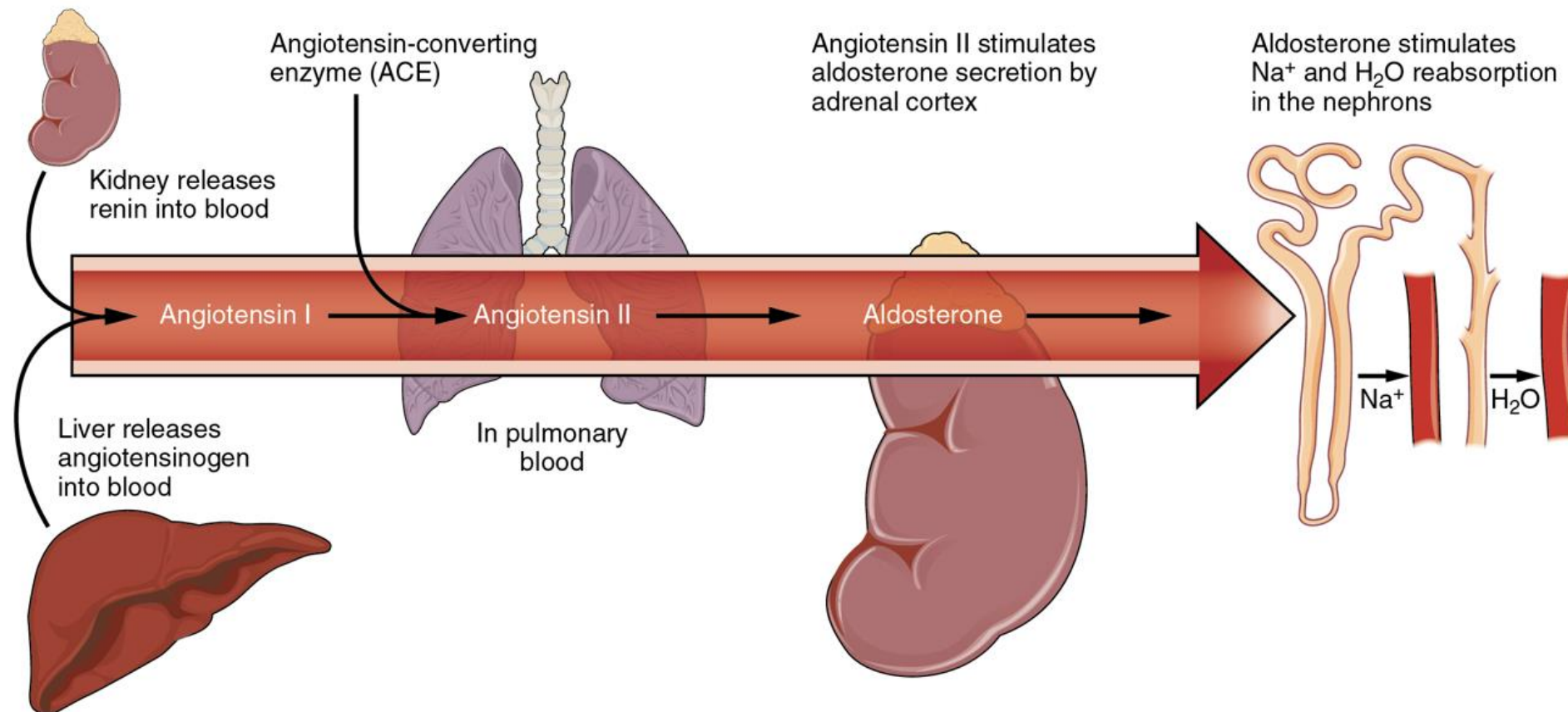
Other Pharmaceuticals and Falls

- There are very few drugs that damage the vestibular system directly
- There are many drugs that affect our sense of balance
 - The presence of one or more of these drugs in a patient history does not mean that is the cause of their balance problem
 - The presence of one or more of these drugs in a patient history does not mean there is no need for vestibular assessment

