Alertness Promoting Pharmacologics – New Agents!

Lynn Marie Trotti, MD, MSc
Associate Professor of Neurology
Emory Sleep Center
Emory University School of Medicine, Atlanta, GA, USA

Conflict of Interest Disclosures for Speakers

☐ 1. I do not have any relationships with any entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients, **OR**

■ 2. I have the following relationships with entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients.

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	
Consultant	
Speakers' Bureaus	
Financial support	
Other	Funds to my institution (none to me) for industry-sponsored research: Jazz, Balance, Harmony

☐ 3. The material presented in this lecture has no relationship with any of these potential conflicts, **OR**

■ 4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

1. Thorpy MJ, et al., Ann Neurol, 2019, 85:359-370
2. Dauvilliers Y, et al., The Lancet Neurology, 2013, 12:1068-1075
3. Trotti LM, et al., Ann Neurol, 2015, 78:454-65

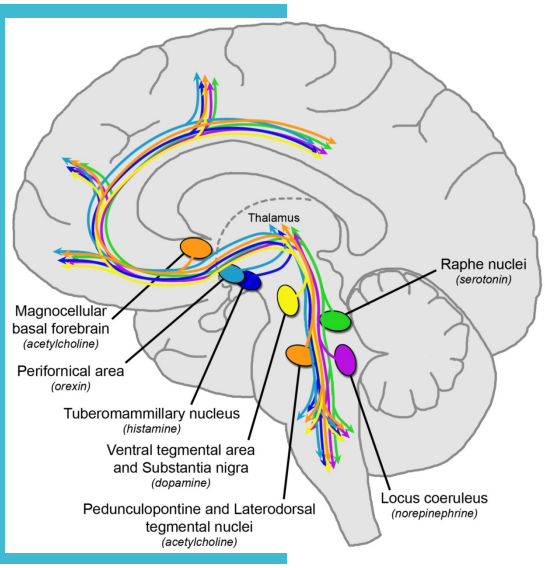
Outline

- 1) Agents approved by the FDA in 2019
  - Solriamfetol
  - Pitolisant
- 2) Agents in development
  - GABA-A receptor modulators
  - Hypocretin receptor agonist

SOLRIAMFETOL

Solriamfetol

- FDA approved March 2019
- Treatment of sleepiness associated with:
  - Narcolepsy (type 1 or 2)
  - Obstructive sleep apnea
- Not currently approved elsewhere
  - Under review by European EMA
- Became available in the US August 2019
- Schedule IV



- ***Solriamfetol is a dual-acting, specific dopamine- and norepinephrine-reuptake inhibitor, via effects on DAT and NET***
- Negligible effects on serotonin reuptake
- No appreciable monoamine release at low doses
  - Some DA release at > 300 mg (rodent equivalent) dose
  - Some serotonin release at supra-maximal doses
- No effects at histamine, orexin

Baladi MG, et al., J Pharmacol Exp Ther, 2018, 366:367-376

TONES 2: Phase 3, parallel group (3 dose), placebo controlled RCT of solriamfetol for narcolepsy

