17th Annual Sleep Medicine Virtual Course

Saturday, March 22, 2025

Management of Hypersomnia Disorders

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Conflict of Interest Disclosures for Speakers

Lynn Marie Trotti, MD, MSc has no relevant financial relationships with ineligible companies to disclose.

Learning Objectives

- Upon completion of this course, attendees should be able to…

1. Discuss currently available treatments for narcolepsy and idiopathic hypersomnia
2. Understand medication factors (e.g., drug interactions, side effects) that impact treatment selection
3. Understand patient factors (e.g., comorbid conditions) that impact treatment selection

FDA approved treatments for (either type of) narcolepsy:

SLEEPINESS

- Non-amphetamine wake-promoting meds:
  - Modafinil
  - Armodafinil
  - Solriamfetol
- Amphetamines/related (some preparations):
  - Methylphenidate
  - Dextroamphetamine/amphetamine
  - Dextroamphetamine
  - Amphetamine
- Oxybates:
  - Sodium oxybate
  - Calcium/magnesium/potassium/sodium oxybate
    - Aka “lower sodium oxybate”
  - Once nightly sodium oxybate
- Histaminergic medications:
  - Pitolisant

CATAPLEXY

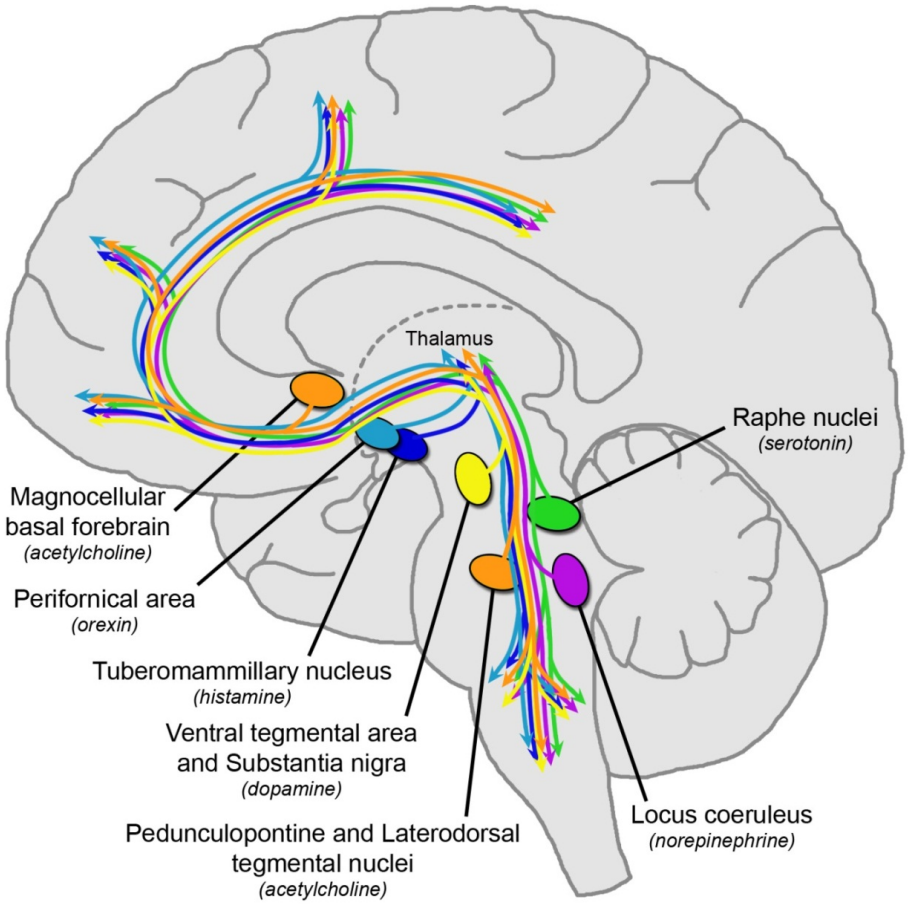
- Oxybates
  - Sodium oxybate
  - Lower sodium oxybate
  - Once nightly sodium oxybate
- Pitolisant

FDA approved treatments for idiopathic hypersomnia:

- Calcium, magnesium, potassium, sodium oxybate

Mechanisms of action

- Primarily dopamine reuptake inhibition (+/- others):
  - Modafinil, armodafinil
- Dopamine & norepinephrine reuptake inhibition:
  - Solriamfetol
- Dopamine & norepinephrine reuptake inhibition & monoamine release:
  - Amphetamines, methylphenidate
- H3 histamine antagonism/inverse agonism:
  - Pitolisant
- GABA-B agonism, GHB agonism
  - Oxybates



Modafinil for narcolepsy

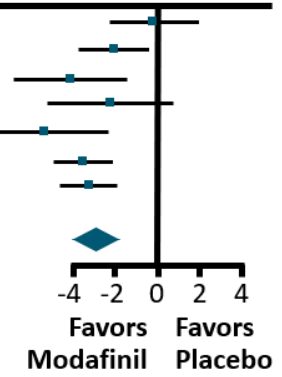
- FDA approved for sleepiness in narcolepsy in 1998, adults only
- Titrate weekly, starting 100 mg/day, up to 200 mg bid
- Liver metabolism, urine excretion
- Common AEs: headache, nausea, anxiety, insomnia

Excessive Daytime Sleepiness (ESS)

Study or Subgroup	Modafinil Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Black 2006	14.5	5.34	63	14.7	5.3	53	14.4%	-0.20 [-2.14, 1.74]
Broughton 1997*	14.5	5.6	75	16.5	4.4	75	17.1%	-2.00 [-3.61, -0.39]
Dauvilliers 2013	11.6	6	33	15.6	4.3	30	10.5%	-4.00 [-6.56, -1.44]
Moldofsky 2000	13.2	5.7	30	15.4	5.8	33	9.1%	-2.20 [-5.04, 0.64]
Saletu 2009*†	10.2	4.1	15	15.4	4	15	8.9%	-5.20 [-8.10, -2.30]
US Modafinil in Narcolepsy Multicenter Study 1998†	13.7	5.7	191	17.1	5	92	20.0%	-3.40 [-4.70, -2.10]
US Modafinil in Narcolepsy Multicenter Study 2000†	12.64	5.1	161	15.8	4.8	85	20.1%	-3.16 [-4.45, -1.87]
Total (95% CI)			**568**			**383**	**100.0%**	**-2.77 [-3.80, -1.73]**

Heterogeneity: $Tau^2 = 0.95$; $Chi^2 = 12.59$, df = 6 ($P = 0.05$); $I^2 = 52\%$
Test for overall effect: Z = 5.24 ($P < 0.0001$)

Epworth Sleepiness

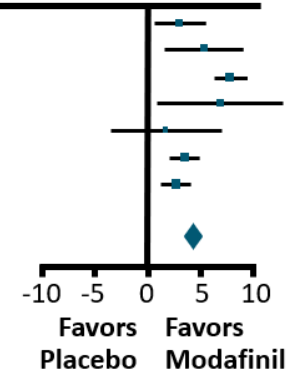


Excessive Daytime Sleepiness (MWT)

Study or Subgroup	Modafinil Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Black 2006	9.86	5.89	63	6.87	6.14	53	10.1%	2.99 [0.79, 5.19]
Broughton 1997*	16.45	12.8	75	11.2	9.8	75	3.7%	5.25 [1.60, 8.90]
Dauvilliers 2013	15.1	2.7	33	7.6	3	30	24.4%	7.50 [6.09, 8.91]
Moldofsky 2000	16.4	13.7	28	9.7	7.9	33	1.5%	6.70 [0.95, 12.45]
Saletu 2009*†	13.3	7.1	15	11.9	6.9	15	1.9%	1.40 [-3.61, 6.41]
US Modafinil in Narcolepsy Multicenter Study 1998†	8.49	6.14	191	5.1	4.7	92	29.0%	3.39 [2.09, 4.69]
US Modafinil in Narcolepsy Multicenter Study 2000†	7.9	5.5	162	5.5	4.5	83	29.5%	2.40 [1.11, 3.69]
Total (95% CI)			**567**			**381**	**100.0%**	**4.14 [3.44, 4.84]**

Heterogeneity: $Chi^2 = 33.30$, df = 6 ($P < 0.00001$); $I^2 = 82\%$
Test for overall effect: Z = 11.61 ($P < 0.0001$)

MWT latency

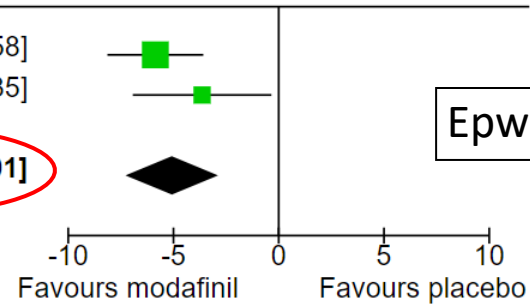


Modafinil for idiopathic hypersomnia

- Two RCTs, both modafinil 200 mg/day (qam or divided)

Study or Subgroup	Modafinil Mean	Modafinil SD	Modafinil Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
Inoue 2021	10	5.23	33	15.86	4.39	37	64.9%	-5.86 [-8.14 , -3.58]
Mayer 2015	9	5.02	17	12.64	4.33	14	35.1%	-3.64 [-6.93 , -0.35]
Total (95% CI)			**50**			**51**	**100.0%**	**-5.08 [-7.16 , -3.01]**

Heterogeneity: Tau² = 0.38; Chi² = 1.18, df = 1 (P = 0.28); I² = 15%
Test for overall effect: Z = 4.80 (P < 0.00001)
Test for subgroup differences: Not applicable

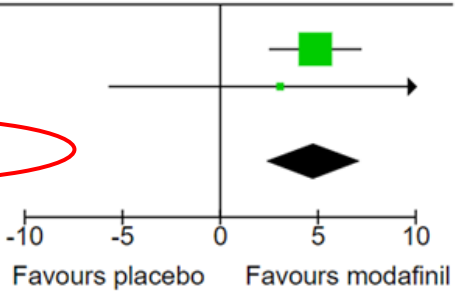


Epworth Sleepiness

MWT latency

Study or Subgroup	Modafinil Mean	Modafinil SD	Modafinil Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
Inoue 2021	11.32	4.71	33	6.46	5.35	37	93.3%	4.86 [2.50 , 7.22]
Mayer 2015	18.44	13.66	15	15.38	10.32	14	6.7%	3.06 [-5.72 , 11.84]
Total (95% CI)			**48**			**51**	**100.0%**	**4.74 [2.46 , 7.01]**

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 4.08 (P < 0.0001)
Test for subgroup differences: Not applicable



