OSA and Excessive Sleepiness
Prevalence, Mechanisms and Treatment

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1. Sogol Javaheri and Shahrokh Javaheri. Update on Persistent Excessive Daytime Sleepiness in OSA. CHEST 2020; 158(2):776-786.
2.
3.

Accreditation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of The American Academy of Sleep Medicine and The Virginia Academy of Sleep Medicine. The American Academy of Sleep Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Meeting with the Giants

In the Memory of Giants

To die, to sleep, perchance to dream…without hypertension:

Dreams of the visionary Christian Guilleminault revisited

S. Javaheri and P. Gay

J Clin Sleep Med 2019;15(9):1261–1270

EDS and OSA

EDS (ENS) is a cardinal symptom of OSA

- What is EDS?
- How to quantitate it?
- How does it manifest in each individual?
- What are the consequences?
- Does it have a benefit?

What is sleepiness and how to define it?

- Subjective ESS
- objective MSLT
- Psychomotor vigilance task (PVT)
  measures neurobehavioral alertness, it is sensitive to sleepiness
- Combination of subjective and objective

Epworth Sleepiness Scale

Using the following scale, circle the *most appropriate number* for each situation.

0 = would doze *less than once a month*
1 = *slight* chance of dozing
2 = *moderate* chance of dozing
3 = *high* chance of dozing

10 considered the threshold
24 is maximum

Situation	Chance of Dozing
Sitting and reading	0 1 2 3
Watching TV	0 1 2 3
Sitting, inactive in a public place (in a theater or in a meeting)	0 1 2 3
As a passenger in a car for an hour without a break	0 1 2 3
Lying down to rest in the afternoon (when circumstances permit)	0 1 2 3
Sitting and talking to someone	0 1 2 3
Sitting quietly after a lunch without alcohol	0 1 2 3
In a car, while stopped for a few minutes in the traffic	0 1 2 3

Add the 8 numbers you have circled **TOTAL** _____

Subjective EDS vs. MSLT

We have reported dissociation between self-reported EDS and objective sleepiness in OSA patients with heart failure with some patients having an MSL of ≤5 minutes despite normal ESS scores

JCSM 2017;13(12):1411–1422

Dissociation between self-reported EDS and objective sleepiness in OSA patients with heart failure

The overall cohort had a pathologic degree of objective sleepiness with MSL of
5.7 (3.5, 8.9) minutes

The overall ESS was within normal range:
7.0 (5.0, 10.0) units

JCSM 2017;13(12):1411–1422

SEDS

1. Truck drivers score 0 on ESS

2. I regularly see patients who nap couple of hours a day with ESS of 5 to 6!

3. Intentional napping is not a metric in ESS questionnaire but can be an important reflection of daytime sleepiness

4. Ask the spouse and family members

5. Ask the spouse to score the ESS

EDS

Caution should be exercised in interpretation of self-reported lack of sleepiness

A Negative Epworth is Epworthless!

What is the current prevalence of Subjective EDS by ESS?

Prevalence of EDS is on the rise

Wisconsin Sleep Cohort study

Of the 6,947 state employees who received the survey, 5,091 (73%) completed and returned it

From these respondents, a sampling frame was constructed from which a stratified random sample of 2,884 persons were chosen

Data for this report were collected between 1988 and June 2011 from 1,520 eligible participants

14% of US population have OSAHS

Peppard et al. American Journal of Epidemiology, 2013

Prevalence of EDS is on the rise

Prevalence of OSA (AHI ≥5 /hour of sleep): 26%

Prevalence of OSA with EDS (ESS>10) : 14%(vs 10.8%, 2 decades ago)

AHI ≥5, ESS score >10
Absolute Increase from a decade ago

Men	**3.5**
Women	**2.2**

Variable manifestations and consequences of EDS

- Drowsy driving, falling asleep at red light, or driving
- Falling asleep immediately on the bed
- Taking naps
- Falling asleep in the moves, watching TV and at work
- Falling asleep as a passenger and on the plane
- Fatigue
- Irritability
- Cognitive dysfunction/memory impairment
- Increased work errors with decreased productivity
- Impaired attention and vigilance
- Reduced quality of life

Prevalence of EDS in well treated OSA with CPAP

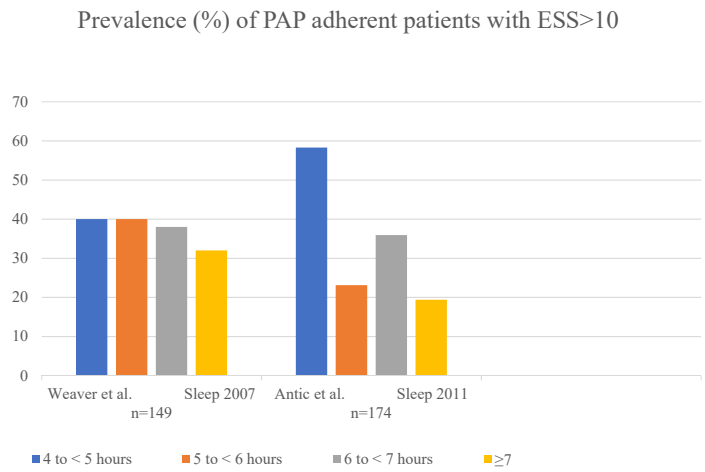
- The estimated prevalence of EDS (ESS >10 units) among PAP adherent subjects

