Sleep Pharmacotherapy - Focus on Drug Interactions

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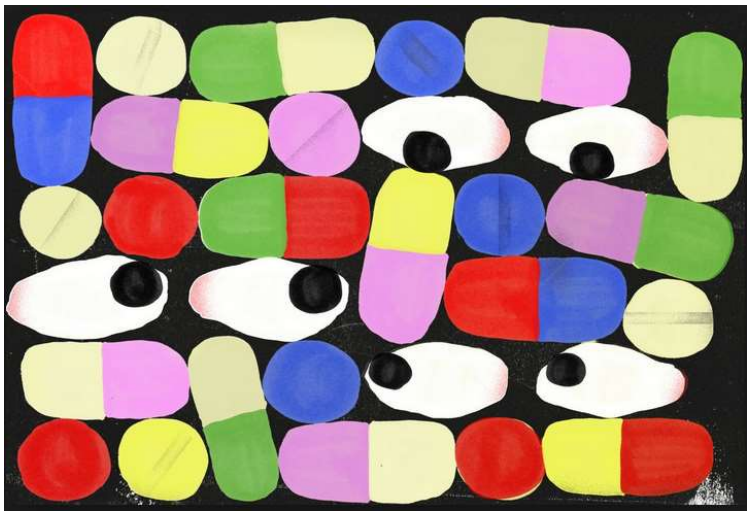
Faculty Disclosure

Mark A. Malesker, Pharm.D.

Dr. Malesker has listed no financial interest/arrangement that would be considered a conflict of interest



Objectives

- Identify pharmacotherapy options for sedation
- Understand the pharmacokinetic profiles of sedative hypnotics
- Review clinically significant sleep pharmacotherapy drug interactions

Outline

- Review of drug interactions
- Sleep Pharmacotherapy
- Sleep therapy pharmacokinetics
- Clinically significant drug interactions

Audience Question #1

- What cytochrome P450 enzyme metabolizes most marketed medications?

- A. CYP1A2
- B. CYP2D6
- C. CYP2C9
- D. CYP3A4

Audience Question #2

- Which has a clinically significant interaction with zolpidem?

- A. Atorvastatin
- B. Doxycycline
- C. Lisinopril
- D. Rifampin

Drug Interactions

- Drug-drug interactions (DDIs)
  - Drugs that interact producing undesirable effects
    - Sometimes used to produce a desirable effect
- Drug-disease
  - Can produce worsening of symptoms
- Drug-food
  - Can block drug effect, absorption, etc.

Review > Consult Pharm. 2018 Nov 1;33(11):649-657. doi: 10.4140/TCP.n.2018.649..

Clinically Significant Food-Drug Interactions

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Abstract

OBJECTIVE: Provide an up-to-date review for health care providers regarding clinically significant food-drug interactions and summarize recommendations for optimal medication administration in older adults and long-term care patients. **DATA SOURCES:** A literature search was performed using MEDLINE, PUBMED, and IPA abstracts to locate relevant articles published between January 1982 and July 2017. DAILYMED was used to identify manufacturer-specific medication administration recommendations. **STUDY SELECTION AND DATA EXTRACTION:** Articles were reviewed for inclusion based on their relevance to this subject matter and the integrity of the information provided. Additionally, the package labeling of included products was reviewed. **DATA SYNTHESIS:** The current recommendations for specific medication administration with regard to food are summarized descriptively. **CONCLUSION:** Clinically significant food-drug interactions are common and have been reported with multiple classes of medications. However, there are a limited number of studies examining food-drug interactions, and the majority of recommendations are made by product-specific manufacturers. Pharmacists should be aware of common food-drug interactions in the community, assisted living, long-term care, subacute care, and hospital settings. To optimize medication therapy and improve therapeutic outcomes, it is important for pharmacists and other health care providers to identify agents with potential for food-drug interactions and to understand the clinical relevance of such interactions.

Types of Interactions

- **Pharmacodynamic**
  - Two drugs act at the same or interrelated receptor sites, resulting in additive, synergistic, or antagonistic effects
- **Pharmacokinetic**
  - Involve changes in the absorption, distribution, metabolism, and excretion of a drug and/or its metabolite

Pharmacodynamic Interactions

- **Antagonism**
  - When one drug blocks the effects of another drug
- **Synergism**
  - When two drugs work better together than the sum of their individual actions (1+1=3)
- **Additivity**
  - When two drugs work together as they would separately (1+1=2)
- **Potentiation**
  - One drug has no effect, but can increase the activity of another drug (0+1=2)

Pharmacokinetic Interactions (1)

- Multiple drugs binding in GI tract
  - Antacids or iron + quinolone or tetracycline
- Alterations in GI pH
  - H_2-antagonist + itraconazole
- Delayed or increased GI motility
  - Anticholinergics, opiates, metoclopramide

