rEDS in patients with OSA

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Disclosures

- Free lance consultant for Bioprojet and other non-competing pharma companies
- Several slides are copied or adapted from the Bioprojet satellite symposium at the 26th congress of the ESRS (Athens, sept 2022)
- I aknowledge gender neutrality but gender specific terms are sometimes used for reasons of convenience

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Agenda

- Why is OSA associated with EDS ?
- How does EDS impact patients ?
- How to diagnose EDS ?
- Predictors and phenotypes of EDS
- From EDS to rEDS
- Effect of primary treatment of OSA on EDS
- Epidemiology of (r)EDS in OSA
- Management principles for rEDS in OSA

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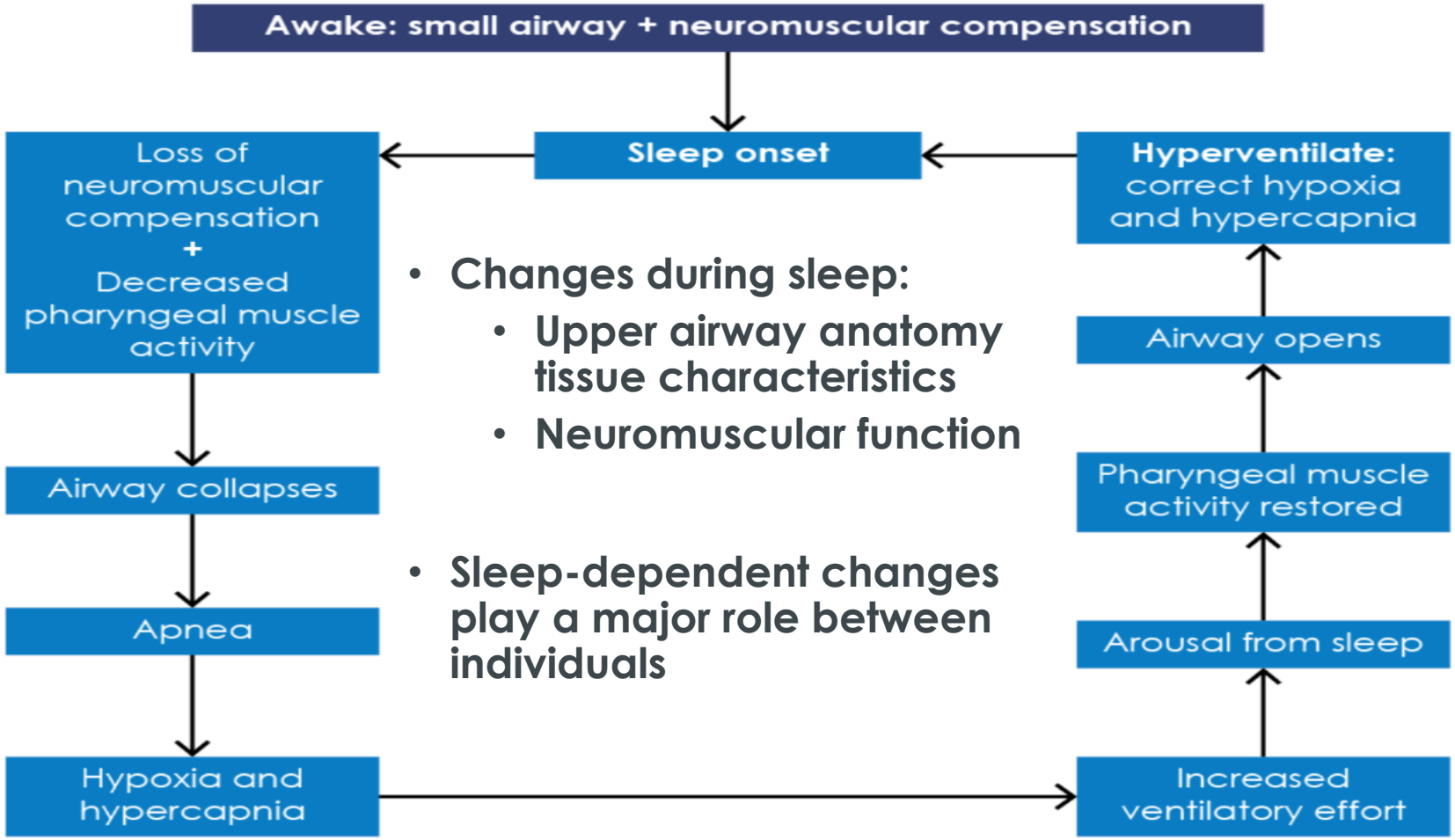
OSA Pathophysiology



Jyotchi I, et al. Obstructive Sleep Apnea: A Pathophysiology and Pharmacotherapy Approach. 2019. [en ligne]. https://www.intechopen.com/books/noninvasive-ventilation-in-medicine-recent-updates/obstructive-sleep-apnea-a-pathophysiology-and-pharmacotherapy-approach (Consulté le 30 janvier 2020).

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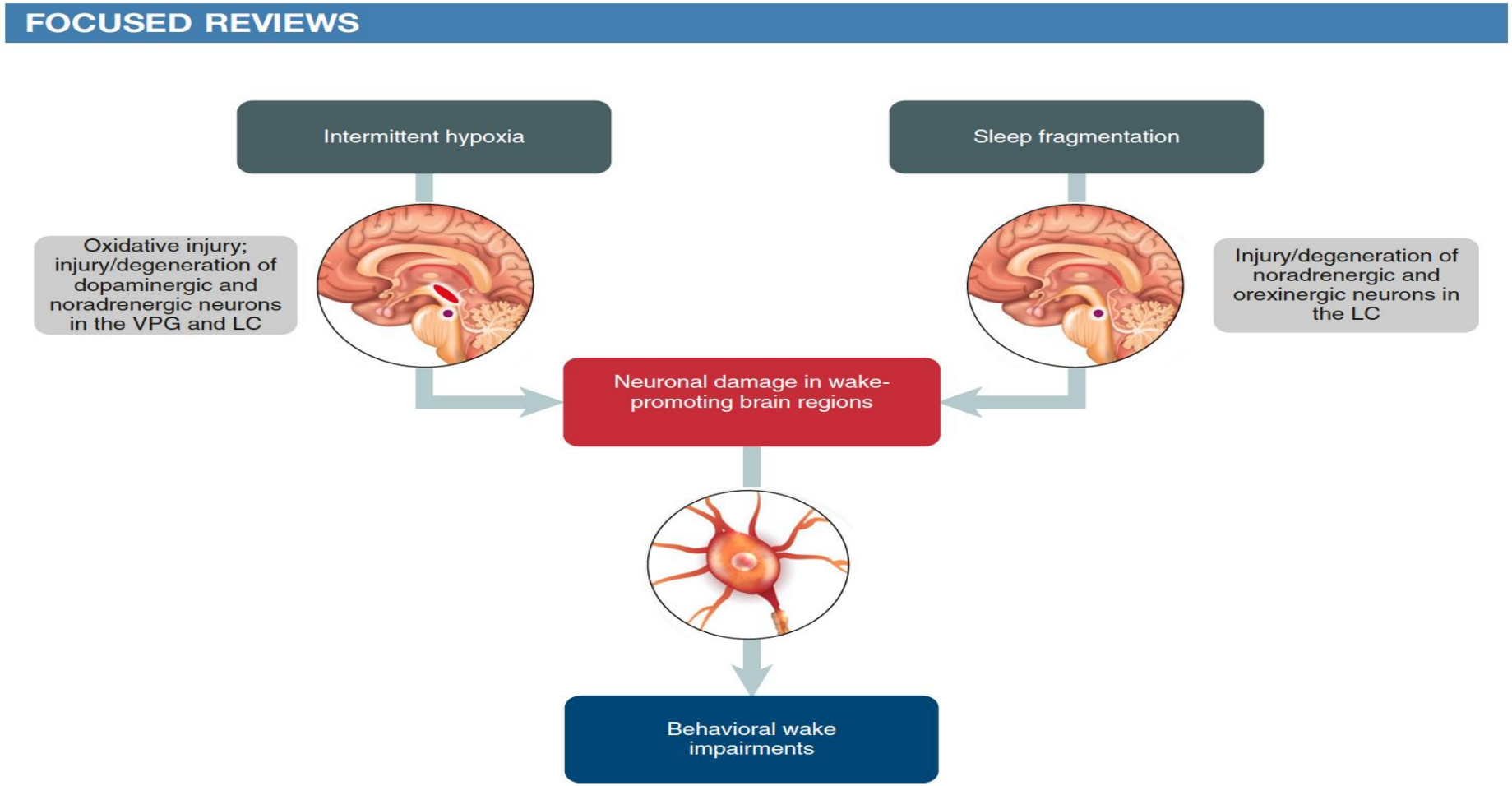
Pathogenesis of EDS in OSA



Lal C, et al. Annals ATS 2021

EDS in OSA : what is means for patients

Excessive daytime sleepiness in OSA
may manifest in multiple adverse behavioral health outcomes

- Falling asleep while driving.
- Fatigue.
- Irritability.
- Diminished cognitive functioning →
- Overall impaired social function.
- Poor quality of life.

Attention
Alertness
Vigilance
Attentiveness
Memory deficit
Impaired executive function
Decreased productivity
Increased work errors.

Sleepiness: Difficulty maintaining alertness during wake periods of a 24-h sleep-wake cycle.

rEDS in OSA : what is means for patients

EDS in OSA: An Update

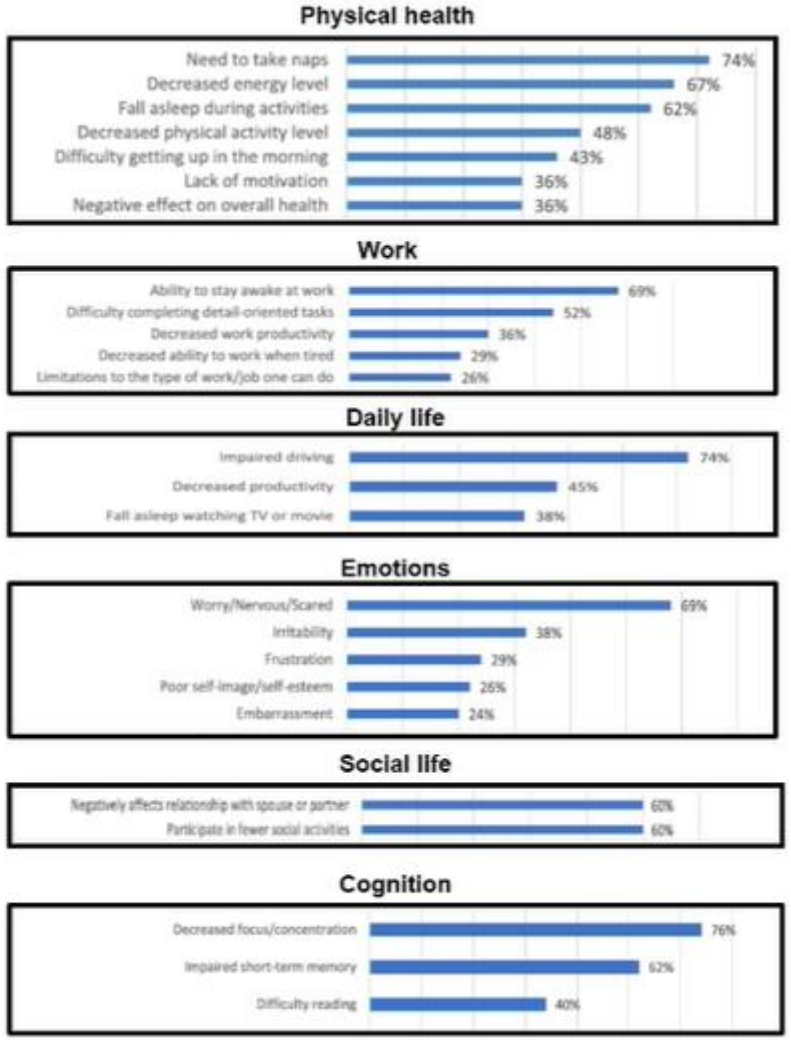
Impact of EDS on HRQOL

- Qualitative research, focus groups in 3 US cities.
- 42 pts. with EDS and OSA.
- 62% currently under PAP or MAD, 33% previously.
- 52% symptoms for ≥1 y., median duration 8.0 yrs. (1-37).
- 32% considered symptoms to be "normal".

- Reasons for seeking medical attention:
  - 67% input from family/ friends.
  - Own concerns 23%.
  - Falling asleep while driving 17%.

- Impact of EDS on HRQOL:
  - Physical health and functioning 95%.
  - Work productivity 90%.
  - Daily functioning 93%.
  - Cognition 90%.
  - Social life/relationships 88%, emotions 71%.

Waldman et al. Health and Quality of Life Outcomes 2020; 18:128.



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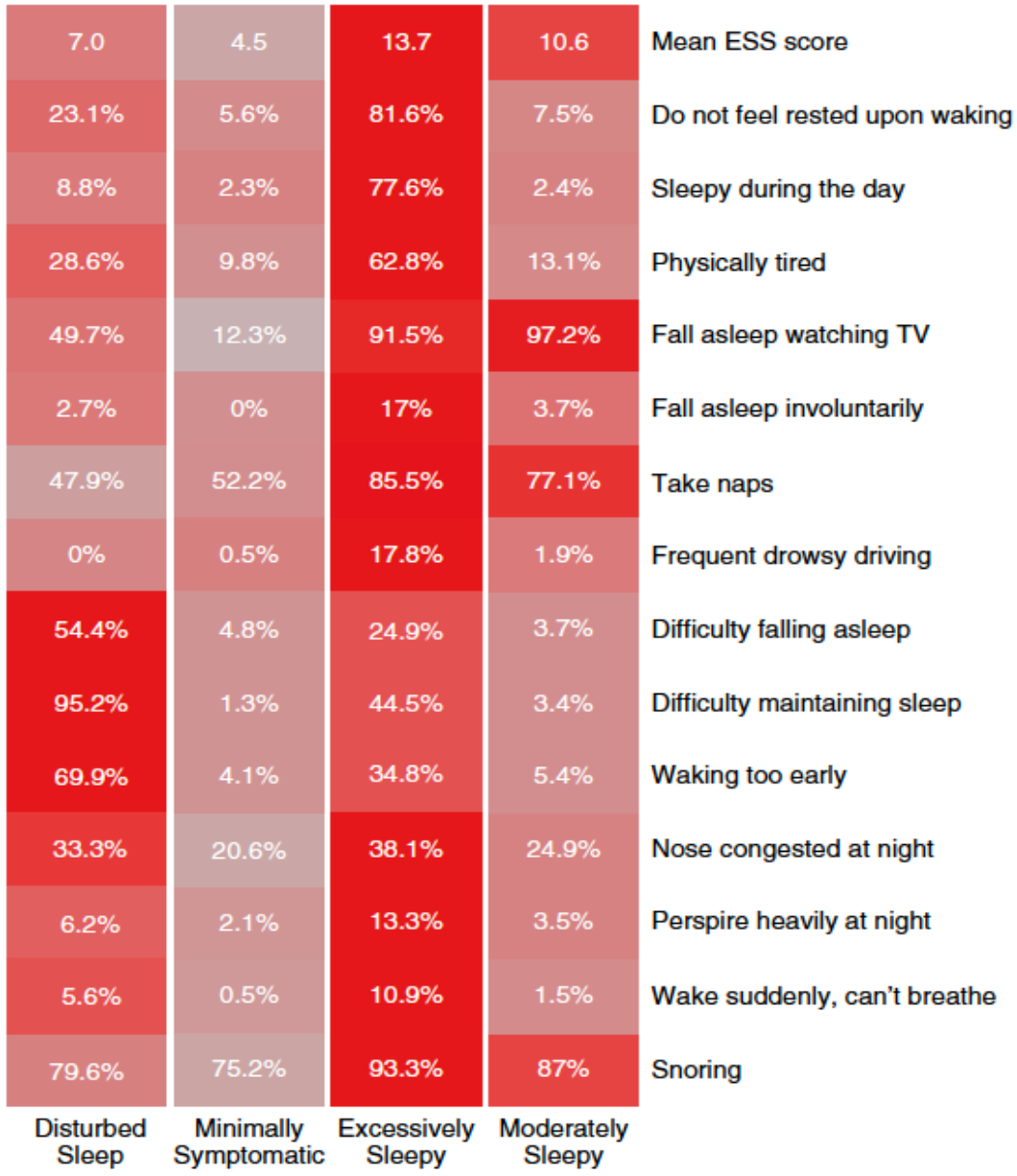
Excessively sleepy OSA patients show the highest symptom burden

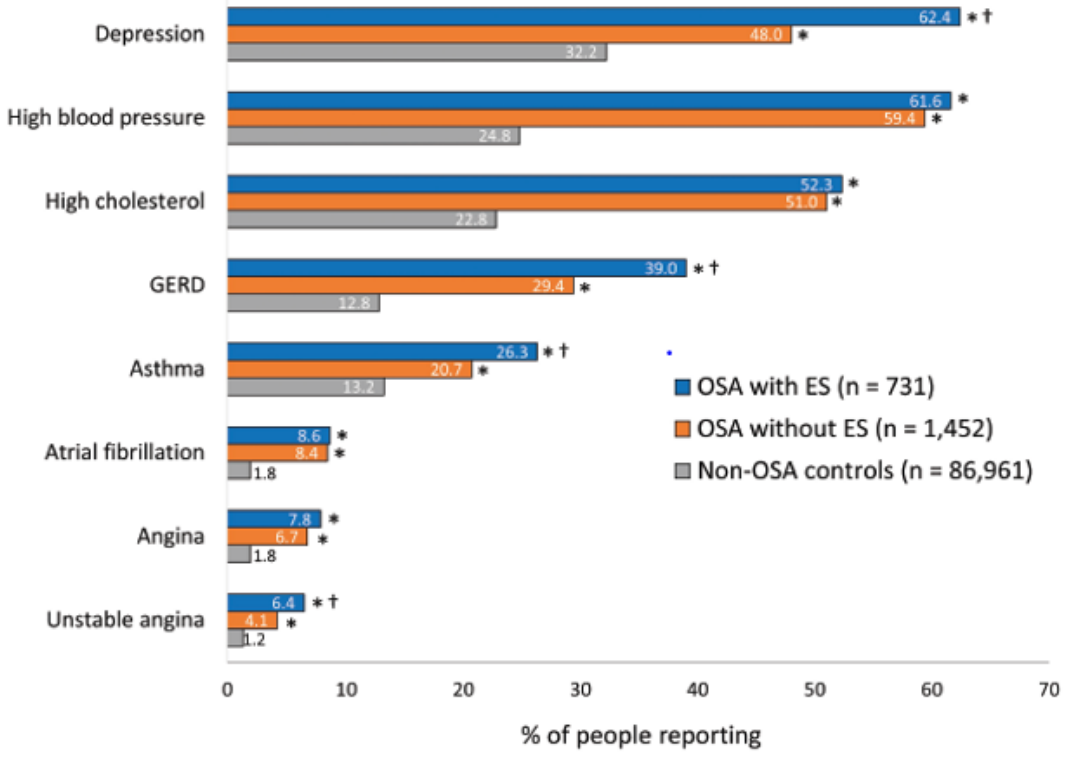
- Substudy from the Sleep Heart Health Study : Multicenter prospective, community based cohort
- 1207 patients with moderate to severe OSA (AHI≥15) vs patients with mild OSA (AHI<5)
- Median follow-up of 11,8 years



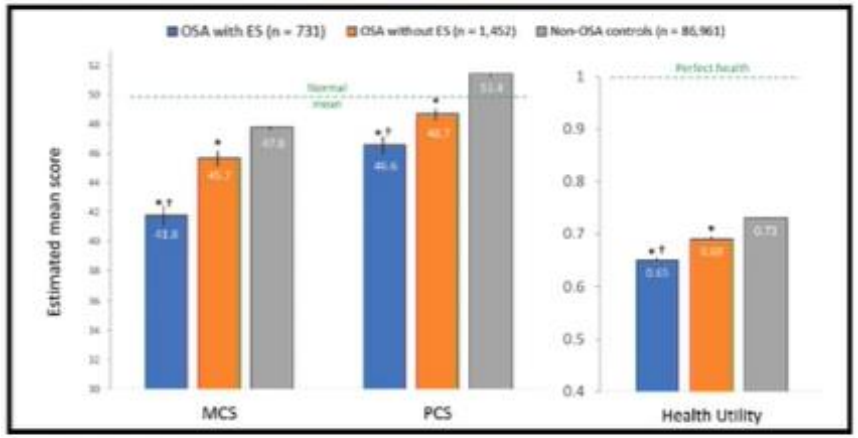
Mazzotti DR, et al. Am J Respir Crit Care Med 2019.

rEDS in OSA : comorbidities

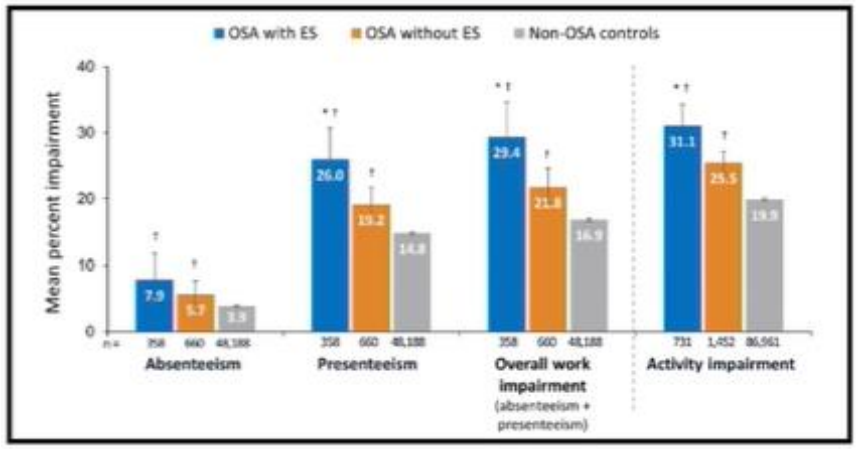
- Cross-sectional 2016 US National Health & Wellness Survey.
- OSA with ESS ≥ 11 (n = 731), OSA w/o ES (n = 1,452), non-OSA controls (n = 86,961).
- Comorbidities, health-related quality of life, productivity.



