Pharmacotherapeutics in Hypersomnia and Insomnia: An Update

Mark Malesker, Pharm.D., FCCP, FCCP, FCCM, FASHP, BCPS
Professor of Pharmacy Practice and Medicine
Creighton University

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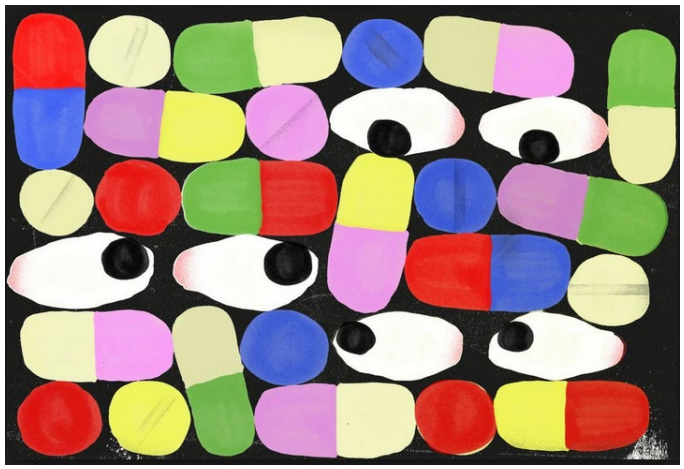
Faculty Disclosure

Mark A. Malesker, Pharm.D.

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



Objectives

- Identify new pharmacotherapy options for sleep disorders
- Understand the impact of medication shortages on sleep pharmacotherapy
- Review clinically significant drug interactions for excessive daytime sleepiness treatments
- Identify new agents in the pipeline for excessive daytime sleepiness

CREIGHTON BLUEJAYS

Outline

- New medication approvals
- Medication shortages
- Amphetamine products
- Methylphenidate products
- Pharmacotherapy for daytime sleepiness
- Clinically significant drug interactions
- Agents in the pipeline

Audience Question #1

- **What cytochrome P450 enzyme metabolizes most marketed medications?**

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

Audience Question #2

- What OTC medication should be avoided with pitolisant?

- A. Acetaminophen
- B. Diphenhydramine
- C. Ibuprofen
- D. Lansoprazole

Daridorexant (Quviviq)

- Treatment of sleep-onset insomnia and/or sleep-maintenance insomnia in adults
  - Suvorexant (Belsomra), Lemborexant (Dayvigo)
- Suppresses the wake drive by competitively inhibiting orexin A and B from binding to OX1R and OX2R
- Dosage is 25 or 50 mg once nightly $\leq$ 30 minutes before bedtime and $\geq$ 7 hours before planned awakening
- Side effects ($\geq$5%): headache, somnolence, fatigue
  - Excessive daytime sleepiness, sleep paralysis, hallucinations reported
- Use with strong CYP3A4 inhibitors or strong or moderate CYP3A4 inducers is not recommended; maximum dose with moderate CYP3A4 inhibitors is 25 mg
- Schedule IV controlled substance
- Modestly more effective than placebo, generally well-tolerated, no active-comparator trials

https://www.quviviq.com/

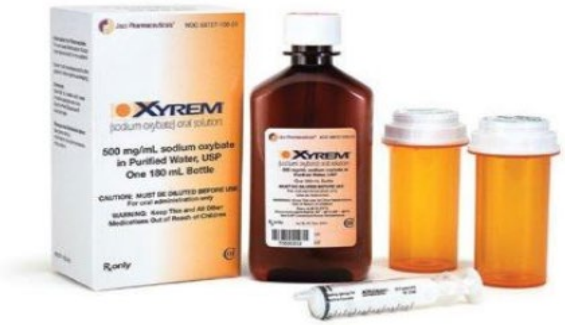
Sodium Oxybate (Lumryz)

- Extended-release oral suspension
  - Packets of 4.5 g, 6 g, 7.5 g, or 9 g
- Dosing
  - Initiate dosage at 4.5 g once per night orally
  - Titrate to effect in increments of 1.5 g per night at weekly intervals
  - Recommended range: 6 g to 9 g once per night orally
- Administration instructions
  - Prepare the dose prior to bedtime; suspend dose in approximately ⅓ cup of water in the mixing cup provided
  - Allow 2 hours after eating before dosing
  - Take dose while in bed and lie down after dosing

https://www.avadel.com/lumryz-prescribing-information.pdf

Sodium Oxybate Products

Sodium oxybate (Xyrem)
0.5 g/mL oral solution



Calcium, magnesium, potassium, sodium oxybates (Xywav)
0.5 g/mL oral solution

Sodium oxybate (Lumryz)
Packets of 4.5 g, 6 g, 7.5 g, 9 g for extended-release oral suspension