(defined as use ≥4 hours per night, for at least 70% of the nights)

has varied among studies ranging from

12% and up to 65%

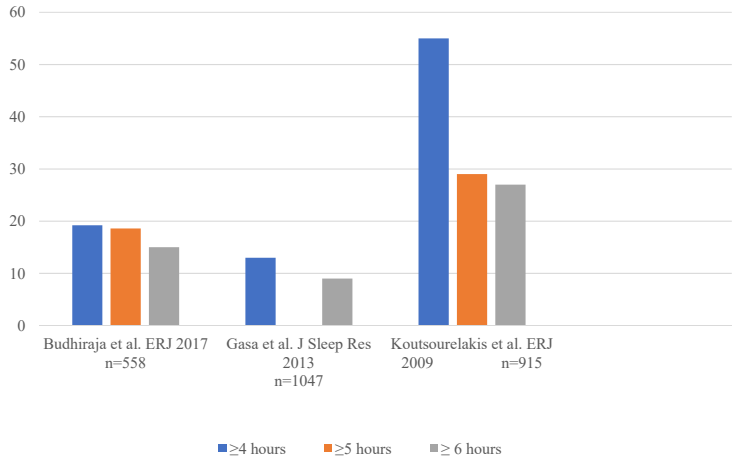
Javaheri S, Javaheri S. Modified from Chest, 2020



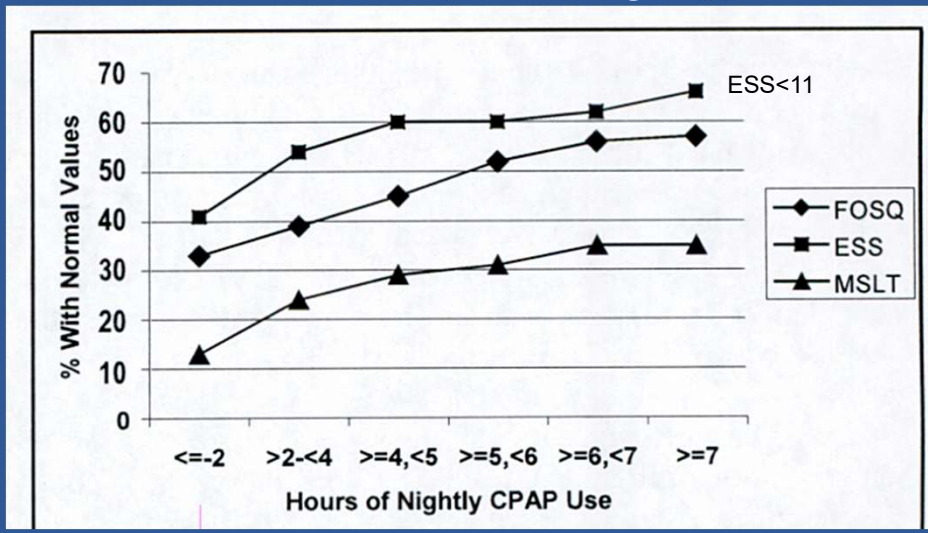
Javaheri S, Javaheri S. Modified from Chest, 2020

Prevalence (%) of PAP adherent patients with ESS>10

Javaheri S, Javaheri S. Modified from Chest, 2020



Dissociation between self-reported EDS and objective sleepiness in OSA without HF (Weaver, Sleep 2007)



Cumulative proportion of participants obtaining normal threshold values on the ESS, MSLT and FOSQ

Prevalence of EDS in well treated OSA with Oral Appliance

- Verbrugge et al performed a prevalence study collecting data from 185 patients with an established diagnosis of OSA treated with a titratable custom-made OA device
- Baseline data: male: female ratio: 129:56; age: 48; BMI= 27 ± 4; AHI: 19 ± 12 ESS score = 10 ± 5
- A full-night polysomnography was performed at baseline and after 3 months of OA therapy
- At 3months : 84 patients (45%) had an AHI of <5
- *32% had ESS ≥ 11 despite complete therapeutic response*
- These subjects had a significantly higher baseline ESS and were younger than those without RES

Sleep Medicine 2014;15: 269-272

Prevalence of EDS in well treated OSA ESS ≥ 11

CPAP (Weaver et al)

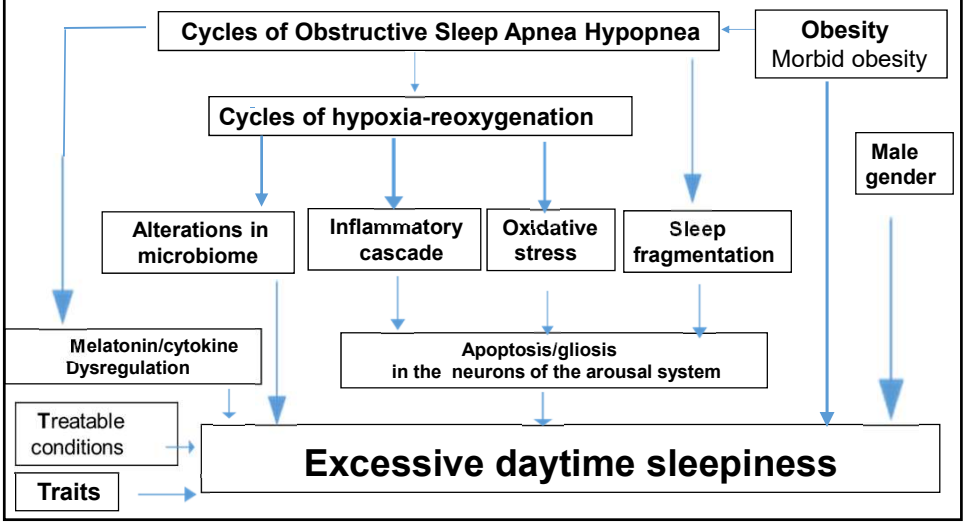
In highly adherent patients using CPAP for 6 to ≤ 7 hours per night, 38%, and in those using the device for ≥ 7 hours, 32 % have residual EDS

Oral Appliance (Verbrugge et al)

32% had EDS despite complete therapeutic response

Pathobiological mechanisms mediating excessive sleepiness in well-treated OSA

Javaheri S, Javaheri S. Modified from Chest, 2020



Potentially treatable conditions associated with persistent EDS in treated OSA

1. ***CPAP issues:*** adherence, mask leak, suboptimal pressure, TECSA
2. ***Oral appliance issues:*** adherence; suboptimal mandibular advancement; TECSA
3. ***Behaviorally induced insufficient sleep***
4. ***Insomnia***
5. ***Depression and/or anxiety***
6. ***Restless leg syndrome and/or periodic limb movements of sleep***
7. ***Circadian rhythm disorders such as shift work disorder***
8. ***Narcolepsy or other hypersomnia disorders***
9. ***Hypothyroidism***
10. ***Somnogenic medications***
11. ***Obesity***

