INSOMNIA

TREATMENT OPTIONS
TREATMENT EFFECTIVENESS

HOW DO WE TX THIS ?

A HX PERSPECTIVE

PHARMACOTHERAPY

46 THE BRITISH MEDICAL JOURNAL. [July 14, 1877.

QUEEN'S HOSPITAL, BIRMINGHAM.
CASES UNDER THE CARE OF DR. SAWYER.

Insomnia.— is usually successfully treated by full doses of bromides conjoined with tincture of ergot and cod-liver oil. If the insomnia be serious, it must be stopped at once by hypnotics, preferably by opium.

PHARMACOTHERAPY

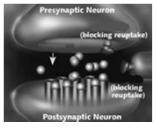
SOME HUMOR RE: PHARMACOTHERAPY
BEFORE WE BEGIN

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., "Silenoir)**

OFF LABEL

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

IN DEVELOPMENT

- **Orexin antagonists** **(e.g., suvorexant)**
- **BZRAs + CBT-I**
- **Stimulants + CBT-I**

Table 1
Basic pharmacology of medications used to treat insomnia

Agent	Trade name	Class	FDA indication	t_{max} (h)	$t_{1/2}$ (h)	Binding profile						Metabolism
						Benzo binding	Anti-H1	MT1-MT2	Anti-5HT2	Anti-alpha-1	Anti-dopa	Anti-mAch	
Flurazepam	Dalmane	Benzodiazepine	Insomnia	0.5–1.5	40–250	+++							CYP2C19, CYP3A4
Quazepam	Doral	Benzodiazepine	Insomnia	2	20–120	+++							CYP3A4, CYP2C19
Estazolam	Prosom	Benzodiazepine	Insomnia	1.5–2	10–24	+++							CYP3A4
Temazepam	Restoril	Benzodiazepine	Insomnia	1–3	8–20	+++							Glucuronide conjugation
Triazolam	Halcion	Benzodiazepine	Insomnia	1–3	2–5.5	+++							CYP3A4, glucuronide conjugation
Clonazepam	Klonopin	Benzodiazepine	Seizures, anxiety	1–2	35–40	+++							CYP2B, CYP3A4, acetylation
Lorazepam	Ativan	Benzodiazepine	Anxiety	1–3	12–15	+++							Glucuronide conjugation
Alprazolam	Xan												[illegible]S, CYP2C19
Diazepam	Valk												CYP2C19, CYP3A4, [illegible]nide conjugation
Chlordiazepoxide	Libr												CYP2C19, CYP3A4, [illegible]nide conjugation
Zolpidem (MR)	Amb												, CYP1A2, CYP2C9
Zaleplon	Sona												le oxidase, CYP3A4
Eszopiclone	Lun												, CYP2E1
Ramelteon	Roz												, CYP2C, CYP3A4
Amitriptyline	Elav												, CYP2C19, CYP2D6,
Doxepin	Sine												CYP2C19, CYP2D6, CYP2C9, CYP1A2
Trazodone	Desyrel	Chlorophenylpiperazine	MDD	1–2	7–15				+++	+++			CYP3A4, CYP2D6, CYP1A2
Mirtazapine	Remeron	Tetracyclic	MDD	0.25–2	20–40		+++		+++				CYP2D6, CYP1A2, CYP3A4
Quetiapine	Seroquel	Dibenzothiazepine	Schizophrenia mania	1	7		++		+	+++	+		CYP2D6, CYP3A4
Olanzapine	Zyprexa	Thiobenzodiazepine	Schizophrenia mania	5	30		+++		+++	++	++	+++	CYP1A2
Risperidone	Risperdal	Benzisoxazole	Schizophrenia mania	1	3–20		+		+++	+++	++		CYP2D6, CYP3A4
Diphenhydramine	Benadryl	Ethanolamine	Allergy, OTC sleep aid	2–3	5–11		+++					+++	CYP2D6, CYP1A2, CYP2C9, CYP2C19
Doxylamine succinate	Unisom	Ethanolamine	Allergy, OTC sleep aid	1.5–2.5	10–12		+++					+++	CYP2D6, CYP1A2, CYP2C9

