

# **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

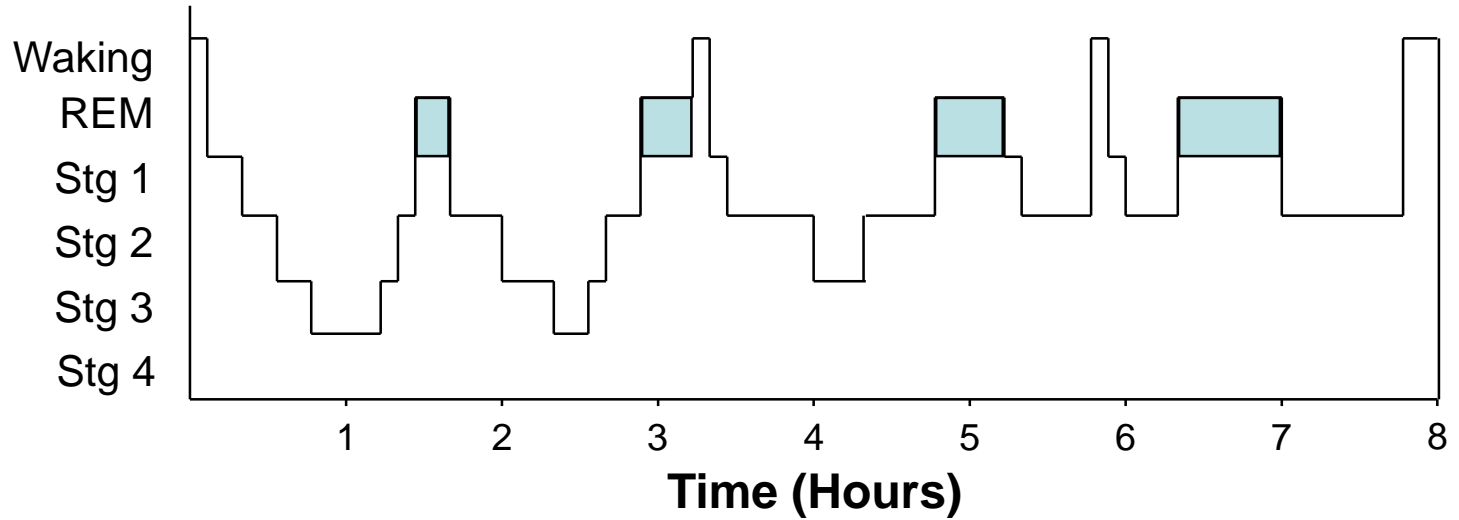
- Sleep alterations reported include:
  - Difficulty falling and staying asleep
  - Increased light, stage 1 sleep
  - Decreased SWS
  - Decreased (<65 min) REM latency
  - Prolonged first REM sleep
  - Increased total REM sleep
- REM and SWS changes not currently believed relevant to insomnia diagnosis or outcome

# Changes in Sleep in MDD

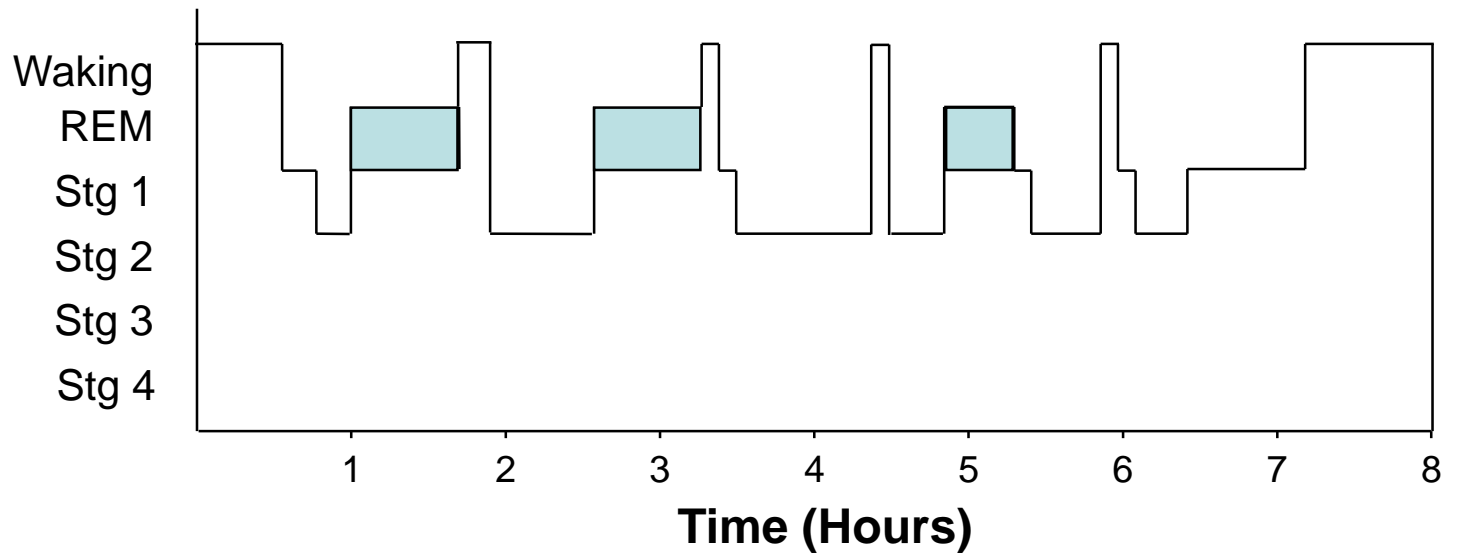
- Decreased amount of sleep
  - Prolonged sleep latency
  - Increased wake time in middle of night
  - Early morning awakenings with inability to return to sleep
  - Reduced sleep efficiency
  - Decreased total sleep time
- Alterations in sleep stages – implications?
  - Decreased slow-wave sleep (stages 3 and 4)
  - Shortened REM latency (<65 minutes)
  - Increased total amount of REM and REM%

# Sleep in MDD

Normal



MDD



# 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



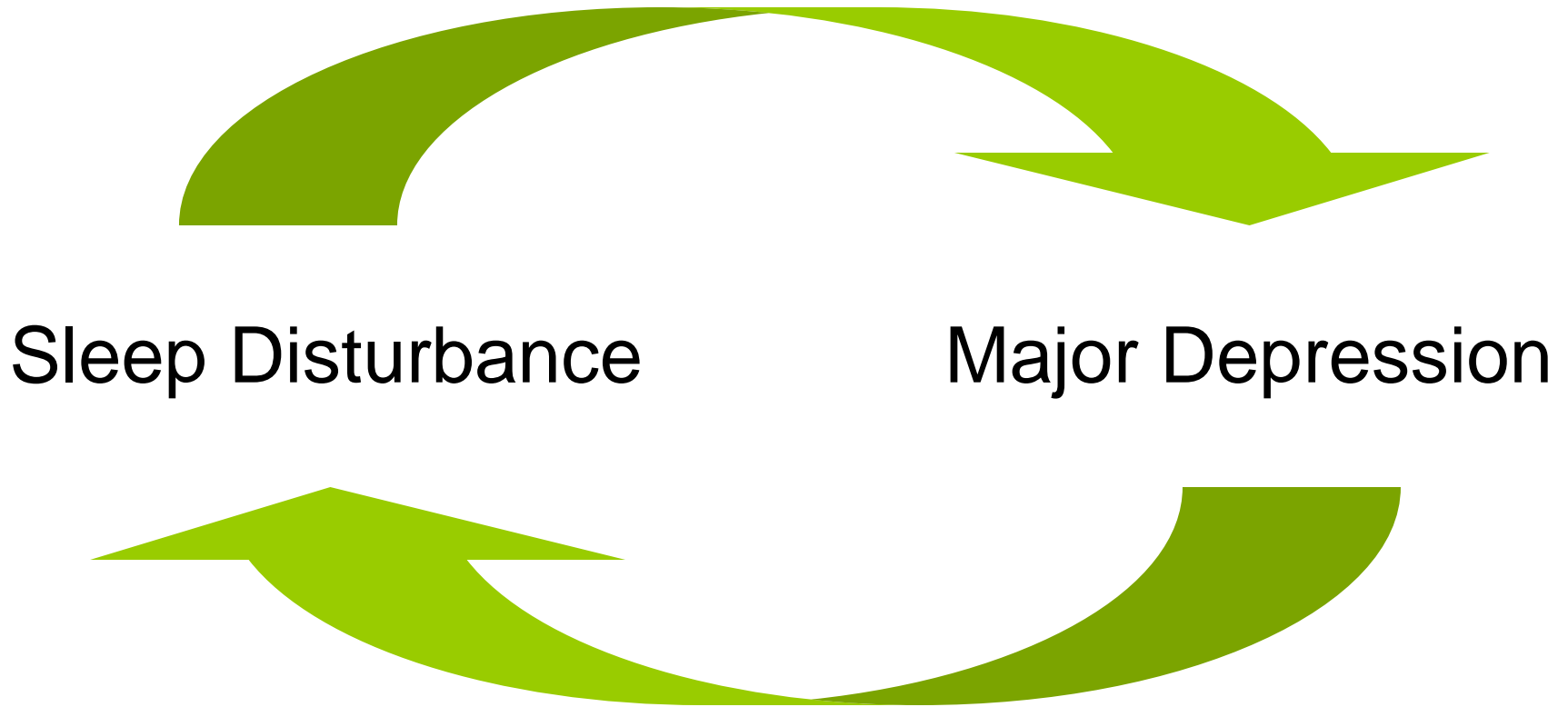
# Evidence for Bidirectionality, Insomnia