Health-related QoL



Productivity



Stepnowski et al, 2019

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rEDS in OSA : comorbidities

Comorbidity (self-reported diagnosis)	OSA/No EDS (ESS, 0–10) n = 1347	OSA/Mild EDS (ESS, 11–12) n = 195	OSA/Moderate EDS (ESS, 13–15) n = 228	OSA/Severe EDS (ESS, 16–24) n = 238
	n (%)	n (%)	n (%)	n (%)
Medical				
Insomnia	270 (20.0%)	47 (24.1%)	66 (28.9%)	73 (30.7%)
Other sleep difficulties	126 (9.4%)	25 (12.8%)	41 (18.0%)	46 (19.3%)
Restless legs syndrome	85 (6.3%)	20 (10.3%)	24 (10.5%)	45 (18.9%)
Parkinson disease	4 (0.3%)	3 (1.5%)	1 (0.4%)	1 (0.4%)
Fibromyalgia	47 (3.5%)	6 (3.1%)	10 (4.4%)	24 (10.1%)
High blood pressure	709 (52.6%)	100 (51.3%)	106 (46.5%)	124 (52.1%)
Atrial fibrillation	67 (5.0%)	14 (7.2%)	16 (7.0%)	16 (6.7%)
High cholesterol	521 (38.7%)	73 (37.4%)	92 (40.4%)	104 (43.7%)
Angina	132 (9.8%)	13 (6.7%)	41 (18.0%)	26 (10.9%)
Unstable angina	35 (2.6%)	9 (4.6%)	15 (6.6%)	10 (4.2%)
Asthma	162 (12.0%)	36 (18.5%)	46 (20.2%)	54 (22.7%)
Gastroesophageal reflux disease	233 (17.3%)	43 (22.1%)	58 (25.4%)	55 (23.1%)
Psychiatric				
Depression	359 (26.7%)	62 (31.8%)	90 (39.5%)	121 (50.8%)
Posttraumatic stress disorder	47 (3.5%)	12 (6.2%)	12 (5.3%)	24 (10.1%)

EDS, excessive daytime sleepiness; OSA, obstructive sleep apnoea.

Jennum et al, 2021

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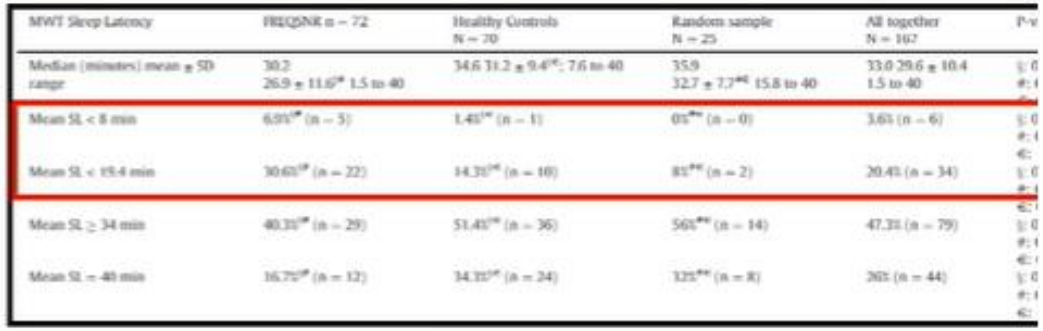
rEDS in OSA : Social impact

Sleepiness and driving risk?

- 2066 truck drivers, structured questionnaire.
- 175 polygraphy, maintenance of wakefulness test.
- 75 subjects with suspected OSA, 75 healthy controls, 25 subjects as random sample.



	FREQSNR n = 72 % 95% CI	Healthy Controls n = 70 % 95% CI	Random sample n = 25 % 95% CI	All together n = 167 % 95% CI
Habitual snorers	86.1 75.9 to 93.1	0 0 to 5.1[a]	32.0 14.9 to 53.5	41.9 34.3 to 49.8
EDT (feeling tired on ≥ 3 d/wk)	31.9 21.4 to 44.0	15.7 8.1 to 26.4	12.0 2.5 to 31.2	22.2 16.1 to 29.2
EDS (feeling sleepy on ≥ 3 days per week)	29.6 19.3 to 41.6	11.4 5.1 to 21.3	12.0 2.5 to 31.2	19.2 13.5 to 26.0
ESS>10	41.7 30.2 to 53.9	22.9 13.7 to 34.4	8.0 1.0 to 26.0	28.9 22.2 to 36.4
AHI≥5	56.9 44.7 to 68.6	20.0 11.3 to 31.2	48.0 27.8 to 68.7	40.1 32.6 to 48.0
AHI≥15	25.0 15.5 to 36.6	4.3 0.1 to 12.0	24.0 9.3 to 45.1	16.2 10.9 to 22.6
AHI≥30	12.5 5.9 to 22.4	1.4 0 to 8.0	8.0 0 to 26.0	7.2 3.8 to 12.2
OSAS: AHI≥5 and EDS	15.3 7.9 to 25.7	0 0 to 5.1[a]	8.0 1.0 to 26.0	7.8 4.2 to 12.9
OSAS: AHI≥5 and ESS>10	26.4 16.7 to 38.1	1.4 0.04 to 7.8	4.0 0.1 to 20.4	12.6 8.0 to 18.7
Moderate OSAS: AHI≥15 and EDS	4.2 0.8 to 11.7	0 0 to 5.1[a]	4.0 0.1 to 20.3	2.4 0.6 to 6.0
Moderate OSAS: AHI≥15 and ESS>10	9.7 4.0 to 19.0	0 0 to 5.1[a]	4.0 0.1 to 20.4	4.8 2.1 to 9.3
AHI≥5 and MWT<19.4min	23.6 14.4 to 35.1	1.4 0.04 to 7.7	4.0 0.1 to 20.4	11.4 7.0 to 17.2
AHI≥15 and MWT<19.4min	11.1 4.9 to 20.7	0 0 to 5.1[a]	0 0 to 13.7[a]	4.8 2.1 to 9.3
AHI≥15 and MWT<8 min	2.8 0.3 to 9.7	0 0 to 5.1[a]	0 0 to 13.7[a]	1.2 0.1 to 4.3

- Moderate OSA common among truck drivers.
- Moderate OSA with sign. objective sleepiness in 10%.

Huhta R et al. Sleep Medicine 2021; 81: 136-1

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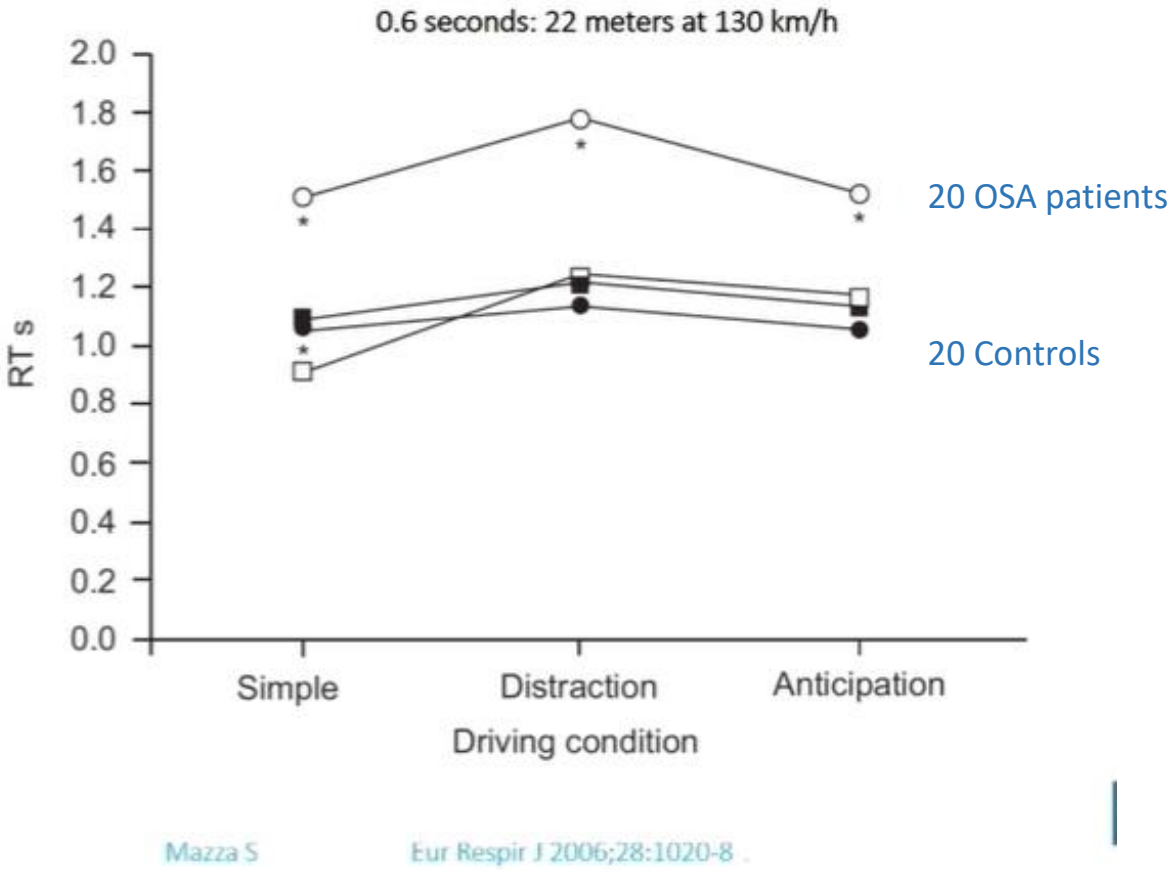
rEDS in OSA : Social impact

Attentional deficits affecting driving capacity are normalized under CPAP treatment



20 OSA patients

20 Controls

Mazza S Eur Respir J 2006;28:1020-8

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rEDS in OSA : Modifiers of disease burden

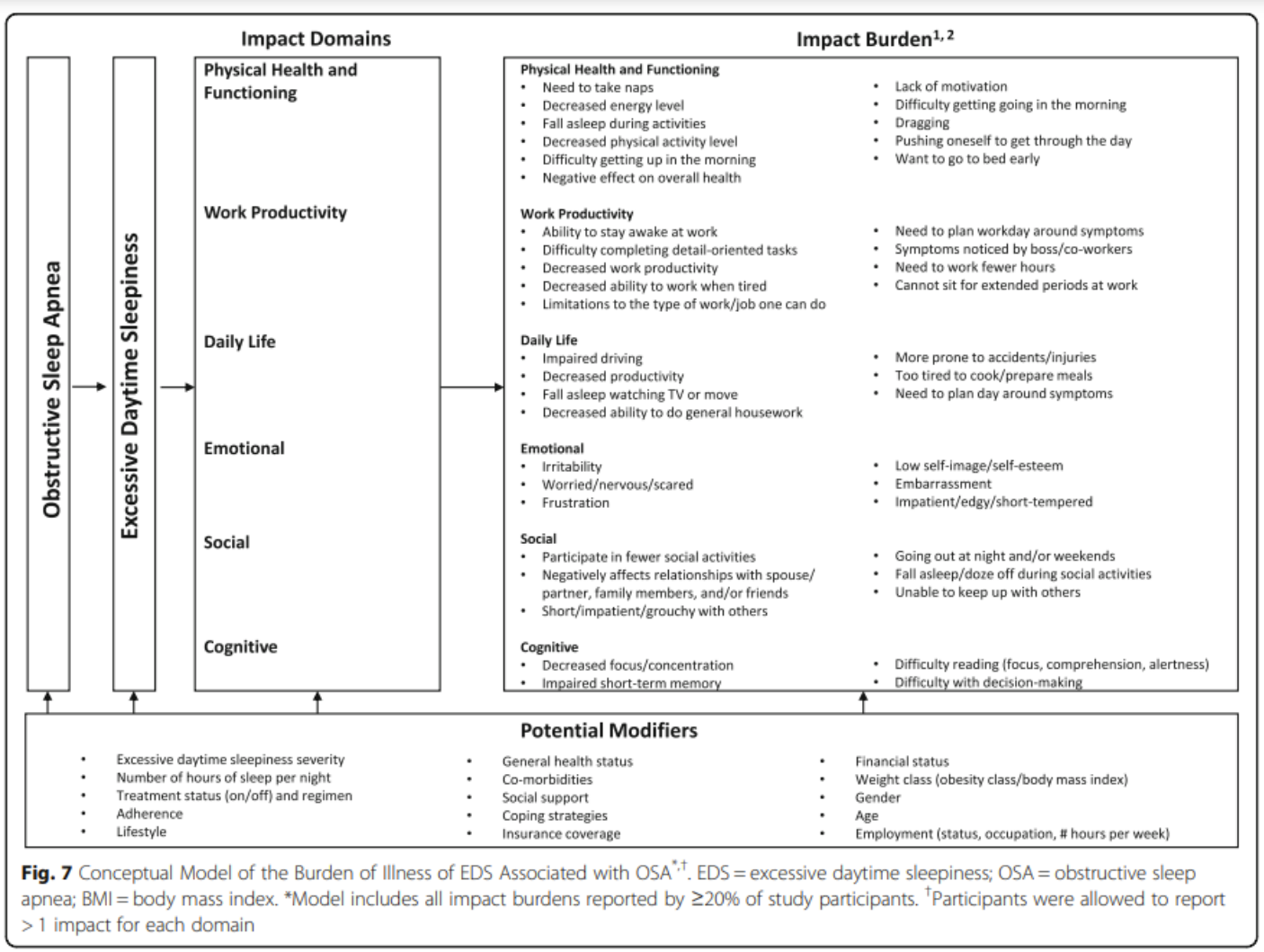

Fig. 7 Conceptual Model of the Burden of Illness of EDS Associated with OSA[*,†]. EDS = excessive daytime sleepiness; OSA = obstructive sleep apnea; BMI = body mass index. *Model includes all impact burdens reported by ≥20% of study participants. [†]Participants were allowed to report > 1 impact for each domain

Waldman et al, 2020

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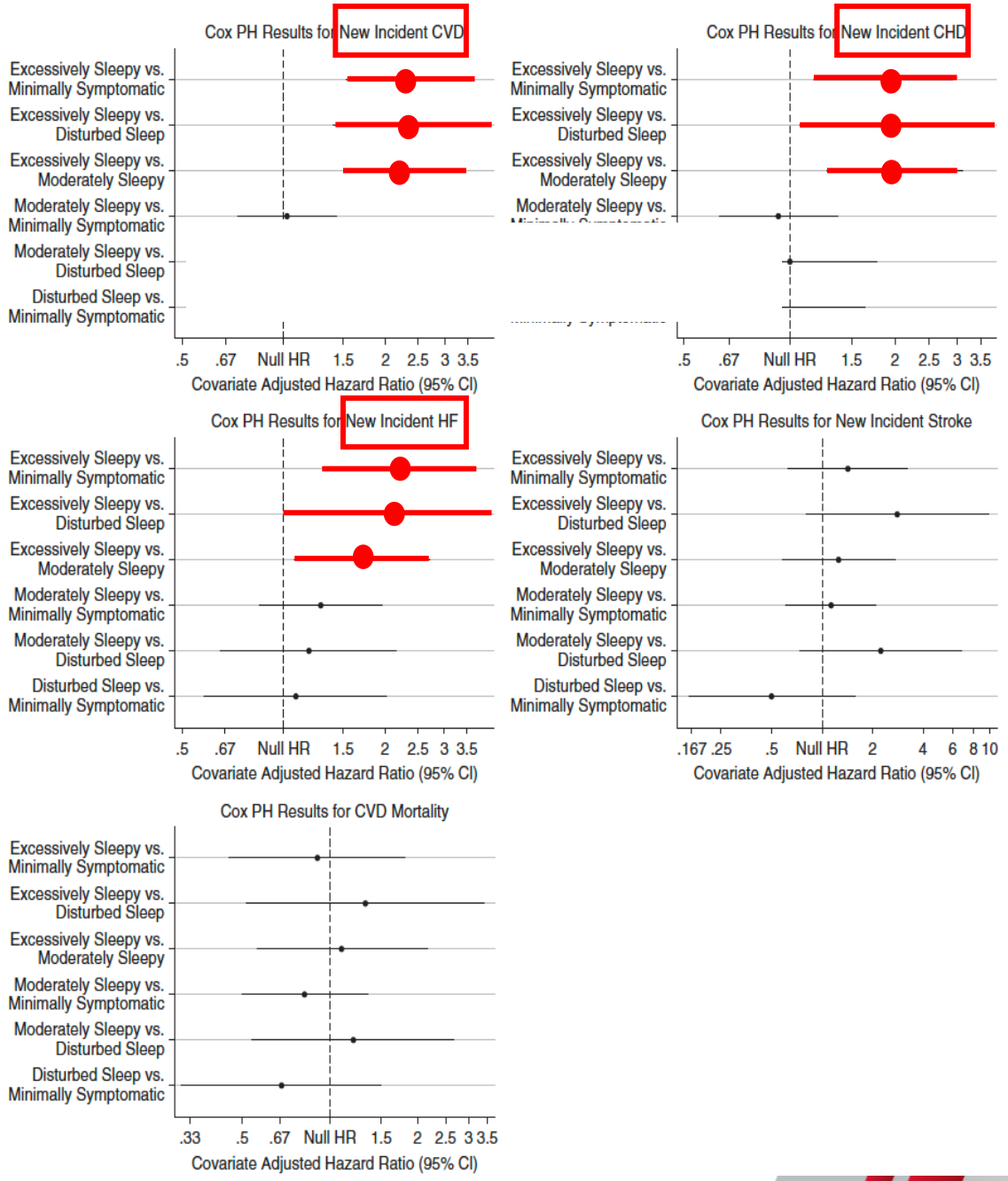
Increased incidence of CVD, CHD and HF in excessively sleepy patients with OSA - Sleep Heart Health Study