Consultant Pharmacist 2000;15:85-92

Pharmacokinetic Interactions (2)

- Inhibition of normal intestinal flora
  - Erythromycin + digoxin
- Protein binding
  - Warfarin + phenytoin
- Inhibition or induction of hepatic metabolism
- Alteration of glomerular filtration, active tubular reabsorption, or passive tubular absorption
  - Lithium and thiazides

Consultant Pharmacist 2000;15:85-92

Factors to Consider When Evaluating the Clinical Significance of Potential Interaction

- Nature of each drug activity at enzyme site (substrate/inhibitor/inducer)
- Potency of the inhibitor/inducer
- Concentration of inhibitor/inducer at enzyme site
- Saturability of the enzyme
- Extent of metabolism of the substrate
- Presence of active metabolites of the substrate
- Therapeutic window of the substrate
- Risk level (elderly)
- Probability of concurrent use

Drugs Aging 2002;19:299-320

Elderly Risk Factors for DIs

- Multiple chronic disease states, #RXs
- Multiple prescribers
- Failure of health professionals to identify DDIs
- Health professionals ignoring computer interaction prompts
- Poor patient compliance with complex drug regimen
- Perception of OTCs as having no DDIs
- Age-related physiological changes altering

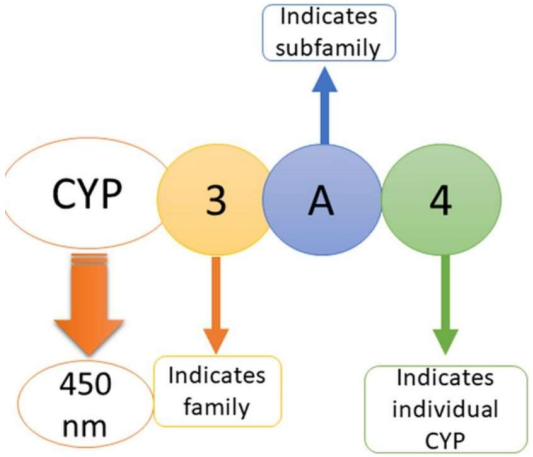
Physiologic Aging Changes Pharmacokinetics

PK Parameter	Age Related Change
Absorption	↑ **Gastric pH** ↓ **GI tract blood flow**
Distribution	↓ **Total body water** ↓ **Plasma protein**
Metabolism	↓ **Hepatic flood flow** ↓ **Microsomal enzyme action**
Excretion	↓ **CrCl** ↓ **Renal blood flow**

