The Aging Mind and Body: Physiology and Sleep

Caring for the Aging patient (and ourselves)

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Disclosure

- Board certified in Adult and Addiction Psychiatry
- Not Geriatric Psychiatry
- No financial arrangements related to the content of this activity

Objectives

- Apply information about the physiological changes with aging for safest prescribing practices
- Apply information about drug metabolism and drug-drug interactions for safest prescribing
- Balance the risks of medications for aging-related sleep disorders when behavioral treatments are unavailable or ineffective, in order to provide the safest possible treatment

The Aging Body: Metabolism

Pharmacokinetics:

- Absorption
- Distribution
- Metabolism
- Excretion[1]

1. Carlo, Andrew D., and Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamic Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.

Preskorn, Sheldon H. *Clinical Pharmacology of SSRI's.* Caddo: Professional Communications, Inc., 1996. Web. 20 Sept. 2015.

Pharmacokinetics: Absorption

- Rate of absorption is slowed more than amount of absorption
- Passive absorption affected by reduced gastric motility/acid secretion, gut blood flow
- Active absorption in gut through enterocyte enzymes:
- CP450 3A4 and P-glycoproteins

Carlo, Andrew D., and Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamic Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.

Absorption: P-glycoproteins

- P-pg. in enterocytes and blood-brain barrier (BBB)
- P-gp function reduced at BBB with age
- Older pts are often on multiple medications that may affect P-gp function: inhibitors may greatly increase concentration of drugs in brain, gut, bile, blood

Carlo, Andrew D., and Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamic Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.

Absorption: P-gp

- P-gp substrates: quinidine, digoxin, lovastatin, SSRI's, venlafaxine, amitriptyline, nortriptyline, doxepin, olanzapine, quetiapine, risperidone, aripiprazole (increased in brain with inhibitors)

- P-gp inhibitors: verapamil (major), garlic (minor-mod), cyclosporine, carbamazepine, olanzapine, quetiapine, fluoxetine, sertraline, paroxetine, venlafaxine, duloxetine, TCA's

- P-gp inducers (lower concentration of substrates): carbamazepine, Depakote, St. John's wort

Carlo, Andrew D., and Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamic Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.
Akamine, Yumiko, et al. "Psychotropic drug-drug interactions involving P-Glycoprotein." *CNS Drugs* 26 (2012): 959-73 *PubMed.* Web. 22 Sept. 2015 (researched by Kimberly Andrews/Laura Molander PIMC Pharmacy.
Sandson, Neil B, et al. "An overview of psychotropic drug-drug interactions." *Psychosomatics* 46 (2005):464-94. *PubMed.* 22 Sept. 2015. (researched by Laura Molander Pharm D, PIMC Pharmacy).

Distribution: Body Water

Concentration of RX is inversely proportional to volume of distribution

Plasma volume declines 8%

Total body water declines 17%

Extracellular fluid declines 40%

Carlo, Andrew D., and Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamic Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.

Distribution

Concentrations of hydrophilic drugs such as lithium, gabapentin, and Water-soluble metabolites of bupropion, venlafaxine will increase

Carlo, Andrew D., nd Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamic Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.

Question 1

1. Fat-soluble drugs have a larger volume of distribution in the elderly
2. Fat-soluble drugs take longer to reach steady state concentrations in the elderly
3. Fat-soluble drugs take longer to be excreted by the elderly

a. All of the above
b. None of the above

Distribution

Half-life is proportional to volume of distribution

Total body fat rises 35%

Lipophilic drugs such as diazepam take longer to reach steady state (may appear to have less efficacy) AND take longer to be excreted

Carlo, Andrew D., nd Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamic Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.

Metabolism

- Conversion of a product into metabolite
- Usually one that is more easily excreted, less toxic
- Flow-limited metabolism is reduced by lower hepatic mass (20-30%), blood flow (20-50%)
- Also reduced by lower bile flow
- Lower rate of glucose, lipid, protein synthesis

Carlo, Andrew D., nd Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamic Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.