- Randomization was stratified by presence/absence of cataplexy

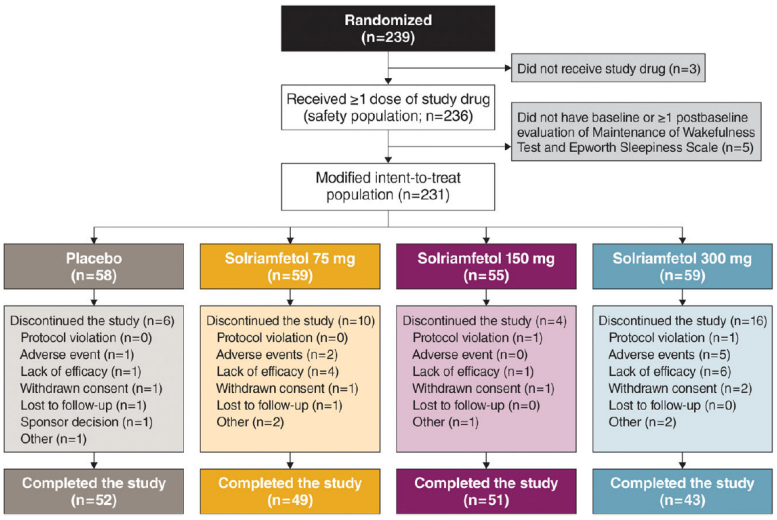


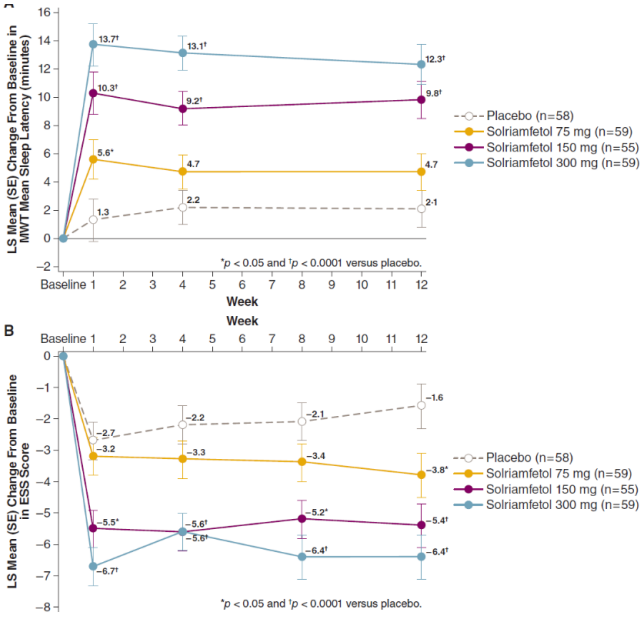
FIGURE 1: Patient disposition.

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

TABLE 1. Baseline Demographic and Clinical Characteristics of the Safety Population

Characteristic	Placebo, n = 59	Solriamfetol 75 mg, n = 59	Solriamfetol 150 mg, n = 59	Solriamfetol 300 mg, n = 59	Total, N = 236
Age, yr	36.0 ± 15.2	36.5 ± 12.8	38.1 ± 13.0	34.3 ± 11.5	36.2 ± 13.2
Sex, n					
M	24 (40.7%)	22 (37.3%)	17 (28.8%)	19 (32.2%)	82 (34.7%)
F	35 (59.3%)	37 (62.7%)	42 (71.2%)	40 (67.8%)	154 (65.3%)
Race, n					
Asian	0	0	3 (5.1%)	3 (5.1%)	6 (2.5%)
Black or African American	10 (16.9%)	12 (20.3%)	6 (10.2%)	5 (8.5%)	33 (14.0%)
White	47 (79.7%)	46 (78.0%)	48 (81.4%)	48 (81.4%)	189 (80.1%)
Other	2 (3.4%)	1 (1.7%)	2 (3.4%)	3 (5.1%)	8 (3.4%)
BMI, kg/m^2	29.1 ± 6.0	27.9 ± 5.4	27.9 ± 5.8	28.1 ± 6.3	28.3 ± 5.9
Presence of cataplexy, n	29 (49.2%)	31 (52.5%)	30 (50.8%)	30 (50.8%)	120 (50.8%)
MWT sleep latency, minutes[a]	6.1 ± 5.6	7.5 ± 5.4	7.7 ± 5.6	8.7 ± 6.2	7.5 ± 5.7
ESS score[b]	17.3 ± 2.8	17.3 ± 3.5	16.9 ± 3.7	17.2 ± 2.8	17.2 ± 3.2