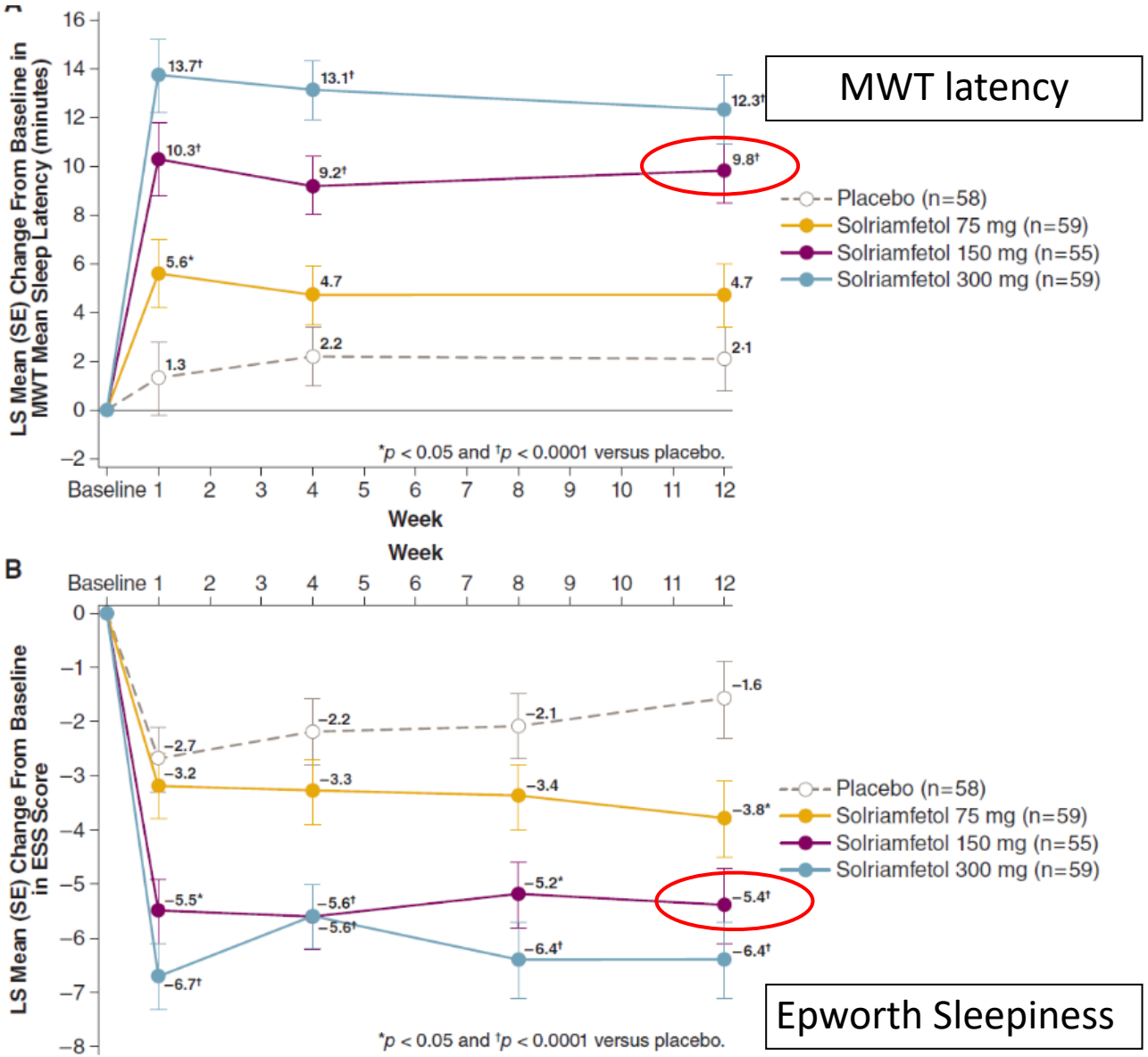
Mayer G, et al., J Sleep Res, 2015, 24:74-81; Inoue Y, et al., Sleep Med, 2021, 80:315-321; Trotti LM, et al., Cochrane Database Syst Rev, 2021, 5:CD012714

Armodafinil

- R-enantiomer of racemic modafinil
- Fewer clinical trials in narcolepsy (none in IH)
- Similar treatment effects and side effects
  - Typically once daily dosing vs twice daily for modafinil
  - Start 125 mg, titrate to 250 mg after 1 week (some people need lower/slower)

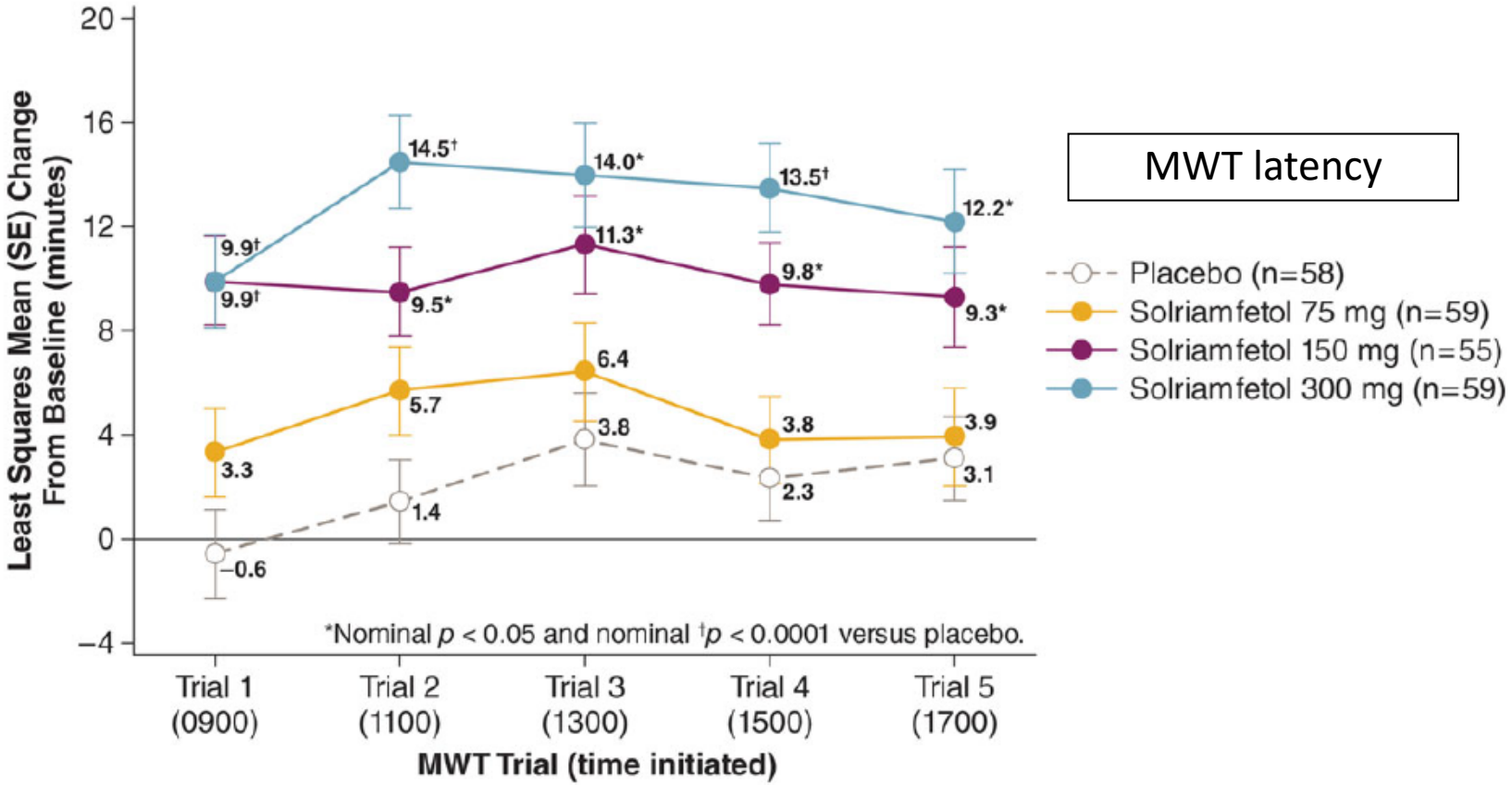
Solriamfetol for narcolepsy

- FDA approved March 2019
- Titrate every 3 days (or slower)
  - 37.5 mg (OSA) or 75 mg (narcolepsy)
  - Max approved dose 150 mg
- Renal excretion
- Common AEs: headache, appetite suppression, anxiety
- Increases in blood pressure:
  - Systolic 1.2 +/- 7.2 mmHg
  - Diastolic 1.5 +/- 4.8 mmHg

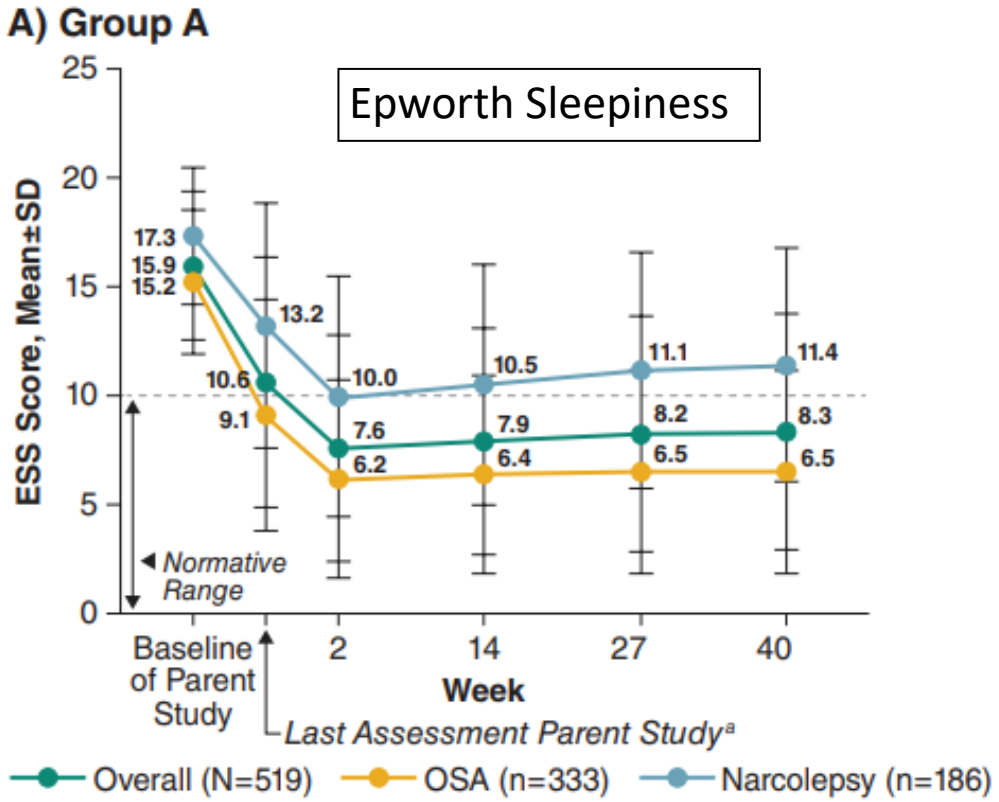


Thorpy MJ, et al., Ann Neurol, 2019, 85:359-370

MWT benefit sustained across the day with single morning dose



Long term follow up of solriamfetol in narcolepsy & OSA



- Drop out due to lack of efficacy:
  - 17.3% in narcolepsy group
  - 3.6% in OSA group
- Drop out due to adverse events:
  - 10.2% in narcolepsy group
  - 9.1% in OSA group

Malhotra, A, et al., Sleep, 2020, 43(2)

