



THE INTERSECTION OF CARDIOMETABOLIC
HEALTH AND SLEEP DISORDERS

The Management of Narcolepsy in Patients with Cardiovascular Risk – Clinical Pearls & Considerations





Prevalence of Cardiovascular & Cardiometabolic Risk Factors in Patients with Narcolepsy

Narcolepsy and Obesity

- Obesity is common in adults with narcolepsy (odds ratio 2.1), and in children with narcolepsy
- Obesity can predispose to cardiometabolic abnormalities and obstructive sleep apnea
- Obesity is most obvious in children and weight increase may occur at time of onset of narcolepsy (precocious puberty occurs more commonly and should be looked for)

Narcolepsy and Diabetes

- In mice, hypocretin may protect against development of insulin resistance
- Narcolepsy patients are at increased risk for insulin resistance and diabetes (odds ratios of 2.4)



Prevalence of Cardiovascular & Cardiometabolic Risk Factors in Patients with Narcolepsy

Blunted Nocturnal Blood Pressure Dipping

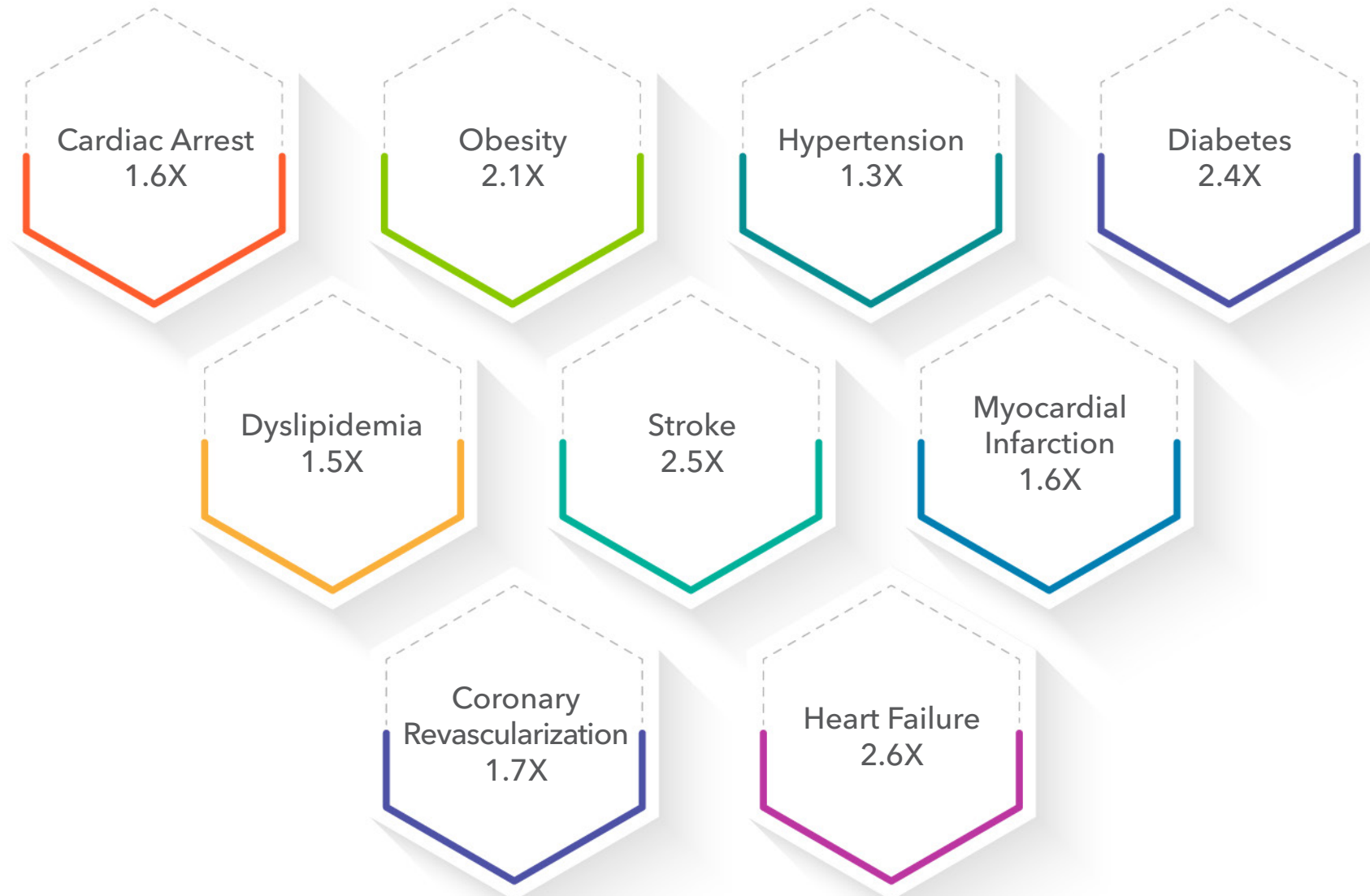
- Defined as a <10% decrease in BP during sleep
- Associated with increased cardiovascular mortality and morbidity, independent of BP and cardiovascular risk factors and chronic heart failure
- More common in patients with narcolepsy vs. controls:
 - 31% vs. 3%
 - Consistent when controlling for sympathetic activity in NREM sleep
 - Associated with increased sleep fragmentation, arousals, PMCS, and PLMS with arousals