Role of, obesity, morbid obesity and Gender

In the WSCS, among adults 30–70 years of age, 14% of men and 5% of women had an AHI ≥5 plus symptoms of daytime sleepiness(OSAHS)

1. EDS directly correlated with BMI

2.The most vulnerable groups were:
Middle aged men (30-49 years old) with BMI ≥40
53% score > 10 on the ESS

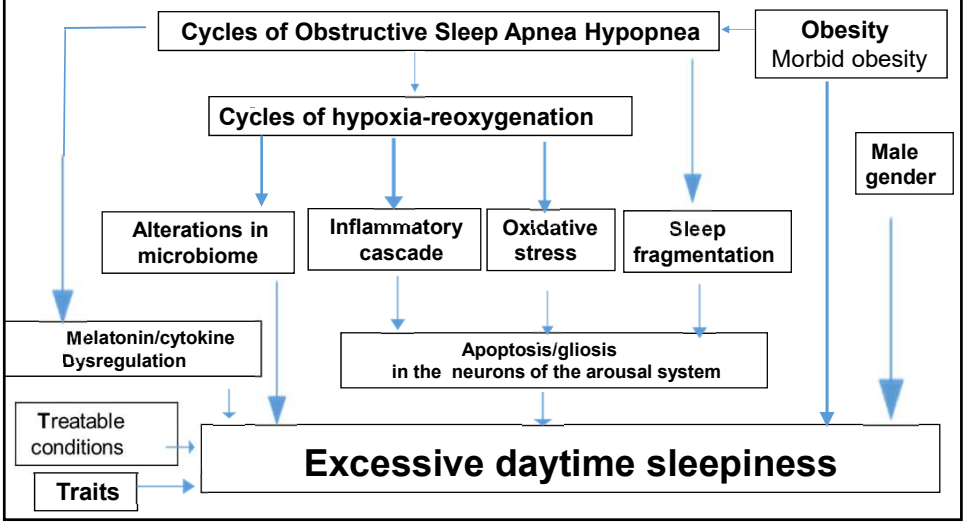
The estimated respective value for *age* and *BMI-matched* women was *16%*

Somnogenic medications

1. OCTs, antihistamines
2. Herbal supplements
3. Benzodiazepines
4. Gabapentinoids
5. Opiates
6. Muscle relaxants
7. Dopamine agonists
8. Anti-depressants and antipsychotics such as doxepin, amitriptyline, and olanzapine
9. Beta blockers

Pathobiological mechanisms mediating excessive sleepiness in well-treated OSA

Javaheri S, Javaheri S. Modified from Chest, 2020



Circadian dysregulation of melatonin and cytokines synthesis/secretion in OSAS

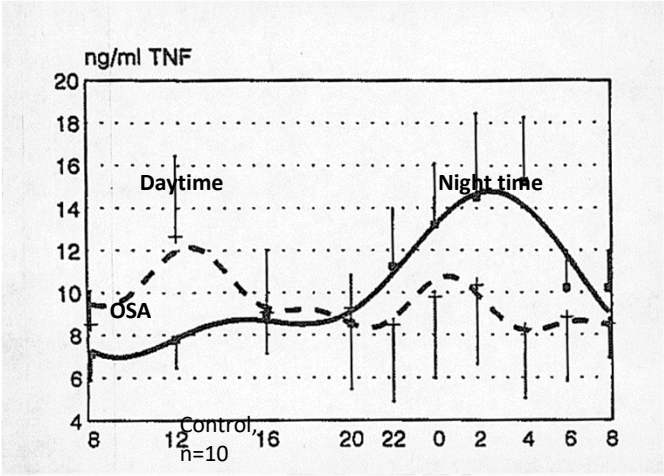
Melatonin dysregulation in OSA

Other studies show dysregulation of melatonin across 24 hours in OSA patients

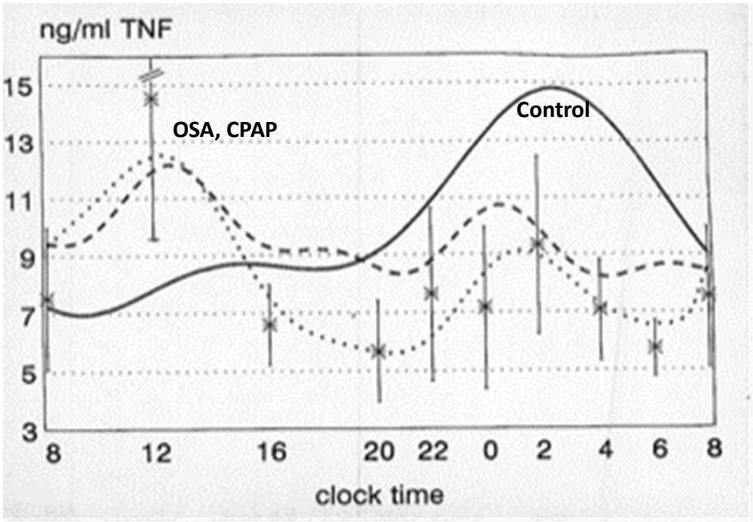
1. Hypoxia decreases melatonin synthesis/secretion
2. Serum melatonin levels remaining flat into morning
3. Elevated serum melatonin level in afternoon hours

Reutrakul et al. Chronobiol Int 2017;34(3):382–392.
Hernández et al. Eur Respir J 2007;30:496-500)\
Ulfberg et al. Afternoon serum-melatonin in sleep disordered breathing. J Intern Med 1998;244(2):163–168).

