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**Perioperative Management  
of the Patient with  
Narcolepsy**

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**Financial Disclosures**

- UpToDate – written 2 sections
- ABIM Sleep Medicine Exam Committee
  - No exam questions will be disclosed during this presentation

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## Objectives

- Define narcolepsy
- Discuss the prevalence and epidemiology of narcolepsy
- Review the pathophysiology and consequences of narcolepsy
- Discuss therapies for narcolepsy
- Consider the implications of narcolepsy and its therapy in the perioperative setting
- Review recommendations for the perioperative management of patients with narcolepsy

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## What is Narcolepsy?

- Lifelong hypersomnia sleep disorder
- ICSD-3 Definitions
  - Narcolepsy Type I
  - Narcolepsy Type II
- Diagnosis requires
  - History
  - PSG followed by a Multiple Sleep Latency Test (MSLT)

*Average time between onset of symptoms and diagnosis is 7 years!*

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## Narcolepsy Type I (ICSD-3)

- **Criteria A and B both must be met:**
  - A. Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.
  - B. The presence of one or both of the following:
    1. - Cataplexy (*to be defined*) AND
      - MSLT with a sleep latency (SOL) of  $\leq 8$  minutes AND
      - MSLT with 2 or more REM periods (SOREMPs) on an MSLT performed according to standard techniques. (*May use SOREMP < 15 minutes on PSG as 1 of the 2 SOREMPs*)
    2. CSF hypocretin-1 concentration\*\* that is either  $\leq 110$  pg/ml (or  $< 1/3$  mean value of normal)      *\*\* No longer available in US*

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## Cataplexy

- Brief (< 2 minutes), usually bilateral, loss of muscle tone with retained consciousness
  - Partial attacks can be subtle with head drooping, jaw sagging, dysarthria
  - Respiratory muscles are usually not involved
  - Muscle twitching, especially in the facial muscles may be seen
- Precipitated by strong, usually positive (i.e. laughter), emotions
- Attacks start abruptly and build over several



<https://www.youtube.com/watch?v=VA6FeiGgLF0>

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## Narcolepsy Type II (ICSD-3)

- Criteria A - E must be met:
  - Daily periods of irrepensible need to sleep or daytime lapses into sleep occurring for at least 3 months.
  - The presence of one or both of the following:
    - MSLT with a mean sleep latency (SOL) of  $\leq$  8 minutes AND
    - MSLT 2 or more REM periods (SOREMPs) on an MSLT performed according to standard techniques.  
*(May use SOREMP < 15 minutes on PSG as 1 of 2).*
  - Cataplexy is *absent*.
  - Either a CSF has not been measured or is measured and normal
  - The hypersomnolence and/or MSLT findings are not better explained by other causes (i.e. insufficient sleep, OSA, etc.)

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## Narcolepsy: Associated Features

- Sleep-related hallucinations (hypnagogic or hypnopompic)
- Sleep-related paralysis (hypnagogic or hypnopompic)
- Disrupted sleep
- Fatigue
- Automatic behaviors

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## Narcolepsy: Prevalence and Epidemiology

- **Prevalence (Type I)**
  - US and Western European 0.02 - 0.18% (*1 in every 2000 in US*)
  - Japan 0.16 - 0.18%

*Estimated that only about 25% of those with narcolepsy have been diagnosed and are on treatment.*
- **Epidemiology**
  - Usual onset teens to early 20s (*can be late onset in 30s*)
  - M=F
  - Associated with obesity (*Type I*)
  - Often associated with other sleep disorders (*i.e. OSA, PLMD, RBD*)

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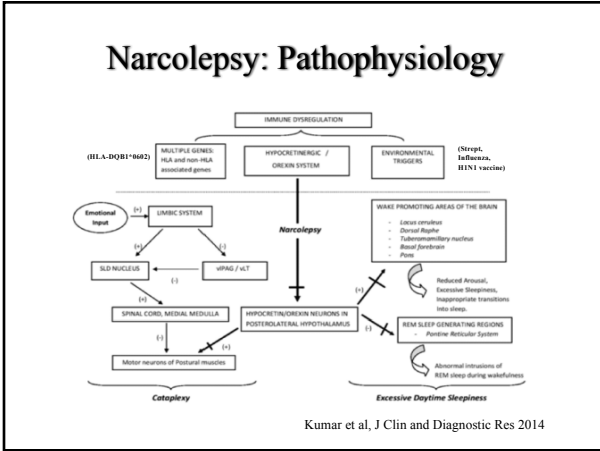
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## Narcolepsy: Consequences

