New Horizons in Sleep Medicine Pharmacotherapy

Psychopharmacology Update: 2024

Maryland Psychiatric Society

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Disclosures

- Advisor/Consultant
  - Eisai Inc
  - Idorsia Pharmaceuticals
  - Johnson & Johnson

Initial Comments

- Pharmacotherapy – one of many sleep disorder treatment approaches, sometimes combined with others
- There are numerous sleep disorders, sometimes with overlapping symptom - make sure the all are addressed
- Sometimes the best treatment is deprescribing
- Best practices:
  - Personalize medication selection
  - Incorporate shared decision making
  - Review expectations and possible adverse reactions
  - Discuss duration of therapy and possible discontinuation plan
  - Always check for drug-drug interactions

Sleep Disorders Reviewed

- Insomnia disorder
- Disorders of central hypersomnolence
  - Narcolepsy
  - Idiopathic hypersomnia
- Parasomnias
- Movements disorders of sleep
- Circadian rhythm sleep-wake disorders
- Sleep-disordered breathing disorders

Pharmacotherapy: Broad Categories

- Dietary supplements
  - Regulated as food
  - No requirement for efficacy evidence
- Over-the-counter (OTC) regulated products
  - FDA regulated
  - Ingredients, manufacturing, prescribing information, labeling, warnings
- Off-label prescription medications
- FDA indicated prescription medications

Insomnia disorder

Insomnia Disorder
Dietary Supplements

- Melatonin
- Everything else – for example
  - Valerian
  - Chamomile
  - Passionflower
  - Hops
  - Lavender
  - Ashwagandha
  - Kava
  - Skullcap
  - Magnesium

Insomnia Disorder: Dietary Supplement Melatonin Products

- Might help with sleep onset, unlikely for sleep maintenance
- Most likely helpful for people with circadian rhythm phase delay (night owls) and non-24-hour disorder
- Limited support for jet lag and shift work
- Try 0.5 to 3 mg – more is not better with melatonin
- Take prior to bedtime (1 to 2 hours)
- But not too early – at least 2 hours after last meal
- Avoid eating late in the evening, even if you're not taking melatonin

Insomnia Disorder
OTC Sleep Aids

- Antihistamines
  - Diphenhydramine
    - Peak concentration: 2 to 3 hours
    - Elimination half-life: 8.5 ± 3.2 hours (short in children; longer in elderly)
  - Doxylamine
    - Peak concentration: 2 to 4 hours
    - Elimination half-life: 10 to 12 hours (longer in elderly)
- Relatively long acting → morning grogginess
- Pharmacodynamics
  - Histamine H_1 receptor antagonists
  - Muscarinic acetylcholine receptor antagonists
  - Tolerance to sedating effects may develop with daily use
- (Non-OTC hydroxyzine similar to above medications)

Insomnia Disorder
Off-Label Prescribed Medications

- Antidepressants (trazodone, mirtazapine, amitriptyline, doxepin)
- Antipsychotics (quetiapine)
- Anxiolytics (alprazolam, clonazepam, lorazepam)
- Antihistamines (prescribed doses higher than OTC)
- Alpha-2-delta ligands (gabapentin, pregabalin)
- Antihypertensives (clonidine)
- Anesthetics (dexmedetomidine, propofol)

Trazodone:
Highlights of Prescribing Information

- **Indications and Usage**: “a selective serotonin reuptake inhibitor indicated for the treatment of major depressive disorder (MDD)”
- **Dosage and Administration**
  - Maximum dose: 400 mg/day in divided doses
  - Should be taken shortly after a meal
  - When discontinued, gradual doses reduction is recommended

- US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Trazodone: Pharmacology

- **Pharmacodynamics**
  - 5-HT_{2A} antagonist (Ki = 35.6 nM)
  - 5-HT_{2B} antagonist (Ki = 78.4 nM)
  - 5-HT_{2C} antagonist (Ki = 224 nM)
  - Serotonin reuptake inhibition (Ki = 367 nM)
  - α_{1A} antagonist (Ki = 153 nM)
  - α_{2C} antagonist (Ki = 155 nM)
  - 5-HT_{1A} partial agonist (Ki = 118 nM)
- **Pharmacokinetics**
  - Peak plasma level (empty stomach) approximately 1 hour
  - Elimination half-life: Biphasic 10–12 hours
  - Active metabolite (CYP3A4): *m*-chlorophenylpiperazine (mCPP)

- US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.
- Bryant SG, et al. *Clin Pharm*. 1982;1(5):406-417.