Circadian variation in TNFα OSAS and circadian rhythms of hormones and cytokines(Entzian et al, BJ, 1996)



Circadian variation in TNFα before and after therapy with CPAP



Pathobiological mechanisms mediating excessive sleepiness in well-treated OSA

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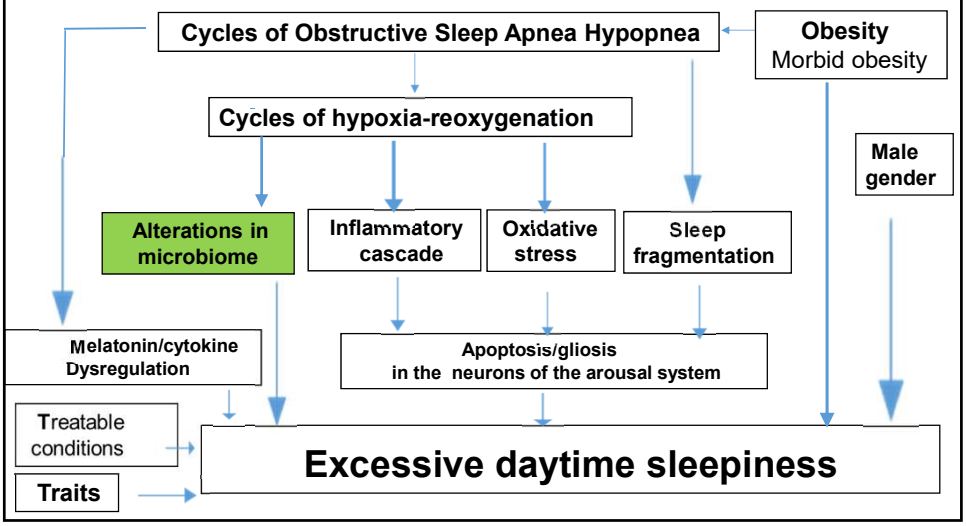


Microbiome-gut-brain axis

Badrana et al. exposed C57Bl/6 J mice to IH or RA for 6W. Fecal matter was collected and frozen

C57Bl/6 J naïve mice were then randomly assigned to a fecal microbiota transfer (FMT) for 3 weeks with either IH or RA fecal slur.

FMT recipients underwent sleep recordings using piezoelectric approaches for 3 consecutive days.

FMT-IH mice exhibited increased sleep duration and the frequency of longer sleep bouts during the dark cycle, suggesting increased sleepiness ($p < 0.0001$ vs. FMT-RA mice).

Badrana M, Khalyfaa A, Aaron Ericssonb A, Gozal D. Fecal microbiota transplantation from mice exposed to chronic intermittent hypoxia elicits sleep disturbances in naïve mice. Experimental Neurology 334 (2020) 113439

Microbiome-gut-brain axis

in subjects with OSA
nasal,oropharyngeal,and gut microbiota
are altered
Based on these studies, we speculate that OSA could promote specific alterations in gut microbiota producing cytokines and inflammatory markers that could contribute to EDS and perhaps persistent EDS in well-treated subjects

Javaheri S and Javaheri S, CHEST 2020

Mechanisms of EDS in well treated OSA

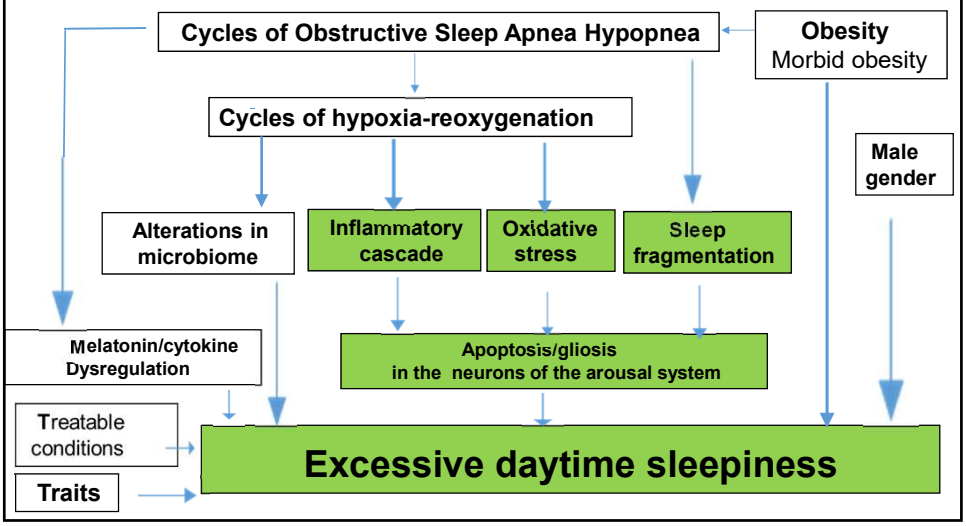
The apnea-related hypoxia and SF/Arousal may alter the gut microbiome diversity and composition, cause dysbiosis.

The established microbiota may then promote the occurrence of some of the OSA-associated morbidities and also contribute to EDS by secreting somnogenic molecules such as ILs