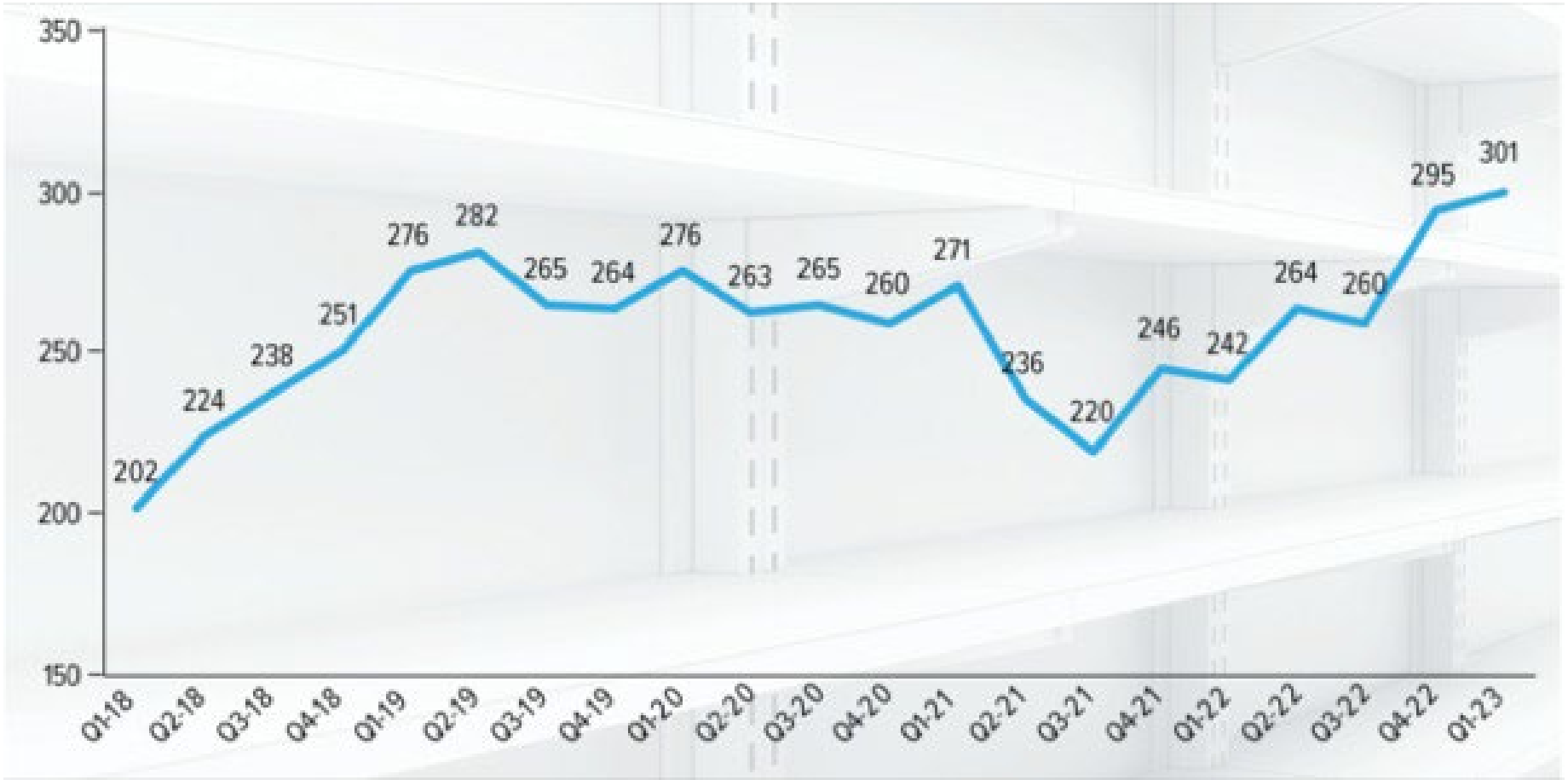
https://www.xywav.com, https://www.xywavhcp.com https://www.lumryzhcp.com