- **Impaired QOL**
  - Sleepiness
    - *Failing in school*
    - *Loss of work*
    - *Driving impairment*
    - *Relationship issues*
- Depression
- Weight gain

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### Narcolepsy: Treatment

- **Sleepiness** (= *stimulants*)
  - Modafinil (*Provigil*) / Armodafinil (*Nuvigil*)
  - Methylphenidate (*Ritalin, Concerta*)
  - Amphetamines
    - Mixed Amphetamine salts (*Adderall*)
    - Dexamphetamine (*Dexedrine*) and Lisdexamfetamine (*Vyvanse*)
  - Sodium Oxybate (*Xyrem*)
- **Cataplexy**
  - Sodium Oxybate (*Xyrem*)
  - REM-suppressing medications (*Effexor, Prozac*)
  - Pitolisant

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### Narcolepsy: Stimulant Treatment

**Modafinil / Armodafinil**

- MOA poorly understood (non-amphetamine, ? via dopamine)
- Reduces sleepiness and improves ESS scores and MWT time
- Well tolerated and low illicit use rates
- Pharmacokinetics
  - Time to peak                      2-5 hrs
  - T<sub>1/2</sub>                                      15 hrs
  - Hepatically metabolized      CYP 450
- SE: headaches, nausea, dry mouth, anorexia, diarrhea, *increased BP (at high doses)*
- No significant withdrawal symptoms.

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### Narcolepsy: Stimulant Treatment

**Methylphenidate**

- MOA via blocking reuptake of NE and dopamine
- Reduces sleepiness and improves ESS scores and MWT time
- Tolerance varies, has high potential for dependence and abuse [Box]
- Pharmacokinetics (*Immediate release*)
  - Time to peak                      1-2 hrs
  - T<sub>1/2</sub>                                      3 hrs
  - De-esterification metabolism
- SE: headaches, nausea, dry mouth, insomnia, irritability, cardiomyopathy, *increased BP, arrhythmias, psychosis, lowers seizure threshold.*
- **Can see withdrawal syndrome.**

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## Narcolepsy: Stimulant Treatment

### Amphetamines

- MOA via release of catecholamines (NE and dopamine)
- Reduces sleepiness and improves ESS scores and MWT time
- Tolerance, dependence and abuse potential all significant [Box]
- Pharmacokinetics (*Immediate release*)
  - Time to peak 3 hrs
  - T<sub>1/2</sub> 10-20 hrs
  - Hepatically metabolized CYP monooxidase/glucuronidation
- SE: headaches, nausea, dry mouth, insomnia, irritability, cardiomyopathy, *increased BP, arrhythmias [Box], psychosis, lowers seizure threshold.*
- **Can see withdrawal syndrome.**

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## Narcolepsy: Cataplexy Treatment

### Sodium Oxybate

- MOA poorly understood (GABA-B receptors?)
- Reduces cataplexy (*weeks*), and improves sleepiness (*ESS and MWT*)
- Tolerance and dependence can develop, abuse potential high [Box]
- Pharmacokinetics
  - Time to peak 30-75 mins
  - T<sub>1/2</sub> 30-60 mins
  - Krebs cycle and beta oxidation
- SE: confusion, dizziness, n/v, sleep walking, *severe CNS depression, respiratory depression (avoid with other CNS depressants).*
- **Can see withdrawal syndrome and rebound cataplexy.**

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## Narcolepsy: Cataplexy Treatment

