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POWERPOINT PRESENTATIONS

Student Lecture #2

Post Traumatic Stress Disorder (PTSD): 1 hour

Audience: Psychiatric nurse practitioner students

DISCLOSURE

- I do not have any conflicts of interest to disclose in relation to this presentation.
- This presentation will include discussion of off-label indications for treatment of PTSD and associated symptoms.

OBJECTIVES

- State the VA/DOD Clinical Practice Guidelines For the Management of Post Traumatic Stress Disorder (PTSD) and Acute Stress Disorder recommendations for the treatment of PTSD
- Name the drug classes and drugs used to treat PTSD
- Describe the adverse effects and clinical pearls for drugs used to treat PTSD
- Recognize the drug classes and drugs to avoid in patients with PTSD
- Identify co-occurring conditions in patients with PTSD
- Examine potential causes of sleep disturbances independent of PTSD

VA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF PTSD AND ACUTE STRESS DISORDER

TREATMENT OF PTSD

PTSD: TREATMENT RECOMMENDATIONS

Trauma-focused Psychotherapy

PTSD: TREATMENT RECOMMENDATIONS

Pharmacotherapy

OR

Non-trauma-focused Psychotherapy

PHARMACOTHERAPY FOR PTSD

PTSD: PHARMACOTHERAPY

Antidepressants have strongest evidence for reducing PTSD symptoms

PTSD: PHARMACOTHERAPY

Recommended Agents
Paroxetine
Sertraline
Fluoxetine
Venlafaxine

PTSD: PHARMACOTHERAPY

Recommended Agents

Paroxetine
Sertraline
Fluoxetine
Venlafaxine

Benefits > harms
Adverse effects: sexual dysfunction, increased sweating, GI upset, drowsiness/fatigue

PTSD: PHARMACOTHERAPY

Neutral Agents

Other Antidepressants → SSRIs, SNRIs, Bupropion, Mirtazapine
Prazosin

Suggest Against

Citalopram

PTSD: PHARMACOTHERAPY

- SSRI
- SNRI
- 5HT Reuptake Inhibitor Antagonist
- Tricyclic Antidepressants
- Monoamine Oxidase Inhibitors

PTSD: PHARMACOTHERAPY

Recommended Agents

Paroxetine
Sertraline
Fluoxetine
Venlafaxine

↓

SSRIs

PHARMACOTHERAPY: SSRIs

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Clinical Pearls

- Paroxetine (Paxil®)
  - ↓ t ½
  - ↑ anticholinergic effects
  - ↑ weight gain
  - ↑↑ drug-drug interactions
- Sertraline (Zoloft®)
  - ↑ GI effects (i.e., diarrhea)
- Fluoxetine (Prozac®)
  - ↑ t ½
  - ↑ activating
  - ↑↑ drug-drug interactions

*Other SSRIs may be beneficial

PTSD: PHARMACOTHERAPY

Recommended Agents

Paroxetine
Sertraline
Fluoxetine
Venlafaxine

↓

SNRIs

PHARMACOTHERAPY: SNRIs

SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS

Clinical Pearls

- Venlafaxine (Effexor®)
  - Off-label use for neuropathic pain associated with diabetes mellitus
  - Increased blood pressure (>225mg/day)

PHARMACOTHERAPY: SSRIs & SNRIs

SELECTIVE SEROTONIN REUPTAKE INHIBITORS
SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS

Adverse Effects

- Nausea
- Headache
- Diarrhea
- Anxiety
- Nervousness
- Sexual Dysfunction
- Agitation
- Dizziness
- Hyponatremia/SIADH
- Serotonin Syndrome

PTSD: PHARMACOTHERAPY

Suggested Agents

Nefazodone
Imipramine
Phenelzine

5HT Reuptake Inhibitor/Antagonist

PHARMACOTHERAPY: NEFAZODONE

SEROTONIN REUPTAKE INHIBITORS/ANTAGONIST

Clinical Pearls

- Nefazodone (Serzone®)
  - Serious potential toxicity, should be managed carefully
  - BBW: hepatoxicity
  - ↑ ↑ drug-drug interactions

*Trazodone: traditionally used for insomnia

PHARMACOTHERAPY: 5HT REUPTAKE INHIBITOR/ANTAGONIST

Adverse Effects

- Orthostatic hypotension
- Nausea
- Constipation
- Dry mouth
- Headache
- Dizziness
- Somnolence
- Priapism

PTSD: PHARMACOTHERAPY

Suggested Agents

Nefazodone
Imipramine
Phenelzine

TCAs

PHARMACOTHERAPY: TCAs

TRICYCLIC ANTIDEPRESSANTS

Clinical Pearls

- Imipramine (Tofranil®)
  - Tertiary amine
    - ↑ anticholinergic effects

- TCAs
  - ↑ ↑ ↑ side effects
  - Serious potential toxicity, should be managed carefully
  - Avoid within 3 months of acute MI
  - Relatively CI in patients with CAD or prostatic enlargement