Drugs & Aging 1998;3:199-209

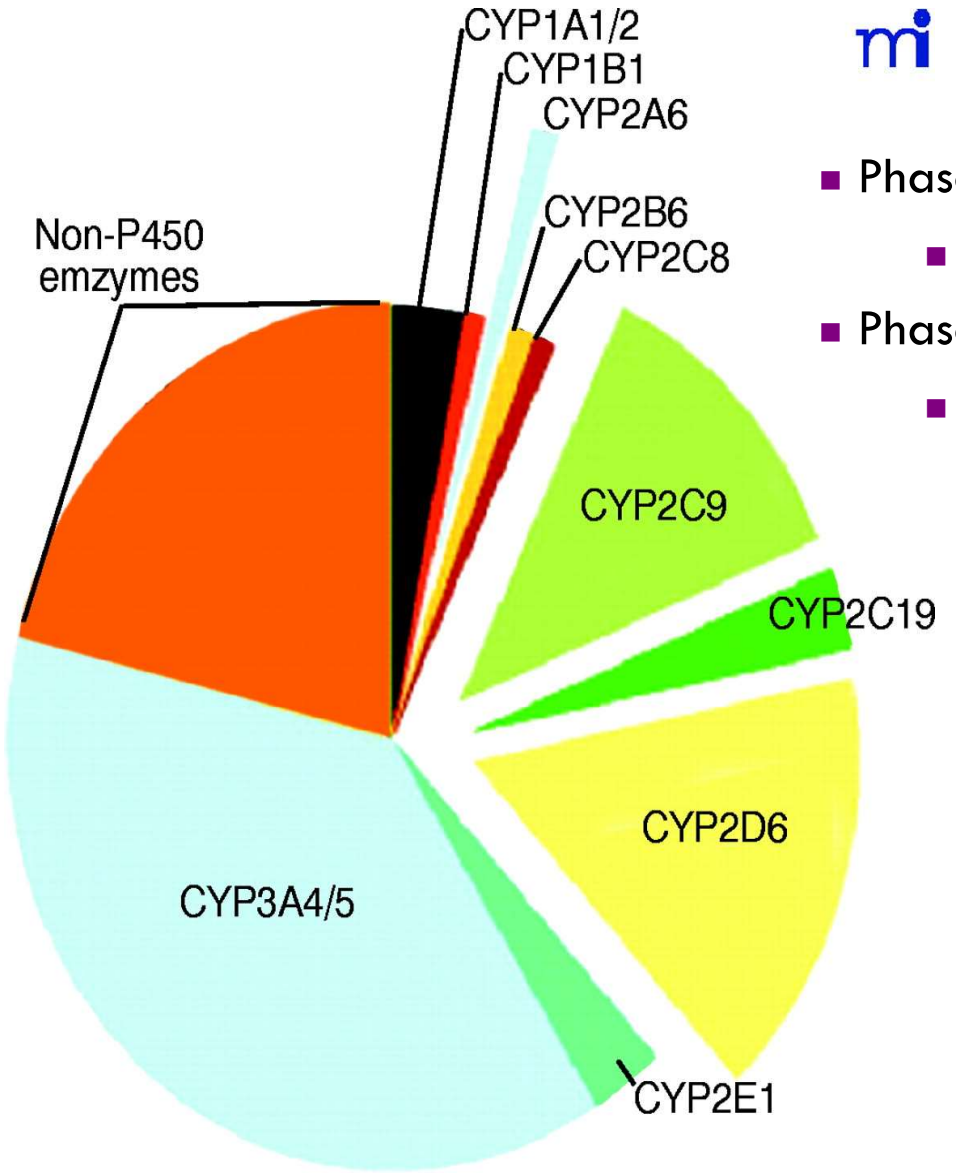
CYP-450 Nomenclature

- **CYP-450 isoenzymes**
  - **Group of heme-containing enzymes embedded primarily in the lipid bilayer of the endoplasmic reticulum of hepatocytes**
  - **Nomenclature suggested in 1987**
    - **CYP1 (family) A (subfamily), 2 (gene)**
- **More than 50 human CYP450 isoenzymes identified to date**
- **CYP3A4, CYP2D6, CYP1A2, CYP2C**
  - **Responsible for drug metabolism**



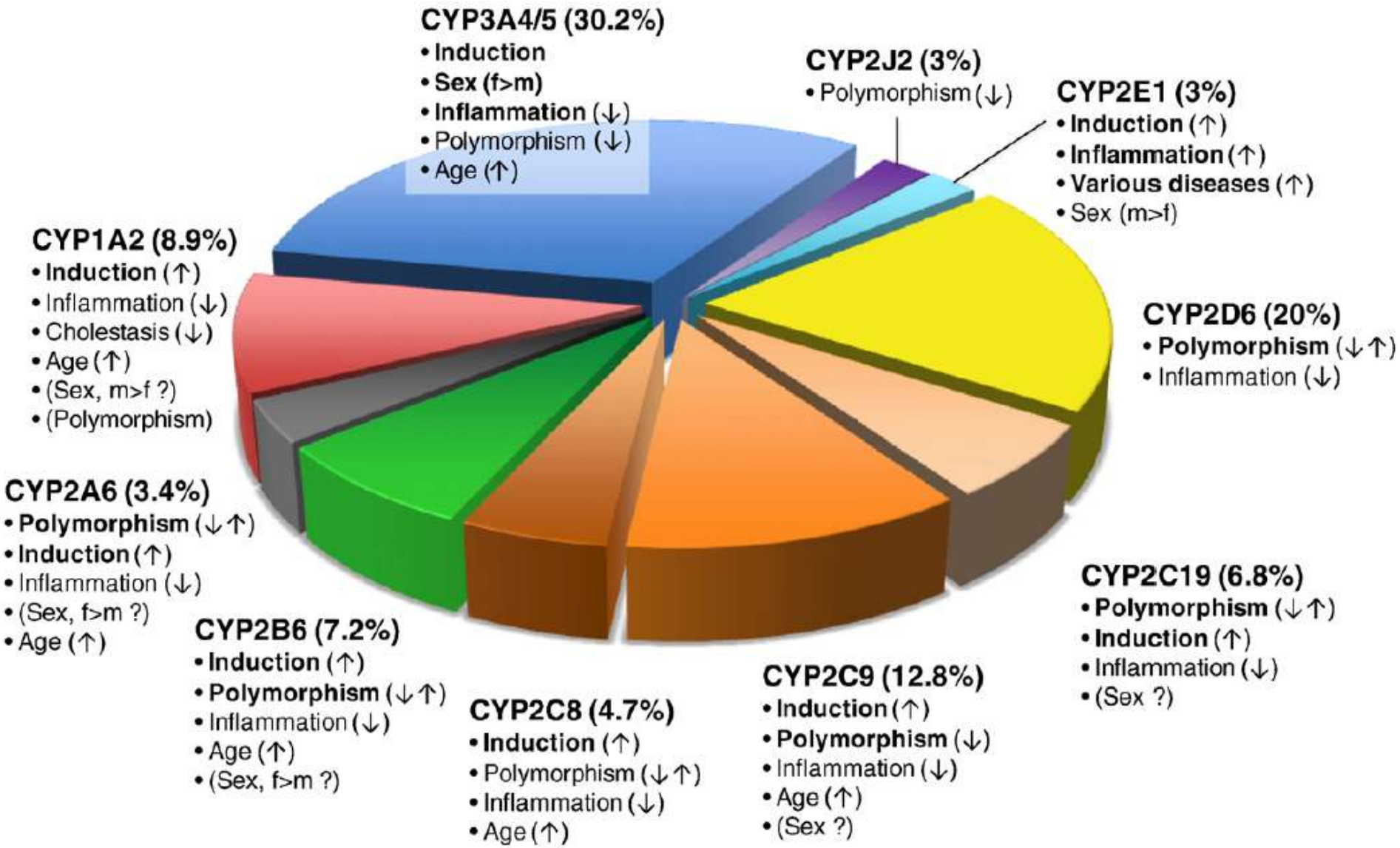
Circulation 2000;101:1749-53, Pharmacotherapy 1998;18(I):84-112, Drug Metabolism Reviews 2002;34:83-448, Intensive Care Med 2009;35:603-612