Trazodone: Highlights of Prescribing Information *Warnings and Precautions*

- Suicidal thoughts and behaviors
- Serotonin syndrome
- Cardiac arrhythmias: Increases the QT interval
- Orthostatic hypotension and syncope
- Increased risk of bleeding
- Priapism (including clitoral priapism*)
- Activation of mania or hypomania
- Potential for cognitive and motor impairment
- Angle-closure glaucoma
- Hyponatremia

Battaglia C, Venturoli S. Persistent genital arousal disorder and trazodone. Morphometric and vascular modifications of the clitoris. A case report. J Sex Med. 2009;6(10):2896-2900. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Insomnia Disorder Regulatory-Approved Medications

- Benzodiazepine receptor agonists
  - Benzodiazepine hypnotics
  - Non-benzodiazepine hypnotics (“Z-drugs”)
- Melatonin receptor agonists
  - Ramelteon
- Selective histamine receptor antagonists
  - Low dose doxepin
- Dual orexin/hypocretin receptor antagonists (DORAs)
  - Suvorexant
  - Lemborexant
  - Daridorexant

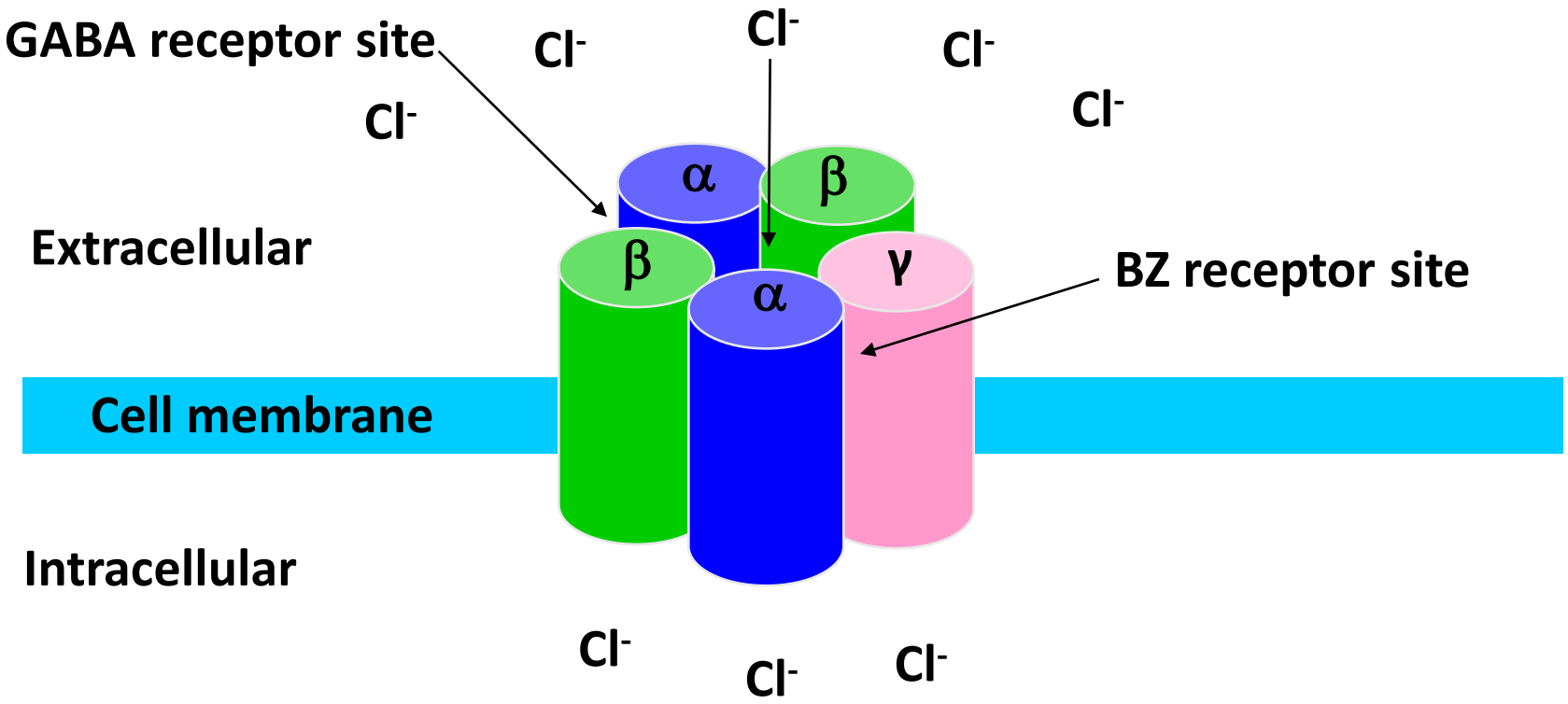
Benzodiazepine Receptor Agonists
Benzodiazepines

