INSOMNIA

TREATMENT OPTIONS

TREATMENT EFFECTIVENESS

HOW DO WE TX THIS?

A HX PERSPECTIVE

PHARMACOTHERAPY
PHARMACOTHERAPY

SOME HUMOR RE: PHARMACOTHERAPY
BEFORE WE BEGIN

PAST AND CURRENT
THERAPEUTIC APPROACH TO
PHARMACOTHERAPY

TREATMENT OPTIONS

CLASSIC THERAPIES
- Benzodiazepines (e.g., temazepam)
- Imidazopyridines (e.g., zolpidem)
  Pyrazolopyrimidine (e.g., zaleplon)
  Pyrrolopyrazine (e.g., eszopiclone)

NEWER THERAPIES
- Melatonin Agonists (e.g., ramelteon)
- Doxepin (e.g., "Silentii")

OFF LABEL
- Antidepressants (e.g., amitriptyline, trazodone)
- Antipsychotics (e.g., quetiapine)

IN DEVELOPMENT
- Orexin antagonists (e.g., suvorexant)
- BZRs + CBT-I
- Stimulants + CBT-I
### WHILE COMPREHENSIVE, WHAT IS MISSING FROM THIS TABLE?

Compiled by Dan Buysse

<table>
<thead>
<tr>
<th>Brand</th>
<th>Dose (mg)</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurazepam</td>
<td>15-30</td>
<td>BZD</td>
</tr>
<tr>
<td>Temazepam</td>
<td>15-30</td>
<td>BZD</td>
</tr>
<tr>
<td>Tranquil</td>
<td>2-6</td>
<td>BZD</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>1-2</td>
<td>non-BZD</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5-10</td>
<td>non-BZD</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5-20</td>
<td>non-BZD</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>5-10</td>
<td>non-BZD</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>5-20</td>
<td>non-BZD</td>
</tr>
<tr>
<td>Riorplone</td>
<td>5-20</td>
<td>non-BZD</td>
</tr>
<tr>
<td>Riorplone</td>
<td>5-20</td>
<td>non-BZD</td>
</tr>
</tbody>
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### BASED ON ½ LIFE WHICH MEDICATION MIGHT BE BEST FOR INITIAL INSOMNIA

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</tr>
<tr>
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<td>1-2</td>
<td>non-BZD</td>
</tr>
<tr>
<td>Zaleplon</td>
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<td>non-BZD</td>
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<td>5-20</td>
<td>non-BZD</td>
</tr>
</tbody>
</table>
PLUSES & MINUSES FOR EACH TREATMENT MODALITY

**Benzodiazepines (e.g., Temazepam)**

+ Good short term efficacy
+ Low interaction profile
+ High LD
+ Minor side effects (depending on 1/2 life)
  - Not recommended for long term use
  - Not curative (gains are lost when Tx is d/c)
  - Rebound insomnia
  - Suppresses SWS or REM
  - Drug dependence (?) MEDICAL JACINT TO AND OR PAIN
PLUSES & MINUSES FOR EACH TREATMENT MODALITY

Imidazopyridines / Non-benzodiazepines
(e.g., Zolpidem, Zaleplon, Zopiclone)

+ Good “short” term efficacy
+ May be used safely up to 6 months (FDA SI REMOVED)
+ Low interaction profile
+ High LD
+ Few side effects
+ Doesn’t suppress SWS or REM
+ Does not result in rebound insomnia

- Not curative (gains are lost when Tx is d/c)
- Parasomnogenesis (pegged to zolpidem)

PLUSES & MINUSES FOR EACH TREATMENT MODALITY

Melatonin Agonists (M1 & M2 receptor agonists)

Ramelteon (Rozerem)

+ “Established” efficacy
+ May be used safely for extended intervals
+ Low interaction profile (except fluvoxamine)
+ High LD
+ Few side effects (possible exception: gonadotrophic hormones)
+ Doesn’t suppress SWS or REM
+ Does not result in rebound insomnia

- Not curative (gains are lost when Tx is d/c)
PLUS & MINUSES FOR EACH TREATMENT MODALITY

**Low Dose Tricyclics – Doxepin (not silenor)***

+ Good short term efficacy (WASO only)
+ Good durability (3 months)
+ No appreciable effects on Sleep Architecture
+ Minor side effects at hypnotic doses (?)
+ Data exists for long term administration in MDD
+ Low abuse potential

- Interacts with other meds (?)
- Possible cardiovascular effects (?)
- Anticholinergic side effects (?)
- Not curative (gains are lost when Tx is d/c)