Sodium Oxybate Dosing

Sodium oxybate (Xyrem) **0.5 g/mL oral solution**	• Initiate 4.5 g per night divided into two doses • Titrate up to 1.5 g per night at weekly intervals • 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later • Dosage range: 6 g to 9 g per night
Calcium, magnesium, potassium, sodium oxybates (Xywav) **0.5 g/mL oral solution**	• Initiate at 4.5 g per night, divided into two doses • Titrate up to 1.5 g per night per week • Dosage range: 6 g to 9 g per night orally, divided into two doses • Doses may be divided equally or unequally and the first dose taken at bedtime and the second dose taken 2.5 to 4 hours later
Sodium oxybate (Lumryz) **Packets of 4.5 g, 6 g, 7.5 g, 9 g for extended-release oral suspension**	• Initiate dosage at 4.5 g once per night • Titrate in increments of 1.5 g per night at weekly intervals • Dosage range: 6 g to 9 g once per night orally

https://www.xywav.com, https://www.xywavhcp.com https://www.lumryzhcp.com

Drug Shortages: National Security Risk



https://www.pharmacypracticenews.com/aimages/2023/PPN0723_022a_10088_600.jpg

U.S. FOOD & DRUG ADMINISTRATION

August 1, 2023

Dear Americans,

As leaders of the U.S. Food and Drug Administration (FDA) and the Drug Enforcement Administration (DEA), we recognize the important role that prescription stimulants play in the treatment of conditions such as attention-deficit/hyperactivity disorder (ADHD), binge eating disorder, and uncontrollable episodes of deep sleep (narcolepsy). The lack of availability of certain medications in recent months has been understandably frustrating for patients and their families.

Given the interest related to access to these medications, we want to provide an update on the ongoing actions being taken to resolve the shortages of prescription stimulant medications. In addition, we want to acknowledge important issues that will need to be addressed through longer-term coordination by a variety of entities involved in this effort. This is not a problem that the FDA and DEA can solve on our own. We are urging all stakeholders to work together to resolve these shortages as quickly as possible.

The FDA and DEA do not manufacture drugs and cannot require a pharmaceutical company to make a drug, make more of a drug, or change the distribution of a drug. That said, we are working closely with numerous manufacturers, agencies, and others in the supply chain to understand, prevent, and reduce the impact of these shortages.

The current shortage of stimulant medications is the result of many factors. It began last fall due to a manufacturing delay experienced by one drug maker. While this delay has since resolved, we are continuing to experience its effects in combination with record-high prescription rates of stimulant medications. Data show that, from 2012 to 2021, overall dispensing of stimulants (including amphetamine products and other stimulants) increased by 45.5 percent in the United States. According to a U.S. Centers for Disease Control and Prevention report, particularly during 2020–2021, when virtual prescribing was permitted on a widespread basis during the COVID-19 Public Health Emergency, the percentages in certain age groups grew by more than 10 percent. We are calling on key stakeholders, including manufacturers, distributors, pharmacies, and payors, to do all they can to ensure access for patients when a medication is appropriately prescribed. We want to make sure those who need stimulant medications have access. However, it is also an appropriate time to take a closer look at how we can best ensure these drugs are being prescribed thoughtfully and responsibly.

Stimulants are controlled substances with a high potential for abuse, which can lead to addiction and overdose. Therefore, there are limits (also known as quotas) set by DEA for how much of these drugs can be produced. However, for amphetamine medications, in 2022, manufacturers did not produce the full amount that these limits permitted them to make. Based on DEA's internal analysis of inventory, manufacturing, and sales data submitted by manufacturers of amphetamine products, manufacturers only sold approximately 70 percent of their allotted quota for the year, and there were approximately 1 billion more doses that they could have produced but did not make or ship. Data for 2023 so far show a similar trend.

We (DEA and the FDA) have called on manufacturers to confirm they are working to increase production to meet their allotted quota amount. If any individual manufacturer does not wish to increase production, we have asked that manufacturer to relinquish their remaining 2023 quota allotment. This would allow DEA to redistribute that allotment to manufacturers that will increase production. DEA is also committed to reviewing and improving our quota process.

The FDA is asking professional groups and healthcare providers to accelerate efforts to support appropriate diagnosis and treatment of ADHD, such as further development of additional clinical guidelines for ADHD in adults. In recognition of this need, FDA awarded a grant to the National Academies of Sciences, Engineering, and Medicine (NASEM) to support a scientific meeting on ADHD in adults and considerations for diagnosis and treatment. FDA also recognizes that further research is needed into the diagnosis and treatment of ADHD and believes that research can help inform the development of alternative treatments and an understanding of the behavioral and societal issues leading to widespread misuse of these medications in certain groups.