- Pharmacodynamics
  - Positive allosteric modulators of GABA responses at the GABA-A receptor complex
  - Multiple GABA-A receptor α subunit subtypes
  - Targeted action in the hypothalamic sleep nuclei
  - Global CNS effects
- Pharmacokinetics
  - Relatively rapidly absorbed
  - Very wide range of elimination half-lives: hours to days
  - Expect prolonged half-life in older adults
  - Most efficacious for sleep onset and maintenance
  - Potential for residual daytime sedation

Benzodiazepine Receptor Agonists Non-Benzodiazepines ("Z-drugs")

- Pharmacodynamics
  - Positive allosteric modulators of GABA responses at the GABAA receptor complex
  - Selected GABA-A receptor α subunit subtypes
  - Targeted action in the hypothalamic sleep nuclei
  - Global CNS effects
- Pharmacokinetics
  - Relatively rapidly absorbed
  - Relatively shorter elimination half-lives: About 1 to 6 hours
  - Expect prolonged half-life in older adults and for zolpidem in women
  - Indications vary for sleep onset and maintenance
  - Limited potential for residual daytime sedation

$GABA_A$ Receptor Complex



Möhler H, et al. *J Pharmacol Exp Ther*. 2002;300(1):2-8. Rowlett JK, et al. *CNS Spectr*. 2004;10(1):40-48.

Melatonin Receptor Agonist: Ramelteon - 1

- Pharmacodynamics
  - Melatonin MT_1 and MT_2 receptor agonist
  - Targeted action in the hypothalamic suprachiasmatic nucleus (SCN)
  - Reduces evening circadian driven arousal
  - Reinforces circadian periodicity
  - Enhances sleep onset
- Pharmacokinetics
  - Relatively rapidly absorbed
  - Relatively short elimination half-life: 1 to 2.6 hours
  - Limited potential for residual daytime sedation

US Food and Drug Administration. Drugs@FDA. www.accessdata.fda.gov/scripts/cder/drugsatfda.

Melatonin Receptor Agonist: Ramelteon - 2

- Indicated for insomnia with sleep onset difficulty
- Adverse events
  - Somnolence (5%)
  - Dizziness (5%)
  - Fatigue (4%)
- No abuse liability
- Avoid with
  - Hepatic impairment (moderate to severe)
  - Fluvoxamine (Luvox) coadministration

US Food and Drug Administration. Drugs@FDA. www.accessdata.fda.gov/scripts/cder/drugsatfda.

Histamine Receptor Antagonist Low-Dose Doxepin - 1

- Pharmacodynamics
  - At very low doses primarily histamine receptor antagonist (avoiding receptor effects associated with higher doses)
  - Histamine is a potent wake-promoting neurotransmitter
  - Enhances sleep by reducing nighttime histamine arousal
- Pharmacokinetics
  - Relatively rapidly absorbed
  - Elimination half-life: About 15.3 hours
  - Limited potential for residual daytime sedation

US Food and Drug Administration. Drugs@FDA. www.accessdata.fda.gov/scripts/cder/drugsatfda.

Histamine Receptor Antagonist Low-Dose Doxepin - 2

- Indicated for the treatment of insomnia characterized by difficulties with sleep maintenance
- Ultra-low dose (3 mg, 6 mg)
- No abuse liability
- Most common adverse effects
  - Somnolence/sedation
  - Nausea
  - Upper respiratory tract infection

US Food and Drug Administration. Drugs@FDA. www.accessdata.fda.gov/scripts/cder/drugsatfda.