Metabolism: CYP Enzymes

- Mitochondrial CYP enzymes originally synthesized steroids and cell membrane components: “steroidogenic”

- Endoplasmic reticulum enzymes evolved to detoxify : toxins, carcinogens, mutagens: “xenobiotics” by adding oxygen to substances, i.e. “phase 1 metabolism”

- CYP’s contain heme, absorb light at 450nm, referred to as CYP450 enzymes

Preskorn, Sheldon H. *Clinical Pharmacology of SSRI’s.* Caddo: Professional Communications, Inc., 1996. Web. 20 Sept. 2015.

CYP450 Enzymes: nomenclature

- Classified by amino acid/structural similarity
- First number is the family, with 40% homology
- Next letter is subfamily w≥ 55% homology
- Last number is code for specific gene
- Example CYP450 2D6

Preskorn, Sheldon H. *Clinical Pharmacology of SSRI's.* Caddo: Professional Communications, Inc., 1996. Web. 20 Sept. 2015.

Metabolism: CYP450 enzymes

CYP450 enzymes most affected by aging are

*1A2 (tobacco, olanzapine, warfarin, caffeine)

3A4/5 (verapamil, alprazolam, carbamazepine)

2C19 (PPI's, diazepam, phenytoin)

Carlo, Andrew D., nd Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamic Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.

CYP450 Enzymes

Greater impact of genetic polymorphisms (increased or decreased enzyme function) and Diet (tobacco, supplements such as SJW, grapefruit juice, etc.) Than impact of aging on enzymes

Carlo, Andrew D., nd Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamics Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.

Juliano, Laura M., Sergi Ferre, Roland R. Griffiths. "The Pharmacology of Caffeine." *The ASAM Principles of Addiction Medicine*. 5th ed. Ries, Richard K., et al, eds. Philadelphia: Wolters Kluwer, 2014. 180-200. Print.

CYP450 Enzymes

The GREATEST RISK to ELDERS is not aging enzymes

It is DRUG-DRUG interactions

The risk of toxicity rises with the number of medications an elder is taking

Carlo, Andrew D., nd Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamic Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.

Excretion

- Slowed by the reduction of liver mass/flow, renal mass/flow
- Increased fat volume
- Reduced enzyme function
- Drug interactions

Pharmacodynamics

- The drug's impact at its target
- Affected by "receptor density, receptor affinity, signal transduction pathways, and cell counter-regulatory processes"

Carlo, Andrew D., nd Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamic Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.

Pharmacodynamics continued

- Brain mass falls 5% per decade after age 40
- Reduced dopamine, $5HT_2A$, α and β adrenergic receptors
- Decreased cholinergic innervation:
- Increased sensitivity to RX

Carlo, Andrew D., nd Jonathan E. Alpert. "Geriatric Psychopharmacology: Pharmacokinetic and Pharmacodynamic Considerations." *Psychiatric Annals* 45.7 (2015): 336-341. Print.

Question 2

1. Medication that helps reduce bladder spasms may cause dementia
2. Low-dose tricyclic antidepressants may cause dementia

a. Both
b. Neither

Anti-Cholinergic Burden Scale (ACB)

- Drugs are scored from 1-3 points based on anticholinergic impact. 2 and 3 have "definite" risk.

- "Each definite anticholinergic (sic-medication)may increase the risk of cognitive impairment by 46% over 6 years.

- For each one point increase in the ACB total score, a decline in MMSE score of 0.33 points over 2 years has been suggested…each 1 point increase in the ACB total score has been correlated with a 26% increase in the risk of death."

anticholinergic burden scale. Web. 25 Sept. 2015.
http://www.preferredphm.com/The-HABC-Mobile-Application.html *Application.html*

CNS Normal Aging

- Increased time to retrieve data from memory
- Increased time to learn new data
- Slower complex reaction time, including response and movement (driving)

Kaiser, Robert M. "Physiological and Clinical Considerations of Geriatric Patient Care." *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 33-59. Print.

