CMHC Cardiometabolic Health Congress

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)

Jennum P et al. Sleep Medicine Reviews. 2021;101440.

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

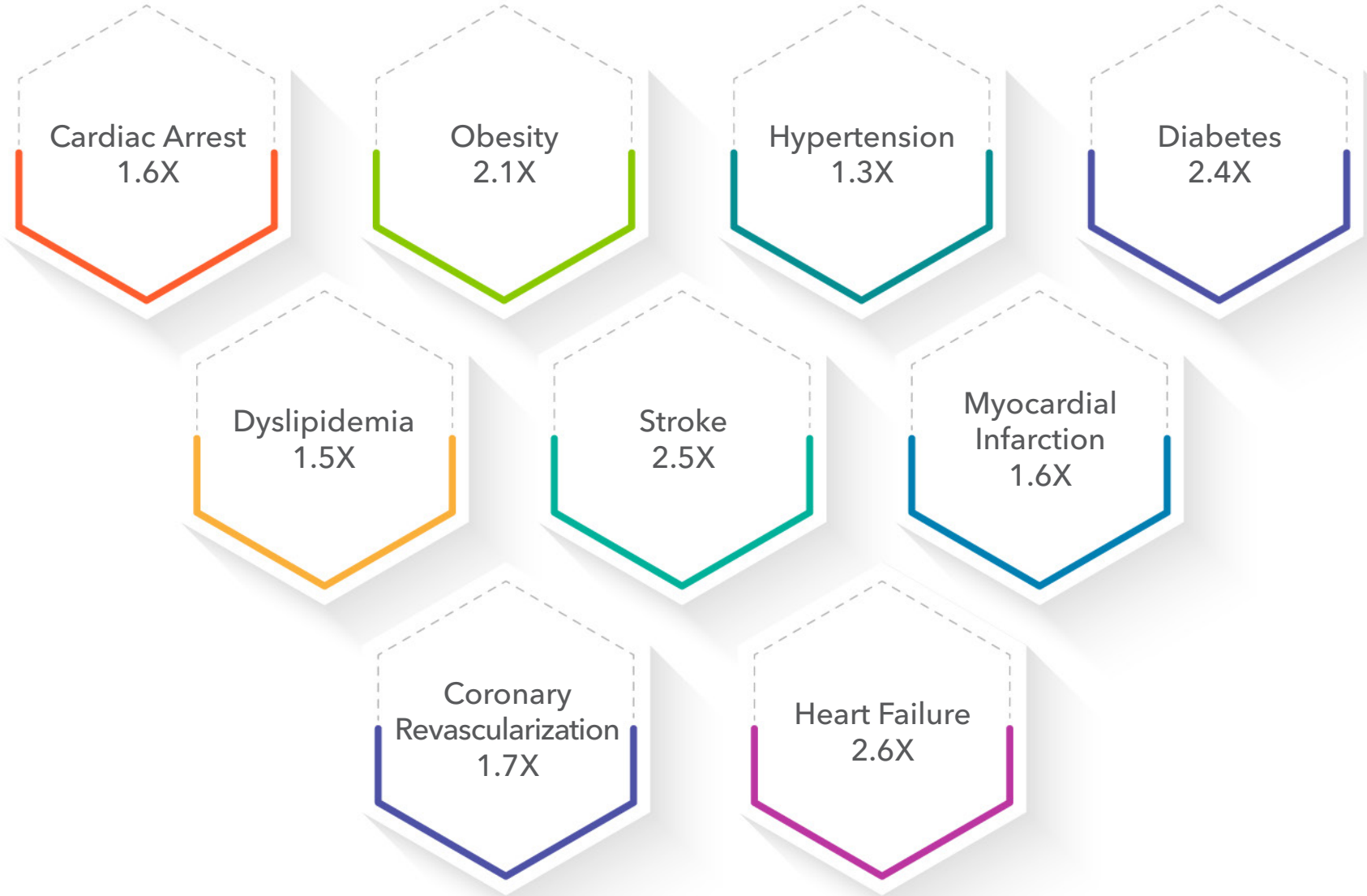
  1.6x higher prevalence of cardiac arrest

