TREATMENT OF HYPERSOMNIAS

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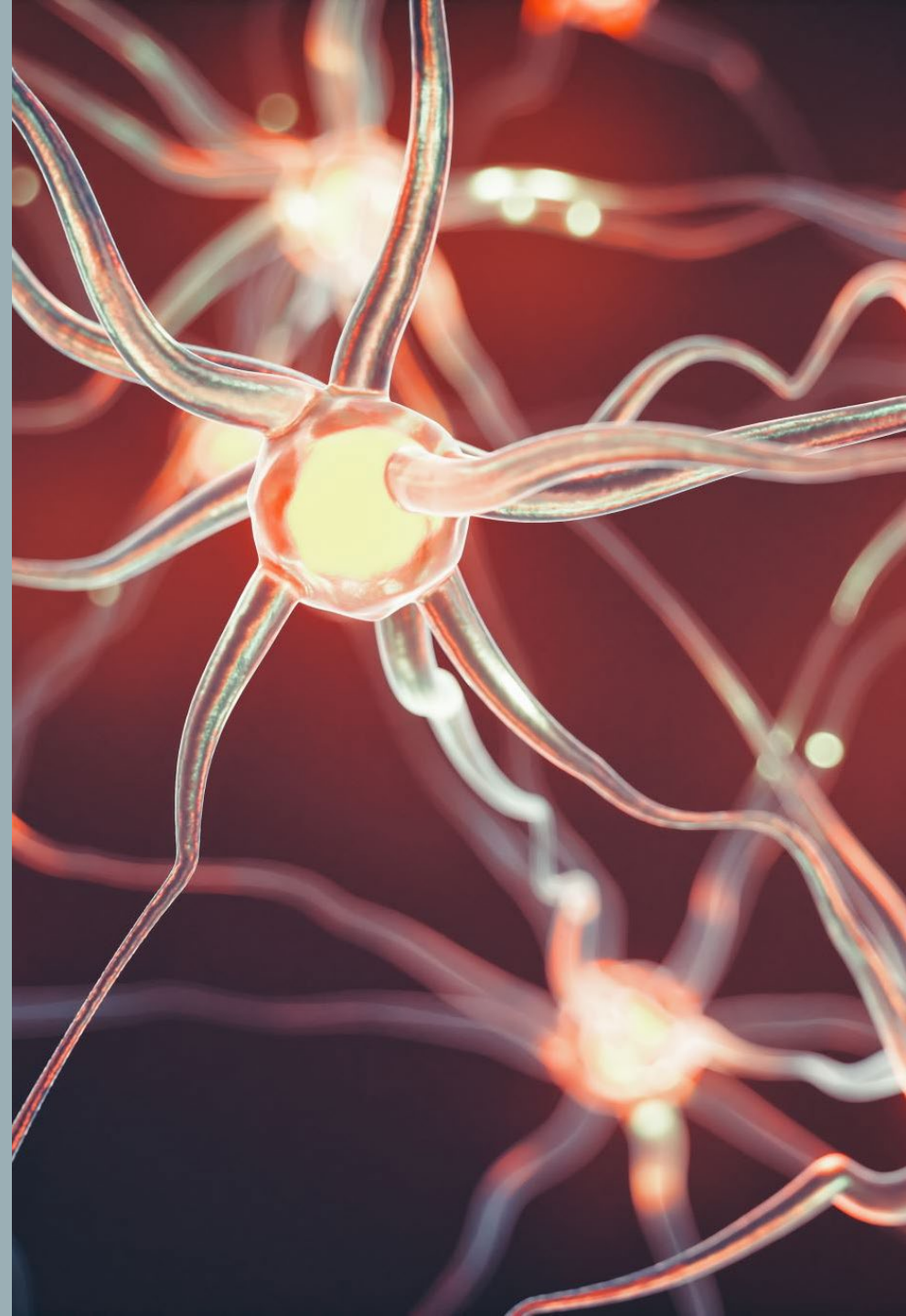


DISCLOSURE INFORMATION

Maryland Sleep Society Presentation Oct 2023

Mark Wu, MD, PhD

- I have no relevant financial relationships to disclose
- I will discuss the following off label use in my presentation: clarithromycin and flumazenil