Narcolepsy and Cardiovascular Disease: Bond Study

- Compared to controls, patients with narcolepsy have:
 - 2.5x higher prevalence of stroke
 - 1.6x higher prevalence of myocardial infarction
 - 1.6x higher prevalence of cardiac arrest
 - 1.7x higher prevalence of coronary revascularization
 - 2.6x higher prevalence of heart failure

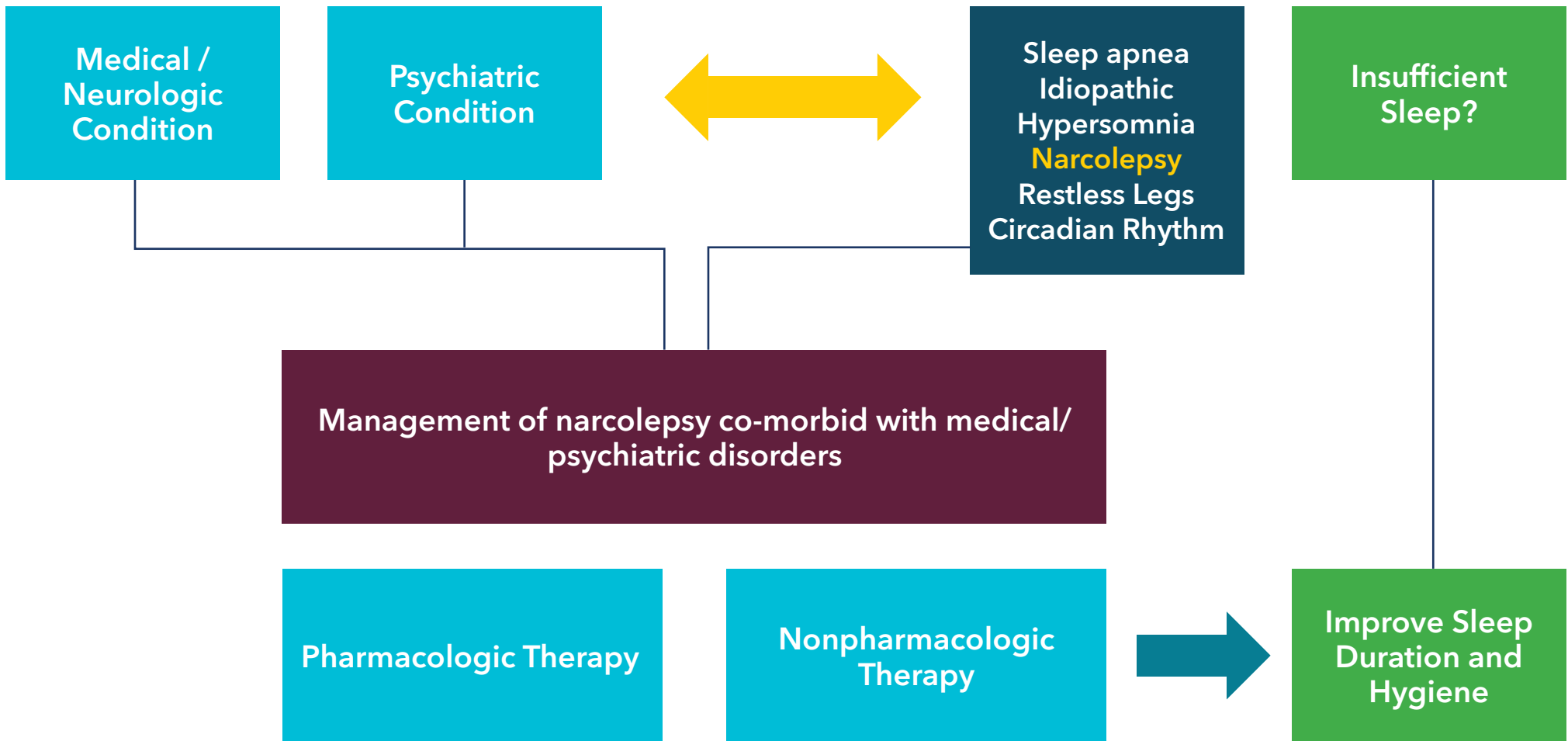


Increased Prevalence of Cardiometabolic Comorbidities in Narcolepsy Patients vs. Controls





Approach to Patient with Excessive Daytime Sleepiness





Two Types of Narcolepsy

Narcolepsy Type 1 (NT1; Narcolepsy with Cataplexy)

- Sleepiness
- At least one of the following:
 - Cataplexy and a positive Multiple Sleep Latency Test (MSLT)*
 - Low CSF orexin-A concentrations

Narcolepsy Type 2 (NT2; Narcolepsy without Cataplexy)

- Sleepiness
- Positive MSLT

Hypnagogic hallucinations, sleep paralysis, and fragmented sleep are more common in Type 1 narcolepsy.

* Positive MSLT: mean sleep latency of ≤ 8 minutes and ≥ 2 sleep-onset REM periods. REM sleep latency < 15 min on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.



Goals of Narcolepsy Treatment

- Reduce daytime sleepiness
- Control ancillary symptoms
 - Cataplexy
 - Nightmares and hallucinations
 - Sleep paralysis
 - Disturbed nocturnal sleep
- Improve psychosocial and work functioning
- Improve safety of patient and public
- Optimize overall long-term health



Behavioral Treatment of Narcolepsy

Sleepiness:

- Take 20-minute naps 2 or 3 times a day
- Avoid driving or other potentially dangerous activities when drowsy
- Avoid large meals and certain sleep-inducing foods, eg, high carbohydrate; fats
- Increase exposure to bright light during the day
- Regularity of sleep and wake times

Cataplexy:

- Avoid emotional situations likely to induce cataplexy
