QUETIAPINE FOR INSOMNIA

Amber Schilling, PharmD

November 7, 20XX

Objectives

- Explain how a diagnosis of insomnia is made
- List several pharmacologic therapies recommended by clinical practice guidelines for the treatment of insomnia, and identify quetiapine's place per these guidelines
- Identify the neurotransmitters involved in the pathophysiology of insomnia and which ones quetiapine may target
- State several potential risks and benefits for quetiapine being used off-label to treat insomnia

Definition & Prevalence

- **Insomnia:** difficulty in initiating or maintaining sleep which produces deficits in daytime function
- 33% of adults report insomnia symptoms
  - 6-10% have symptoms that meet diagnostic criteria
- More prevalent among females vs males (1.5: 1)
- 50% of patients with insomnia have a comorbid psychiatric disorder
  - Depression, Anxiety, Schizophrenia, Bipolar, Substance Abuse, Post-Traumatic Stress Disorder
- Often chronic (potential for long-term drug therapy)

Schutte-Rodin S, *J Clin Sleep Med* (2008)
DSM-V, American Psychiatric Association (2013).
Anderson SL et al, *Am J Health-Syst Pharm* (2014).

Image:
http://www.psihoterapeutul.ro/2012/02/06/insomnia/insomnia-cartoon/

Risk Factors

Vulnerable individuals

- Anxiety/worry-prone personalities
- "Light" sleepers
- Tendency to repress emotions
- Female gender (Birth of new baby, menopause)
- Advancing Age

Precipitating events

- Illness, bedridden w/ painful injury
- Separation (death of loved one)
- Chronic daily stress

Environmental factors

- Noise
- Light
- High/low temps
- High altitudes

DSM-V, American Psychiatric Association (2013).

Health Consequences

- Decreased quality of life, work productivity
  - Increased economic burden
- Memory, judgment, and impulse control impairments
- Deficiencies in immune system and healing process
- Increased risk of
  - Accidents (MVA, work-related)
  - Major Depressive Disorder, Anxiety, Suicide
  - Substance abuse
  - Hypertension
  - Myocardial Infarction
  - Tension ha, pain, GI problems

DSM-V, American Psychiatric Association (2013).
Anderson SL et al, *Am J Health-Syst Pharm* (2014).
Schutte-Rodin S et al, *J Clin Sleep Med* (2008).

Van Cauter, *J Clin Edocrin & Metab* (1992).
Durmer et al, *Seminars in Neurology* (2005).
Thomas M et al, *J Sleep Res* (2000).

Diagnosis (DSM-IV / V)

- **Primary Insomnia (DSM-IV) / Insomnia Disorder (DSM-V)**
  - Diagnosis is based on the patient's perceptions of their symptoms
    - **Subjective** Diagnosis
  - Symptoms:
    - Occur despite adequate opportunity for sleep
    - Are not attributable to other substances or medications
    - **Are not adequately explained by a comorbid mental disorder**
    - Cannot be better explained by another sleep-wake disorder (Narcolepsy, Sleep Apnea, Jet Lag, Shift-Work Disorder, etc.)

DSM, Diagnostic and Statistical Manual of Mental Disorders

DSM-IV, American Psychiatric Association (2000).
DSM-V, American Psychiatric Association (2013).

Diagnosis (DSM-V)

≥1 Nighttime Symptom(s)

Nighttime Symptom	Possible Manifestation
Difficulty initiating sleep	• Taking longer than 20-30 mins to fall asleep • Hyper-focused efforts on trying to sleep impairs ability to sleep
Difficulty maintaining sleep	• Frequent awakenings
Early morning awakening with inability to return to sleep	• Awaking before total sleep time reaches 6.5 hours

PLUS

Daytime Impairment(s)
• Social, occupational, educational, behavioral, etc. • Fatigue, decreased energy, mood disturbances

Duration
≥ 3 nights/wk , x ≥ 3 months (DSM-V) x ≥ 1 month (DSM-IV, Guidelines)

DSM-V, American Psychiatric Association (2013).

Polysomnography

- Objective measure; not required for diagnosis
- Sleep study test
  - Brain function (EEG)
    - Sleep stages (NREM, REM, Wakefulness)
  - Eye movements (EOG)
    - When sleep occurs
    - REM → rapid eye movements
  - Skeletal movements (EMG)
  - Heart Rate & Rhythm (EKG)
  - Respirations
  - O2 sats
  - Snoring (Sound Probe)

Image: www.oregon.gov

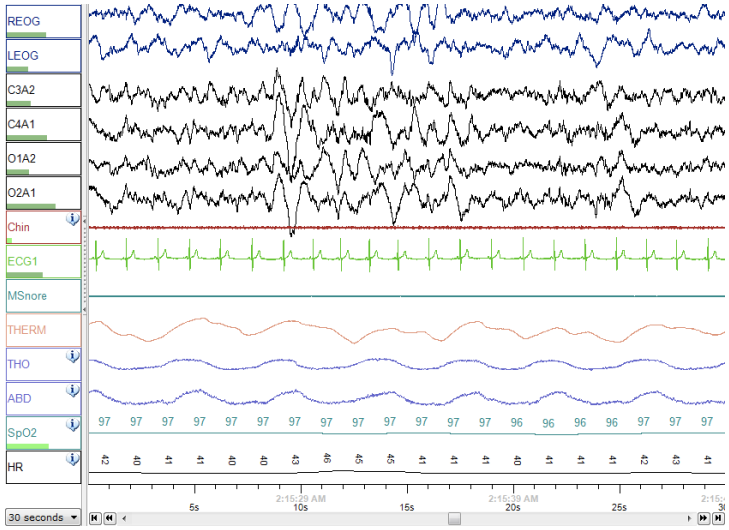


Image: Wikipedia

EEG, electroencephalogram; EOG, electro-oculogram; EMG, electromyogram; EKG, electrocardiogram

Armon C, Medscape (2014).

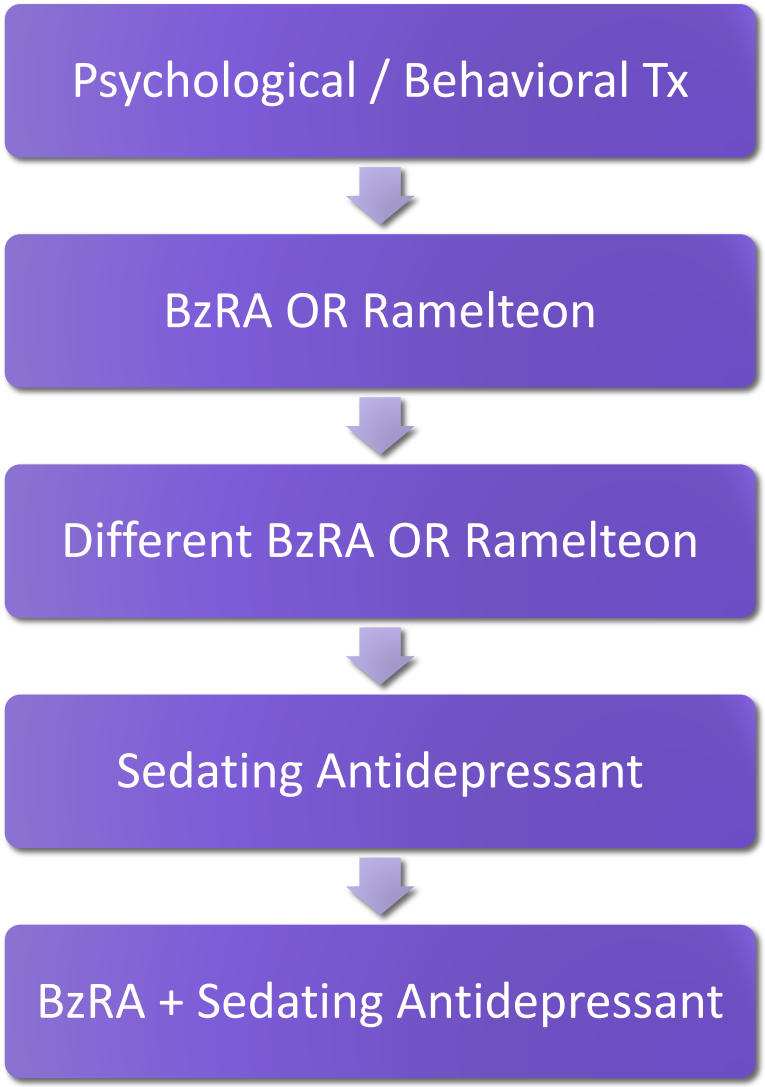
Treatment: Clinical Practice Guidelines

- At baseline and throughout treatment, patient should:
  - Keep a sleep diary
  - Complete sleep quality questionnaires
    - Insomnia Severity Index (ISI)
    - Pittsburgh Sleep Quality Index (PSQI)
    - (there are others)
  - "Frequent…patient feedback is an important component of treatment."

