CURRENT TREATMENT OF ADULT NARCOLEPSY

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Treatment goals

- Reduce excessive sleepiness
- Control cataplexy
  - Other associated REM-related symptoms (sleep paralysis, hypnagogic and hynopompic hallucinations)
- Improve nighttime sleep
- Reduce psychosocial problems

Behavioral therapy

**cataplexy**
- Avoiding emotions
  - Loss of emotions

**Wakefulness**
- Voluntary naps
  - refreshing for 1-4h
  - no difference short and long
- Caffeine, Cola
- Diets?
- Sports
- Regular life and sleep times
  - accident reduction
  - excessively?
  - Rich in proteins
  - moderate, short

Acceptance of narcolepsy is essential
EDS and irresistible sleep attacks

Modafinil

- $\alpha_1$ adrenergic stimulation
- Indirect and direct interaction of dopaminergic system
- Involvement of serotoninergic/gabaergic mechanisms
  - Can block dopamine transporters (DT) (Young et al., Biol Psychiatry 2010)

- Elimination half-life: 10-12 h
- No interaction with AD and stimulants
- Combination with methylphenidate, d-amphetamine or SO common
Modafinil

- Side effects
  - Mood changes, irritability, palpitation, sweating, tremor, nausea, nervousness, headache, insomnia (some disappear after some weeks)
- No tolerance
- No abuse potential
- Induction of cytochrome P450 enzymes – increased metabolism of oral contraceptives (must contain 50 ug ethinylestradiol at least) (Palovaara 2000)
- Skin rash
- No teratogenicity studies – therefore not indicated during pregnancy
Methylphenidate

- Induces dopamine release
- No effect on monoamine storage
- Elimination half life 2-7h (2-3x daily)

- 5 reports evidence class II-III
  - Controlled study (Yoss & Daly 1959)
  - Controlled study (Parkes & Fenton 1973)
  - Long term study (Honda 1979) n=106
  - Controlled study with 10, 30, 60 mg/d): MWT sleep latency increase in 80% (60 mg). In the Digit Symbol Test, Wilkinson addition Test, n=13, sign. Changes compared to baseline (Mitler 1986)
  - 1 retrospective study (n 487) (Guilleminault 1993)

Approved for treatment of narcolepsy
- Extended release
GHB, Sodium oxybate

- Endogenous metabolite of GABA
- Neuromodulator
  - GABA
  - Dopamine
  - Serotonin
  - Endogenous opioids
- Evidence for role as neurotransmitter
  - Synthesized in neurons, stored in vesicles, released via depolarization into synaptic cleft, reuptake, specific receptors
- Elimination half-life 90-120 min
- Control of cataplexy
- Enhancement of daytime alertness
- Improved nighttime sleep

4 class I studies: 4-9 g twice a night
Side effects of GHB and SO

• Dizziness
• Nausea
• Confusion
• Gait problems when waking up
• Vomiting
• Enuresis
• Sleepwalking
Mazindol

- Imidazolidine derivative
- Weak releasing agent for dopamine
- Blocks dopamine and norepinephrine uptake with high affinity
- Elimination half-life 10 h, plasma half-life lasts 30 h
- reduces sleepiness at a dose of 2+2 mg/day in 53–60% of subjects.
- Class IV evidence studies: significant improvement of subjective sleepiness in 50–75% of patients (Parkes and Schachter, 1979; Iijima et al., 1980; Vespignani et al., 1984; Alvarez et al., 1991; Nittur et al., 2013)

Adverse effects
- Rare cases of pulmonary hypertension and valvular abnormalities
- Approval only in France
- (third line treatment with close monitoring)
- Not recommended in pregnancy
Stimulant recommendation

1. Line: Modafinil (100-400 mg/d) at 2 doses, rarely 600 mg
2. Line: Methylphenidate 10-60 mg
3. Line: Common practice in the US: Sodium oxybate
   Always combine with behavioural treatment
Cataplexy treatment

Mechanism of Antidepressants in the Treatment of Cataplexy

• Postulated to act through inhibition of REM phenomena
• Anticataplectic effect correlates with inhibition of norepinephrine reuptake
• Other effects: improvement of sleep paralysis, hallucinations

# Cataplexy

Commonly Used Antidepressant Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>CNS Activity</th>
<th>FDA Indicated</th>
</tr>
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<tbody>
<tr>
<td>TCAs</td>
<td></td>
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<tr>
<td>• Protriptyline</td>
<td>Norepinephrine and serotonin agonist, Cholinergic antagonist</td>
<td>No</td>
</tr>
<tr>
<td>• Imipramine</td>
<td></td>
<td></td>
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<tr>
<td>• Clomipramine</td>
<td></td>
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<tr>
<td>SSRIs</td>
<td></td>
<td></td>
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<tr>
<td>• Fluoxetine</td>
<td>Serotonin agonist (and some norepinephrine agonism)</td>
<td>No</td>
</tr>
<tr>
<td>• Paroxetine</td>
<td></td>
<td></td>
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<tr>
<td>• Sertraline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine-XR</td>
<td>Norepinephrine and serotonin agonist</td>
<td>No</td>
</tr>
</tbody>
</table>

Clomipramine

- Metabolizing rapidly into desmethyl clomipramine, an active metabolite with adrenergic reuptake inhibition
- Most widely evaluated for cataplexy
- 1 class I (Mitler 1986), 4 class IV studies (Chen 1995, Guilleminault 1976, Shapiro 1975, Schachter 1980)
- Complete abolition or decrease in severity and frequency of cataplexy at 25-75 mg/d

