New Approaches to Insomnia and Depression

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Disclosures

• My content will include reference to commercial products; however, generic and alternative products will be discussed whenever possible.

• Consulting: Abbott, AstraZeneca, Attentiv, Teva, Eisai,, Jazz, Janssen, Merck, Neurocrine, Novartis, Otsuka, Lundbeck, Roche, Somnus, Sunovion, Somaxon, Transcept, Vantia

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Overview

• The relationship of insomnia and depression
• General treatment strategy
• Available data on the treatment of insomnia in patients with insomnia and depression
• Trying to make sense of the findings
• Conclusions
90% with MDD Have Sleep Problem: DSM-IV Major Depression

• 2-week period of depressed mood or loss of interest
• Clinically significant distress or impairment of functioning
• Symptoms not due to substance abuse or medical condition
• 4 or more of the following symptoms:
  – Insomnia/hypersomnia
  – Weight loss/decreased appetite
  – Psychomotor agitation/retardation
  – Fatigue/loss of energy
  – Worthlessness and guilt
  – Diminished concentration/indecisiveness
  – Thoughts of death and suicide

Major Depressive Disorder

• Sleep alterations reported include:
  – Difficulty falling and staying asleep
  – Increased light, stage 1 sleep
  – Decreased SWS
  – Decreased (<65 min) REM latency
  – Prolonged first REM sleep
  – Increased total REM sleep

• REM and SWS changes not currently believed relevant to insomnia diagnosis or outcome

Gillin et al., Arch Gen Psychiatry 1979; Kupfer et al., Arch Gen Psychiatry 1985; Walter et al., Biol Psychiatry 1989;
Berger et al., Biol Psychiatry 1982; Tsuno et al., J Clin Psych. 2005
Changes in Sleep in MDD

• Decreased amount of sleep
  – Prolonged sleep latency
  – Increased wake time in middle of night
  – Early morning awakenings with inability to return to sleep
  – Reduced sleep efficiency
  – Decreased total sleep time

• Alterations in sleep stages – implications?
  – Decreased slow-wave sleep (stages 3 and 4)
  – Shortened REM latency (<65 minutes)
  – Increased total amount of REM and REM%
Sleep in MDD

MDD

Normal

Waking
REM
Stg 1
Stg 2
Stg 3
Stg 4

Time (Hours)
Insomnia in MDD: Symptom or Co-Morbid Conditions?

• Are sleep problems best thought of as symptoms or conditions that are co-morbid with psychiatric disorders?

• Long considered symptoms: 1983 NIH Consensus Conference:
  • Chronic insomnia is caused by medical and psychiatric disorders
  • Insomnia-specific treatment is not needed
  • Treating the “underlying disorder” should address the insomnia
Evidence for Bidirectionality, Insomnia Independence - Insomnia:

- Increases the risk of future depression
- Decreases antidepressant response
- Is independent risk factor for suicidality, attempts and completed suicide in MDD pts
  - Insomnia is a stronger predictor of near-lethal suicide attempts than a specific suicide plan
    - Relative risk of suicide death in studies up to 2.4
- Is the most frequent residual symptom in antidepressant responders
- Residual insomnia increases relapse risk

Bidirectional Effects

Sleep Disturbance  Major Depression
Strategies for Treatment of Insomnia in Depressed Patients

• Monotherapy with sedating antidepressant
  – Mirtazapine: 15–45 mg qhs; tricyclic antidepressant
    • **Advantages:** Single medication — good compliance?
    • **Disadvantages:** Limited antidepressant options; risks residual daytime sedation, weight gain, etc.

• Nonsedating antidepressant plus:
  – Sedating antidepressant: trazodone: 50–200 mg qhs; mirtazapine 15–30 mg qhs; low-dose tricyclic antidepressant
  – Hypnotic agent
    • **Advantages:** greater flexibility in antidepressant selection; More predictable rapid sleep improvement; can d/c sedating agent and continue antidepressant
    • **Disadvantages:** Compliance? Cost
  – Cognitive behavioral therapy for insomnia (CBTI)

Cognitive Behavioral Insomnia Therapy

• Multiple components frequently administered in combination
  – Sleep Hygiene
  – Stimulus Control
  – Sleep Restriction
  – Cognitive Therapy
  – Relaxation Techniques
Sleep Hygiene Education

- Caffeine - sources & effects
- Nicotine
- Role of exercise
- Light bedtime snack (milk, peanut butter)
- Alcohol, tobacco & other substances
- Environment: light, noise, temperature
CBTI+Antidepressant Meds in MDD

- MDD patients receiving CBTI along with escitalopram had a greater depression remission rate than those administered a control behavioral intervention along with escitalopram (62% vs 33%)
- Two trials recently completed of anti-depressant meds plus CBTI
  - Improvement in insomnia mediates MDD improvement; Detailed results pending

