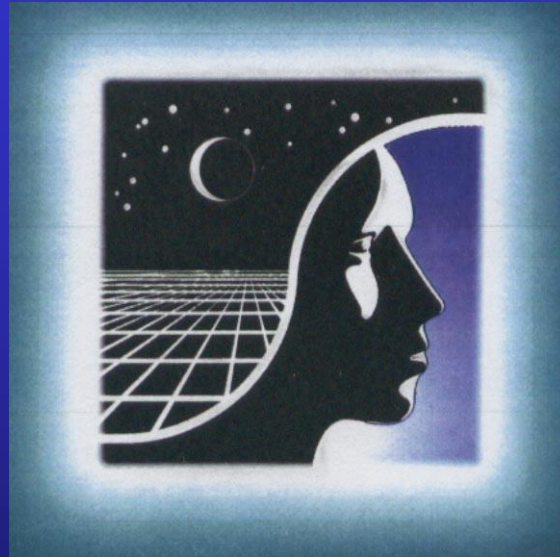


INTÉRÊT DE LA DÉTERMINATION DES PHÉNOTYPES DANS LE SYNDROME D'APNÉE OBSTRUCTIVE DU SOMMEIL (SAOS)



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INTRODUCTION

WHAT DO WE KNOW ?

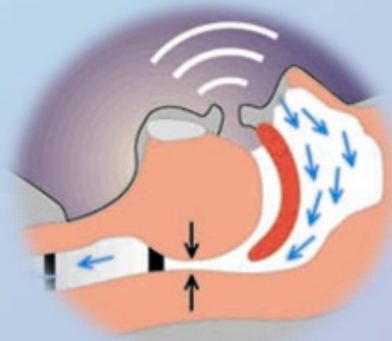
- OSA is a highly prevalent disorder characterized by repetitive obstruction of the upper airway during sleep which leads to intra-thoracic pressure swings, sleep fragmentation and intermittent hypoxia.
- Providing a mechanistic framework for the association of OSA with a range of clinical morbidity including metabolic and Cardio Vascular disease , cognitive impairment, and increased rates of mortality.
- Ongoing epidemiological studies suggest prevalence rates have increased over the last 20 years, with recent study (HypnoLaus) showing that it affects up to 27% of women and 43% of men aged 50-70 years and 9% in women and 26% in men in the 30-49 years-old category. Largely attributed to increasing obesity rates and aging, two major risk factors for OSA.