Sleep Diary Component	Definition
Sleep Onset Latency (SOL)	Time it takes to fall asleep once in bed
Total Sleep Time (TST)	Total amount of time spent asleep
Sleep Efficiency (SE)	Percent of time in bed spent asleep (TST/TotalTimeInBed) (>90% is considered normal)
Number of awakenings	---

Schutte-Rodin S et al, *J Clin Sleep Med* (2008).

Treatment: Clinical Practice Guidelines



Schutte-Rodin S et al, *J Clin Sleep Med* (2008).

Anti-epileptics, Anti-psychotics:

- Use only when patient would benefit from primary action as well as sedating effect

Not recommended:

- Barbiturates
- Chloral hydrate & derivatives
- OTC Sleep Aids
  - Anti-histamines, Herbals

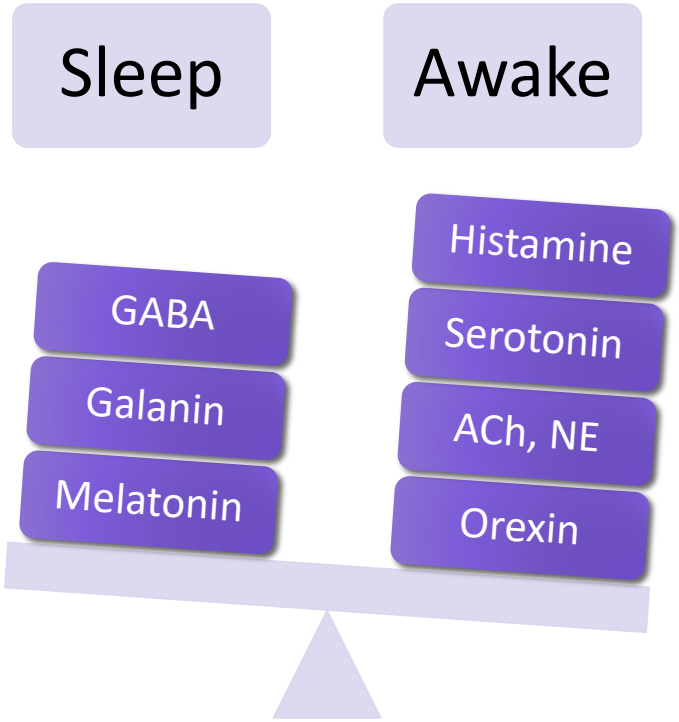
BzRA, Benzodiazepine Receptor Agonist (BDZ's and non-BDZ's)

Pathophysiology

2 Neurotransmitter Systems in the Brain

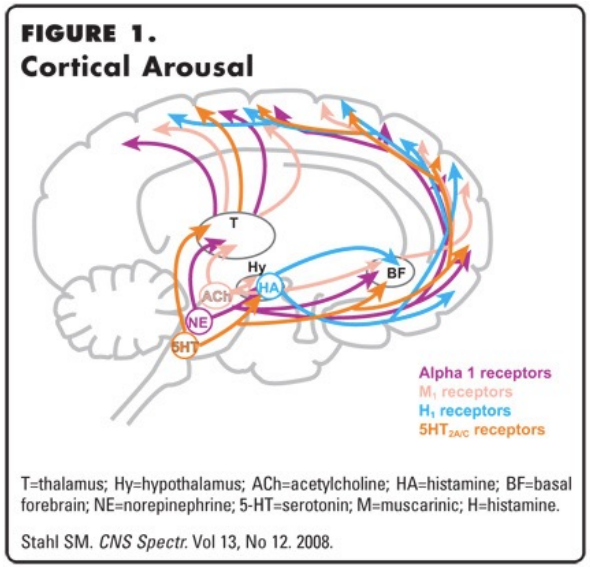
- Wake-promoting
- Sleep-promoting

Wake-promoting neurons project widely throughout brain to activate the cortex



GABA=Inhibitory NT

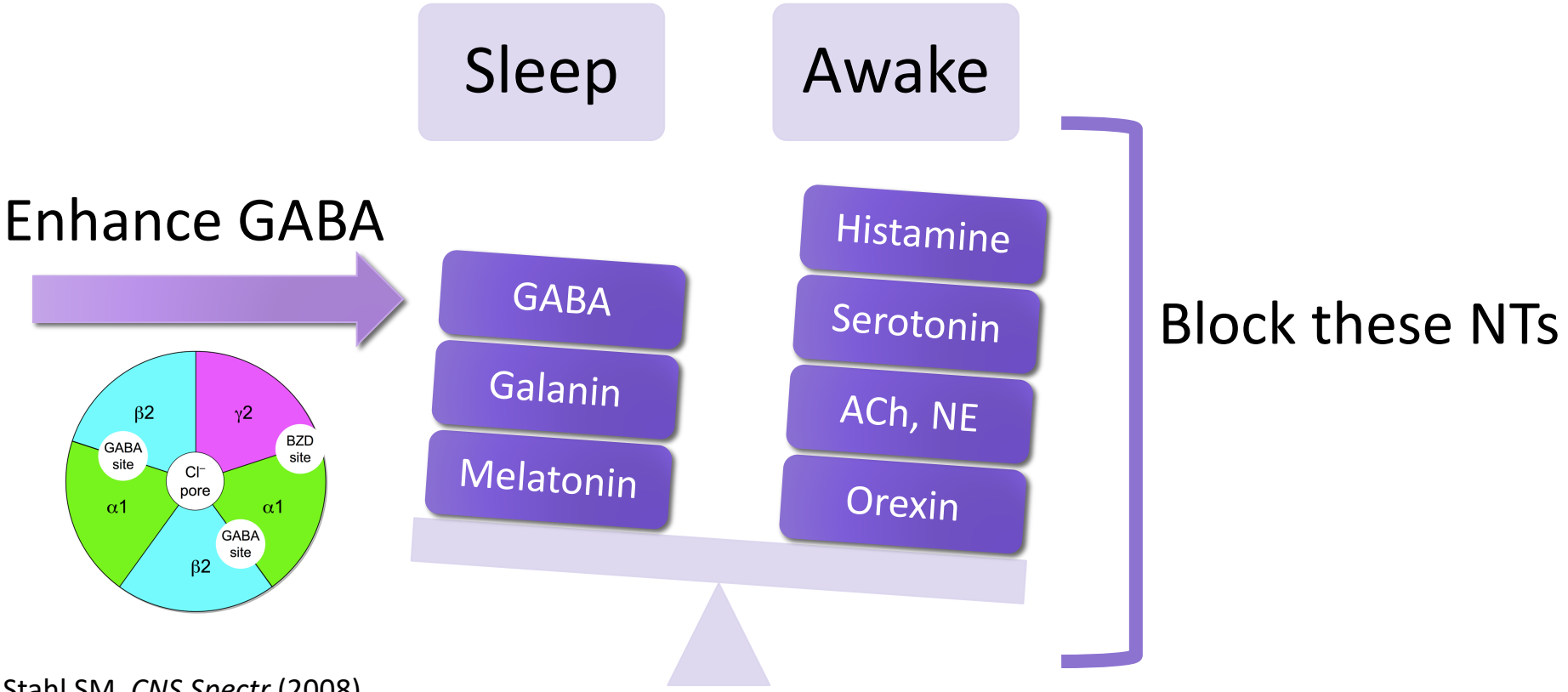
Sleep-promoting neurons project to all regions of the cortex where wake-promoting neurons are located



Stahl SM, *CNS Spectr* (2008).