- Substudy from the Sleep Heart Health Study : Multicenter prospective, community based cohort
- 1207 patients with moderate to severe OSA (AHI≥15) vs patients with mild OSA (AHI<5)
- Median follow-up of 11,8 years



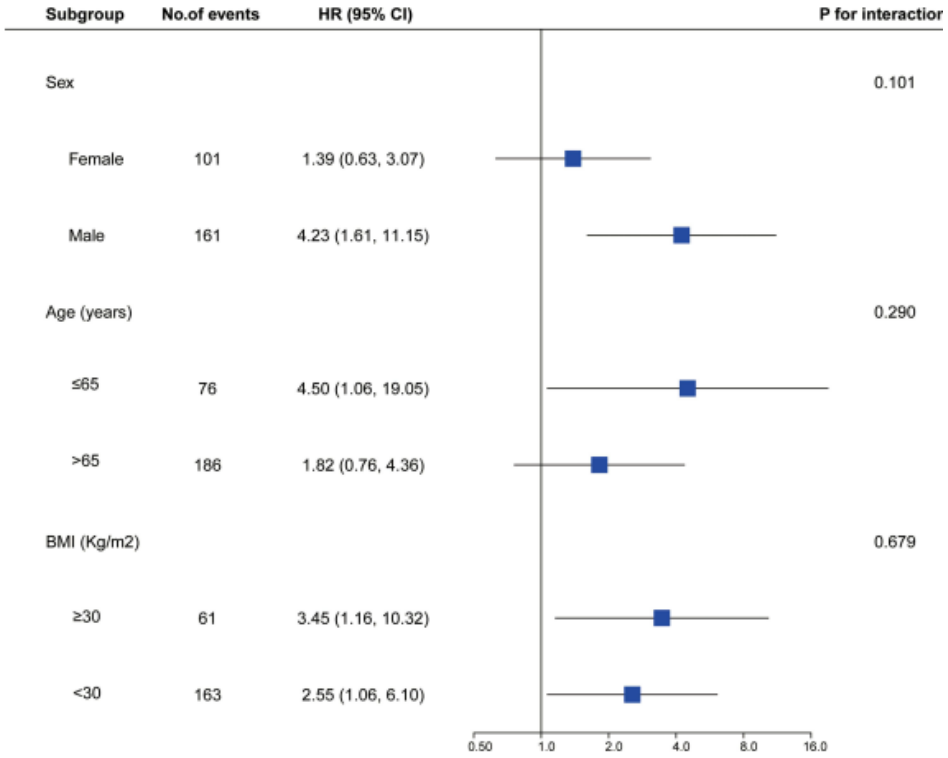
CVD: cardiovascular disease ; CHD: coranary heart disease ; HF: heart failure

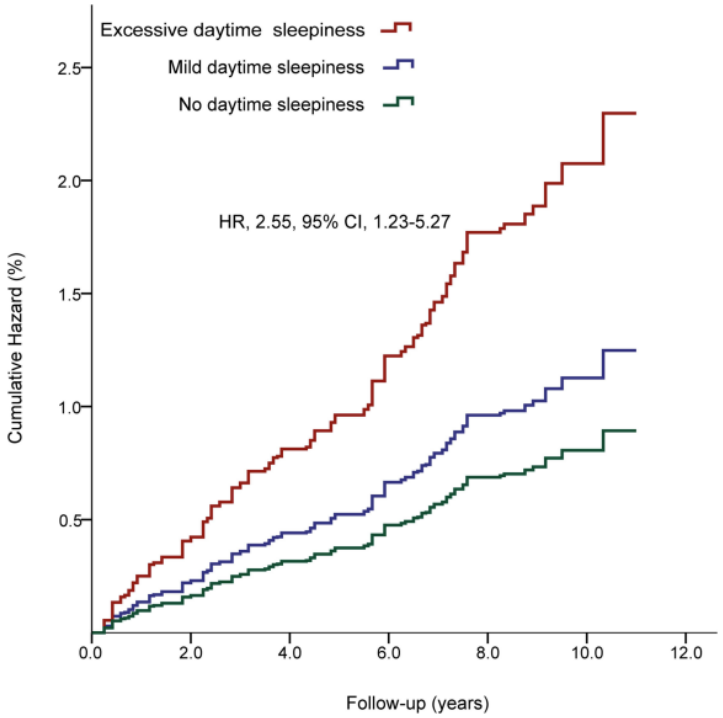
Mazzotti DR, et al. Am J Respir Crit Care Med 2019.

Mortality of EDS (16% with OSA)

Excessive daytime sleepiness and cardiovascular mortality?

- Prospective study, 10,330 adult participants.
- National Health Nutrition Examination Survey, 2005-2008, follow-up until 2015.
- Self-reported feeling of being overly sleepy often or always, 18.5% of US adults.
- HR of cv. death in EDS 2.85 (95% CI, 1.33-6.09).
- Corrected for sociodem. factors, comorbidities, cv. risk factors incl. depression





Associations between EDS and risk of cv. mortality stratified by sex, age and BMI in fully adjusted model.

Li J et al. Nature and Science of Sleep 2021: 13: 1049-1059 .

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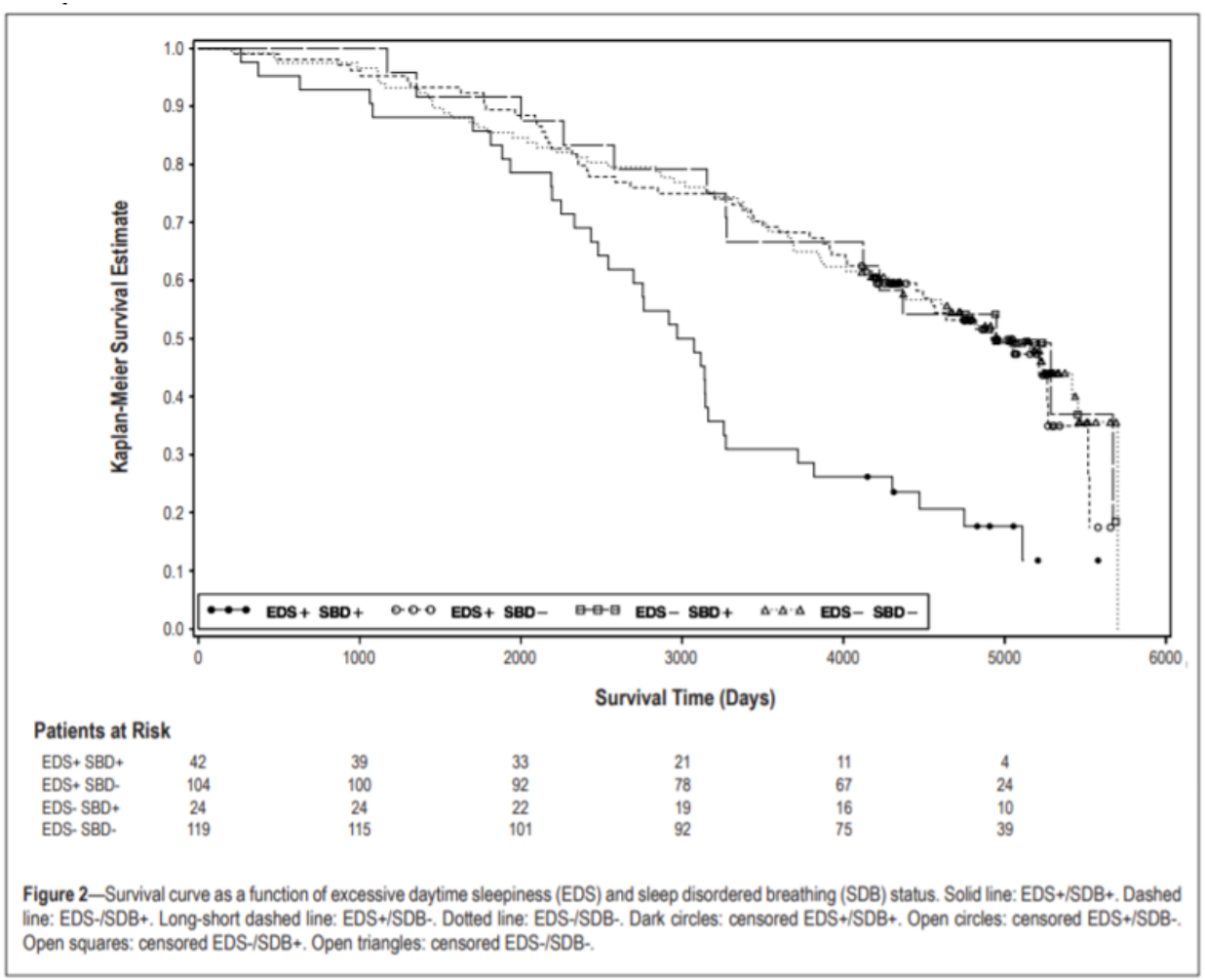
rEDS in OSA : Mortality

- 289 persons > 65 yrs recruited from the Philadelphia area
  - 146 with self-reported EDS
  - 143 without self-reported EDS
- FU for 13,4 years
- PSG to determine OSA (AHI≥20)
- SDB+/EDS+ vs SDB-/EDS- : HR = 2.7



Patients at Risk

EDS+ SBD+	42	39	33	21	11	4
EDS+ SBD-	104	100	92	78	67	24
EDS- SBD+	24	24	22	19	16	10
EDS- SBD-	119	115	101	92	75	39

Figure 2—Survival curve as a function of excessive daytime sleepiness (EDS) and sleep disordered breathing (SDB) status. Solid line: EDS+/SDB+. Dashed line: EDS-/SDB+. Long-short dashed line: EDS+/SDB-. Dotted line: EDS-/SDB-. Dark circles: censored EDS+/SDB+. Open circles: censored EDS+/SDB-. Open squares: censored EDS-/SDB+. Open triangles: censored EDS-/SDB-.

Gooneratne et al, 2011

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rEDS in OSA : Definitions

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What is EDS ?

What is excessive daytime sleepiness?

- The inability to stay awake during the day
- Should be distinguished from fatigue
- Many possible causes:
  - Depression, obesity, diabetes, hypothyroidism
  - Neurological conditions such as Parkinson's disease
  - Short/lack of sleep, poor sleep hygiene, shift work
  - Medication such as opiates, antiepileptic, antidepressants
  - Alcohol, caffeine, other recreational drugs
  - Sleep disorders: OSA, periodic leg movements, narcolepsy, UARS

rEDS in OSA : Definitions

- **Excessive daytime sleepiness**
  - Daytime sleepiness is defined as excessive when it causes a subjective complaint or interferes with function.
  - The International Classification of Sleep Disorders, third edition (ICSD-3) defines EDS as the inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentionally or at inappropriate times almost daily for at least three months
- **Hypersomnia**
  - The terms hypersomnia and hypersomnolence are sometimes used interchangeably with EDS.
  - The ICSD-3 defines hypersomnolence as excessive sleepiness when wakefulness is expected, and hypersomnia as a disorder characterized by hypersomnolence
- **Fatigue**
  - Fatigue refers to a subjective lack of physical or mental energy.
  - Clinical fatigue incorporates three components :
    - inability to initiate activity (perception of generalized weakness, in the absence of objective findings)
    - reduced capacity to maintain activity (easy fatigability);
    - difficulty with concentration, memory, and emotional stability (mental fatigue)

American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd ed, American Academy of Sleep Medicine, 2014.

Markowitz AJ, Rabow MW. Palliative management of fatigue at the close of life: "it feels like my body is just worn out". JAMA 2007; 298:217.

Tools to evaluate EDS

Commonly used tools for evaluating EDS			
Tool	**Type**	**Measurement**	**Cutoff Value Suggestive of EDS**
Maintenance of Wakefulness Test	Objective	Ability to stay awake (40-min session)	Sleep latency ≤19 min
Oxford Sleep Resistance Test	Objective	Ability to stay awake (40-min session)	N/A*
Mean Sleep Latency Test	Objective	Ability to fall asleep (20-min nap opportunity)	Sleep latency ≤8 min
Psychomotor Vigilance Task	Objective	Sustained attention (i.e., reaction time, lapses in attention)	N/A†
Epworth Sleepiness Scale	Objective	Sleep propensity in daily situations‡	Score > 10
Stanford Sleepiness Scale	Objective	Degree of sleepiness at a point in time§	Score > 3
Karolinska Sleepiness Scale	Objective	Degree of sleepiness at a point in time‖	Score ≤ 7

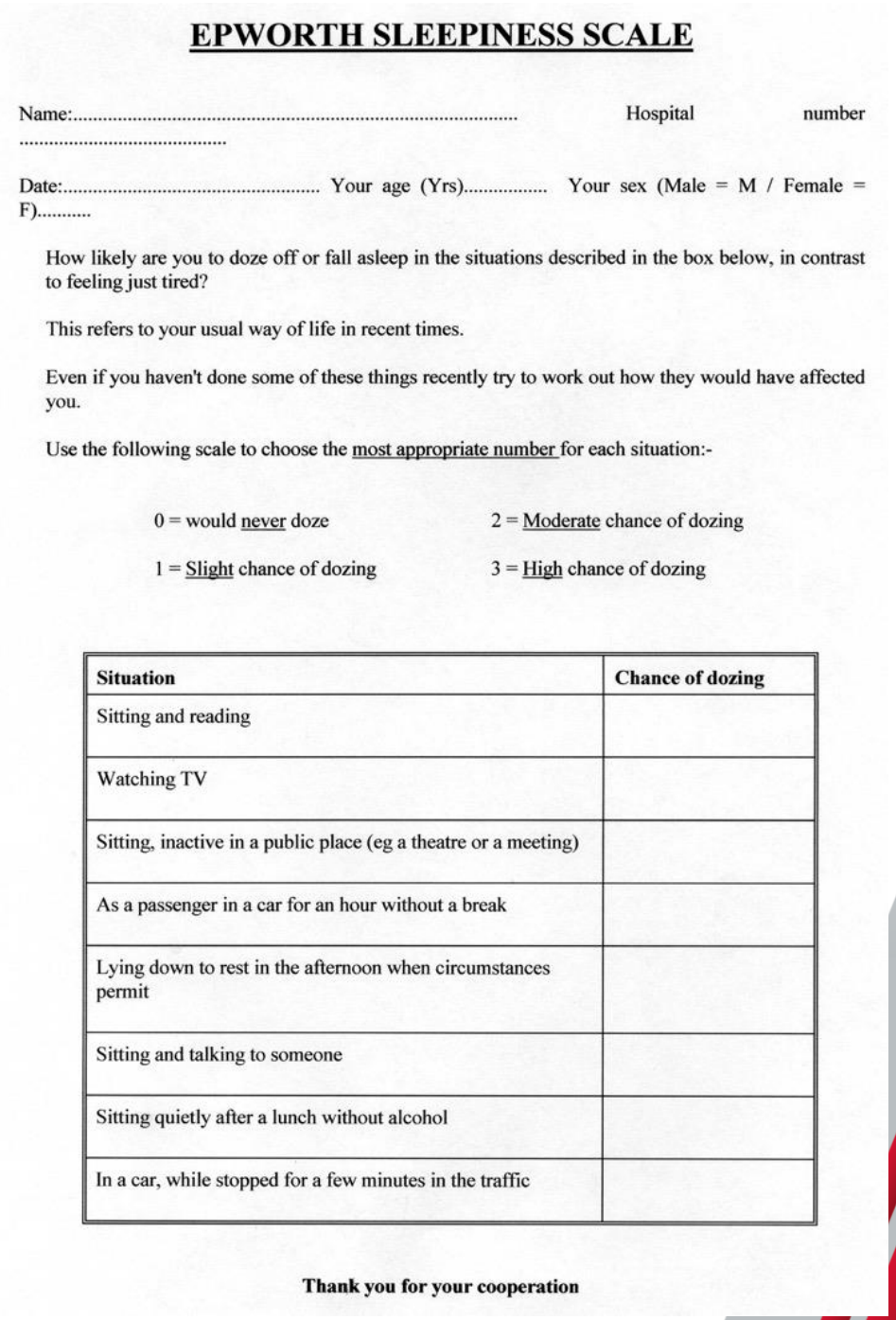
Berlin Questionnaire
Pichot Fatigue
Acti-watch

Lal C, et al. Ann Am Thorac Soc 2021.

Epworth Sleepiness Scale (ESS)

- Situational questions - not the same as asking “are you sleepy”. No quality of life assessment
- A patient may think they are not sleepy, but still score highly on the ESS
- A total score of 0-9 is considered normal, and 10-24 abnormal
- However, 15% of randomly selected adults score 10 or more. Clearly is a grey area, 9-12 - borderline

Invented by Murray Johns at the Epworth Hospital in Australia



EPWORTH SLEEPINESS SCALE

Name:..... Hospital number .....

Date:..... Your age (Yrs)..... Your sex (Male = M / Female = F).....

How likely are you to doze off or fall asleep in the situations described in the box below, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:-

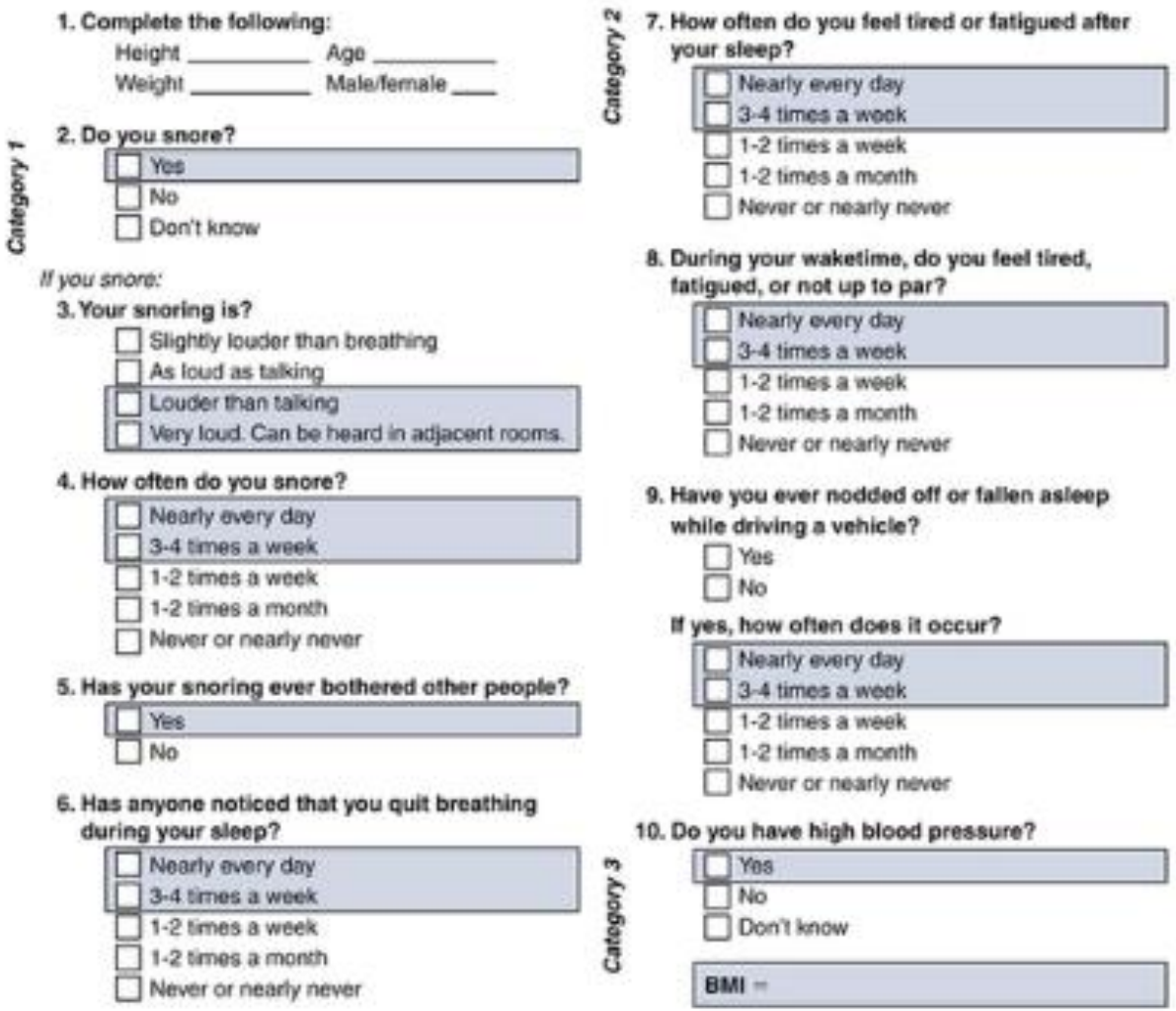
0 = would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

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

Thank you for your cooperation

Epworth sleepiness scale. https://epworthsleepinessscale.com/about-the-ess/

Berlin questionnaire



Category 1

1. **Complete the following:**
   Height _____ Age _____
   Weight _____ Male/female ____

2. **Do you snore?**
   - [ ] Yes
   - [ ] No
   - [ ] Don't know

If you snore:

3. **Your snoring is?**
   - [ ] Slightly louder than breathing
   - [ ] As loud as talking
   - [ ] Louder than talking
   - [ ] Very loud. Can be heard in adjacent rooms.