Methylphenidate and Amphetamines

- Very long clinical use in treating narcolepsy +/- idiopathic hypersomnia

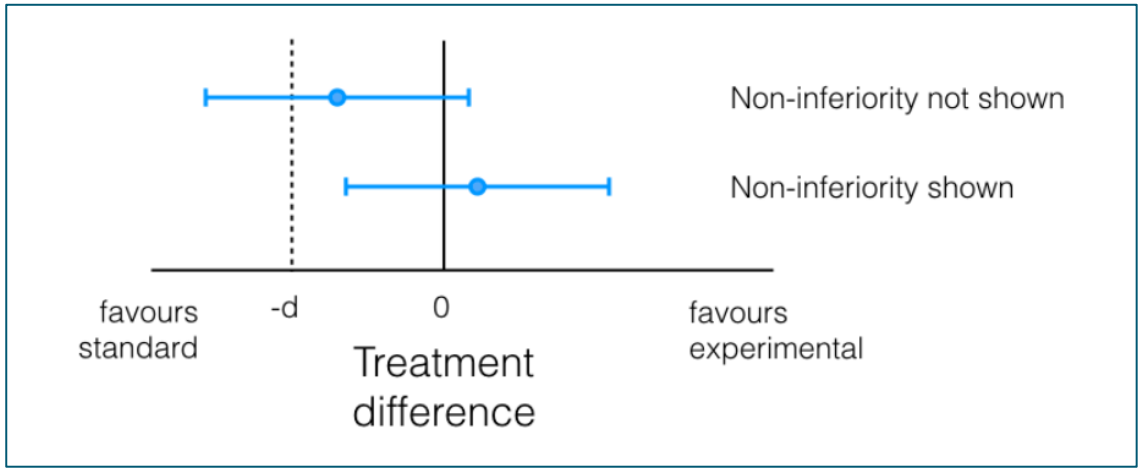
	Clinical series	Sample size	Response rate
Methylphenidate	-Ali 2009	N = 61 with IH	41% remained on methylphenidate with complete response
Amphetamine-Dextroamphetamine	-Ali 2009	N = 8 with IH	25% remained on amphetamine-dextroamphetamine with complete response
Dextroamphetamine	-Ali 2009 -Anderson 2007	N = 15 with IH	33% responded to dextroamphetamine

- Limited clinical trial evidence
- Many preparations

Ali M, et al., J Clin Sleep Med, 2009, 5:562-8; Anderson KN, et al., Sleep, 2007, 30:1274-81

Modafinil vs amphetamine-dextroamphetamine non-inferiority trial

- 44 participants, 22 randomized to each medication
  - 75% IH, 25% NT2
- Non-inferiority trial, primary outcome ESS, non-inferiority threshold 2 points



- Modafinil 100 mg qam up to 200 mg bid
- Amphetamine-dextroamphetamine 10 mg qam up to 20 mg bid

Trotti LM et al, 2024, CNS Drugs, 38(11):909-920; image from https://www.sealedenvelope.com

Modafinil vs amphetamine-dextroamphetamine non-inferiority trial

Efficacy outcomes

- Similar magnitude of Epworth improvement
  - 5.0 (+/- 2.7) points with modafinil
  - 4.4 (+/- 4.7) points with amphetamine-dextroamphetamine
- Non-inferiority of amphetamine-dextroamphetamine was NOT demonstrated (p = 0.11).
- Secondary outcomes:
  - Amphetamine-dextroamphetamine WAS non-inferior to modafinil for:
    - Much/very much improved on cognitive dysfunction
    - Much/very much improved on sleep inertia
    - Sleep Inertia Questionnaire
    - Hypersomnia Severity Index

Safety outcomes

- Dropouts due to adverse events
  - 31.8% for modafinil
    - two severe events
  - 9.1% for amphetamine-dextroamphetamine
  - p = 0.13
- AEs experienced by at least 5%
  - Anxiety more common with modafinil
  - Appetite suppression with amphetamine-dextroamphetamine

Trotti LM et al, 2024, CNS Drugs, 38(11):909-920

Pitolisant for narcolepsy

- FDA-approved August 2019
- Increase dose no more often than q7 days
  - Week 1: 8.9 mg
  - Week 2: 17.8 mg
  - Week 3: 35.6 mg
- Full benefit seen in ~4-8 weeks at fixed dose
- Liver metabolism, renal excretion
- Common AEs: headache, insomnia, nausea
- QT prolongation
- Specialty pharmacy

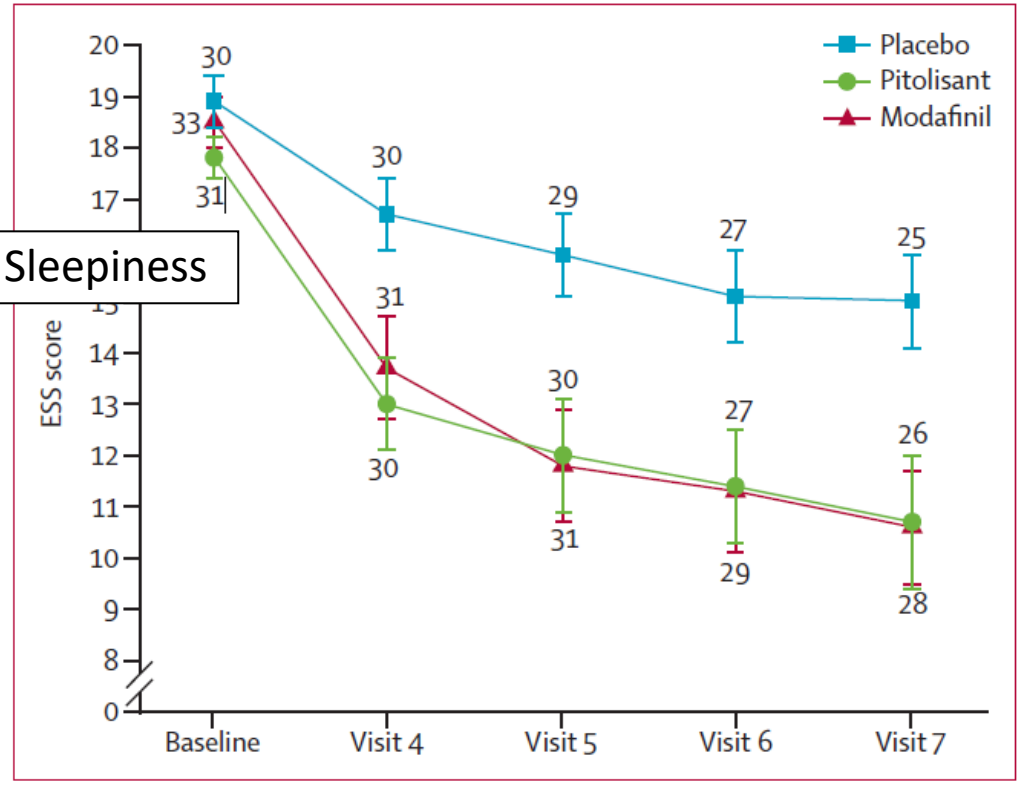
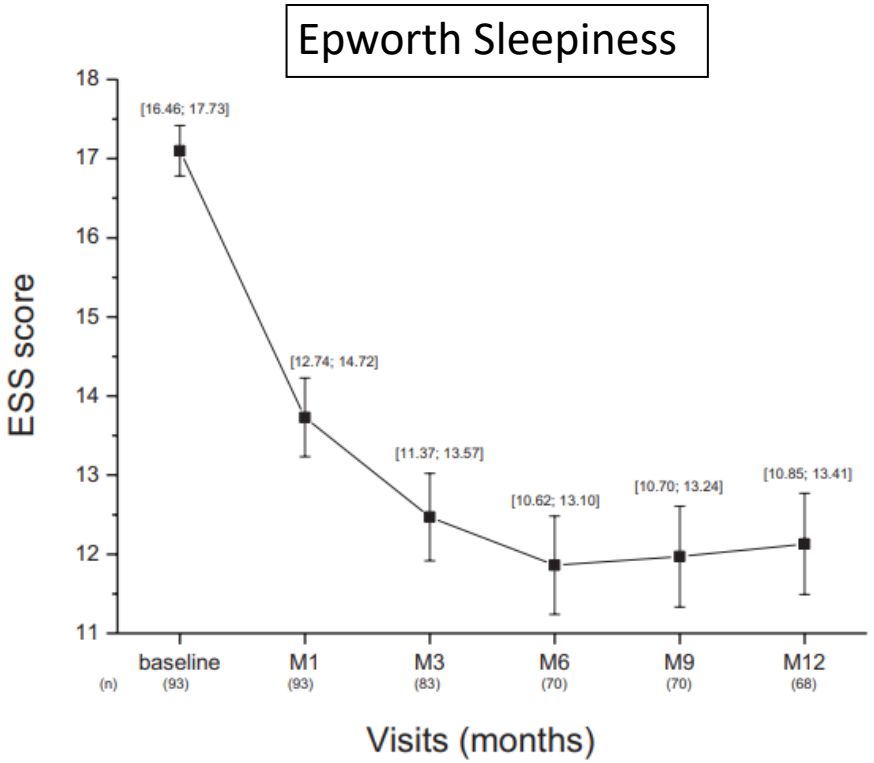


Figure 3: Changes in Epworth sleepiness scale (ESS) score

Dauvilliers Y, et al., The Lancet Neurology, 2013, 12:1068-1075

Long term use of pitolisant for narcolepsy



- Open-label, single arm, previously treated or new to pitolisant (up to 40 mg), 1 year
- 102 people with narcolepsy with or without cataplexy (~75% with cataplexy); continued other meds
- Primary outcome was TEAEs at 12 months
  - 57% reported any TEAE; 43% likely related
  - Most common: headache, insomnia, weight gain, anxiety, depression, nausea
  - 7% serious AE – all judged unrelated except 1 miscarriage
- 33% stopped pitolisant early
  - Lack of efficacy in 20% of whole group
  - AEs in 11%

Pitolisant for idiopathic hypersomnia

- Phase 3 randomized withdrawal trial, adults with IH
- During open label run in, 83% of participants were responders (ESS reduction at least 3 points)
  - Average ESS change from baseline -9.4 points
- BUT, no significant difference between pitolisant and placebo during 4-week blinded withdrawal
- 88% continued the 12-month extension phase
- No new safety signals

https://ir.harmonybiosciences.com/news-releases/news-release-details/harmony-biosciences-announces-topline-data-phase-3-intune-study

Oxybates

- Taken at night to target sleepiness & cataplexy the next day

- Three preparations:
  - Sodium oxybate (twice nightly) – FDA approved 2002
    - Available as a generic
  - Ca/Mg/K/Na oxybate – FDA approved 2020
    - ~90% less sodium than sodium oxybate at max dose
  - Once nightly sodium oxybate – FDA approved 2023
    - Full dose at bedtime

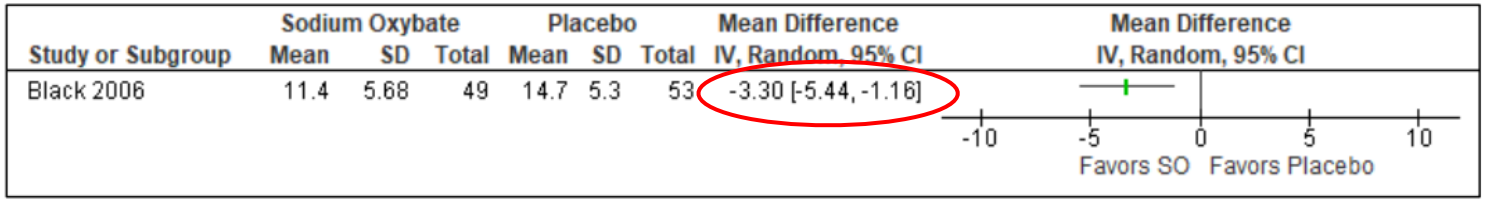
- Liquid or reconstituted granules
- Start 2.25 gm bid nightly or 4.5 gm once nightly formulation
  - Increase by not more than 1.5 gm total nightly qweek
- Take interactions with sedating medications & substances seriously