Treatment Approaches

- Insomnia: Excessive wake-promoting tone
- To treat:



Stahl SM, *CNS Spectr* (2008).
Image of GABA receptor: http://en.wikipedia.org/wiki/GABAA_receptor

Binding Profiles

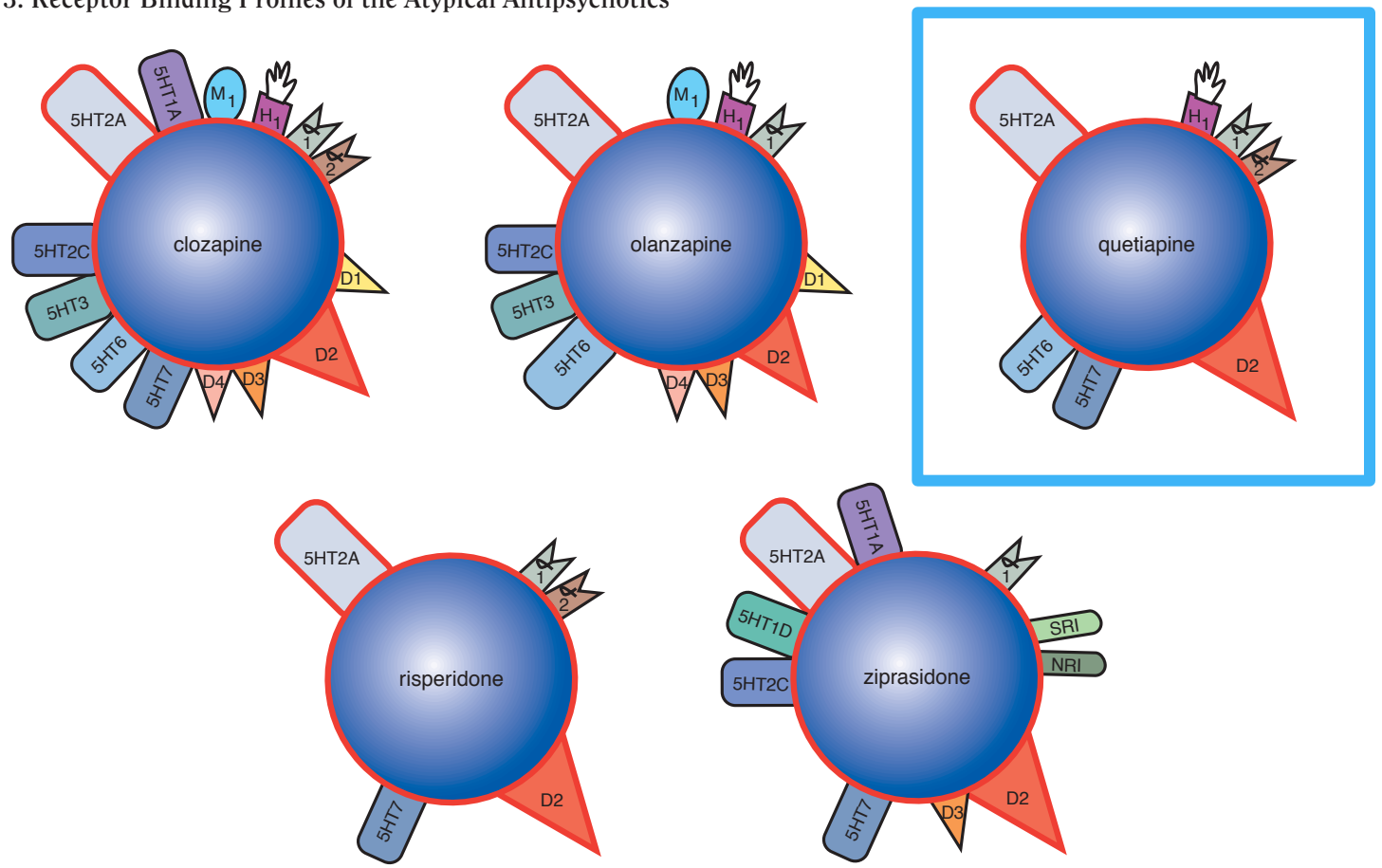
Agent	BDZ Binding	Anti-H1	MT1-2	Anti-5HT2	Anti-alph1	Anti-dopa	Anti-cholinergic	Anti-orexin
BDZs	+++							
Non-BDZ BzRA	+++							
Remelteon			+++					
Doxepin		+++			+++		+	
Amitriptyline		+++			+++		+++	
Trazodone				+++	+++			
Mirtazepine		+++		+++				
Quetiapine		++		+	+++	+		
Diphenhydramine		+++					+++	
Doxylamine		+++					+++	
(Suvorexant)								+++

Krystal, *Sleep Med Rev* (2009).

BDZ, Benzodiazepine; H1, histamine Type 1; MT1-2, Melatonin Type 1 and 2; 5HT2, serotonin Type 2

Second Generation Anti-Psychotics

Figure 3. Receptor Binding Profiles of the Atypical Antipsychotics[a]



[a]Reprinted with permission from Stahl.[11]
Abbreviations: α_1 = α_1-adrenergic, α_2 = α_2-adrenergic, D = dopamine, 5HT = serotonin, H = histamine, M = muscarinic, NRI = norepinephrine reuptake inhibitor, SRI = serotonin reuptake inhibitor.

Stahl SM, *Primary Care Companion J Clin Psychiatry* (2003).

Quetiapine

Receptor Blocked	Effect of the Blockade
D2	Anti-psychotic
5-HT2a	Anti-psychotic **Sedation** Incr DA release in Nigrostriatal Pathway Decr platelet aggregation
H1	**Sedation** Weight Gain
Alpha-1	Vasodilation → hypotension, reflex tachycardia
Alpha-2 (autoreceptor)	Increase in NE
5-HT6	Unknown
5-HT7	Unknown

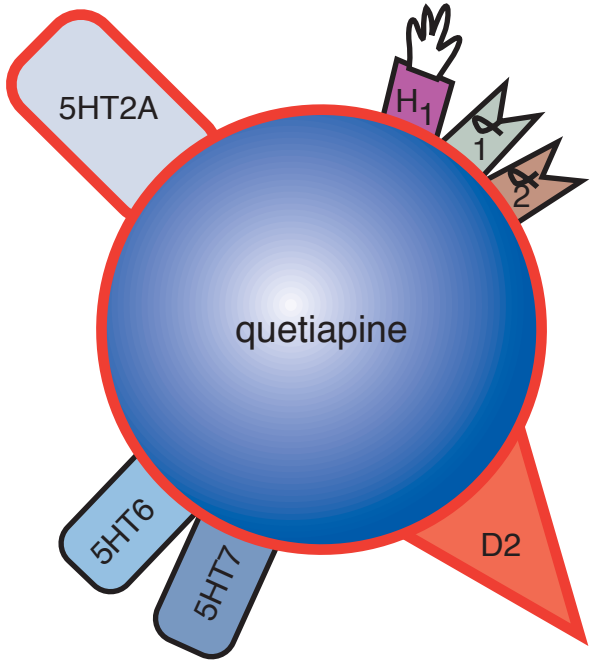


Image: Stahl SM, *Primary Care Companion J Clin Psychiatry* (2003).