4. **How often do you snore?**
   - [ ] Nearly every day
   - [ ] 3-4 times a week
   - [ ] 1-2 times a week
   - [ ] 1-2 times a month
   - [ ] Never or nearly never

5. **Has your snoring ever bothered other people?**
   - [ ] Yes
   - [ ] No

6. **Has anyone noticed that you quit breathing during your sleep?**
   - [ ] Nearly every day
   - [ ] 3-4 times a week
   - [ ] 1-2 times a week
   - [ ] 1-2 times a month
   - [ ] Never or nearly never

Category 2

7. **How often do you feel tired or fatigued after your sleep?**
   - [ ] Nearly every day
   - [ ] 3-4 times a week
   - [ ] 1-2 times a week
   - [ ] 1-2 times a month
   - [ ] Never or nearly never

8. **During your waketime, do you feel tired, fatigued, or not up to par?**
   - [ ] Nearly every day
   - [ ] 3-4 times a week
   - [ ] 1-2 times a week
   - [ ] 1-2 times a month
   - [ ] Never or nearly never

9. **Have you ever nodded off or fallen asleep while driving a vehicle?**
   - [ ] Yes
   - [ ] No

   If yes, how often does it occur?
   - [ ] Nearly every day
   - [ ] 3-4 times a week
   - [ ] 1-2 times a week
   - [ ] 1-2 times a month
   - [ ] Never or nearly never

Category 3

10. **Do you have high blood pressure?**
    - [ ] Yes
    - [ ] No
    - [ ] Don't know

BMI =

- Sleep Disturbed Breating (SDB) evaluation in primary care
- 3 categories of questions

Scoring questions: Any answer within box outline is a positive response.

Scoring categories:
Category 1 is positive with 2 or more positive responses to questions 2-6 ☐
Category 2 is positive with 2 or more positive responses to questions 7-9 ☐
Category 3 is positive with 1 positive response and/or a BMI >30 ☐

Final result: 2 or more positive categories indicates a high likelihood of sleep disordered breathing.

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Pichot Fatigue Score

Pichot's Fatigue Scale (to assess fatigue)

Ref « assessment scales and tools in General Medicine" March 2002 (translated from the French version for the "Sommeil et médecine générale" website)

- Tiredness is a feeling of physical and mental weakening that usually occurs after a sustained effort and that consequently requires a period of rest.
- Pathological tiredness is referred to when people find it harder to carry out their daily activities than in their usual condition.
Pichot's subjective scale has been proposed to assess the importance of this handicap.

First name:..... Family name.....

Date of birth.....

Test date.....Current medication.....

.

Among the eight following proposals, select those that best correspond to your feeling:

0 = not at all, 1 = a little, 2 = moderately, 3 = much, 4 = extremely,

- I have no energy..... 0 1 2 3 4
- Everything requires an effort..... 0 1 2 3 4
- I feel weak in some parts of my body..... 0 1 2 3 4
- My legs and arms feel weary..... 0 1 2 3 4
- I feel tired without any reason..... 0 1 2 3 4
- I feel like lying down to rest..... 0 1 2 3 4
- I find it difficult to concentrate..... 0 1 2 3 4
- I feel exhausted, stiff and heavy..... 0 1 2 3 4

Total (out of 32):.....

A score above 22 reveals excessive fatigue, you may suffer from inefficient sleep.

NB. This test doesn't give a diagnosis but can help to assess your general level of fatigue Report it to your physician to discuss the causes and consequences of such a state of exhaustion

Pichot fatigue scale. https://www.sommeil-mg.net/spip/questionnaires/pichot.pdf.

Objective tests during investigation of EDS

OSleR (Oxford Sleep Resistance)

Actiwatch and sleep diary

Assesses sleeping and activity pattern.

Worn continuously for 2 weeks at home and reviewed with a sleep diary

Full PSG and MSLT (Multiple Sleep Latency Test) or MWT (Maintenance of Wakefulness Test)

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OSleR test

Other evaluation of Excessive Daytime Sleepiness (EDS)

- **OSLER test** (duration 40 min max, x3) to measure time to fall asleep
  - A simplified MWT: simple easy reliable tool, doesn't require EEG
  - Semi-recumbent position in dark room
  - RESPOND (touch a button) to LED flashes 1 sec every 3 sec
  - Test is terminated after 7 consecutive LED flashes without response: patient asleep
  - 3 sessions in a day
  - 2 types of results: Latency (minutes) and Error number

Krieger AC et al, Comparison of the MWT to a modified behavioral test (OSLER) in the evaluation of daytime sleepiness
J Sleep Res 2004;13:407-11

Predictors and phenotypes of EDS

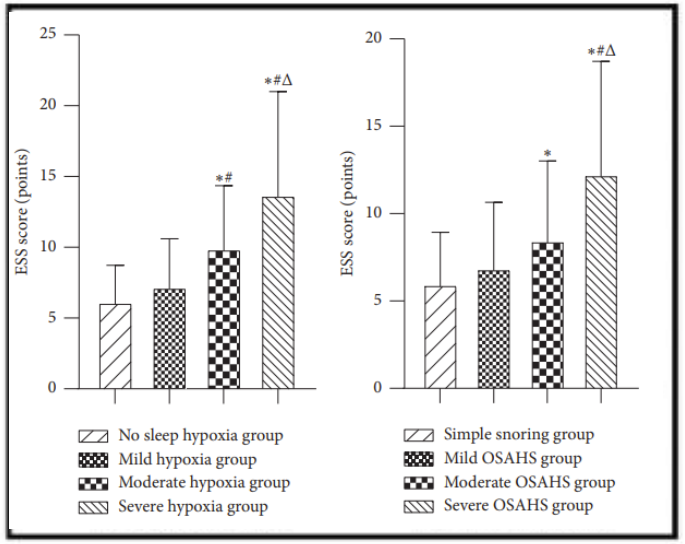
EDS in OSA: An Update

What does influence sleepiness?

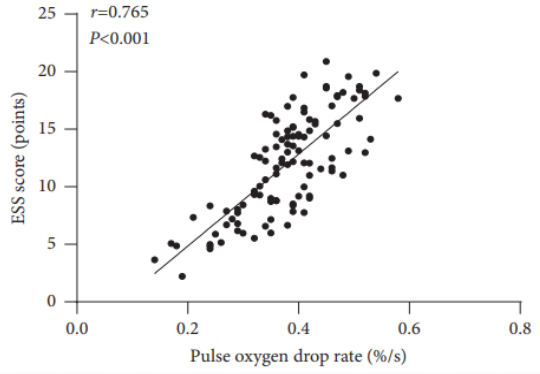
- 246 consecutive OSA pts., PSG.
- Grouping by AHI, ESS and minimum SaO_2.
- No sleep hypoxia: 33; mild h.: 34; moderate h.: 119; severe h.: 60.
- Moderate OSA: 48; severe OSA: 113.
- Lethargy group (ESS >10): 118; no lethargy group (ESS ≤10): 128.

- ESS score associated with hypoxia and OSA severity.
- Multiple logistic regression analysis:
  - AHI and CT90%: independent risk factors for daytime sleepiness.
  - Positive correlation between ESS and SaO_2 decline in severe OSA.

Hypoxia plays a role



Factors	β	SE	Wald	P value	OR (95% CI)
AHI	0.774	0.375	4.428	0.023	2.184 (1.058 – 4.425)
CT90%	1.473	0.474	9.747	0.003	4.365 (1.733 – 11.010)



Zhang F et al. Evidence-Based Compl Altern Med 2021; doi.org/10.1155/2021/6345734

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Predictors and phenotypes of EDS

Excessive Daytime Sleepiness In Obstructive Sleep Apnoea: An Update

Sleepiness in REM-dependent OSA?

- 1863 consecutive pts. with presumed diagnosis of OSA.
- 102 REM-dependent OSA,190 REM-independent OSA.
- Matching regarding sex and age.

- REM-OSA: 2x lower median AHI, similar ESS.

- Daily sleepiness may be stronger associated with apneas/hypopneas occurring in REM than nREM sleep.

REM-sleep plays a role

	REM-dependent OSA (n = 102)	REM-independent OSA (n = 190)	p-value
M:F ratio	42:60	96:94	0.091
Age at diagnosis	53.0 ± 10.8	54.1 ± 10.5	0.403
BMI [kg/m²]	32.0 ± 6.3	29.9 ± 4.5	**0.003**
TST [hours]	5.9 ± 1.0	5.8 ± 1.1	0.549
REM sleep stage time of TST [%]	21.7 ± 7.0	20.8 ± 6.7	0.274
Sleep time in supine position of TST [%]	55.4 ± 25.2	39.2 ± 19.8	**<0.001**
AHI_{TST}	6.1 (3.4–10.0)	12.2 (7.6–18.8)	**<0.001**
AHI_{back}/AHI_{side}	2.0 (0.0–5.0)	17.9 (9.2–35.1)	**<0.001**
AHI_{REM}/AHI_{nREM}	6.0 (4.0–10.4)	0.6 (0.1–1.5)	**<0.001**
$AHI_{REM\text{-}related}$	3.8 (1.9–5.7)	1.2 (0.4–2.7)	**<0.001**
AHI_{nREM}	31.7 (19.0–53.2)	9.0 (4.8–15.0)	**<0.001**
AHI_{back}	1.0 (0.3–3.0)	1.1 (0.0–5.2)	0.176
AHI_{side}	5.7 (2.3–16.1)	16.0 (10.2–27.3)	**<0.001**
Arousal Index	13.5 (9.1–19.0)	19.0 (13.5–27.9)	**<0.001**
Mean desaturation SpO_2 [%]	88.8(87.0–90.2)	88.3 (87.0–89.3)	0.345
Minimal SpO_2 saturation [%]	82.1 (75.3–85.0)	81.4 (78.0–85.0)	0.531
ESS score	9.0 (6.0–11.0)	8.0 (4.8–11.0)	0.109
ESS score ≥ 10	31.4%	28.9%	0.689

Gabryelska A et al. Scientific Reports 2020; 10:34.

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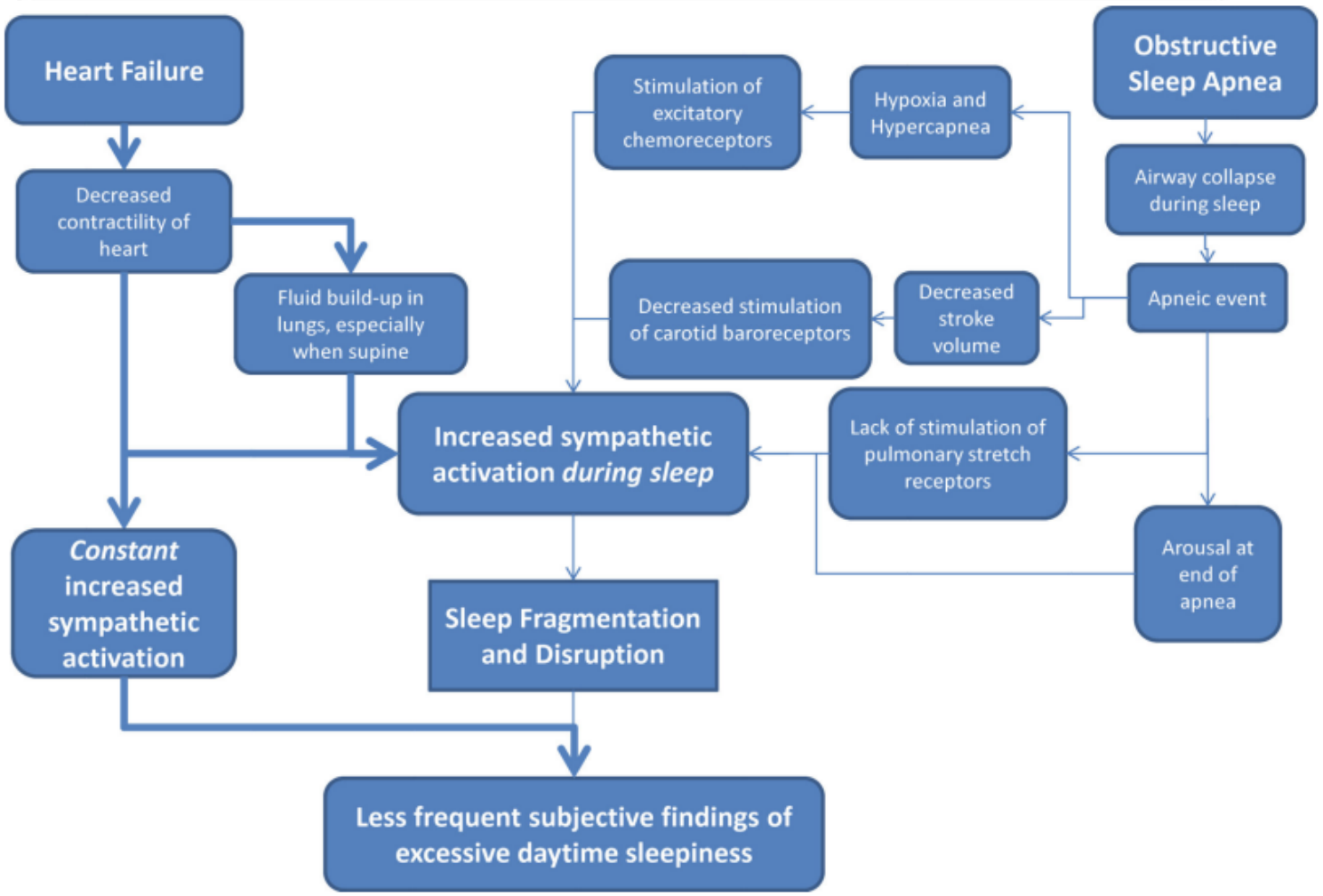
Predictors and phenotypes of EDS

- Patients with heart failure and OSA
  - often have disrupted sleep,
  - often do not complain of EDS.
- Possible explanations for lack of EDS.

Sympathetic activation



Pak VM et al. J Sleep Res. 2019; 28(5): e12778.

Predictors and phenotypes of EDS

EDS in OSA: An Update

Gender differences of EDS?

- **Significant variability of EDS, independent of AHI.**
- **Retrospective study, 578 m., 270 f., suspected OSA.**
- **Home sleep test.**

Table 1 Whole sample. Correlations between ESS and sleep study variables

	Age	BMI	No. of apneas	No. of hypopneas	AHI	Max. dur. of apnea	Max. dur. of hypopnea	Mean dur. of apnea	Mean duration of hypopnea	No. of desaturations	% time Sat < 90%	% time Snoring
ESS	− .109	.104	.118	.099	.142	.070	.018	.057	.020	.124	.103	.068

The significance is 5%

Table 2 Men's group. Correlations between ESS and sleep study variables

	Age	BMI	No. of apneas	No. of hypopneas	AHI	Max. dur. of apnea	Max. dur. of hypopnea	Mean dur. of apnea	Mean duration of hypopnea	No. of desaturations	% time Sat < 90%	% time Snoring
ESS	− .057	.107	.129	.115	.158	.073	.042	.074	.037	.145	.130	.079

The significance is 5%

Table 3 Women's group. Correlations between ESS and sleep study variables

	Age	BMI	No. of apneas	No. of hypopneas	AHI	Max. dur. of apnea	Max. dur. of hypopnea	Mean dur. of apnea	Mean duration of hypopnea	No. of desaturations	% time Sat < 90%	% time Snoring
ESS	− .208	.104	.059	.047	.069	.049	− .038	− .010	− .019	.034	− .025	.040

- **Male:**
  - **Correlation between ESS and BMI, AHI, oxygen desaturations, tSO_2 <90%.**
- **Women:**
  - **No correlation between any sleep parameter or BMI and ESS.**
  - **Negative correlation between age and EDS.**

Men's sleepiness more influenced by OSA and sleep variables compared to women.

Honig E et al. Sleep and Breathing 2021; 25:1837-1842.

From EDS to rEDS in OSA

OSA related causes

- Poor mask fitting,
- Suboptimal pressure settings,
- Nasal congestion,
- Mask leak,
- Aerophagia,
- Dry mouth,
- Treatment-emergent central sleep apnea.

Sleep disorders, other than OSA

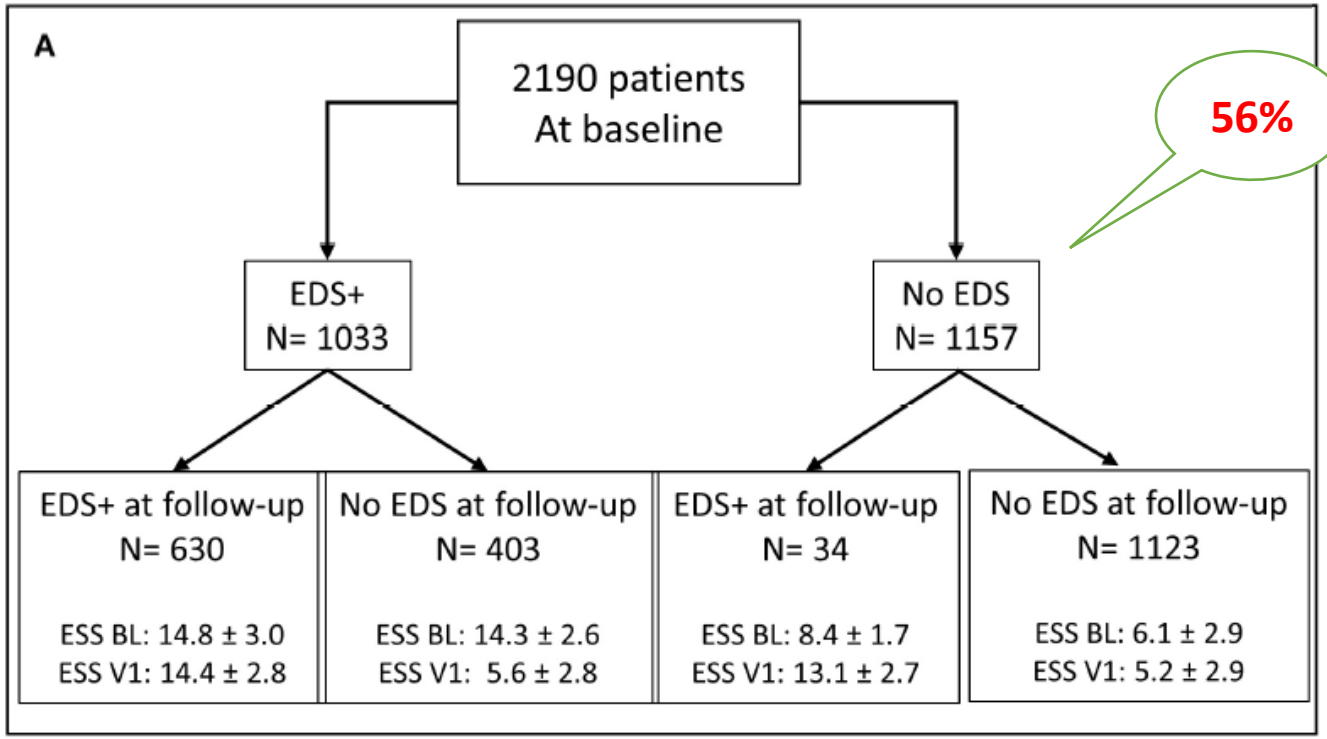
- Inadequate sleep hours
  - Behaviorally induced insufficient sleep
  - Insomnia
  - Circadian rhythm disorders such as shift work disorder
- Restless leg syndrome/ periodic limb movements
- Narcolepsy or other hypersomnia disorders

Non-sleep disorders

- Depression
- Anxiety
- Obesity
- Hypothyroidism
- Somnogenic medications.