Javaheri S and Javaheri S, CHEST 2020

Pathobiological mechanisms mediating excessive sleepiness in well-treated OSA

Javaheri S, Javaheri S. Modified from Chest, 2020



Sleep and Wake Neurons Interaction

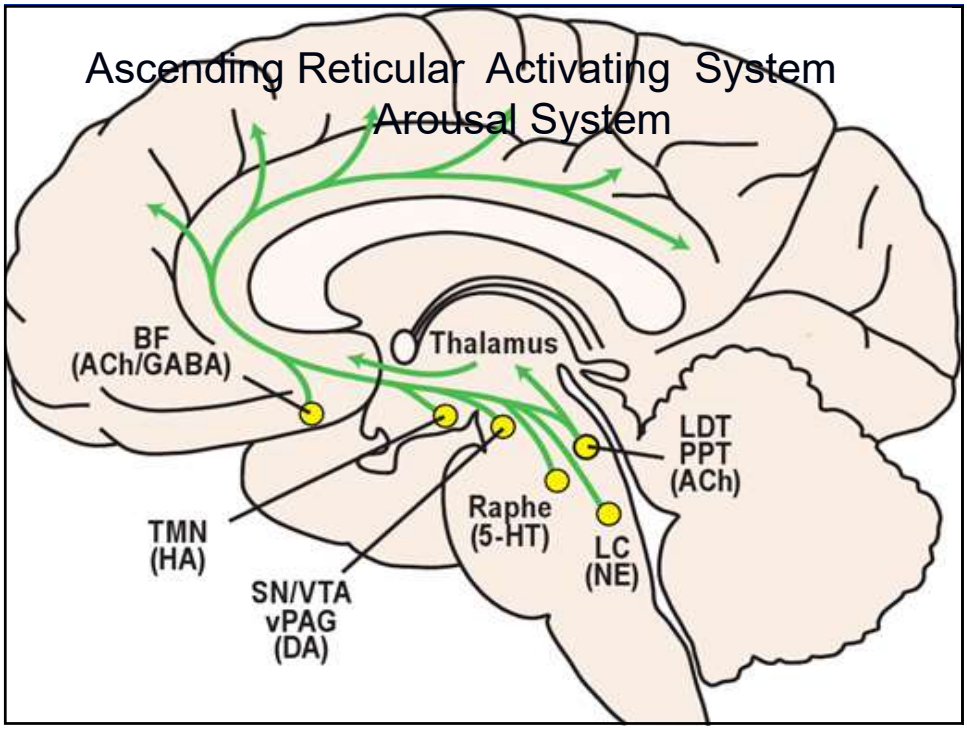
Many neurochemical systems interact to generate wakefulness and sleep.

Wakefulness is promoted by neurons in the pons, midbrain, and posterior hypothalamus that produce:

acetylcholine(basal forebrain), norepinephrine (LC), dopamine (substantia nigra, ventral tegmental area, and ventral periaqueductal gray) , serotonin(raphe nuclei), histamine(TMN), and orexin/hypocretin(hypothalamus).

Most of these ascending arousal systems diffusely activate the cortex and other forebrain targets.

España RA, Scammell TE. Sleep Neurobiology from a Clinical Perspective Sleep2011; 34: 845–858



Adverse Consequences of Chronic Sleep Fragmentation and Arousals
(Javaheri and Gay, JCSM, 2019)

1. Day time sleepiness and impaired cognitive dysfunction

2. Autonomic dysregulation with increased sympathetic activation and withdrawal of parasympathetic activity

3. Induced overnight arousals elevating blood pressure in man

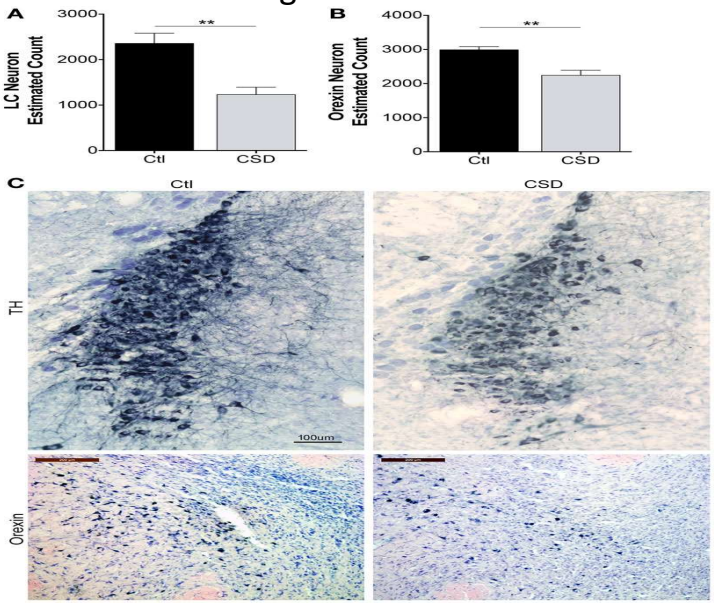
4. In animal models, chronic sleep fragmentation induces inflammation, structural vascular changes and hypertension

5. in animal models, sleep fragmentation causes dysbiosis with potentially adverse consequences

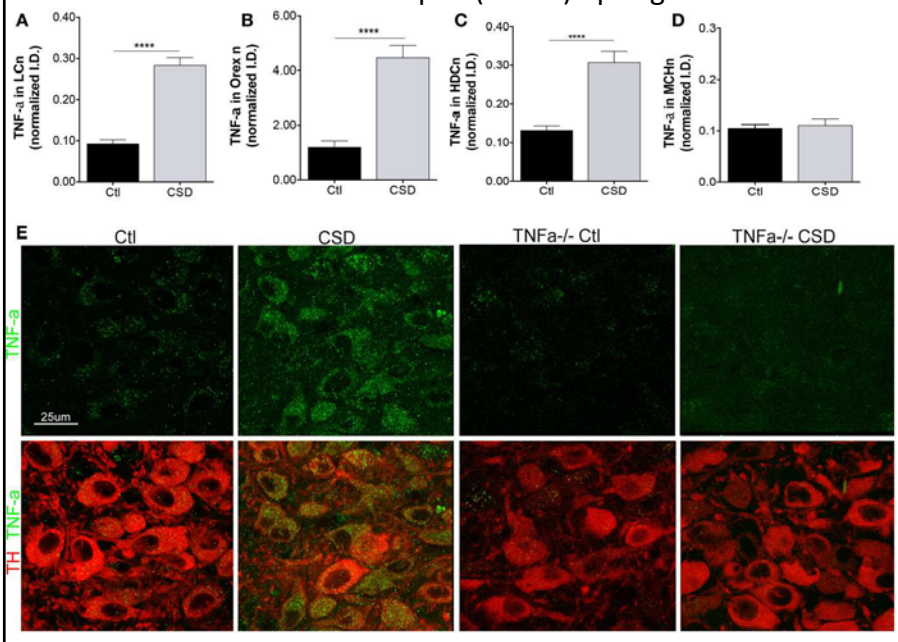
6. In animal models, sleep fragmentation causes inflammation, apoptosis and gliosis of the wake neurons. This could be the reason for persistent EDS in well treated subjects with OSA