SE of Quetiapine

Rare	Low Risk	Medium Risk
• Extrapyramidal SE • Prolactin Elevation	• Anti-Cholinergic SE	• QTc Prolongation • Weight Gain • DM2 • Hyperlipidemia • Orthostatic Hypotension • Sedation

Muench J et al, *American Family Physician* (2010)

Second Generation Antipsychotics, *Lexi-Drugs* (2014)

Quetiapine

Brand Names	Seroquel®, Seroquel®XR
FDA Approved Indications	Schizophrenia Bipolar I Disorder Major Depressive Disorder (as adjunct) → XR only *Ages 10yo and up only
Half-life (elimination)	Parent: 6-7hr Active Metabolite (norquetiapine): 12hr
Black Box Warnings	1. Increased risk of death in elderly patients with dementia-related psychoses 2. Increased risk of suicidal thoughts and behavior in patients <24yo
Available Dosage Forms and Strengths	Oral Tablet: **25, 50, 100**, 200, 300, 400mg Oral Tablet (XR): 50, 150, 200, 300, 400mg
Patent Expiry	March 2012

Seroquel (quetiapine fumarate), Full Prescribing Information, AstraZeneca, Revised Oct 2013.
Seroquel XR (quetiapine fumarate), Full Prescribing Information, AstraZeneca, Revised Oct 2013.
GoodRx. www.goodrx.com (Accessed October 9, 2014)

Quetiapine

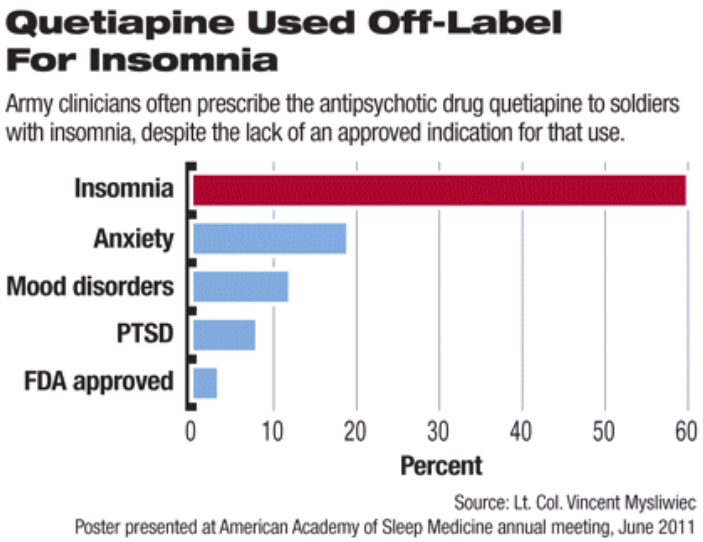
- Controversies
  - April 2010: AstraZeneca payed $520 million to the federal government to settle a civil lawsuit
    - AstraZeneca aggressively promoted Seroquel® to physicians for unlabeled uses (one of which was “sleeplessness”)

US Department of Justice, *Justice News* (Apr 2010).

The Clinical Controversy

- Is quetiapine's off-label use for insomnia appropriate when the patient has no other comorbid psychiatric illnesses?

Quetiapine was prescribed more often for insomnia than for its FDA approved indications (2011)



Kime, www.armytimes.com, (2012)
Bar Graph: Krystal, *Sleep Med Rev* (2009)
Levin, *Psychiatric News* (2011

Quetiapine 6th most prescribed agent for insomnia, but few trials supporting its use

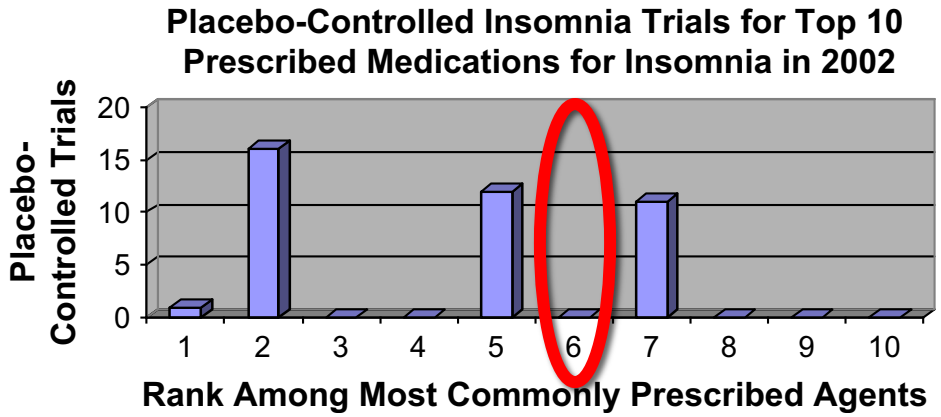


Fig. 1. Agent rank: 1: trazodone, 2: zolpidem, 3: amitriptyline, 4: mirtazapine, 5: temazepam, 6: quetiapine, 7: zaleplon, 8: clonazepam, 9: hydroxyzine, 10: alprazolam.

The Clinical Controversy

- Possible reasons why quetiapine has been used as alternative to guideline-based recommended treatments:
  - BzRA (BDZ and non-BDZ)
    - Controlled substances
    - Habit-forming: risk of psychological / physiologic dependence with long-term use
    - Anterograde amnesia (pt may not have slept well, but cannot remember)
    - Hallucinations
    - Next-day Hangover effect (less common with non-BDZ, but can still occur)
    - Complex sleep-related behaviors (potentially hazardous)
      - Driving, Cooking, Eating, Making Phone Calls (all while asleep)
  - Remelteon
    - Expensive

Lexi-Drugs (2014)

Review of the Literature

- Use of quetiapine for Primary Insomnia:
  - Only 2 clinical trials to date
  - No trials comparing quetiapine to an active treatment

Authors	Trial Name	Intervention	# of patients
Wiegand et al (2008)	Quetiapine in primary insomnia: a pilot study	Quetiapine 25mg (all pts)	18
Tassniyom et al (2010)	Quetiapine for primary insomnia: a double blind, randomized controlled trial	Quetiapine 25mg vs Placebo	13

- For a frame of reference:
  - BzRA's:
    - Decrease sleep latency by 10-20 mins
    - Increase total sleep time by 30-60 mins
  - Ramelteon
    - Decrease sleep latency by 5 mins
    - Increase total sleep time by 7 mins

Buscemi et al, *J Gen Int Med* (2007)
Holbrook et al, *CMAJ* (2000)
Kuriyama et al, Sleep Med (2014)

Wiegand et al (2008)

METHODS	
Trial Design	Single-center, open label pilot study (Germany)
Interventions	Quetiapine 25mg QHS x6weeks • Dose could be increased PRN
Inclusion Criteria	Primary Insomnia (DSM-IV)
Exclusion Criteria	Not specified
Endpoints Measured • Primary/Secondary Not Stated	Total Sleep Time, Sleep Latency, Sleep Efficiency, REM Sleep Latency, Slow Wave Sleep • Polysomnography • Sleep Diaries, Questionnaires (PSQI)
Statistical Analyses	Wilcoxon's Test Alpha not specified, but assumed = 0.05 2-tailed alpha Beta (power) not specified

Wiegand et al, *Psychopharmacology* (2008)

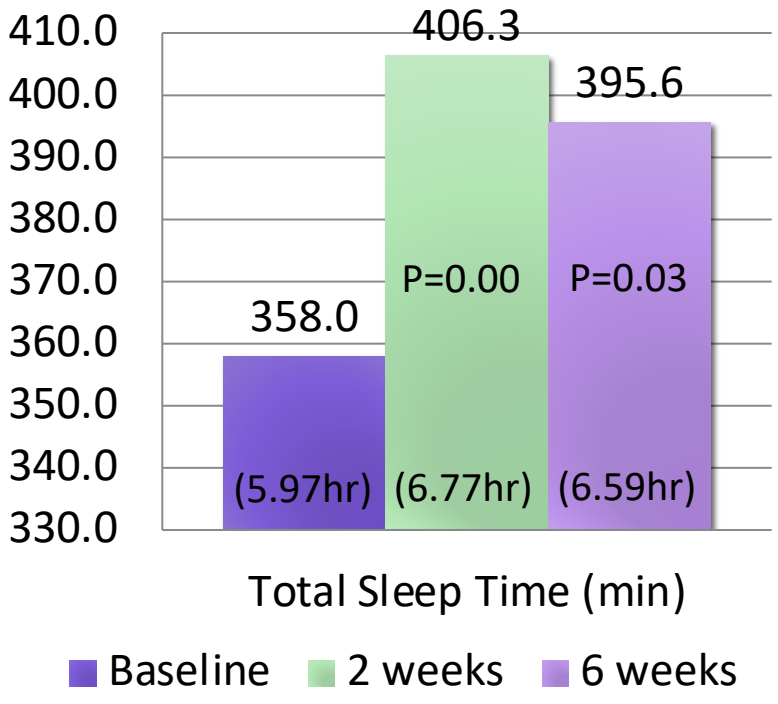
Wiegand et al (2008)