Mechanism OF OBSTRUCTIVE SLEEP APNEA

Snores

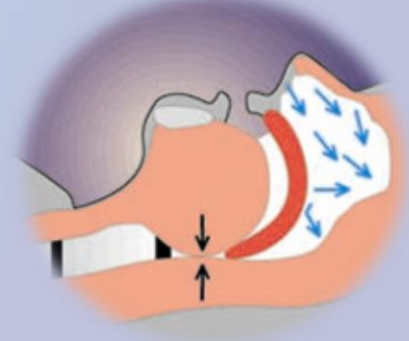


Normal



Partial Collapse

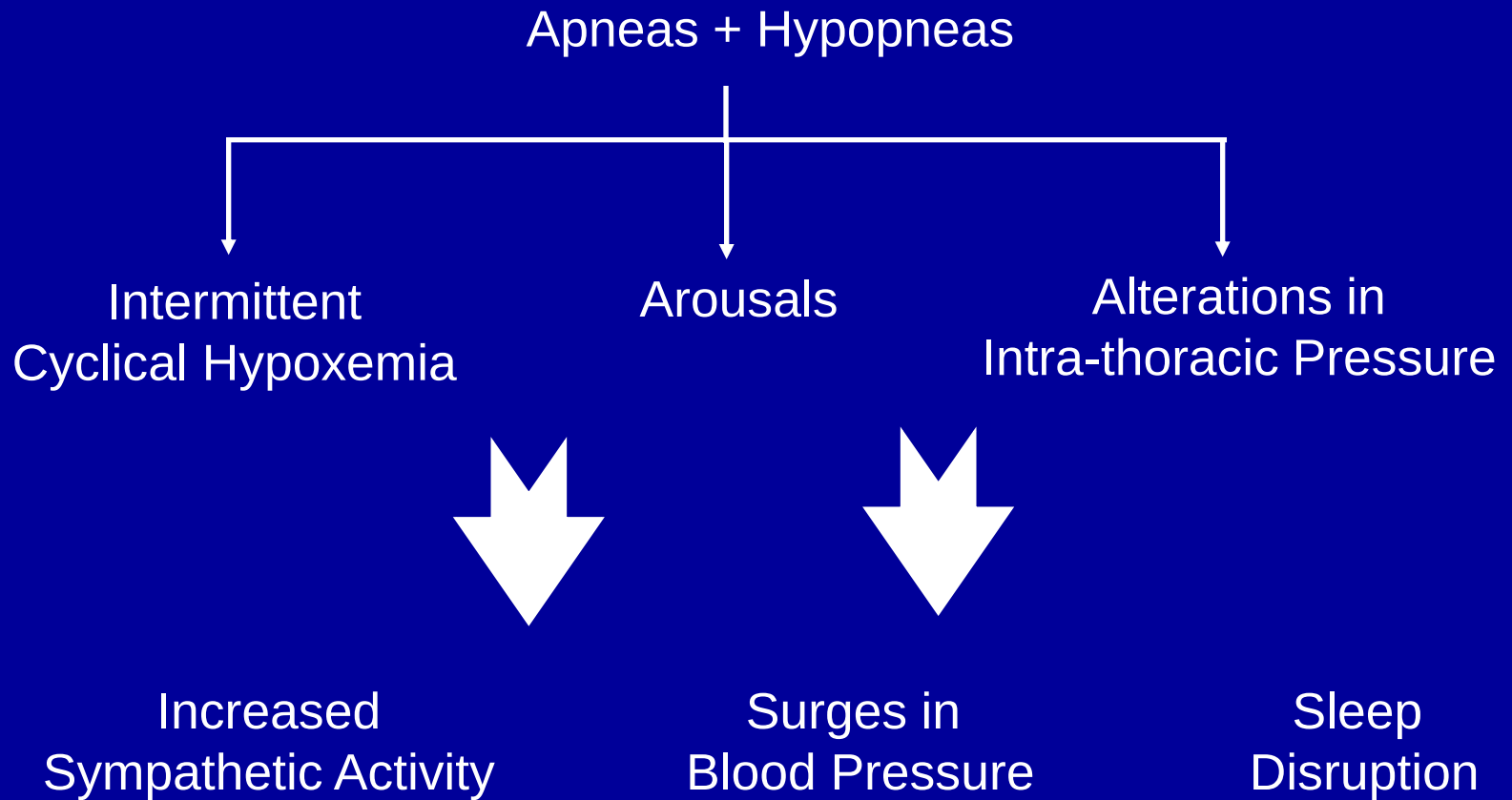
Hypopneas



Complete Collapse

Apneas

Acute Pathophysiologic Consequences



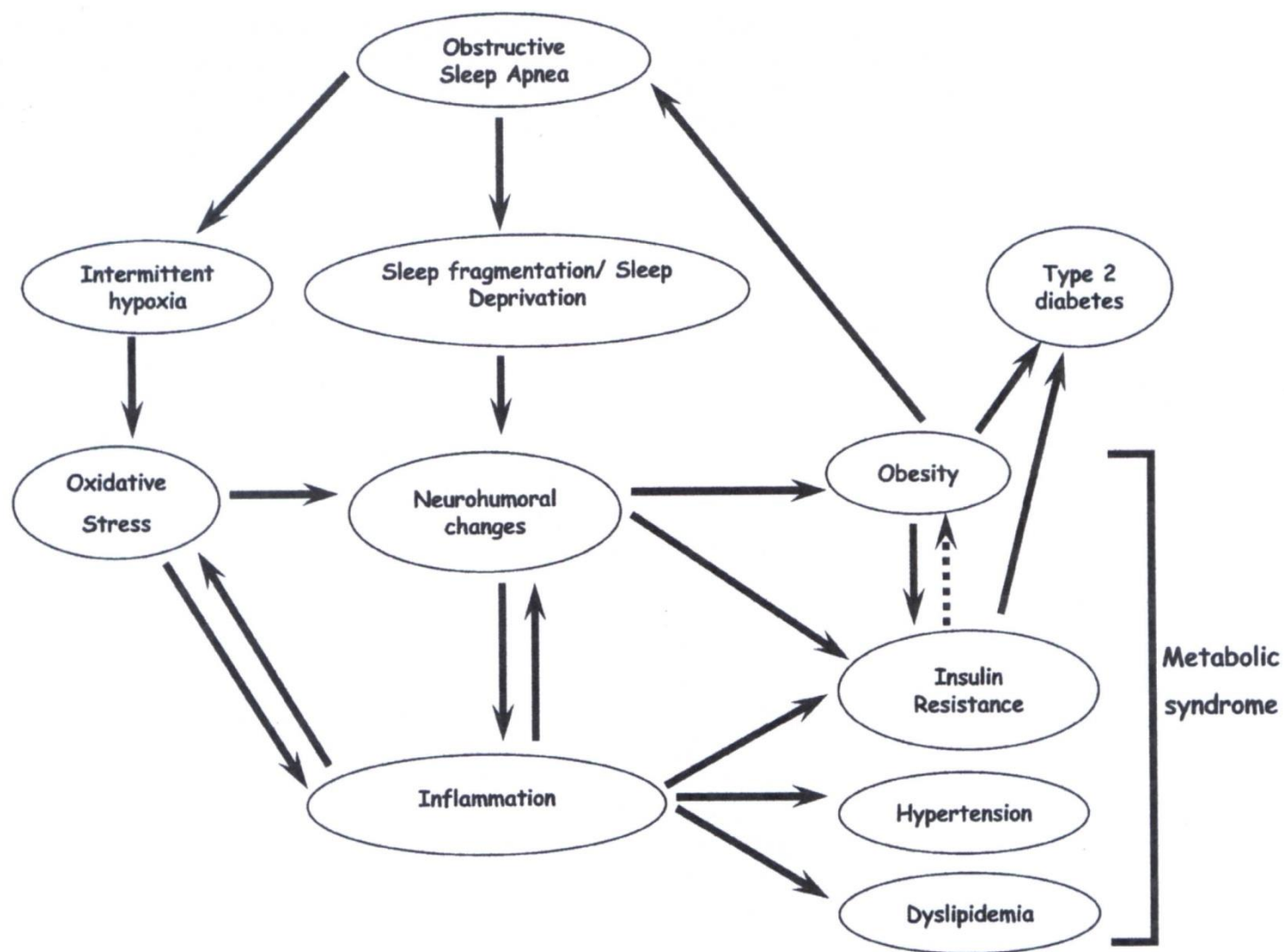


Figure 1. Possible mechanistic links between obstructive sleep apnea, metabolic syndrome, and type 2 diabetes.

REMINDER

UPPER AIRWAY PATENCY.

- The patency of the upper airway (UA) is dependent on:
 - The upper airway size, soft tissue volume and craniofacial anatomy: Macroglossia, retrognathism, obesity, adenotonsillar hypertrophy....
 - Extraluminal pressure (adipose tissue)
 - and compliance.
 - Reflex activation of the upper airway **dilator muscles** provoked by negative intra-pharyngeal pressures during inspiration.
 - Recent evidence has demonstrated that a fluid shift from the lower limbs to the UA takes place in OSA contributing to UA edema.
- UA obstruction involves **MORE THAN ONE SPECIFIC SITE OF THE UA** in the majority of OSA patients.

REMINDER

- **DURING SLEEP** there is an increased susceptibility of the upper airway to collapse because:
 - There is a **normal** decrease of:
 - Neuronal excitatory input to pharyngeal dilator muscles,
 - & Reflex activation of the upper airway **dilator muscles** provoked by negative intra-pharyngeal pressures during inspiration is substantially diminished during sleep.
 - IN OSA it is abnormally reduced resulting in hypotonic pharyngeal muscles and increased risk of pharyngeal collapse.

INTRODUCTION

CPAP

- Current available treatments have been shown to improve both the physiologic and the metabolic consequences of OSA and possibly even increase survival in some cases.
- However in many cases the current treatments are:
 - Either poorly tolerated (both initially and long-term adherence) (eg, CPAP: Current Gold-Standard treatment for OSA)
 - indeed although advances in CPAP and mask technology can improve CPAP comfort and tolerance, failure rates are still high > 50%.
 - Moreover “in real world” even with good adherence, not all patients will experience health benefits from CPAP therapy.