PHARMACOTHERAPY: TCAs

TRICYCLIC ANTIDEPRESSANTS

Adverse Effects

- Dry mouth
- Dry eyes
- Constipation
- Orthostatic hypotension
- Tachycardia
- Ventricular arrhythmias
- Weight gain
- Drowsiness
- Photosensitivity

PTSD: PHARMACOTHERAPY

Suggested Agents
Nefazodone
Imipramine
Phenelzine

MAOIs

PHARMACOTHERAPY: MAOIs

MONOAMINE OXIDASE INHIBITORS

Clinical Pearls

- Phenelzine (Nardil®)
  - CI in heart failure, hypertension, hepatic impairment, severe renal impairment
  - ↑ drug-drug interactions
  - ↑ drug-food interactions

PHARMACOTHERAPY: MAOIs

MONOAMINE OXIDASE INHIBITORS

Adverse Effects

- Postural hypotension, ↓ heart rate, edema
- Sedation and sleep disturbances
- Headache
- Dry mouth, constipation, upset stomach, weight gain
- Sexual dysfunction
- Hypertensive crisis

PHARMACOTHERAPY: MAOIs

MONOAMINE OXIDASE INHIBITORS

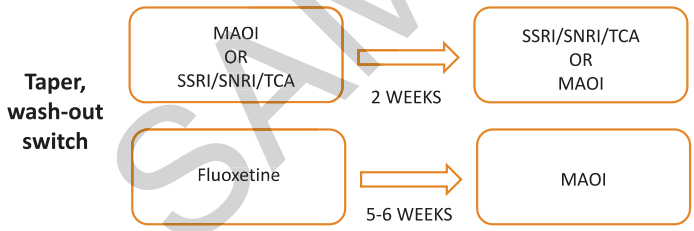
DRUG-DRUG INTERACTIONS	VS	DRUG-FOOD INTERACTIONS
▪ Serotonergic agents; serotonin syndrome ▪ Antidepressants, opioids, linezolid, carbamazepine, methylene blue, triptans ▪ Sympathomimetic agents; increased blood pressure, hypertensive crisis, seizures ▪ Decongestants, stimulants, TCAs, SNRIs, bupropion, appetite suppressants, tramadol		▪ Tyramine containing foods; hypertensive crisis  AGED TO PERFECTION

ANTIDEPRESSANTS: BLACK BOX WARNING

Increase risk of suicidal thinking and behavior in children, adolescents, and young adults (up to 24 years of age)

PHARMACOTHERAPY: SWITCHING ANTIDEPRESSANTS

Direct switch	Taper, immediate switch	**Taper, wash-out switch**	Cross-taper switch



PHARMACOTHERAPY: DISCONTINUING ANTIDEPRESSANTS

- Goal: avoidance of discontinuation symptoms
  - No one "size fits all" approach

Taper! ↓ **TDD 25% per week**

- High risk patients
  - 5-8 weeks of therapy
  - Higher doses of antidepressants
  - Compliance issues
  - Antidepressants with short t ½ (paroxetine)
  - Venlafaxine!!!

PHARMACOTHERAPY: DISCONTINUING ANTIDEPRESSANTS

Discontinuation Symptoms

- **F**lu-like symptoms
- **I**nsomnia
- **N**ausea
- **I**mbalance
- **S**ensory disturbances
- **H**yperarousal

- **TCA** – lack sensory abnormalities, equilibrium issues
- **MAOI** – more severe: worsening depression, confusion, anxiety, catatonia

PHARMACOTHERAPY: AGENTS TO AVOID

Antipsychotics
Benzodiazepines
Cannabinoids

Avoid Starting

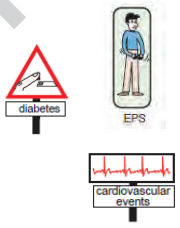
Discuss Discontinuation

AGENTS TO AVOID: ANTIPSYCHOTICS

- Suggest against due to lack of strong evidence for efficacy and known adverse effect profiles and associated risks

Side Effects/Risks

1. Metabolic side effects
2. Extrapyramidal symptoms
3. Geriatric considerations



AGENTS TO AVOID: ANTIPSYCHOTICS

Metabolic Side Effects

- Hyperglycemia
- New onset diabetes
- Weight gain
- ↑ lipid concentrations
- Hyperprolactinemia