### REM Suppressing Agents

- MOA via blocking reuptake of NE and/or serotonin
- Reduces cataplexy (though not well studied nor FDA approved)
- Little tolerance, dependence or abuse potential
- Pharmacokinetics
  - Time to peak and T<sub>1/2</sub> varies by drug, all are metabolized by the liver
  - SSRI: Venlafaxine, Fluoxetine, Atomoxetine (NE)
  - TCAs: Protriptyline, Clomipramine
- SE: SSRI - nausea, HA, insomnia  
TCAs - dry mouth, sweating, dizziness, somnolence, *orthostatic hypotension, cardiotoxicity, seizures*
- **Can see mild withdrawal syndrome and rebound cataplexy.**

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### Narcolepsy and Perioperative Concerns

- While narcolepsy is relatively uncommon, perioperative providers are likely to see these patients
  - It is not expected that these providers screen for or diagnose narcolepsy
- There has been concern raised about patients with narcolepsy undergoing anesthesia/sedation
  - ? Hypersomnolence -> prolonged emergence and postop hypersomnia
  - ? Increased perioperative cataplexy and sleep paralysis
  - ? Drug interactions with anesthetics, drug withdrawal effects
  - ? Impact on pain control
  - ? Autonomic dysfunction

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### Narcolepsy and Perioperative Concerns

- Are narcolepsy and/or it's therapy associated with increased perioperative risk for adverse events?
- What is the perspective of patients with narcolepsy undergoing surgery?
- What is the familiarity of perioperative providers with narcolepsy and it's therapies?
- How should patients with narcolepsy be optimally managed in the perioperative setting?

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### Narcolepsy and Perioperative Concerns

- Case report in 1977 of a patient undergoing ovarian cyst removal, who had a history of sleep paralysis;
  - During a previous admission, she had an episode of sleep paralysis for which she was given CPR.
  - During this admission, had an uneventful surgery
  - PostOp, experienced 3 episodes of sleep paralysis described as being found nonresponsive, glassy eyed, and with irregular breathing.
  - Was given physostigmine IV for each with response, and once responsive, described sleep paralysis episodes.

Spector et al, Anesthesiology 1977

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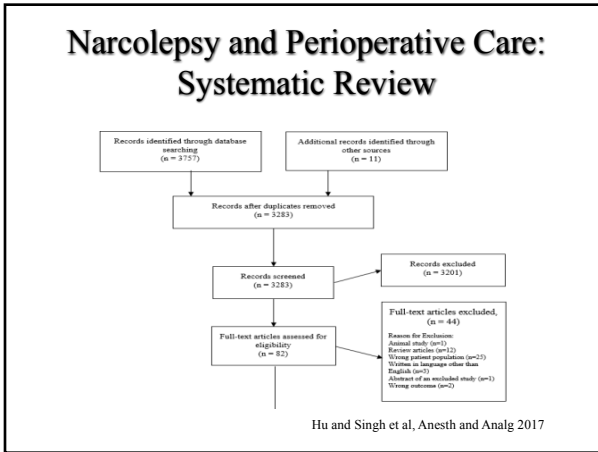
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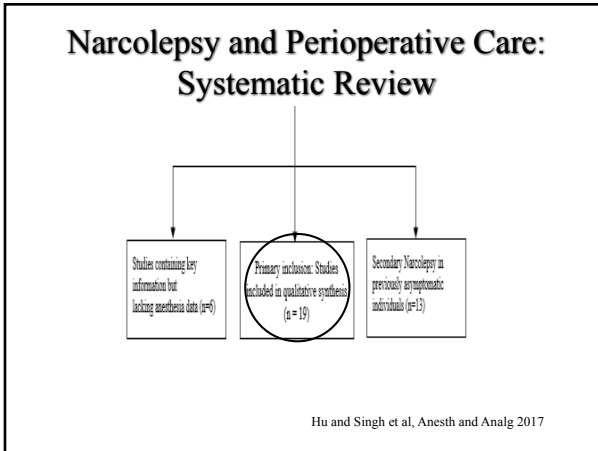
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- ### Narcolepsy and Perioperative Care: Systematic Review
- 19 studies (n=49) for primary analysis
    - Mostly case reports, but 2 small case series and 1 series of 27 patients
    - None of the reports were prospective or had control groups
    - Variety of medications used as stimulants (mostly methylphenidate and amphetamines)
      - 91% continued medications preoperatively
    - No patient used sodium oxybate for cataplexy (small number on SSRIs or TCAs)
    - Variety of surgeries were performed
- Hu and Singh et al, Anesth and Analg 2017