The Aging Body

- Reduced homeostasis: “the ability…to maintain a steady state”
- Baroreceptor reflex weakens (ability to maintain BP)
- Increased risk for dehydration: impaired thirst response, reduced ADH release with volume loss, reduced renal sensitivity to ADH

Kaiser, Robert M. “Physiological and Clinical Considerations of Geriatric Patient Care.” *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 33-59. Print.

The Aging Body

- Reduced vision as lens thickens, opacifies,
- Pupils shrink, become more rigid
- Hearing loss affects discernment of speech
- Increased norepinephrine results in less CV sensitivity:
- Lower max HR, force of contraction, ability of vessels to dilate

Kaiser, Robert M. "Physiological and Clinical Considerations of Geriatric Patient Care." *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 33-59. Print.

The Aging Body

- Slower bone marrow response to blood loss or infection
- Increased platelet sensitivity, clotting factors
- Thymus shrinks, reduced T and B cell response to challenges

Kaiser, Robert M. "Physiological and Clinical Considerations of Geriatric Patient Care." *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 33-59. Print.

The Aging Body

- Decreased muscle mass, increased fat/adipocytes, free fatty acids, adipocytokines
- Reduced insulin sensitivity
- Reduced dilation of stomach, small bowel, slowed food transit
- Coordination of swallowing with loss of ganglion cells

Kaiser, Robert M. "Physiological and Clinical Considerations of Geriatric Patient Care." *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 33-59. Print.

Aging and Sleep: Between a Rock and a Hard Place?

- Sleep changes start in late 30's, early 40's:

- Decline in "total sleep time, reduced sleep efficiency…decreased slow wave and REM sleep, and increased stage 1 and 2 (light) sleep...tendency to fall asleep and awaken earlier"

- Most notable change in elders is "frequent interruption of sleep by periods of wakefulness."

Krystal, Andrew D., Thakur, Mugdha E. "Sleep and Circadian Rhythm Disorders." *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 435-457. Print.

Sleep and Aging

- Over half of elders “report chronic sleep difficulties”
- “Sleep disturbances affect quality of life, increase the risk of accidents and falls, and are among the leading reasons for long-term-care placement.”
- Most common causes are “sleep apnea, periodic limb movement disorder, and medical and psychiatric disorders that lead to secondary sleep-related symptoms.”

Krystal, Andrew D., Thakur, Mugdha E. “Sleep and Circadian Rhythm Disorders.” *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 435-457. Print.

Common Sleep Disorders in Aging

- Sleep apnea: cessation/partial decrease of breathing resulting in hypoxia, terminated with arousal/gasping
- "Clinically significant" periodic limb movement disorder is present in 30-45% of people of those over 60: "repetitive muscular contractions" such as kicking
- Movements causing arousal/hour are higher in elders

Krystal, Andrew D., Thakur, Mugdha E. "Sleep and Circadian Rhythm Disorders." *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 435-457. Print.

Restless Leg Syndrome

- Present in up to 28% of those over 65
- Irresistible urge to move is worse at night, at rest, relieved by movement
- Twice as frequent in older women than men
- Diagnosed by history, not polysomnography
- Increased with diabetes, iron-deficiency, pregnancy,
- and meds that reduce dopamine, raise serotonin (antidepressants/antipsychotics/anti-emetics)

Krystal, Andrew D., Thakur, Mugdha E. "Sleep and Circadian Rhythm Disorders." *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 435-457. Print.

Physical Causes of Insomnia

- 63-72% of elders attributed insomnia to nocturia
- Pain: improves with better sleep in some studies
- Be very cautious using sleep RX with COPD, and in combination with opiates

Krystal, Andrew D., Thakur, Mugdha E. "Sleep and Circadian Rhythm Disorders." *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 435-457. Print.

Question 3

- 1. Insomnia causes 22% of car crashes
- 2. Insomnia doubles the risk of diabetes and depression
- 3. Insomnia impairs learning and chromatin remodeling

a. All of the above
b. None of the above

Risks of Insomnia

- “2 fold increased risk of obesity, diabetes, hypertension, incident cardiovascular disease, stroke, depression, substance abuse, and all-cause mortality in multiple studies.”