MDD = major depressive disorder; $t_{1/2}$ includes the half-lives of the parent compound and major active metabolites; OTC = over-the-counter; information in table from Refs. [8,9,]
Anti-5HT2-Serotonin Type 2 Receptor Antagonist; Anti-alpha-1 - Alpha 1 Adrenergic Antagonist; Anti-Dopa - Dopamine Antagonist; Anti-H1 - Antihistamine; Anti-mAch - Muscarinic Cholinergic Antagonist; Benzo – Benzodiazepine; CYP - Cytochrome P450; ETOH – Alcohol; MR – Modified release; MT1-MT2 - Melatonin Type 1 and Type 2 Receptor Antagonist; $t_{1/2}$ - Half-life; t_{max} - Time to maximum blood level.]

WHILE COMPREHENSIVE, WHAT IS MISSING FROM THIS TABLE ?

Krystal Sleep Medicine Reviews 13 (2009) 265–274

Drugs Indicated for Insomnia

Generic	Brand	$T_{1/2}$ (Hours)	Dose (mg)	Drug Class
Flurazepam	Dalmane	48-120	15-30	BZD
Temazepam	Restoril	8-20	15-30	BZD
Triazolam	Halcion	2-6	0.125-0.25	BZD
Estazolam	Prosom	8-24	1-2	BZD
Quazepam	Doral	48-120	7.5-15	BZD
Zolpidem	Ambien	1.5-2.4	5-10	non-BZD
Zaleplon	Sonata	1	5-20	non-BZD
Eszopiclone	Lunesta	5-7	1-3	non-BZD
Zolpidem Ext. Rel.	Ambien CR	1.5-2.4*	6.25-12.5	non-BZD
Ramelteon	Rozerem	1.5-5	8	MT agonist

Compiled by Dan Buysse

BASED ON ½ LIFE WHICH MEDICATION MIGHT BE BEST FOR <u>INITIAL INSOMNIA</u>

Generic	Brand	$T_{1/2}$ (Hours)	Dose (mg)	Drug Class
Flurazepam	Dalmane	48-120	15-30	BZD
Temazepam	Restoril	8-20	15-30	BZD
Triazolam	Halcion	2-6	0.125-0.25	BZD
Estazolam	Prosom	8-24	1-2	BZD
Quazepam	Doral	48-120	7.5-15	BZD
Zolpidem	Ambien	1.5-2.4	5-10	non-BZD
Zaleplon	Sonata	1	5-20	non-BZD
Eszopiclone	Lunesta	5-7	1-3	non-BZD
Zolpidem Ext. Rel.	Ambien CR	1.5-2.4*	6.25-12.5	non-BZD
Ramelteon	Rozerem	1.5-5	8	MT agonist

Compiled by Dan Buysse

BASED ON ½ LIFE WHICH MEDICATION MIGHT BE BEST FOR <u>MIDDLE INSOMNIA</u>

Generic	Brand	$T_{1/2}$ (Hours)	Dose (mg)	Drug Class
Flurazepam	Dalmane	48-120	15-30	BZD
Temazepam	Restoril	8-20	15-30	BZD
Triazolam	Halcion	2-6	0.125-0.25	BZD
Estazolam	Prosom	8-24	1-2	BZD
Quazepam	Doral	48-120	7.5-15	BZD
Zolpidem	Ambien	1.5-2.4	5-10	non-BZD
Zaleplon	Sonata	1	5-20	non-BZD
Eszopiclone	Lunesta	5-7	1-3	non-BZD
Zolpidem Ext. Rel.	Ambien CR	1.5-2.4*	6.25-12.5	non-BZD
Ramelteon	Rozerem	1.5-5	8	MT agonist