## 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

Fawcett J. *J Clin Psychiatry*.1988;49;Suppl 7-8; Fawcett J, et al. *Am J Psychiatry*.1990;147(9):1189-1194; Reynolds CF, et al. *Am J Psychiatry*. 1997;154:958-962; Breslau N, et al. *Biol Psychiatry*.1996;39:411-418; Ford DE, Kamerow DB. *JAMA*.1989;262(11):1479-1484; Adam K, et al. *J Psychiatr Res*. 1986;20(4):301-306; Vgontzas AN, et al. *J Clin Endocrinol Metab*.2001;86(8):3787-3794; Ford DE, Cooper-Patrick L. *Depress Anxiety*.2001;14(1):3-6; Roberts RE, et al. *Am J Psychiatry*. 2000;157(1):81-88; Fava GA, et al. *J Affect Disord*. 1990;19:149-152; Nierenberg AA, et al. *J Clin Psychiatry*. 1999;60:221-225; Weissman, et al. *Gen Hosp Psych*. 1997. Hall et al., *Psychosomatics*. 1999; McCall et al., *Sleep Medicine* 2010

# Bidirectional Effects



# 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)

Nowell PD, Buysse DJ. *Depress Anxiety*. 2001;14:7-18; Nierenberg AA, et al. *Am J Psychiatry*. 1994;15:1069-1072; Dording CM, Mischoulon D, Petersen TJ, et al. *Ann Clin Psychiatry*. 2002;14:143-147; Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26:249-260.

# 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

# 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:

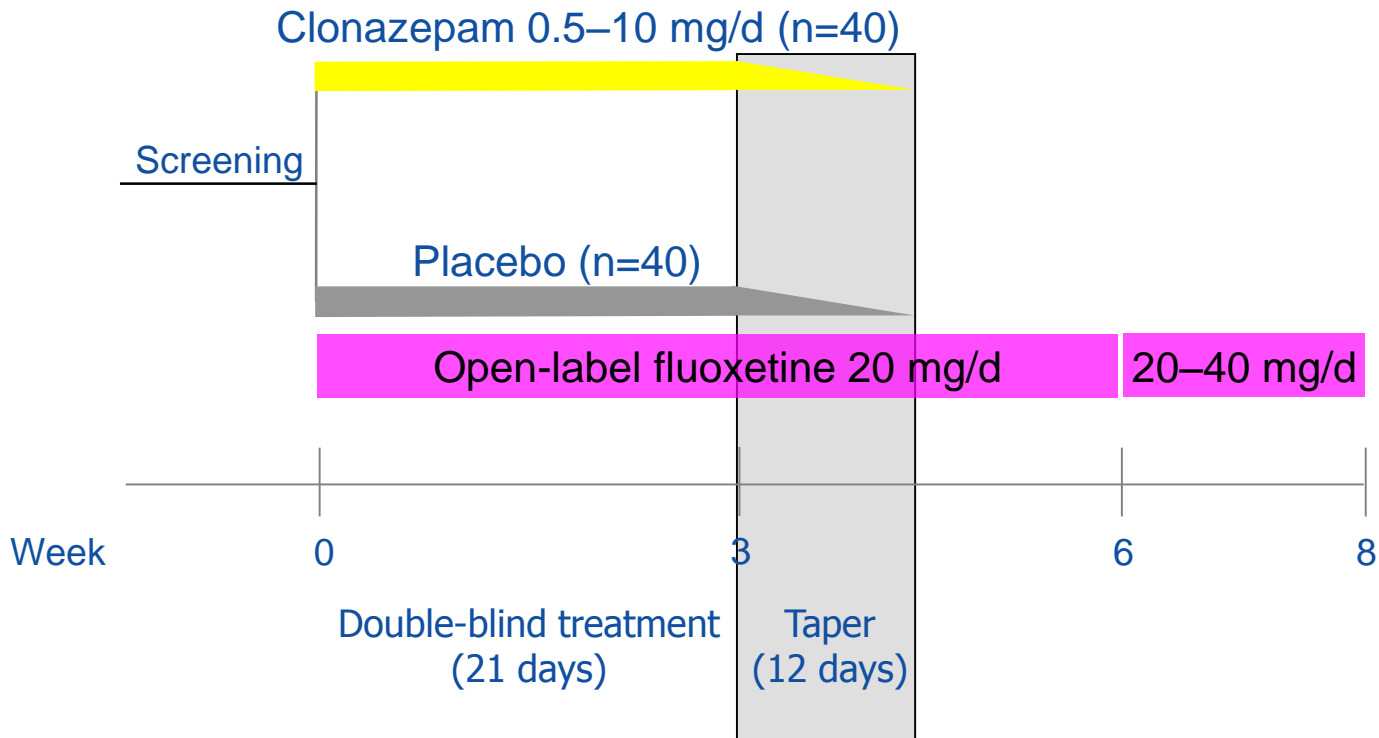
- Trazodone
- Zolpidem
  - Improved reported function and QOL



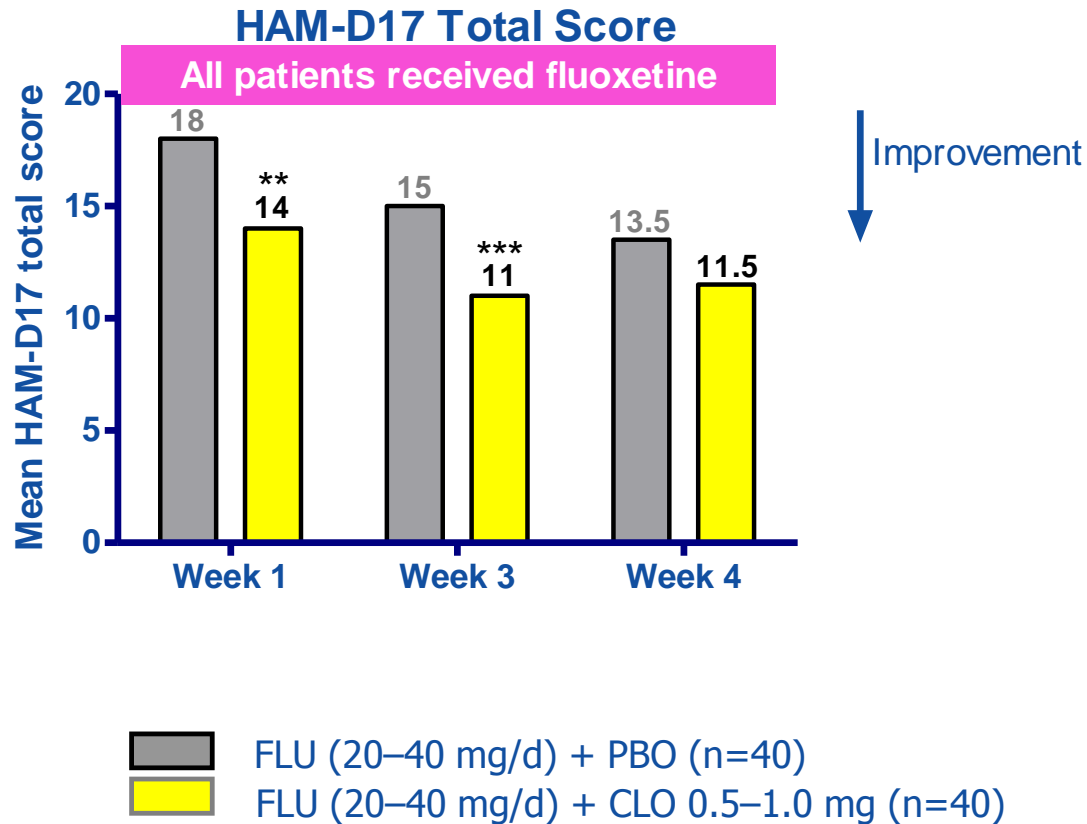
# Trials of Antidepressant/Sleep Agent Co-Therapy