INTRODUCTION

WEIGHT LOSS

- Are difficult to achieve and even harder to maintain (eg, weight loss)
 - Can reduce the AHI by an average 71%.
 - But complete resolution is still uncommon (less than 38%), residual AHI in the moderate severity range.
- However weight loss offset the wealth of obesity-related health problems and should always be part of any treatment plan.

INTRODUCTION

ORAL APPLIANCES, UPPER AIRWAY SURGERY, POSITIONAL THERAPY

- Or only resolve OSA in a portion of patients with variable and unpredictable efficacy (eg,
- **Oral appliances: mandibular advancement splints (MAS),**
 - They work by repositioning the tongue and bringing the mandible forward, thereby increasing the overall volume of the airway.
 - May have a higher adherence compared to CPAP.
 - Limitations: high cost, dental exclusion.
- **Upper airway surgery,**
 - Most often last resort options.
 - Uvulopalatopharyngoplasty, tongue reduction, maxillomandibular surgery, hyoid repositioning, turbinate reduction...
 - Variable and largely unpredictable efficacy.
 - Risks associated with surgery.
- **Positional therapy:**
 - Range of gadgets.
 - Variable adherence and efficacy.

BUT!!!

- All the above standard treatment options are directed at improving upper airway anatomy and have variable efficacy.
- Moreover,
 - The diagnosis,
 - Assessment of severity,
 - And management of OSA,
- remain intimately linked to a single indicator: **the Apnea-Hypopnea index (AHI)**. This single indicator alone may not capture the diverse spectrum of the condition.

OSA IS A MULTIFACTORIAL DISORDER.

- There are 4 important components that determine OSA pathogenesis:
 - **1- ANATOMICAL COMPROMISE:**
 - Some degree of “impaired” upper airway anatomy is a prerequisite for OSA development (narrow, crowded, collapsible upper airway) :
 - Size and shape of the craniofacial structures
 - Enlarged upper airway soft tissues
 - Obesity
 - but there is clearly more.
 - Recent evidence has identified several **NON ANATOMIC FACTORS** (or traits) that also play an important role in OSA pathogenesis.

OSA IS A MULTIFACTORIAL DISORDER

These factors include:

- 2- An **OVERSENSITIVE VENTILATORY CONTROL SYSTEM**(ie, ventilatory control instability or **HIGH LOOP GAIN**)
 - During sleep PaCO_2 tightly regulates ventilation via afferent feedback from chemoreceptors. A patient with a high loop gain has an excessively large ventilatory response to very small changes in CO_2 , leads to hypocapnia, subsequent reductions in respiratory drive which can perpetuate recurrent upper airway collapse.
 - 30% of OSA patients
 - **POTENTIAL THERAPIES:**
 - Oxygen therapy.
 - Carbonic anhydrase inhibitors: Acetazolamide.

OSA IS A MULTIFACTORIAL DISORDER

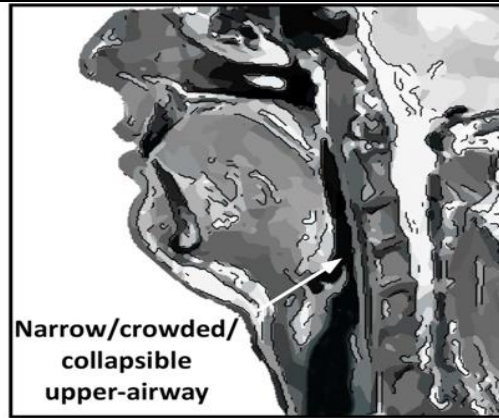
- 3- **A LOW RESPIRATORY AROUSAL THRESHOLD:**
 - Wake up too easily to small changes in intrathoracic pressure preventing the opportunity for sufficient ventilatory drive to accumulate and recruit the upper airway dilator muscle.
 - 30-50% of all OSA patients and >85% of non obese patients.
- **POTENTIAL THERAPIES:**
 - Hypnotic agents: Eszopiclone, Zopiclone, Trazodone... but still experimental.