- Adverse effects: dry mouth, sweating, constipation, tachycardia, weight increase, hypertension, difficulty urinating, impotence
- Teratogenicity: low, but risk of atropine intoxication in infants
- Withdrawal cataplexy, status cataplecticus, tolerance
Norepinephrine/serotoninergic reuptake inhibitors

Venlafaxine
- 4 subjects at 150-375 mg/d for 2-7 months (Smith 1996)
- Improvement of eds and cataplexy reported by all np
- side effects: increased heart rate and blood pressure
- Tolerance
- Not recommended in pregnancy

Mazindol
- 1 class I evidence study with 2x2 mg/d without effect on cataplexy
- 1 class IV evidence study (Ijima 1986) with improvement of cataplexies in 50-85% np
- Retrospective analysis (Nittur et al., 2012): Mazindol has a long-term, favorable benefit/risk ratio in 60% of drug-resistant hypersomniacs, including a clear benefit on cataplexy (-50%).
Sodium Oxybate: Open-Label Extension Trial
Efficacy in Cataplexy Over 12 Months

N=117 Start. N=80 End.
P<0.001 vs baseline.

Stimulant medications maintained.

Major associated symptoms

Hypnagogic hallucinations and sleep paralysis
- Reduction of daily numbers of hh and sp

Poor sleep
- 25-30 mg/kg decreased subjective arousal (Lammers 1993) and sleep fragmentation
- Sign. Decrease of night time awakening
- Improvement of nocturnal sleep quality
- Increase of slow wave sleep

- Triazolam (class III)
  - (Thorpy 1992) improvement with triazolam 0.25 mg

- Clonazepam and temazepam (class III)
  - improve nocturnal sleep in 10/12 patients, but not eds
  - (Kansagra, JCSM 2013)
Establish accurate diagnosis of narcolepsy with or without cataplexy; check for possible co-morbidity

- **Excessive daytime sleepiness**
  - Modafinil 100-400 mg/day
  - Sodium oxybate 4.5-9 mg/day
  - Methylphenidate 10-60 mg/day
  - Planned daytime naps

- **Cataplexy**
  - Sodium oxybate 4.5-9 mg/day
  - Clomipramine 10-75 mg/day

- **Hallucinations & Sleep paralysis**
  - Other TCAs / SSRIs / Venlafaxine / Noradrenalin re-uptake inhibitors

- **Poor sleep**
  - Sodium oxybate 4.5-9 mg/day
  - Clomipramine 10-75 mg/day
  - Avoidance of known triggers

- **Parasomnias**
  - Benzodiazepines / other hypnotics

- **Associated features**
  - Modafinil 100-400 mg/day
  - Conventional medications

Give patients as much information as possible. Regular follow-up

OSA: Conventional medication
PLMS: L-dopa, sodium oxybate / bromocriptine
Depression: Conventional medication
Inverse h3 receptor agonist

Schwartz 2011

<table>
<thead>
<tr>
<th></th>
<th>At inclusion</th>
<th>After treatment</th>
</tr>
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<tbody>
<tr>
<td>Narcolepsy</td>
<td>17.2 ± 0.7</td>
<td>12.4 ± 0.9*</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>16.6 ± 0.7</td>
<td>10.8 ± 1.1*</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
<td>15.7 ± 0.9</td>
<td>9.8 ± 1.5*</td>
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Number (n) of diurnal somnolence and sleep episodes in narcoleptic patients
# Pitolisant (Wakix)

Dauvilliers et al., Lancet Neurology 2014

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pitolisant (N=31)</th>
<th>Modafinil (N=33)</th>
<th>Placebo (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>11 (35%)</td>
<td>6 (18%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (10%)</td>
<td></td>
<td></td>
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<tr>
<td>Abdominal discomfort/pain</td>
<td>2 (6%)</td>
<td>6 (18%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (3%)</td>
<td>4 (12%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (3%)</td>
<td>4 (12%)</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>1 (3%)</td>
<td>2 (6%)</td>
<td></td>
</tr>
<tr>
<td>Weight increased</td>
<td>1 (3%)</td>
<td></td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Withdrawal syndrome at V8 *</td>
<td></td>
<td></td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>
Effect of oral JZP-110 (ADX-N05) treatment on wakefulness and sleepiness in adults with narcolepsy

Richard K. Bogan a,*, Neil Feldman b, Helene A. Emsellem c, Russell Rosenberg d, Yuan Lu e

JZP-110 Stimulanz; dopaminerge + noradrenerge Aktivität; Phenylalaninderivat

Baseline MWT: 5.3 ± 3.1 Min., ESS: 17.6 ± 3.5
The effect of intranasal orexin-A (hypocretin-1) on sleep, wakefulness and attention in narcolepsy with cataplexy
Weinhold SL et al., Brain 2014

REM stability re-established
Design and Synthesis of Non-Peptide, Selective Orexin Receptor 2 Agonists

Takashi Nagahara, Tsuyoshi Saitoh, Noriki Kutsunuma, Yoko Irukayama-Tomobe, Yasuhiro Ogawa, Daisuke Kuroda, Hiroaki Gouda, Hidetoshi Kumagai, Hideaki Fujii, Masashi Yanagisawa, and Hiroshi Nagase

Binding mode. hydrogen docking in red

ICB injection in OX1/2 R KO mice