- Clonazepam
- Eszopiclone
- Zolpidem CR

# Trial design: Clonazepam in patients with insomnia and MDD

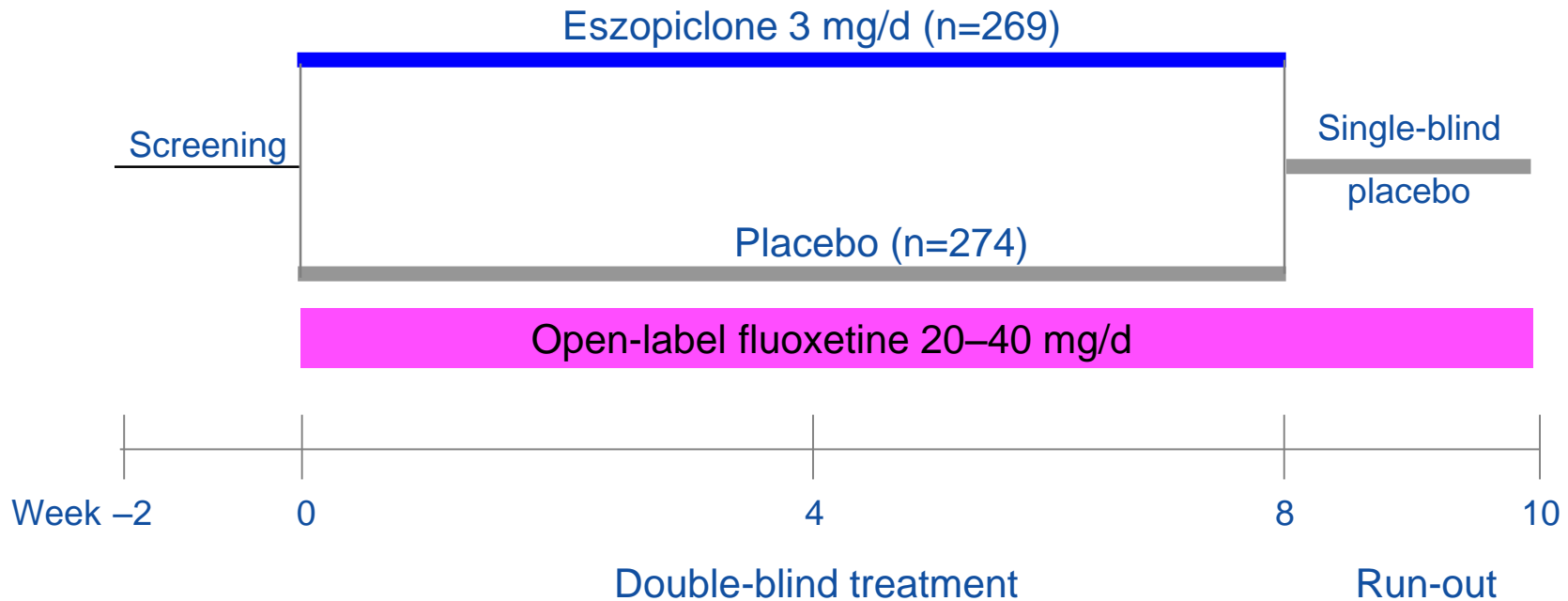


# Clonazepam: Depression outcomes in patients with insomnia and MDD

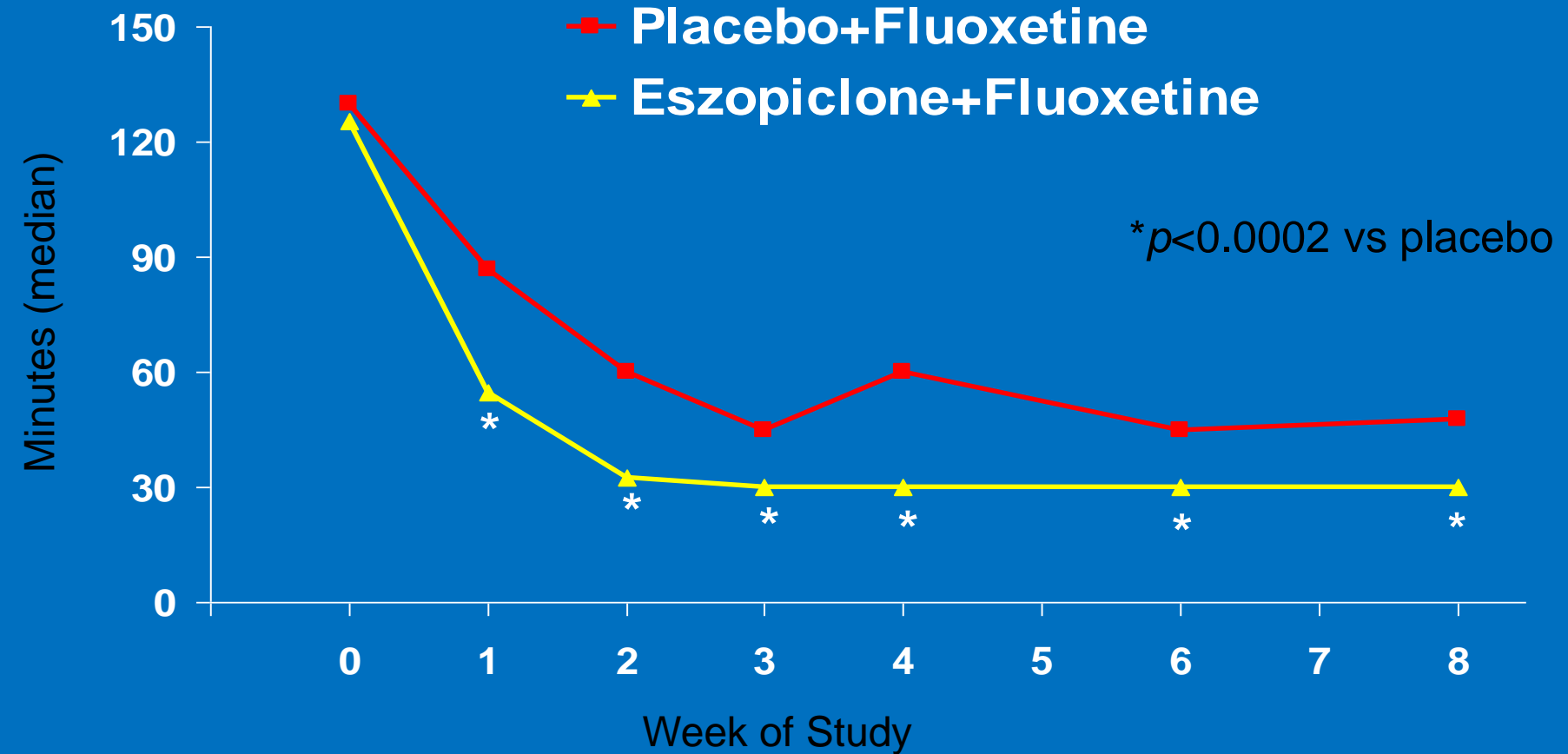


\*\*p<0.01, \*\*\*p<0.001 vs fluoxetine + placebo