- May contribute to 22% of vehicle “crashes, 16% near-crashes,”

- “impaired learning…chromatin remodeling, insulin resistance”

NIH. National Center on Sleep Disorders Research. *National Institutes of Health Sleep Disorders Research Plan.* 1 June 2011. Web. 12 Oct. 2015.

Insomnia and Suicide

- Insomnia, hypersomnia, and nightmares increase suicide risk independent of depression
- Insomnia is caused by excessive arousal
- Insomnia causes “cognitive distortions” that contribute to a sense of helplessness and hopelessness in the face of stressors

McCall, W. Vaughn. “The correlation between sleep disturbance and suicide.” *Psychiatric Times.* Sept. 2015: 18-21. UBM Medical, LLC. Print.

Treating Insomnia

- Infirmity, isolation, sensory losses, boredom, napping, “dysfunctional beliefs about sleep” may combine to disrupt sleep/wake cycle, good health, sleep habits

- Safest treatment by FAR is cognitive behavioral treatment: as or more effective as meds in some studies

- More enduring effect on sleep than meds

Krystal, Andrew D., Thakur, Mugdha E. “Sleep and Circadian Rhythm Disorders.” *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 435-457. Print.

Non Pharmacologic Approaches to Insomnia

Cognitive behavioral therapy for insomnia (CBT-I):

- "Learn about factors that enhance sleep, examine beliefs and practices that interfere with sleep, and adopt behaviors that foster sleep"
- Apps: CBTI-coach, SleepRate, Sleepio[1]
- CBTforInsomnia.com[2]

1. Lamber, Lynne. "Apps, Online Programs Can Expand Availability of CBT for Insomnia." *Psychiatric Times.* 21 Aug. 2015: 20-12. UBM Medical, LLC. Review of American Academy of Sleep Medicine and the Sleep Research Society meeting June 2015, Seattle. Print.

2. Jacobs, Gregg D. *CBT for Insomnia. @2015 CBT.* Web. 12 Oct. 2015.

Sleep Restriction Therapy

- Goal is to reduce time in bed spent not sleeping
- Sleep log for 2-3 weeks to calculate total sleep time
- Time in bed allowed is total sleep time plus “normal nocturnal wakefulness”
- Time in bed increases in 15-20 minute increments after sleep is over 85-90% of time in bed (if fatigue persists)

Krystal, Andrew D., Thakur, Mugdha E. “Sleep and Circadian Rhythm Disorders.” *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 435-457. Print.

Sedative Hypnotics in Aging

"Prescribing sedative-hypnotic drugs is not routinely recommended for older patients with a sleep disorder. Geriatric patients…are at higher risk of iatrogenic complications because of polypharmacy, comorbidities, relative renal and hepatic insufficiency, and other physiologic changes leading to alterations in drug exposure and metabolism."

Hong, Irene S., et al. "Sedative-hypnotics for sleepless geriatric patients." *Current Psychiatry* Oct 13.10 (2014): 36-39, 46-50, 52. *Frontline Medical Communications Inc.* Web. 11 Aug. 2015.

FDA-Approved Insomnia Drugs

"Amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital, chloral hydrate, diphenhydramine, doxylamine, doxepin, estazolam, flurazepam, lorazepam, quazepam, temazepam, triazolam, eszopiclone, zaleplon, zolpidem, ramelteon, and suvorexant."

Hong, Irene S., et al. "Sedative-hypnotics for sleepless geriatric patients." *Current Psychiatry* Oct 13.10 (2014): 36-39, 46-50, 52. *Frontline Medical Communications Inc.* Web. 11 Aug. 2015.