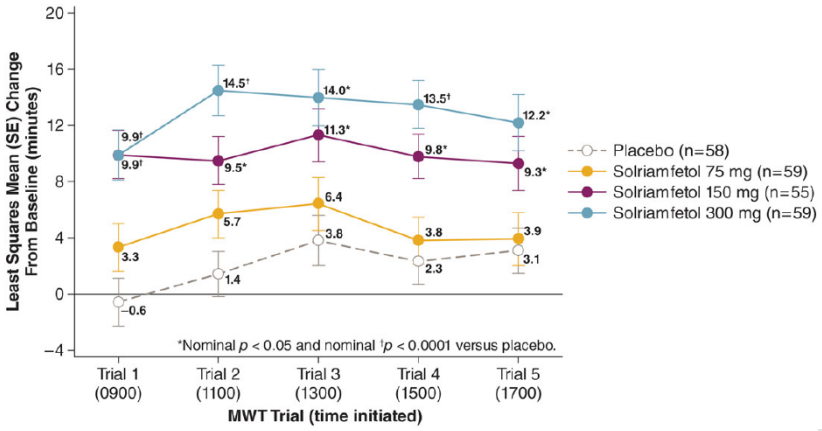
Thorpy MJ, et al., Ann Neurol, 2019, 85:359-370



- Co-primary endpoints of ESS & MWT met for doses of 150 mg & 300 mg
  - MWT not significant for 75 mg
- Compared to placebo:
  - ESS improved 2.2-4.7 points
  - MWT improved 2.6-10.1 minutes
- Broadly similar benefit in NT1 and NT2
- FDA approved with starting dose of 75 mg, maximum dose 150 mg

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

MWT benefit sustained across the day with single am dosing



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

TONES2: Phase 3, parallel group (4 doses), placebo-controlled RCT of solriamfetol for OSA

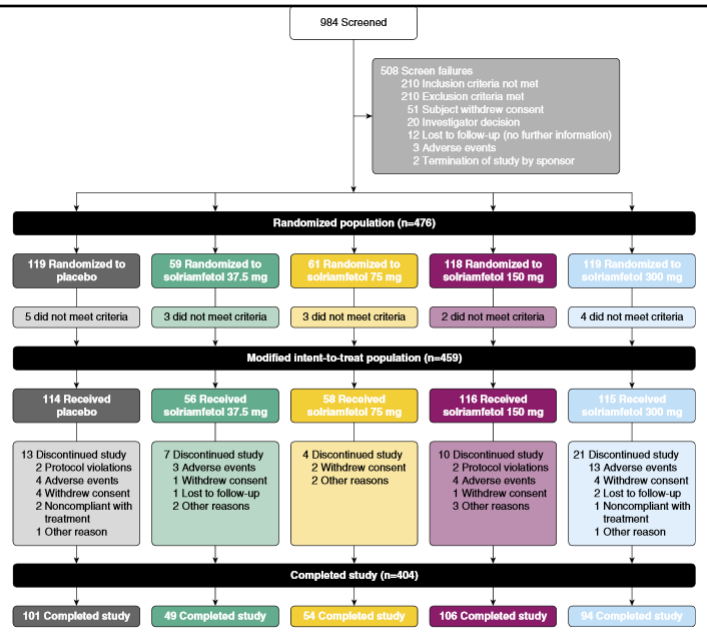
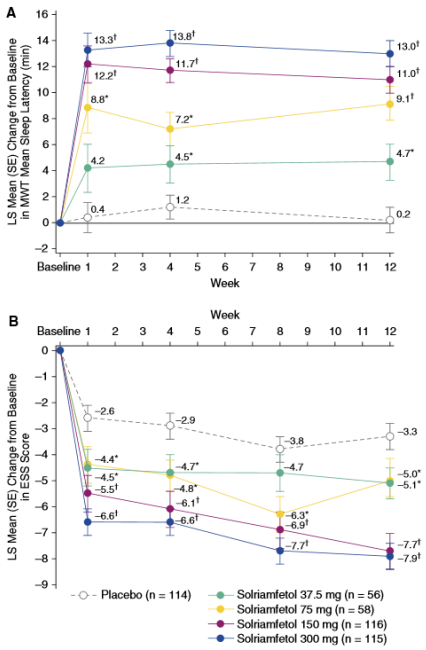


Figure 1. Participant disposition (Consolidated Standards of Reporting Trials diagram). Fifteen participants in the randomized population did not have baseline or one or more postbaseline evaluations of Maintenance of Wakefulness Test sleep latency or Epworth Sleepiness Scale score, and two did not receive solriamfetol. These participants did not meet the prespecified criteria for inclusion in the modified intent-to-treat population.