Manber et al., Sleep. 2008
Available Data on Insomnia Pharmacotherapy

- Studies of sedating antidepressants don’t specifically assess sleep effects
  - Don’t indicate utility of treating sleep
- No studies of Sedating antidepressant + Non-sedating antidepressant
- Studies of treatment of residual insomnia with drug for sleep + antidepressant
  - Zolpidem, Trazodone
- “Hypnotic” + Non-sedating antidepressant
  - clonazepam, eszopiclone, zolpidem CR
Improvement in Residual Insomnia in SSRI-Treated Patients with MDD

Greater improvement in sleep compared with placebo found with adjunctive:

- Trazodone
- Zolpidem
  - Improved reported function and QOL

Trials of Antidepressant/Sleep Agent Co-Therapy

- Clonazepam
- Eszopiclone
- Zolpidem CR
Trial design: Clonazepam in patients with insomnia and MDD

Screening

Clonazepam 0.5–10 mg/d (n=40)

Placebo (n=40)

Open-label fluoxetine 20 mg/d

20–40 mg/d

Week

0

3

6

8

Double-blind treatment (21 days)

Taper (12 days)

Clonazepam:
Depression outcomes in patients with insomnia and MDD


**p<0.01, ***p<0.001 vs fluoxetine + placebo
Trial design:
Eszopiclone in patients with insomnia and MDD

- Screening
- Eszopiclone 3 mg/d (n=269)
- Placebo (n=274)
- Open-label fluoxetine 20–40 mg/d

Single-blind placebo

Double-blind treatment

Run-out

Week –2  0  4  8  10

Sleep Latency (LOCF)

*Placebo+Fluoxetine
Eszopiclone+Fluoxetine*

$p<0.0002$ vs placebo

$p$ values reflect results from change from baseline analyses using ANCOVA.
WASO (LOCF)

Minutes (median)

- Placebo+Fluoxetine
- Eszopiclone+Fluoxetine

* $p<0.007$ vs placebo
† $p<0.05$ vs placebo

$p$ values reflect results from change from baseline analyses using ANCOVA.
Total Sleep Time (LOCF)

- **Placebo+Fluoxetine**
- **Eszopiclone+Fluoxetine**

*p values reflect results from change from baseline analyses using ANCOVA.*

*P<0.0001 vs placebo*
Change from Baseline in HAM-D17

All Items

<table>
<thead>
<tr>
<th></th>
<th>Week 8</th>
<th>Week 10</th>
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<tbody>
<tr>
<td>Placebo+Fluoxetine</td>
<td>-10.9</td>
<td>-12.9</td>
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<tr>
<td>Eszopiclone+Fluoxetine</td>
<td>-12.2</td>
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Excluding Insomnia Items

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<tr>
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<th>Week 8</th>
<th>Week 10</th>
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<tbody>
<tr>
<td>Placebo+Fluoxetine</td>
<td>-9.2</td>
<td>-10.4</td>
</tr>
<tr>
<td>Eszopiclone+Fluoxetine</td>
<td>-9.5</td>
<td>-11.1</td>
</tr>
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</table>

$p$ values reflect results from change from baseline analyses using ANCOVA
Antidepressant Response and Remission (LOCF)

Response (50% HAM-D17 decrease)

- Week 4: Placebo+Fluoxetine 30, Eszopiclone+Fluoxetine 36, p=0.14
- Week 8: Placebo+Fluoxetine 48, Eszopiclone+Fluoxetine 59, p=0.009

Remission (HAM-D17 ≤ 7)

- Week 4: Placebo+Fluoxetine 19, Eszopiclone+Fluoxetine 22, p=0.29
- Week 8: Placebo+Fluoxetine 33, Eszopiclone+Fluoxetine 42, p=0.03
Improvement in MDD Not Seen with Zolpidem CR

- Identical study carried out with zolpidem CR and sleep was improved but no improvement in depression vs placebo

Sheehan et al., 2009
Study design:
Zolpidem CR in patients with insomnia and MDD

Zolpidem controlled-release 12.5 mg/d (n=190)

Placebo (n=190)

Responders ≥50% improvement in HAM-D17

Open-label escitalopram 10 mg/d

Screening

Week

-1 0 4 8 10 12 16 20 24 26

Double-blind treatment

Responder-randomized treatment

Run-out

Zolpidem CR:
Sleep outcomes in patients with insomnia and MDD

**p<0.001, ***p<0.0001 vs escitalopram + placebo

Zolpidem CR: Depression outcomes in patients with insomnia and MDD

All patients received escitalopram

<table>
<thead>
<tr>
<th>Week 4</th>
<th>Week 8</th>
</tr>
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<tbody>
<tr>
<td>ESC 10 mg/d + PBO (n=190)</td>
<td>ESC 10 mg/d + ZOL CR 12.5 mg (n=190)</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>Improvement</td>
</tr>
<tr>
<td>HAM-D17 total score</td>
<td></td>
</tr>
<tr>
<td>-8.1</td>
<td>-10.9</td>
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<tr>
<td>-9.1</td>
<td>-11.3</td>
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<tr>
<td>-15</td>
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</table>

Fava M, et al. Poster presented at the 22nd Annual APSS Meeting (SLEEP); June 2008
How Do We Explain Eszopiclone vs Zolpidem CR Difference?