How big is the problem of EDS in OSA ?

- Retrospective analysis of RES (ESS >10).
- European Sleep Apnea Database.
- 4,853 pts, 54.8 ± 11.8 yrs, 26.1% females.
- Median follow-up: 5 months.



Bnsignore et al. 2021

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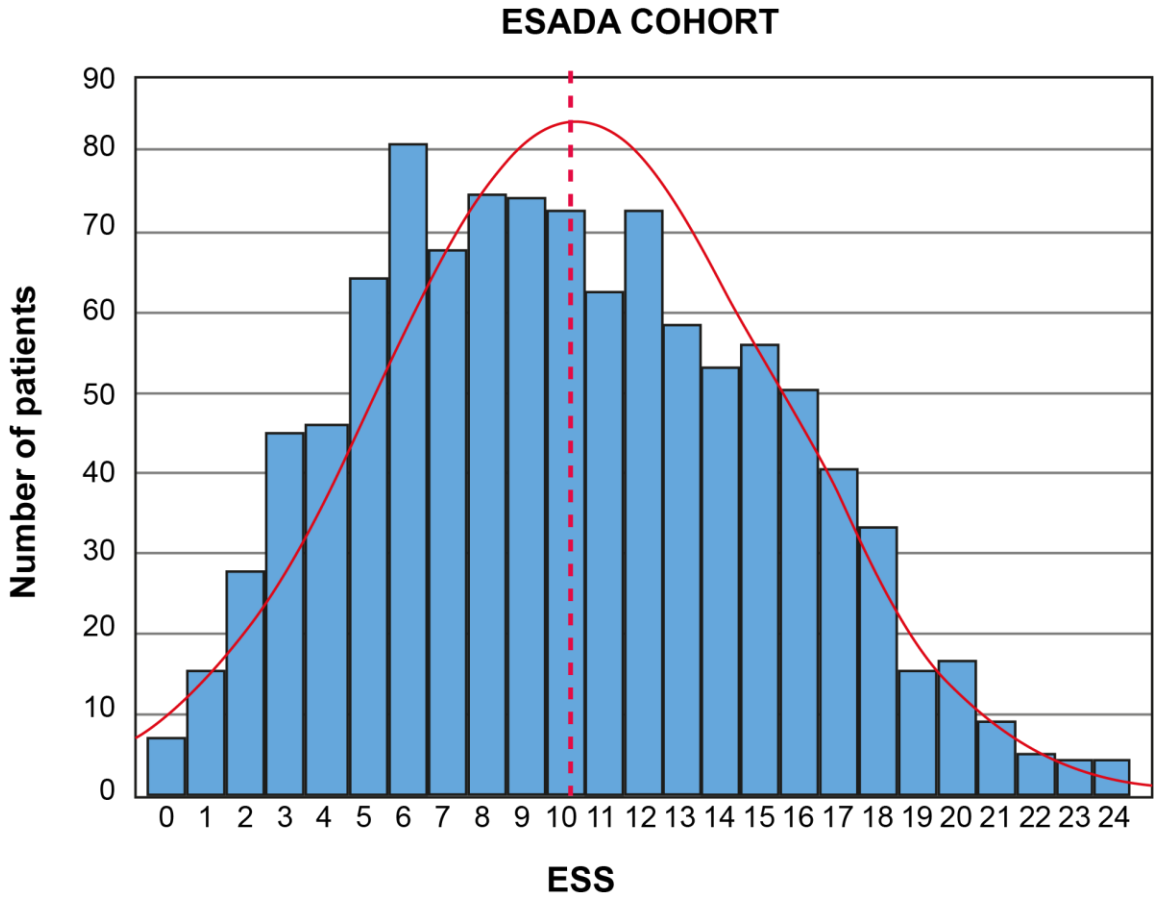
How big is the problem of EDS in OSA ?



ESS>10 before CPAP: 479/1050 (=46%)

Verbraecken J. J Sleep Res 2014.

OSA treatments: guidelines

1- **Lifestyle changes** such as losing weight, positional therapy, avoidance of alcohol & sedatives

2- **CPAP: continuous positive airway pressure** or a similar machine that uses positive airway pressure to help breathe

3- **Oral breathing devices (or OA** = oral appliance)**:** Mandibular Advanced Orthosis (MAO) and tongue-retaining devices (TRD) or other devices (such as nasal dilators)

4- **Surgery (rare)**: uvulopalatopharyngoplasty, MMA = maxillomandibular advancement

5- Very rarely Hypoglossal (XII) nerve stimulation

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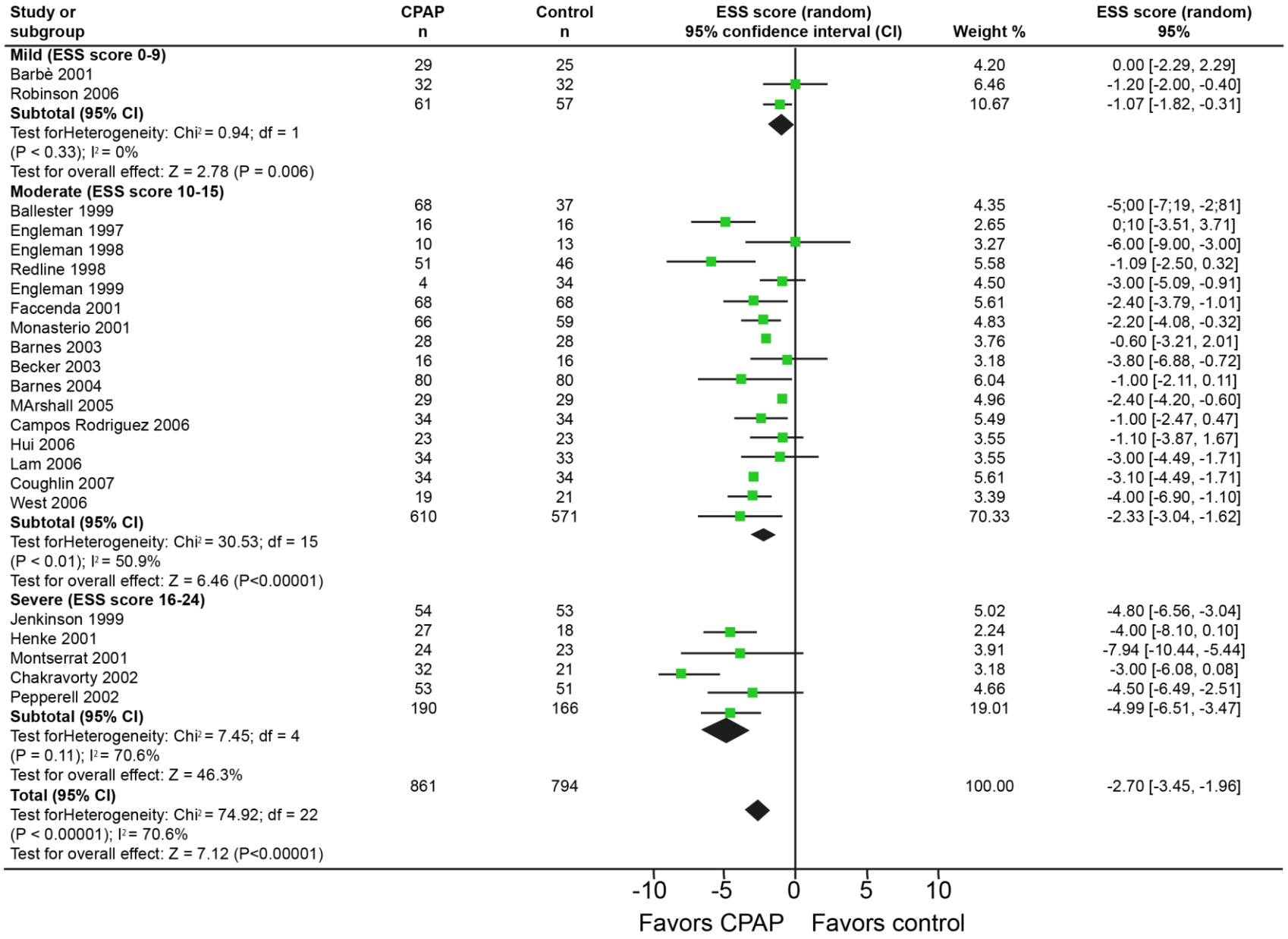
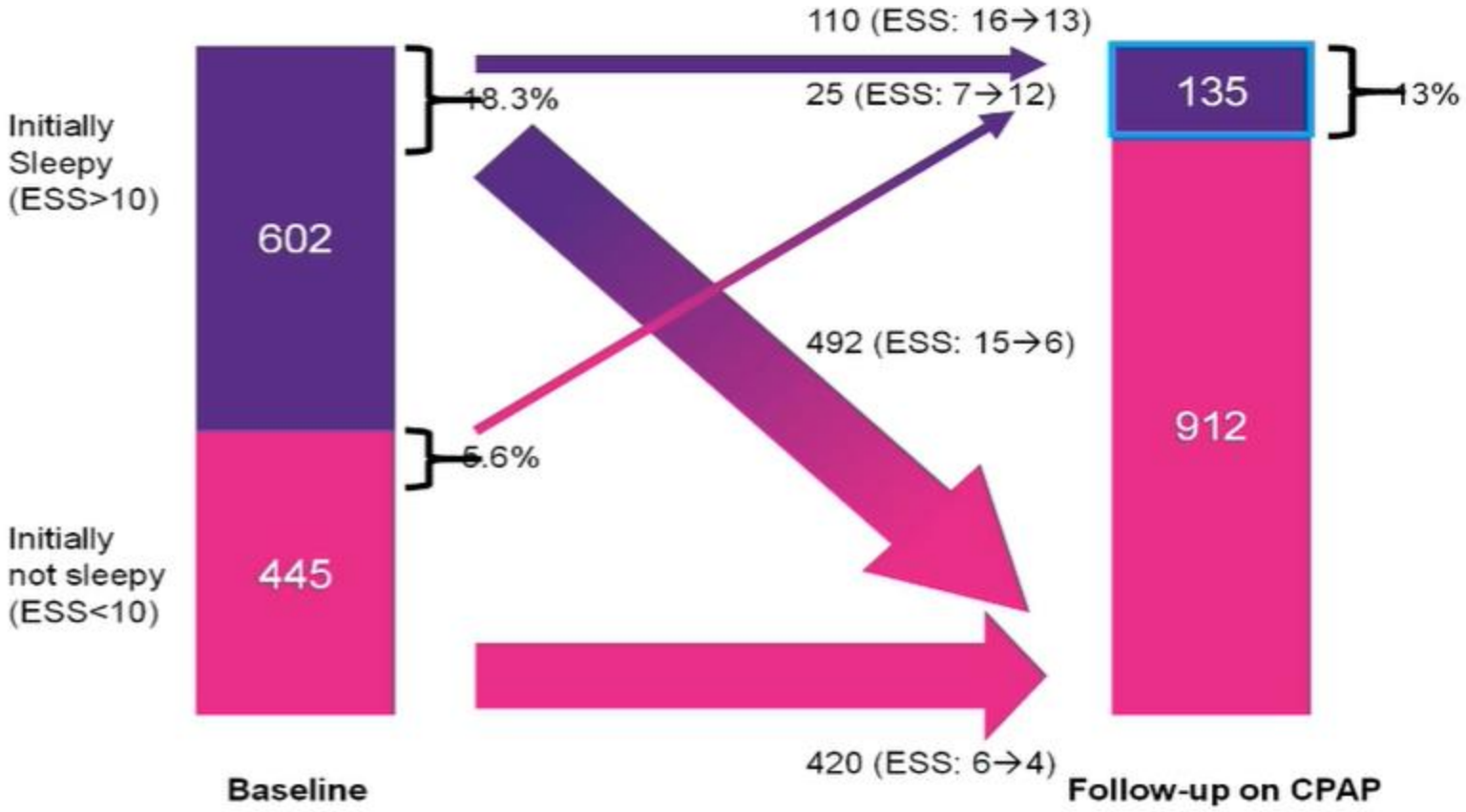
Epstein LJ et al Clinical guideline for the evaluation, management and long term care of obtsructuve apnea in adults
J Clin Sleep Med 2009, 5(3): 263-276
Others

CPAP decreases EDS in OSA



McDaid C, et al. Sleep Med Rev 2009.

Residual excessive sleepiness under CPAP



Epworth Sleepiness Scale score ≥ 11 in a context of a well managed OSA treatment

Gasa M J Sleep Res 2013; 22:389-97

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CPAP-resistant syndrome

	RES+(n = 135, 13%)	*RES−(n = 912, 87%)*	*P-value*
Anthropometrics			
Age (years)	56.12 ± 11.55	57.56 ± 12.57	0.0909
Male/female (%)	60/40	71/29	**<0.01**
BMI (kg m^{-2})	31.14 ± 6.11	32.08 ± 6.65	NS
Subjective scale values at baseline			
ESS	14.17 ± 4.65	10.91V5.06	**<0.0001**
Depression	4.14 ± 3.91	3.08 ± 3.35	**<0.01**
Fatigue	14.50 ± 9.09	11.18 ± 7.91	**<0.0001**
General health	5.22 ± 2.39	5.98 ± 2.45	**<0.001**
Co-morbidities			
Hypertension (%)	45.19	50.55	NS
Arrhythmia (%)	8.15	8.44	NS
Stroke (%)	1.48	3.18	NS
Heart failure (%)	2.96	1.71	NS
Peripheral arterial disease (%)	2.22	1.97	NS
Ischaemic cardiomyopathy (%)	6.67	7.68	NS
Diabetes (%)	14.1	17.4	NS
PLM treatment (%)	0.74	0.33	NS
OSA severity			
Baseline AHI (events h^{-1})	40.60 ± 20.61	42.95 ± 19.45	**<0.05**
Oxygen desaturation index (nb h^{-1})	31.71 ± 23.22	34.99 ± 22.87	NS

Gasa M J Sleep Res 2013; 22:389-97

Aspects of CPAP management

1.Getting the patient onto a machine

2.Getting the patient to use it

3.Getting the patient to *continue* to use it

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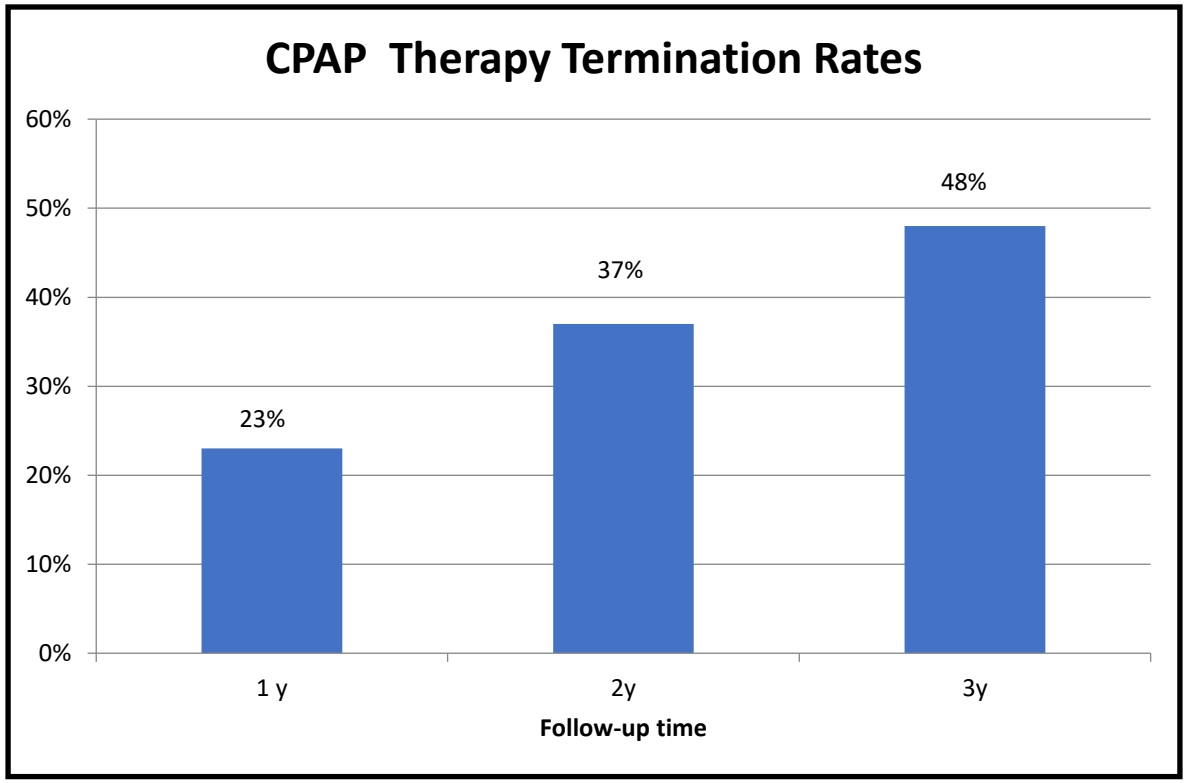
Untreated OSA (after diagnosis): extent of the problem?

Rate of CPAP Stop in real practice after 3 years



Pépin JL, et al. J Clin Med 2021.

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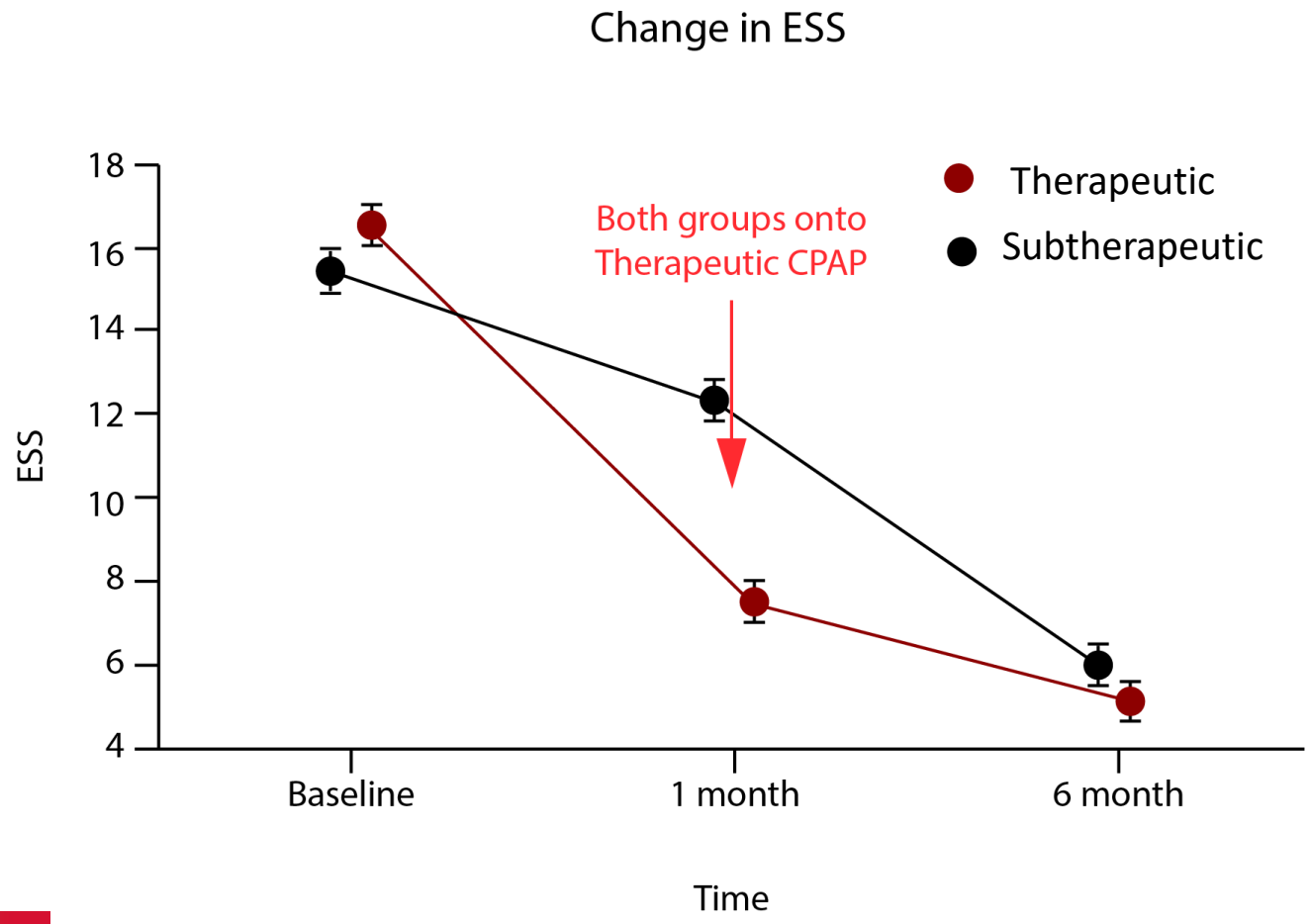
Change in ESS with (sub)therapeutic CPAP



- 107 patients with symptomatic OSA (≥10/hr AHI ; ESS≥10) randomised to either therapeutic or sub-therapeutic nasal CPAP for 1 month
- Both groups on therapeutic CPAP for a further 5 months

Jenkinson C, et al. Lancet 1999.