Schweitzer PK, et al., Am J Respir Crit Care Med, 2019, 199:1421-1431



- Co-primary outcome of ESS & MWT significantly better than placebo at all doses
- Similar benefits on ESS and MWT (compared to placebo) as in narcolepsy study:
  - ESS improved 1.9-4.7 points (all doses significant)
  - MWT improved 4.5 to 12.8 minutes (all doses significant)
- FDA approved with lower starting dose of 37.5 mg but same maximum dose of 150 mg

Schweitzer PK, et al., Am J Respir Crit Care Med, 2019, 199:1421-1431

Solriamfetol adverse events

	Narcolepsy	OSA
Serious AE	1 unrelated in solriamfetol	3 unrelated in solriamfetol; 2 unrelated in placebo
Drop out due to AE	5.1% (vs 1.7% in placebo)	7.3% (vs 1.7% in placebo)
AE in ≥5% of solriamfetol group – *increase above placebo rate*	Headache: 16.1% Nausea: 9% Low appetite: 9% Dry mouth: 3.9% Nasopharyngitis: 3.9% Anxiety: 3.4%	Anxiety: 7.0% Low appetite: 6.8% Nausea: 2.0% Headache: 1.7%

Thorpy MJ, et al., Ann Neurol, 2019, 85:359-370; Schweitzer PK, et al., Am J Respir Crit Care Med, 2019, 199:1421-1431

Solriamfetol increases HR and BP

	Solriamfetol (all doses)	Placebo
Heart Rate		
--Narcolepsy study	2.4 +/- 6.5	0.5 +/- 6.7
--OSA study	2.9 (1.7 to 4.1)	0.1 (-0.9 to 1.1)
Systolic BP		
--Narcolepsy study	1.2 +/- 7.2	0.6 +/- 8.1
--OSA study	2.5 (0.4 to 4.6)	-0.2 (-1.7 to 1.4)
Diastolic BP		
--Narcolepsy study	1.5 +/- 4.8	-0.6 +/- 5.2
--OSA study	1.5 (0.3 to 2.7)	0 (-0.9 to 1.0)

Thorpy MJ, et al., Ann Neurol, 2019, 85:359-370; Schweitzer PK, et al., Am J Respir Crit Care Med, 2019, 199:1421-1431

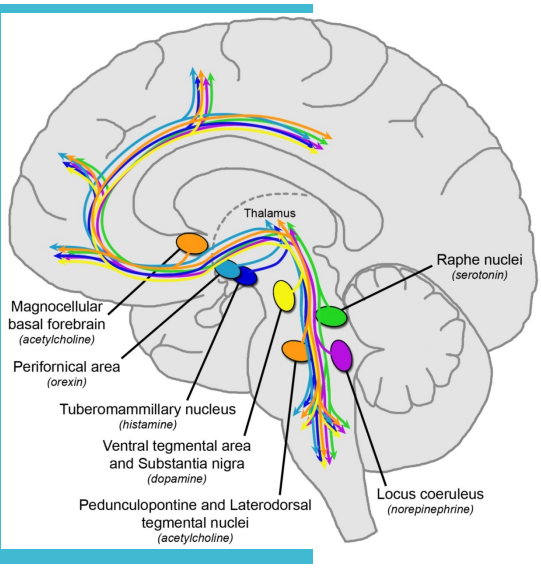
Other notes about solriamfetol

- Increase dose no more often than q3 days
- Half-life 7.1 hours
- Renally excreted unchanged
  - Must be renally dosed and avoid use if GFR < 15
- No peds approval
- Caution if:
  - Vascular disease/risk
  - Substance abuse history
  - Bipolar or psychosis (unstudied)
- Drug-drug interactions based on dopamine & HTN effects