<table>
<thead>
<tr>
<th></th>
<th>PRE-POST Δ</th>
<th>PRE-POST Δ</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SUB</td>
<td>OB</td>
</tr>
<tr>
<td>SL</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>NWAK</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>WASO</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>TST</td>
<td>15</td>
<td>25</td>
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</table>
PLUS & MINUSES FOR EACH TREATMENT MODALITY

**Antidepressants (e.g., Amitriptyline, Trazodone)**

+ Good short term efficacy (?)
+ Minor side effects at hypnotic doses (?)
+ Data exists for long term administration in MDD
+ Low abuse potential
  - Interact with other meds (?)
  - Possible cardiac toxicity (?)
  - Anticholinergic side effects (?)
  - PLMs as an iatrogenic effect (more so w/ amitriptyline)
  - Off label prescription for Primary Insomnia
  - Not curative (gains are lost when Tx is d/c)
  - Rebound insomnia (?)
    - suppresses REM (not so much trazodone)
    - Priapism

**HOW DO HYPNOTICS COMPARE WITH SEDATING ANTIDEPRESSANTS?**

I would have guessed ...

**TRAZODONE AND ZOLPIDEM TREATMENT OF PRIMARY INSOMNIA**

Walsh, Hum Psychopharmacol, 1998

Subjective Sleep Latency

```
<table>
<thead>
<tr>
<th>Week</th>
<th>Zolpidem</th>
<th>Trazodone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Week 1</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>Week 2</td>
<td>40</td>
<td>30</td>
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```

Subjective Total Sleep Time