AASM and AGS Recommendations

- Avoid barbiturates, chloral hydrate, meprobamate (low therapeutic index, overdose/dependence risks)

- Avoid off-label drugs (anticonvulsants, antidepressants, antipsychotics) "if possible, because of limited evidence supporting their use" for sleep

Am. Geriatrics Society: AVOID benzodiazepines, avoid "Z" drugs with history of falls, fractures

Hong, Irene S., et al. "Sedative-hypnotics for sleepless geriatric patients." *Current Psychiatry* Oct 13.10 (2014): 36-39, 46-50, 52. *Frontline Medical Communications Inc.* Web. 11 Aug. 2015.

Sleep Meds and Aging

- 24.8-27.9% “sleep related office visits were” by patients 65 or older[1]
- SCREENING TOOL OF OLDER PERSON’S PRESCRIPTIONS (STOPP): Does not recommend benzodiazepines, antipsychotics, first generation antihistamines due to “postural imbalance”[2]

2. “PHARMACIST’S LETTER.” *PRESCRIBER’S LETTER.* Therapeutic Research Center. Web. 11 Aug. 2015.

1. Hong, Irene S., et al. “Sedative-hypnotics for sleepless geriatric patients.” *Current Psychiatry* Oct 13.10 (2014): 36-39, 46-50, 52. *Frontline Medical Communications Inc.* Web. 11 Aug. 2015.

“Sedative Hypnotic Medication Use and the Risk of Motor Vehicle Crash”

- 409,171 adults in an “integrated health care plan” med use compared to crash records in WA state
- 5.8% received new sedative hypnotic rx
- Increased risk of crash with temazepam HR 1.27
- Trazadone HR 1.91, zolpidem HR 2.20 “equivalent to
- BAL 0.06-0.11%
- “3 fold increased risk premature mortality”, 4 fold in first year of treatment.

Hansen, Ryan N., and Boudreau, Denise M., et al. “Sedative Hypnotic Medication Use and the Risk of Motor Vehicle Crash.” *AM J Public Health.* 105.8 (2015):e64-e69. Web. 9 Sept. 2015.

Hypnotics with Studies in the Elderly

- 2-12 week double-blind placebo controlled studies “have established the risk-benefit profile for”:
- Flurazepam, triazolam, temazepam, eszopiclone, zaleplon, zolpidem, ramelteon, doxepin
- “Data on adverse effects…in older adults” are available for the above except triazolam

Krystal, Andrew D., Thakur, Mugdha E. “Sleep and Circadian Rhythm Disorders.” *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 435-457. Print.

Long term studies in Elders

- Zaleplon 5-10mg: 'no significant risks…or significant discontinuation effects" with up to 1 year use[1]
- 5mg recommended for elders[2]
- Suvorexant: a subset of subjects in a 1 year study were elders
- Approved at lower than study doses

2. McCall, Catherine, and John W. Winkleman. "The Use of Hypnotics to Treat Sleep Problems in the Elderly." *Psychiatric Annals* 45.7 (2015): 342-7. Print.

1. Krystal, Andrew D., Thakur, Mugdha E. "Sleep and Circadian Rhythm Disorders." *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 435-457. Print.

Suvorexant

- Orexin/hypocretin dual receptor antagonist: OX_1r, OX_2r
- two RDBPC trials in elders at 15 and 30mg
- FDA-approved doses: 10-20mg,
- 10mg recommended for elders
- Sleep paralysis, cataplexy (sudden loss of muscle tone)
- Next day sedation, driving impairment: take at least 7 hours before wake up time (half life 10-22 hours!)

McCall, Catherine, and John W. Winkleman. "The Use of Hypnotics to Treat Sleep Problems in the Elderly." *Psychiatric Annals* 45.7 (2015): 342-7. Print.

Sleep Meds continued

- The American Academy of Sleep Medicine recommends “an initial treatment of 2 to 4 weeks, followed by re-evaluation of continued need for treatment.”

- AASM recommends “short or intermediate-acting” non BNZ receptor agonists or “ramelteon for initial…management of primary insomnias and insomnias comorbid with other conditions.”

Hong, Irene S., et al. “Sedative-hypnotics for sleepless geriatric patients.” *Current Psychiatry* Oct 13.10 (2014): 36-39, 46-50, 52. *Frontline Medical Communications Inc.* Web. 11 Aug. 2015.

