Fighting to Stay Awake:
Advances in Narcolepsy and
Idiopathic Hypersomnia

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Central Disorders of Hypersomnolence

- Narcolepsy type I
- Narcolepsy Type II
- Idiopathic Hypersomnia
- Kleine-Levin Syndrome
- Hypersomnia due to a medical condition
- Hypersomnia due to medication or substance
- Hypersomnia due to a psychiatric disorder
- Insufficient sleep syndrome

An accurate diagnosis is needed in order to choose the appropriate therapy

Narcolepsy Type I

- 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
  - Cataplexy and MSLT of <8 minutes and >2 SOREM periods on MSLT. A SOREM on preceding PSG may replace 1 SOREM on MSLT
  - CSF hypocretin 1 level concentration either <110 pg/ml or <1/3 of mean normal values

CRITERIA A AND B MUST BE MET


Narcolepsy Type II

- A. Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months
- B. MSL of <8 minutes and >2 SOREM periods on MSLT. A SOREM on preceding PSG may replace 1 SOREM on MSLT
- C. Cataplexy is absent
- D. Either CSF hypocretin 1 level not measured or is >110 pg/ml or >1/3 of mean normal values
- E. Hypersomnolence and/or MSLT findings not better explained by other causes

CRITERIA A-E MUST BE MET

Narcolepsy

- Clinical features:
  - Excessive daytime sleepiness (EDS) 100%
  - **Cataplexy** (Narcolepsy Type I) 60-100%
  - Hypnagogic hallucinations 60%
  - Sleep paralysis 50-60%

Narcolepsy

- Prevalence 0.05 %
- Male predominance
- Mean age of onset ~20s
- 1-2% patients have a 1st degree relative affected
Comorbid Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Men (%)</th>
<th>Women (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA</td>
<td>10 (24.4)</td>
<td>12 (17.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>UARS</td>
<td>7 (17.0)</td>
<td>5 (7.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>RLS</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>PLMD</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>RBD</td>
<td>0 (0.0)</td>
<td>2 (2.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>Bruxism</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Parasomnias</td>
<td>6 (14.6)</td>
<td>15 (22.1)</td>
<td>0.34</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>7 (17.1)</td>
<td>11 (16.2)</td>
<td>0.90</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>13 (31.7)</td>
<td>22 (32.4)</td>
<td>0.94</td>
</tr>
<tr>
<td>Depression</td>
<td>21 (51.2)</td>
<td>40 (58.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>ADHD</td>
<td>8 (19.5)</td>
<td>2 (2.9)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Neurologic disorders</td>
<td>6 (14.6)</td>
<td>29 (42.6)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>2 (4.9)</td>
<td>7 (10.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Fibromyalgia or chronic pain syndromes</td>
<td>1 (2.4)</td>
<td>7 (10.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
<td>0 (0.0)</td>
<td>7 (10.3)</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

Won et al, J Clin Sleep Med 10 (2014)

Lifestyle Impairment

<table>
<thead>
<tr>
<th>Activity</th>
<th>Percentage</th>
<th>Men (n = 41)</th>
<th>Women (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work/school underperformance</td>
<td>60.2</td>
<td>68.8</td>
<td></td>
</tr>
<tr>
<td>Reduced social activity</td>
<td>67.5</td>
<td>54.5</td>
<td></td>
</tr>
<tr>
<td>Problems with driving</td>
<td>41.5</td>
<td>44.1</td>
<td></td>
</tr>
<tr>
<td>Substance abuse</td>
<td>9.9</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>Negatively impacts, personal relationships</td>
<td>71.4</td>
<td>64.1</td>
<td></td>
</tr>
<tr>
<td>Reduced exercise activity</td>
<td>30.1</td>
<td>15.9</td>
<td></td>
</tr>
</tbody>
</table>

Won et al, J Clin Sleep Med 10 (2014)
Risk of Narcolepsy After H1N1 Influenza Vaccine

AS03 Adjuvanted AH1N1 Vaccine Associated with an Abrupt Increase in the Incidence of Childhood Narcolepsy in Finland