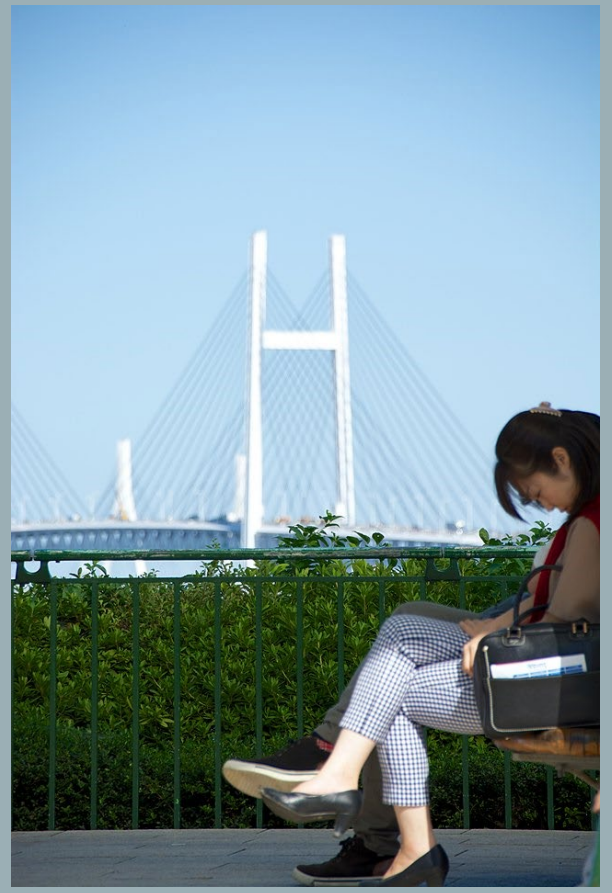
OVERVIEW

- Evaluation of the Sleepy Patient
- Primary Hypersomnias
  - Narcolepsy, Idiopathic Hypersomnia, Klein-Levin Syndrome
- Example Cases
- Review of Treatment Options for Hypersomnias
  - Non-pharmacological approaches
  - Pharmacological approaches

EVALUATION OF THE SLEEPY PATIENT

1. Sleepiness vs fatigue.

2. DDx:
   - -insufficient sleep (esp long sleepers)
   - -medical disorders (e.g., hypothyroidism)
   - -psychiatric disorders (esp atypical depression or bipolar depression)
   - -medications
   - -sleep disorders (e.g., OSA, RLS, etc.)
   - -circadian rhythm disorders



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PRIMARY HYPERSOMNIAS: NARCOLEPSY

1. Epidemiology: Prevalence ~1:2,000, M=F, usually starts teens/early 20s

2. Clinical Features: Disordered regulation of REM sleep: sleep paralysis, hypnogogic/hypnopompic hallucinations
   Type 1: cataplexy
   Type 2: no cataplexy

3. Diagnosis: History, PSG/MSLT (<8 mins, ≥2 SOREMs)

4. Pathophysiology: Loss of orexin signaling in Type 1
   Unclear in Type 2

Scammell (2015) NEJM 373: 2654-2662

PRIMARY HYPERSOMNIAS: IDIOPATHIC HYPERSOMNIA

1. Epidemiology: Prevalence ~1:10,000, F>M (3:1), usually starts teens/early 20s

2. Clinical Features: Often associated with long sleep duration
   Naps are unrefreshing
   Sleep inertia, "mental fog" on awakening

3. Diagnosis: History, PSG/MSLT (<8 mins)

4. Pathophysiology: Unknown

Arnulf et al (2023) Sleep Med Rev 69: 101766

NARCOLEPSY VS IDIOPATHIC HYPERSOMNIA

SYMPTOMS	Narcolepsy Type 1	Narcolepsy Type 2	Idiopathic Hypersomnia
Excessive Daytime Sleepiness	**YES**	**YES**	**YES**
Sleep Paralysis and Hallucinations	**YES**	Sometimes	Occasionally
Cataplexy	**YES**	**NO**	**NO**
Difficulty Staying Asleep at Night	**YES**	Sometimes	**NO**
Refreshing Naps	**YES**	Sometimes	Occasionally
Sleep Inertia	Occasionally	Sometimes	**YES**

www.hypersomniafoundation.org

Khan and Trotti (2015) Chest 148: 262-273

PRIMARY HYPERSOMNIAS: KLEIN-LEVIN SYNDROME

1. Epidemiology: Prevalence ~1-2 per million, M>F (3:1), usually starts in teens

2. Clinical Features: Relapsing-remitting 1-2 wk episodes with hypersomnia, cognitive impairment, psychiatric and behavioral disturbances (hyperphagia and hypersexuality).
   Relapses occur every 1-12 months for ~ 14 years
   Usually resolves after 30 yro

