Perioperative Management of the Patient with Narcolepsy

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

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!

Narcolepsy Type I (ICSD-3)

- Criteria A and B both must be met:
  A. Daily periods of irresistible 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 <= 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 <=110 pg/ml (or < 1/3 mean value of normal)  ** No longer available in US
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 seconds

https://www.youtube.com/watch?v=Vd6FiatSgFk

Narcolepsy Type II (ICSD-3)

- Criteria A - E 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:
     - MSLT with a mean sleep latency (SOL) of <= 8 minutes AND
     - MSLT 2 or more REM periods (SOREMPs) on an MSLT performed according to standard techniques. (May see SOREM < 15 minutes on PSG as 1 of 2).
  C. Cataplexy is absent.
  D. Either a CSF has not been measured or is measured and normal
  E. The hypersomnia and/or MSLT findings are not better explained by other causes (i.e. insufficient sleep, OSA, etc.)

Narcolepsy: Associated Features

- Sleep-related hallucinations (hypnagogic or hypnopompic)
- Sleep-related paralysis (hypnagogic or hypnopompic)
- Disrupted sleep
- Fatigue
- Automatic behaviors
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 0)
  - Often associated with other sleep disorders (e.g. OSA, PLMD, RBD)

Narcolepsy: Pathophysiology

Kumar et al, J Clin and Diagnostic Res 2014

H LA - DQB1*0602

Narcolepsy: Consequences

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

### 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
  - T1/2: 15 hrs
  - Hepatically metabolized: CYP 450
- **SE:** headaches, nausea, dry mouth, anorexia, diarrhea, increased BP (at high doses)
- No significant withdrawal symptoms.

#### 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
- **Pharmacokinetics (Immediate release)**
  - Time to peak: 1-2 hrs
  - T1/2: 3 hrs
  - De-esterification metabolism
- **SE:** headaches, nausea, dry mouth, insomnia, irritability, cardiomyopathy, increased BP, arrhythmias, psychosis, lowers seizure threshold
- Can see withdrawal syndrome.
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
- Pharmacokinetics (Immediate release)
  - Time to peak: 3 hrs
  - T1/2: 10-20 hrs
  - Hepatically metabolized: CYP monoxygenase/glucuronidation
- SE: headaches, nausea, dry mouth, insomnia, irritability, cardiomyopathy, increased BP, arrhythmias (tachycardia), psychosis, lowers seizure threshold
- Can see withdrawal syndrome.

Narcolepsy: Cataplexy Treatment

**Sodium Oxybate**
- MOA poorly understood (GABA-B receptors?)
- Reduces cataplexy (tends), and improves sleepiness (ESS and MWT)
- Tolerance and dependence can develop, abuse potential high
- Pharmacokinetics
  - Time to peak: 30-75 mins
  - T1/2: 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.

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 T1/2 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.
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.

Narcolepsy and Perioperative Concerns

• Are narcolepsy and/or its 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 its therapies?
• How should patients with narcolepsy be optimally managed in the perioperative setting?

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
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
Narcolepsy and Perioperative Care: Systematic Review

• Background Data
  - Age: 47 ± 14 yrs
  - % Male: 61%
  - BMI: 31 ± 5 kg/m²
  - Comorbidities: HTN, HL, PVD, COPD, migraine HAs
  - Narcolepsy db: 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

Narcolepsy and Perioperative Care: Systematic Review

• Complications
  - Unable to perform a meta-analysis
  - Intraoperative:
    - HTN (1) and Hypotension (1)
    - Bradycardia (5)
    - Cataplexy (1) during LE procedure under RA
  - Postoperative (11%):
    - Pain (13)
    - PONV (7)
    - Fever (3)
    - EDS (2)
    - Sleep paralysis (1)
    - HTN (1)
    - ST depression (3)
    - Desaturation (1)
    - Respiratory support (1)
    - Agitation (1)

Hu and Singh et al, Anesth and Analg 2017

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
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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Narcolepsy patients</th>
<th>Control patients</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of general surgery, min</td>
<td>101 (52)</td>
<td>99 (79)</td>
<td>0.77</td>
</tr>
<tr>
<td>Duration of hospital stay, days</td>
<td>3 (0-16)</td>
<td>3 (0-16)</td>
<td>0.65</td>
</tr>
<tr>
<td>Duration of intubation, min</td>
<td>3 (0-6)</td>
<td>3 (0-6)</td>
<td>0.80</td>
</tr>
<tr>
<td>Intensive care and/or mechanical unit</td>
<td>0 (0.30)</td>
<td>1 (1.28)</td>
<td>0.45</td>
</tr>
<tr>
<td>Extubation</td>
<td>0 (0.30)</td>
<td>1 (1.28)</td>
<td>0.45</td>
</tr>
<tr>
<td>Extubation after sedation or intubation</td>
<td>0 (0.30)</td>
<td>1 (1.28)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

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

Calvo-Ferrandeiz et al, J Sleep Res 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-Ferrandeiz et al, J Sleep Res 2017
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: 1,266 members of Narcolepsy Network and 4,000 members of Facebook group of Narcolepsy Network

1,162 respondents

10/19/17

Patient’s Concerns

Preoperative Counseling

Narcolepsy and Perioperative Care: The Patient’s Perspective

Hershner et al, in prep
Narcolepsy and Perioperative Care: The Patient’s Perspective

Patient-reported Outcomes

[Graph showing patient-reported outcomes]

Hershner et al, in prep

Narcolepsy and Perioperative Care: Periop Provider Comfort Level

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
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

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
  - 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

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)
  (Franzosi et al, JCSM 2013)
- Screening for OSA in patients with narcolepsy should be considered (preoperative clinic or otherwise)
http://www.sasmhq.org

Thank You