Extrapyramidal Symptoms

- Akathisia
- Pseudo-parkinsonism
- Dystonia
- Tardive Dyskinesia

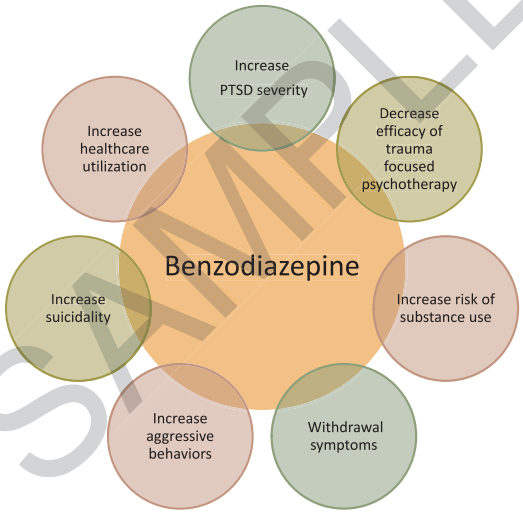
Geriatric Considerations

- Increased risk of stroke in the elderly
- Increase risk of death in elderly patients with dementia

AGENTS TO AVOID: BENZODIAZEPINES

- Ineffective for the treatment and prevention
- High risk, low benefit
- Avoid initiation and discuss discontinuation

AGENTS TO AVOID: BENZODIAZEPINES



AGENTS TO AVOID: BENZODIAZEPINES

Advise
- Educate about risks

Assess
- Readiness to discontinue

Assist
- Provide written taper schedule

AGENTS TO AVOID: BENZODIAZEPINES

Benzodiazepine Tapering Strategies

1. Gradually taper the original benzodiazepine
2. Substitute with longer-acting benzodiazepine then gradually taper
3. Taper to lower dose of original benzodiazepine then switch to longer-acting

AGENTS TO AVOID: BENZODIAZEPINES

<u>Slow taper</u> (3-6 months) is preferred and associated with total cessation of benzodiazepine use in about two-thirds of patients

AGENTS TO AVOID: BENZODIAZEPINES

Potential Withdrawal Symptoms

During Taper	Less Common	Rare
• Insomnia/nightmares • Anxiety/irritability • Depression • Muscle stiffness • Flu-like symptoms • Paresthesia • GI disturbances	• Depersonalization • Decreased memory/concentration • Weakness	• Delusions/hallucinations /delirium • Visual disturbances • Seizures

Patients may experience withdrawal after 4 weeks of use

Timeline: 1 to 7 days and can last 4 to 14 days

AGENTS TO AVOID: CANNABINOIDS

- Lack of large, well-designed studies evaluating the efficacy of cannabinoids in patients with PTSD
- Preliminary evidence showed improvement in PTSD nightmares
- Potential benefits are offset by serious side effects

Not recommended due to lack of evidence, known adverse effects, and associated risks

AGENTS TO AVOID: CANNABINOIDS

Short Term
- Poor focus, memory, reaction time
- Difficulty with problem solving
- Hallucinations, paranoia, anxiety

Long Term
- Memory problems, trouble learning new things
- Depression, hallucinations, paranoia, anxiety, worsening PTSD symptoms
- Addiction

TREATMENT OF PTSD WITH CO-OCCURRING CONDITIONS

- Presence of co-occurring disorder(s) should NOT prevent patients from receiving guideline-recommended treatments for PTSD (i.e., SUD and co-occurring sleep disturbances)

Sleep disturbances

CO-OCCURRING CONDITIONS: SLEEP DISTURBANCES

Sleep disturbances (insomnia/nightmares) are found in 90-100% of patient's with PTSD

Examine Potential Causes!

- Obstructive sleep apnea
- Restless leg syndrome
- Early morning awakening
- Alcohol

PTSD: INSOMNIA

Cognitive Behavioral Therapy For Insomnia (CBT-I)

PTSD: NIGHTMARES

- Significant impact on patients with PTSD!
  - Intrusion
  - Trauma-related feelings and thoughts
  - Avoidance
  - Arousal

PTSD: NIGHTMARES

Prazosin

- Global symptoms; suggest against
- Nightmares associated with PTSD; recommendation is neutral
- May still be effective option in some patients with PTSD

PHARMACOTHERAPY: PRAZOSIN

ALPHA-1-BLOCKER

Clinical Pearls

- Dosed at bedtime
- How to dose: 1 – 2mg QHS with an increase of 1mg every 3 to 7 days
- Only increase dose if nightmares are still present and adverse effects are absent or mild
- Dosing range: 1 – 20mg with average effective dose of 9 – 13mg daily

PHARMACOTHERAPY: PRAZOSIN

ALPHA-1-BLOCKER

Adverse Effects

- First dose hypotension
- Orthostatic hypotension
- Dizziness
- Somnolence
- Headache
- Lightheadedness
- Urinary incontinence

SUMMARY

- First-line treatment for PTSD is trauma-focused psychotherapy
- Second-line treatment is pharmacotherapy or non-trauma-based psychotherapy
- Choose pharmacotherapy that helpful not harmful
  - Paroxetine, sertraline, fluoxetine, and venlafaxine
  - Avoid starting and discuss discontinuation of antipsychotics, benzodiazepines, and cannabinoids
- Co-occurring conditions do not preclude treatment for PTSD
- Evaluate the patient as a whole and consider alternative etiologies for co-occurring conditions, such as sleep disturbances

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Thank you!
Questions?