Non Benzodiazepine Receptor Agonists/“Z” drugs

- Zaleplon and Zolpidem bind alpha $_1$ GABA$_A$ receptors, increasing chloride conductance: hypnotic and amnestic

- Eszopiclone “may be less selective for GABA$_A$ subtypes” (help with anxiety as well as sleep)

- Benzodiazepines bind at alpha$_{1\text{-}3,5}$ GABA$_A$

McCall, Catherine, and John W. Winkleman. “The Use of Hypnotics to Treat Sleep Problems in the Elderly.” *Psychiatric Annals* 45.7 (2015): 342-7. Print.

Eszopiclone and Zolpidem

- No “long-term efficacy and safety” data in elderly
- FDA lowered recommended doses of zolpidem for women by 50% in 2014 due to next day impairment from slower metabolism
- Zolpidem 5mg for elderly
- Eszopiclone 1mg for elderly

Hong, Irene S., et al. “Sedative-hypnotics for sleepless geriatric patients.” *Current Psychiatry* Oct 13.10 (2014): 36-39, 46-50, 52. *Frontline Medical Communications Inc.* Web. 11 Aug. 2015.

Krystal, Andrew D., Thakur, Mugdha E. “Sleep and Circadian Rhythm Disorders.” *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 435-457. Print.

Question 4

- 1. Preferred treatment of insomnia in elders is with cognitive-behavioral interventions
- 2. If that fails or does not help, use short-acting hypnotics for 2-3 weeks and reassess
- 3. Be very cautious about hypnotics with a history of falls, cognitive impairment

a. All of the above
b. None of the above

AASM-recommended hypnotics

- Zaleplon half life 1 hour
- Zolpidem half life 2.5-3 hours
- (VERSUS eszopiclone due to its half life of 6 hours)

Ramelteon half life 1-2.6 hours, metabolite 2-5 hours

Hong, Irene S., et al. "Sedative-hypnotics for sleepless geriatric patients." *Current Psychiatry* Oct 13.10 (2014): 36-39, 46-50, 52. *Frontline Medical Communications Inc.* Web. 11 Aug. 2015.

Ramelteon

Ramelteon: melatonin MT1, MT2 receptor agonist

Half life 1-2.6 hours, metabolite 2-5 hours

8mg recommended geriatric dose for sleep onset insomnia

Successful for delirium prevention among hospitalized elders in one study

Prolactin may rise, cortisol, testosterone may decline

Hong, Irene S., et al. "Sedative-hypnotics for sleepless geriatric patients." *Current Psychiatry* Oct 13.10 (2014): 36-39, 46-50, 52. *Frontline Medical Communications Inc.* Web. 11 Aug. 2015.

Adverse Reactions for AASM meds

- Potential for complex sleep-related behavior, suicidal ideation, hallucinations are listed for all non benzodiazepine agonists, suvorexant, and ramelteon

- Amnesia listed for all but ramelteon

Epocrates.com. *Athenahealth.com,* 2015. Web. 18 Oct. 2015.

What about Low Dose Doxepin?

- Under 10mg, effect is mostly antihistaminergic
- FDA-approved for sleep maintenance insomnia
- Half life 15.3 hours
- 3-6mg, 3mg recommended for elders
- Two RDBPC studies in elders (4 and 12 weeks):did not “induce significant adverse effects”

McCall, Catherine, and John W. Winkleman. “The Use of Hypnotics to Treat Sleep Problems in the Elderly.” *Psychiatric Annals* 45.7 (2015): 342-7. Print.

What about fairly low-dose doxepin?

- 3,434 people over 65 followed more than 7 years
- “Greater risk for dementia with over 3 years of”:
- 10mg doxepin daily
- 4mg chlorpheniramine
- 5mg oxybutynin
- “10 year cumulative dose-response” increased risk of dementia and Alzheimer’s dementia ($p<.0001$)
- Effects may persist after cessation of drug

Gray, Shelly L., et al. Cumulative Use of Strong Anticholinergics and Incident Dementia.” *JAMA Internal Medicine. AMA.* Published online 26 Jan 2015. Web. 15 Oct. 2015.