FDA has already taken steps to support the development of alternative treatment options. In 2020, for instance, FDA permitted marketing of a game-based digital therapeutic to improve attention function in children with ADHD. This device offers a non-drug option for improving symptoms associated with ADHD in children. There are also non-stimulant medications approved to treat ADHD, including one approved in 2021. Additionally, to address continuing concerns of misuse, addiction and overdose of prescription stimulants, the FDA recently issued a drug safety communication and required updates to the labeling to standardize prescribing information and clearly inform patients, caregivers and healthcare professionals of these risks.

FDA and DEA will continue to do all we can to prevent stimulant drug shortages, limit their impact, and resolve them as quickly as possible. We will consider additional actions to prevent non-medical use and identify efforts to better understand and strengthen the supply chain. We also hope that we can all work together to assure that those who need stimulant medications can get them based on the best clinical knowledge about when they are effective, and avoid them when there is no indication for their use.

We will continue to work together and with all of you to mitigate this drug shortage and provide up to date information.

Sincerely,

Robert M. Califf, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration

Anne M. Milgram
Administrator
Drug Enforcement Administration

https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm

U.S. FOOD & DRUG ADMINISTRATION

Home / Drugs / Drug Safety and Availability / FDA Announces Shortage of Adderall

FDA Announces Shortage of Adderall

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Information about Nitrosamine Impurities in Medications

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Drug Safety Communications

Food and Drug Administration Overdose Prevention Framework

Drug Shortages

FDA Drug Safety Podcasts

August 1, 2023: FDA Actions to Address Shortages in Prescription Stimulants

On October 12, 2022, FDA posted a shortage of the immediate release formulation of amphetamine mixed salts, commonly referred to by the brand name Adderall or Adderall IR, on our drug shortage website. FDA is in frequent communication with all manufacturers of amphetamine mixed salts, and one of those companies, Teva, is experiencing ongoing intermittent manufacturing delays. Other manufacturers continue to produce amphetamine mixed salts, but there is not sufficient supply to continue to meet U.S. market demand through those producers.

Amphetamine mixed salts, including Adderall, are FDA-approved for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. Until supply is restored, there are alternative therapies including the extended-release version of amphetamine mixed salts available to health care professionals and their patients for amphetamine mixed salts' approved indications. Patients should work with their health care professionals to determine their best treatment option.

What is FDA doing to address the shortage of Adderall?

Content current as of:
08/01/2023

Regulated Product(s)
Drugs

From 2012 to 2021, overall dispensing of stimulants
(including amphetamine products and other stimulants) increased by 45.5 percent

Amphetamine Formulations

Product	Formulation
Dextroamphetamine (DextroStat, Zenzedi, Procentra)	Tablets, oral solution
Dextroamphetamine ER (Dexedrine Spansule)	Capsule
Mixed amphetamine salts (Adderall)	Tablet
Mixed amphetamine salts ER (Adderall XR)	Capsule
Lisdesamfetamine (Vyvanase)	Capsule, tablet
Racemic amphetamine sulfate (Evekeo, Evekeo ODT)	Tablets, ODT
Mixed amphetamine salts ER liquid (Dyanvel)	Oral suspension
Mixed amphetamine salts ER ODT (Adzenys XR ODT)	Tablets, ODT
Mixed amphetamine salts ER suspension (Adzenys ER)	Oral suspension
Triple-bead mixed amphetamine salts (Mydayis)	Capsule

Methylphenidate Formulations (1)

Product	Formulation
Immediate release (Ritalin, Methylin)	Tablet, oral solution, chew tablet
Extended release (Metadate)	Tablet
Dexmethylphenidate (Focalin)	Tablet
Dexmethylphenidate ER (Foxalin XR)	Capsule
Controlled delivery capsules (Metadate CD)	Capsule
LA capsules (Ritalin LA)	Capsule
Osmotic release oral system (Concerta)	Tablet
Transdermal (Daytrana)	Transdermal
ER suspension (Quillivant XR)	Oral suspension
ER capsules (Aptensio XR	Capsule

Methylphenidate Formulations (2)