Student Lecture #3

Sleep Disorders: 2 hour

Audience: Psychiatric nurse practitioner students

Management of Sleep-Wake Disorders

Part I: Insomnia

Objectives

1. Identify the drugs used to treat insomnia per the American Academy of Sleep Medicine
2. Describe the pharmacologic treatments for insomnia
3. List the key adverse effects of pharmacologic treatments for insomnia
4. Discuss the clinical pearls associated with the drug/drug classes used to treat insomnia

Insomnia Treatment

Insomnia: Pharmacotherapy

Recommended by American Academy of Sleep Medicine:

- Sleep onset:
  - Ramelteon, triazolam, zaleplon
- Sleep maintenance:
  - Doxepin, suvorexant
- Sleep onset and maintenance:
  - Eszopiclone, temazepam, zolpidem

Insomnia: Pharmacotherapy

Not Recommended by American Academy of Sleep Medicine:

- Sleep maintenance nor onset:
  - Diphenhydramine
  - Melatonin
  - Tiagabine
  - Trazodone
  - L-tryptophan
  - Valerian

Insomnia: Pharmacotherapy

LENGTH OF TREATMENT
Intended for short-term use (≤4 to 8 weeks), preferably in conjunction with nonpharmacologic. Limit long-term use to cases for which nonpharmacologic treatments are not available or not effective and benefits are felt to outweigh risks.

Benzodiazepines

C-IV

- FDA approved:
  - Sleep onset or maintenance: **temazepam** (Restoril®), estazolam (ProSom®), flurazepam (Dalmane®), quazepam (Doral®)
  - Sleep onset: **triazolam** (Halcion®)
- MOA
  - $GABA_A$ receptor agonists

Benzodiazepines

C-IV

- Adverse effects
  - Drowsiness, sedation, psychomotor impairment (i.e., increased risk of falls), disorientation, depression, confusion, irritability, aggression, paradoxical excitation/disinhibition, impairment of memory and recall
  - Rebound insomnia
  - Tolerance can develop over time to the sedative effects
  - Abuse and dependence; 15-40% report severe withdrawal symptoms after cessation of long-term use

Benzodiazepines

C-IV

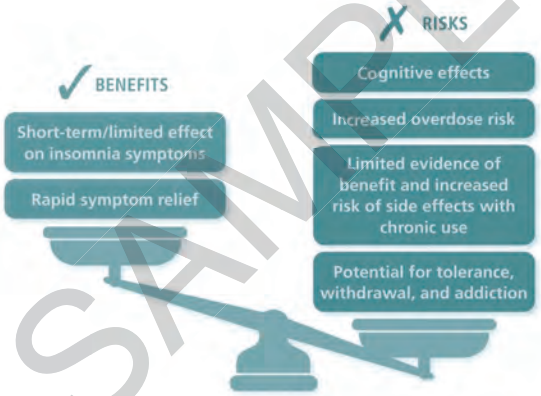
Benzodiazepines: US BOXED WARNING

Risks from concomitant use of opioids

Abuse, misuse, addiction

Dependence and withdrawal reactions

Benzodiazepines



Benzodiazepines

In General, AVOID Benzodiazepines If the Patient Has:

- ✗ A substance use disorder
- ✗ PTSD
- ✗ Chronic respiratory disease
- ✗ Sleep apnea
- ✗ A history of traumatic brain injury
- ✗ Dementia or is over age 60
- ✗ A prescription for other CNS depressants such as opioids

Non-Benzodiazepine Receptor Agonists (NBRA)

C-IV

- FDA approved:
  - Sleep onset or maintenance: **eszopiclone (Lunesta®), zolpidem ER (Ambien CR®)**
  - Sleep onset: **zolpidem IR (Ambien®), zaleplon (Sonata®)**

- MOA: Enhance inhibitory action of GABA at the GABA-A receptor complex, have greater selectivity for certain GABA-A subunit types which may limit the range of side effects as well as therapeutic effects (i.e., less anxiolytic effects)

NBRA

C-IV

- Adverse effects
  - Complex sleep-related behaviors (BBW), next-day impairment, withdrawal effects (fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramping/abdominal pain, nervousness, panic attacks), severe injuries (related to drowsiness and reduced consciousness leading to falls/injuries), headache, GI discomfort, and abuse dependence

NBRA

C-IV

- Eszopiclone:
  - Sedation onset: Rapid (~10 minutes)
  - Half-life: ~6 hours
  - Dosing: 1mg QHS PRN (max 2mg/day)
  - >10%: headache, distortion of taste
  - Take immediately prior to bedtime or after the patient has gone to bed and is having difficult falling asleep
  - Do not take with or immediately following a high-fat meal.