OSA IS A MULTIFACTORIAL DISORDER

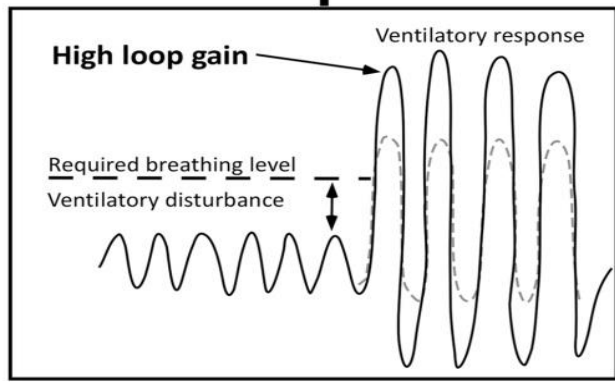
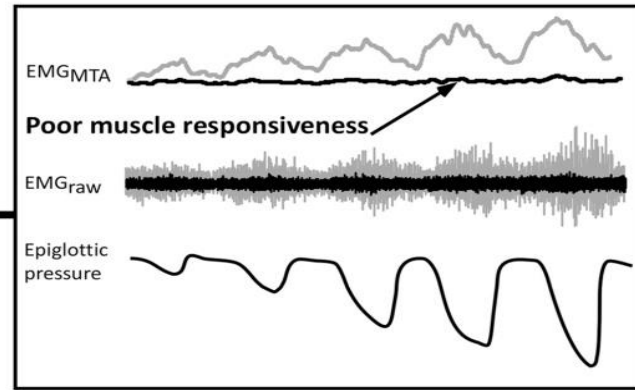
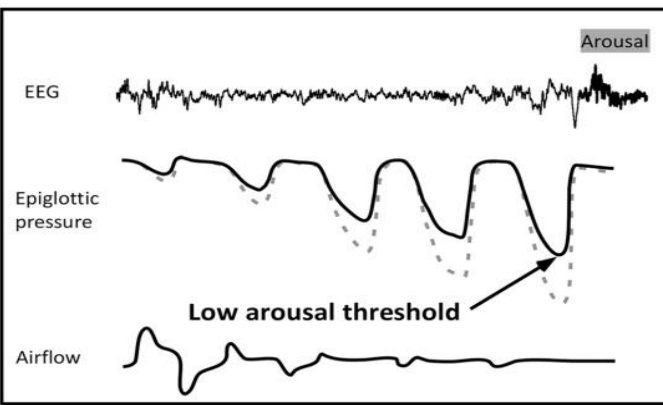
- **4-POOR PHARYNGEAL MUSCLE RESPONSIVENESS OR EFFECTIVENESS DURING SLEEP.**
- One third of OSA patients demonstrate reduced activation of upper airway dilator muscles in response to the increasingly negative airway collapsing pressures.
- **POTENTIAL THERAPIES:**
 - Hypoglossal nerve stimulation
 - Muscle training
 - Pharmacologic experimental therapies: Potassium channel blockers, Desipramine (tricyclic antidepressant with combined serotonergic, noradrenergic and antimuscarinic effects)