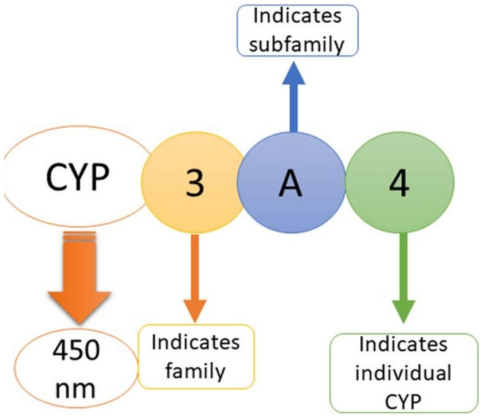
Product	Formulation
ER chew tabs (QuilliChew ER)	Chew tablet
ER ODT (Cotempla XR ODT)	ODT
DR/ER (Jornay PM)	Capsule
ER capsules (Adhansia XR)	Capsule
Serdexmethylphenidate/dexmethylphenidate (Azstarys)	Capsule

Types of Drug 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

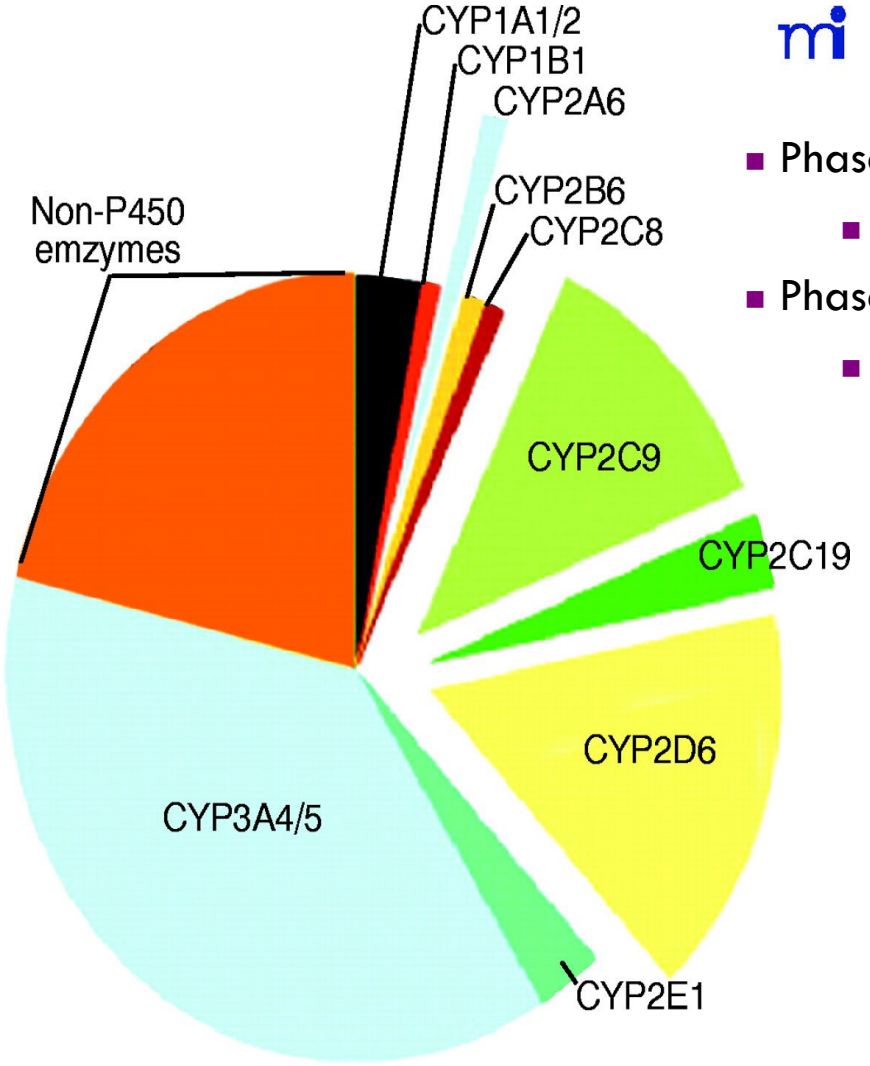
CYP-450 Nomenclature

- 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

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

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-HT_3 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)

Excessive Daytime Sleepiness Treatments

- Armodafinil (Nuvigil)
- Modafinil (Provigil)
- Solriamfetol (Sunosi)
- Pitolisant (Wakix)
- Sodium oxybate (Xyrem, Lumryz)
- Mixed oxybates (Xywav)
- Amphetamine (multiple formulations)
- Methylphenidate

Armodafinil Pharmacology

- Dopamine and norepinephrine reuptake inhibitor
- Hepatic metabolism via multiple pathways, including amine hydrolysis and CYP3A4/5; metabolites include R-modafinil acid and modafinil sulfone
- Elimination in urine < 10% as metabolites