7. In man , chronic SF is associated with telomere shortening which could result in premature aging

Reduced neuron estimates for locus coeruleus and orexinergic neurons in CSD



Tumor necrosis factor-alpha (TNF-α) up-regulation in WAN



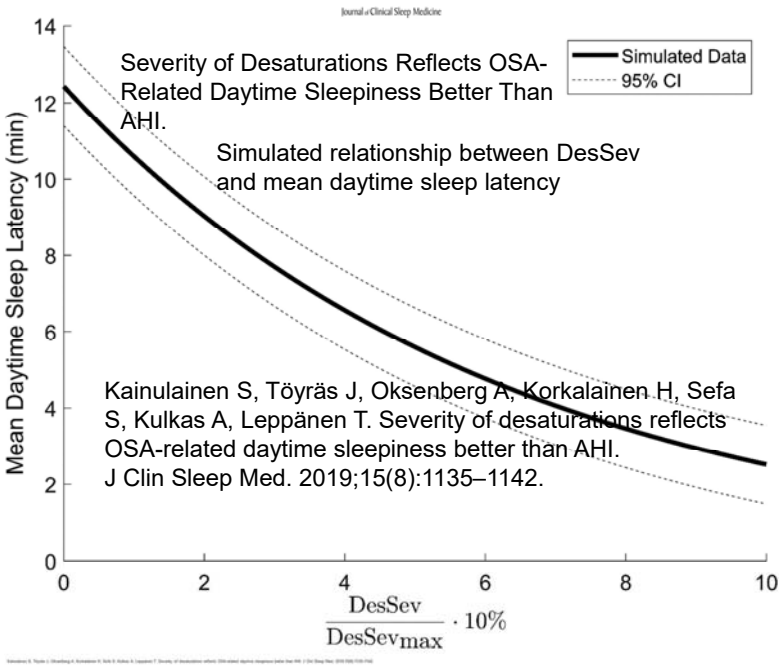
Selective Loss of Catecholaminergic Wake–Active Neurons in a Murine Sleep Apnea Model

Long-term intermittent hypoxia protocol

Reductions in ambient oxygen level from 21to 10% for 5 seconds every 90s, resulting in fluctuations in oxyhemoglobin saturation from 94–98% to 76–84% lasting 2–7 s, 10 h of the lights-on period for 8 weeks modeling patterns observed in severe OSA

6 months after recovery from 8 weeks exposure to hypoxia/reoxygenation Irreversible injury in two wake-active dopaminergic neurons in the ventral peri-aqueductal gray and noradrenergic neurons in the locus ceruleus (40% loss)
Wake impairments are irreversible.

Zhu Y, Fenik P, Zhan G, Mazza E, Kelz M, Aston-Jones G, Veasey SC. Selective Loss of Catecholaminergic Wake–Active Neurons in a Murine Sleep Apnea Model. J Neuroscience, 2007 • 27(37):10060–10071



Mechanisms of EDS in well treated OSA

Long-term exposure to repeated episodes of desaturation, sleep fragmentation and arousals, all associated with cycles of apnea-recovery may permanently damage neuronal arousal system by inflammation, apoptosis and gliosis

Medications to treat EDS

Caffeine

Amphetamines

Modafinil and armodafinil

Solriamfetol

Pitolisant

GABA –A Inhibitors

Javaheri S, Javaheri S, Update on Persistent Excessive Daytime Sleepiness in Obstructive Sleep Apnea. CHEST, 2020

Schinkelshoek, Fronczek, Lammers. Update on the Treatment of Idiopathic Hypersomnia Current Sleep Medicine Reports. 2019; 5:207–214

According to the FDA
400 milligrams of caffeine per day is the recommended maximum for healthy adults

This is the equivalent to about 4 to 5 cups of coffee

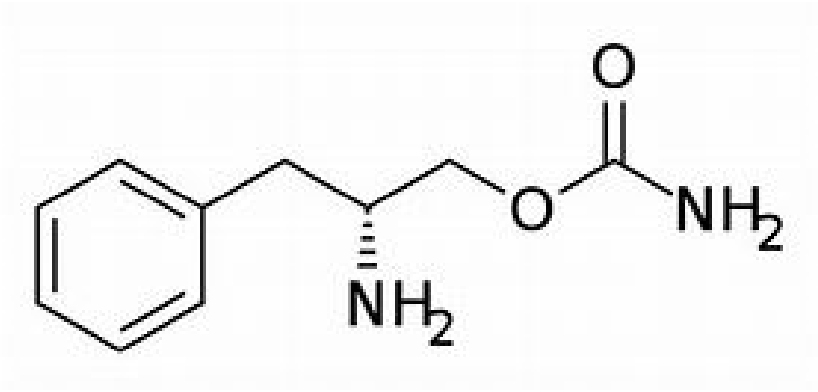
The FDA cites 1,200 milligrams as a level that may produce toxic effects such as seizures

Solriamfetol (JZP-110)

- **A new combined dopamine transporter (DAT)/norepinephrine transporter (NET) inhibitor**
- **Clinical trial data suggest that simultaneous antagonism of both DAT and NET may impart a more robust alerting effect than imparted by highly-selective DAT inhibitors with agents that do not serve as substrates for transporter uptake and do not induce significant monoamine release.**