NBRA

C-IV

- Zolpidem:
  - Sedation onset: ~30 minutes (IR formulation)
  - Half-life (IR, ER): ~2.5 hours
  - Dosing:
    - Sleep onset/sleep maintenance (with 7-8 planned hours of sleep):
      - ER tablet: 6.25mg (females) or 6.25 to 12.5mg (males) QHS (max 12.5mg/day)
      - IR, spray, sublingual tablet: 5mg (females), 5-10mg (males) QHS (max 10mg/day)
      - Of note, IR, spray, sublingual off-label for sleep maintenance
  - >10%: headache, drowsiness, dizziness
  - Take immediately before bedtime due to rapid onset of action
  - Do not administer with or immediately after a meal
  - Take when at least 7 to 8 hours remaining before planned time of awakening.
  - Do not administer during the same night

NBRA

C-IV

- Zaleplon:
  - Sedation onset: ~30 minutes
  - Half-life: 1 hour
  - Dosing: 5-10mg QHS PRN (max of 20mg/day)
  - >10%: headache
  - Administer immediately before bedtime or when the patient is in bed and can't fall asleep
  - Do not take with or immediately following a high-fat meal

NBRA's: US BOXED WARNING

Complex sleep behaviors: sleep walking, sleep-driving, and engaging in other activities while not fully awake. Some of these events may result in serious injuries, including death

NBRA

C-IV

NBRA's: US BOXED WARNING

Complex sleep behaviors: sleep walking, sleep-driving, and engaging in other activities while not fully awake. Some of these events may result in serious injuries, including death

Orexin Receptor Antagonist

C-IV

- FDA approved
  - Sleep onset or maintenance: **Suvorexant (Belsomra®)**
- MOA
  - Orexin receptor antagonist, highly selective at orexin type 1 and orexin type 2 receptors

Orexin Receptor Antagonist

C-IV

- Adverse effects
  - 1-10%: diarrhea, xerostomia (more common in females), abnormal dreams (more common in females), dizziness, drowsiness (more common in females), headache (more common in females), cough, upper respiratory tract infection (more common in females)
  - Warnings/precautions: daytime somnolence, sleep paralysis, hypnagogic or hypnopompic hallucinations, cataplexy-like symptoms

- Clinical pearls
  - Onset of action: 30-minutes
  - Half-life: ~12 hours
  - Dosing: 10mg daily PRN (max 20mg/day)
  - Take 30 minutes prior to bedtime with at least 7 hours of planned sleep
  - Contraindicated in patients with narcolepsy

Melatonin Receptor Agonist

- FDA approved:
  - Sleep onset: **Ramelteon (Rozerem®)**
- MOA
  - Melatonin type 1 and melatonin type 2 receptor agonist
- Adverse effects
  - Morning sleepiness, dizziness, fatigue, or exacerbated insomnia, GI upset, next-day somnolence, and hyperprolactinemia
- Clinical pearls
  - Onset: ~30 minutes
  - Half-life: ~1-2.6 hours, active metabolite ~2-5 hours
  - Dosing: 8mg QHS PRN (max 8mg/day)
  - Take within 30 minutes of bedtime
  - Maximum effects may require up to 3 weeks of use
  - Duration: efficacy is supported for up to 6 months of continuous use
  - Administer on an empty stomach

Tricyclic Antidepressant (TCA)

- FDA approved:
  - Sleep maintenance: **Doxepin (Silenor®)**

- MOA: Increases the synaptic concentration of serotonin and norepinephrine in the central nervous system by inhibition of their reuptake by the presynaptic neuronal membrane, antagonizes the histamine (H1) receptor for sleep maintenance

Tricyclic Antidepressant (TCA)

- Adverse effects:
  - Neurologic (sedation, reduced seizure threshold), anticholinergic (blurred vision, urinary retention, dry mouth, constipation, cognitive impairment/delirium), cardiovascular (cardiotoxicity, orthostatic hypotension, tachycardia), weight gain, sexual dysfunction

- Clinical pearls:
  - Onset: improvement in sleep in as early as the first night
  - Duration of action: ~7 hours
  - Administer 30 minutes prior to bedtime
  - Do not take within 3 hours of food
  - Lethal in overdose
  - Anticholinergic!

Tricyclic Antidepressant (TCA)

Antidepressants: Black box warning

Increase risk of suicidal thinking and behavior in children, adolescents, and young adults (up to 24 years of age)

Conclusion

- There are various FDA approved medications to treat sleep onset and sleep maintenance insomnia

- If pharmacotherapy is warranted it should be utilized in combination with non-pharmacotherapy

- AASM guidelines recommend short-term use of pharmacotherapy with chronic use only being considered if
  - CBT inaccessible/ineffective, maintain long-term gains with medication and who are monitored closely

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Questions?!