3. Diagnosis: History

4. Pathophysiology: 1st episode (and sometimes recurrent episodes) often triggered by infection,

Arnulf et al. (2012) Lancet Neurol 11: 918-928

CASE 1

HPI: At initial presentation, 50 yro F with history of narcolepsy (type 2)
-Sleepiness began at 46 yro, severe sleepiness, ESS=20
-Sleep cycle: 11pm-5am, TST 6am. However, extending sleep time up to 12 hrs has no effect
-Naps– 3-4 per week (2-3 hrs duration), unrefreshing.
-No cataplexy, SP, or HH
-Does experience sleep inertia
-Mood: "depressed", + anhedonia, but no SI.

PMH:

HTN	depression
HLD	fibromyalgia
Raynuad's syndrome	

CASE 1

Medications:

Buproprion
Furosemide prn
Duloxetine
Pravastatin
Aripiprazole
HCTZ prn
Losartan
Dextroamphetamine/amphetamine (Adderall) XR 30 mg PO qd
Sodium oxybate (Xyrem) 3g bid

FH/SH: No known family members with sleep disorders. Married, works as a nurse manager. Denies smoking, alcohol. 2 caffeinated beverages, last one at dinner.

Tests: PSG: TST 457 mins, SE: 89%, RDI=3
MSLT (4 naps): mean sleep latency: 2.8 mins, 4/4 SOREMs

Diagnosis: Narcolepsy type 2

CASE 1

Medications Tried and Course:

-Modafinil– mildly helpful
-Armodafinil- mildly helpful
-Adderall- less helpful
-Xyrem- significant improvement, but had significant BLE edema when taking

-Patient later diagnosed with hyperaldosteronism and treated for that, which improved BLE edema

-Switched from Adderall to Dexedrine up to 60 mg PO qam, switched from Xyrem to Xywav:
-ESS improved from 20 to 16 (able to work, but still with residual sleepiness)
-BLE edema markedly improved
-sleeping 8-9 hrs/night.

CASE 2

HPI: 29 yro M h/o seasonal allergies complains of EDS
-describes both EDS and fatigue, but mostly EDS
-started in middle school, has gradually worsened over the past 20 yrs
-Sleeps from 11pm-7am, TST: 8 hrs. A few brief awakenings during night.
-No improvement when extending TST to 12 hrs.
-Denies cataplexy, has had a few episodes of SP, possible HH
-Brief naps are refreshing
-No sleep inertia
-Mood: "good"
-ESS: 17

PMH: seasonal allergies

CASE 2

FH: Mother has insomnia, father has OSA.

SH: Single, works as engineer. Denies smoking, rare EtOH use, 0-1 caffeinated beverages, last one in the morning.

Testing: Extended PSG: TST: 547 mins, SE=84.3%, RDI=5.6
MSLT: mean sleep latency 4.6 mins, 0/5 SOREMs

However, previous work suggests poor test-retest reliability for SOREM classification

Dx: Idiopathic hypersomnia vs narcolepsy type 2?

Trotti et al. (2013) J Clin Sleep Med 9: 789-795

CASE 2

Medications Tried and Course:

-Modafinil– tachycardia, felt jittery

-Methylphenidate LA (10-20 mg PO qam)– anxiety, difficulty thinking

-Solriamfetol (75 mg, then 150 mg)– better tolerated, significant improvement in EDS without adverse side effects.