Sodium oxybate (original) for narcolepsy

- REMS program (all oxybates)
- Common AEs (all oxybates): nausea, enuresis, somnolence, anxiety
- Take sedating interactions seriously

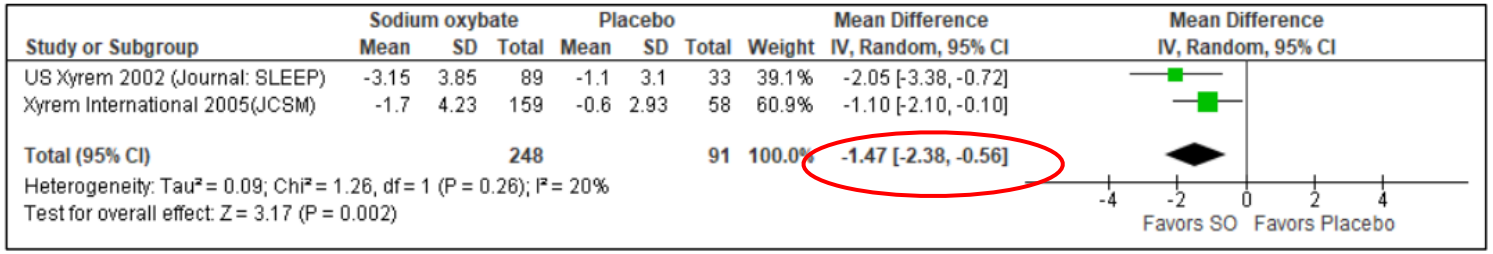
Epworth Sleepiness

Figure S19. ESS determined excessive daytime sleepiness, in response to sodium oxybate vs. placebo in adult patients with unspecified narcolepsy.



Data obtained from personal communication with JAZZ pharmaceuticals.

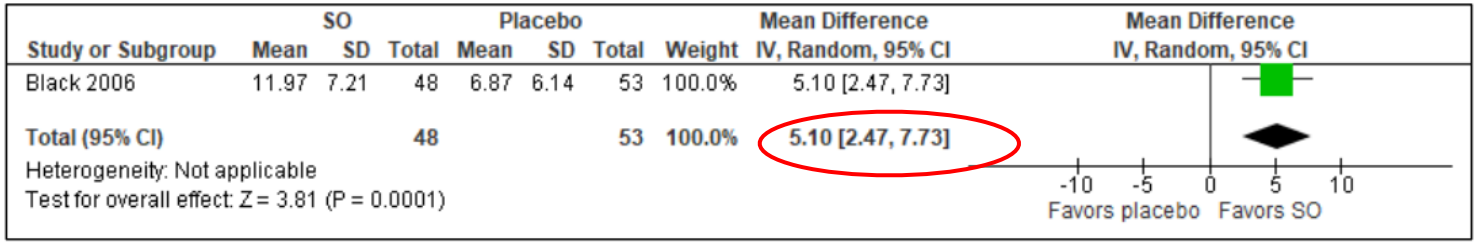
Figure S20. ESS determined excessive daytime sleepiness, in response to sodium oxybate (various doses) in adult patients with NT1.



Sodium oxybate data is pooled doses data in both studies. Results are a change from baseline. Data obtained by personal communication.

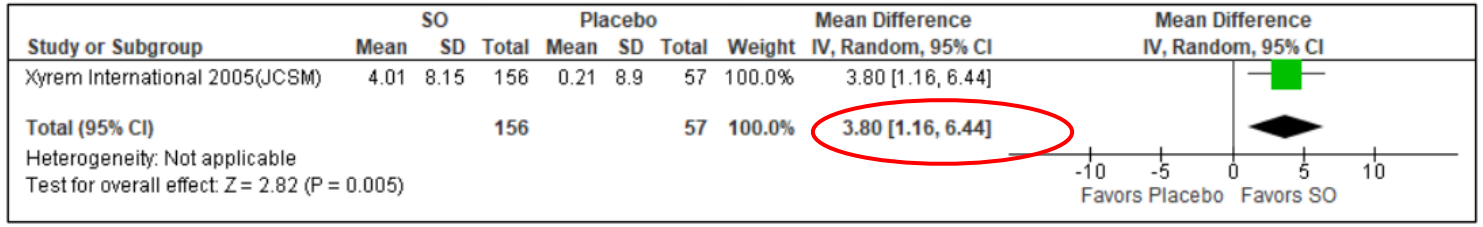
Sodium oxybate (original) for narcolepsy

Figure S23. MWT determined excessive daytime sleepiness, in response to sodium oxybate vs. placebo in adult patients with unspecified narcolepsy.



MWT latency

Figure S22. MWT determined excessive daytime sleepiness, in response to sodium oxybate vs. placebo in adult patients with NT1.



MWT latency

Xyrem 2005 (JCSM) - pooled data (change from baseline) of all doses shown here. Median data converted to mean (SD)

Cataplexy

Outcome: CATAPLEXY

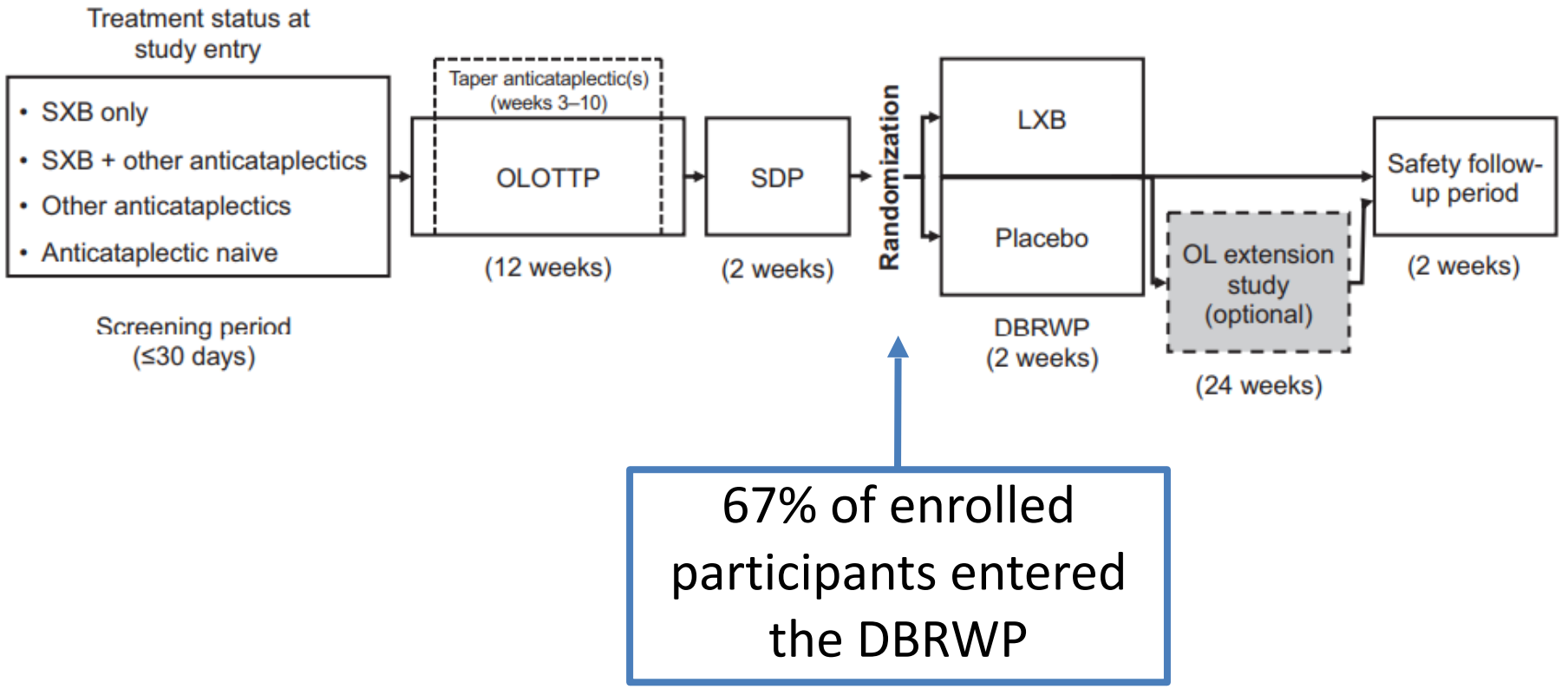
Table S40. Weekly number of cataplexy attacks in RCTs, in response to sodium oxybate (various doses) in adult patients with NT1.

Study	Study design	Study duration	No. of subjects		Data (mean, SD)				% difference in cataplexy reduction
					Intervention		Placebo		
			Pts. on SO	Pts on placebo	Baseline	Post treatment (% mean reduction)	Baseline	Post treatment (% mean reduction)	
US Xyrem 2002 (SLEEP)	RCT	4 weeks	97	33	32.67± 36.68	19.39 ± 36.0 (40.64%) *	35.1± 47.1	24.0 ± 28.4 (31.6%) *	9.04%
Xyrem International 2005(Sleep Medicine)	RCT	8 weeks	169	58	36.66 ± 61.60	18.35 ± 53.21 (49.9%)	35.01 ± 51.80	20.75 ± 19.63 (40.73%)	9.17%

*[(post-treatment mean/pre-treatment mean) -1 x 100]

Xyrem International 2005(Sleep Medicine) and US Xyrem 2002- SO data is pooled dose data

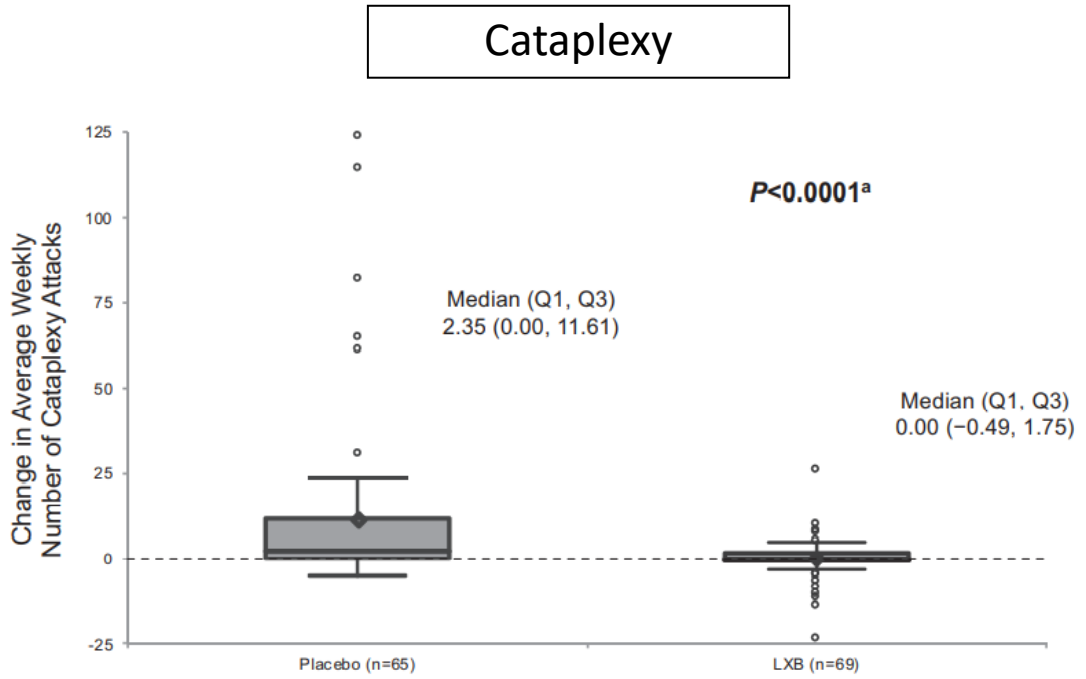
Lower sodium oxybate: Randomized, withdrawal studies