Other Pharmaceuticals and Falls

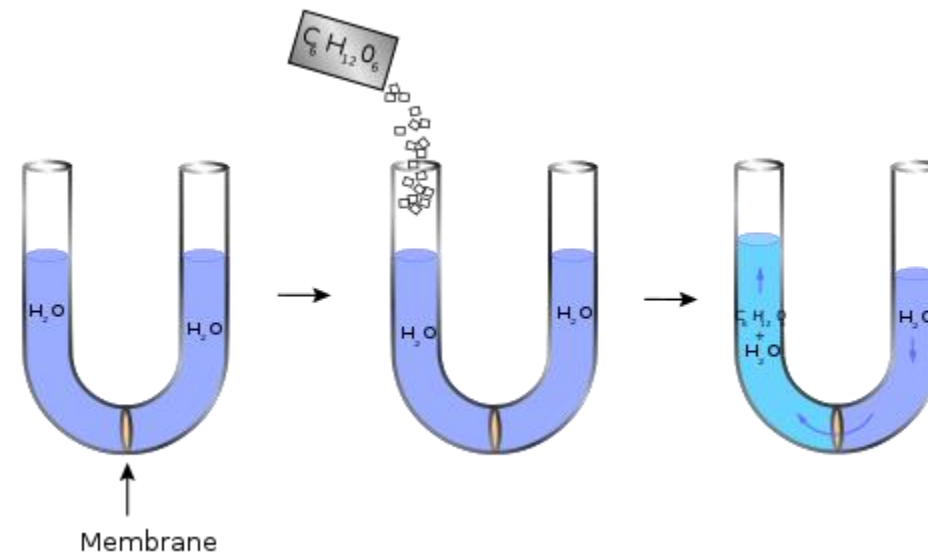
- **Drugs that produce orthostatic hypotension**
 - May produce dizziness/lightheadedness
 - May well lead to falls
 - These would explain a symptom that is not an audiological problem
- **These drugs include**
 - Diuretics
 - Other antihypertensives
 - Many cardiac drugs
 - nitrates

Blood Pressure Control



Osmotic Draw

- **Osmosis**
 - Where concentrations are high then water follows
 - Pouring sugar in draws water to form higher column

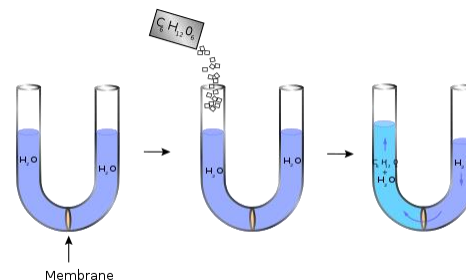


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Osmotic Draw

- **Osmosis**

- Osmotic laxatives draw water out of the body into the gut
 - Dehydration is a side effect
- Diuretics draw water out of the blood vessels into the urine
 - Less volume of blood -> lower blood pressure



Blood Pressure Control

- Angiotensin II also stimulates neural control of blood vessels *via* β -receptors
 - causes arteries to contract
 - less volume for blood -> higher blood pressure
 - increases heart contraction rate and intensity
 - more output of blood -> higher blood pressure
 - stimulates calcium release inside cardiac and vascular muscles
 - more calcium -> "squeeze" heart and vessels -> higher blood pressure

Blood Pressure Control

- **Incidental to today's topic**
 - antidiuretic hormone released by the pituitary
 - atrial natriuretic peptide releases by heart atria
 - brain natriuretic peptide released by heart ventricles

Blood Pressure Control

- We can roll a bowling ball easily
- We cannot throw a bowling ball up in the air easily



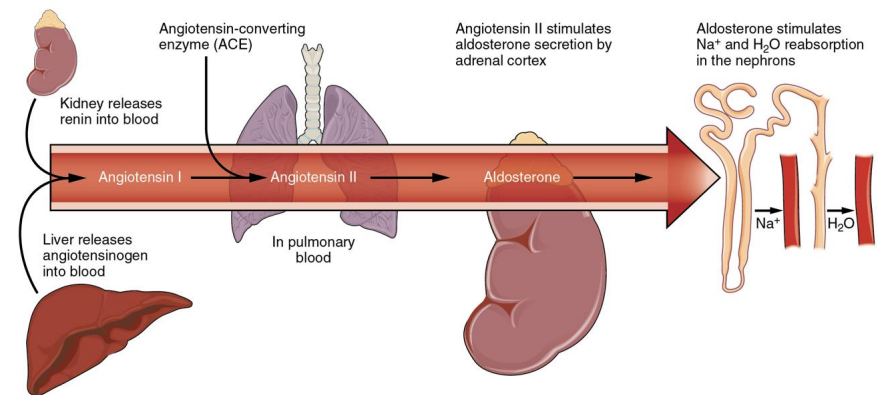
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Blood Pressure Control