CASE 3

HPI: The pt is a 22 yro F with history of recurrent episodes of EDS
Episodes started in high school
Episodes last several days to several weeks, occur 6x/yr
-sleep 16-18 hrs/day,
-increased eating, especially junk foods
-increased irritability
-no obvious increase in sexual behaviors
Between episodes, feels normal. At baseline, sleeps 10 hrs/night.
Some of these episodes are associated with viral illnesses
Has been diagnosed with multiple potential psychiatric conditions:
depression, anxiety, ADD, bipolar d/o, dissociative conditions.
No cataplexy, SP, or HH
ESS=9 at baseline

CASE 3

PMH: IgA deficiency, mild asthma, multiple psychiatric diagnoses

FH/SH: No known sleep disorders. Single, currently not working or going to school. Denies smoking, EtOH. Drinks caffeinated beverages rarely.

Testing: PSG: TST 518 mins, 98% SE, N1 0%, N2 28%, N3: 54%, REM: 18%, RDI=1
MSLT: mean sleep latency=13.5 mins, 0/4 SOREMs.

Dx: Klein-Levin Syndrome

1) Recurrent hypersomnia (EDS lasting 2 days-4 weeks, ≥1x/yr, normal between episodes, and no other cause for hypersomnia)
2) At least one of the following: cognitive abnormalities (confusion, hallucinations), abnormal behavior, hyperphagia, hypersexuality

CASE 3

Medications Tried and Course:

-Adderall XR 30 mg PO qam
-Trazodone 50 mg PO qhs
-Lexapro 10 mg PO qd
-Lamictal 200 mg PO qd
-Lithium (levels are monitored by psychiatrist)
-Has been on lithium since 2017, with no obvious change in frequency of episodes.
-Recommended reducing polypharmacy and reducing stimulants to as-needed.
-Started using Adderall 5-15 mg between episodes
-Over the course of 3 years, episodes started decrease in frequency 1-2 per year.

TREATMENT APPROACHES FOR HYPERSOMNIAS: OVERVIEW

1. Non-pharmacological approaches
2. Pharmacological approaches
    a) Stimulants
    b) Sleep-promoting agents
    c) Miscellaneous

NON-PHARMACOLOGICAL APPROACHES

1. Stimulant drug holidays (once a week)

2. Brief naps
   -2 15 min naps, mid-AM and early PM
   -For patients with narcolepsy, who find brief naps refreshing

Wikimedia Commons

PHARMACOLOGICAL APPROACHES: STIMULANTS

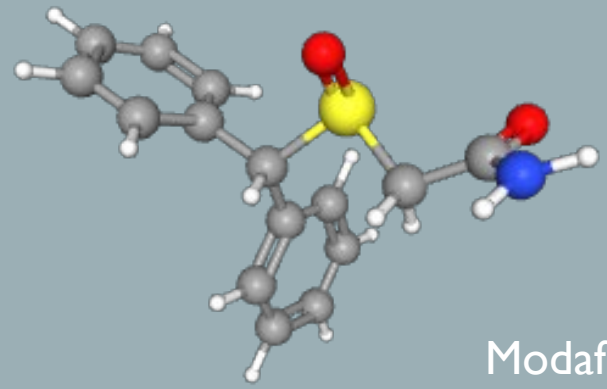
1. Stimulants
   a) Modafinil and armodafinil
   b) Methylphenidate
   c) Amphetamines
   d) Pitolisant
   e) Solriamfetol

Duration, Mechanism of action, Potency, Side Effects

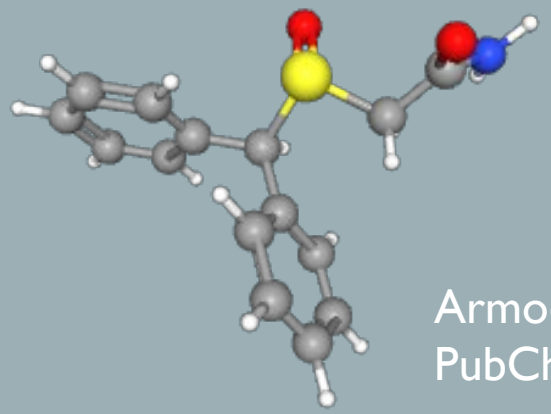
MODAFINIL AND ARMODAFINIL

a) Modafinil: d- and l- isomers
Armodafinil: d-isomer of modafinil
-considered first-line therapy

-Duration: armodafinil longer acting, once a day dosing
-Mechanism: likely decreases reuptake of DA
-Potency: typically less potent than methylphenidate and amphetamines
-Side Effects: tends to be well tolerated
-HA, rash
-reduces effectiveness of OCPs, hormone-based birth control