Bogan RK, et al., Sleep, 2021;44:zsaa206

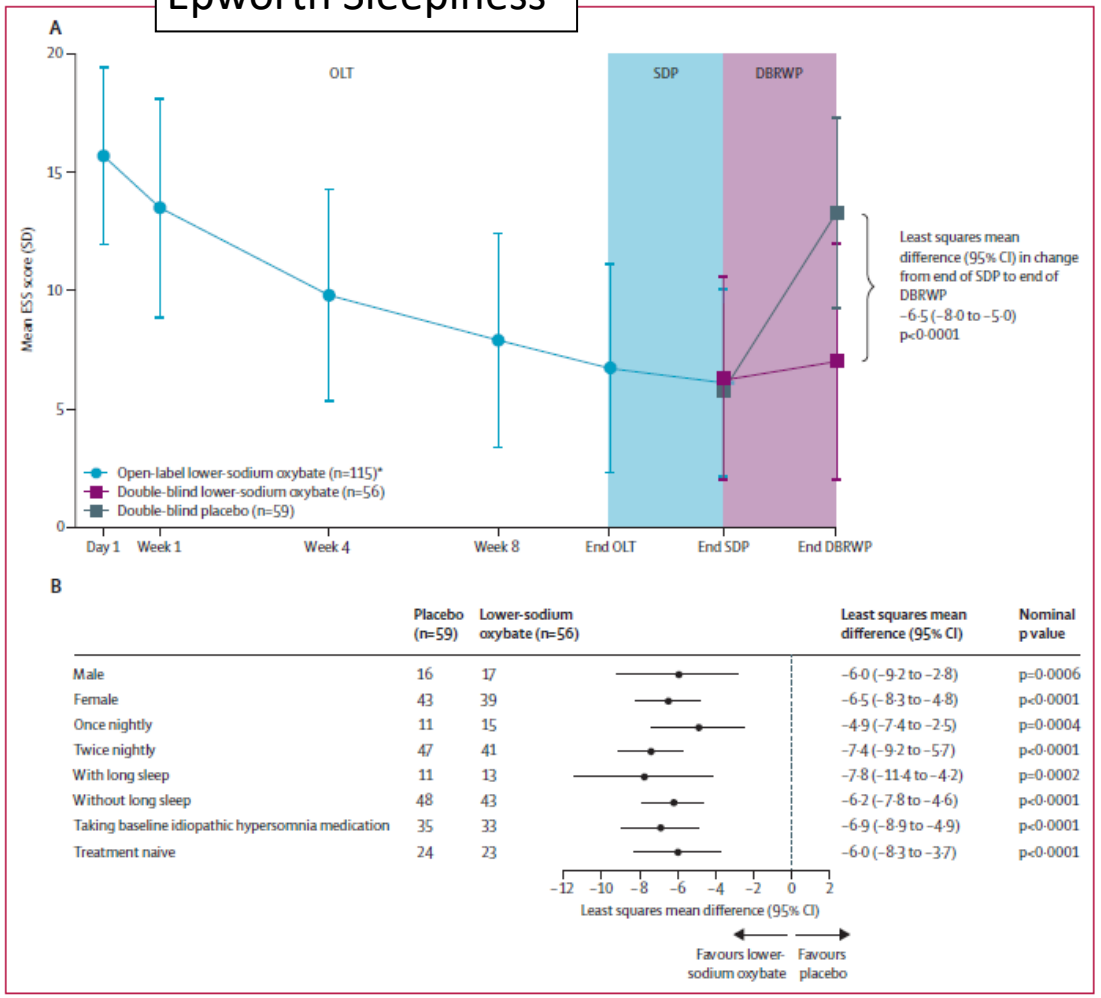
Ca, Mg, K, Na oxybate for narcolepsy

- During DBRWP:
  - Epworth Sleepiness
    - Worsened by 3.0 (+/- 4.7) in placebo
    - Stable (mean 0.0 +/- 2.9) in oxybates
    - P < 0.0001
  - Weekly cataplexy
    - Increased by 11.5 (+/- 24.8) in placebo
    - Increased by 0.1 (+/- 5.8) in oxybates
    - P < 0.0001



Ca, Mg, K, Na oxybate for idiopathic hypersomnia

Epworth Sleepiness



- 114 mild TEAEs
- 77 moderate TEAEs
- 1 severe (unrelated)

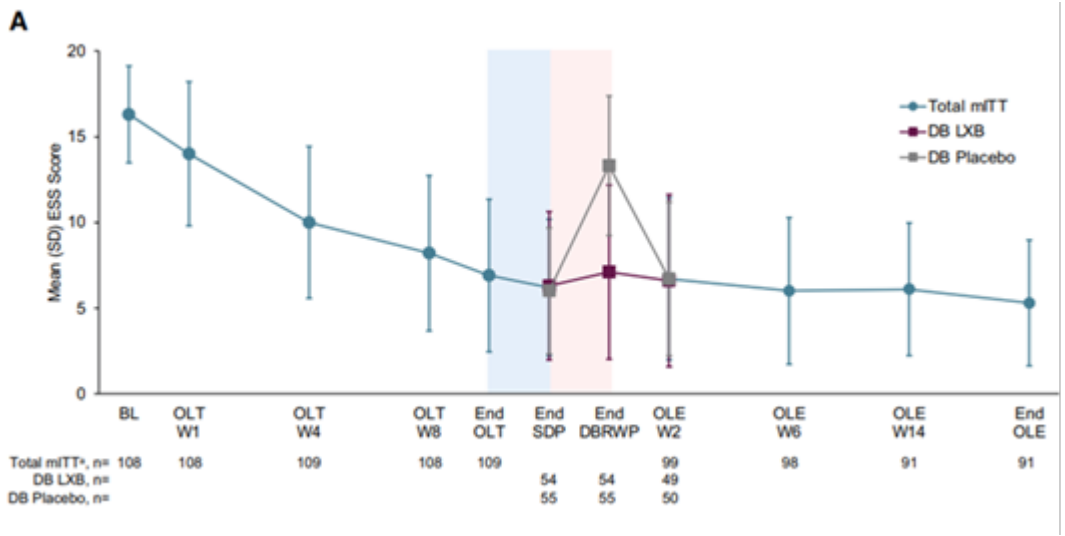
- 4 people had 9 serious TEAEs (unrelated)

- 17% (26/154) dropped out due to TEAEs (including 3 in extension)
  - Half (13/26) of these had at least one psychiatric TEAE leading to drop out

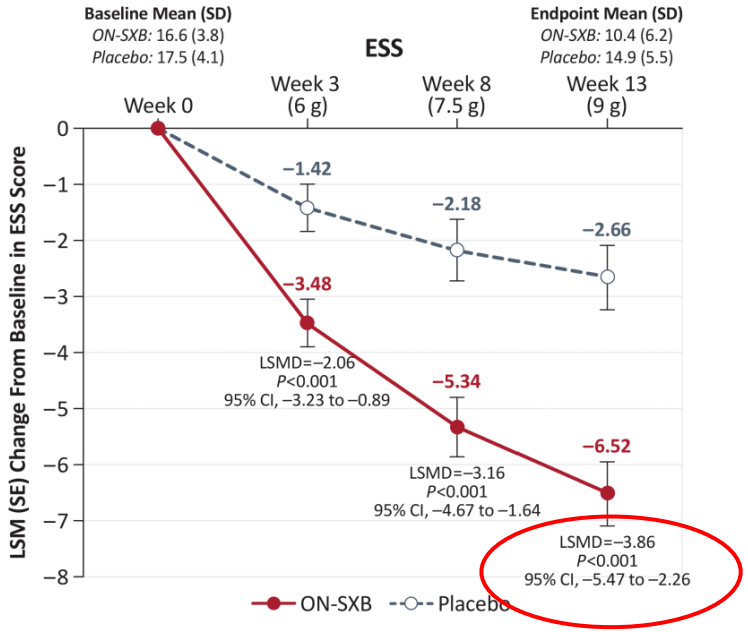
Long-term follow-up of IH lower sodium trial

- 154 participants took at least one LXB dose
- 106 entered the open label extension
- 95 finished the open label extension
- → ~62% of people who started LXB were still taking at the end of ~40 weeks
- (5 participants on SXB at study entry not include in these results)

Epworth Sleepiness

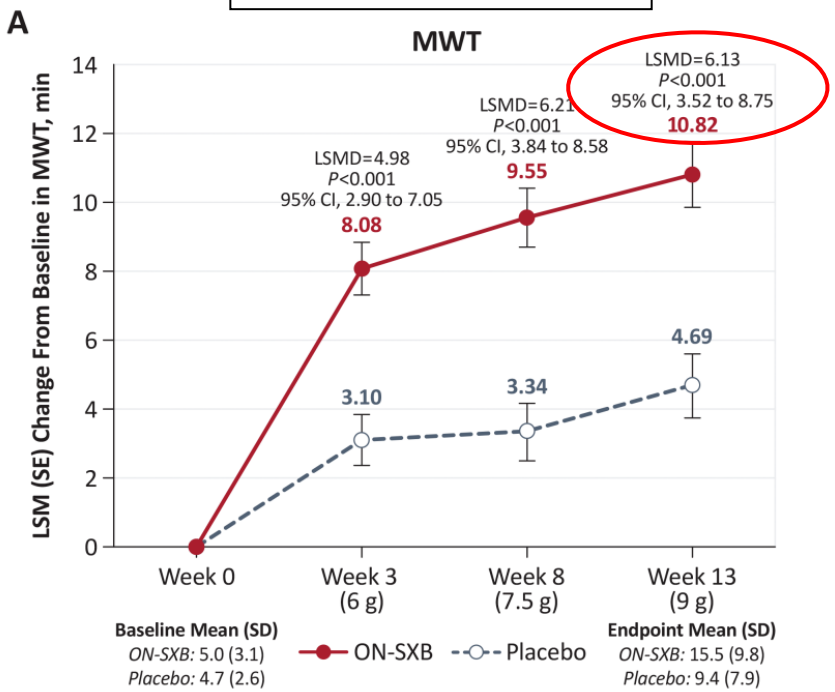


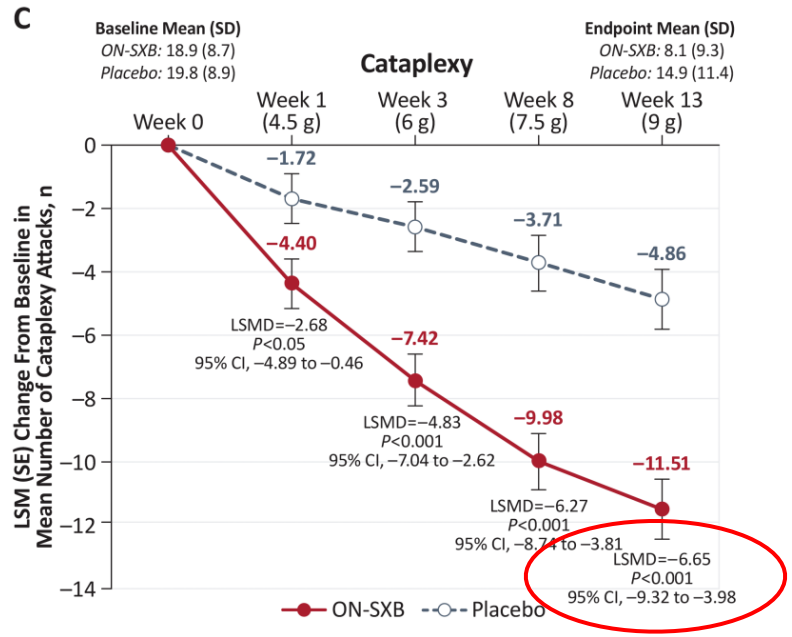
Once Nightly Sodium Oxybate for narcolepsy



Epworth Sleepiness

MWT latency





Cataplexy

Kushida C, et al, Sleep 2022;45:zsab200.