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021875s023lbl.pdf

Armodafinil Interactions (1)

- Clearance of drugs that are substrates for CYP3A4/5 (steroidal contraceptives, cyclosporine, midazolam, and triazolam) may be increased by armodafinil via induction, which results in lower systemic exposure
  - Steroidal contraceptives (ethinyl estradiol)
    - Use alternative or concomitant methods of contraception while taking armodafinil and for one month after discontinuation of armodafinil treatment
  - Cyclosporine blood concentrations may be reduced

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021875s023lbl.pdf

Armodafinil Interactions (2)

- Elimination of drugs that are substrates for CYP2C19 (phenytoin, diazepam, propranolol, omeprazole, and clomipramine) may be prolonged by armodafinil via inhibition of metabolic enzymes, with resultant higher systemic exposure
  - Dose reduction of these drugs may be required when these drugs are used concomitantly with armodafinil

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021875s023lbl.pdf

Armodafinil Interactions (3)

- More frequent monitoring of prothrombin times/INR should be considered whenever armodafinil is co-administered with warfarin
- Caution should be used when concomitantly administering MAO inhibitors and armodafinil

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021875s023lbl.pdf

Modafinil Pharmacology

- Dopamine and norepinephrine reuptake inhibitor
- Primarily hepatic metabolism via amide hydrolysis and lesser extent via CYP 3A4/5
- Urine elimination <10% as metabolites

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf

Modafinil Interactions (1)

- Clearance of drugs that are substrates for CYP3A4/5 (steroidal contraceptives, cyclosporine, midazolam, and triazolam) may be increased by modafinil via induction, which results in lower systemic exposure
  - Steroidal contraceptives (ethinyl estradiol)
    - Use alternative or concomitant methods of contraception while taking modafinil and for one month after discontinuation of armodafinil treatment
  - Cyclosporine: blood concentrations may be reduced

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf

Modafinil Interactions (2)

- Elimination of drugs that are substrates for CYP2C19 (phenytoin, diazepam, propranolol, omeprazole, and clomipramine) may be prolonged by modafinil via inhibition of metabolic enzymes, with resultant higher systemic exposure
  - Dose reduction of these drugs may be required when these drugs are used concomitantly with modafinil

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf

Modafinil Interactions (3)

- More frequent monitoring of prothrombin times/INR should be considered whenever armodafinil is co-administered with warfarin
- Caution should be used when concomitantly administering MAO inhibitors and armodafinil

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf

Solriamfetol Pharmacology

- Dopamine and norepinephrine reuptake inhibitor
- Minimal metabolism
- Urine elimination (95% unchanged)

https://www.sunosihcp.com/assets/files/sunosi.en.uspi.pdf

Solriamfetol Interactions

- Contraindicated in patients receiving concomitant treatment with monoamine oxidase (MAO) inhibitors, or within 14 days following discontinuation of MAOIs, because of the risk of hypertensive reaction
  - Isocarboxazid, phenelzine, tranylcypromine
- Warnings and precautions
  - BP and HR increases - measure HR and BP prior to initiating and periodically throughout treatment
  - Control hypertension before and during therapy
  - Avoid use in patients with unstable cardiovascular disease, serious heart arrhythmias, or other serious heart problems

https://www.sunosihcp.com/assets/files/sunosi.en.uspi.pdf

Pitolisant Pharmacology

- Histamine-3 receptor antagonist/inverse agonist
- Hepatic metabolism via CYP2D6 primarily, metabolized to lesser extent via CYP3A4
- Urine elimination (90%, <2% unchanged), feces 2.3%

https://wakixhcp.com/pdf/wakix-tablets-pi.pdf

Pitolisant Dosing

- **Hepatic impairment**
  - Moderate hepatic impairment: Initial dosage is 8.9 mg once daily
  - Titrate to a maximum dosage of 17.8 mg once daily after 14 days
- **Renal impairment**
  - Moderate (CrCl of 30-50 mL/min) or severe (CrCl 15-29 mL/min) impairment: Initial dosage is 8.9 mg once daily
  - Titrate to maximum dosage of 17.8 mg once daily after 7 days
  - End-stage renal disease (CrCl < 15 mL/min): Not recommended
- **Poor Metabolizers of CYP2D6**
  - Maximum recommended dosage is 17.8 mg once daily

https://wakixhcp.com/pdf/wakix-tablets-pi.pdf

Pitolisant Interactions (1)