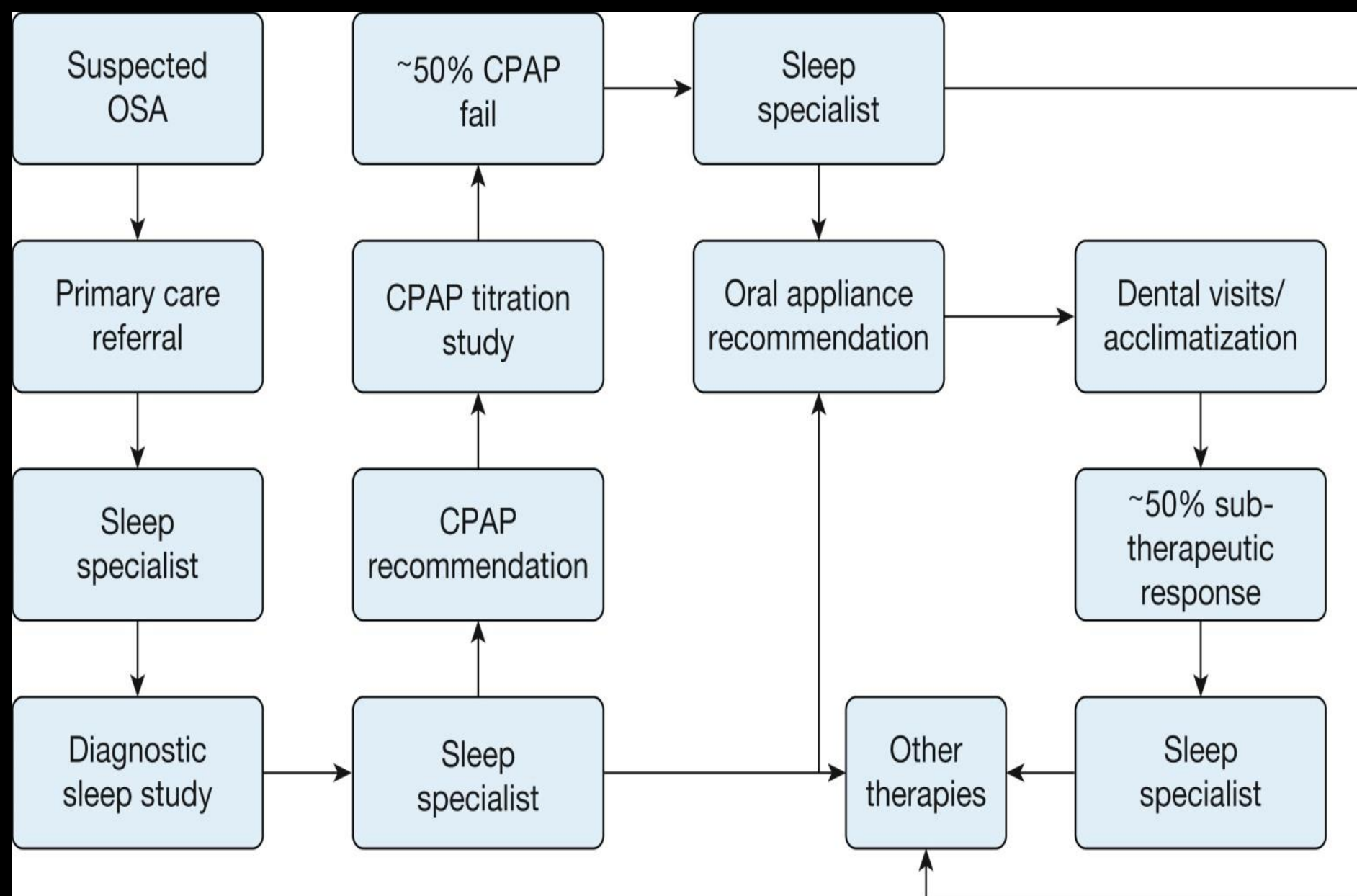
OSA IS A MULTIFACTORIAL DISORDER

- Non-anatomic mechanisms play an important role in the majority (69%) of OSA patients particularly in certain groups (eg, non obese patients)
- OSA patients have their own unique combination of pathophysiological mechanisms that contribute to their disease.



OSA





PHENOTYPIC APPROACHES TO OSA

- The aims of phenotyping include improving understanding of disease mechanisms, predicting response to therapy, and the risk for adverse events
- “Phenotype is a category of patients with OSA distinguished from others by a single or combination of disease features”
- Phenotyping strategies can be grouped by features:
 - ❖ Clinical
 - ❖ Anatomical
 - ❖ Polysomnographic
 - ❖ Biomarkers
 - ❖ Measurement of treatment effectiveness
 - ❖ Models of care.

PHENOTYPIC APPROACHES TO OSA

CLINICAL PHENOTYPES

- 3 groups according to SYMPTOMS PRESENTATION
 - Asymptomatic: highest prevalence of Cardio vascular disease.
 - Excessively sleepy
 - Disturbed sleep: insomnia symptoms.
- No difference in terms of AHI.
- Studies have shown that the disturbed sleep group requires additional targeted therapy to address the insomnia complaints in addition to CPAP.

PHENOTYPIC APPROACHES TO OSA

ANATOMICAL PHENOTYPES

- **AGE :**

- OSA in the elderly may represent distinct physiological phenotype: consistently lack of association between OSA and increased of Hypertension or A.Fib in this group. Overnight rostral shift of fluids to the neck...
- Menopausal women: REM-associated OSA, Hormone replacement therapy.