Hanna Nohynek,1,3 Jukka Jokinen,2 Markku Partinen,2 Outi Vaarala,1 Turku Kijjarrainen,1 Jonas Sundman,1 Sari-Leena Himanen1,2 Christer Mublin1,2 Ilkka Jolkkonen,1,2 Pälvi Olsén,1,2 Outi Saarenpää-Heikkinen,2 Tenä Kilpi2

Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis

Elizabeth Miller consultan epidemiologist2, Nick Andrews senior scientist1, Lesley Sleekers public health researcher1, Julia Stowe research fellow1, Anne Marie Weedone public health researcher1, John Shneerson consultant physician1, Christopher Verity consultant paediatric neurologist1

Risk of Narcolepsy Associated with Inactivated Adjuvanted (AS03) A/H1N1 (2009) Pandemic Influenza Vaccine in Quebec

Jacques Montepaschi1, Dominique Petit2, Marie-Josée Quinn2, Manale Ouakki2, Genève Deceuninck4, Alex Desautels1, Emmanuel Mignon2, Philippe De Wals3

Secondary Narcolepsy

- Multiple Sclerosis
- Brainstem tumors
- CNS infections
- Stroke
- Nieman-Pick
- Parkinson’s disease
**Idiopathic Hypersomnia (IH)**

- A. Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months
- B. Cataplexy is absent
- C. MSLT shows <2 SOREM or no SOREM periods
- D. Presence of at least one of the following
  - MSLT shows MSL <8 minutes
  - TST -24 hour >660 minutes
- E. Insufficient sleep ruled out
- F. Hypersomnolence and MSLT findings not explained by another sleep, medical or psychiatric disorder or use of drug or medications

**CRITERIA A-E MUST BE MET**

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**Treatment, Practical Considerations**

- Age, sex, BMI
- Severity of symptoms
- Lifestyle
- Cost of therapy
- Comorbid conditions
  - Cardiovascular disease
  - Pregnancy
  - Psychiatric disorders
**EDS, Non-pharmacologic Therapy**

- Sleep hygiene
- Short scheduled naps
- Avoid sedative drugs
- Caffeine
- Light therapy
- Strategies to prevent sleep-related injuries

**Caffeine**

- Binds to adenosine receptors – stimulating cholinergic neurons
- Peak plasma in 15-120 minutes
- Half life 2-5 hours
- More than 150 mg is needed to affect sleep
- >250 mg/day can elicit agitation, anxiety, tachycardia
- >1000 mg can be associated with confusional states

<table>
<thead>
<tr>
<th>Drink</th>
<th>Caffeine content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Americano Coffee</td>
<td>154mg/12 oz</td>
</tr>
<tr>
<td>Cafe Mocha</td>
<td>152-175mg/12 oz</td>
</tr>
<tr>
<td>Cappuccino</td>
<td>154mg/12 oz</td>
</tr>
<tr>
<td>Coffee</td>
<td>163-250mg/8oz</td>
</tr>
<tr>
<td>Espresso</td>
<td>77mg/1.5 oz</td>
</tr>
<tr>
<td>Latte</td>
<td>154-225mg/12 oz</td>
</tr>
<tr>
<td>Classic Cola</td>
<td>34mg/12 oz</td>
</tr>
<tr>
<td>Diet Cola</td>
<td>46mg/12 oz</td>
</tr>
<tr>
<td>Lime Soda</td>
<td>46-121mg/12 oz</td>
</tr>
<tr>
<td>Iced tea</td>
<td>48mg/20 oz</td>
</tr>
<tr>
<td>Black tea</td>
<td>110mg/8 oz</td>
</tr>
<tr>
<td>Green tea</td>
<td>40mg/6 oz</td>
</tr>
<tr>
<td>Energy drink</td>
<td>422mg/1.9 oz</td>
</tr>
</tbody>
</table>