PITOLISANT

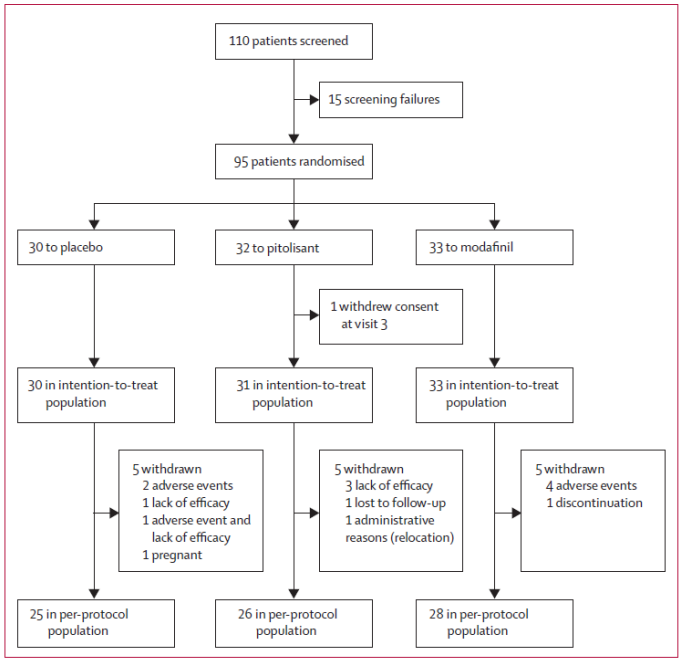
Pitolisant

- FDA-approved August 2019
- Treatment of sleepiness associated with:
  - Narcolepsy (type 1 or 2)
- Approved by European EMA (for narcolepsy) since March 2016
- Will be available in the US soon
- Unscheduled by FDA



- ***Pitolisant is an antagonist/inverse agonist of H3 histamine receptors***
- Increases histaminergic neurotransmission

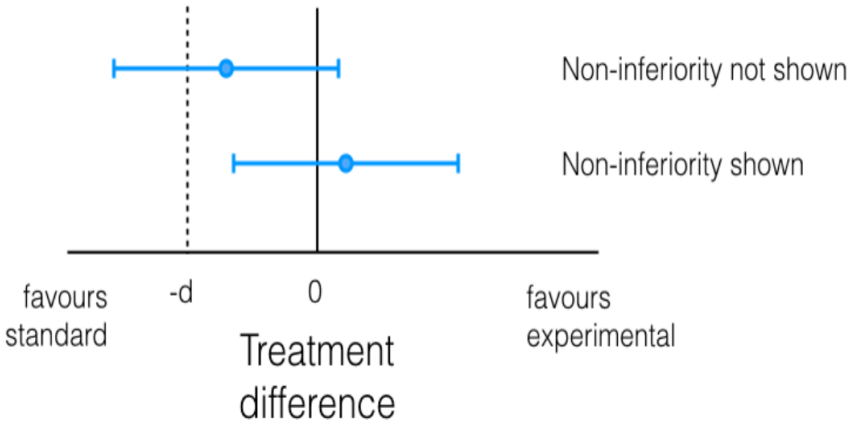
HARMONY1: Pitolisant for sleepiness in people with narcolepsy



- Pitolisant: 10 mg → 20 mg → 40 mg
- Modafinil: 100 mg → 200 mg → 400 mg

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

Study design: Superiority vs placebo; Non-inferiority vs modafinil



Baseline Characteristics

	Placebo	Pitolisant	Modafinil
Age	39.5	33.0	40.0
% Men	43	65	55
MSL	5.4	3.7	4.9
ESS	18.9	17.8	18.5
% with cataplexy	80	81	82
% prior modafinil	43	42	33