Thank you!

Management of Sleep-Wake Disorders

Part II: Other

Objectives

1. Identify the drugs used to treat sleep related movement disorders, hypersomnia, circadian rhythm sleep-wake disorders, and parasomnias per the American Academy of Sleep Medicine
2. Describe the pharmacologic treatments for sleep related movement disorders, hypersomnia, circadian rhythm sleep-wake disorders, and parasomnias
3. List the key adverse effects of pharmacologic treatments for sleep related movement disorders, hypersomnia, circadian rhythm sleep-wake disorders, and parasomnias
4. Discuss the clinical pearls associated with the drug/drug classes used to treat sleep related movement disorders, hypersomnia, circadian rhythm sleep-wake disorders, and parasomnias

Other Sleep Disorders

- Sleep Related Movement: Restless Leg Syndrome (RLS)
- Hypersomnia: Narcolepsy, Idiopathic
- Circadian Rhythm Sleep-Wake Disorders: Intrinsic & Extrinsic
- Parasomnias: REM Sleep Behavior Disorder

Sleep Related Movement Disorders: Restless Leg Syndrome

Restless Leg Syndrome: Pharmacologic Therapy

Standard recommendation by American Academy of Sleep Medicine:

- Dopamine agonists
  - Pramipexole
  - Ropinirole

- Alternatives (can treat): Levodopa, cabergoline (only if others trialed first), opioids, gabapentin enacarbil

Pramipexole (Mirapex®)

FDA Indications	• Restless leg syndrome (IR formulation only)
MOA	• Nonergot dopamine agonist with specificity for the D_2 subfamily dopamine receptor and has also been shown to bind to D_3 and D_4 receptors
Onset, Duration	• Onset: peak plasma levels ~1-2 hours after intake, once dose effective dose achieved onset is rapid (first dose) • Duration: 6-8 hours
Dosing	• 0.125mg daily, 2-3 hours prior to bedtime • May increase dose by 0.25mg every 4-7 days • Max 0.75mg/day
Warnings & Precautions	• Dyskinesia, impulse control disorders, neuroleptic malignant syndrome, orthostatic hypotension, pleural/retroperitoneal fibrosis, postural deformity, psychotic effects, retinal changes, somnolence
Adverse Effects	• Augmentation, possible link to heart failure, n/v, dopamine agonist withdrawal syndrome, constipation, headache, insomnia, asthenia
Clinical Pearls & Patient Education	• Administer with or without food to decrease nausea • If augmentation occurs, give earlier in the day, divide into multiple daily dosing, or consider alternative therapy

Ropinirole (Requip®)

FDA Indications	• Restless leg syndrome (IR formulation only)
MOA	• Precise mechanism of action of ropinirole is unknown, it is believed to be due to stimulation of postsynaptic dopamine D_2-type receptors within the caudate putamen in the brain
Onset, Duration	• Onset: peak plasma levels 1-2 hours after intake, once dose effective dose achieved onset of action rapid (after 4-10 days) • Duration: 6-8 hours
Dosing	• 0.25 mg once daily 1 to 3 hours before bedtime • Dose may be increased after 2 days to 0.5 mg once daily, and after 7 days to 1 mg once daily • Max 4mg/day
Warnings & Precautions	• Dyskinesia, impulse control disorders, orthostatic hypotension, pleural/retroperitoneal fibrosis, psychotic effects, retinal changes, somnolence
Adverse Effects	• Augmentation, n/v, withdrawal syndrome, syncope, nasopharyngitis, headache, asthenia, back pain
Clinical Pearls & Patient Education	• Administer with or without food • If augmentation occurs, give earlier in the day, divide into multiple daily dosing, or consider alternative therapy

Gabapentin Enacarbil (Horizant®)

FDA Indications	• Restless leg syndrome
MOA	• Prodrug of gabapentin • Structurally related to GABA, however does not bind to GABA-A or GABA-B and it does not appear to influence degradation or uptake of GABA • Exact mechanism in RLS unknown
Onset, Duration	• Onset: ~one-week • Duration: duration of action is unclear, but half-life is 5-6 hours
Dosing	• 300-600mg daily at 5PM
Warnings & Precautions	• CNS depression, multiorgan hypersensitivity, respiratory effects (i.e., respiratory depression), suicidal ideation, DRESS
Adverse Effects	• Dizziness, drowsiness, headache, sedated state, irritability, decreased libido, peripheral edema
Clinical Pearls & Patient Education	• Administer with food • If doses >600mg/day are used, recommend tapering to avoid withdrawal seizures • Do not interchange with gabapentin