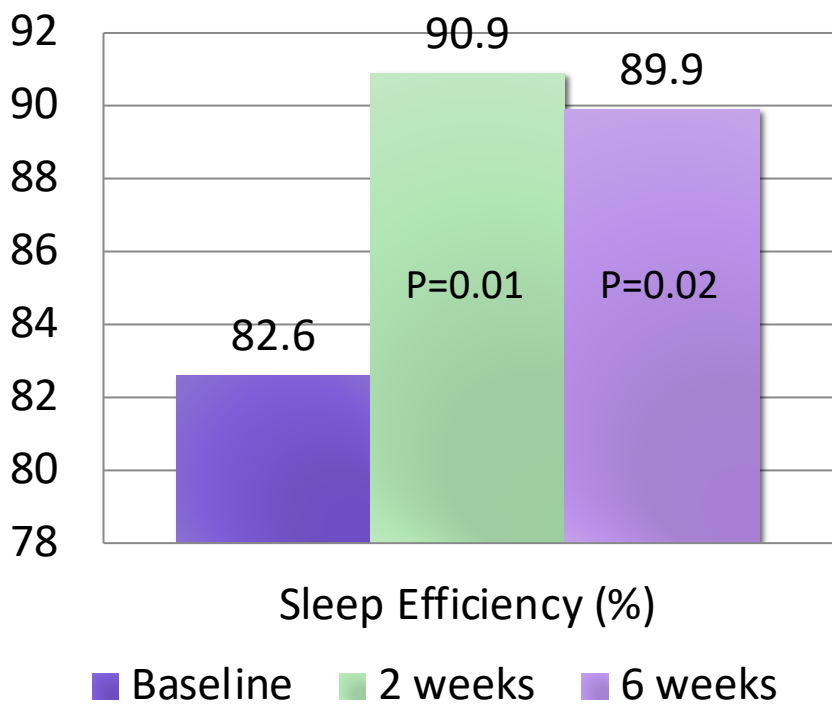
RESULTS	
Enrollment	18 patients
Monitoring	Baseline, 2 weeks, 6 weeks
Doses of quetiapine utilized	10 pts → 25mg for entire 6 weeks 7 pts → dose was increased to 50mg 1 pt → dose was increased to 75mg
Endpoints	Statistically significant improvements compared to baseline at both 2wks, 6wks: • Increase in TST (polysomnography, PSQI) • Increase in Sleep Efficiency (polysomnography, PSQI) • Increase in sleep quality (PSQI) No significant improvement from baseline: • Sleep Latency, REM Sleep Latency, Slow Wave Sleep (polysomnography)
Side Effects Reported	Dry Mouth Next morning hangover effect

Wiegand et al (2008)

RESULTS

- Polysomnography data
- Values reported are means
- p values reflect change from baseline



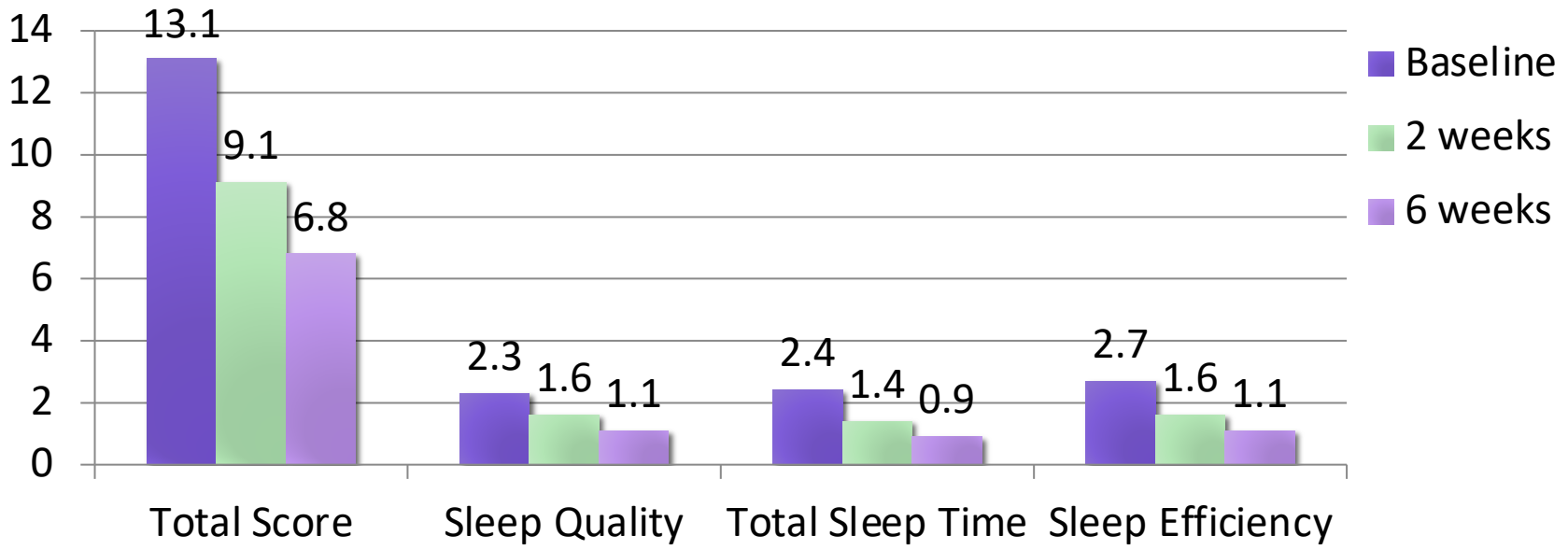


Wiegand et al, *Psychopharmacology* (2008)

Wiegand et al (2008)

RESULTS

- PSQI Scores
- Values reported are mean scores
- The lower the score, the better the patient perceives they are sleeping
- All p values were 0.00 and reflect change from baseline score



Wiegand et al, *Psychopharmacology* (2008)

Wiegand et al (2008)

STRENGTHS / LIMITATIONS	
Strengths	Objective and subjective parameters utilized (polysomnography and patient questionnaires) Endpoints measured consistent with guideline recommendations Groundwork for future studies
Limitations	Small number of patients Open label (no placebo, no active control) Baseline characteristics not provided (external validity unknown) Not statistically robust • Alpha had to be inferred • No mention of power, sample size calculation • Primary and Secondary endpoints not delineated • Power could be an issue for variables where no significance was found Short duration Metabolic side effects not seen, but unknown if monitored

Wiegand et al (2008)

AUTHOR'S CONCLUSIONS

- Majority did NOT require dose escalation (efficacy seen for 6weeks at 25mg)
- Quetiapine may be a viable pharmacologic treatment option for insomnia

OWN CONCLUSIONS

Low-dose quetiapine given over a 6week period:

- Improved patient's perception of their sleep
- Increased total sleep time by approx 40 mins
- Increased sleep efficiency (probably 2/2 increase in TST)
- Did not help patients initiate sleep
- Did not significantly increase slow wave or REM sleep
- Did not produce any serious side effects

Interpret results with caution

Wiegand et al, *Psychopharmacology* (2008)

Tassniyom et al (2010)

METHODS	
Trial Design	Randomized, double-blind, placebo-controlled (Thailand)
Study Dates	January 2007 – December 2007
Interventions	Quetiapine 25mg –OR– Placebo QHS X2 weeks
Inclusion Criteria	Primary Insomnia (DSM-IV) Age 16-65
Exclusion Criteria	Any other psychiatric diagnosis Meds that could cause sedation Orthostatic hypotension, Liver disease, Thyroid disease, Heart disease, H/o seizure, Cognitive Impairment, Pregnancy, Unable to keep sleep diary or answer questionnaires