Contribution of Major Human P450s to Phase I Metabolism



- Phase I
  - Oxidation/Reduction/Hydrolysis
- Phase II
  - Conjugation

Fraction of Clinically Used Drugs Metabolized by P450 Isoforms and Factors Influencing Variability



Pharmacology & Therapeutics 138 (2013) 103–141

Substrates, Inhibition, and Induction

- Some meds metabolized by more than one isoenzyme
  - S-warfarin 2C9
  - R-warfarin CYP3A4, CYP1A2
- Inhibition
  - Result of competitive binding at the enzyme's binding site
  - Onset and offset of enzyme inhibition are dependent on the half-life and time to steady state of the inhibitor drug
- Induction
  - Occurs when hepatic flow is increased or the synthesis of more CYP-450 enzymes is stimulated

Drugs Removed or Restricted in USA Because of Drug Interactions

- Terfenadine (Seldane), February 1998
- Astemazole (Hismanal), July 1999
- Cisapride (Propulsid), January 2000

CYP3A4 Isoenzyme Substrates

- Quinidine
- Lidocaine
- R-warfarin
- Carbamazepine
- Sertraline
- Methadone, meperidine
- Alprazolam
- Calcium channel blockers
- Macrolides
- Tricyclic antidepressants
- Estrogen, OC's
- Corticosteroids
- HMG-CoA inhibitors
- Cyclosporine
- Erythromycin
- Fentanyl
- Protease inhibitors
- Chemotherapeutic agents
- Azole antifungals
- 5-HT3 antagonists

CYP3A4 Isoenzyme Inhibitors

- Amiodarone
- Antifungals
- Cimetidine
- Grapefruit juice
- Macrolide antibiotics
- Ritonavir
- Calcium channel blockers
- Nefazodone
- Omeprazole
- Protease inhibitors
- Metronidazole
- SSRIs
- Delavirdine

CYP3A4 Isoenzyme Inducers

- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone
- Rifampin

CYP2D6 Isoenzyme Substrates

- Codeine
- Antiarrhythmics
- Antidepressants
- Benzodiazepines
- Antipsychotics
- Metoprolol
- 5-HT_3 antagonists

CYP2D6 Isoenzyme Inhibitors

- Amiodarone
- Quinidine
- Propafenone
- Chronic alcohol ingestion
- Paroxetine, fluoxetine, duloxetine
- Bupropion
- Ritonavir
- Cimetidine

CYP2D6 Isoenzyme Inducers

- Carbamazepine
- Phenobarbital
- Primidone
- Phenytoin
- Rifampin

CYP1A2 Isoenzyme Substrates

- Caffeine
- Theophylline
- R-Warfarin
- Antidepressants (TCAs + mirtazapine)
- Antipsychotics (olanzapine, clozapine)
- NSAIDs
- Acetaminophen

CYP1A2 Isoenzyme Inhibitors

- Amiodarone
- Cimetidine
- Ciprofloxacin
- Macrolides
- Fluvoxamine
- Grapefruit juice
- Ketoconazole
- Isoniazid
- SSRIs

CYP1A2 Isoenzyme Inducers

- Phenobarbital
- Phenytoin
- Rifampin
- Carbamazepine
- Cigarette smoking
- Charbroiled meat

CYP2C Isoenzyme Substrates

- Oral antidiabetic agents (2C9)
- NSAIDs (2C9)
- Clopidogrel (2C19)
- Amitriptyline
- Losartan (2C9)
- Omeprazole
- Phenytoin (2C9)
- S-warfarin (2C9)