- Regularity of sleep and wake times

Psychosocial support:

- Family support
- Narcolepsy network
- Education: www.sleepfoundation.org



Initial Treatment Considerations for Pharmacotherapy

- What is the severity of symptoms?
 - Effects on work/school performance?
- Lifestyle of the patient
 - How might that affect a dosing schedule?
 - When is alertness most important (e.g. evening commute, classes)
- **Age and medical comorbidities**
 - Hypertension or heart disease? (dangers of classic stimulant meds and black box warnings)
 - Obesity, metabolic disorders
 - Sleep apnea
 - Depression/mental health issues?



Therapeutic Interventions for Narcolepsy

Alerting Medications

| Medication | Mechanism of action |
|--|---|
| Caffeine ^[a] | Adenosine receptor antagonist |
| Methylphenidate ^{[b]*} , amphetamines ^{[c]*} | Sympathomimetic; enhance neurotransmission of dopamine, norepinephrine, serotonin |
| Modafinil ^{[d]*} , armodafinil ^{[e]*} | Dopamine reuptake inhibitor |
| Oxybate ^{[f]*} (SXB, LXB, OnSXB) | GABA _B agonist |
| Solriamfetol ^{[g]*} | Dopamine-norepinephrine reuptake inhibitor |
| Pitolisant ^{[h]*} , Samelisant [†] | Histamine H ₃ antagonist/inverse agonist |
| Reboxetine [†] | Selective norepinephrine reuptake inhibitor |

***FDA approved to treat excessive sleepiness associated with narcolepsy.**

†Investigational; not FDA-approved for any indication.

a. Aldosari MS, et al. Clin Nutr. 2018;37:S208; b. Ritalin® (methylphenidate) PI 2019; c. Adderall® (amphetamine and dextroamphetamine) PI 2007; d. Provigil® (modafinil) PI 2015; e. Nuvigil® (armodafinil) PI 2018; f. Xyrem® (sodium oxybate) PI 2018; g. Sunosi™ (solriamfetol) PI 2019; h. Kimura H, et al. An orexin 2 receptor-selective agonist. J. Sleep. 2019;42(suppl 1):A23.