Modafinil
PubChem



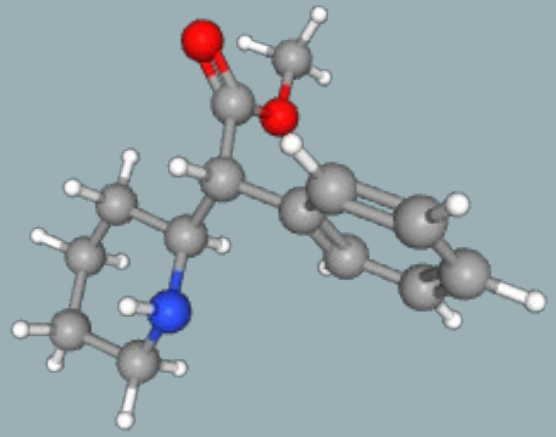
Armodafinil
PubChem

Thorpy, M..J. (2015) Curr Treat Options Neurol 17:20

METHYLPHENIDATE

b) Methylphenidate (Ritalin/Concerta)- contains d- and l-isomers
Dexmethylphenidate (Focalin)- d-isomer of methylphenidate.

-Duration: relatively short acting, controlled release formulations available
-Mechanism: inhibit DAT
-Potency: moderate, dexmethylphenidate more potent
-Side Effects: insomnia, dizziness, palpitations.

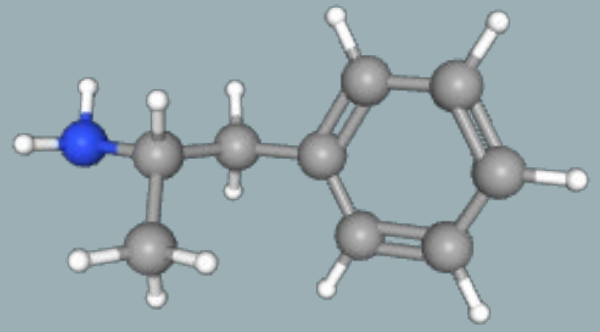


Methylphenidate
PubChem

Thorpy, M..J. (2015) Curr Treat Options Neurol 17:20

AMPHETAMINES

c) Mixed amphetamine salts (Adderall): d- and l- isomers
Dextroamphetamine (Dexedrine): d-isomer of amphetamine
Lisdexamphetamine,(Vyvanse): inactive prodrug of Dexedrine



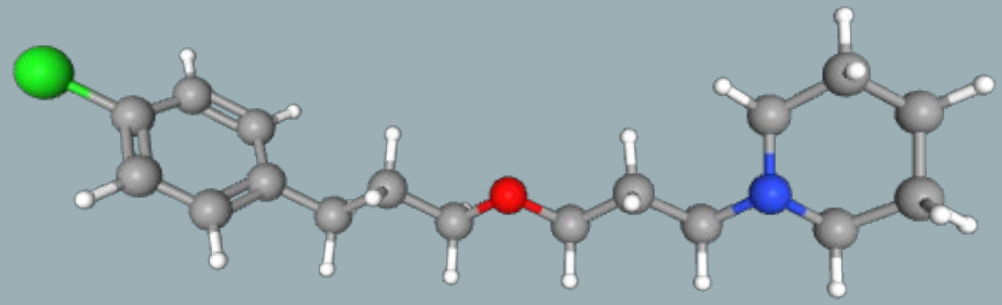
Amphetamine
PubChem

-Duration: relatively short acting, controlled release formulations available, Lisdexamphetamine is longer acting.
-Mechanism: inhibit DAT, DAT reverse transport, inhibit NET, NET reverse transport
-Potency: strong, dextroamphetamine more potent
-Side Effects: palpitations, tachycardia, hypertension, insomnia, weight loss.
-Lisdexamphetamine may be better tolerated

NEWER STIMULANTS: PITOLISANT

d) Pitolisant (Wakix)