CYP2C Isoenzyme Inhibitors

- Amiodarone (2C9)
- Cimetidine (2C9)
- Fluconazole
- Fluoxetine, fluvoxamine (2C9)
- Metronidazole
- Omeprazole (2C9, 2C19)
- Zafirlukast (2C9)

Pharmacotherapy of Insomnia

- Benzodiapine receptor agonists
- Benzodiazepines
- Selective histamine receptor antagonist
- Melatonin receptor agonist
- Orexin receptor antagonist
- Alternate medications
- OTC sleep aids
- Dietary supplements

What People Take for Insomnia

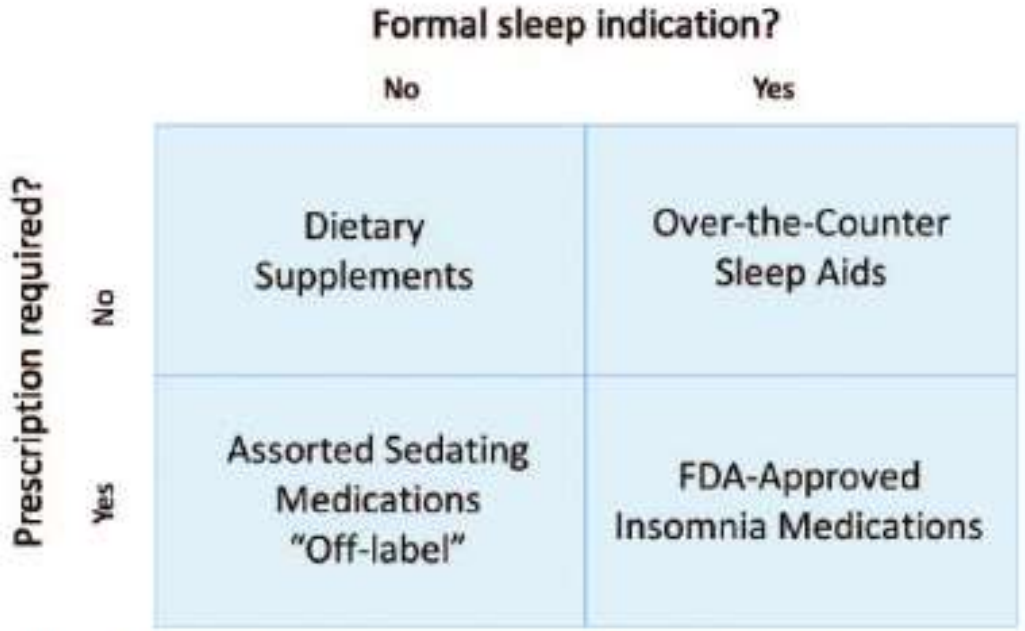


Figure 1. Categories of compounds that people take to try to treat insomnia based on indication and requirement for prescription. FDA indicates Food and Drug Administration.

Sleep Med Clin 2018;13:169-182, Journal of Central Nervous System Disease 2018;10:1-7

Benzodiazepine Receptor Agonists

- Eszopiclone (Lunesta)
- Zaleplon (Sonata)
- Zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist)

Eszopiclone

Agent	Onset	Half-Life (Hours)	Duration	Adult Dose	Elderly Dose
Eszopiclone (Lunesta)	**15-30 min**	**5-7**	**Intermediate**	**1-3 mg**	**1-2 mg**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021476s030lbl.pdf

Eszopiclone Metabolism

- **CYP3A4 and CYP2E1 via demethylation and oxidation**

https://www.sunovion.ca/monographs/lunesta.pdf

Eszopiclone Drug Interactions

- Additive effects with CNS depressants
  - Antipsychotics, antidepressants, opiates, alcohol
- Rifampin may increase metabolism (inducer)
- CYP 3A4 inhibitors (clarithromycin, itraconazole, ketoconazole, nelfinavir, ritonavir, conivaptan, amiodarone) may decrease metabolism (3A4), do not exceed 2 mg dose

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021476s030lbl.pdf

Zaleplon

Agent	Onset	Half-Life (Hours)	Duration	Adult Dose	Elderly Dose
Zaleplon (Sonata)	< 30 min	1	Ultra-short	10-20 mg	5 mg

https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020859s011lbl.pdf

Zaleplon Metabolism

- Primarily metabolized by aldehyde oxidase to form 5-oxo-zaleplon
- Metabolized to a lesser extent by cytochrome P450 (CYP) 3A4 to form desethylzaleplon

https://labeling.pfizer.com/ShowLabeling.aspx?id=710

Zaleplon Interactions

- Additive effects with CNS depressants
  - Antipsychotics, antidepressants, opiates, alcohol
- Rifampin, phenytoin, fosphenytoin, carbamazepine, phenobarbital may increase 3A4 metabolism
- CYP3A4 inhibitors (erythromycin, ketoconazole) may decrease metabolism
- Cimetidine inhibits both aldehyde oxidase and CYP3A4
  - Reduce dose with long term exposure