- Co-administration with strong CYP2D6 inhibitors
  - For patients receiving strong CYP2D6 inhibitors, initiate pitolisant at 8.9 mg once daily and increase after 7 days to a maximum dosage of 17.8 mg once daily
  - For patients on a stable dose of pitolisant, reduce the pitolisant dose by half upon initiating strong CYP2D6 inhibitors

https://wakixhcp.com/pdf/wakix-tablets-pi.pdf

Pitolisant Interactions (2)

- Co-administration with strong CYP3A4 inducers
  - Concomitant use of strong CYP3A4 inducers decreases pitolisant exposure by 50%
  - Assess for loss of efficacy after initiation of a strong CYP3A4 inducer
  - For patients stable on 8.9 mg or 17.8 mg once daily, increase the dose of pitolisant to double the original daily dose (17.8 mg or 35.6 mg, respectively) over 7 days
  - If concomitant dosing of a strong CYP3A4 inducer is discontinued, decrease pitolisant dosage by half

https://wakixhcp.com/pdf/wakix-tablets-pi.pdf

Pitolisant Interactions (3)

- Histamine-1 (H1) Receptor Antagonists
- Clinical implication
  - Pitolisant increases the levels of histamine in the brain; therefore, H1 receptor antagonists that cross the blood-brain barrier may reduce effectiveness
- Prevention or management
  - Avoid centrally acting H1 receptor antagonists

https://wakixhcp.com/pdf/wakix-tablets-pi.pdf

Pitolisant Interactions (4)

- CYP3A4 Substrates
- Clinical implication
  - Pitolisant is a borderline/weak inducer of CYP3A4 - reduced effectiveness of CYP3A4 substrates may occur when used concomitantly
  - The effectiveness of hormonal contraceptives (ethinyl estradiol) may be reduced when used with pitolisant and effectiveness may be reduced for 21 days after discontinuation of therapy
- Prevention or management
  - Patients using hormonal contraception should be advised to use an alternative non-hormonal contraceptive method during treatment with pitolisant and for at least 21 days after discontinuation of treatment

https://wakixhcp.com/pdf/wakix-tablets-pi.pdf

Pitolisant Interactions (5)

- Warnings and Precautions
  - QT Interval Prolongation: Increases in QT interval
    - Avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval
    - Monitor patients with hepatic or renal impairment for increased QTc

Sodium Oxybate Metabolism

- CNS depressant
- Metabolized by GHB dehydrogenase and beta-oxidation to inactive metabolites and ultimately carbon dioxide and water
- Clearance of GHB is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration
- Less than 5% unchanged in urine, negligible fecal excretion

https://www.avadel.com/lumryz-prescribing-information.pdf

Sodium Oxybate (Xyrem)

- Do not use in combination with alcohol or sedative hypnotics
- Initial Xyrem dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking Xyrem
- Monitor patient response closely and adjust dose accordingly if concomitant use of Xyrem and divalproex sodium is warranted

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021196s030lbl.pdf

Calcium, Magnesium, Potassium, Sodium Oxybates (Xywav)

- Contraindicated for use in combination with alcohol or sedative hypnotics
- When initiating divalproex sodium in patients taking a stable dosage of Xywav, a reduction of the Xywav dosage by at least 20% is recommended with initial concomitant use
- When initiating Xywav in patients already taking divalproex sodium, a lower starting dosage of Xywav is recommended
  - Subsequently, the dosage of Xywav can be adjusted based on individual clinical response and tolerability

https://pp.jazzpharma.com/pi/xywav.en.USPI.pdf

Sodium Oxybate (Lumryz)

- Contraindicated for use in combination with alcohol or sedative hypnotics
- Use of other CNS depressants may potentiate the CNS-depressant effects
- Co-administration with alcohol is contraindicated because of respiratory depression
- Consumption of alcohol may also result in a more rapid release of the dose of sodium oxybate

https://www.avadel.com/lumryz-prescribing-information.pdf

Amphetamine Pharmacology

- Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space
- Metabolism is oxidative deamination to inactive metabolite

https://dailymed.nlm.nih.gov

Amphetamine Interactions

- MAOI antidepressants are contraindicated
  - MAOIs potentiate the effects of amphetamine
  - Do not administer during or within 14 days after use of MAOI
- Alkalinizing agents (GI antacids and urinary)
  - These agents increase blood levels of amphetamine
- Acidifying agents (GI and urinary)
  - These agents reduce blood levels of amphetamine
- Adrenergic blockers, antihistamines, antihypertensives, phenobarbital, phenytoin, veratrum alkaloids, and ethosuximide
  - Effects may be reduced by amphetamines
- Tricyclic antidepressants, norepinephrine, and meperidine
  - Effects may be potentiated by amphetamines