# Trial design: Eszopiclone in patients with insomnia and MDD

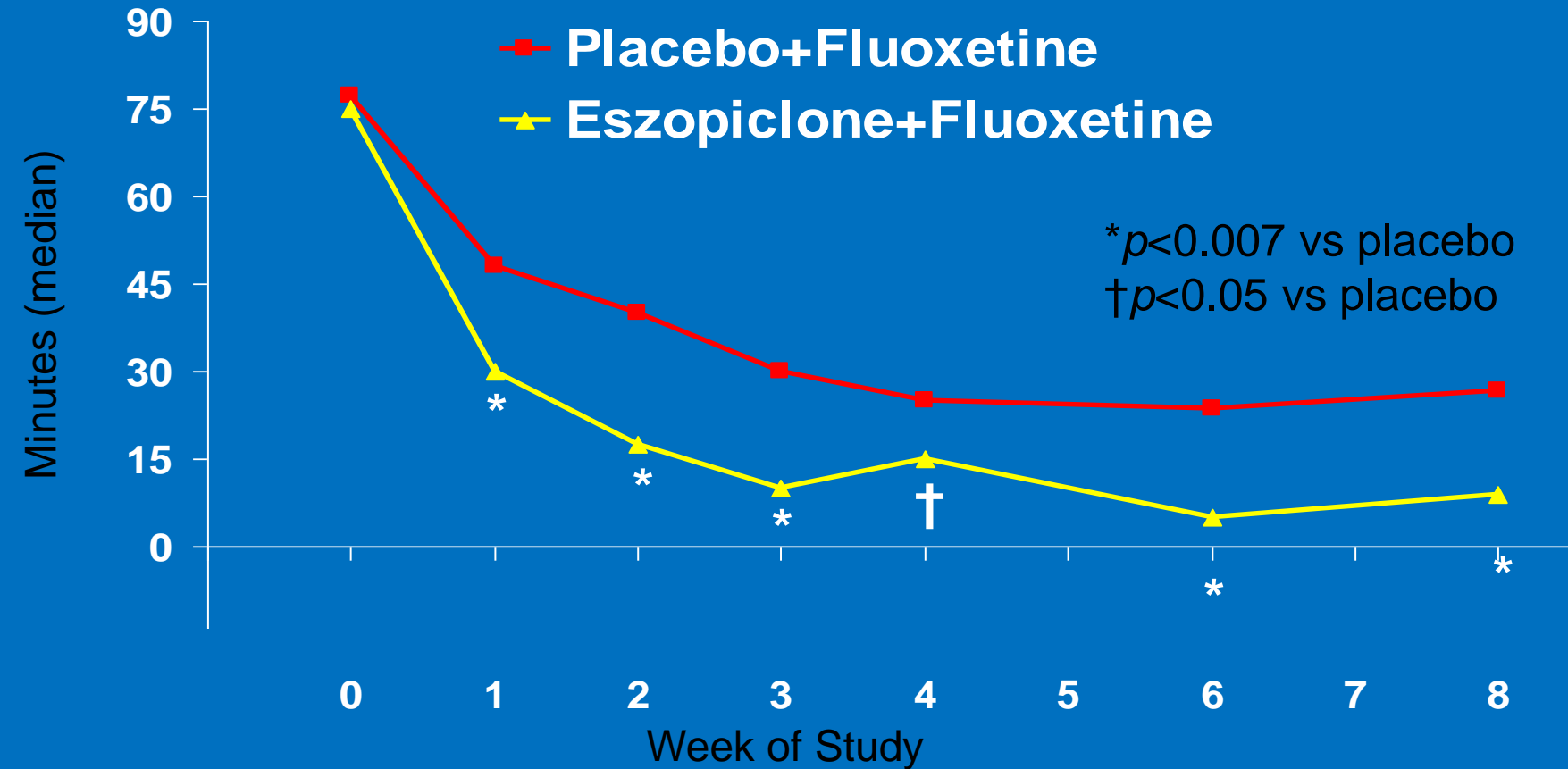


# Sleep Latency (LOCF)



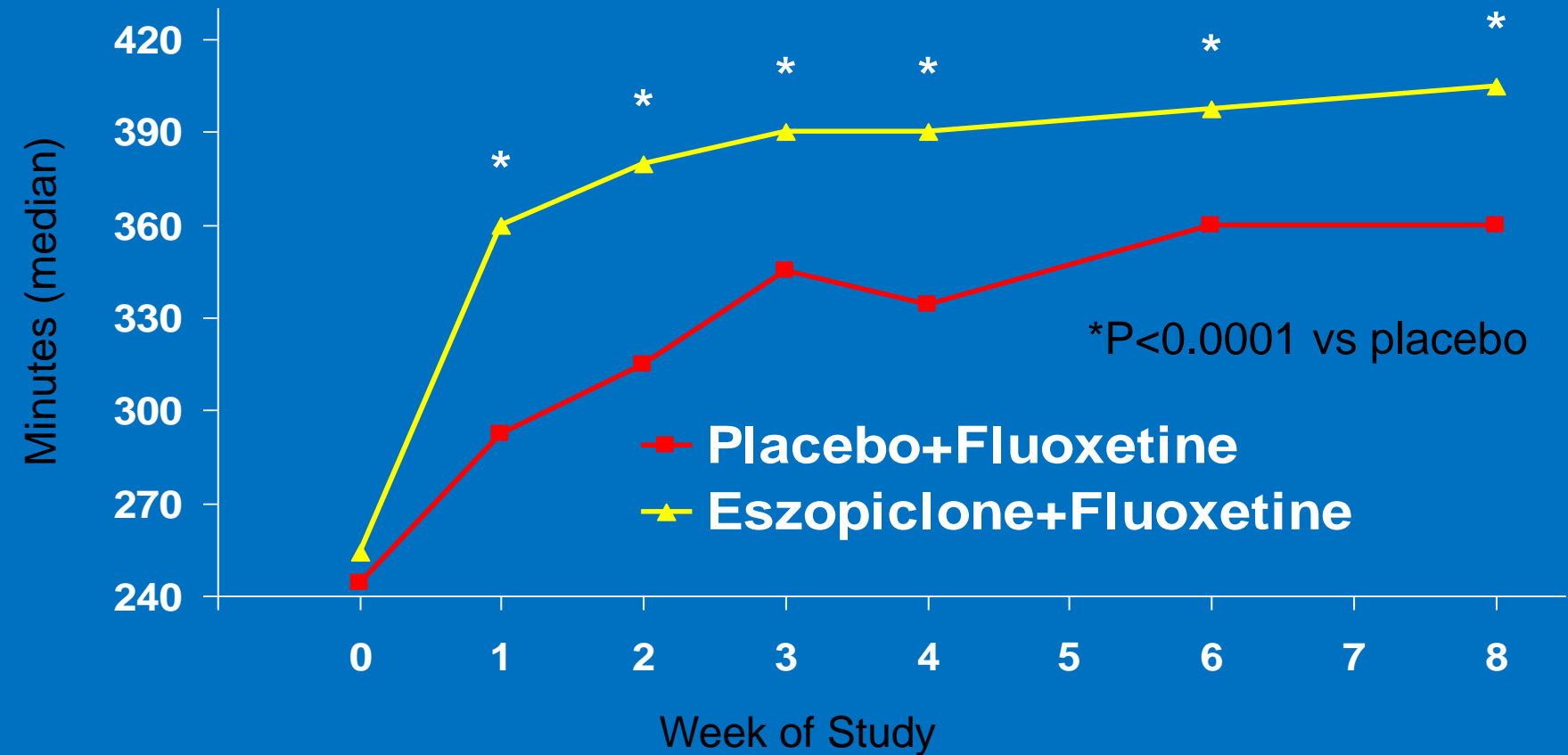
$p$  values reflect results from change from baseline analyses using ANCOVA.

# WASO (LOCF)



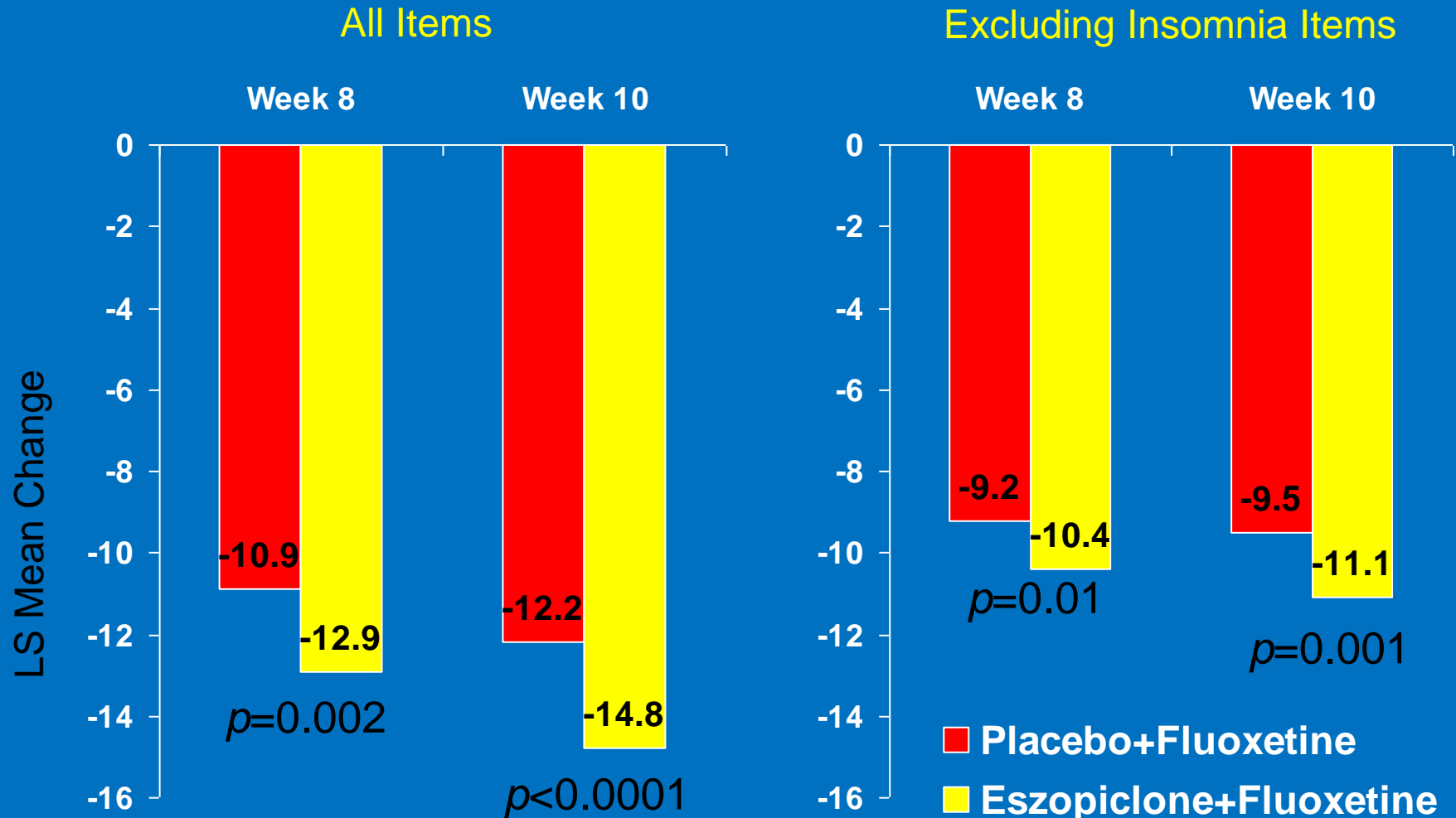
$p$  values reflect results from change from baseline analyses using ANCOVA.