  1.7x higher prevalence of coronary revascularization

  2.6x higher prevalence of heart failure

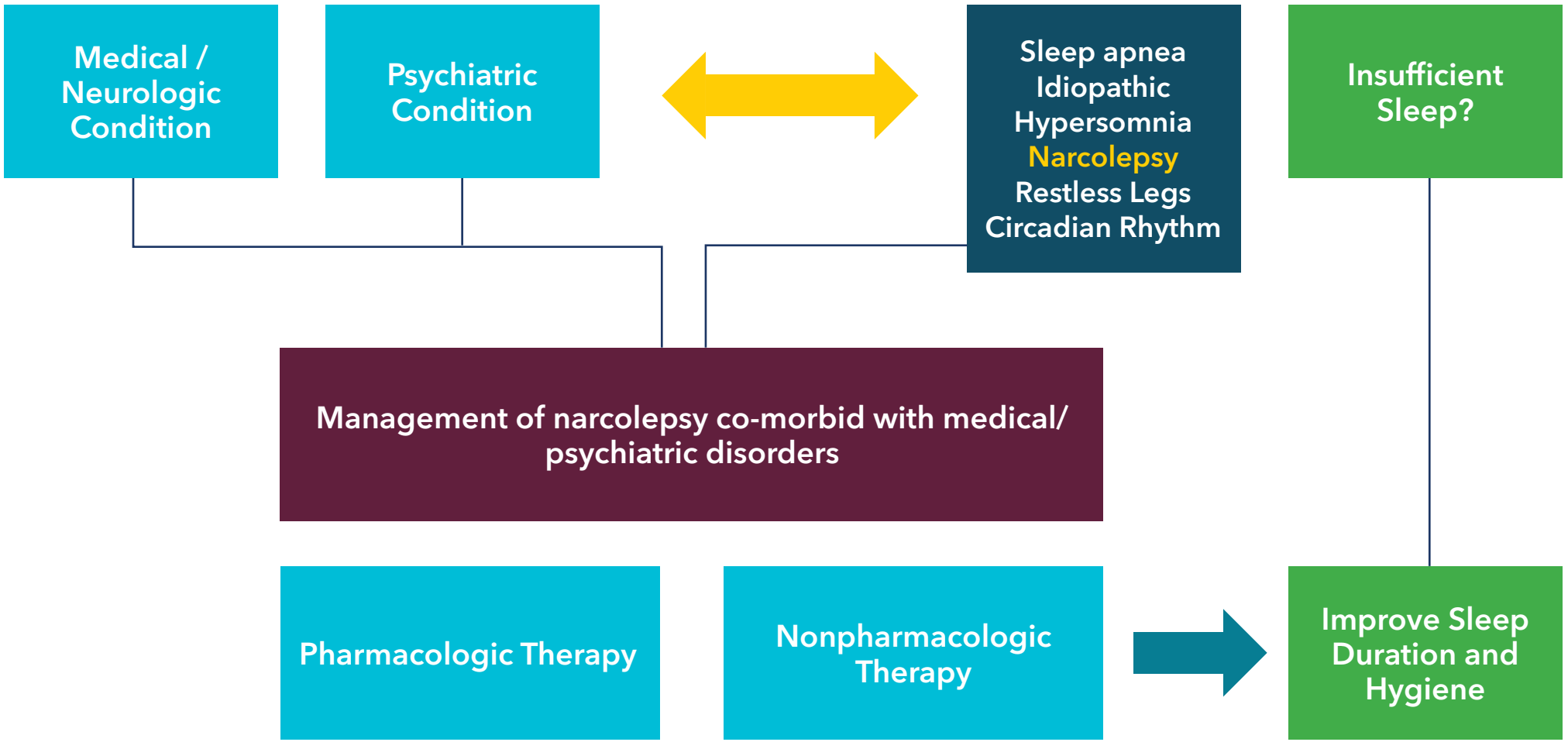
Jennum P et al. *Sleep Medicine Reviews*. 2021;101440.

Increased Prevalence of Cardiometabolic Comorbidities in Narcolepsy Patients vs. Controls



Jennum P et al. *Sleep Medicine Reviews*. 2021;101440.

Approach to Patient with Excessive Daytime Sleepiness



Pigeon WR, et al. J Psychosom Res. 2003;54:61-69. Kupfer DJ, et al. N Engl J Med. 1997;336:341-346;Consensus Conference (1984). JAMA. 251:2410-2414. Morgenthaler T, et al. Sleep. 2007;30:1705-1711; McWhirter D, et al. Psychiatry (Edgmont). 2007;4:26-35.

Two Types of Narcolepsy

Narcolepsy Type I (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 perdiods. REM sleep latency < 15min 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

Thorpy MJ, Dauvilliers Y. Sleep Med. 2015;16:9-18.

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,]. 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.

Bhattarai J, Sumerall S. Sleep Sci. 2017;10(1):19-27

AASM Practice Parameters for Narcolepsy Recommendations 2021

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

Maski K et al, JCSM, 2021, https://doi.org/ 10.5664/jcsm.9328; Morgenthaler TI, et al. Sleep. 2007;30:1705-1711.

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

Jennum P et al. Sleep Medicine Reviews. 2021;101440.

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