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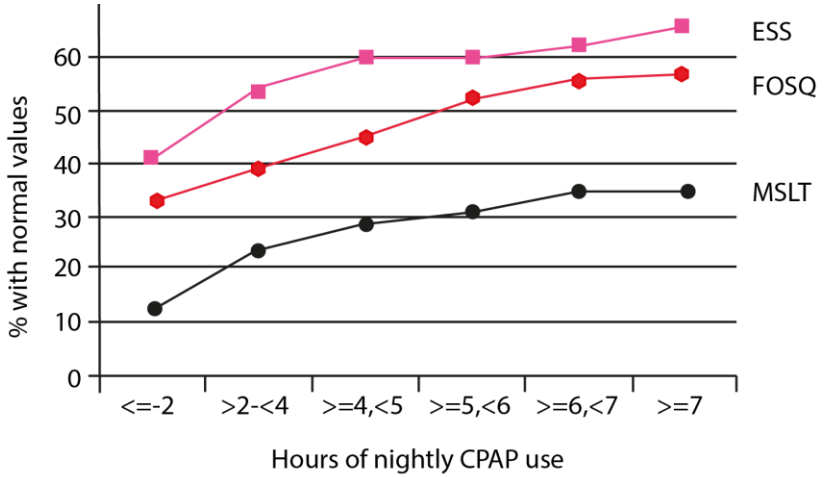
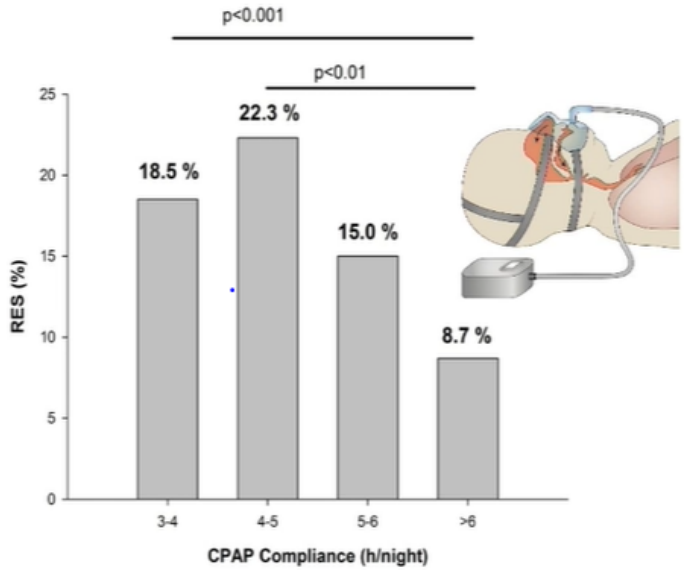
Change in ESS with hours of nightly use of CPAP





- Weaver et al, 2007: about 20% of the patients remained sleepy after 3 months of CPAP use for 8 h/night
- Pepin et al, 2009: about 6% of CPAP-treated OSA patients remained sleepy after CPAP for 1 year
- Residual sleepiness on CPAP ranged between 13% and 40% in other studies (Antic et al, 2011; Gasa et al, 2013; Budhiraja et al, 2017)

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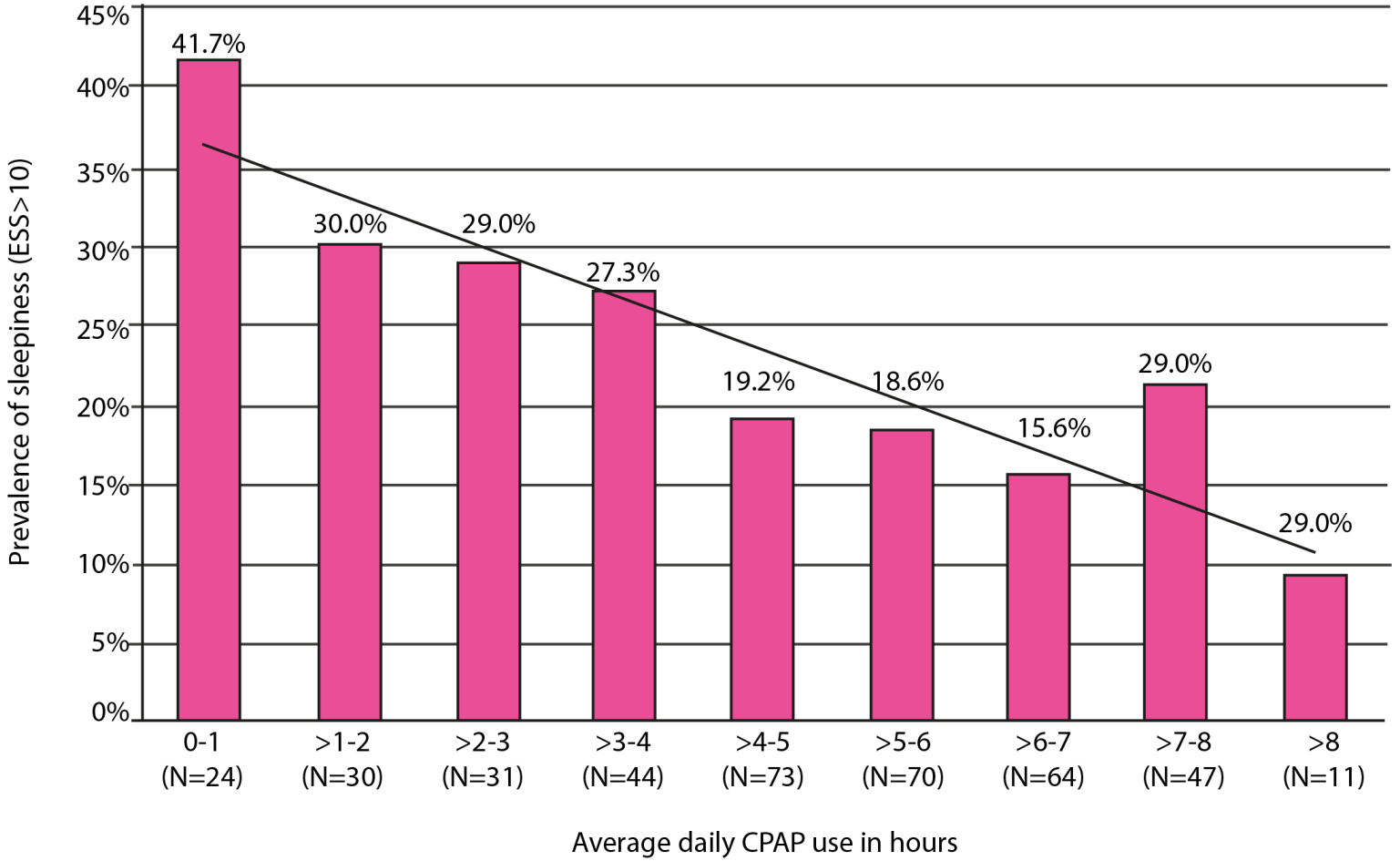
Prevalence of EDS post CPAP treatment



Weak relationship with baseline AHI or ESS

Javaheri S, et al. Chest 2020.

Residual EDS post CPAP treatment: ESADA cohort

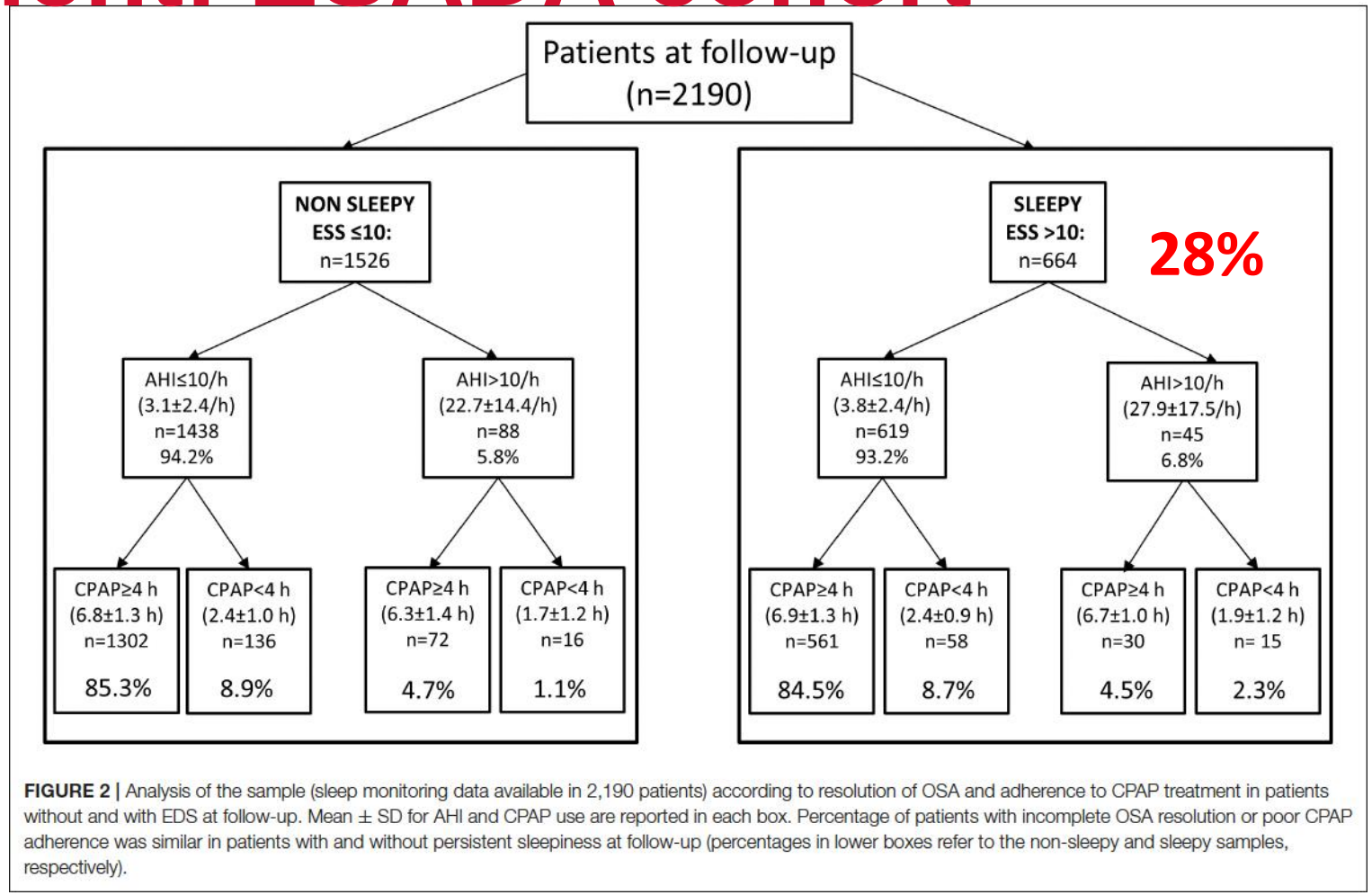
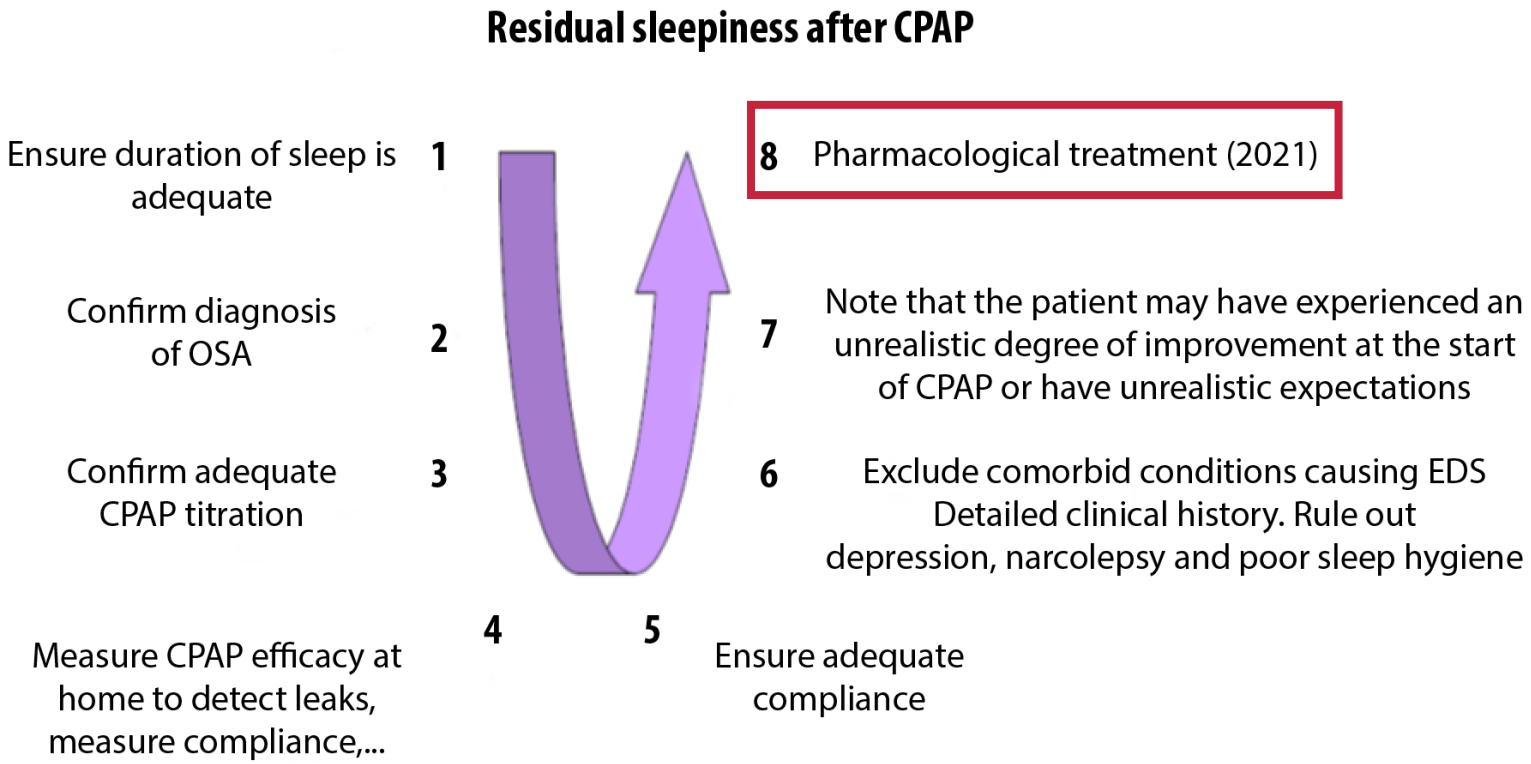


FIGURE 2 | Analysis of the sample (sleep monitoring data available in 2,190 patients) according to resolution of OSA and adherence to CPAP treatment in patients without and with EDS at follow-up. Mean ± SD for AHI and CPAP use are reported in each box. Percentage of patients with incomplete OSA resolution or poor CPAP adherence was similar in patients with and without persistent sleepiness at follow-up (percentages in lower boxes refer to the non-sleepy and sleepy samples, respectively).

Bonsignore M, et al. Frontiers in Neurology 2021.

Management of residual EDS

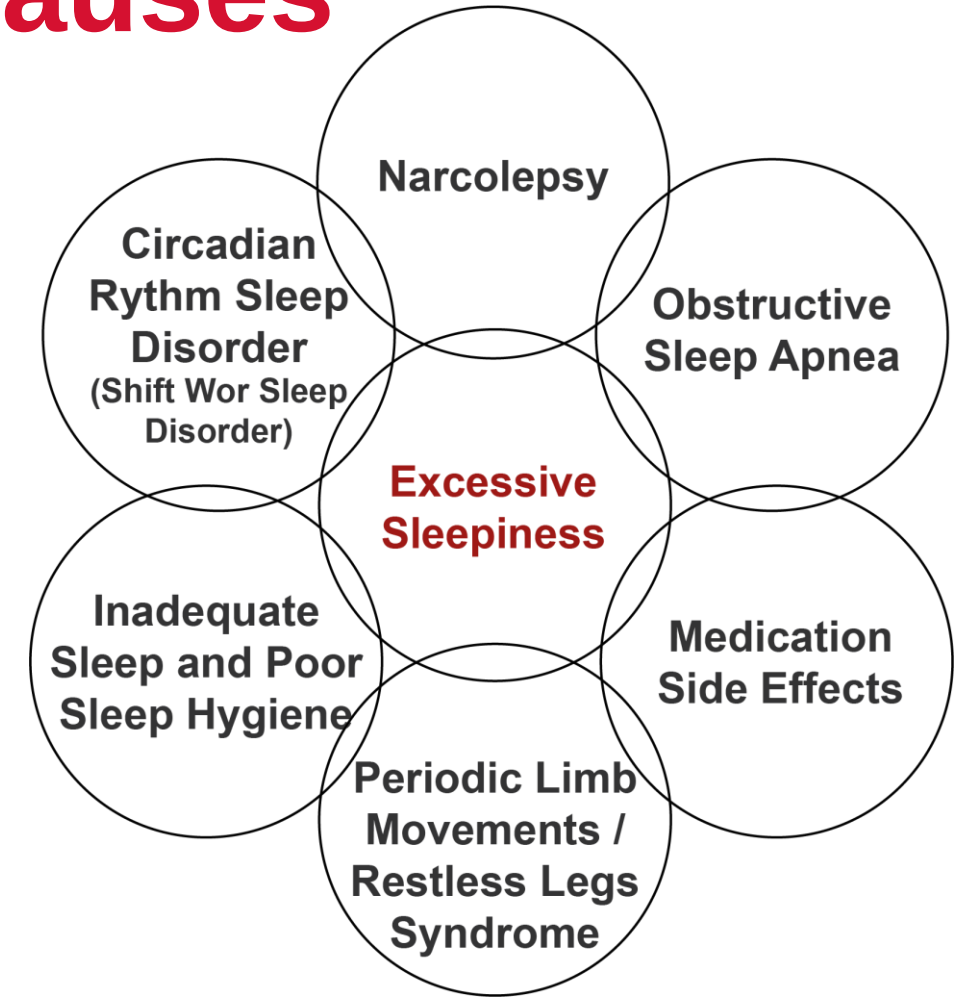


Hypotiroidism, circadian rhythm disorders, psychiatric a illness, chronic medical condition, medications, illicit drugs use

Suggested procedure to be followed in patients with persistent sleepiness after CPAP

Santamaria J, et al. Sleep Medicine Reviews 2007.