# Total Sleep Time (LOCF)



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

# Change from Baseline in HAM-D17

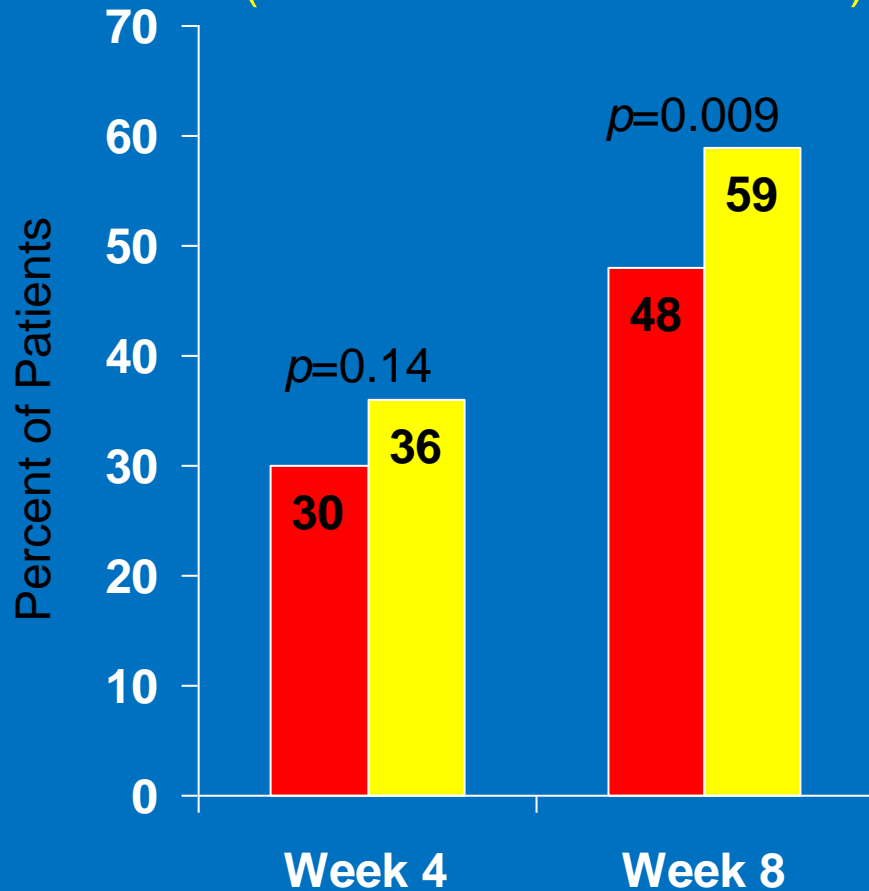


p values reflect results from change from baseline analyses using ANCOVA

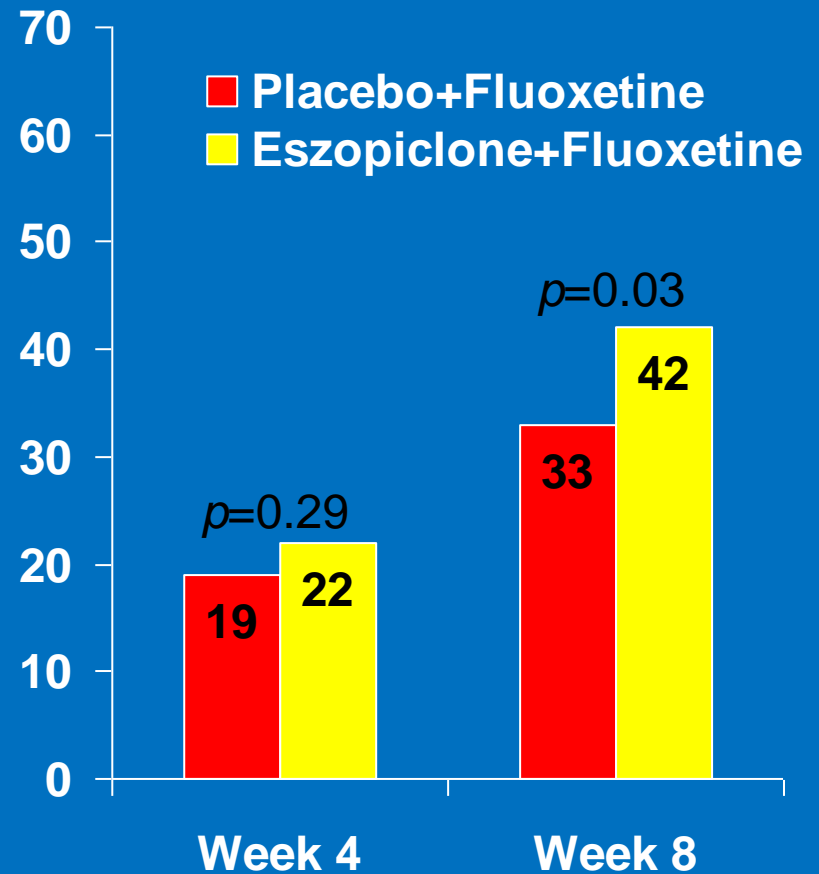


# Antidepressant Response and Remission (LOCF)

Response  
(50% HAM-D17 decrease)



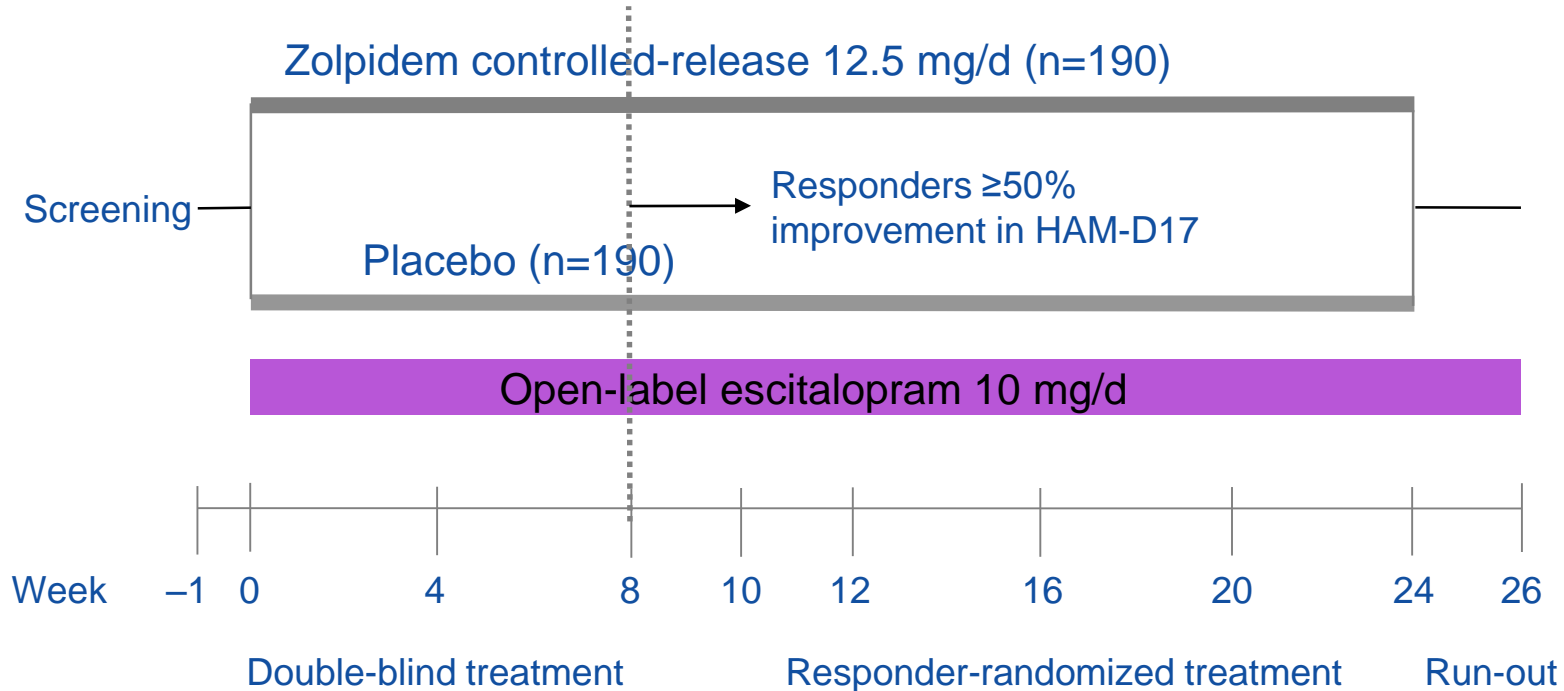
Remission  
(HAM-D17 ≤ 7)