http://www.caffeineinformer.com

**EDS, Pharmacotherapy**

- Wake promoting agents
- CNS stimulants-Amphetamines and Methylphenidate
- Sodium Oxybate
- Novel Therapies
AASM Practice Parameters
Narcolepsy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Modafinil</td>
<td>Narcolepsy</td>
<td>Standard</td>
</tr>
<tr>
<td>Armodafinil</td>
<td>Narcolepsy</td>
<td>Standard</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Narcolepsy</td>
<td>Guideline</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Narcolepsy</td>
<td>Guideline</td>
</tr>
<tr>
<td>D-amphetamine</td>
<td>Narcolepsy</td>
<td>Guideline</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Narcolepsy</td>
<td>Guideline</td>
</tr>
<tr>
<td>Sodium Oxybate</td>
<td>Narcolepsy</td>
<td>Standard</td>
</tr>
</tbody>
</table>

Morgenthaler et al. Sleep 30 (2007)

Modafinil
- Used in the U.S since 1998
- Classified as a Schedule IV controlled substance
- Low dependency

Armodafinil
- Used in the U.S since 2007
- Classified as a Schedule IV controlled substance
- Low dependency
Modafinil-Armodafinil

- Inhibition of dopamine reuptake
- Children and women
- Not FDA approved for <18 yo
- Pregnancy Risk Category C
- wwwPROVIGILpregnancyregistry.com
- wwwNUVIGILpregnancyregistry.com

Modafinil

Approved by the FDA for the treatment of excessive daytime sleepiness associated with:

- Narcolepsy type I and II
- Shift Work Sleep Disorder
- Persistent excessive daytime sleepiness associated with sleep apnea

Armodafinil

- Narcolepsy type I and II
- Pediatric ADHD
- Shift Work Sleep Disorder
Off-Label Uses

- Idiopathic hypersomnia
- ADHD
- Depression
- Fibromyalgia
- Multiple Sclerosis
- Parkinson’s disease
- Myotonic dystrophy

Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Modafinil</th>
<th>Armodafinil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak plasma</strong></td>
<td>2-4 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td><strong>Concentration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td>15 hours</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>60% to albumin</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>P450 liver</td>
<td>CYP liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Urine</td>
<td>Urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relation to food</strong></td>
<td>Delay peak concentration by 1 hour</td>
<td>Delay peak concentration by 2-4 hours</td>
</tr>
</tbody>
</table>
Modafinil vs Armodafinil

200 mg single dose

Armodafinil can sustain a higher plasma concentration than Modafinil late in the day despite similar half life

200 mg multiple doses


MODAFINIL

- 100-200 mg PO
- Max 200-400 mg/day
- Single or split dose
- Hepatic impairment, reduce dose to half
- Geriatric population, reduce dose

ARMODAFINIL

- 50-150-200-250 mg PO
- 150-250 mg/day
- Single dose in am
- Hepatic impairment, reduce dose
- Geriatric population, reduce dose
**Modafinil Single vs Split Dose**

Schwartz et al., J Neuropsychiatry Clin Neurosci 17 (2005)

**Effect of Modafinil in IH**

Anderson et al., Sleep 10 (2007)
Effect of Armodafinil in Narcolepsy

Schwartz et al, Neuropsychiatr Dis Treat. 6 (2010)

Modafinil vs Armodafinil in Narcolepsy

Does Modafinil Improve Driving Performance?

- 14 patients with Narcolepsy or IH
- Modafinil 400 mg or placebo 5 days prior to driving test

Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>Modafinil</th>
<th>Armodafinil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>34%</td>
<td>14-23%</td>
</tr>
<tr>
<td>Nausea</td>
<td>11%</td>
<td>6-9%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Back pain</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>1%</td>
<td>1-4%</td>
</tr>
</tbody>
</table>
Disease-Related Concerns

Contraindications
- Left ventricular hypertrophy

Use with caution
- Mitral valve prolapse
- Tourette syndrome
- Psychiatric disorders
- Hepatic impairment
- Myocardial infarct

CNS Stimulants

Amphetamines
- Dextroamphetamine
- Levoamphetamine
- Lisdexamphetamine
- Methamphetamine