Medications for Cataplexy

- Sodium oxybate and low-sodium oxybate (also EDS)
- Histamine H3 receptor antagonist/agonist
 - Pitolisant
- Antidepressants
 - TCAs: clomipramine hydrochloride, protriptyline
 - SSRIs: fluoxetine, paroxetine
 - NRI/NERIs: atomoxetine, reboxetine
 - SSNRI: venlafaxine



Pharmacotherapy for Narcolepsy: Both EDS and Cataplexy

Sodium Oxybate

- Improves nocturnal sleep.
 - Increases slow wave sleep.
 - Reduces arousals and awakenings.
- Can eliminate cataplexy.
- Reduces vivid dreams, nightmares and hallucinations.
- Reduces sleep paralysis.
- Improves overall cognitive functioning.



AASM Practice Parameters for Narcolepsy Recommendations 2021

| Intervention | Recommendation | Excessive daytime sleepiness | Cataplexy | Disease severity | Quality of life |
|-------------------|----------------|------------------------------|-----------|------------------|-----------------|
| Modafinil | Strong | x | | x | x |
| Pitolisant | Strong | x | x | x | |
| Sodium oxybate | Strong | x | x | x | |
| Solriamfetol | Strong | x | | x | x |
| Armodafinil | Conditional | x | | x | |
| Dextroamphetamine | Conditional | x | x | | |
| Methylphenidate | Conditional | x | | x | |



Cardiovascular Risks of Commonly-Used Narcolepsy Treatments

Solriamfetol

- Renal excretion (95%): reduced dose in renal disease/caution in geriatric population with impaired renal excretion
- Avoid use in unstable cardiovascular disease
- Associated with slight increases in heart rate and blood pressure

Pitolisant

- Increases QTc interval, avoid use in patients who: a) are taking other drugs that prolong QTc interval, or b) have risk factors for prolonged QTc interval
- Avoid use in patients with severe hepatic impairment
- Dose adjustments are needed in patients with hepatic impairment or poor metabolizers of CYP2D6

Sodium Oxybate

- Regular sodium oxybate significantly contributes to daily sodium intake (6-9 g/night of sodium oxybate contributes 1100-1640mg to daily sodium intake) and can increase risk of cardiovascular events (particularly stroke) regardless of baseline blood pressure
- This is a challenge in patients with hypertension or cardiovascular risk—the American Heart Association (AHA) recommends a total daily sodium intake of <1500 mg as ideal and 2300mg as the upper limit to maintain blood pressure and cardiovascular health
- Lower sodium oxybate, which reduces sodium by 92% compared to sodium oxybate and has similar efficacy in cataplexy and EDS may be an option in this setting

Modafinil

- Associated with greater usage of antihypertensive medications
- Concurrent use of modafinil and solriamfetol is contraindicated in patients with unstable heart disease, serious heart arrhythmias, and other serious cardiovascular conditions

Methylphenidate

- Associated with increased heart rate, blood pressure, and arrhythmias

Antidepressants

- Many antidepressants prescribed off-label for cataplexy have potential cardiovascular concerns, including clomipramine, venlafaxine, and protriptyline



Summary of Management Approaches

- **Co-morbid medical and psychiatric disorders**
- **Risk of cardiovascular side effects**

Excessive daytime sleepiness

- Structured nocturnal sleep
- Naps: scheduled and PRN
- Sympathomimetic stimulants
 - Selective NE and DA reuptake inhibitors (solriamfetol)
- Non-sympathomimetic agents: modafinil, armodafinil, sodium oxybate
- Histaminergic (pitolisant)

Cataplexy

- Sodium Oxybate
- Low sodium oxybate
- Pitolisant
- Antidepressants (TCA or SSRI)

Sleep fragmentation

- Sleep hygiene
- Sodium Oxybate

General

- Personal and family counseling
- Support
- Sleep hygiene