- **SEX, ETHNICITY:**

- Males are 2-3 times more likely to have OSA than females: Android anatomy.
- OSA in various ethnic populations: Asians: craniofacial skeletal restriction, surgical treatment?
- Obesity.

Table 1
OSA Phenotypes and Corresponding Endotypes^a

OSA Phenotypes	Predominant Endotypes		
OSA in elderly patients	Low arousal threshold	Rostral fluid shift	Hyporesponsive genioglossus
			Anatomical (abnormal fat distribution)
OSA in males	Anatomical (android obesity)		Rostral fluid shift (age >40 y)
OSA in fluid overloaded states	Rostral fluid shift		
OSA in menopausal women	Anatomical (abnormal fat distribution)		
Ethnic OSA phenotypes			
African Americans	Anatomical (obesity)		
Asians	Anatomical (abnormal craniofacial morphology)		
Caucasians	Anatomical (both obesity and abnormal craniofacial morphology)		
REM-related OSA phenotype	Hyporesponsive		
	Genioglossus		
Supine-related OSA phenotype	Anatomical		Hyporesponsive genioglossus

^aLinking underlying pathologic mechanisms with phenotypes of OSA.

Table 2
OSA With Low and High Arousal Threshold

Low Arousal Threshold	High Arousal Threshold
Higher propensity to wake up from sleep	Lower propensity to wake up from sleep
More likely to have mild-to-moderate OSA	Predominantly associated with severe OSA
Sedatives may be beneficial	Sedatives may evoke a respiratory arrest
Associated with less hypoxia due to reduced apnea duration	More prone to hypoxia due to prolonged apneas

Abbreviation: OSA, obstructive sleep apnea.

PHENOTYPIC APPROACHES TO OSA

POLYSOMNOGRAPHIC: PHYSIOLOGIC PHENOTYPES

- The **PALM scale** was developed to provide a framework for deeper phenotyping of OSA based on physiology and to complement existing measures such as AHI. It is performed using a modified polysomnography technique.
- Measurement of multiple causative traits:
 - Anatomical predisposition, measured by the passive critical closing pressure (**P**_{crit})
 - **A**_{rousal} threshold
 - **L**_{oop} gain
 - Upper airway **M**_{uscle} responsiveness.
- Supine position-related OSA.
- It provides new targets for treatment
- But complex and still experimental.

Table 5
Differences Between REM-Related and Supine-Related OSA

REM-Related OSA	Supine-Related OSA
Females	Males
Older in age	Younger in age
Higher mean BMI	Lower mean BMI
Genioglossal hyporesponsiveness	Unfavorable airway geometry due to smaller craniofacial volume (midline obstruction such as thyroid, retroglossal thyroid, or tonsillar enlargement needs to be excluded)
	Reduced lung volume

Abbreviations: BMI, body mass index; OSA, obstructive sleep apnea; REM, rapid eye movement.

PHENOTYPIC APPROACHES TO OSA BIOMARKERS

- “OMICS “ APPROACHES are of interest
 - To develop diagnostic markers of disease,
 - Identification of susceptibility to comorbidities
 - And predict responses to treatment.
- Still experimental.
- MEASUREMENT OF TREATMENT EFFECTIVENESS
- Duration of use of the treatment: early CPAP removal.
- Incorporate patient preferences.
- Technologic advancement: cloud-based technologies, big data,...
- This phenotyping will facilitate a more comprehensive personalized approach to inform treatment decision such as combination therapy as an efficacious alternative.
- BUT NEED for simplified phenotypic tools to advance tailored therapy.

Obstructive Sleep Apnea

Anatomical Trait

Small, collapsible upper airway

Nonanatomical Traits

Poor upper airway muscle response

High loop gain

Low arousal threshold

Targeted therapeutic options

- CPAP
- MAS
- Upper airway surgery
- Weight loss
- Position modification

- Hypoglossal nerve stimulation
- Noradrenergic/anti-muscarinic drugs?