1. *approved for narcolepsy*



Pitolisant
PubChem

2. Several Phase III Trials show improvement of EDS and cataplexy

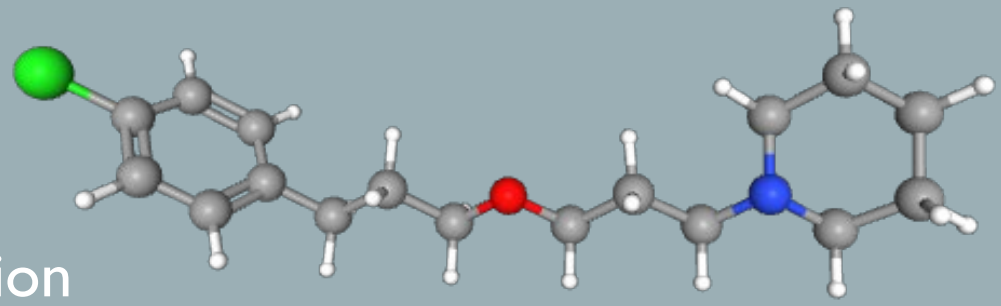
3. Harmony CTP-- RCT of 105 Type 1 narcolepsy pts
   - -Cataplectic attacks/wk: 9.2 to 2.3
   - -ESS improved: 17.4 to 12
   - -Placebo works about half as well

Szakacs et al (2017) Lancet Neurol 16: 200-207

NEWER STIMULANTS: PITOLISANT

d) Pitolisant (Wakix)

-Duration: Half-life 20 hrs, once daily dosing
-Mechanism: H3 receptor antagonist/inverse agonist
-Potency: milder
-Side Effects: generally well-tolerated, potential interaction with OCPs, can prolong QT (caution in patients with heart disease)
-Other: CYP3A4 metabolized



Pitolisant
PubChem

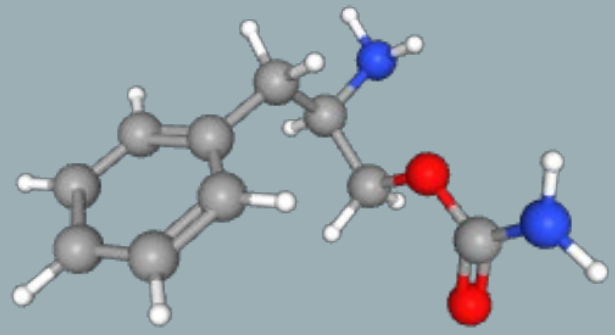
Szakacs et al (2017) Lancet Neurol 16: 200-207
Earl, D.C. and Van Tyle, K.M. (2020). Curr Opin Pulm Med 26: 629-633.

NEWER STIMULANTS: SOLRIAMFETOL

e) Solriamfetol (Sunosi)

1. *approved for EDS from narcolepsy or from OSA*

2. TONES study- RCT of ~ 200 narcolepsy pts (Type 1 or 2)
   - -Placebo, 75 mg, 150 mg, 300 mg groups
   - -Improvement of MWT by 7.7 mins, relative to placebo
   - -Improvement of ESS by 3.8, relative to placebo



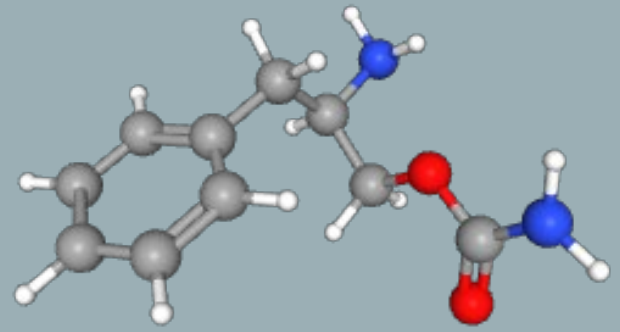
Solriamfetol
PubChem

Thorpy et al (2019) Ann Neurol 85: 359-370

NEWER STIMULANTS: SOLRIAMFETOL

e) Solriamfetol (Sunosi)

-Duration: Half-life 7 hrs, once daily dosing
-Mechanism: DA and NE reuptake inhibitor
-Potency: milder
-Side Effects: generally well-tolerated, mild incr in SBP/DBP
(caution in patients with unstable CV disease)
-Other: renally cleared, contraindicated with recent MAOi use



Solriamfetol
PubChem

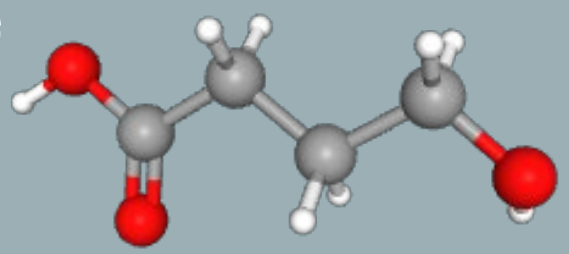
Thorpy et al (2019) Ann Neurol 85: 359-370
Earl, D.C. and Van Tyle, K.M. (2020). Curr Opin Pulm Med 26: 629-633.