OSA + somnolence can be due to several causes



Schwartz JRL. J Clin Psychiatry 2004.

Predictors of EDS in general population

- 16.583 persons Pen State Cohort
- 1741 healthy persons (20-100yrs) uderwent PSG to assess association between EDS and OSA
- Depression is the most significant risk factor for EDS in general population; this association is the strongest in younger people and decreases with age

Predictors of sleepiness in the general population

Bixler et al. J Clin Endocrinol Metab 2005; 90: 4510-4515

Parameter	ES	*P*	OR	
Depression	10.6	<0.001	6.85	+
Log BMI (kg/m^2)	4.3	<0.001		
+1 SD			1.45	+
+2 SD			2.10	
Age	3.6	<0.001		
+1 SD			0.61	-
+2 SD			0.38	
Typical sleep duration	3.2	0.001		
+1 SD			0.76	-
+2 SD			0.58	
Diabetes (glucose > 126)	2.3	0.019	1.87	+
Smoke	1.9	0.060	1.53	
OHI > 15	1.2	0.255	1.70	

ES, Effect size.

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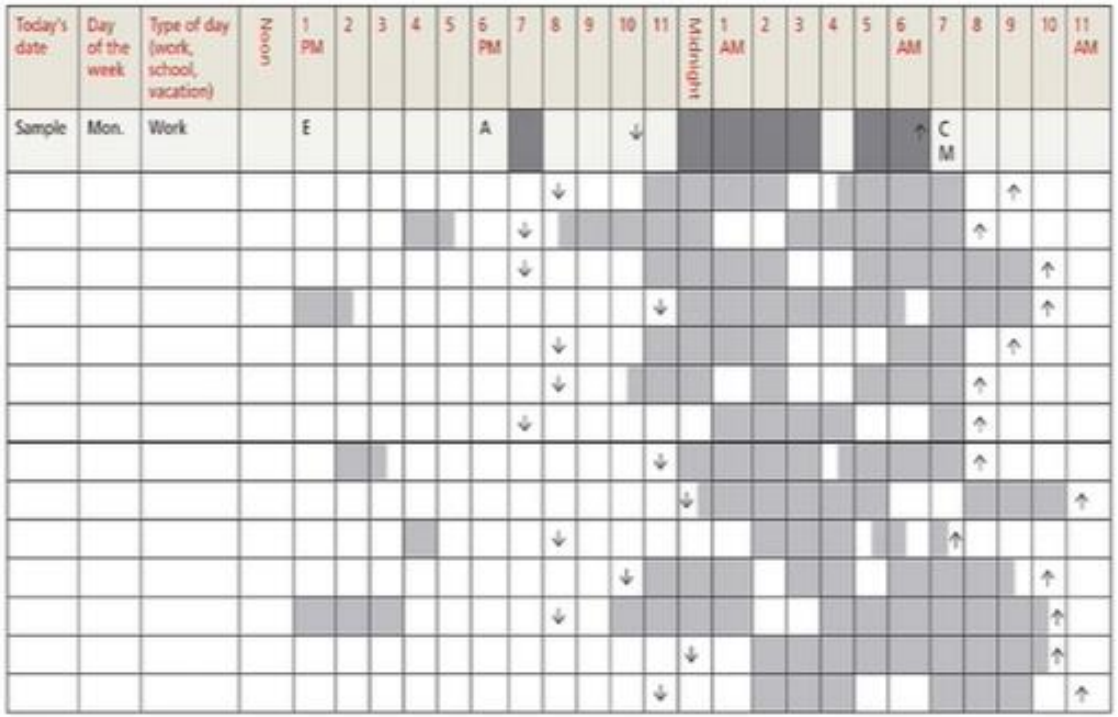
Elimination of competing etiologies of EDS



Medications
Antihistamines
Anxiolytics
Antidepressants
Anticonvulsants
Beta blockers
Mood stabilizers
Antipsychotics
Opioids
Sedative-hypnotics

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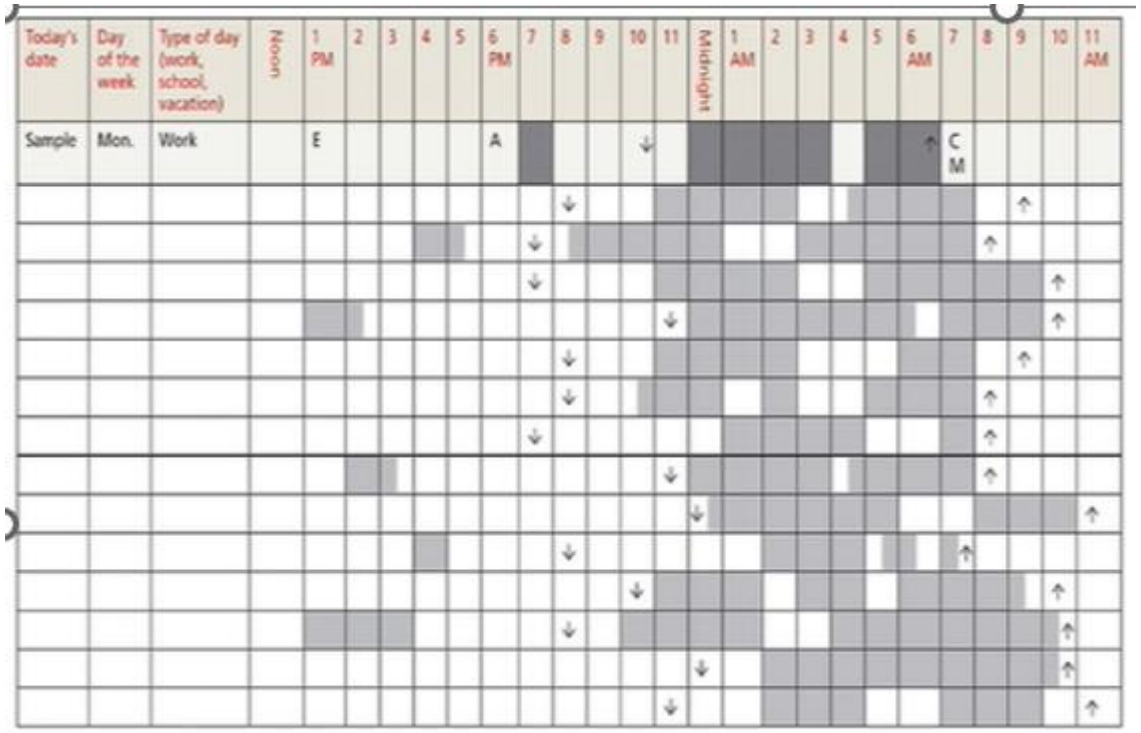
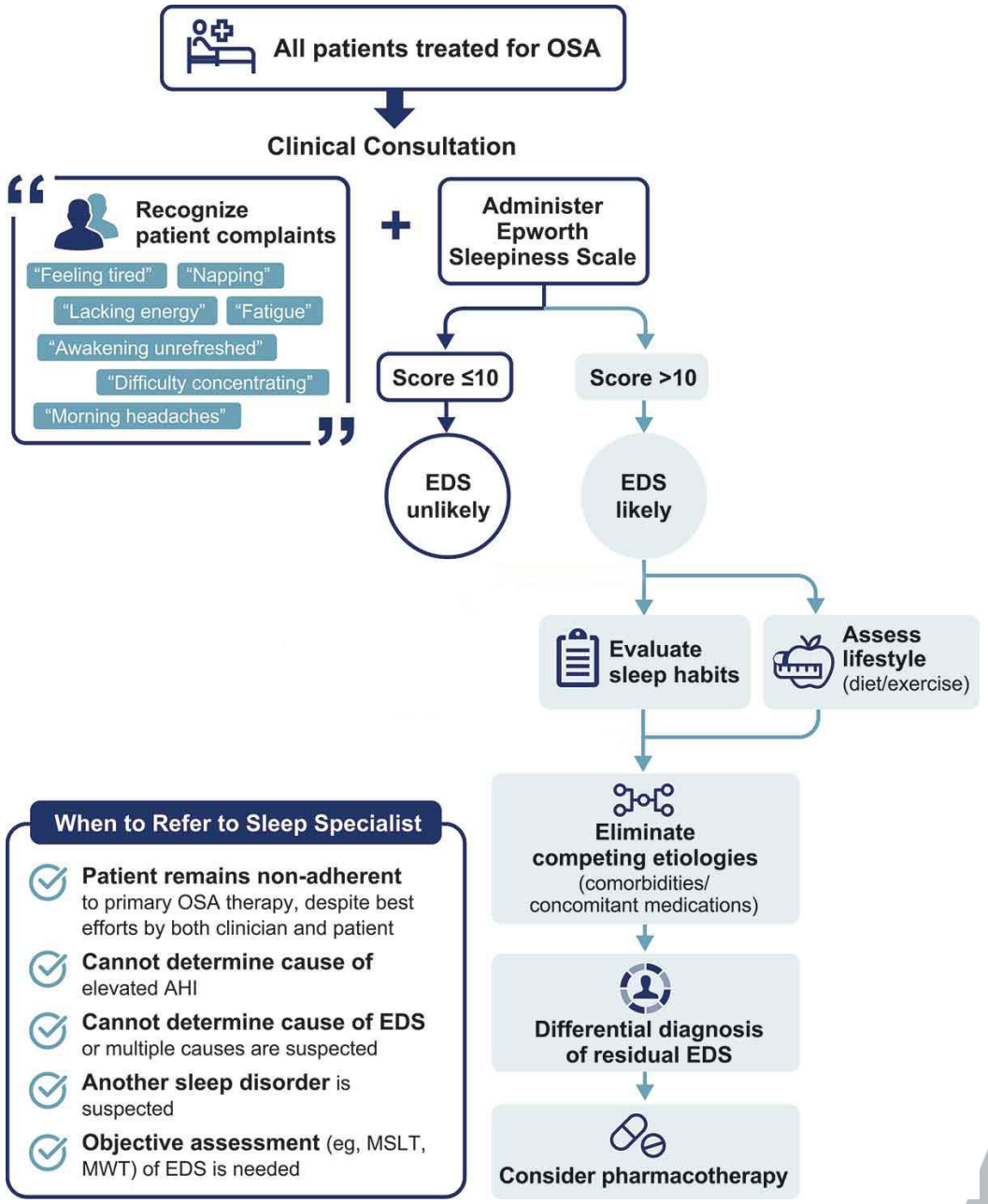
Elimination of competing etiologies of EDS

Suboptimal treatment of OSA	**Inadequate adherence, non-normalisation of breathing (AHI), inappropriate ventilatory support**
Lifestyle factors	Insufficient sleep, diet, exercise
Sleep disorders	Narcolepsy, idiopathic hypersomnie, Kleine-Levin syndrome, circadian rhythm sleep-wake disorders, restless legs syndrome, periodic limb movement disorder
Psychiatric disorders	Depression, anxiety, substance use
Medical disorders	Diabetes, hypothyroidism, renal disease, hepatic encephalopathy, cancer, inflammatory conditions, encephalitis, neurogenerative disorders, head trauma, stroke
Medications	Alpha-2 antagonists, antihistamines, anxiolytics, antidepressants, anticonvulsants, antidiarrhea agents, antiemetics, antimuscarinics/antispasmodics, antiparkinsonian agents, antipsychotics, antitussives, barbiturates, benzodiazepines, beta-blockers, genito-urinary smooth muscle relaxants, mood stabilizers, opioids, sedative-hypnotics, skeletal muscle relaxants

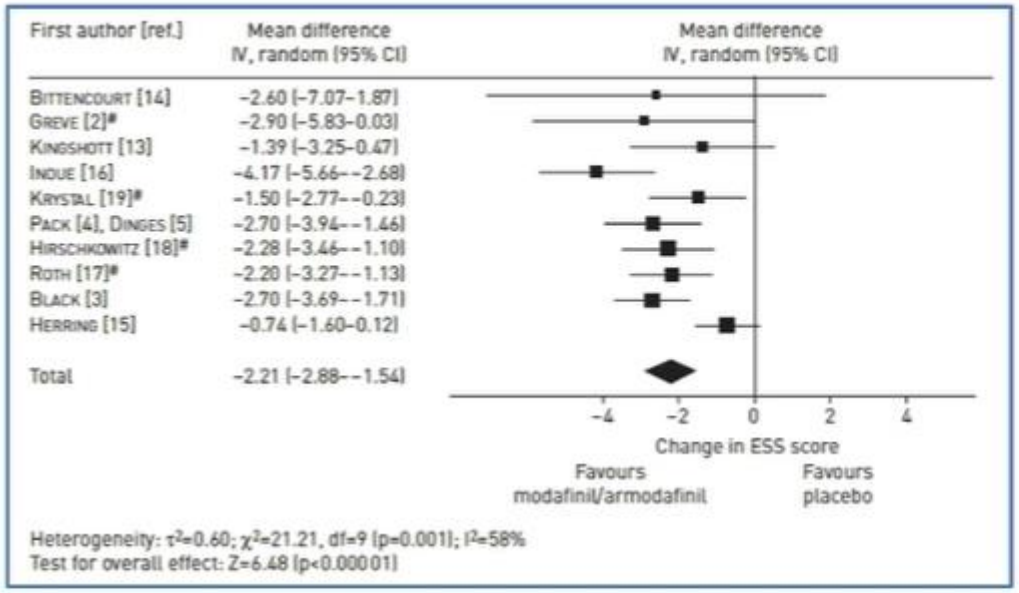


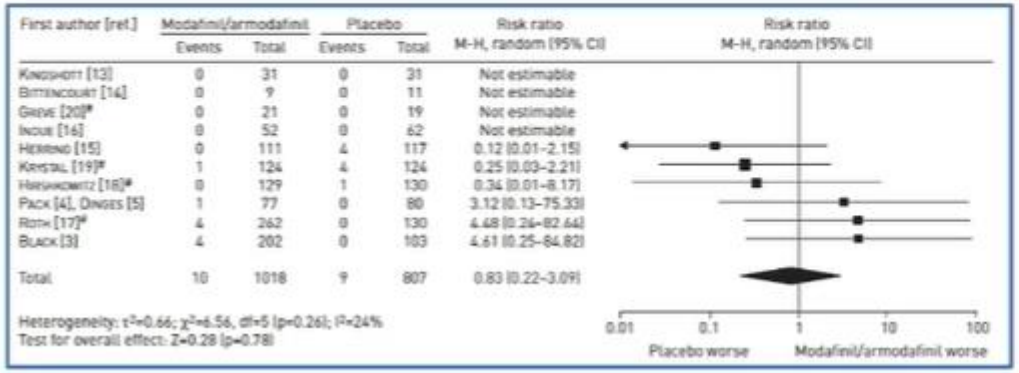
How to manage EDS in a specialist sleep clinic?



Rosenberg R, et al. Postgrad Med 2021.

Pharmacotherapy for EDS (1)





Modafinil/armodafinil in OSA: a systematic review and meta-analysis

- Improved RES (Epworth: -2 points) and objective tests (MWT: +3 min)
- In 2011 EMA withdrew both drugs from the market because of side effects

Chapman et al. Eur Respir J 2016

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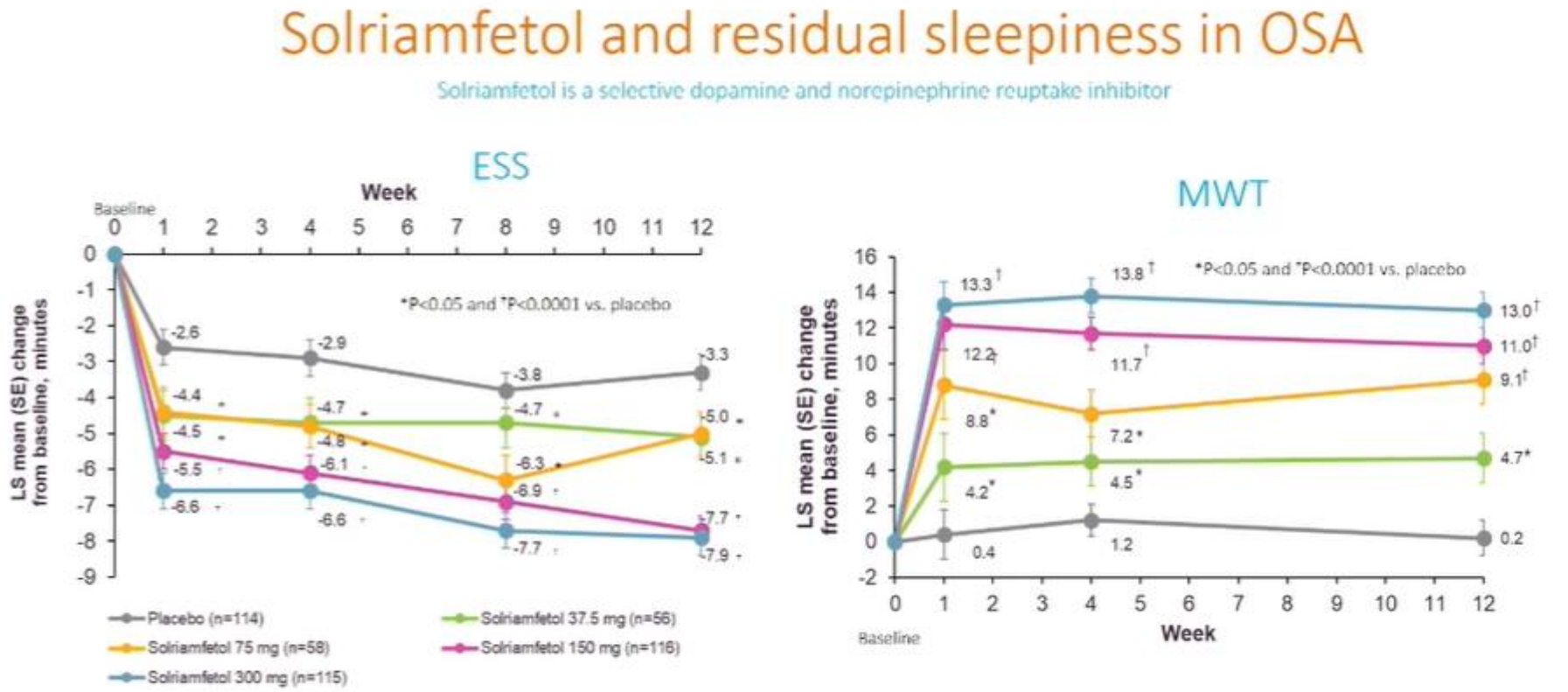
Pharmacotherapy for EDS (2)



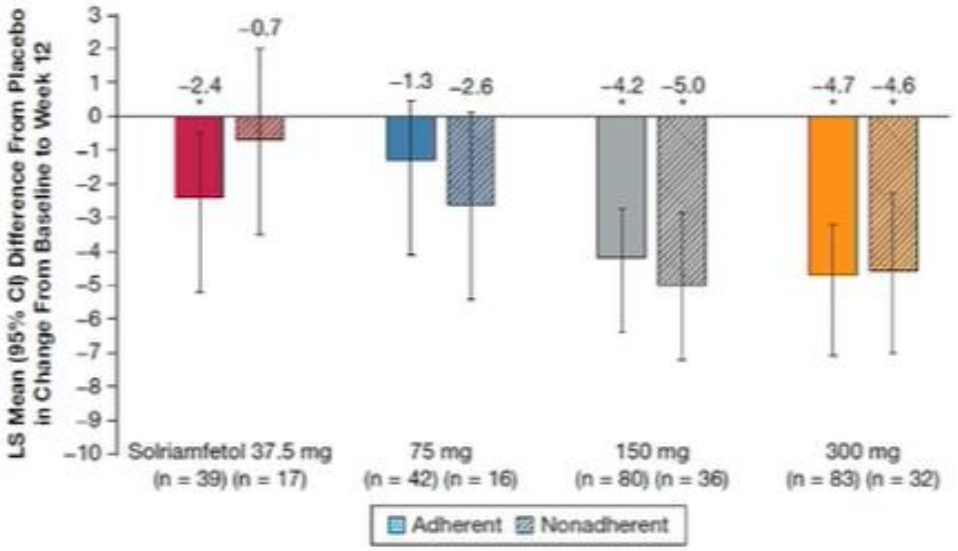
The highest dose of solriamfetol (300mg) causes an average increase of 2.5 mmHg in systolic blood pressure and 1.5 mmHg in diastolic blood pressure.