- Supplemental O₂
- Acetazolamide

- Sedatives

Personalized Treatment of Obstructive Sleep Apnea

Traditional therapy model

Recognition + Diagnosis

Archetypal Presentation

- daytime sleepiness
- snoring
- witnessed apnoea
- obesity

Diagnosis

polysomnography
→ obtain AHI

Treatment

Prescribe **CPAP**

Follow-up

Monitor CPAP
adherence &
efficacy
(residual AHI)

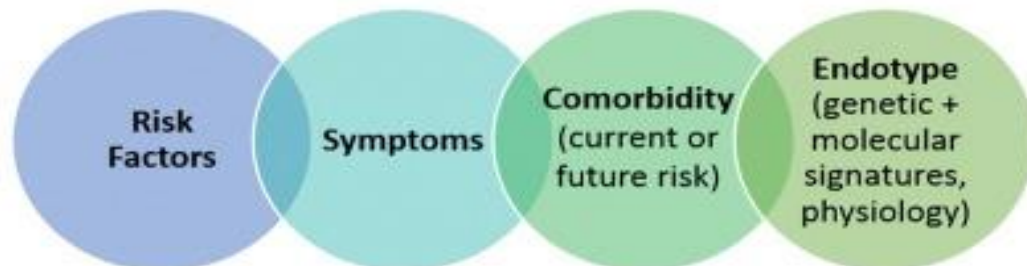
Reconsider CPAP

Reinforce CPAP

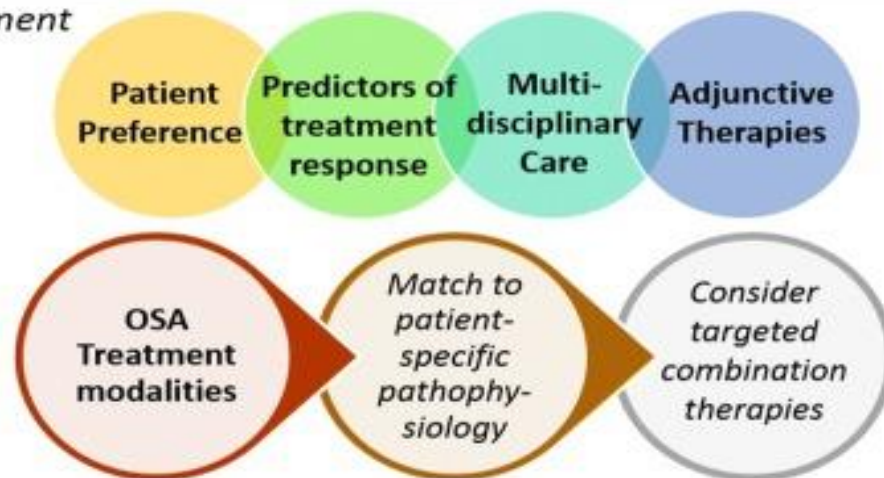
Try Alternative
Therapy

Future of tailored therapy

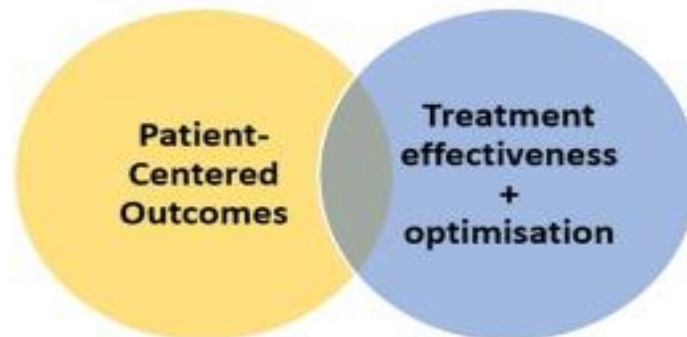
Diagnosis + Prognosis



Treatment



Follow-up



LAST MINUTE

- FDA Clears Solriamfetol (Sunosi) for Narcolepsy, OSA
- Megan Brooks
- Match 21 , 2019

CONCLUSION

- These new concepts:
 - have shed the light on:
 - The heterogeneity of OSA pathogenesis,
 - The efficiency of combination therapy
 - They represent an exciting opportunity to move beyond the current one-size-fits-all approach and beyond just focus on AHI.
 - And opened the doors of a new era of personalized OSA treatment.

THANK YOU