Tassniyom et al, *J Med Assoc Thai* (2010)

Tassniyom et al (2010)

METHODS, cont'd	
Primary Endpoints	Total Sleep Time (TST) → sleep diary Sleep Latency (SL) → sleep diary Daytime alertness and functioning Sleep satisfaction
Secondary Endpoint	Side Effects
Statistical Analyses	16 pts required $p<0.05$ for statistical significance Block randomization (block size = 4) Independent t-test Beta (power) not specified

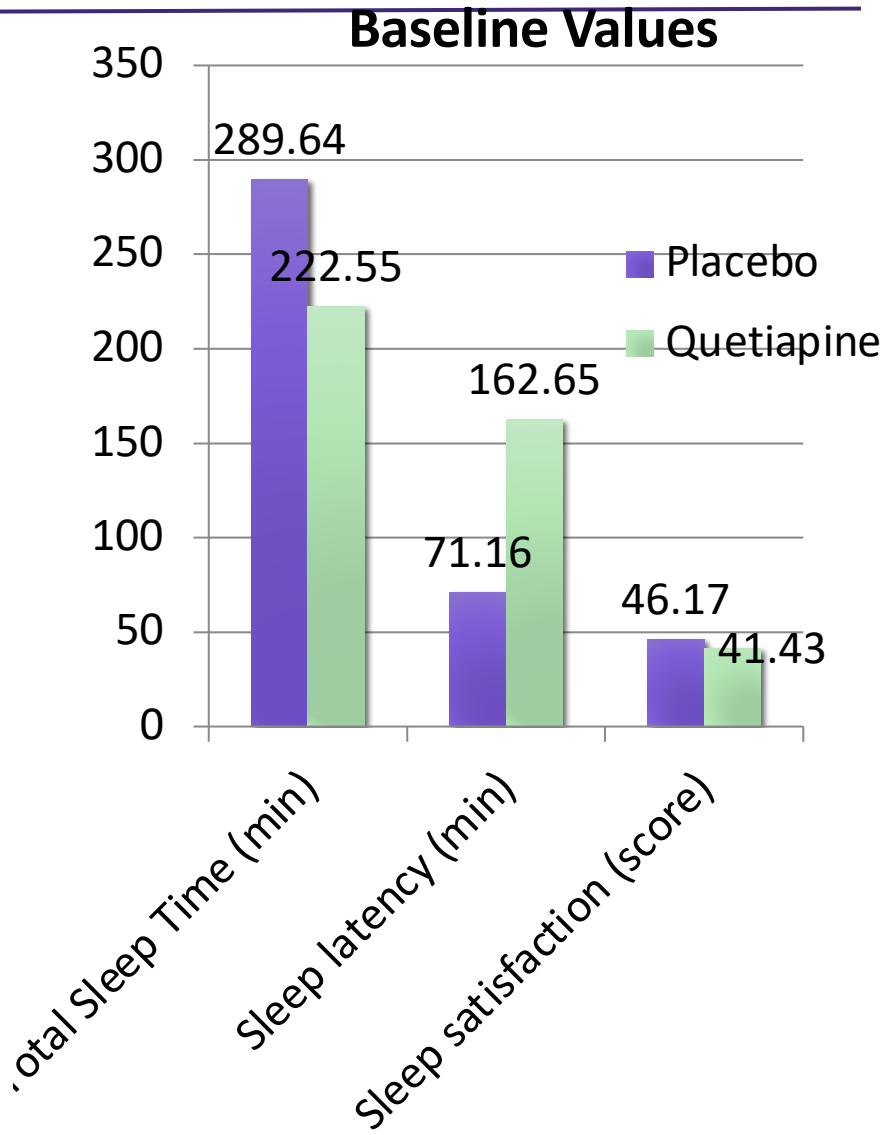
Tassniyom et al, *J Med Assoc Thai* (2010)

Tassniyom et al (2010)

RESULTS	

Enrollment	16 patients randomized
	• 13 completed study
	  • n=7 (quetiapine)
	  • n=6 (placebo)

Baseline Characteristics	Mean age: 45.95 yrs (range, 25-62) More females More severe insomnia symptoms at baseline in quetiapine group
Endpoints	None were statistically significant
Side Effects	Dry lips Daytime drowsiness

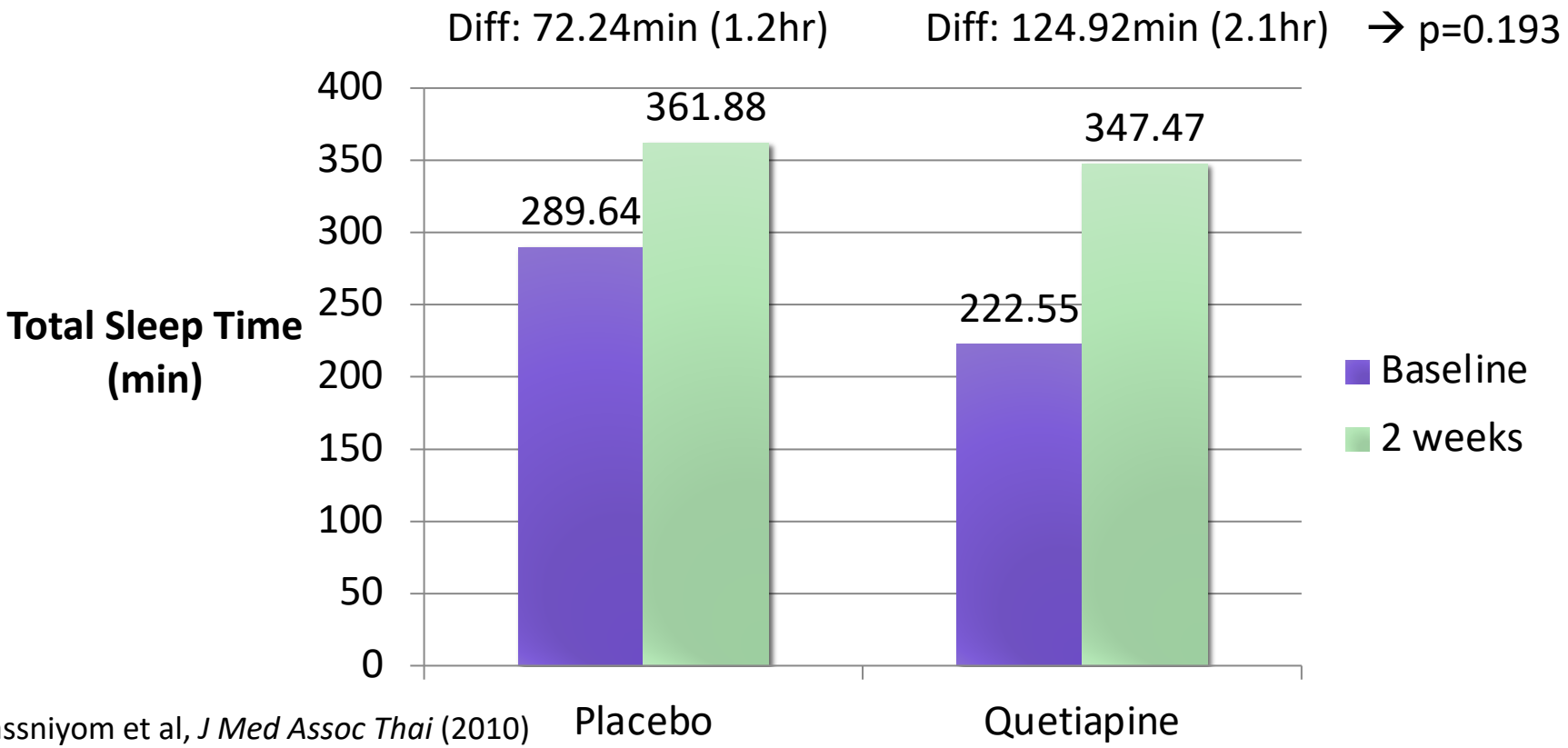


Tassniyom et al, *J Med Assoc Thai* (2010)