Compiled by Dan Buysse

BASED ON ½ LIFE WHICH MEDICATION MIGHT BE BEST FOR <u>LATE INSOMNIA</u>

Generic	Brand	$T_{1/2}$ (Hours)	Dose (mg)	Drug Class
Flurazepam	Dalmane	48-120	15-30	BZD
Temazepam	Restoril	8-20	15-30	BZD
Triazolam	Halcion	2-6	0.125-0.25	BZD
Estazolam	Prosom	8-24	1-2	BZD
Quazepam	Doral	48-120	7.5-15	BZD
Zolpidem	Ambien	1.5-2.4	5-10	non-BZD
Zaleplon	Sonata	1	5-20	non-BZD
Eszopiclone	Lunesta	5-7	1-3	non-BZD
Zolpidem Ext. Rel.	Ambien CR	1.5-2.4*	6.25-12.5	non-BZD
Ramelteon	Rozerem	1.5-5	8	MT agonist

Compiled by Dan Buysse

PLUSES & MINUSES FOR EACH TREATMENT MODALITY

<u>Benzodiazepines (e.g., Temazepam)</u>

+ 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 (?) ASIDE: ANXIETY 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)

PLUSES & MINUSES FOR EACH TREATMENT MODALITY

Melatonin Agonists (M1 receptor agonists)

+ "Established" efficacy
+ May be used safely for extended intervals
+ Low interaction profile (except fluvaxamine)
+ 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)

(SUB-OB ISSUE)

	PRE-POST Δ SUB	PRE-POST Δ OB	Δ
SL	10	15	-5
NWAK	1	2	-1
WASO	5	15	-10
TST	15	25	-10

PLUS & MINUSES FOR EACH TREATMENT MODALITY

Low Dose Tricyclics – Doxepin (not silenior)

+ 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)

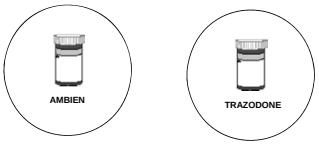
PLUS & MINUSES FOR EACH TREATMENT MODALITY

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

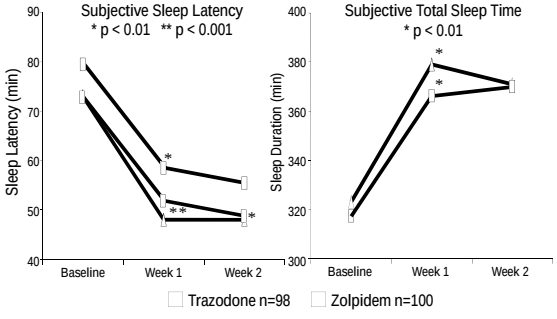
HOW DO HYPNOTICS COMPARE WITH SEDATING ANTIDEPRESSANTS ?



