Conventional (and not-so-conventional) Treatments for Idiopathic Hypersomnia

Lynn Marie Trotti, MD, MSc
Chair, HF Medical Advisory Board
Associate Professor of Neurology, Emory University School of Medicine

List of FDA approved treatments for IH:
List of FDA approved treatments for narcolepsy:

- Non-amphetamine wake-promoting meds:
  - Provigil (modafinil)
  - Nuvigil (armodafinil)
- Amphetamines and related:
  - Ritalin/Ritalin SR/Metadate ER/Methylin/ (methylphenidate)
  - Adderall (dextroamphetamine/amphetamine)
  - Dexedrine/Dexedrine ER/Procentra/Zenzedi (dextroamphetamine)
- Xyrem (sodium oxybate)
Modafinil for IH or narcolepsy: Easier to stay awake

![Bar chart showing minutes MWT Mean Sleep Latency for Control, EDS Placebo, and EDS Modafinil groups.](image)

- EDS Placebo: P < 0.01
- EDS Modafinil: P < 0.001

13 PWN, 14 with IH, 14 controls

Modafinil 200 mg bid vs placebo (RCT cross-over)


Modafinil improves, but doesn’t normalize, safety risk

![Schematic representation of the on-road driving test.](image)

Figure 2—Schematic representation of the on-road driving test. A Continental system continuously records the actual position of the car within the traffic lane by tracking the relative distance of the car from the delineated stripe in the right of the road. Primary outcomes are Inappropriate Line Crossings (ILC) and Standard Deviation of Lateral Position (SDLP) (cm).

- Placebo: * *
- Modafinil: *

Modafinil for IH (without long sleep time)

Days –7 to 28: sleep-wake diary twice daily

Days –1 to 1: wash-out

V1 day –7

Study inclusion

CGI

MWT

ESS

CGI

Day 1 baseline

V2 day 1

V3 day 8

V4 day 15

V5 day 21

V6 day 28

MWT

ESS

CGI

Modafinil for IH (without long sleep time)

Figure 2. Epworth Sleepiness Scale (ESS) scores for modafinil and placebo. The solid line represents ESS scores for the placebo groups (n = 14) over time, the dashed line modafinil (n = 17). #P < 0.1; *P < 0.05; **P < 0.005. Signs between the lines indicate group differences, signs above or below a line indicate the comparison with baseline. V = visit.

Figure 3. Mean Maintenance of Wakefulness test (MWT) sleep latency. V = visit. *P < 0.05 compared to baseline; solid line = placebo; dashed line = modafinil.

Modafinil vs Armodafinil

Clinical series of patients with IH show 63% (124/197) remain on modafinil with good response

Modafinil package insert; Trotti LM, Sleep Med Clinics, 2017

Stimulants for IH

<table>
<thead>
<tr>
<th></th>
<th>Clinical series</th>
<th>Sample size</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>-Ali 2009</td>
<td>N = 61</td>
<td>-41% remained on methylphenidate with complete response</td>
</tr>
<tr>
<td>Amphetamine-</td>
<td>-Ali 2009</td>
<td>N = 8</td>
<td>-25% remained on amphetamine-dextroamphetamine with complete response</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>-Ali 2009,</td>
<td>N = 15</td>
<td>-33% responded to dextroamphetamine</td>
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<td></td>
<td>-Anderson 2007</td>
<td></td>
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</tbody>
</table>

25% of IH patients are unable to achieve good symptom control with “standard” medications

Trotti LM, Sleep Med Clinics, 2017
Unconventional (but published) treatments for IH

Sodium oxybate for IH (compared to people with narcolepsy)

<table>
<thead>
<tr>
<th></th>
<th>IH (n = 46 ever prescribed; 85% actually took)</th>
<th>NT1 (n = 42)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max total dose (gm/night)</td>
<td>4.3 +/- 2.2</td>
<td>6.6 +/- 2.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Single evening dose</td>
<td>66%</td>
<td>21%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ESS change</td>
<td>-3.5 +/- 4.5</td>
<td>-3.2 +/- 4.2</td>
<td>NS</td>
</tr>
<tr>
<td>Improvement in sleep drunkenness</td>
<td>24/34 (71%)</td>
<td>3/7 (43%)</td>
<td>NS</td>
</tr>
<tr>
<td>Continued treatment</td>
<td>47%</td>
<td>32%</td>
<td></td>
</tr>
</tbody>
</table>

IH patients took less
IH patients often took only one dose
But sleepiness improved
And so did sleep drunkenness

Leu-Semenescu S, 2016, Sleep Medicine
Clarithromycin: A randomized, double blind, placebo controlled trial

20 subjects

Clarithromycin 500 mg c breakfast & lunch

Matched Placebo

Clarithromycin 500 mg c breakfast & lunch

Two weeks One week Two weeks

Funded by the American Sleep Medicine Foundation

Primary outcome measure: median reaction time (psychomotor vigilance task)

P = NS

Secondary outcome measures: Epworth Sleepiness Scale

![Graph showing ESS scores for BL, placebo week 1, placebo week 2, clarithromycin week 1, and clarithromycin week 2.](image)

P < 0.005
CL < PL = B


Compounded flumazenil

![Image of compounded flumazenil bottles and pills.](image)
Clinical experience with flumazenil (n = 153)

- Benefit reported by 63%
- Ongoing treatment in 39%
- ESS change (n = 40):
  - baseline 15.0 +/- 4.7
  - flumazenil 10.3 +/- 5.1
  - p < 0.0001

Levothyroxine and IH (with long sleep time)

- Case series
- 9 patients with IH + LST
- NORMAL thyroid function
  - TSH average 1.71
  - range 0.66-3.42
- Levothyroxine 25 mcg

Trotti LM, JCSM, 2016
Shinno H, Sleep Med, 2011
Transcranial direct current stimulation in untreated patients with IH

- 8 previously untreated IH patients
- 3 stimulations per week x 4 weeks, performed between 8 and 11 am
- 5.75 point decrease in ESS, 7/8 reporting improvement in sleepiness, and improvements in reaction times on attention test

Galbiati A, Archives italiennes de biologie, 2016;

Thank you!