Tassniyom et al (2010)

RESULTS, cont'd

Total Sleep Time
- Not statistically significant, but could be clinically significant
- Clear placebo effect

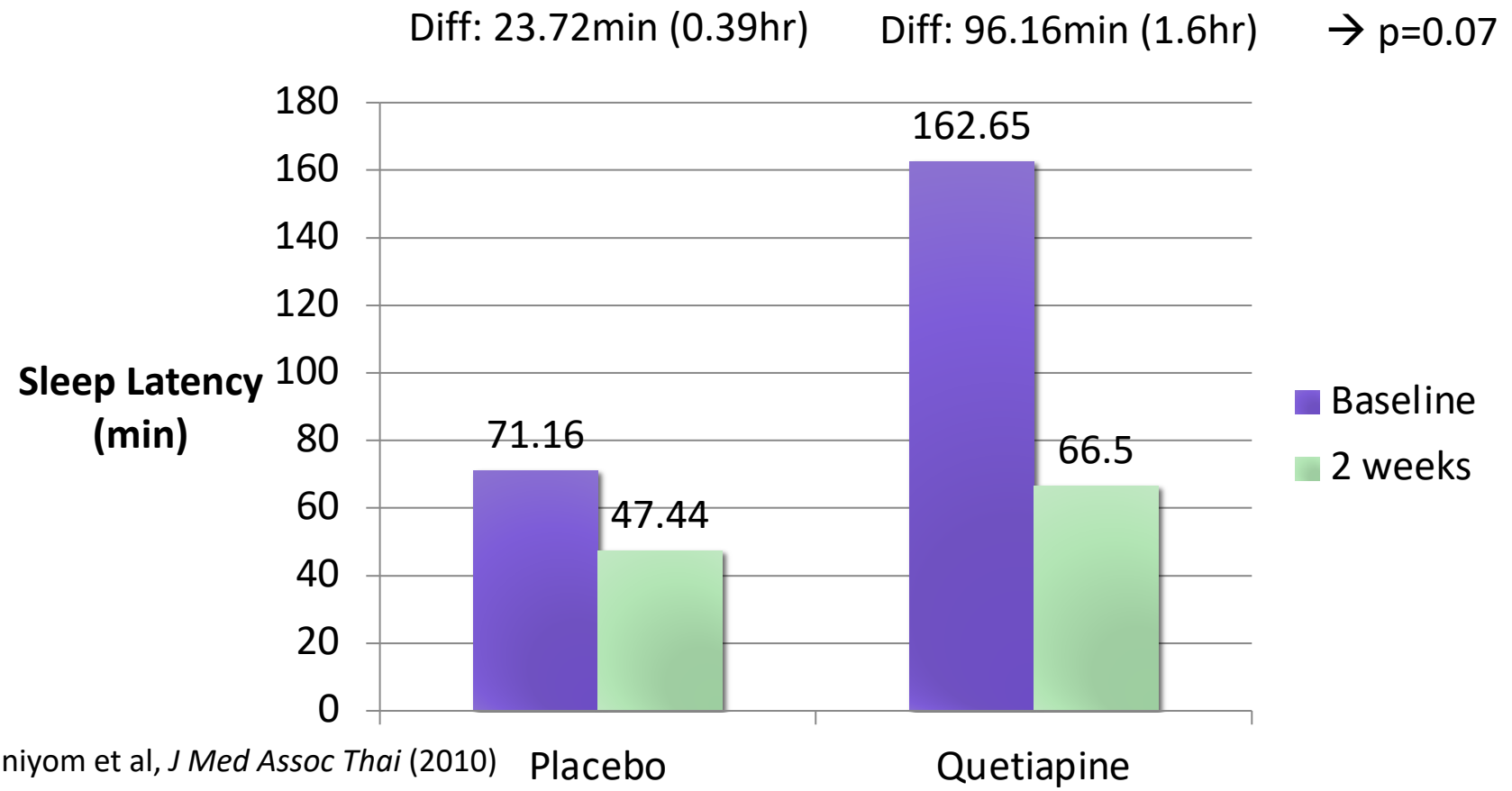


Tassniyom et al, *J Med Assoc Thai* (2010)

Tassniyom et al (2010)

RESULTS, cont'd

Sleep Latency
- Not statistically significant, but could be clinically significant



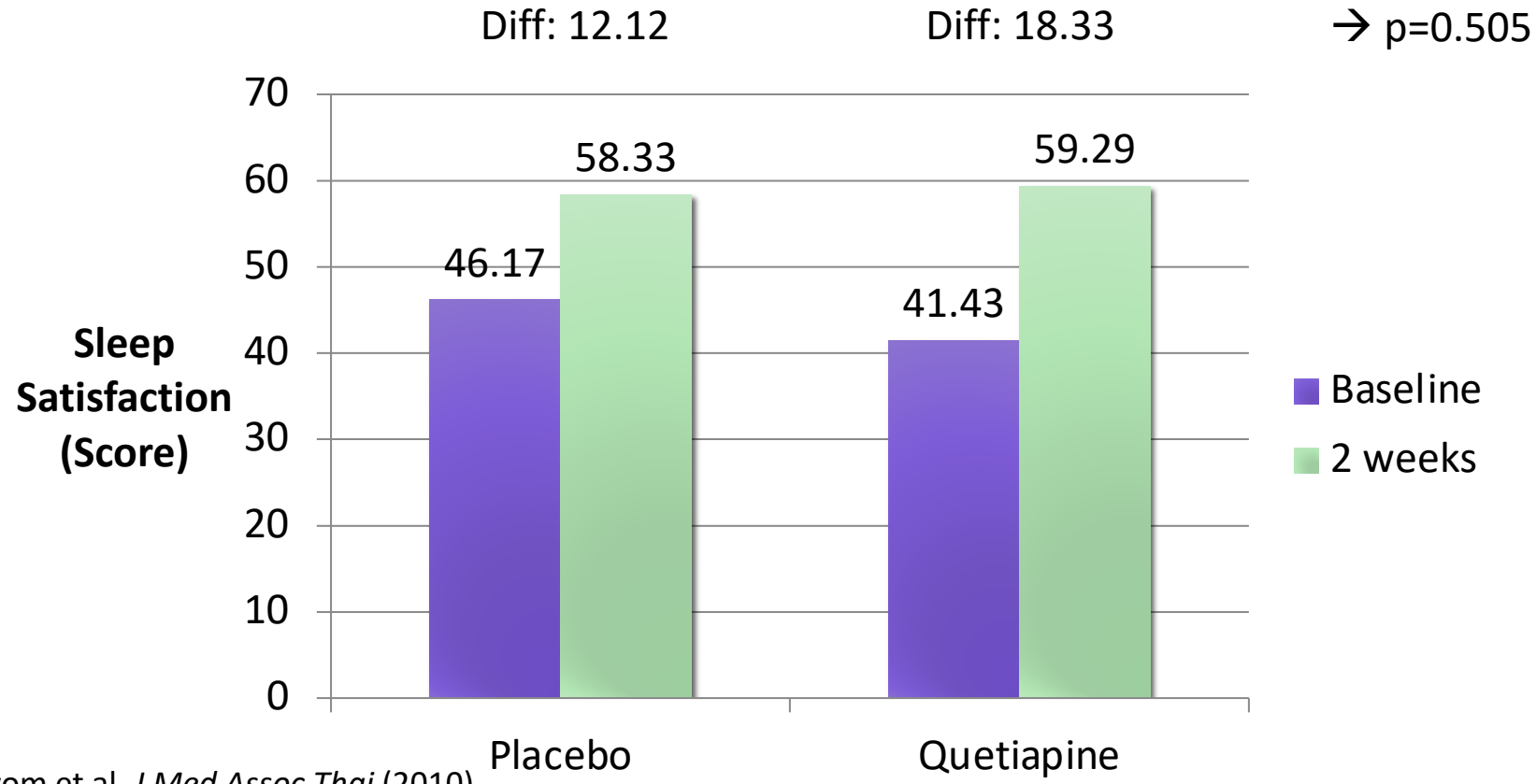
Tassniyom et al, *J Med Assoc Thai* (2010)