Orexin Receptor Antagonists
New and Emerging Compounds

- Suvorexant
  - FDA approved in 2014
  - Dual orexin receptor antagonist (DORA)
- Lemborexant
  - FDA approved in 2019
  - Dual orexin receptor antagonist (DORA)
- Daridorexant
  - FDA approved 2022
  - Dual orexin receptor antagonist (DORA)
- Seltorexant
  - Investigational for comorbid depression and insomnia
  - Single orexin receptor antagonist (2-SORA)

Belsomra Prescribing Information, 2018. Dayvigo Prescribing Information, 2019. Quviviq Prescribing Information, 2022. Brooks S, et al. *J Psychopharmacol*. 2019;33(2):202-209.

Dual Orexin Receptor Antagonists (DORAs) -1

- Pharmacodynamics
  - Dual orexin receptor (OX1 and OX2) antagonist
  - Hypothalamic neurons with peptides orexin-A and orexin-B project to cortex and wake-promoting nuclei to reinforce and stabilize wakefulness
  - DORAs promote sleep by decreasing orexin-associated CNS arousal
- Pharmacokinetics
  - Relatively rapidly absorbed
  - Elimination half-lives: Range from about 8 to 19 hours
  - Dose-dependent potential for residual daytime sedation

US Food and Drug Administration. Drugs@FDA. www.accessdata.fda.gov/scripts/cder/drugsatfda.

Dual Orexin Receptor Antagonists (DORAs) -2

- Indication: For the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance
- FDA approvals: 2014 to 2022
- Contraindication: narcolepsy
- Adverse reactions: somnolence
- Schedule IV controlled substance

US Food and Drug Administration. Drugs@FDA. www.accessdata.fda.gov/scripts/cder/drugsatfda.

	LEMBOREXANT	SUVOREXANT	DARIDOREXANT
Approval	2019	2014	2022
Indication	Difficulty with sleep onset and/or sleep maintenance	Difficulty with sleep onset and/or sleep maintenance	Difficulty with sleep onset and/or sleep maintenance
Available doses	5, 10	5, 10, 15, 20	25, 50
Contraindications	Narcolepsy	Narcolepsy	Narcolepsy
Most common adverse reaction	Somnolence	Somnolence	Headache, fatigue, somnolence
Pharmacokinetics Half-life (hours)	17, 19	12	8
DEA Schedule	IV	IV	IV

Belsomra Prescribing Information, 2020. Dayvigo Prescribing Information, 2020. Quviviq Prescribing Information, 2022

FDA-Approved Insomnia Medications, Part 1

Generic name	Brand name	Available doses (mg)	Elimination half-life (hours)
Benzodiazepine Receptor Agonists			
Benzodiazepines Immediate Release			
Estazolam	ProSom	1, 2	10 to 24
Flurazepam	Dalmane	15, 30	2.3 (active metabolite: 48 - 160)
Quazepam	Doral	7.5, 15	39 (active metabolite 73)
Temazepam	Restoril	7.5, 15, 22.5, 30	3.5 to 18.4
Triazolam	Halcion	0.125, 0.25	1.5 to 5.5
Nonbenzodiazepines Immediate Release			
Eszopiclone	Lunesta	1, 2, 3	~6 (~9 in elderly)
Zaleplon	Sonata	5, 10	1
Zolpidem	Ambien	5, 7.5, 10	~2.5
Nonbenzodiazepines Extended Release			
Zolpidem ER	Ambien CR	6.25, 12.5	2.8 in males (longer in females)
Nonbenzodiazepines Alternate Delivery			
Zolpidem oral spray	Zolpimist	5, 10	2.7 – 3.0
Zolpidem sublingual	Edluar	5, 10	~2.5
Zolpidem sublingual	Intermezzo	1.75, 3.5	~2.5

US Food and Drug Administration. Drugs@FDA. www.accessdata.fda.gov/scripts/cder/drugsatfda.