Methylphenidate

Enhance neurotransmission of DA, NE and 5-HT
Amphetamines

- Sympathomimetic amines, promote release of catecholamines (DA and NE)
- Measured in urine or blood
  - Detectable for ~ 24 hours
  - High dose may be detectable for ~2-3 days
- Pregnancy Risk Factor Category C
- Schedule II controlled substances
  - High potential for abuse
  - Use with severe restrictions
  - Severe psychological or physical dependence

### Amphetamines

<table>
<thead>
<tr>
<th>Dextroamphetamine</th>
<th>Dextroamphetamine + Levoamphetamine</th>
<th>Lisdexamfetamine</th>
<th>Methamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Dexedrin</em> 60 mg</td>
<td><em>Adderall</em> 60 mg</td>
<td><em>Vyvanse</em> 70 mg</td>
<td><em>Desoxyn</em> 60 mg</td>
</tr>
<tr>
<td>Generic IR, ER</td>
<td>IR, XR</td>
<td>IR</td>
<td>IR</td>
</tr>
</tbody>
</table>

- Amphetamines are most likely to result in tolerance
- Methamphetamine and Dextroamphetamines are more likely to be used illicitly
- Half-life elimination: Adults: ~10 to 12 hours
**Methylphenidate**

<table>
<thead>
<tr>
<th>Ritalin</th>
<th>Ritalin LA</th>
<th>Ritalin SR</th>
<th>Concerta</th>
<th>Metadate CD</th>
<th>Metadate ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,10, 20 mg</td>
<td>10,20,30, 40 mg</td>
<td>20 mg</td>
<td>18,27,36, 54 mg</td>
<td>10,20,30, 40,50, 60 mg</td>
<td>20, 30, 40 mg</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>Maximum dose</td>
<td>Maximum dose</td>
<td>Maximum dose</td>
<td>Maximum dose</td>
<td>Maximum dose</td>
</tr>
<tr>
<td>60 mg</td>
<td>60 mg</td>
<td>60 mg</td>
<td>72 mg</td>
<td>60 mg</td>
<td>60 mg</td>
</tr>
</tbody>
</table>

**Methamphetamines for Narcolepsy**

MSLT (min)
Methamphetamine 5-60 mg vs Placebo

Miller et al., Sleep. 16 (1993)
Adverse Effects

- Anxiety
- Agitation
- Depression
- HTN
- Tachycardia
- Sudden Death
- Weight loss

Disease-Related Concerns

Contraindications

- Glaucoma
- Peripheral vasculopathy
  - Raynaud’s
- Pre-existing structural cardiac abnormalities
  - Cardiomyopathy
  - Arrhythmia

Use with caution

- HTN
- Epilepsy
- Psychosis
- Mania
- History of drug abuse
- Tourette’s or other tics
Monitoring Parameters

- CBC
- EKG
- Blood Pressure
- Heart rate
- Depression
- Weight

F/U recommended every 3-6 months, unless clinically indicted

Amphetamine Withdrawal Symptoms

- Withdrawal symptoms depend on time span, frequency, dosage, tolerance, and individual physiology
- Often seen:
  - Anger/Irritability/Anxiety
  - Depression/Mood swings/Psychosis
  - Suicidal thoughts
  - Weight gain
  - Poor concentration/Foggy thinking
  - Craving
  - Crying spells
  - Dizziness
  - Fatigue
  - Headaches
Ohio Automated Rx Reporting System

OARRS

• Monitors information for suspected abuse or diversion
• Drugs monitored include control substances in schedule II, III, IV and V
• To be used:
  - Prior to start new therapy
  - Patient on multiple drugs
  - Check at least annually

Sodium Oxybate

• Approved for EDS and cataplexy in patients >16 yrs
• Sodium salt of γ-hydroxybutyrate
  - High sodium load 1638 mg in 9 g dose
• Unknown MOA: GABA<sub>B</sub> and GHB receptors
• Schedule III control substance
• Pregnancy Category C
How to Use Sodium Oxybate

- Taken in 2 equal doses at night at least 2 hr after eating
- 1 wk between dosage increases; Follow-up every 3 mo