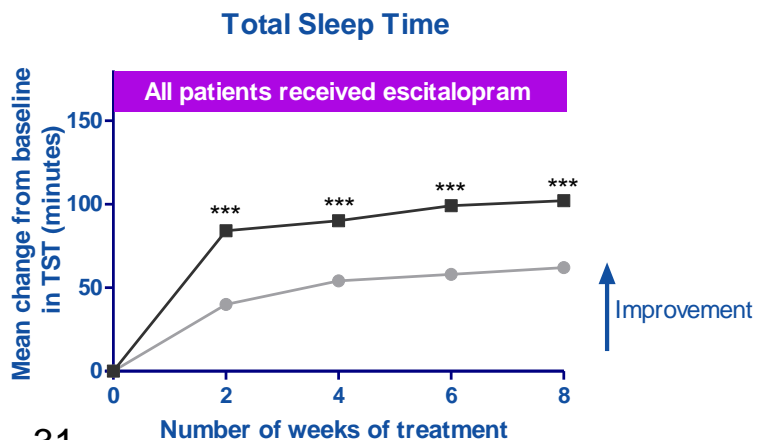
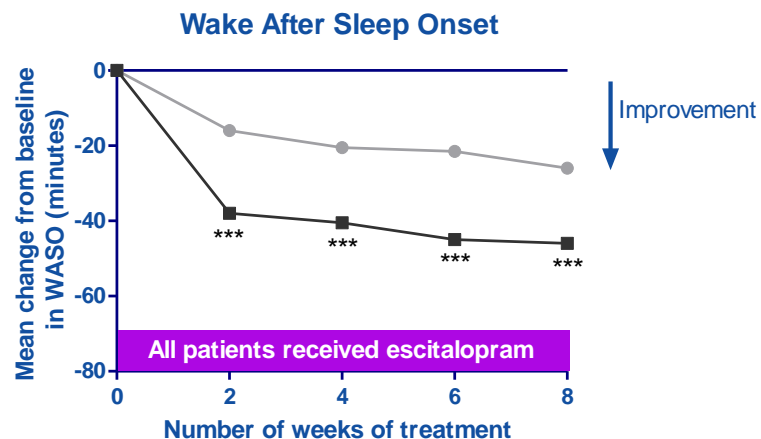
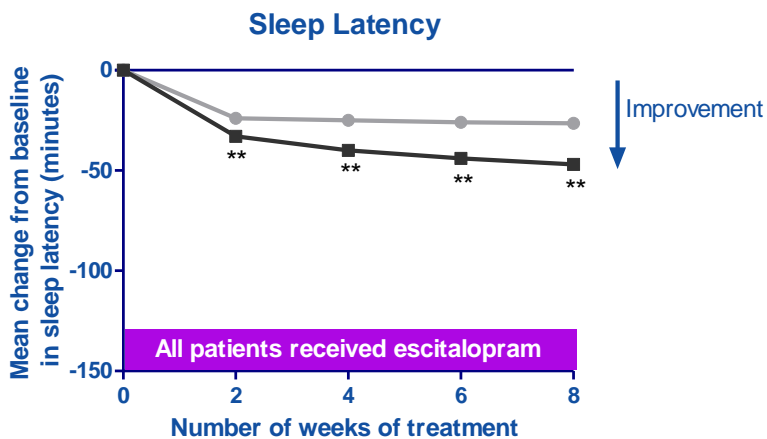
# Improvement in MDD Not Seen with Zolpidem CR

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

# Study design: Zolpidem CR in patients with insomnia and MDD



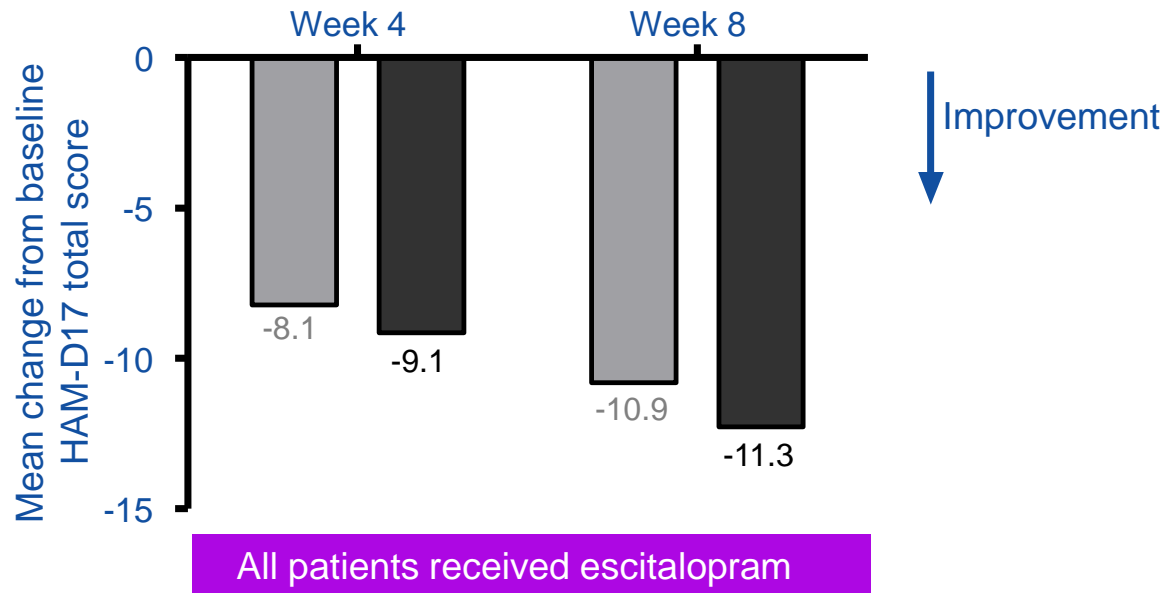
# Zolpidem CR: Sleep outcomes in patients with insomnia and MDD



- ESC 10 mg/d + PBO (n=190)
- ESC 10 mg/d + ZOL CR 12.5 mg (n=190)

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

# Zolpidem CR: Depression outcomes in patients with insomnia and MDD



- ESC 10 mg/d + PBO (n=190)
- ESC 10 mg/d + ZOL CR 12.5 mg (n=190)