• Sleep effect sizes are comparable but significant difference in associated effect on depression.

• Improvement in depression may not be mediated by improvement in sleep; and Either:
  – Eszopiclone is an antidepressant and Zolpidem CR is not
  – Zolpidem CR is an anti-antidepressant and Eszopiclone is not
BENEFIT SUSTAINED FOR AT LEAST 2 WEEKS POST DISCONTINUATION OF INSOMNIA THERAPY

Figure 2—HAM-D-17 Response and Remission Rates at Weeks 8 and 10. Note: p-values reflect Chi-square results.
Discontinuation Effects
WASO

Week 8 = last week of DB treatment
Discontinuation Effects
TST

Week 8 = last week of DB treatment
Mechanism of ESZ vs Zolpidem Difference?

• **Benzodiazepines** Temazepam, Flurazepam, Triazolam etc.
  – A group of compounds with related chemical structure
  – Mechanism of action:
    • GABA receptor comprised of 5 peptides that form channel which controls the flow of chloride ions in and out of the neuron.
    • Generally, Cl concentration greater outside than inside the neuron. GABA binding opens the channel and resulting inward flux of CL hyperpolarizes neuronal membrane causing inhibition
    • Benzodiazepines bind to a binding site on α subunit of GABA receptor complex and enhance this GABA-mediated inhibition

• “**Non-Benzodiazepines**” Zolpidem, zaleplon, eszopiclone, indiplon
  – A group of compounds unrelated to selves or benzos
  – Mechanism of action:
    • Same as benzos, relatively greater α subunit binding specificity
The GABA Receptor Complex
GABA-A Subunit-Specific Effects

- The effects of binding to α subunits differ because of location of GABA receptors containing them
  - Greater binding to α subunits of GABA receptors in the cerebellum will result in greater effect on balance.
  - Greater binding to α subunits of GABA receptors in the amygdala will result in greater effect on anxiety.
  - Evidence of differential binding in animals
    - Limited human data on differential α subunit binding
GABA Alpha Subunit Subtypes
## Animal Data on Effects of GABA Alpha Subunit Binding

<table>
<thead>
<tr>
<th>Alpha subunit</th>
<th>Agents with Significant Effects</th>
<th>Possible Adjunctive Therapeutic Effects</th>
<th>Potential Adverse Effects</th>
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</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Triazolam, Temazepam, Flurazepam, Estazolam, Quazepam, Zaleplon, Zolpidem, Zolpidem CR, Eszopiclone</td>
<td>Anti-Convulsant</td>
<td>Cognitive Impairment, Ataxia</td>
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<tr>
<td>$\alpha_2$</td>
<td>Triazolam, Temazepam, Flurazepam, Estazolam, Quazepam, Eszopiclone</td>
<td>Anxiolytic, Myorelaxant, Antidepressant?</td>
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<tr>
<td>$\alpha_3$</td>
<td>Triazolam, Temazepam, Flurazepam, Estazolam, Quazepam, Eszopiclone</td>
<td>Anxiolytic, Myorelaxant, Antidepressant?</td>
<td></td>
</tr>
<tr>
<td>$\alpha_4$</td>
<td></td>
<td>Analgesia</td>
<td>Ataxia, Amnesia</td>
</tr>
<tr>
<td>$\alpha_5$</td>
<td>Triazolam, Temazepam, Flurazepam, Estazolam, Quazepam</td>
<td>Myorelaxation</td>
<td>Cognitive Impairment Tolerance</td>
</tr>
</tbody>
</table>

Conclusions

• Targeting pharmacologic treatment specifically to insomnia can significantly improve sleep and reported daytime function and QOL
  – Further studies needed to determine
    • Optimal duration of treatment
    • If treating insomnia decreases relapse rate
Conclusions

• Effects of treating insomnia on antidepressant response are variable
  – Esz but not Zolp appears to augment antidepressant effect; Clonazepam?

• Further studies needed:
  – To confirm antidepressant effect of ESZ and mechanism ($\alpha_2$, $\alpha_3$ ?)
    » To determine if antidepressant benefit is sustained and if there is decreased risk of relapse
    » To determine if ESZ alone is antidepressant
    » With other ($\alpha_2$, $\alpha_3$ ?) agents
  – Relationship between antidepressant and sleep effects
    » Do drugs with sleep benefit and antidepressant effects have greater augmentation effect?