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Hypersomnia: Narcolepsy, Idiopathic

Narcolepsy: Pharmacologic Therapy

Recommended by American Academy of Sleep Medicine:

- Modafinil
- Pitolisant
- Sodium oxybate
- Solriamfetol

- Alternatives (suggested): armodafinil, dextroamphetamine, methylphenidate,

Idiopathic Hypersomnia: Pharmacologic Therapy

Recommended by American Academy of Sleep Medicine:

- Modafinil

- Alternatives (suggested): clarithromycin, methylphenidate, pitolisant, sodium oxybate,

Other: Pharmacologic Therapy

Suggested by American Academy of Sleep Medicine	
Kleine-Levin Syndrome	• Lithium

Hypersomnia Secondary to Medical Conditions	• Dementia with Lewy Bodies:
	  • Armodafinil
	• Parkinson's Disease
	  • Modafinil, sodium oxybate
	• TBI
	  • Armodafinil, modafinil
	• Myotonic Dystrophy
	  • Modafinil
	• Multiple Sclerosis
	  • Modafinil

C-IV

Modafinil(Provigil®)/Armodafinil (Nuvigil®)

FDA Indications	• Narcolepsy-related excessive daytime sleepiness (EDS), • Obstructive sleep apnea EDS • Shift work sleep disorder EDS
MOA	• Binds to dopamine transporter to inhibit reuptake • Lower affinity for dopamine receptors compared to amphetamines
Warnings & Precautions	• Serious rash (Stevens-Johnsons Syndrome), toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) • Angioedema/anaphylaxis, psychiatric symptoms, cardiovascular events
Onset, Duration	• Onset: within one-hour • Duration: ~6-8 hours
Adverse Effects	• Headache, decreased appetite, abdominal pain, n/v, increased blood pressure (clinical trials), anxiety, suicidal thoughts
Clinical Pearls & Patient Education	• Effects similar to traditional CNS stimulants, but improved tolerability and reduced risk of abuse and tolerance • Take on an empty stomach, in the morning • Modafinil may need to be split into BID to control evening symptoms, armodafinil longer half-life and dosed daily • May decrease effectiveness of birth control

Pitolisant (Wakik®)

FDA Indications	• Narcolepsy (cataplexy or EDS)
MOA	• Unclear, but may be mediated through its activity as an antagonist/inverse agonist at histamine-3-receptors
Warnings & Precautions	• May prolong QT interval, avoid use in patients with known QT prolongation or concomitant use with other agents that prolong the QT. • Avoid in those with know cardiac arrythmia
Onset, Duration	• Onset: may take up to ≥8 weeks to achieve clinical response • Duration: Half-life of ~20 hours
Adverse Effects	• Headache, insomnia, nausea, anxiety
Clinical Pearls & Patient Education	• Take in the morning upon awakening • May decrease effectiveness of birth control

C-III Sodium Oxybate (Xyrem®)

FDA Indications	• Narcolepsy (cataplexy or EDS)
MOA	• CNS depressant and GABA-B agonist that may modulate GABA-A and GABA-C • Improves nocturnal sleep, thereby improving daytime alertness
Onset, Duration	• Onset: Rapid (≤5 to 15 minutes), cataplexy improves within days, but may take 8-12 weeks to achieve optimal response • Duration: 2-3 hours, requires dose throughout night
Dosing	• 2.25g QHS after in bed, 2.25g administered 2.5 to 4 hours later • May increase nightly by 1.5g at weekly intervals • Max 9g/night
Warnings & Precautions	• Behavioral/psychiatric effects • CNS depression • Parasomnias • Withdrawal symptoms: most data from illicit use (delirium, tremor, seizures, insomnia, restless, anxiety, psychosis, lethargy, nausea, muscle cramps, increased heart rate
Adverse Effects	• Confusion, headache, dizziness, n/v, weightloss, urinary incontinence
Clinical Pearls & Patient Education	• Administer on empty stomach ≥2 hours after eating • High sodium content (3g dose = 546mg sodium)

C-III Sodium Oxybate (Xyrem®)

US BOXED WARNING

Central nervous system depression

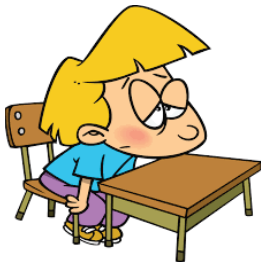
Abuse and misuse

Restricted access (REMS)

C-IV Solriamfetol (Sunosi®)