PHARMACOLOGICAL APPROACHES: SLEEP-PROMOTING

2. Sleep-promoting medications
   a) Sodium oxybate (Xyrem)
   b) Calcium, magnesium, potassium, and sodium oxybates (Xywav)
   c) Sodium oxybate extended release suspension (Lumryz)

OXYBATES

b) -Sodium oxybate (Xyrem)- sodium salt of gamma-hydroxybutyrate
-Ca^{2+}, Mg^{2+}, K^{+}, Na^{2+} oxybates (Xywav)- >90% less sodium salt
-Sodium oxybate, extended release suspension (Lumryz)
Treats both EDS and cataplexy



Sodium oxybate
PubChem

-Duration: short acting, dosed twice nightly, except Lumryz (once nightly)
-Mechanism: induces very deep NREM sleep, likely by activating $GABA_B$ receptors
-Potency: strong inducer of sleep
-Side Effects: HA, nausea, mood issues? Avoid EtOH and other sedatives.
Evaluate for sleep apnea before prescribing

Thorpy, M..J. (2015) Curr Treat Options Neurol 17:20

NEWER OXYBATES: XYWAV

1. FDA-approved for treatment of narcolepsy AND idiopathic hypersomnia

2. Phase 3 trial 2022, N=154.
   -3 mo titration, 2 wk stable dose, then 2 wks of placebo vs continued treatment
   -Note: participants can likely detect the difference between drug vs placebo
   -Primary endpoint– ESS 15.7 to 6.1
   -when switched to placebo, ESS worsened but stayed stable on those continuing treatment

Dauvilliers et al (2022) Lancet Neurol 21: 53-65

NEWER OXYBATES: LUMRYZ

1. FDA-approved for treatment of EDS or cataplexy in narcolepsy pts

2. REST-ON Study– Phase III RCT of ~200 pts
   - -at 9g vs placebo
     - -MWT: 10.8 min vs 4.7 min
     - -decr catapletic attacks/wk: -11.5 (18.9→7.4) vs -4.9 (19.8→14.9)

Kushida et al (2022) Sleep 1-11

PHARMACOLOGICAL APPROACHES: MISCELLANEOUS

3. Miscellaneous
   a) Venlafaxine and Clomipramine
   b) Clarithromycin
   c) Flumazenil

SPECIFIC TREATMENTS: NARCOLEPSY

Treatment for Cataplexy-

1. Sodium oxybate
2. Pitolisant (Wakix)

a) -Venlafaxine: SNRI (can get rebound cataplexy when discontinued abruptly)
-Clomipramine: (sedation and dry mouth, but potent for cataplexy)