https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020859s011lbl.pdf

Zolpidem Products

Agent	Onset	Duration	Adult Dose	Elderly Dose
Zolpidem (Ambien)	30 min	Short	5 mg for Female 5-10 mg for Male	5 mg
Zolpidem CR (Ambien CR)	30 min	Intermediate	6.25 mg for Female 6.25-12.5 mg for Male	6.25 mg
Zolpidem SL (Edluar)	30 min	Short	5 mg for Female 5-10 mg for Male	5 mg
Zolpidem SL (Intermezzo)	30 min	Short	1.75 mg for Female 3.5 mg for Male	1.75 mg
Zolpidem Solution (Zolpimist)	30 min	Short	5 mg for Female 5-10 mg for Male	5 mg

Zolpidem Metabolism

- **Hepatic methylation and hydroxylation via CYP3A4 (~60%), CYP2C9 (~22%), CYP1A2 (~14%), CYP2D6 (~3%), and CYP2C19 (~3%) to 3 inactive metabolites**

https://products.sanofi.us/ambien/ambien.pdf

Zolpidem Interactions

- CNS depressants, including alcohol - possible adverse additive CNS-depressant effects
- Opioids: Concomitant use may increase risk of respiratory depression
- Imipramine: Decreased alertness observed
- Chlorpromazine: Impaired alertness and psychomotor performance observed
- CYP3A4 inducers (rifampin or St. John's wort) - combination use may decrease effect
- Ketoconazole: combination use may increase effect

https://products.sanofi.us/ambien/ambien.pdf

Benzodiazepines

Agent	Onset	Half-Life (Hours)	Duration	Adult Dose	Elderly Dose
Triazolam (Halcion)	15-30 min	1.5 – 5.5	Short	0.125 -0.25 mg	0.125 mg
Estazolam (ProSom)	15-60 min	10 – 24	Intermediate	1-2 mg	0.5-1 mg
Temazepam (Restoril)	45-60 min	10 – 17	Intermediate	15-30 mg	7.5-15 mg
Flurazepam (Dalmane)	30-60 min	50 – 100	Long	15-30 mg	7.5 mg
Quazepam (Doral)	20-45 min	25 – 41	Long	15 mg	7.5 mg

Triazolam Metabolism

- **The initial step in metabolism is cytochrome P450 3A (CYP 3A)-mediated hydroxylation to form 1-hydroxytriazolam and 4-hydroxytriazolam, which are subsequently conjugated to form glucuronides**

https://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&id=586

Triazolam Interactions

- Contraindicated with concomitant CYP450 3A inhibitors - ketoconazole, itraconazole, nefazodone, ritonavir, indinavir, nelfinavir, saquinavir, and lopinavir
- Use with Opioids: Increase the risk of respiratory depression
- Use with Other CNS Depressants: Produces additive CNS depressant effects
- Use with CYP 3A4 Inhibitors: Increased risk of adverse reactions

https://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&id=586

Estazolam Metabolism

- The metabolism of estazolam to the major circulating metabolite 4-hydroxy-estazolam is catalyzed by CYP3A

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a1e3b4bf-22e9-430a-a768-4d86ae886c9e

Estazolam Interactions

- Contraindicated with ketoconazole and itraconazole (3A4 inhibitors)
- 3A4 inhibitors (nefazodone, fluvoxamine, and erythromycin) would be expected to increase plasma concentrations
- CYP3A inducers (such as carbamazepine, phenytoin, rifampin and barbiturates) would be expected to decrease plasma concentrations

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a1e3b4bf-22e9-430a-a768-4d86ae886c9e

Temazepam Metabolism

- **Hepatic; undergoes phase II metabolism**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/018163s067lbl.pdf

Temazepam Interactions

- The concomitant use opioids increases the risk of respiratory depression
- Additive CNS depressant effects

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/018163s067lbl.pdf

Flurazepam Metabolism

- **Hepatic to N_1-desalkyl-flurazepam (T ½ 74 to 160 hours)**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/016721s076lbl.pdf

Flurazepam Interactions

- **Additive CNS depressant effects**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/016721s076lbl.pdf

Quazepam Metabolism

- Hepatic via CYP3A4, CYP2C9, CYP2C19
- Two active plasma metabolites are 2-oxoquazepam (T ½ 39 hours) and N-desalkyl-2-oxoquazepam (T ½ 73 hours)

https://doralrx.com/docs/Doral-500494-10-2021-01-15-Clean.pdf

Quazepam Interactions

- Concomitant use of opioids increases the risk of respiratory depression
- CNS Depressants: downward dose adjustment may be necessary due to additive effects

https://doralrx.com/docs/Doral-500494-10-2021-01-15-Clean.pdf

Melatonin Receptor Agonist

Agent	Onset	Duration	Adult Dose	Elderly Dose
Ramelteon (Rozerem)	15-30 min	Short	8 mg	8 mg