https://dailymed.nlm.nih.gov

Methylphenidate

- Blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space
- Metabolized primarily by de-esterification to inactive metabolite α-phenyl-piperidine acetic acid (PPAA)
- Because methylphenidate is not metabolized by cytochrome P-450 isoenzymes to a clinically important extent, inducers or inhibitors of CYP isoenzymes are not expected to substantially affect the pharmacokinetics

https://dailymed.nlm.nih.gov

Methylphenidate Interactions

- Should not be used in patients being treated (currently or within the proceeding two weeks) with MAO Inhibitors (CONTRAINDICATIONS, Monoamine Oxidase Inhibitors)
- Because of possible effects on blood pressure, use cautiously with pressor agents
- Methylphenidate may decrease the effectiveness of drugs used to treat hypertension
- Human pharmacologic studies have shown that racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, phenytoin, primidone), and tricyclic drugs (imipramine, clomipramine, desipramine)
  - Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate
  - It may be necessary to adjust the dosage and monitor plasma drug concentration (or, in case of coumarin, coagulation times), when initiating or discontinuing methylphenidate

https://dailymed.nlm.nih.gov

New Treatments

- AXS-12 (Reboxetine)
- TAK-861
- TAK-994
- Clarithromycin
- Mazindol

AXS-12 (Reboxetine)

- Axsome Therapeutics, Inc.
- Highly selective and potent norepinephrine reuptake inhibitor being developed for the treatment of narcolepsy
- SYMPHONY (Study Evaluating a Mechanistic Approach to Treating Narcolepsy) study, a phase 3 randomized, multicenter, double-blind, placebo-controlled, parallel-group trial of AXS-12
  - Enrollment in the trial is ongoing

https://classic.clinicaltrials.gov/ct2/show/NCT05059223

TAK-861

- Takeda
- Oral orexin receptor type 2 agonist
- Recruiting Phase III for narcolepsy type 1, narcolepsy type 2

https://classic.clinicaltrials.gov/ct2/show/NCT05687903?cond=narcolepsy&draw=3&rank=18

TAK-994

- Takeda
- Oral orexin receptor-2-selective agonist
- Phase 2 trial published in NEJM July 27, 2023
- Greater improvements on sleepiness and cataplexy than placebo over 8 week period in narcolepsy type 1, more hepatoxic effects led to trial discontinuation

https://classic.clinicaltrials.gov, N J Engl J Med 2023;389:309-321

Clarithromycin

- Sponsor: Emory University
- Macrolide antibiotic
- Antibiotic-mediated Improvements in Vigilance: Mechanisms of Action of Clarithromycin in Hypersomnia Syndromes, Phase II
- Clarithromycin dosed as 500 mg twice daily, once upon awakening and once with lunch, for 14 days

https://classic.clinicaltrials.gov/ct2/show/NCT04026958?cond=narcolepsy&draw=12&rank=104

Mazindol Extended Release

- NSL Pharmaceutics
- Triple monoamine reuptake inhibitor and partial orexin-2 receptor agonist
- FDA approved for weight loss in 1973, later voluntarily withdrawn due to low sales
- Oral treatment for narcolepsy
- Randomized controlled double-blind phase 2 trial (NCT05055024) just completed

https://classic.clinicaltrials.gov/ct2/results?cond=mazindol&term=&cntry=&state=&city=&dist=&Search=Search

Audience Question #3

- A QT interval prolonging medication (levofloxacin) should be avoided with _____?

- A. Armodafinil
- B. Modafinil
- C. Pitolisant
- D. Solriamfetol

Audience Question #4

- Which treatment needs monitoring of blood pressure and heart rate prior to starting therapy, then periodically?

- A. Armodafinil
- B. Modafinil
- C. Solriamfetol
- D. Sodium oxybate

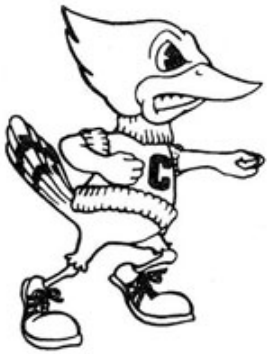
The End

1924

1941

1955

1957



1970

1972

2013