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### Narcolepsy and Perioperative Care: Systematic Review

- **Background Data**
  - Age 47 +/- 14 yrs
  - % Male 61%
  - BMI 31 +/- 5 kg/m<sup>2</sup>
  - Comorbids HTN, HL, PVD, COPD, migraine HAs
  - Narcolepsy dx 27 +/- 14 yrs
- **Anesthesia**
  - Induction propofol (49%), thiopental (42%), fentanyl (22%)
  - GA inhalational (78%), TIVA (22%)
  - NMB nondepolarizing agents
  - Reversal 20% (neostigmine and glycopyrrolate)

Hu and Singh et al, Anesth and Analg 2017

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### Narcolepsy and Perioperative Care: Systematic Review

- **Complications**
  - Unable to perform a meta-analysis
  - **Intraoperative:**
    - HTN (1) and Hypotension (1)
    - Bradycardia (1)
    - Cataplexy (1) during LE procedure under RA
  - **Postoperative (31%):**
    - Pain (13)
    - PONV (3)
    - Fever (3)
    - EDS (2)
    - Sleep paralysis (1)
    - HTN (1)
    - ST depression (1)
    - Desaturation (1)
    - Respiratory support (1)
    - Agitation (1)

Hu and Singh et al, Anesth and Analg 2017

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### Narcolepsy and Perioperative Care: Systematic Review

- 2 studies (n=486 deliveries) and 1 case report of OB cases
- Compared to Narcolepsy Type 2, Narcolepsy Type 1 had higher rates of:
  - Weight gain during pregnancy
  - Impaired glucose tolerance
  - Anemia
- 5 episodes (1%) of cataplexy were documented during deliveries
  - 1 report of status cataplecticus
  - 2 reports of emergency C-sections

Hu and Singh et al, Anesth and Analg 2017

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### Narcolepsy and Perioperative Care: Case-control Study

- Single institution retrospective 1:2 matched control study design
  - Matched by age, gender, type and year of surgery
- 76 patients with narcolepsy included
  - More likely to be stimulants (74% vs. 4%\*)
  - More likely to be on antidepressants (46% vs. 28%\*)
  - More likely to have OSA (41% vs. 19%\*)
  - No difference in co-morbidity index, BMI or anesthetic age use (except for ketamine)
  - Note, only 1 patient on sodium oxybate

\* P< 0.05

Cavalcante et al, J Clin Anesthesia 2017

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### Narcolepsy and Perioperative Care: Case-control Study

Outcomes for patients with and without narcolepsy.

Outcome	Narcoleptic patients (n = 76)*	Controls (n = 152)*	P Value
<b>Phase I recovery</b>			
Duration of phase I recovery, min	101 (52)	99 (56)	0.77
Opioids, mg IV ME	5 (0-10)	5 (0-10)	0.85
Respiratory depression <sup>b</sup>	5 (6.6%)	12 (7.9%)	0.80
Intensive care unit or monitored unit admission <sup>c</sup>	8 (10.5%)	11 (7.2%)	0.45
<b>First 48 h after PACU discharge</b>			
Intensive care unit admission from ward <sup>d</sup>	1 (1.3%)	1 (0.7%)	>0.99
EET activation <sup>e</sup>	5 (6.6%)	2 (1.3%)	0.04
<b>30-d postoperative outcomes</b>			
Thromboembolic event	0	0	>0.99
Myocardial infarction	0	1 (0.7%)	>0.99
Death	0	1 (0.7%)	>0.99
Hospital length of stay, d	3 (2-5)	3 (2-5)	0.57

- No difference in intraoperative complications
- 5 ERT activations due to: hypotension (3), sepsis (1) and respiratory depression (1)