American Academy of Sleep Medicine Clinical Practice Guideline (2021)

	Adult Narcolepsy	Pediatric Narcolepsy	Idiopathic hypersomnia
Modafinil	**Strong**	Conditional	**Strong**
Armodafinil	Conditional	--	--
Methylphenidate	Conditional	--	Conditional
Dextroamphetamine	Conditional	--	--
Sodium oxybate	**Strong**	Conditional	Conditional
Solriamfetol	**Strong**	--	--
Pitolisant	**Strong**	--	Conditional
Clarithromycin	--	--	Conditional

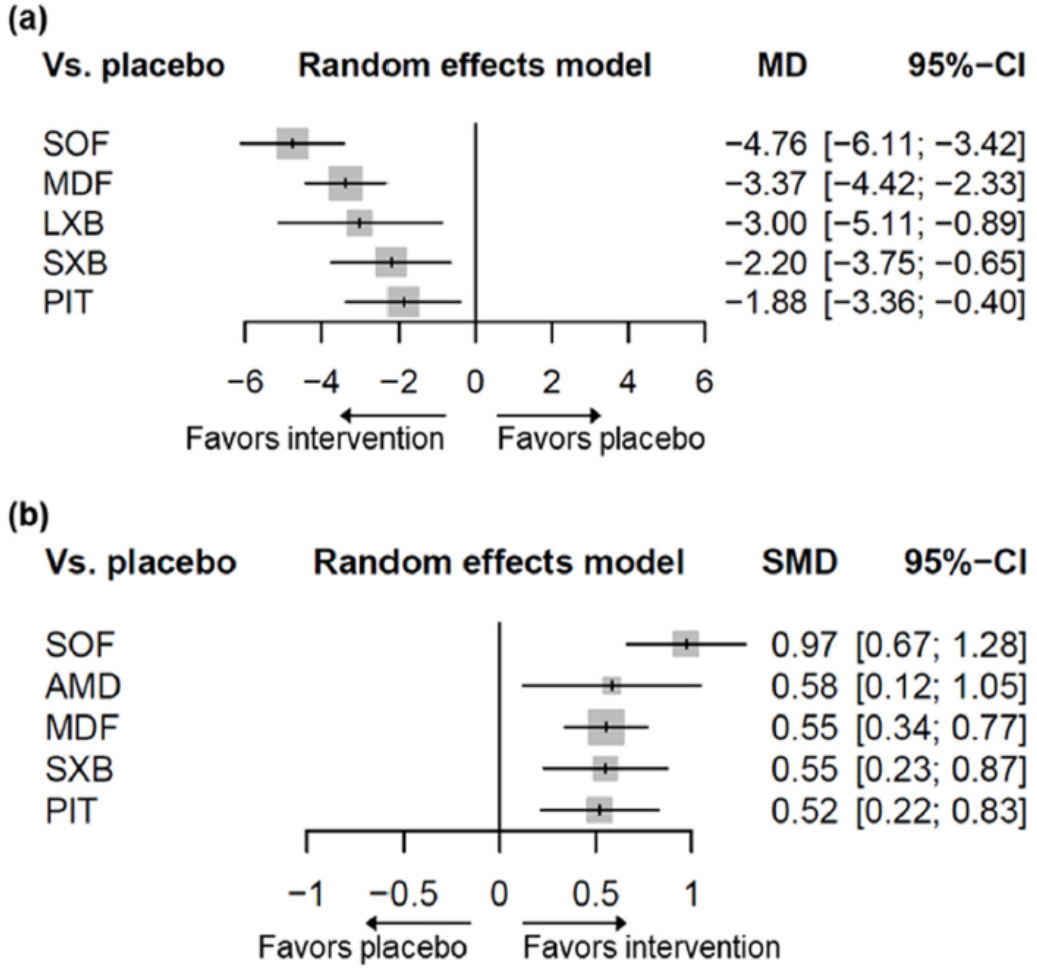
- Moment in time
  - Prior to Ca, Mg, K, Na oxybate studies, once-nightly Na oxybate studies, and IH pitolisant study
  - Prior to several peds FDA approvals
- Published literature
  - No recs based solely on expert consensus
    - Antidepressants for cataplexy

Maski K, et al., Journal of Clinical Sleep Medicine, 2021, 17:1881-1893

Which treatment for which patient?

- Targeting specific symptoms
  - Sleepiness, cataplexy, disrupted nocturnal sleep, severe sleep inertia
  - Cognition? Brain fog? Long sleep durations? Fatigue?
- Drug-drug interactions
- Side effect risks
- Comorbid conditions

Network meta-analysis: Sleepiness



Epworth Sleepiness

MWT latency

- Does not include amphetamines or methylphenidate
- Significant differences:
  - Epworth: SOF > PIT, SXB
  - MWT: SOF > PIT, MDF
- Abbreviations:

-SOF: solriamfetol

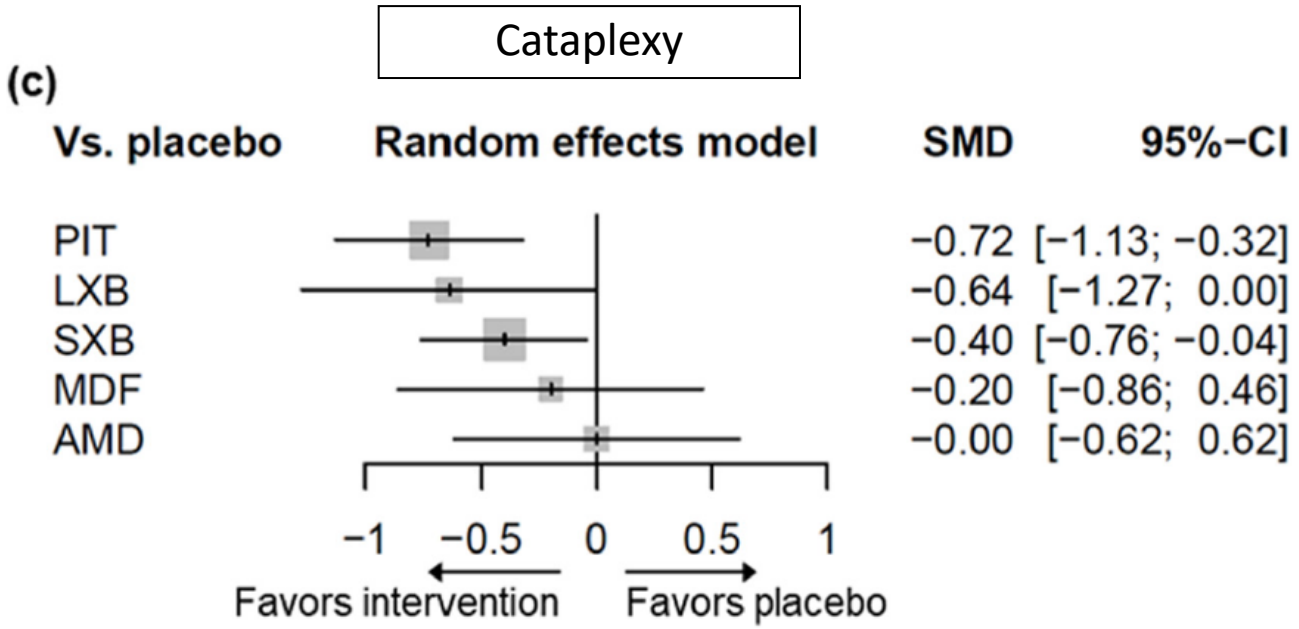
-MDF: modafinil

-LXB: lower sodium oxybate

-SXB: sodium oxybate

-PIT: pitolisant

Network meta-analysis: Cataplexy



- Does not include SSNRIs (e.g., venlafaxine), SSRI (e.g., fluoxetine)
- Some oxybate studies had randomized withdrawal design

Deciding among medications for cataplexy

- Anti-depressants
  - Only treat cataplexy, not sleepiness (so not preferred for those desiring monotherapy)
  - Dual therapeutic benefit in people with depression
- Oxybates
  - Treat both cataplexy and sleepiness
  - Very rare suicidality – use with caution in people with recent/uncontrolled depression
- Pitolisant
  - Treats both cataplexy and sleepiness
  - Inducer of cytochrome P450 3A4; requires dose reduction when used with bupropion
  - Didn’t cause/worsen depression in clinical trials

Disrupted nocturnal sleep

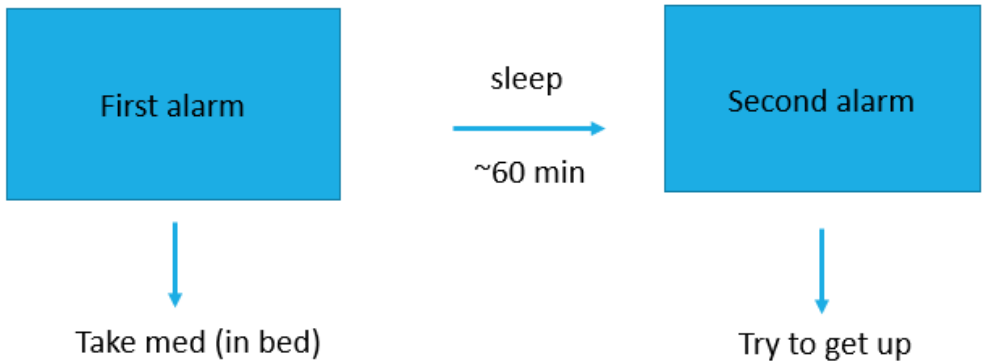
- Consider comorbid causes, e.g., obstructive sleep apnea
- Consider iatrogenic (medication) effects
- If pharmacology to improve DNS is needed, consider oxybates
- Other medications that could treat DNS do not target sleepiness or cataplexy