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

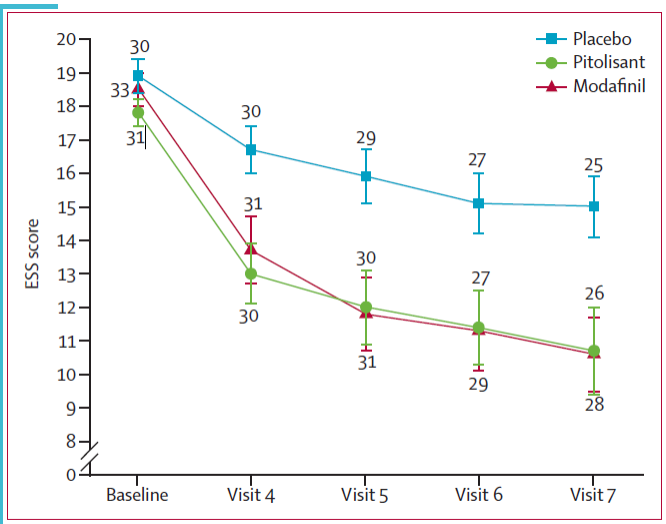


Figure 3: Changes in Epworth sleepiness scale (ESS) score

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

	Placebo		Modafinil	
	Mean difference (95% CI)	P-value	Mean difference	P-value
ESS	3.0 points (0.4 to 5.6)	0.02	-0.12 points (-2.7 to +2.5)	NS
MWT	1.5 min (1.0 to 2.1)	0.04	-0.77 min (-0.52 to -1.13)	NS

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

	Placebo (N=30)	Pitolisant (N=31)	Modafinil (N=33)
Adverse events			
Headache	6 (20%)	11 (35%)	6 (18%)
Insomnia	0	3 (10%)	0
Abdominal discomfort or pain	0	2 (6%)	6 (18%)
Nausea	2 (7%)	2 (6%)	1 (3%)
Diarrhoea	0	1 (3%)	4 (12%)
Dizziness	0	1 (3%)	4 (12%)
Anxiety	0	0	2 (6%)
Irritability	0	1 (3%)	2 (6%)
Weight increased	2 (7%)	1 (3%)	0
Amphetamine-like withdrawal symptoms	0	0	3 (10%)
Serious adverse events			
Abdominalk pain or discomfort	0	1 (3%)	1 (3%)
Abnormal behaviour	0	0	1 (3%)
Amphetamine-like withdrawal symptoms	0	0	1 (3%)
Inner ear disorders	0	0	1 (3%)
Lymphoadenopathy	0	0	1 (3%)

Data are number of patients (%).

Table 3: Adverse events

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

HARMONY-CTP: Pitolisant and cataplexy RCT

Cataplexy at least 3/wk

- RCT pitolisant vs placebo
- Same doses as in EDS trial, similar sample size (105 ITT)
- Allowed to continue SXB and antidepressants
- Primary outcome – weekly cataplexy rate
  - Pitolisant → 75% reduction from baseline
  - Placebo → 38% reduction from baseline
- Similar AEs – HA, irritability, anxiety, nausea
- No serious AEs

Szakacs Z, et al., Lancet Neurol, 2017, 16:200-207

HARMONY3: open-label, 1 year follow up

- 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%
- Persistent benefit; lowest ESS scores at 6 months