FDA-Approved Insomnia Medications, Part 2

Generic name	Brand name	Available doses (mg)	Elimination half-life (hr)
Selective melatonin receptor agonist			
Ramelteon	Rozerem	8	1 – 2.6
CR Melatonin	Circadin	2	3.5 – 4.0
Selective histamine H_1 receptor antagonist			
Doxepin	Silenor	3, 6	15.3
Dual orexin receptor antagonist			
Daridorexant	Quviviq	25, 50	8
Lemborexant	Dayvigo	5, 10	17 - 19
Suvorexant	Belsomra	5, 10, 15, 20	12

US Food and Drug Administration. Drugs@FDA. www.accessdata.fda.gov/scripts/cder/drugsatfda.

Disorders of central hypersomnolence

Narcolepsy (Types 1 and 2)

Idiopathic hypersomnia

FDA Approved Indications for Excessive Daytime Sleepiness and Cataplexy

	Medication	Narcolepsy EDS	Narcolepsy cataplexy	Idiopathic hypersomnia	Obstructive sleep apnea EDS	Shift work disorder	
Provigil	Modafinil	✓			✓	✓	DAYTIME
Nuvigil	Armodafinil	✓			✓	✓	
Ritalin	Methylphenidate	✓					
Adderall	Amphetamine formulations	✓					
Sunosi	Solriamfetol	✓			✓		
Wakix	Pitolisant	✓	✓				
Xyrem, Lumryz	Sodium oxybate	✓	✓				NIGHTTIME
Xywav	Mixed oxybate salts	✓	✓	✓			

Disorders of Central Hypersomnolence Excessive Daytime Sleepiness (EDS)

- Daytime dosing
  - Methylphenidate formulations
  - Amphetamine formulations
  - Modafinil/armodafinil
  - Solriamfetol
  - Pitolisant
  - Caffeine (non-prescription, dietary supplement and drug)
- Bedtime dosing – oxybates, all liquid formulations
  - Sodium oxybate (twice nightly)
  - Calcium, magnesium, potassium, sodium oxybates (Mixed oxybate salts or low-sodium oxybates, twice nightly)
  - Extended-release sodium oxybate (once nightly)

Disorders of Central Hypersomnolence
Cataplexy in Narcolepsy

- FDA-approved for cataplexy
  - Sodium oxybate (twice nightly, once nightly (ER))
  - Low-sodium oxybate (mixed oxybate salts, twice nightly)
  - Pitolisant
- Off-label for cataplexy
  - SNRIs (especially venlafaxine)
  - SSRIs
  - Selective norepinephrine reuptake inhibitor (atomoxetine)
  - TCAs (clomipramine, protriptyline)

Central Disorders of Hypersomnolence New Horizons

- Expanded indications for idiopathic hypersomnia
- Orexin agonists (at least 14 in Phase III trials)
  - **OX2R**
  - OX1R
  - Dual receptor
- Histamine H3 receptor antagonists
- Selective norepinephrine reuptake inhibitor (reboxetine)
- Modafinil plus astroglial connexin inhibitor
- Flumazenil (GABA-A receptor antagonist)
- Clarithromycin (negative GABA-A allosteric modulator)

Parasomnias

Non-REM related

REM related

Parasomnias
REM sleep related

- No FDA-approved medications with indications for REM sleep parasomnia treatment
- REM-sleep behavior disorder
  - Consider medication discontinuation (e.g., antidepressants)
  - Melatonin (doses up to 15 mg)
  - Clonazepam (0.5 to 1.0 mg)
  - Acetylcholinesterase inhibitors (donepezil, rivastigmine)
- Nightmare disorder
  - Consider medication discontinuation
  - Prazosin – mixed support for PTSD nightmares
  - Possible benefit: clonidine, gabapentin, topiramate, trazodone, terazosin, olanzapine, and risperidone

Parasomnias
Non-REM sleep related

- No FDA-approved medications with indications for Non-REM sleep parasomnia treatment
- Sleep terrors, sleepwalking, confusional arousals, sexsomnia, sleep related eating disorder (SRED)
- Medication options
  - Clonazepam (0.5 to 1.0 mg)
  - Melatonin
  - SRED: topiramate, clonazepam, selected antidepressants

Movement disorders of sleep

Restless legs syndrome

Periodic limb movement disorder

Movement Disorders of Sleep
Restless Legs Syndrome (RLS)