Solriamfetol

$C_{10}H_{14}N_2O_2$



[2 R]-2-amino-3-phenylpropylcarbamate hydrochloride

derived from phenylalanine

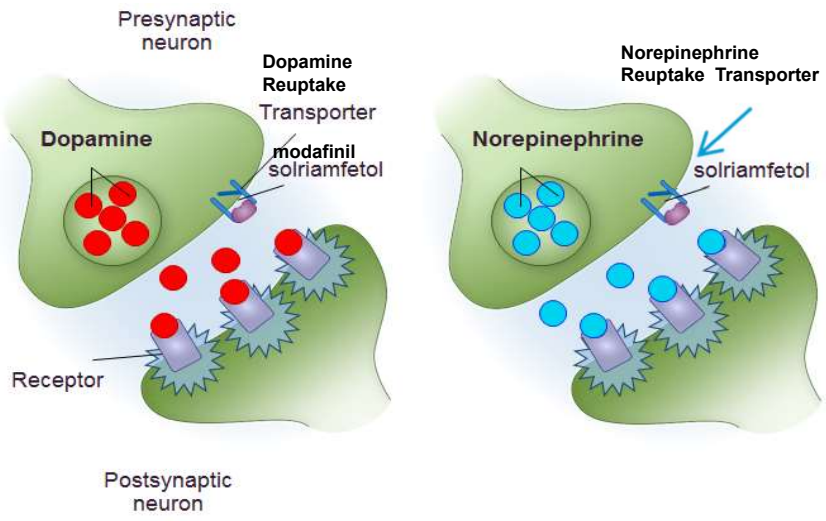
Mechanisms of Action of Wake-Promoting Agents

	Affinity/selectivity
Traditional Stimulants (e.g. Ritalin, Dexedrine)	Non-selective for the DAT, NET, and SERT[1]
Wake-Promoting Agents (e.g. Modafinil)	DAT selective[2]
Solriamfetol (JZP-110)[a]	Low affinity, DAT and NET selective[3-7]

[a]Based on data from animal models.
DA, dopamine; DAT, dopamine transporter; MOA, mechanism of action; NE, norepinephrine; NET, noradrenaline transporter; SERT, serotonin transporter.

1. Rothman RB, et al. *Synapse.* 2001;39(1):32-41. 2. Wisor J. *Front Neurol.* 2013;4:139. 3. Janowsky A. Study report; 2000. 4. Janowsky A. Study report; 2006b. 5. Pullan S. Study report; 2006a. 6. Chester K. Study report; 2006. 7. Pullan S. Study report; 2006d. 8. Dupuis P. Study report; 2001. 9. Janowsky A. Study report; 2006a. 10. Loland CJ, et al. *Biol Psychiatry.* 2012;72:405-413. 11. Schmitt KC, et al. *J Neurochem.* 2008;107:928-940. 12. Schmitt KC, et al. *PloS One.* 2011;6(10):e25790. 13. Hasan S, et al. *Neuropsychopharmacology.* 2009;34(7):1625-1640.

Mechanism of Action of modafinil and solriamfetol



Solriamfetol Trials
Treatment of Excessive Sleepiness in OSA

1. OSA 12 week study Primary Outcome Measures

MWT and ESS: Change in the mean sleep latency time (in minutes),and ESS scale From baseline to week 12

2. Withdrawal trial

3. 6- month long-term trial

Schweitzer PK, Rosenberg R, Zammit GK, et al. Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3). A Randomized Controlled Trial. Am J Respir Crit Care Med 2019;199(11):1421–1431

Strollo PJ Jr, Hedner J, Collop N, et al. Solriamfetol for the Treatment of Excessive Sleepiness in OSA: A Placebo-Controlled Randomized Withdrawal Study. Chest 2019;155(2):364–374

MalhotrA, Shapiro C, Jean-Louis Pepin JL, Hedner J, Ahmed M, Foldvary-Schaefer N, Strollo Jr PJ, Geert Mayer G, Sarmiento K, Baladi M, Chandler P, Lee L, Schwab R. Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea SLEEPJ, 2020, 1–11

. In a twelve-week double-blind randomized placebo-controlled trial (TONES 3) Schweitzer et al , Am J Respir Crit Care Med, 2019

476 patients with OSA were randomized to receive placebo once a day or solriamfetol at doses of 37.5, 75, 150, and 300 mg.

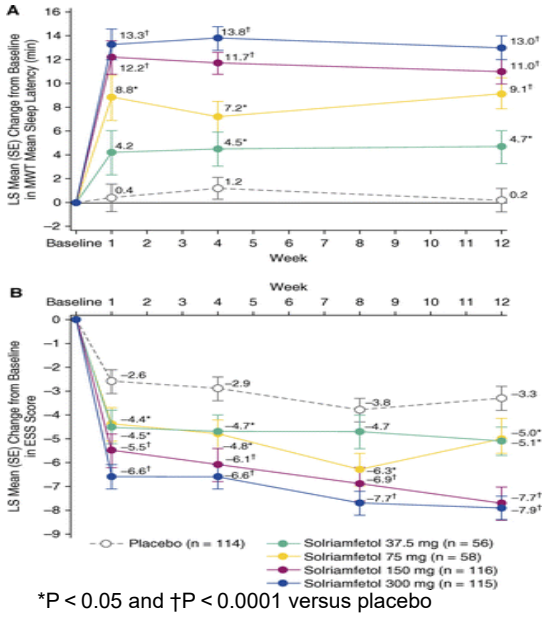
Of the 474 participants who were randomized, 404 (85%) completed the study.

The coprimary endpoints were changes from baseline at week 12 in MWT and ESS

Solriamfetol resulted in dose-dependent increases in MWT sleep latency and reductions in ESS.