- **Blood delivery to the brain when we stand**
 - When we stand there it is harder for blood to pump to the brain
 - Orthostatic hypotension
 - We get dizzy
 - May fall
 - Ordinarily our blood pressure regulation system reacts
 - Antihypertensive medications blunt this response

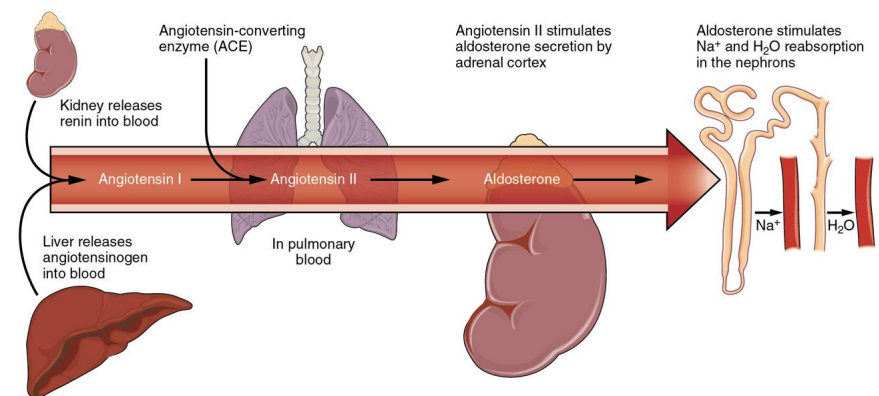
ACE Inhibitors

- lisinopril
- benazepril
- ramipril
- quinapril
- enalapril



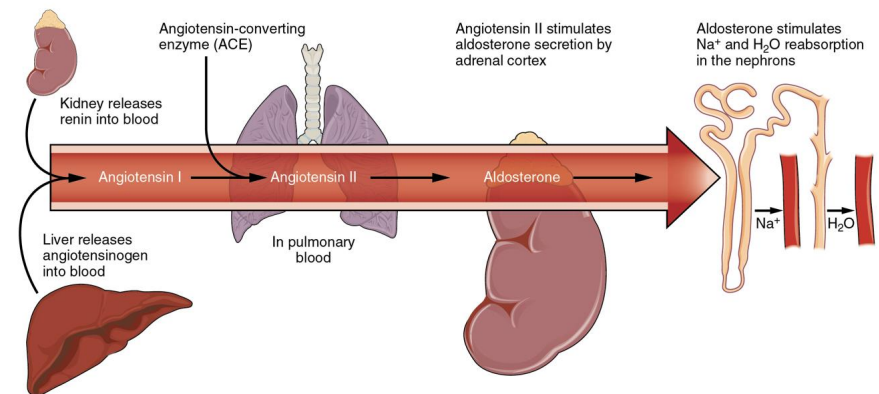
Angiotensin Receptor Blockers

- losartan
- valsartan
- olmesartan
- irbesartan
- telmisartan



Loop Diuretics

- furosemide (Lasix)
- torsemide
- bumetanide
- ethacrinic acid (Edecrin)
- most of these are cochleotoxic
- Diuretic
- hydrochlorothizide



β-blockers

- metoprolol
- carvedilol
- atenolol
- propranolol
- labetalol
- nebivolol
- bisoprolol

Calcium Channel Blockers

- decrease intensity of contraction of cardiac and vascular smooth muscle
- amlodipine
- diltiazem
- nifedipine
- verapamil
- felodipine

Cardiac Drugs

- **nitrates**
 - Allow vasodilatation
 - isosorbide
 - nitroglycerin
 - isosorbide dinitrate
- **digoxin**
- **digitalis**

Osmotic Laxatives

- These will be intravascularly depleting
 - orthostatic hypotension
- docusate
- polyethylene glycol 3350 (Miralax)
- lactulose
- bisacodyl
- psyllium

Nonbenzodiazepine hypnotics

- Affectionately known as the Z-drugs
- Indicated for
 - Sleep/sedation
 - Anxiety
- zolpidem (Ambien)
- eszopiclone (Lunesta)
- zaleplon (Sonata)