Ramelteon Metabolism

- CYP1A2 is the major isozyme involved in the hepatic metabolism of ramelteon; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree

www.accessdata.fda.gov/drugsatfda_docs/label/2010/021782s011lbl.pdf

Ramelteon Interactions

- Fluvoxamine (strong CYP1A2 inhibitor): increases AUC for ramelteon and should not be used in combination
- Rifampin (strong CYP enzyme inducer): decreases exposure to and effects of ramelteon
- Ketoconazole (strong CYP3A4 inhibitor): increases AUC for ramelteon; administer with caution
- Fluconazole (strong CYP2C9 inhibitor): increases systemic exposure of ramelteon; administer with caution
- Donepezil increases systemic exposure of ramelteon; patients should be closely monitored when ramelteon is co administered with donepezil
- Doxepin increases systemic exposure of ramelteon; patients should be closely monitored when ramelteon is co administered with doxepin
- Alcohol: Causes additive psychomotor impairment; should not be used in combination

www.accessdata.fda.gov/drugsatfda_docs/label/2010/021782s011lbl.pdf

Histamine Receptor Antagonist

Agent	Onset	Duration	Adult Dose	Elderly Dose
Doxepin (Silenor)	30 min	Long	3-6 mg	3 mg

Doxepin (Silenor) Metabolism

- Primarily metabolized by hepatic cytochrome P450 isozymes CYP2C19 and CYP2D6, and to a lesser extent, by CYP1A2 and CYP2C9
- Inhibitors of these isozymes may increase the exposure of doxepin
- Not an inhibitor of any CYP isozymes at therapeutically relevant concentrations
- The ability to induce CYP isozymes is not known

Doxepin (Silenor) Interactions

- Should not be administered in patients on MAOIs within the past two weeks
- Cimetidine: increases exposure to doxepin
- Alcohol: sedative effects may be increased with doxepin
- CNS Depressants and Sedating Antihistamines: sedative effects may be increased with doxepin
- Tolazamide: a case of severe hypoglycemia has been reported

www.silenor.com/

Alternative Medication Insomnia Treatments

Agent	Onset (Min)	Half-Life (H)	Dose (mg/day) Adult/Elderly
Amitriptyline (Elavil)	30	13-36	10-75/10 initial
Doxepin (Sinequan)	30	15-20	10-50/10 initial
Mirtazapine (Remeron)	NA	20-40	15/15
Trazodone (Desyrel)	30-60	6.4-11.6	50-150/25 initial

Amitriptyline Metabolism

- Metabolized mainly via CYP2C19 and CYP2D6 pathways
- Metabolism by CYP2C19 results in active metabolites, including nortriptyline

Amitriptyline Interactions

- CYP2D6 inhibitors (quinidine; cimetidine)
- CYP2D6 inducers (rifampin, carbamazepine)
- Caution with coadministration of SSRIs
- Serotonin Syndrome - increased risk when co-administered with SSRI, SNRI, triptans
- Additive anticholinergic effects
- Additive CNS depression
- Increase the risk of QTc prolongation

Mirtazapine Metabolism

- **Extensively hepatic via CYP1A2, CYP2D6, CYP3A4, and via demethylation and hydroxylation**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020415s029,%20021208s019lbl.pdf

Mirtazapine Interactions

- Contraindication - Concomitant use of MAOIs or use within 14 days of stopping MAOI
- Warning (Serotonin Syndrome) - increased risk when co-administered with SSRI, SNRI, triptans
- Strong CYP3A inducers: Dosage increase may be needed
- Strong CYP3A inhibitors: Dosage decrease may be needed
- Cimetidine (CYP1A2, CYP2D6, and CYP3A inhibitor)
  - Dosage decrease may be needed
- Warfarin: monitor INR during concomitant use
- Increase the risk of QTc prolongation

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020415s029,%20021208s019lbl.pdf

Trazodone Metabolism

- Metabolized, via oxidative cleavage, to an active metabolite, m-chlorophenylpiperazine (mCPP) by CYP3A
- 89 to 95% protein bound

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018207s032lbl.pdf

Trazodone Interactions

- Contraindication - Concomitant use of MAOIs, or use within 14 days of stopping MAOI
- Warning (Serotonin Syndrome) - increased risk when co-administered with SSRI, SNRI, triptans
- CNS Depressants: may enhance effects of alcohol, barbiturates, or other CNS depressants
- CYP3A4 Inhibitors: consider dose reduction based on tolerability
- CYP3A4 Inducers: increase in dosage may be necessary
- Digoxin or Phenytoin: monitor for increased digoxin or phenytoin serum levels
- Warfarin: monitor for increased or decreased PT