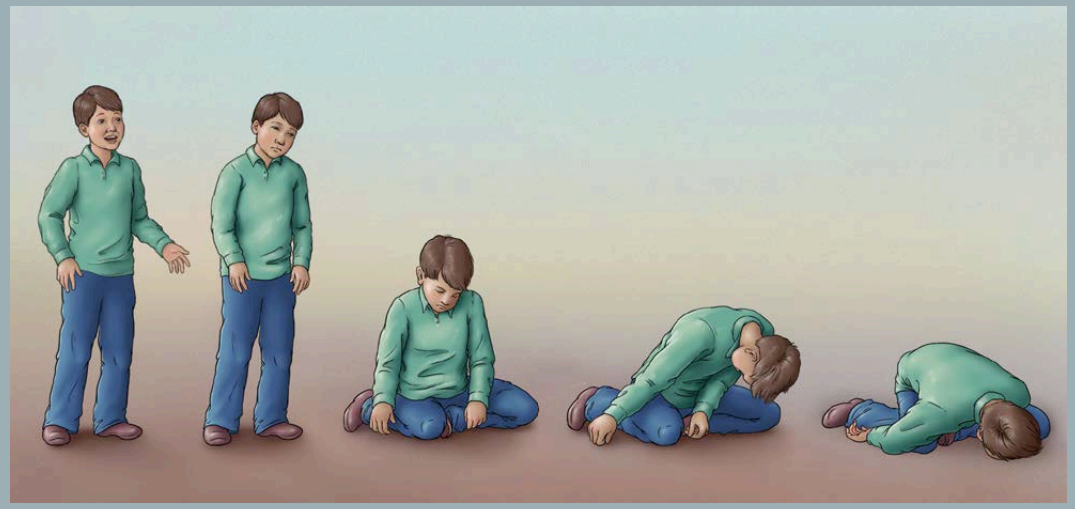


Figure 1. Cataplexy, from Scammell (2015) NEJM 373: 2654-2662

SPECIFIC TREATMENTS: IDIOPATHIC HYPERSOMNIA

b) Clarithromycin

-5 week small randomized, placebo-controlled double blind crossover trial of clarithromycin 500 mg bid.
-PVT (primary endpt)– no effect
-ESS: 14.1 placebo, 10.1 clarithromycin

Trotti et al (2015) Ann Neurol 78: 454-465
Maski et al. (2021) J Clin Sleep Med 17: 1881-1893.

SPECIFIC TREATMENTS: IDIOPATHIC HYPERSOMNIA

b) Clarithromycin

-Duration: short acting, bid dosing
-Mechanism: antibiotic and negative allosteric modulator of $GABA_A$ receptors
-Potency: mild, some patients report improvement of mental fog
-Side Effects: diarrhea, nausea, GI upset, metallic taste, vomiting. Potential concern for long-term use, antibiotic resistant bacteria?, gut flora issues? (probiotics)

Trotti et al (2015) Ann Neurol 78: 454-465

SPECIFIC TREATMENTS: IDIOPATHIC HYPERSOMNIA

c) Flumazenil

-not recommended by AASM guidelines

-retrospective chart review of 153 pts, ~63% experienced benefit (decr ESS by 4.7), and 39% stayed chronically on treatment.

-Duration: short acting, qid dosing

-Mechanism: antagonize BZD binding site of $GABA_A$ receptors

-Potency: mild-moderate?

-Side Effects: common, but generally mild, dizziness, anxiety, HA, insomnia. Potential serious side effects include seizures or arrhythmias (seen with IV flumazenil).

Trotti et al (2016) J Clin Sleep Med 12: 1389-1394.
Maski et al. (2021) J Clin Sleep Med 17: 1881-1893.

SPECIFIC TREATMENTS: IDIOPATHIC HYPERSOMNIA

c) Flumazenil

-Contraindicated in patient using BZD or history of BZD abuse.
-Sign consent form, work with a compounding pharmacy
-6 mg sublingual lozenges qid, then increase by one lozenge q5 days up to a maximum of 2 lozenges qid.
-can also be provided as topical cream

Trotti et al (2016) J Clin Sleep Med 12: 1389-1394.

SPECIFIC TREATMENTS: KLEIN-LEVIN SYNDROME

1. During episodes
    1. Modafinil (but controversial, bc can exacerbate behavioral/psychiatric symptoms).
    2. Can try risperidone if experiencing psychotic symptoms or benzodiazepines if experiencing anxiety

2. Between episodes (if frequent, disabling episodes).
    1. Lithium (but requires careful monitoring).

Trotti et al (2015) Ann Neurol 78: 454-465

TAKE HOME POINTS

1. Try to disentangle sleepiness from fatigue.
2. PSG/MSLT criteria are helpful, but not necessarily definitive.
3. There may be overlap between Narcolepsy Type 2 and Idiopathic Hypersomnia
4. Remember non-pharmacological approaches (stimulant holidays and brief naps)
5. For stimulants, try modafinil/armodafinil first. D isomer drugs tend to more potent.
6. Xywav is approved for Narcolepsy and Idiopathic Hypersomnia
7. Pitolisant (Wakix) can treat EDS and cataplexy
8. Consider the newer stimulants for patients sensitive to side effects
9. For patients with refractory Idiopathic Hypersomnia, consider clarithromycin or possibly flumazenil.

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