# 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

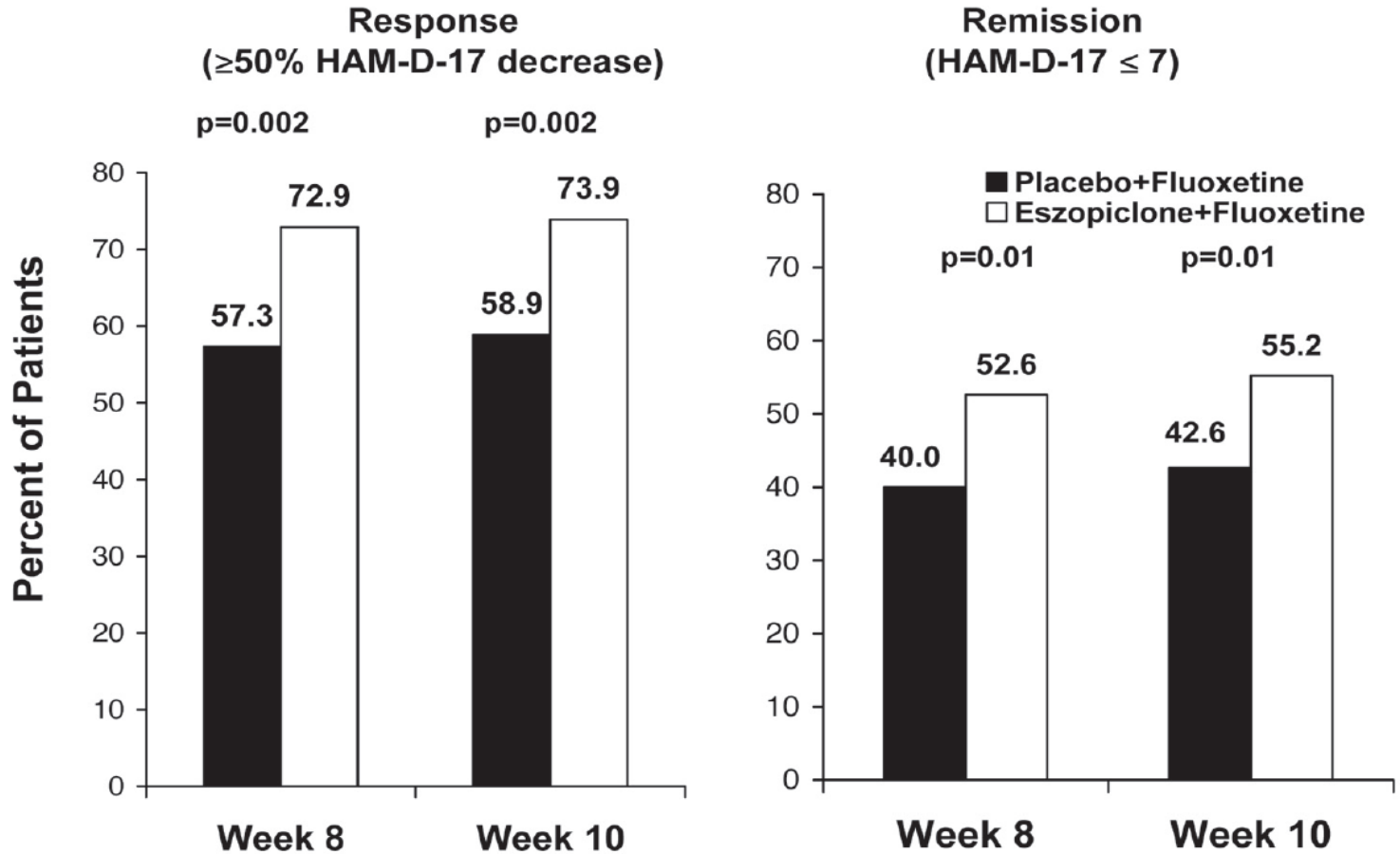
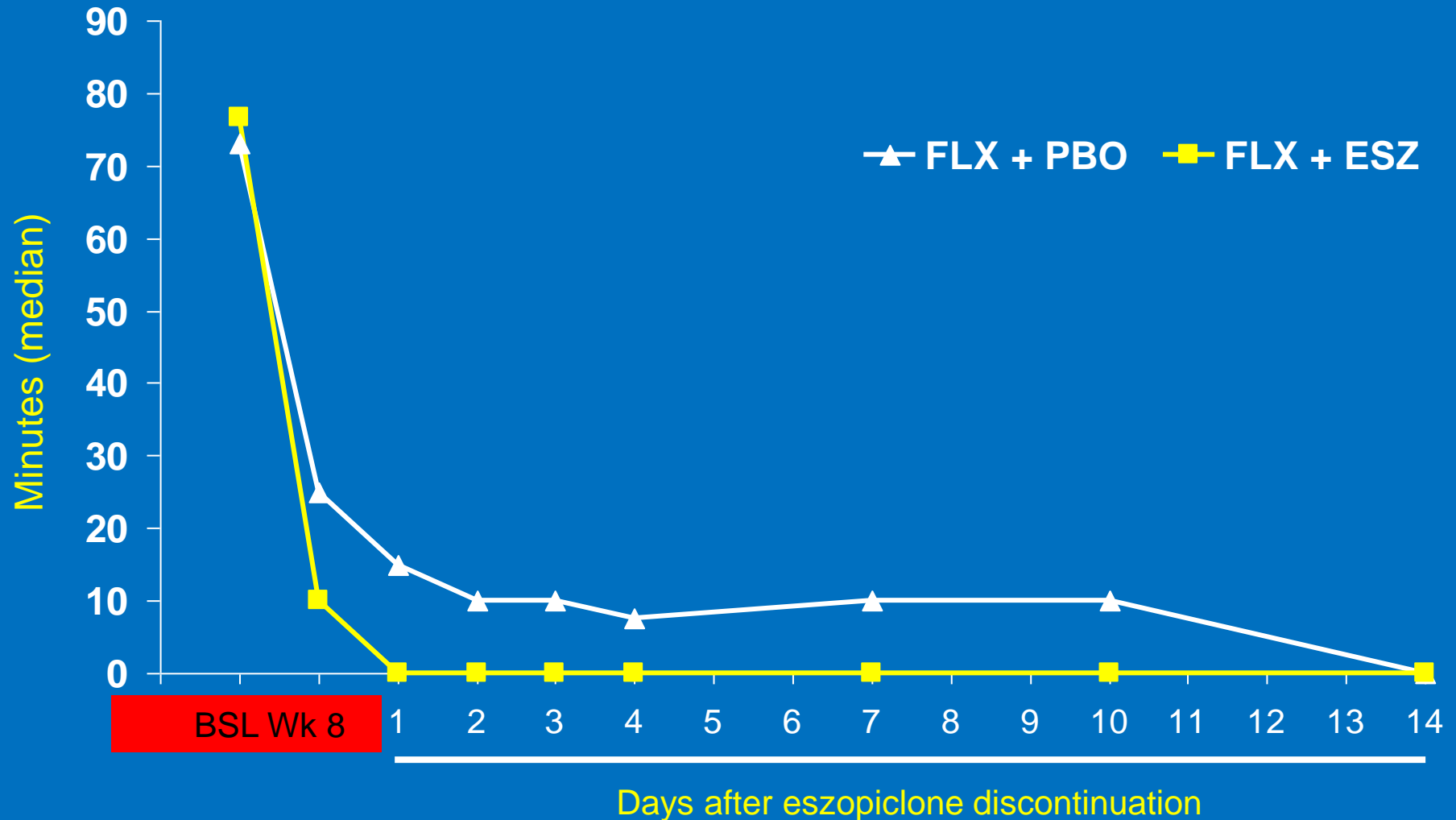


Figure 2—HAM-D-17 Response and Remission Rates at Weeks 8 and 10. Note: p-values reflect Chi-square results.