I would have guessed …

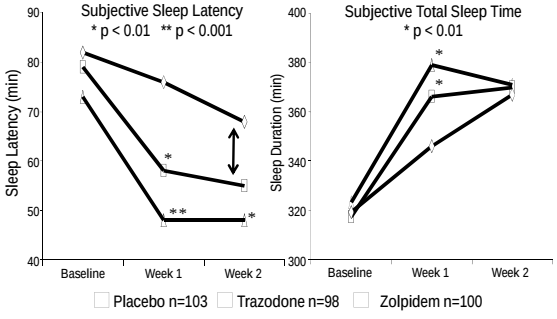
TRAZODONE AND ZOLPIDEM TREATMENT OF PRIMARY INSOMNIA

Walsh, *Hum Psychopharmacol*, 1998



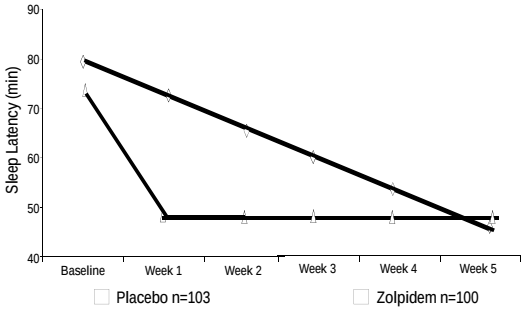
TRAZODONE AND ZOLPIDEM TREATMENT OF PRIMARY INSOMNIA

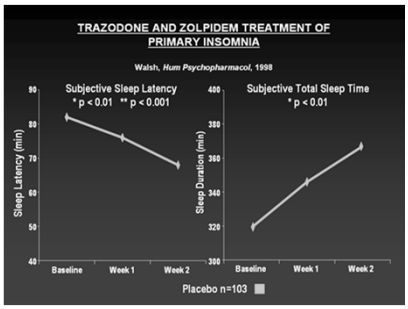
Walsh, *Hum Psychopharmacol*, 1998



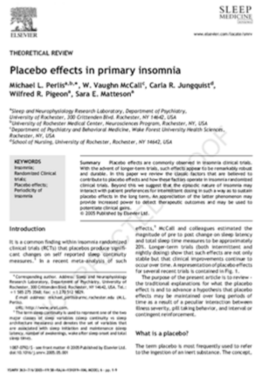
TRAZODONE AND ZOLPIDEM TREATMENT OF PRIMARY INSOMNIA

Walsh, *Hum Psychopharmacol*, 1998





"What's up with placebos and insomnia ?!!"



SLEEP MEDICINE

THEORETICAL REVIEW

Placebo effects in primary insomnia

Michael L. Perlis[a,b,*], W. Vaughn McCall[c], Carla R. Jungquist[d], Wilfred R. Pigeon[a], Sara E. Matteson[a]

[a]Sleep and Neurophysiology Research Laboratory, Department of Psychiatry, University of Rochester, 300 Crittenden Blvd. Rochester, NY 14642, USA
[b]University of Rochester Medical Center, Neurosciences Program, Rochester, NY, USA
[c]Department of Psychiatry and Behavioral Medicine, Wake Forest University Health Sciences, Rochester, NY, USA
[d]School of Nursing, University of Rochester, Rochester, NY 14642, USA

KEYWORDS
Insomnia;
Randomized Clinical trials;
Placebo effects;
Periodicity of insomnia

Summary Placebo effects are commonly observed in insomnia clinical trials. With the advent of longer-term trials, such effects appear to be remarkably robust and durable. In this paper we review the classic factors that are believed to contribute to placebo effects and how these factors operate in insomnia randomized clinical trials. Beyond this we suggest that the episodic nature of insomnia may interact with patient preferences for intermittent dosing in such a way as to sustain placebo effects in the long term. An appreciation of the latter phenomenon may provide increased power to detect therapeutic outcomes and may be used to potentiate clinical gains.

Introduction

It is a common finding within insomnia randomized clinical trials (RCTs) that placebos produce significant changes on self reported sleep continuity measures.[1] In a recent meta-analysis of such effects,[1] McCall and colleagues estimated the magnitude of pre to post change on sleep latency and total sleep time measures to be approximately 20%. Longer-term trials (both intermittent and nightly dosing) show that such effects are not only stable but that clinical improvements continue to occur over time. A representation of placebo effects for several recent trials is contained in Fig. 1.

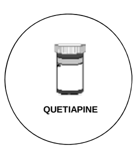
The purpose of the present article is to review – the traditional explanations for what the placebo effect is and to advance a hypothesis that placebo effects may be maintained over long periods of time as a result of a peculiar interaction between illness severity, pill taking behavior, and interval or contingent reinforcement.

What is a placebo?

The term placebo is most frequently used to refer to the ingestion of an inert substance. The concept,

WHAT ABOUT ANTIPSYCHOTICS ?

WHAT ABOUT QUETIAPINE ?



Psychopharmacology (2008) 196:337–338
DOI 10.1007/s00213-007-0968-8

LETTER TO THE EDITORS

Quetiapine in primary insomnia: a pilot study

Michael H. Wiegand · Florentina Landry · Torsten Brückner · Corina Pohl · Zdenko Veselý · Thomas Jahn

Received: 21 September 2007 / Accepted: 26 September 2007 / Published online: 6 October 2007

In the treatment of primary insomnia, benzodiazepines and non-benzodiazepine hypnotics are not a first-line medication, mainly due to the dependency risk, especially in long-term treatment. Sedating antidepressants are widely used as an alternative treatment (Wiegand 1999). However, these compounds have several side effects and tend to interact with other drugs, which is a problem especially in elderly patients.