```
<table>
<thead>
<tr>
<th>Week</th>
<th>Zolpidem</th>
<th>Trazodone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Week 1</td>
<td>380</td>
<td>340</td>
</tr>
<tr>
<td>Week 2</td>
<td>320</td>
<td>300</td>
</tr>
</tbody>
</table>
```

*p < 0.01   **p < 0.001
TRAZODONE AND ZOLPIDEM TREATMENT OF PRIMARY INSOMNIA

Walsh, Hum Psychopharmacol, 1998

Subjective Sleep Latency

* p < 0.01  ** p < 0.001

Placebo n=103  Trazodone n=98  Zolpidem n=100

“What's up with placebos and insomnia?!!”
WHAT ABOUT ANTIPSYCHOTICS?

WHAT ABOUT QUETIAPINE?
WHAT ABOUT PROSPECTIVE SAMPLING DATA
BOTTOM LINE
THE JURY IS STILL OUT ON THIS
**PHARMA WARS 2004-2008**

**TREATMENTS IN RnD**

NEW THERAPIES 2004-2008
- Single Isomer Versions of “BZRAs” (Eszopiclone)
- Modified Release Versions of “BZRAs” (Zolpidem-CR)
- Orexin Antagonists
- Longer ½ life melatonin agonists
- 5HT2A antagonists
- NK antagonists
- Atypical BZRAs (bind on cell body vs. the synapse)
- GABA Re-uptake Inhibitors & GABA Agonists

**IN SUM**

BZRAs HAVE GOOD EFFICACY
AND APPEAR REASONABLE SAFE

SADs APPEAR TO HAVE GOOD EFFICACY
THOUGH THERE ARE CONCERNS ABOUT ADVERSE EVENTS

MELATONIN AGONISTS ARE “IFFY”

ANTIPSYCHOTICS
“THE JURY IS OUT”
SO WHAT ABOUT

COMPARATIVE EFFICACY IN GENERAL (ZOLP)
COMPARATIVE EFFICACY BY TYPE / SUBTYPE

<table>
<thead>
<tr>
<th></th>
<th>NIH – 1983</th>
<th>NIH – 2005</th>
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</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Insomnia is a symptom, not a</td>
<td>Insomnia is a disorder, typically</td>
</tr>
<tr>
<td></td>
<td>primary disorder</td>
<td>correlated with other disorders</td>
</tr>
<tr>
<td>Treatment</td>
<td>Treat the primary disorder</td>
<td>Chronic insomnia exists and merits</td>
</tr>
<tr>
<td></td>
<td>(insomnia symptoms are</td>
<td>treatment</td>
</tr>
<tr>
<td></td>
<td>sometimes addressed,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sometimes ignored)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypnotics should generally be</td>
<td></td>
</tr>
<tr>
<td></td>
<td>used only for short-term</td>
<td></td>
</tr>
<tr>
<td></td>
<td>treatment</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Chronic insomnia occurs in the</td>
<td>Insomnia is associated with</td>
</tr>
<tr>
<td></td>
<td>context of medical/psychiatric</td>
<td>significant impairment in function</td>
</tr>
<tr>
<td></td>
<td>disorders</td>
<td>and quality of life</td>
</tr>
</tbody>
</table>
AND NOW A WORD FROM OUR SPONSOR
When proven ineffective, the sandman is replaced by the boulder guy

PLUS & MINUSES FOR EACH TREATMENT MODALITY

Behavior Therapy

+ Good “short” & long term efficacy
+ No issues re: drug interactions (?)
+ Does not alter sleep architecture [or maybe it does]
+ No rebound insomnia
+ No abuse potential
+ No issues re: LD

- Takes between 3 - 8 weeks
- Transient worsening of symptoms (1-2 weeks)
- Requires substantial patient compliance
- Only effective as practiced by specialists (?)
DOES THIS STUFF WORK?

There is now an overwhelming preponderance of evidence that Cognitive Behavioral Therapy for insomnia (CBT-I) is efficacious, effective, as efficacious as sedative hypnotics during acute treatment (4-8 weeks), and is more efficacious in the long term (following treatment).
Morin et al. 
Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. 

Murtagh et al. 
Identifying effective psychological treatments for insomnia: a meta-analysis. 
RCT DATA AIN’T THE REAL WORLD!

ECT  CLINIC

EFFECTIVENESS

AN EXAMPLE


EFFECTIVENESS

EFFECT SIZES PRE-TO-POST WITH CBT-I
WHY ARE THE TST EFFECTS SO POOR?

HERE'S WHY

HOW DOES PHARMACOTHERAPY WITH BZRs COMPARE WITH COGNITIVE BEHAVIORAL THERAPY?

IS THIS AN ACCURATE REPRESENTATION?

MEDICAL TX FOR INSOMNIA  CBT TX FOR INSOMNIA
I THINK NOT

RELATIVE EFFICACY
HOW DO MEDICAL AND BEHAVIORAL INTERVENTIONS COMPARE?

[Table with data]

[Graph with data]

[Text in the image]

20
RELATIVE EFFICACY
HOW DO MEDICAL AND BEHAVIORAL INTERVENTIONS COMPARE?


COMPARATIVE EFFICACY

PERCENT CHANGE WITH ACUTE TX

EFFECT SIZE DIFFERENCES WITH ACUTE TX
CBT & PCT HAVE “EQUIPOTENCY” IN SHORT RUN

AND

CBT HAS BETTER EFFICACY IN THE LONG RUN
(MAYBE – ASK AT BREAK)

WHAT ABOUT INDIVIDUAL RESULTS?

CASE EXAMPLES ON DAY 3

WHAT ABOUT MODE OF DELIVERY?
EFFECTIVENESS

EFFECT SIZES PRE-TO-POST WITH CBT-I

![Chart showing effect sizes pre-to-post with CBT-I for different conditions.](chart.png)
EFFECTIVENESS

EFFECT SIZES PRE-TO-POST WITH CBT-I

Célyne Bastien – JCP 2004, Vol. 72, No. 4, 653-659
Efficacy

PRE-TO-POST % CHANGE WITH CBT-I

NOTE: EFFECT SIZES WERE ALSO STUDIED

Yamadera et al. 2013 Sleep and Biological Rhythms

Though we have said it before it bears repeating

In an ideal world, the choice of therapy would be based on the following very simple principles:

- Pharmacotherapy is indicated in the instances where the condition is acute and the need for immediate symptom reduction is the primary consideration. This indication also carries with it the possibility that short-term treatment for acute insomnia may have some prophylactic value against the development of chronic insomnia. That is, if sedative hypnotics are more frequently prescribed for such things as off-label insomnia related to acute medical illness or insomnia secondary to transient life stressors (e.g., bereavement), such a strategy may prevent the engagement of behavioral strategies which are thought to perpetuate insomnia and lead to conditioned arousal. Behavioral treatment is indicated in the instances where the condition is chronic and/or in acute cases where 1) pharmacotherapy is contraindicated, e.g., in pediatric or geriatric patients, 2) when there is a potential for drug interactions, or 3) when patients present with a history of substance abuse.

FOR A SURPRISINGLY GOOD 30K VIEW OF TX

BREAK
EFFECTIVENESS

EFFECT SIZES PRE-TO-POST WITH CBT-I

[Bar chart showing effect sizes pre-to-post with CBT-I for different variables: SL, NOA, WASO, TST.

Arch Gen Psychiatry. 2009 Jul;66(7):652-6]