Falls and Insomnia

- “There is evidence for an associations of falls with benzodiazepines, non benzodiazepines, and medications with anticholinergic and antiadrenergic effects…there are also studies suggesting that untreated insomnia increases the risk for falls.”

- “How to take into account the risk of falls caused by being awake at night versus the risk of falls cause by medication”??

Krystal, Andrew D., Thakur, Mugdha E. “Sleep and Circadian Rhythm Disorders.” *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 435-457. Print.

Trazadone

- Lower doses (25-50mg) cause sedation from antihistamine, 5HT-$_2$A, alpha 1-adrenergic antagonism: cognitive, sedative, hypotensive side effects[1]

- Doses over 150mg are antidepressant (5HT-$_2$c antagonism, SRI), though lower doses may rarely trigger activation[2]

2. Stahl, Stephen M. *Stahl's Essential Psychopharmacology. 4th ed.* Cambridge: Cambridge University Press, 2015. 322-325, 457-8. Print.

1. Krystal, Andrew D., Thakur, Mugdha E. "Sleep and Circadian Rhythm Disorders." *The American Psychiatric Publishing Textbook of Geriatric Psychiatry.* 5th ed. Steffens, David C., Don G. Blazer, Mugdha E. Thakur, eds. Washington, D. C.: American Psychiatric Publishing, 2015. 435-457. Print.

Trazadone continued

- Low risk of weight gain or sexual side effects (except rare risk of priapism) compared to SSRI's
- Not habit-forming, weight-neutral
- Arrhythmia, angle-closure glaucoma
- At higher doses, similar side effects to SSRI's (hyponatremia, serotonin withdrawal with abrupt cessation, increased bleeding risk)

Stahl, Stephen M. *Stahl's Essential Psychopharmacology. 4th ed.* Cambridge: Cambridge University Press, 2013. 322-325, 457-8. Print.

Mirtazapine

- $5HT_2A$, histamine antagonism (sedating effect)
- $5HT_2c$ antagonism (weight gain)
- $alpha_2$ antagonism potently boosts norepinephrine, serotonin release (antidepressant)
- $5HT_3$ antagonism reduces nausea/vomiting/diarrhea
- 7.5-45mg for depression

Stahl, Stephen M. *Stahl's Essential Psychopharmacology. 4th ed.* Cambridge: Cambridge University Press, 2013. 317-22. Print.

Mirtazapine continued

- Improved subjective sleep quality, reduced sleep fragmentation
- No change in “wake time after sleep onset, total sleep time, sleep efficiency” with impaired motor response hypotension, weight gain
- Rare marrow suppression, warnings about torsades de pointes, angle-closure glaucoma, hypersensitivity reactions

McCall, Catherine, and John W. Winkleman. “The Use of Hypnotics to Treat Sleep Problems in the Elderly.” *Psychiatric Annals* 45.7 (2015): 342-7. Print.

Ropinirole

- Dopamine agonist used for Parkinson disease:
- 24mg maximum dose
- Restless legs syndrome: 4mg maximum
- Risk of impulse control disorders is much higher with ropinirole, pramipexole than levodopa, especially with higher doses, Parkinson disease.

Taylor, Jacob, and Gregory Pontone. "Implications of Impulse Control Disorder in Parkinson Disease." *Psychiatric Times.* Aug. 2015: 10-12. UBM Medical, LLC. Print.

Ropinirole continued

- Impulsive behavior may start slowly: gambling, hyper sexuality, binge eating, spending, travel
- My trigger/worsen psychosis, especially with Parkinson disease
- Ask directly about behaviors

Taylor, Jacob, and Gregory Pontone. "Implications of Impulse Control Disorder in Parkinson Disease." *Psychiatric Times.* Aug. 2015: 10-12. UBM Medical, LLC. Print.

Thank you!