At 12 weeks, at 150 mg, there was an 11 minute increase in mean MWT sleep latency and an 8 unit reduction in mean ESS from baseline of

Effect of various doses of solriamfetol on mean changes from baseline in MWT sleep latency in minutes and (B) change in ESS for all treatment groups



*P < 0.05 and †P < 0.0001 versus placebo

Pharmacokinetics of Solriamfetol

- The oral bioavailability of solriamfetol is approximately 95%.
- Peak plasma concentration of solriamfetol occurs at a median Tmax of 2 hours (range 1.25 to 3.0 hours) post-dose under fasted conditions
- Ingestion of solriamfetol with a high-fat meal results in minimal change in Cmax and AUC; however, a delay of approximately 1 hour in Tmax is observed
- The apparent mean elimination half-life is about 7.1 hours.
- Solriamfetol steady state is reached in 3 days
- ***Renally excreted***

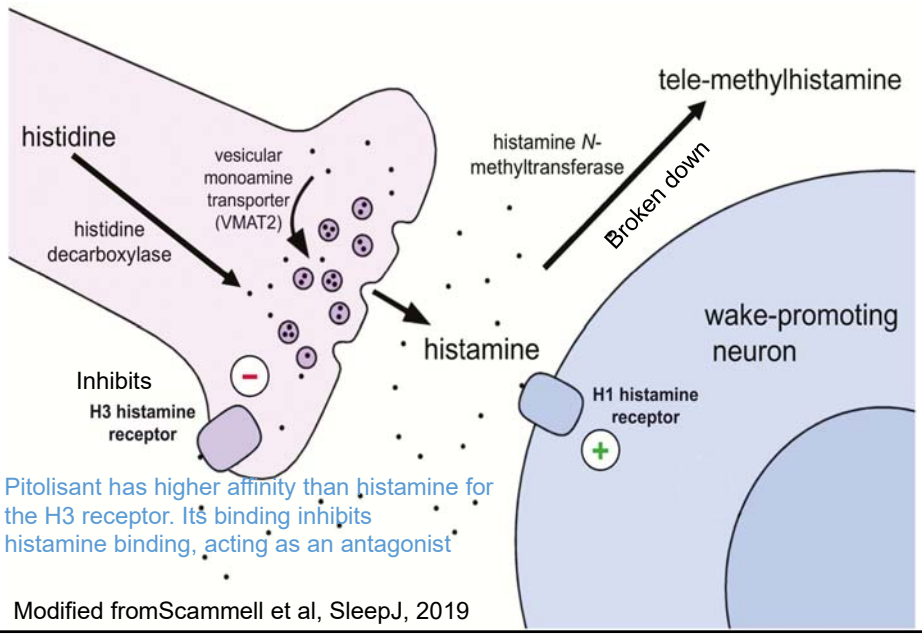
Elimination and metabolism of of Solriamfetol

- *Metabolism: Solriamfetol is minimally metabolized in humans and approximately 95% of the dose is recovered in urine as unchanged solriamfetol, and 1% or less of the dose was recovered as the minor inactive metabolite N-acetyl solriamfetol*
- Population PK analysis indicated that age, gender, and race do not have clinically relevant effects on the pharmacokinetics of solriamfetol
- No dose adjustments were made in clinical studies that enrolled patients ages 65 and above

Solriamfetol : Take-home messages

1. Start dose: half tablet (37.5 mg in am)
2. Tmax: 2 hours
3. Half life: 7.1 hours
4. Dose increase: no sooner than 3 days
5. Renal route of excretion
6. Lack of drug interaction
7. Careful FU. Checking BP and HR

Histamine Signaling Pathway in the Tuberomammillary Nucleus



Modified fromScammell et al, SleepJ, 2019

Pitolisant for Daytime Sleepiness in Obstructive Sleep Apnea Patients Refusing CPAP
A Randomized Trial (Dauvilliers et al Am J Respir Crit Care Med)

Phase 3, prospective double-blind, placebo-controlled, parallel-group multicenter study evaluated the efficacy and safety of pitolisant over 12 weeks in adult moderate to severe OSA (n=200, AHI ≥15/h) patients experiencing EDS (Epworth Sleepiness Scale, ESS ≥12), refusing CPAP, and without significant cardiovascular disease.

In an international multicenter, double-blind, randomized (3:1), placebo-controlled, parallel-design trial

pitolisant at 5, 10, or 20 mg once a day or placebo, taken on an empty stomach within 1 hour of waking in the morning. Treatment was initiated at 5 mg during 2-week titration period, escalating the dose based on efficacy and tolerance and then followed with the selected dose for a further 10 weeks

Primary endpoint: change in the Epworth Sleepiness score.

Secondary endpoints: maintenance of wakefulness assessed by the Oxford Sleep Resistance Test, clinical global impressions of severity, patient's global opinion, EQ-5D quality-of-life, and Pichot Fatigue questionnaire scores

Results

268 obstructive sleep apnea patients (75% male; mean age: 52 years, AHI= 49/hour, baseline sleepiness score: 15.7) were randomized (200 pitolisant; 68 placebo) and analyzed in intention to treat

The primary endpoint, change in ESS from baseline to end of intervention (LOCF ESS)

was -6.3 in the pitolisant group and -3.6 in the placebo group ($p<0.001$)

The ESS score was more reduced with pitolisant than with placebo
-2.8 (95% CI: [-4.0;-1.5]) ($p<.001$).

Wake maintenance tests were not improved

Results

The Pichot fatigue score was reduced with pitolisant.

The overall impact of pitolisant was confirmed by both physicians' and patients questionnaires.

Adverse event incidence, mainly headache, insomnia, nausea, and vertigo, was similar in the pitolisant and placebo groups with no cardiovascular or other significant safety concerns.

Conclusions

Pitolisant significantly reduced self-reported daytime sleepiness, fatigue and improved patient-reported outcomes and physician disease severity assessment in sleepy patients with obstructive sleep apnea refusing or non-adherent to continuous positive airway pressure.

Pitolisant: Take home message

Approved for narcolepsy and improves cataplexy

Tmax = 3 h after oral administration.

Plasma half-life of ~10–12 h

Steady state within 5–6 days

Pitolisant is metabolized in the liver mediated by CYP 450 Enz: CYP3A4 and CYP2D

Pitolisant is a CYP3A4, CYP2B6, and CYP1A2 inducer and a CYP2D6 and OCT1 inhibitor

Drug interaction and QT interval prolongation