Schweitzer PK et al, 2019

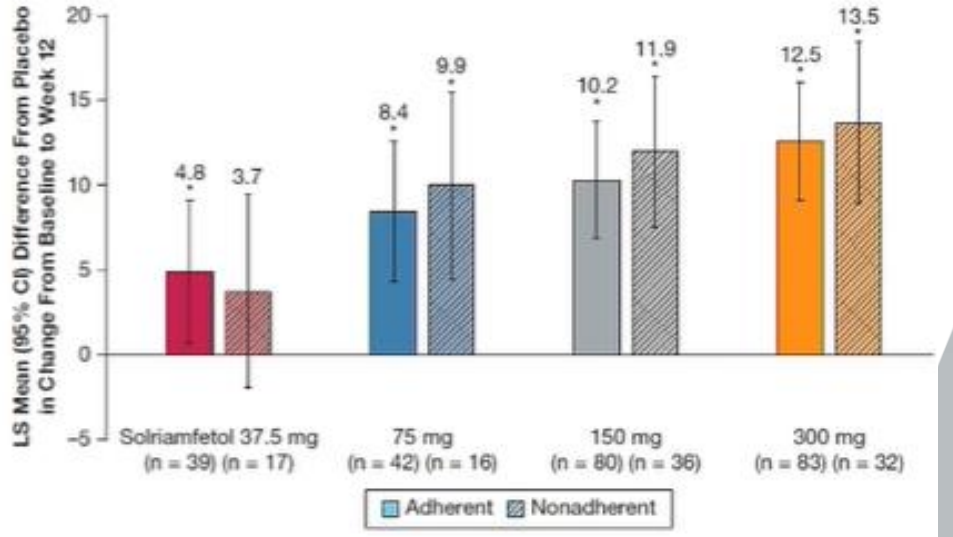
Pharmacotherapy for EDS (3)

Solriamfetol and residual sleepiness in CPAP non-adherent patients

ESS



MWT

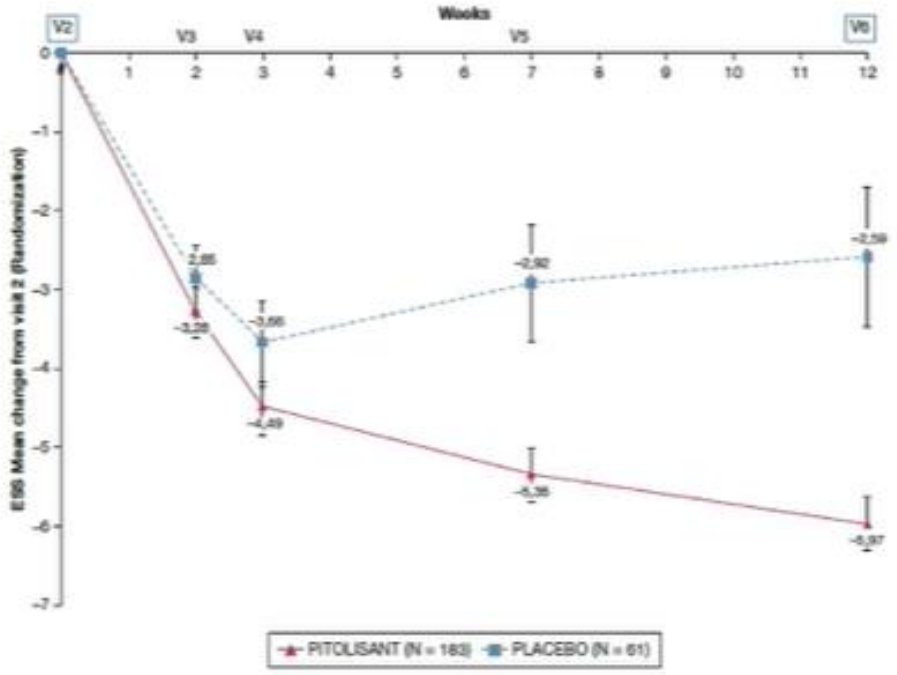


Schweitzer PK et al, 2021

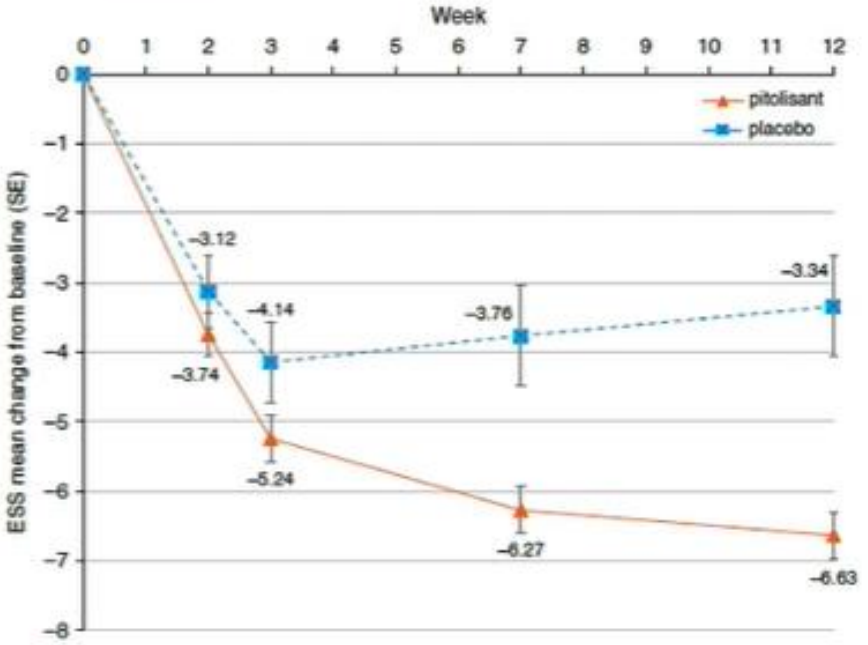
Pharmacotherapy for EDS (4)

Pitolisant for residual EDS in OSA

HAROSA I- Patients with residual EDS and good adherence to CPAP (Pepin et al, Chest 2021)



HAROSA II: Patients with EDS who refused CPAP (Dauvilliers et al, AJRCCM 2020)



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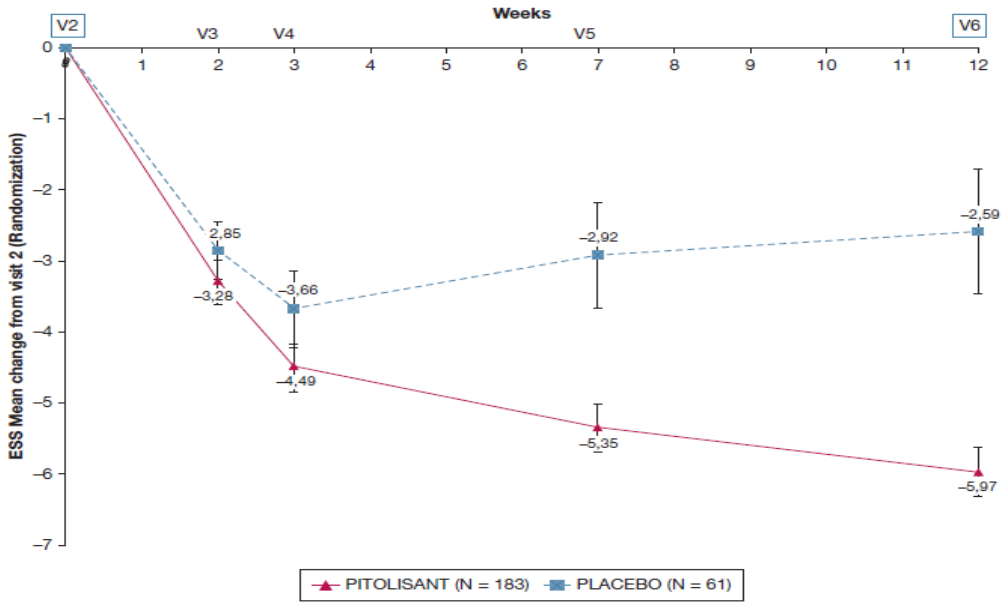
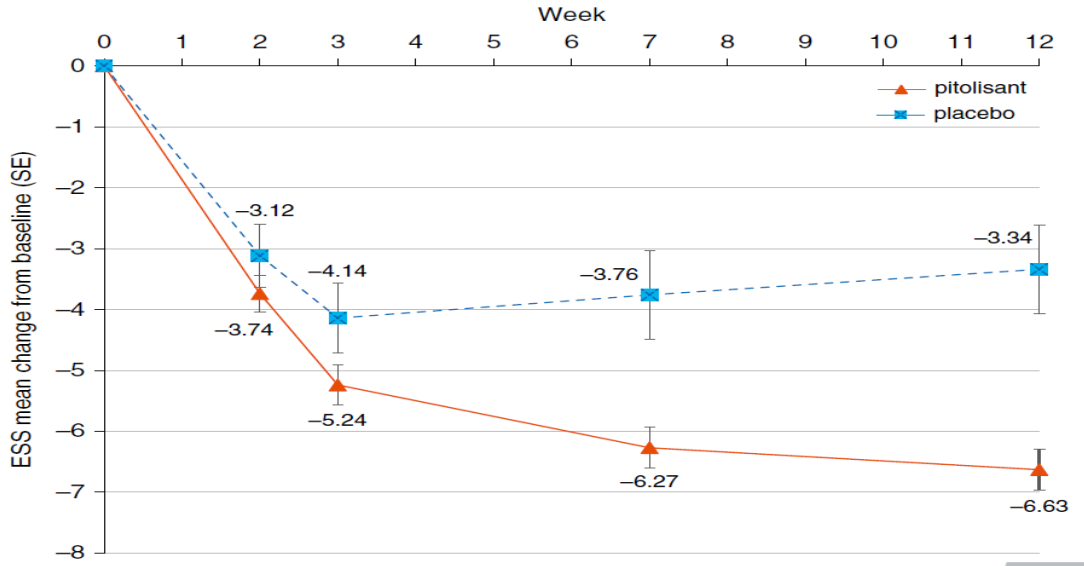
Pharmacotherapy for EDS (4)

HAROSA I- Patients with residual EDS and good adherence to CPAP (Pepin et al, Chest 2021)



ESS mean change (pitolisant-placebo):
-2.6 (CI 95%[-3.9;-1.4]; p< 0.001)

HAROSA II: Patients with EDS who refused CPAP (Dauvilliers et al, AJRCCM 2020)



Pitolisant 201 pts – Placebo 67
ESS mean change (pitolisant-placebo) :
-2.8 (95% CI: [-4.0;-1,5]; p<0.001)

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What with sleepy OSA patients refusing CPAP ?

PRO waking agents

- Major improvement in symptoms
- No problem in patients accepting CPAP
- In patients refusing CPAP, non-pharmacological (diet, naps, ..) or non-CPAP treatment (MAD, positional therapy, ...) may help reduce EDS
- Continued follow up gives a chance to challenge the patient to accept CPAP therapy

CON waking agents

- Waking agent is a symptomatic, not a primary OSA treatment
- With the waking agent, the patient will never take again the CPAP or accept it
- Treatment with WPA should be initiated at least after 3 months of CPAP (Bonsignore et al 2021)
- Need to convince patients to be treated with CPAP or MAD

From Bonsignore ML – ESRS 2022

Summary : EDS in OSA

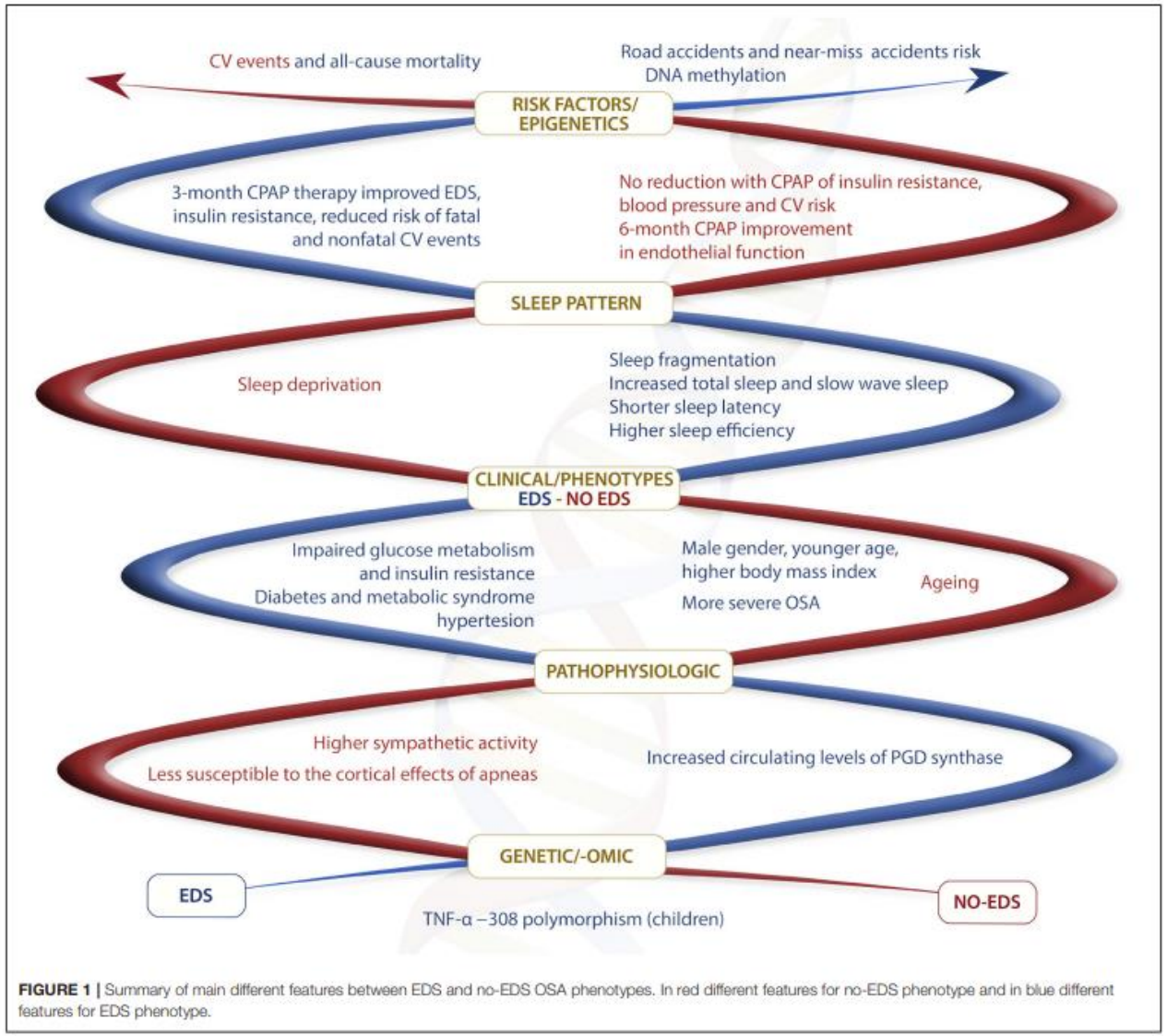

FIGURE 1 | Summary of main different features between EDS and no-EDS OSA phenotypes. In red different features for no-EDS phenotype and in blue different features for EDS phenotype.

Garbarino et al, 2019

- **Common - but not universal - symptom.**
- **Predictors: Male gender, younger age, high BMI.**
- **Causes: Hypoxemia and sleep fragmentation.**
- **Association with**
  - **Incident cardiovascular disease.**
  - **All-cause mortality.**
  - **Metabolic syndrome and diabetes.**

- **CPAP effects on consequences in EDS-OSA,**
  - **but inconsistent in no-EDS pts.**
- **No-EDS patients**
  - **Less susceptible to cortical apnea effects.**

- **Single disease with different phenotypes?**
- **Different diseases with different**
  - **Genetic/epigenetic determinants?**
  - **Pathogenic mechanisms?**
  - **Prognosis?**

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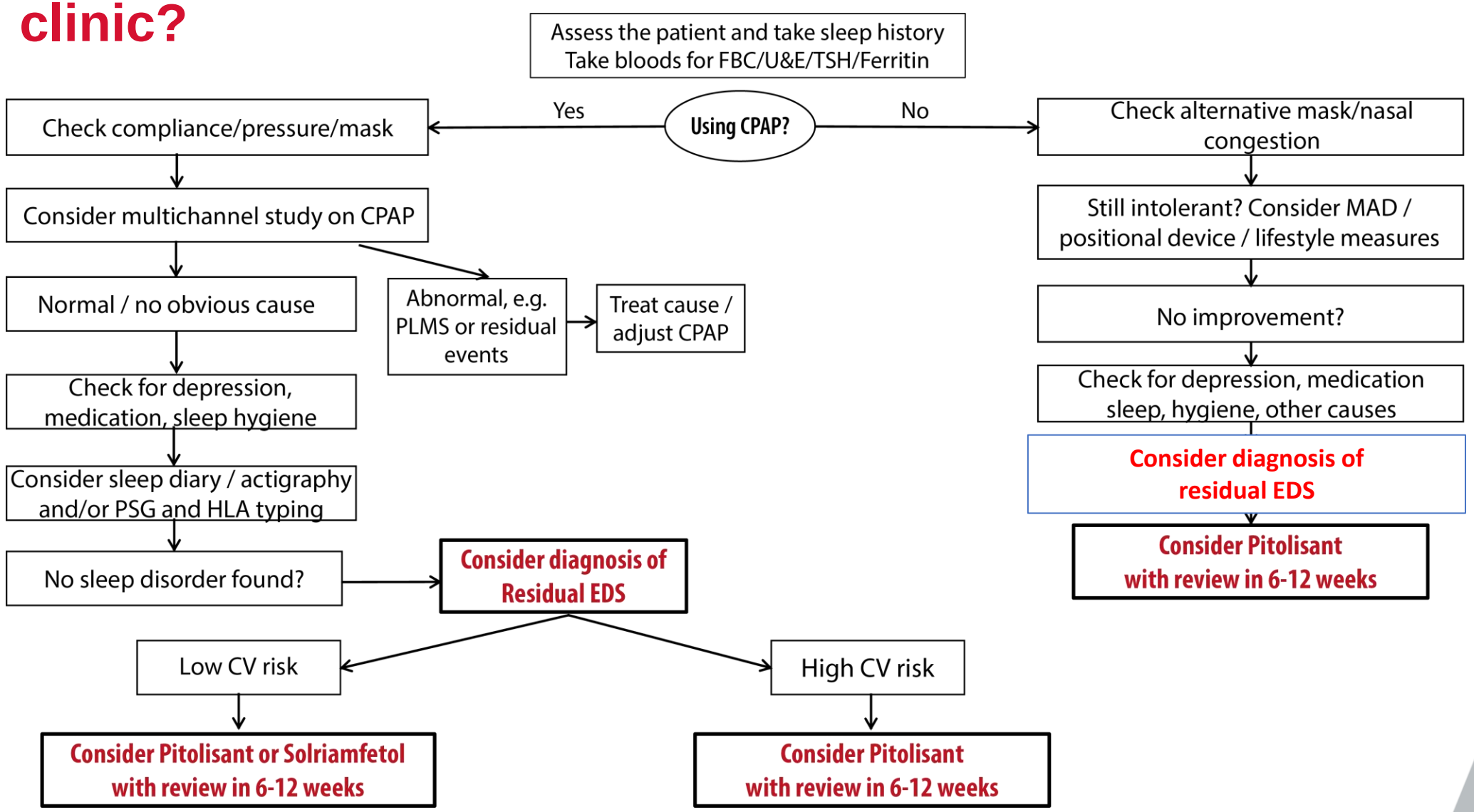
Summary : How to manage EDS in a specialist sleep clinic?



Craig S, et al. 2022

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