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018207s032lbl.pdf

Orexin Receptor Antagonists

Agent	Onset	Half-Life (H)	Adult Dose	Elderly Dose
Suvorexant (Belsomra)	30 min	12	10-20 mg	10-20 mg
Lemborexant (Dayvigo)	< 30 min	17-19	5-10 mg	5-10 mg
Daridorexant (Quviviq)	< 30 min	8	25-50 mg	25-50 mg

Suvorexant (Belsomra) Metabolism

- **Metabolism by CYP3A is the major elimination pathway**

https://www.merck.com/product/usa/pi_circulars/b/belsomra/belsomra_pi.pdf

Suvorexant (Belsomra) Interactions

- CYP3A inhibitors: Recommended dose is 5 mg when used with moderate CYP3A inhibitors
  - Amprenavir, aprepitant, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil
  - Dose can be increased to 10 mg once per night if the 5 mg dose is not effective
- Not recommended for use in patients taking strong CYP3A inhibitors
  - Ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin, conivaptan
- Strong CYP3A inducers: Efficacy may be reduced
- Digoxin: monitor digoxin concentrations

https://www.merck.com/product/usa/pi_circulars/b/belsomra/belsomra_pi.pdf

Lemborexant (Dayvigo) Metabolism

- **Primarily metabolized by CYP3A4, and to a lesser extent by CYP3A5**

Lemborexant (Dayvigo) Interactions

- Strong/moderate CYP3A inhibitors: avoid concomitant use
  - Strong CYP3A inhibitors: itraconazole, clarithromycin
  - Moderate CYP3A inhibitors: fluconazole, verapamil
- Weak CYP3A inhibitors: The maximum recommended dose is 5 mg
- Strong or moderate CYP3A inducers: Avoid concomitant use
  - Strong CYP3A inducers: rifampin, carbamazepine, St. John's wort
  - Moderate CYP3A inducers: bosentan, efavirenz, etravirine, modafinil
- Decreases the AUC of drugs that are CYP2B6 substrates (bupropion, methadone)

www.dayvigo.com

Daridorexant (Quviviq) Metabolism

- Primarily metabolized by CYP3A4 (89%)
  - Other CYP enzymes individually contribute to less than 3% of metabolic clearance of daridorexant

www.quviviq.com/

Daridorexant (Quviviq) Interactions

- Strong CYP3A4 inhibitors: Avoid concomitant use
- Moderate CYP3A4 inhibitors: Maximum recommended dose is 25 mg
- Moderate or Strong CYP3A4 inducers: Avoid concomitant use

www.quviviq.com/

OTC Insomnia Treatments

Agent	Onset (Min)	Half-Life (H)	Dose (mg/day) Adult/Elderly
Diphenhydramine	30-60	2.4-9.3	25-50 / Avoid
Doxylamine	30	10	25 / Avoid

OTC = over the counter

Diphenhydramine Products

Agent	Dosage Form	Strengths	Usual Adult Daily Dose
Diphenhydramine (Sominex, Nytol, Benadryl)	Tabs	12.5 mg, 25 mg	25-50 mg
Diphenhydramine (Sominex)	Capsule	25 mg, 50 mg	25-50 mg
Diphenhydramine	Liquid, Elixir, Syrup	12.5 mg/ml	25-50 mg

Diphenhydramine

- Metabolism
  - Extensively hepatic via CYP2D6, minor demethylation via CYP1A2, CYP2C9, and 2C10
- Interactions
  - Use cautiously with inducers or inhibitors of CYP2D6
  - Additive anticholinergic effects
  - Additive CNS depression

Doxylamine Products

Agent	Dosage Form	Strengths	Usual Adult Daily Dose
Doxylamine (Unisom)	Tabs	25 mg	25 mg

Doxylamine

- Metabolism
  - Hepatic by N-dealkylation to metabolites
- Interactions
  - Additive anticholinergic effects
  - Additive CNS depression

Melatonin

- Metabolism
  - CYP1A2, CYP1A1 and the extrahepatic CYP1B1
- Interactions
  - Use with strong CYP1A2 inducers or inhibitors is not recommended

Audience Question #3

- How is eszopiclone metabolized?

- A. CYP1A2
- B. CYP2D6
- C. CYP2C19
- D. CYP3A4

Audience Question #4

- What is the dose of suvorexant in a patient taking concurrent itraconazole?

- A. 5 mg
- B. 10 mg
- C. 20 mg
- D. Dose is not recommended

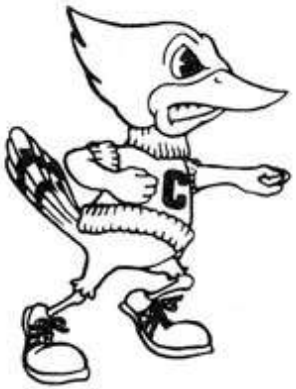
The End

1924

1941

1955

1957



1970

1972

2013