Severe sleep inertia

- Oxybates
  - IH clinical trial of lower sodium oxybate
    - Sleep inertia worsened 22 points (out of 100 point VAS) with randomization to placebo
- Other bedtime medications
  - Stimulants
  - Bupropion XL
  - Flumazenil
  - DR/ER methylphenidate
    - Absorbed in colon
    - 50% released 10-14 hrs after ingestion
    - 50% released 14-20 hrs after ingestion

- Phase shifting approaches for those who are delayed

- Med timing:



Dauvilliers Y, et al., Lancet Neurol, 2022; supplemental material; Schenck CH et al, JCSM, 2021, 17(4):653-657

Key drug-drug Interactions

CYP 3A4 inducers Reduce effectiveness of 3A4 substrates (including hormonal contraception and morning after pill)	QT prolongation	Oversedation/ respiratory depression
• Modafinil • Armodafinil • Pitolisant	• Pitolisant • Some antidepressants • Clarithromycin	• Oxybates (all formulations)

Medication considerations

Medication	Serious AEs	Black box warnings	DEA schedule	Peds FDA approval?	Other sleep FDA approvals
Modafinil/ armodafinil	Drug rashes, mania, psychosis, hallucinations, suicidal ideation, dependency/abuse potential		IV	No; higher risk SJS	OSA, shift work
Solriamfetol	Dependency/abuse potential		IV	No	OSA
Methylphenidate & amphetamines	Drug rashes, TTP, HTN, MI, stroke, arrhythmia, seizures, angioedema, priapism, glaucoma, rhabdo, hepatotoxicity, vasculopathy, mania, psychosis, hallucinations, suicidal ideation, dependency/abuse potential	**Abuse, dependence; CVD/death with misuse**	II	Varies	--
Pitolisant	QT prolongation, anaphylaxis		--	Yes	--
Oxybates	CNS depression, respiratory depression, depression, suicidality, psychosis, paranoia, hallucinations, sleepwalking, apnea, dependency/abuse potential	**CNS depression, respiratory depression; death with misuse**	III, with REMS program	Yes	IH (lower sodium oxybate)
SNRIs (venlafaxine)/ SSRIs (fluoxetine)	Suicidality, mania, serotonin syndrome, bleeding, drug rashes, seizures, hypoNa, HTN, arrhythmia, QT prolongation, cardiomyopathy, ILD, pancreatitis, blood dyscrasias, hepatotoxicity	**Suicidality risk in those <25 years old**	--	No (for narcolepsy)	--

People with narcolepsy often have comorbid psychiatric conditions

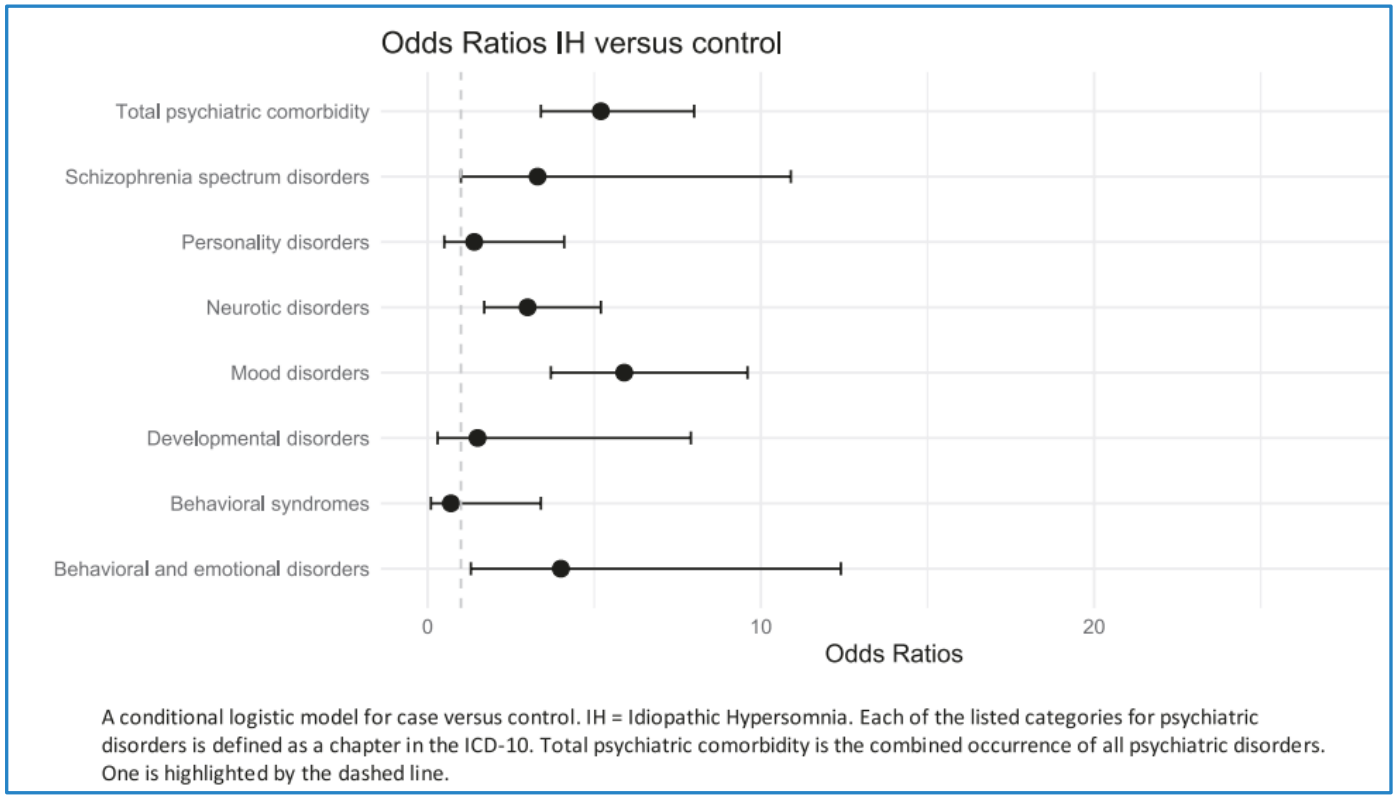
Table 2. Psychiatric Comorbidity Prevalence (CCSM Level 2 Categories)[a] and Selected Subcategories for Patients With a Narcolepsy Diagnosis Versus Matched Controls

	Patients With Comorbidity		
CCSM 5 Mental Illness Categories	Controls (n = 46,559)	Narcolepsy (n = 9,312)	OR (95% CI)[b]
5.1 Adjustment disorders	5.4%	11.2%	2.3 (2.1–2.4)
5.2 Anxiety disorders	11.9%	25.1%	2.5 (2.4–2.7)
5.3 Attention deficit, conduct, and disruptive behavior disorders	1.3%	7.3%	6.2 (5.6–7.0)
5.4 Delirium, dementia, and amnestic and other cognitive disorders	1.5%	4.6%	3.8 (3.3–4.3)
5.7 Impulse control disorders not elsewhere classified	0.1%	0.2%	1.9 (1.1–3.2)
5.8 Mood disorders	13.8%	37.9%	4.0 (3.8–4.2)
5.8.1 Bipolar disorders	2.1%	8.3%	4.4 (3.9–4.8)
5.8.2 Depressive disorders	13.0%	35.8%	3.9 (3.7–4.1)
5.9 Personality disorders	0.2%	1.1%	5.8 (4.3–7.7)
5.10 Schizophrenia and other psychotic disorders	0.9%	3.4%	3.8 (3.3–4.4)
5.11 Alcohol-related disorders	1.3%	1.9%	1.4 (1.2–1.7)
5.12 Substance-related disorders	1.2%	4.0%	3.5 (3.0–4.0)
5.13 Suicide and intentional self-inflicted injury[c]	0.2%	1.0%	4.1 (3.1–5.4)
5.15 Other miscellaneous mental disorders	4.0%	14.5%	4.1 (3.8–4.4)

- Largest ORs for:
  - Attention deficit/conduct = 6.2
  - Personality disorders = 5.8
  - Bipolar = 4.4

- Narcolepsy n = 9312, matched control n = 46559
- US medical claims data (Medicare and private)

People with IH often have comorbid psychiatric conditions



A conditional logistic model for case versus control. IH = Idiopathic Hypersomnia. Each of the listed categories for psychiatric disorders is defined as a chapter in the ICD-10. Total psychiatric comorbidity is the combined occurrence of all psychiatric disorders. One is highlighted by the dashed line.

- Odds ratio for having a psychiatric disorder diagnosis in the 10 years before IH diagnosis, vs matched population controls
  - *but remember average diagnostic delay in IH is 10.6 years
- Consider IH versus hypersomnia comorbid to psychiatric disorder

Haubjerg Østerby NC et al, 2024, Sleep Advances, zpae073; Anderson J et al, 2024, JCSM, epub ahead of print

Consider co-morbid psychiatric disorders when selecting medication

	substance abuse	depression	mania/bipolar	psychosis	agitation	anxiety
modafinil/ armodafinil	-	-	-	-		
methylphenidate	-		-	-	XX (if severe)	XX (if severe)
amphetamines	-		-	-		
oxybates	XX (EtOH, sedating)	-	-	-	-	-
pitolisant						
solriamfetol	-		-	-		

- CONTRAINDICATION (XX) or CAUTION (-) USING MEDICATION IF PRESENT (from package insert)

People with narcolepsy commonly have comorbid medical conditions

Overall comorbidity comparison by CCSM categories[a] – controls versus narcolepsy.

CCSM Category[a]	Excess prevalence	OR[b] (95% CI)
Infectious and parasitic diseases (01)	14.1%	1.9 (1.8, 2.0)
Neoplasms (02)	10.3%	1.6 (1.5, 1.6)
Endocrine, nutritional, and metabolic diseases, and immunity disorders (03)	17.9%	2.8 (2.6, 2.9)
Diseases of the blood and blood-forming organs (04)	13.1%	2.1 (2.0, 2.2)
Mental illness (05)	31.1%	3.8 (3.6, 4.0)
Diseases of the nervous system/sense organs (excluding narcolepsy; 06)	20.7%	3.7 (3.4, 3.9)
Diseases of the circulatory system (07)	16.6%	2.6 (2.5, 2.8)
Diseases of the respiratory system (08)	17.3%	3.7 (3.4, 3.9)
Diseases of the digestive system (09)	21.4%	2.7 (2.5, 2.8)
Diseases of the genitourinary system (10)	13.1%	2.2 (2.1, 2.3)
Complications of pregnancy, childbirth, and the puerperium (11)	−0.4%	NS
Diseases of the skin and subcutaneous tissue (12)	14.4%	1.8 (1.8, 1.9)
Diseases of the musculoskeletal system and connective tissue (13)	17.5%	3.5 (3.2, 3.7)
Congenital anomalies (14)	7.1%	2.2 (2.1, 2.4)
Certain conditions originating in the perinatal period (15)	0.1%	NS
Injury and poisoning (16)	20.2%	2.4 (2.3, 2.5)
Symptoms, signs, and ill-defined conditions and factors influencing health status (17)	8.0%	4.3 (2.8, 4.8)

- Narcolepsy n = 9312, matched control n = 46559
- US medical claims data (Medicare and private)