Cavalcante et al, J Clin Anesthesia 2017

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### Narcolepsy and Perioperative Care: Case-control Study

- Single institution retrospective 1:4 control study design
- 25 patients with narcolepsy (59 pregnancies) vs. 75 controls (164 pregnancies) found narcolepsy:
  - More likely to have single pregnancies\*
  - More likely to develop gestational DM\*
  - No difference in complications during or after delivery
  - Note, 6 patients on stimulants and none sodium oxybate

\* P< 0.05

Calvo-Ferrandez et al, J Sleep Res 2017

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## Narcolepsy and Perioperative Care: The Patient's Perspective

- Data to date limited to retrospective cases, which may limit reported outcomes
- Patient perspectives and concerns are valid and important quality measures

Survey sent to:  
1266 members of Narcolepsy Network and  
6000 members of Facebook group of Narcolepsy Network

1162 respondents

1020 respondents had narcolepsy and  
underwent a procedure under  
sedation/general anesthesia

Hershner et al, in prep

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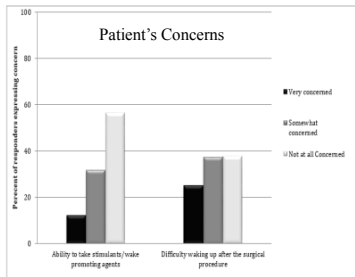
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## Narcolepsy and Perioperative Care: The Patient's Perspective



Hershner et al, in prep

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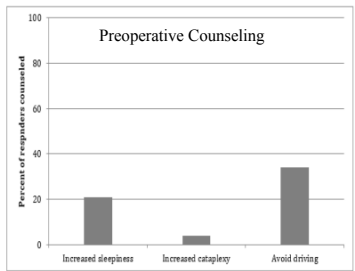
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## Narcolepsy and Perioperative Care: The Patient's Perspective



Hershner et al, in prep

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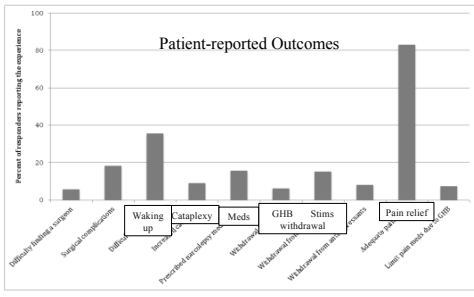
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### Narcolepsy and Perioperative Care: The Patient's Perspective



Hershner et al, in prep

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### Narcolepsy and Perioperative Care: Periop Provider Comfort Level



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### Perioperative Management of Patients with Narcolepsy: Recommendations

- Preoperative counseling
  - Continuation of preoperative medications
  - Possible worsening of symptoms postoperatively
    - Driving avoidance
- Continue regular narcolepsy medications
  - Controls symptoms
  - Prevents withdrawal

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### Perioperative Management of Patients with Narcolepsy: Recommendations

- Consider use of RA alone or with sedation over GA when appropriate
  - Avoids drug-drug interactions
  - ? limits intraoperative complications
- Consider depth of anesthesia monitoring such as BIS
  - Helps to prevent awareness or delayed emergence
  - Can be useful if cataplexy occurs while under RA
- Consider use of TIVA and shorter acting anesthetic agents whenever appropriate

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### Perioperative Management of Patients with Narcolepsy: Recommendations

- Use of multimodal analgesia and avoid use of long-acting opioid medications
- Postoperative vigilance for worsening narcolepsy sx's
  - Consider Sleep Medicine consultation
- We have limited knowledge about perioperative management of patients on sodium oxybate
- OB patients may be at risk of increased cataplexy with delivery
  - Consider Sleep Medicine consultation

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### Perioperative Management of Patients with Narcolepsy: Recommendations

- Narcolepsy and OSA may coexist!
  - Up to 25% of patients with narcolepsy may have co-morbid OSA  
Sansa et al, Sleep Med 2010  
 Frauscher et al, JCSM 2013
- Screening for OSA in patients with narcolepsy should be considered (preoperative clinic or otherwise)

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<http://www.sasmhq.org>

Thank You

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