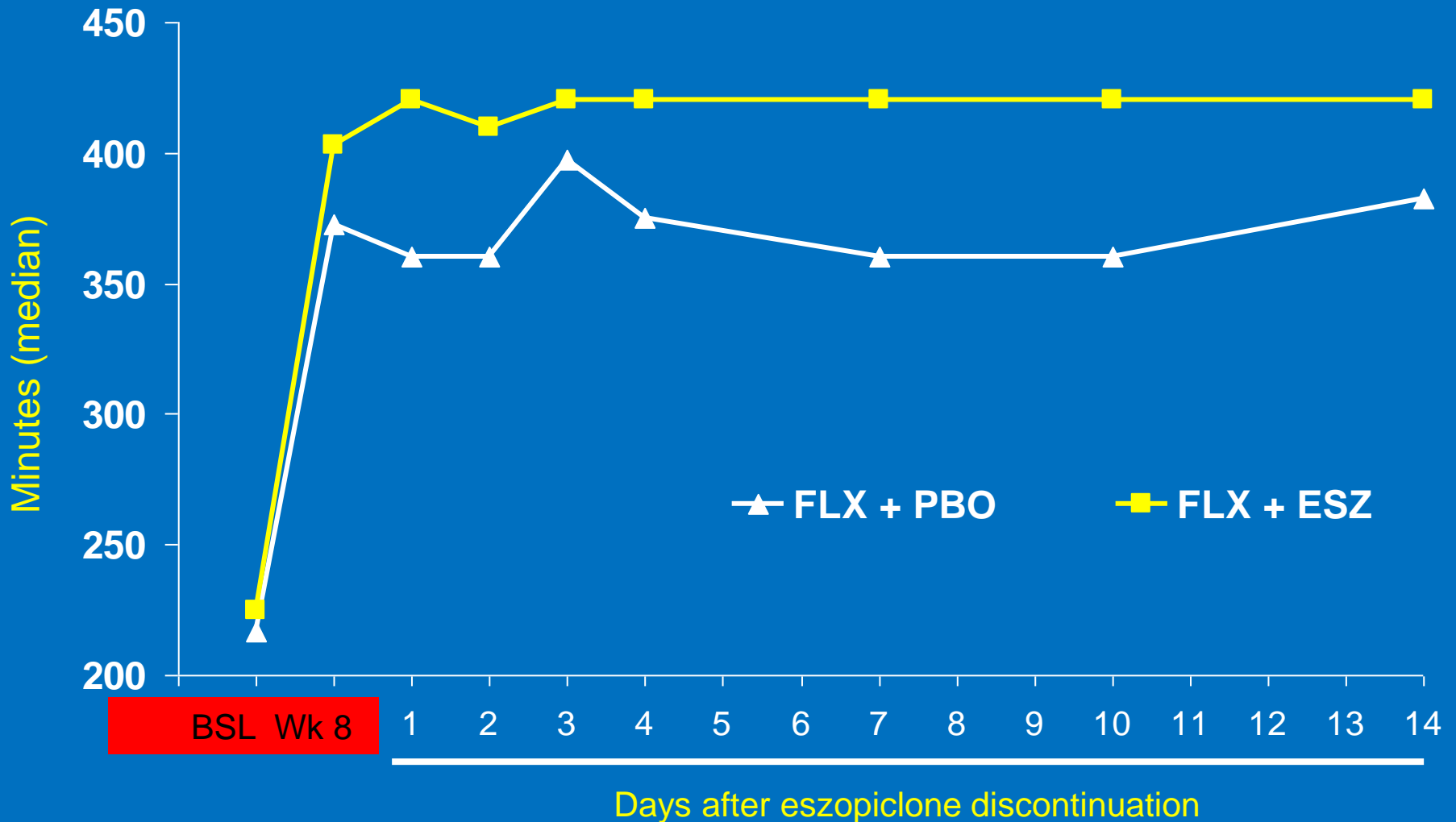
# Discontinuation Effects WASO



Week 8 = last week of DB treatment



# Discontinuation Effects TST

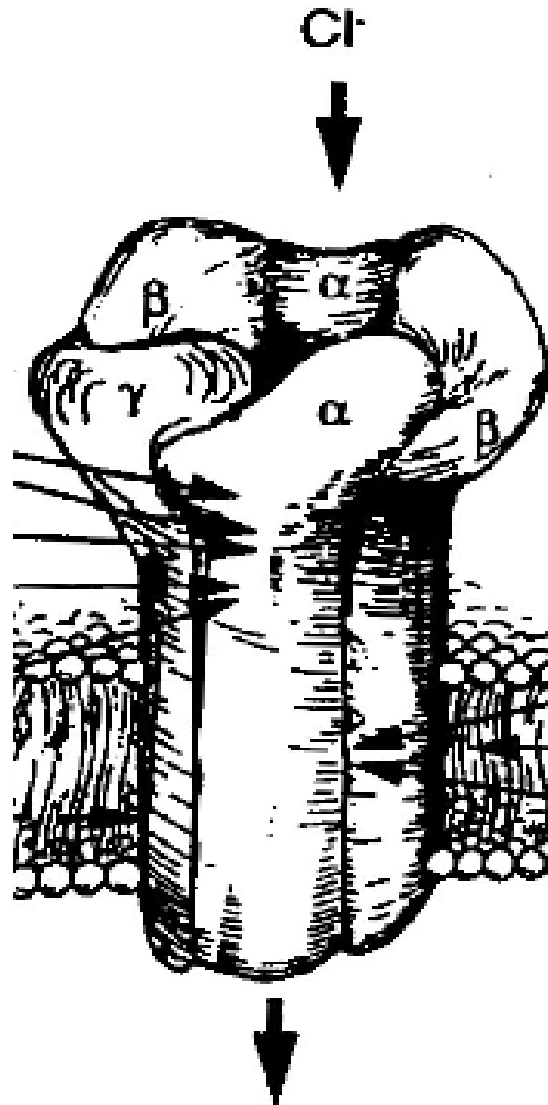


Week 8 = last week of DB treatment

# Mechanism of ESZ vs Zolpidem Difference?

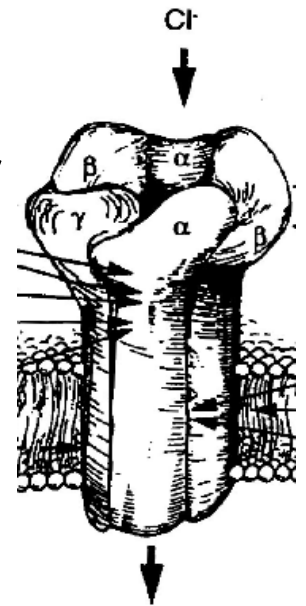
- **Benzodiazepines** Temazepam, Flurazepam, Triazolam etc.
  - A group of compounds with related chemical structure
  - Mechanism of action:
    - GABA receptor comprised of 5 peptides that form channel which controls the flow of chloride ions in and out of the neuron.
    - Generally, Cl concentration 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  $\alpha$  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  $\alpha$  subunit binding specificity

# The GABA Receptor Complex

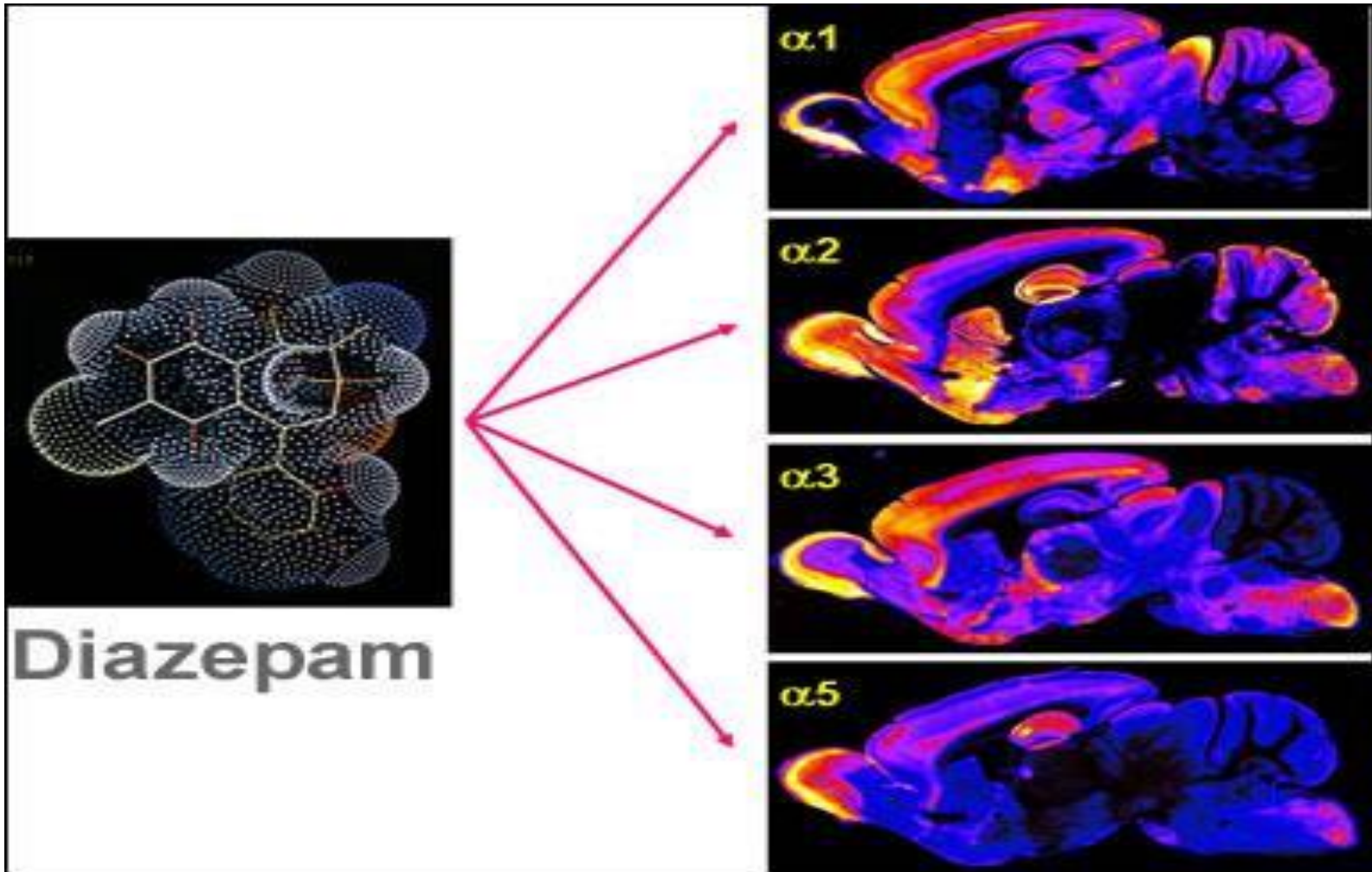


# GABA-A Subunit-Specific Effects

- The effects of binding to  $\alpha$  subunits differ because of location of GABA receptors containing them
  - Greater binding to  $\alpha$  subunits of GABA receptors in the cerebellum will result in greater effect on balance.
  - Greater binding to  $\alpha$  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  $\alpha$  subunit binding



# GABA Alpha Subunit Subtypes



# Animal Data on Effects of GABA Alpha Subunit Binding

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

Mohler et al., *J Pharmacol Exp Ther*, 2002; Kopp et al., *Proc Natl Acad Sci*. 2004; Van Rijnsgever et al., *J Neurosci*. 2004; Chandra et al., *Proc Natl Acad Sci*. 2006; Crestani et al., *Neuropharmacology*, 2002; Griebel et al., *J Psychopharmacol*. 1998

# 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?