- Always review iron studies and ferritin and follow guidelines for possible oral or intravenous iron formulations
- Consider discontinuation of contributing medications, including antidepressants and antipsychotics
- FDA-approved RLS medications
  - Dopamine agonists
    - Pramipexole (Mirapex)
    - Ropinirole (Requip)
    - Rotigotine patch (Neupro)
  - Alpha-2-delta ligands
    - Gabapentin enacarbil

Movement Disorders of Sleep
AASM 2024 RLS Clinical Guidelines - 1

- STRONG FOR
  - Gabapentin enacarbil
  - Gabapentin
  - Pregabalin
  - IV ferric carboxymaltose
- CONDITIONAL FOR
  - Various IV and oral iron formulations
  - Dipyridamole
  - Extended-release oxycodone and other opioids

Movement Disorders of Sleep
AASM 2024 RLS Clinical Guidelines - 2

- CONDITIONAL AGAINST
  - Standard use of
    - Levodopa
    - Pramipexole
    - Ropinirole
    - Rotigotine patch
  - Bupropion
  - Carbamazepine
  - Clonazepam
  - Valerian
  - Valproic acid
- STRONG AGAINST
  - Cabergoline

Circadian rhythm sleep-wake disorders

Intrinsic

Extrinsic

Circadian Rhythm Sleep-Wake Disorders

- Intrinsic Disorders
  - Advance Sleep-Wake Phase Disorder (ASWPD)
  - Delayed Sleep-Wake Phase Disorder (DSWPD)
  - Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD)
  - Irregular Sleep-Wake Rhythm Disorder (ISWRD)
- Extrinsic Disorders
  - Shift Work Disorder
  - Jet Lag Disorder

Circadian Rhythm Sleep-Wake Disorders Intrinsic Disorders

- FDA-approved medications
  - Non-24-Hour Sleep-Wake Rhythm Disorder: Tasimelteon (Hetlioz)
- American Academy of Sleep Medicine Clinical Guidelines (2015)
  - Strategically timed melatonin
    - Delayed Sleep-Wake Phase Disorder
    - Non-24-Hour Sleep-Wake Rhythm Disorder

Circadian Rhythm Sleep-Wake Disorders
Shift Work Disorder (SWD)

- FDA-approved for excessive sleepiness associated with SWD
  - Modafinil
  - Armodafinil
- American Academy of Sleep Medicine Clinical Guidelines (2007)
  - Modafinil during the night shift
  - Melatonin prior to daytime sleep
  - Caffeine to enhance alertness during the night shift

Circadian Rhythm Sleep-Wake Disorders
Jet Lag Disorder

- No medications are FDA-approved for Jet Lag Disorder
- American Academy of Sleep Medicine Clinical Guidelines (2007)
  - Melatonin administered at the appropriate time is indicated to reduce symptoms of jet lag and improve sleep
  - Short-term use of a benzodiazepine receptor agonist hypnotic is indicated for the treatment of jet lag-induced insomnia
  - Caffeine is indicated as a way to counteract jet lag-induced sleepiness

Sleep-related breathing disorders

Obstructive sleep apnea

Central sleep apnea

Obstructive Sleep Apnea (OSA)
Primary Treatment – New Horizons

- No FDA-approved medications for upper airway collapsibility
- Indirect benefits from weight loss medications (e.g., tirzepatide)
- Investigational
  - Noradrenergic-antimuscarinic combinations
    - atomoxetine, reboxetine, or milnacipran
    - oxybutynin, aroxybutynin, or hyoscine
  - Intranasal options
    - Leptin
    - Oxytocin

Obstructive Sleep Apnea (OSA) Excessive Daytime Sleepiness (EDS)

- FDA-approved for OSA EDS – assuming primary treatment active (e.g., CPAP)
  - Modafinil
  - Armodafinil
  - Solriamfetol

Central Sleep Apnea (CSA)
Primary Treatment – New Horizons

- No FDA-approved medications for CSA but medications might improve primary underly causes such as heart failure
- Discontinuation of opioids may be best approach for selected patients
- Off-label/investigational
  - Acetazolamide – promotes metabolic acidosis and increases apneic threshold for carbon dioxide
  - Theophylline – respiratory stimulant
  - Buspirone – may promote ventilatory stability by modulating chemosensitivity to CO2