Z-drugs

- The exact association between the Z-drugs and falls is unclear
- The highest association is between falls and zopiclone
 - zopiclone is not approved by the US FDA
 - zopiclone is not available in the US
 - that drug may tarnish the reputation of the other Z-drugs
 - there is an association between Z-drugs and falls

Drug Association With Falls

- **Fall risk of drugs is usually found by meta-analysis of a number of studies**
 - More often these meta-analyses group drugs into classes to judge fall risk
 - There simply are not enough studies of a single drug
 - Consider all of the possible adverse effects of a drug
 - Impractical to study each individual drug for each adverse effect
 - Drug manufacturer unlikely to desire to study adverse effects

Drug Association With Falls

- **Fall risk is generally low**
 - Odds ratios of 1.25 to 1.5
 - If higher the drug likely carries too much risk in general for approval
 - If it affects equilibrium to that extent it probably affects other systems too
- **zopiclone is used in Canada**
 - When fall risk combined with other drugs in class raises apparent risk of class

Other Pharmaceuticals and Falls

- **Benzodiazepines**
 - Indicated for
 - Anxiety
 - Sleep/sedation
- **alprazolam (Xanax)**
- **clonazepam (Klonopin)**
- **lorazepam (Ativan)**
- **diazepam (Valium)**
- **temazepam (Restoril)**

Other Pharmaceuticals and Falls

- **Rohypnol (roofies)**
 - A benzodiazepine
 - Strongly amnestic
 - Not approved by the US FDA
 - Not legally available in the US
 - The date rape drug

Antidepressants

- **Many increase activity of neurotransmitters**
 - Serotonin
 - Norepinephrine
 - Changing the way these act on the brain lead to antidepressant action
- **Selective Serotonin reuptake inhibitors (SSRI)**
 - Increase serotonin in nerve synapse
- **Serotonin Norepinephrine Reuptake Inhibitors (SNRI)**
 - Increase serotonin and norepinephrine in nerve synapse

SSRI Antidepressants

- sertraline (Zoloft)
- escitalopram (Lexapro)
- fluoxetine (Prozac)
- citalopram (Celexa)
- paroxetine (Paxil)

SNRI Antidepressants

- duloxetine (Cymbalta)
- venlafaxine (Effexor)
- desvenlafaxine (Pristiq)

Serotonin Receptor Antagonist

- **This sounds backwards**
 - Decreases serotonin action on receptor
 - There are serotonin receptor subtypes
 - This drug seems to enhance overall serotonin and norepinephrine activity
- **mirtazapine (Remeron)**

Antipsychotics

- quetiapine
- aripiprazole
- risperidone
- lurasidone
- ziprasidone
- haloperidol
- prochlorperazine

Antiepileptics

- carbamezipine
- phenytoin
- phenobarbital

Other Pharmaceuticals and Falls

- **Parkinson disease drugs**
 - ropinirole
 - diphenhydramine
 - pramipexole
 - benztropine
 - carbidopa;levodopa

Polypharmacy

- **Use of more than one drug**
 - Often more than one patient problem to treat
 - Sometimes multiple drugs to treat a problem
- **Drugs that cause falls generally have low fall risk**
 - When administering multiple drugs with fall risk the overall fall risk can increase dramatically
 - Or fall risk drugs combined with current or past use of vestibular risk drugs

Beers List is a famous and reliable list of drugs for geriatric patients and considers fall risk heavily

J Am Geriatr Soc. 2012 April ; 60(4): 616–631. doi:10.1111/j.1532-5415.2012.03923.x.

American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults:

The American Geriatrics Society 2012 Beers Criteria Update Expert Panel

Christine M. Campanelli

The American Geriatrics Society, New York, New York

British Geriatric Society List

- [Medicines and Falls in Hospital - British Geriatrics Society](#)
- A very nice list of drugs that are associated with fall risk
 - A .pdf file that names names
 - Color coded according to level of risk

Article with good information about drugs associated with fall risk

Geriatric Polypharmacy Pharmacist as Key Facilitator in Assessing for Falls Risk



Michelle A. Fritsch, PharmD^{a,*}, Penny S. Shelton, PharmD^b

Clin Geriatr Med 33 (2017) 205–223

<http://dx.doi.org/10.1016/j.cger.2017.01.003>

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