Black J et al, Sleep Medicine, 2017, 33:13-18

Consider co-morbid medical disorders when selecting medication

	CVD/ CHF	cardiac structural	arrhythmias	Long QT or FH	pulmonary disease	tics	seizure	glaucoma	hyperthyroid	Liver dosing	Kidney dosing
modafinil/ armodafinil	-	XX (LVH, MVP)								HD	
methylphenidate	XX	XX	XX			XX	-	XX	-		
amphetamines	XX	XX	XX			-	-	-	-		some RD
oxybates	- (if sodium)				-					HD	
pitolisant	XX		XX	XX						HD	RD
solriamfetol	XX		XX								RD

- CONTRAINDICATION (XX) or CAUTION (-) USING MEDICATION IF PRESENT

Dosing and Pharmacokinetics

Daytime Medications	Half-life	Dosing	Maximum Dose
Modafinil	15 hrs	AM/noon	400 mg/day*
Armodafinil	15 hrs	AM	250 mg/day*
Solriamfetol	7.1 hrs	AM	150 mg/day*
Methylphenidate	2.5-7 hrs	AM (100% ER), AM/noon (IR, IR/ER)	72 mg/day (100% ER), 60 mg/day (IR, IR/ER)
Amphetamines	Varied	AM (lisdexamfetamine), AM/noon (others)	70 mg/day (lisdexamfetamine); Typically 60 mg/day (others)
Pitolisant	7.5-24.2 hrs	AM	35.6 mg

Nighttime Medications	Half-life	Dosing	Maximum Dose
Sodium oxybate	30-60 min	Bedtime, then 2.5 to 4 hours later	4.5 g BID nightly
Ca/Mg/K/Na oxybate	30-60 min	Bedtime, then 2.5 to 4 hours later (for IH, bedtime or BID nightly)	4.5 g BID nightly (6 g if once nightly)
Once nightly sodium oxybate	30-60 min (but ER)	Bedtime	9.0 g once nightly
Methylphenidate DR/ER	5.9 hrs	8 PM	100 mg

Consider non-pharmacologic strategies as adjunct treatments

	NT1	NT2	IH
Scheduled naps	Yes	⟷	Not typically
Accommodations	Naps, cognitive	⟷	Late start, cognitive
Counseling/support (SE, safety)	Yes, CBT-H?		
Patient groups	Wake Up Narcolepsy, Narcolepsy Network, Project Sleep		Hypersomnia Foundation

How effective do patients perceive non-pharmacologic strategies to be?

		Narcolepsy (n=242)	Idiopathic Hypersomnia (n =129)
Caffeine	% using	73%	82%
	effectiveness	4.1	3.3*
Naps	% using	87%	81%
	effectiveness	5.0	2.7*
Scheduled night sleep	% using	76%	75%
	effectiveness	4.6	3.0*
Nicotine	% using	25%	20%
	effectiveness	4.1	3.2*
Exercise	% using	54%	58%
	effectiveness	4.6	2.2*

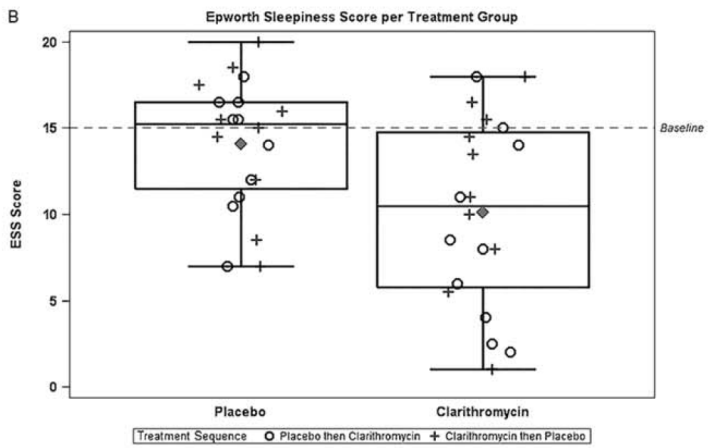
Effectiveness 0-10 scale; * = $p < 0.05$

Data from Neikrug A et al, Behav Sleep Med, 2017, 15:158-71

Considerations in treatment-refractory cases

- Other diagnoses
  - Circadian
  - Mood
  - Fatigue
  - Autonomic dysfunction
  - Medical comorbidities
- Combination therapy
- Clarithromycin
  - FDA warning for people with CAD
- Flumazenil
- Clinical trials/pipeline

Epworth Sleepiness



Trotti LM et al, Annals of Neurology, 2015, 78(3):454-65

Treatment during conception/pregnancy

Consider the balance of harms:

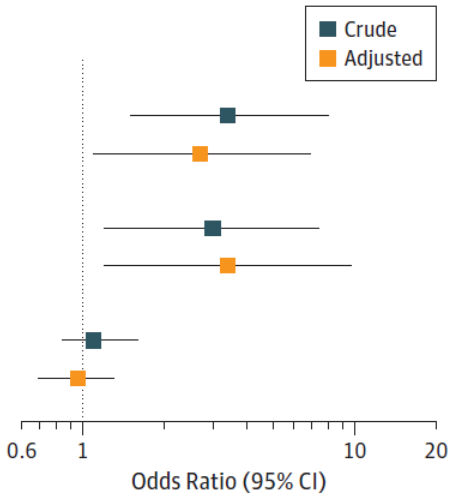
- Harms of medication
- Harms of not taking medication
  - Safety
  - Functional status, relationships, work, education
  - Quality of life

Narcolepsy medications & pregnancy

- Modafinil/armodafinil now considered NOT safe during pregnancy
  - Mixed data
  - US registry data suggests risk of MCM 13% (vs 3% baseline risk)
  - 3x higher risk than with methylphenidate
- Full list of meds/safety data at HypersomniaFoundation.org

Figure. Risk of Congenital Malformations From First-Trimester Modafinil Exposure

Comparisions	No. of Major Congenital Malformations	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Modafinil vs unexposed			
Modafinil	6	3.4 (1.5-7.4)	
Unexposed	32 466		2.7 (1.1-6.9)
Modafinil vs methylphenidate			
Modafinil	6	3.0 (1.2-7.4)	
Methylphenidate	43		3.4 (1.2-9.7)
Methylphenidate vs unexposed			
Methylphenidate	43	1.1 (0.84-1.6)	
Unexposed	32 466		0.69 (0.69-1.3)



Kaplan S, et al., JAMA Intern Med, 2021, 181:275-277; Damkier P, et al., JAMA, 2020, 323:374-376

Other considerations during conception/pregnancy

- Lowest dose, least often
- Change meds before conception not after

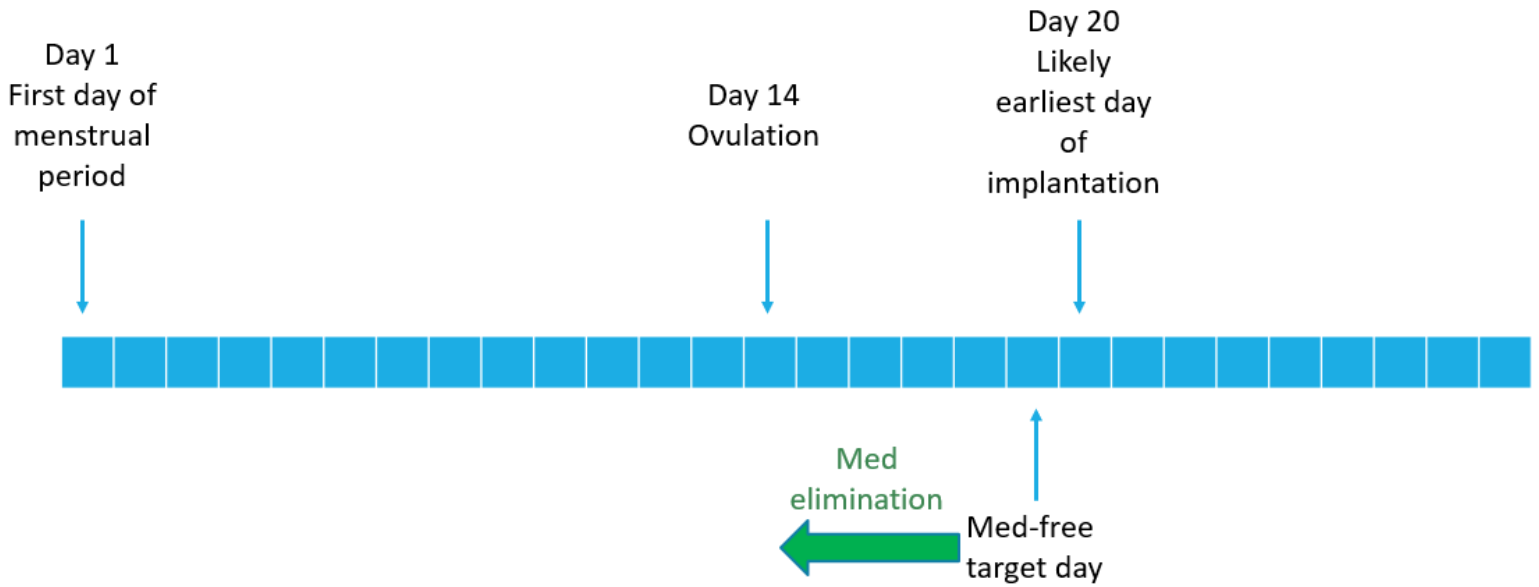
- Preconception MFM consultation

- Different accommodations during pregnancy:
  - Driving safety
  - Sleep inertia/getting to work on time
  - Reduced hours
  - Shifted hours
  - More breaks
  - Is short term disability an option?

- Consider the safety zone during attempts at conception

Safety zone calculations*

*assumes a regular, 28-day cycle, and predictable drug elimination



- For example, amphetamine salts
  - Half-life up to 14 hours
  - Time to eliminate ~ 3 days
- Day 19 is med-free target day
- Safety zone is days 1-16

Medications during breastfeeding

Medication	LactMed Data	LactMed Summary/Quotes
Modafinil/ armodafinil	• Very low armodafinil levels in milk (n = 1) • No AEs during breastfeeding with modafinil (n < 6)	• Use with careful monitoring or use alternate
Sodium oxybate	• No AEs (n = 2) • Levels minimal by 4-5 hours after dose	• "Nursing should usually be withheld from the time of the first dose to 4-6 hours after the second dose and breastfeeding can be continued during the day."
Methylphenidate	• Milk/blood levels very low (n ~10) • No AEs (n ~10) • Effects on neurodevelopment unknown • Large doses could suppress production	• "If methylphenidate is required by the mother, it is not a reason to discontinue breastfeeding."
Dextroamphetamine	• Milk levels low (n = 5) • No AEs (n = 4) • Neurodevelopment unknown • Large doses could suppress production	
Solriamfetol	• No data	• "If solriamfetol is required by the mother, it is not a reason to discontinue breastfeeding."
Pitolisant	• No entry	
Venlafaxine	• Metabolite found in infant plasma but no proven SE reported • Watch for sedation and poor weight gain	
Fluoxetine	• Average amount in milk higher than other SSRIs • Colic/drowsiness reported	• Not a reason to discontinue breastfeeding • Continue if already on fluoxetine for pregnancy, else other SSRI

Drugs and Lactation Database (LactMed): NIH. ncbi.nlm.nih.gov/books/NBK501922. Accessed 11/8/2023

Thank you!