Tassniyom et al (2010)

RESULTS, cont'd

Sleep Satisfaction (Visual Analog Scale)

- Not statistically significant, but could be clinically significant
- Placebo effect



Tassniyom et al, *J Med Assoc Thai* (2010)

Tassniyom et al (2010)

STRENGHTS / LIMITATIONS	
Strengths	Sleep diaries utilized for data (incr external validity)
Limitations	No objective measures employed (polysomnography) May have been under-powered • No statistical differences found • # patients analyzed smaller than amt required Metabolic side effects not seen, but unknown if monitored Author-reported: • Small sample size • Short study duration (2wks)

Tassniyom et al, *J Med Assoc Thai* (2010)

Tassniyom et al (2010)

AUTHOR'S CONCLUSIONS

- Trends toward sleep improvement despite no statistical significance
- Increase in sleep time by 2hr and decrease in sleep latency by 1.5hr clinically important

OWN CONCLUSIONS

Low-dose quetiapine given over a 2week period:

- May help a patient fall asleep faster
- May increase total sleep time
- Did not produce any serious side effects

Interpret results with caution

Tassniyom et al, *J Med Assoc Thai* (2010)

Metabolic Consequences

- Low dose ≠ low risk

Cates et al (2009)	
Trial Type	Retrospective Chart Review
Sample Size	N=43
Baseline Characteristics	All had comorbid psychiatric disorders All on at least 1 other anti-psychotic or antidepressant 22 on SGA • 13 receiving SGA known to have moderate-high risk of weight gain
Quetiapine dose for insomnia (recv'd on top of other psychotropic drugs)	35 received 100-200mg QHS 8 received 25-50mg QHS X11 months (mean duration)
Results	Significant increase in weight (p=0.037) • Mean = +4.9lbs Significant increase in BMI (p=0.048) • Mean = +0.8pts

Cates et al, *Community Ment Health J* (2009)

Other Effects

- Low-dose quetiapine may cause motor disturbances and decrease in REM

Cohrs et al (2004)	
Trial Type	Randomized, double-blind, placebo-controlled, cross-over
Sample Size	N=14
Baseline Characteristics	Healthy males (non-insomniacs)
Quetiapine dose	25mg, 100mg X9nights
Results	Significant increase in periodic leg movements at 100mg dose Significant reduction in REM at 100mg dose Significant improvements in TST, sleep efficiency, and other sleep parameters at both doses

Cohrs et al, *Psychopharmacology* (2004)

Other Effects

- Abuse Potential
  - The only atypical antipsychotic that has evidence for abuse
  - Prison Systems
    - Drug-seeking behaviors w/ quetiapine
      - Threatening suicide if quetiapine is discontinued
      - Faking psychotic symptoms in order to obtain quetiapine
  - Street Names:
    - Quell
    - Snoozeberries
    - Susie-Q
    - Baby Heroin
    - Q-ball (when combined with cocaine and given IV)
    - Maq-ball (combined with marijuana)

Waters BM et al, Am J Psychiatry (2007).
Pinta ER et al, Am J Psychiatry (2007).
Sansone RA et al, Psychiatry (2010).
Pierre JM et al, Am J Psychiatry (2004).
Anderson SL et al, *Am J Health-Syst Pharm* (2014).

Cost Comparisons

- Guideline-based treatments vs Quetiapine

Agent	Cost per tablet or capsule ($)
Zolpidem	$0.17 (10mg) $0.26 (5mg)
Quetiapine	$0.24 (25mg)
Temazepam	$0.29 (15mg, 30mg)
Triazolam	$0.30 (0.25mg)
Zaleplon	$0.50 (5mg) $0.53 (10mg)
Eszopiclone	$0.78 (1mg)
Zolpidem ER	$2.25 (6.25mg)
Zolpidem SL (Edluar®)	$6.92 (5mg)
Zolpidem SL (Intermezzo®)	$7.94 (1.75mg)
Ramelteon (Rozerem®)	$8.80 (8mg)

GoodRx. www.goodrx.com (Accessed November 5, 2014)

Summary & Recommendations

- More studies are needed
  - Larger # of patients, longer duration, more statistically robust
- The same monitoring that is recommended for higher doses should be utilized
  - Blood Pressure, Weight, BMI, Waist Circumference, QTc prolongation, Blood Glucose, Lipids, Motor Impairments, CBC, TSH

Potential Risks	Potential Benefits
Very few studies exist demonstrating safety, efficacy	Studies seem to show a trend toward efficacy and improvements are similar to those observed in BzRA
Unknown risk of metabolic effects, QTc prolongation at low doses → should assume that the risk is equivalent until proven otherwise	Relatively inexpensive compared to other recommended treatments
May have abuse potential	Not currently a controlled substance

Questions

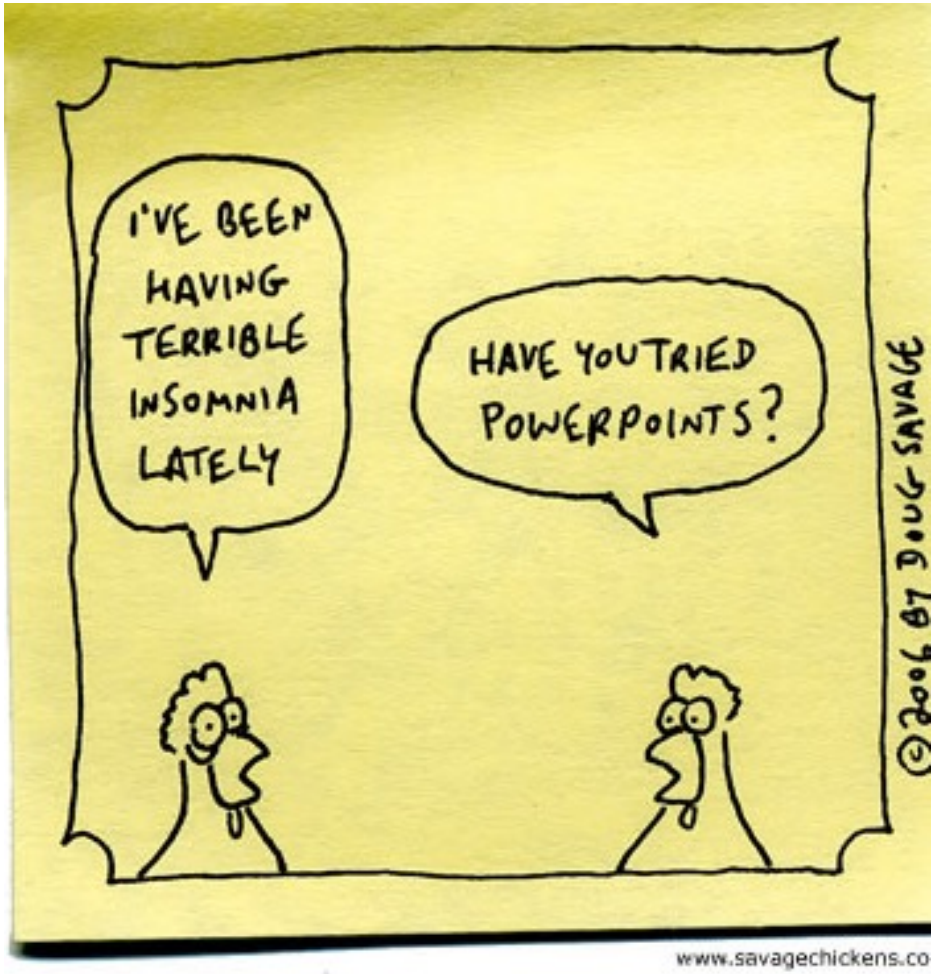


Image: http://www.savagechickens.com/2006/01/sleepy-time.html