**Dosing calculator**

<table>
<thead>
<tr>
<th>1st Dose</th>
<th>2nd Dose</th>
<th>Total Nightly Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.25 g</td>
<td>2.25 g</td>
<td>4.5 g</td>
</tr>
<tr>
<td>3 g</td>
<td>3 g</td>
<td>6 g</td>
</tr>
<tr>
<td>3.75 g</td>
<td>3.75 g</td>
<td>7.5 g</td>
</tr>
<tr>
<td>4.5 g</td>
<td>4.5 g</td>
<td>9 g</td>
</tr>
</tbody>
</table>

**Effective dose range**

XYREM (sodium oxybate) PI

Reduction in ESS

*Reduction in ESS*

Sodium Oxybate Side Effects

Precautions

- Depressed patients
- Do not combine with alcohol or CNS depressant medication
- Avoid in patients with untreated OSAS

BLACK BOX WARNING
Associated with CNS adverse events, respiratory depression, coma and death
**Drug Combination**


**Cataplexy**

- Specific to Narcolepsy Type I
- Increase inhibitory and reduce excitatory signaling of motor neurons in the brain and spinal cord resulting in inhibition of skeletal motor neuron and absence of DTR
- Bilateral, symmetric sudden loss of muscle tone with preserved awareness
- Precipitated by emotions
- From jaw drop, facial twitch, buckling knees to complete fall
- Frequency varies from several per weeks to 1/year
- Onset after ~1 year of EDS
Cataplexy, Pharmacotherapy

- SNRI
  - Vanlafaxine
  - Duloxetine
- SSRI
  - Fluoxetine
  - Paroxetine
- Tricyclic
  - Protriptyline
  - Clomipramine
  - Imipramine
- Sodium Oxybate - First line of treatment

Reduction in Cataplexy Attacks

Pregnancy

• 75 sleep specialist
• 20 years of experience
• 5 narcolepsy pts/week

• 1 patient on modafinil and sodium oxybate: extremely preterm baby
• 1 patient on dextroamphetamine: pregnancy aborted due to major fetal heart abnormalities

Ongoing Research For EDS and Cataplexy

• Clarithromycin 250-1000 mg/day
  - Enhances GABA-A function
  - Used in 53 pts, 64% improved (Trotti et al. J Psychopharmacol 28 (2014))

• Mazindol
  - Tricyclic
  - 139 pts with decreased ESS from 17 to 5 points (Nittur et al. Sleep Medicine 14 (2013))
Ongoing Research For EDS and Cataplexy

- **Flumazenil**
  - BDZ antagonist
  - 153 pts, ESS decreased from 17 to 4 in 39% pts. (Trotti et al. J Psychopharmacol 28 (2014))

- **Pitolisant**
  - Histamine 3 antagonist
  - 4 pts, 10-40 mg daily, ESS decreased from 14.3 to 9.5. (Inocente et al, Clin Neuropharm. (2012))

- **Hypocretine/orexin replacement therapy**
  (Wu et al, Sleep Res Online. 1 (2000))

- **Baclofen**
  - GABA B agonist may reduce cataplexy
    (Black et al, J Neurosci. 19 (2014))

- **Transcranial direct current stimulation (tDCS)**
  - Noninvasive brain stimulation
  - Enhance the excitability of the frontal cortex that can improve vigilance
Assessing Efficacy of Treatment

- Sleepiness and Vigilance
  - ESS
  - MSLT
  - MWT
  - Diary to evaluate frequency of daytime episodes

Individual Tailoring of Therapy

- Discuss expectation prior to therapy
- Discuss cost difference, generic availability
- Discuss side effects, risk of dependence and tolerance
- Assess comorbid conditions, stimulants may exacerbate cardiovascular disease, psychiatric disorders and DM, sodium oxybate may exacerbate OSAS, RLS and psychiatric disorders.
- Discuss pregnancy risk
Individual Tailoring of Therapy

- Changing therapy from sympathomimetic drugs to wake promoting agents is safe and feasible
- Combinations of long- and short-acting forms of stimulants may be indicated and effective for some patients
- Polysomnographic re-evaluation of patients should be considered if symptoms of sleepiness increase
- Regular follow-up of patients every 3-6 months is advised