FDA Indications	• EDS associated with narcolepsy or obstructive sleep apnea
MOA	• Unclear, efficacy may be related to activity as selective dopamine and norepinephrine reuptake inhibitor • Does not promote monoamine release as traditional stimulants
Onset, Duration	• Onset: Observed early as one-hour post-dose in clinical trials • Duration: effects observed for up to 9 hours
Dosing	• 75mg daily (narcolepsy) or 37.5mg daily (OSA) may increase at 3 days intervals up to 150mg/day
Warnings & Precautions	• May cause dose dependent increases in blood pressure an heart rate avoid use in patients with unstable cardiovascular disease, serious heart arrhythmias, or other serious heart problems • Psychiatric symptoms, including anxiety, insomnia, irritability reported with use
Adverse Effects	• Headache, nausea, decreased appetite, insomnia, anxiety
Clinical Pearls & Patient Education	• Administer once daily upon awakening • Avoid administration within 9 hours of planned bedtime because of the potential to interfere with sleep

Circadian Rhythm Sleep-Wake: Extrinsic & Intrinsic



Extrinsic Circadian Rhythm Sleep-Wake Disorder: Pharmacologic Therapy

Indicated by American Academy of Sleep Medicine	
Shift work disorder	• Modafinil is indicated to enhance alertness during the night shift
Jet lag disorder	• Melatonin administered at the appropriate time is indicated to reduce symptoms and improve sleep following travel across multiple time zones
Delayed sleep phase disorder	• Properly timed melatonin administration is indicated as a therapy
Free running circadian rhythm sleep disorder	• Timed melatonin administration is indicated for therapy in blind individuals

Melatonin (OTC)

Not-FDA Approved	
MOA	• Natural hormone the body secretes that helps to maintain sleep-wake cycle • Agonist at melatonin receptors, including those in the suprachiasmatic nucleus (SCN) • Melatonin facilitates sleep onset by decreasing the typical evening SCN-driven arousal, and helps to reinforce circadian periodicity
Onset, Duration	• Onset: Observed early as one-hour post-dose in clinical trials • Duration: effects observed for up to 9 hours
Dosing	• 0.5-10mg QHS
Adverse Effects	• Nightmares, dizziness, daytime sleepiness, headache, short-term feelings of depression, irritability, and stomach cramps
Clinical Pearls & Patient Education	• Given 1-2 hours before bedtime • The safety of long-term melatonin use has not be established in controlled studies

Intrinsic Circadian Rhythm Sleep-Wake Disorder: Pharmacologic Therapy

Recommendations by American Academy of Sleep Medicine	
Advanced sleep-wake phase disorder	• No evidence to support the use of sleep-promoting medications, melatonin or wakefulness promoting medications
Delayed sleep-wake phase disorder	• Insufficient evidence to support the use of sleep-promoting medications
Non-24-hour sleep-wake rhythm disorder	• No evidence to support the use of sleep promoting/wakefulness medications • Suggested to use strategically timed melatonin in blind adults • Insufficient evidence to support the use of melatonin in sighted adults
Irregular sleep-wake rhythm disorder	• Avoid the use of sleep-promoting medications to treat demented elderly patients • Avoid use of melatonin as a treatment in older people with dementia

Tasimelteon (Hetlioz®)

FDA Indications	• Non-24-hour sleep-wake disorder
MOA	• Agonist of melatonin receptors MT_1 and MT_2 (greater affinity for the MT_2 receptor than the MT_1 receptor) • Agonism of MT_1 is thought to preferentially induce sleepiness, while MT_2 receptor activation preferentially influences regulation of circadian rhythms
Onset, Duration	• Onset: Effects may take week or months • Duration: Half-life ~1-2 hours, duration unclear
Dosing	• 20mg once daily, 1 hour prior to bedtime
Warnings & Precautions	• CNS depression
Adverse Effects	• Headache, nightmares, unusual dreams, upper respiratory infections, urinary tract infections
Clinical Pearls & Patient Education	• Administer with food • Take at the same time each night, skip dose if you can't take at approximately the same time

Parasomnia: REM Sleep Behavior Disorder

REM Sleep Behavior Disorder (RBD): Pharmacologic Therapy

- Treatment options per American Academy of Sleep Medicine
  - Zopiclone, benzodiazepines (other than clonazepam), Yi-GAN San, desipramine, clozapine, carbamazepine, sodium oxybate
  - Of note, evidence is very limited with only a few subjects having been studied

Parasomnia: Nightmare Disorder

Nightmare Disorder: Pharmacologic Therapy

- Treatment options per American Academy of Sleep Medicine
  - PTSD associated nightmares:
    - Atypical antipsychotics (olanzapine, risperidone, aripiprazole), clonidine, cyproheptadine, fluvoxamine, gabapentin, nabilone, phenelzine, prazosin, topiramate, trazodone, and tricyclic antidepressants
  - Nightmare disorder:
    - Nitrazepam, prazosin, and triazolam.
    - Not recommended for the treatment of nightmare disorder:
      - Clonazepam and venlafaxine.

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Questions?!

Thank you!

Management of Sleep-Wake Disorders

Part II: Other