Dauvilliers Y, et al., Sleep, 2019, epub ahead of print

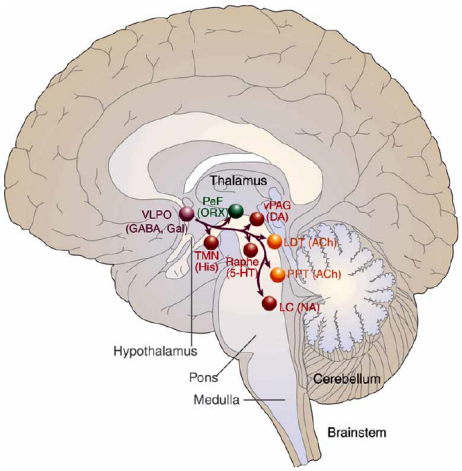
Other notes about pitolisant

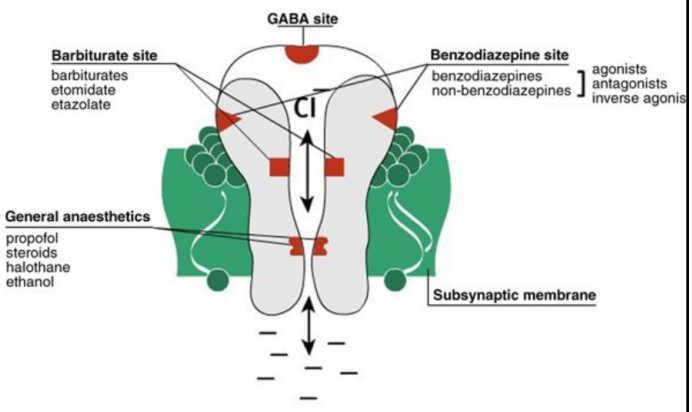
- Increase dose no more often than q7 days
  - Week 1: 8.9 mg
  - Week 2: 17.8 mg
  - Week 3: 35.6 mg
  - Full benefit seen in ~4-8 weeks at fixed dose
- Half-life 20 hours
- No peds approval

Other notes about pitolisant

- Metabolized by CYP2D6 > 3A4, then excreted in urine
  - Dose reduction for moderate liver or kidney disease
  - Avoid use in severe liver or kidney disease
- Caution if:
  - Prolonged QT interval
  - Co-medication with meds that increase QT interval
  - At 35.6 mg dose, QT increases by 4.2 msec
- Drug-drug interactions based on 2D6 and 3A4
- MUST USE BACK UP OR ALTERNATE TO ORAL CONTRACEPTION
- Specialty pharmacy

GABA-A RECEPTOR MODULATORS





Schwartz JR, et al., Curr Neuropharmacol, 2008, 6:367-78; Gommers D, et al., Critical Care, 2008, 12:S4

GABAergic agents in development (or being repurposed)

	Why?	Published evidence	Current status
Flumazenil	Negative allosteric modulator of GABA	Case series (n = 150; response rate 60%)	Off-label use of compounded flumazenil in rare, treatment-refractory hypersomnia patients
Clarithromycin	GABA antagonist properties	Pilot, crossover, placebo-controlled RCT (n = 20)	Phase 2 clinical trial for idiopathic hypersomnia & narcolepsy without cataplexy ongoing
BTD-001	GABA antagonist	--	Phase 2 clinical trial for idiopathic hypersomnia ongoing
GR-3027	GAMSA	--	Phase 2a for idiopathic hypersomnia recently completed

Rye DB, et al., Sci Transl Med, 2012, 4:161ra151; Trotti LM, et al, J Clin Sleep Med, 2016, 12:1389-1394;Trotti LM, et al., Ann Neurol, 2015, 78:454-65

HYPOCRETIN (OREXIN) RECEPTOR AGONIST

TAK925

- Direct orexin replacement may be challenging
- Selective orexin 2 receptor agonist
  - Orexin 2 knock out (but not Orexin 1) → narcoleptic phenotype in mice
- Significant increase in wake time in:
  - Mice
  - Marmosets
  - Cynomolgus monkeys
  - No increase in wake time in Orexin 2 knock out mice
- Significant reduction in W→R transitions in mice
- Sustained benefit with 14 day administration
- Ongoing trials:
  - Narcolepsy
  - Idiopathic hypersomnia
  - OSA

Yukitake H, et al., Sleep, 2018, 41:A1; Suzuki M et al, Sleep, 2018, 41:A1

Thank you