For these reasons, neuroleptics play an increasing role in the management of chronic insomnia. In clinical practice, the use of neuroleptics in acute and chronic insomnia is traditionally widespread, e.g., melperone, pipamperone, promethazine, etc., especially in elderly insomniacs, as a sleeping medication. However, this is based on unsystematic clinical experience rather than on data: Systematic studies on the efficacy of neuroleptics in this indication are extremely limited. This is true for older compounds as well as for the more advanced and in many respects advantageous compounds like risperidone, olanzapine, and quetiapine.

Among the newer, "atypical" antipsychotics, quetiapine appears to be a specially promising "candidate" for the treatment of chronic insomnia in general and primary insomnia in particular. This dibenzothiazepin derivate has antagonistic effects on several central neurotransmitter systems: serotonin ($5\text{-}HT_{1A}$ and $5\text{-}HT_2$), dopamine (D_1 and D_2), histamine (H_1), and on adrenergic α_1 and α_2 receptors. There is virtually no action on cholinergic, muscarinergic, and benzodiazepine receptors. This special profile suggests a favorable effect on sleep, especially the combination of a $5\text{-}HT_2$ receptor and an H_1 receptor blockade. Some antidepressants have a similar profile, e.g., mirtazapine, trazodone, and trimipramine. All of these compounds are used in the treatment of chronic insomnia (unrelated to depression).

Quetiapine's favorable effect on sleep in healthy probands as well as in depressed patients has been demonstrated by an increasing number of studies (e.g., Wetter et al. 2002; Cohrs et al. 2004; Calabrese et al. 2005; Sokolski and Brown 2006; Todder et al. 2006; Baune et al. 2007; Endicott et al. 2007.)

In an open pilot study, we treated 18 outpatients suffering from primary insomnia with quetiapine for 6 weeks. After a washout period of 1 week, medication was given at bedtime. The dose was 25 mg initially; in seven patients, it was increased to 50 mg, in one patient, to 75 mg. Sleep parameters were measured by repeated polysomnographies. Subjective sleep quality was assessed by means of the Pittsburgh Sleep Quality Index (PSQI; Buysse et al. 1989) and sleep diaries. Cognitive effects were assessed by means of a neuropsychological test battery.

The results demonstrated that quetiapine in a comparably low dose improved objective and subjective sleep parameters in patients with primary insomnia (Table 1). This improvement was already present after 2 weeks' medication, and then increased after 6 weeks' medication. The improvement was most clear in the subjective sleep variables as assessed by means of the PSQI and the patients' sleep diaries. The

M. H. Wiegand (✉) · F. Landry · T. Brückner · Z. Veselý
Sleep Disorders Center, Technical University of Munich,
Ismaninger Str. 22,
81675 Munich, Germany
e-mail: michael.wiegand@lrz.tum.de

C. Pohl · T. Jahn
Clinical and Experimental Neuropsychology Unit, Department of Psychiatry and Psychotherapy, Technical University of Munich,
Ismaninger Str. 22,
81675 Munich, Germany

Springer

Table 1 Selected objective and subjective sleep parameters resulting from polysomnography and PSQI ratings

	T_1 (baseline)	T_2 (2 weeks med.)	p	T_3 (6 weeks med.)	p
Objective sleep quality (polysomnography)					
Subjective sleep quality (PSQI scores)					
Total score	13.1±2.3	9.1±3.3	0.00	6.8±3.3	0.00

Presented are means±SD. "p" refers to the change from baseline (Wilcoxon's test, two-tailed).
REM Rapid eye movements, *SPT* sleep period time, *PSQI* Pittsburgh Sleep Quality Inventory

WHAT ABOUT PROSPECTIVE SAMPLING DATA

NAME: ____________ DATE: ____________

COMPLETE IMMEDIATELY BEFORE BED CONCERNING HOW YOU FELT TODAY:

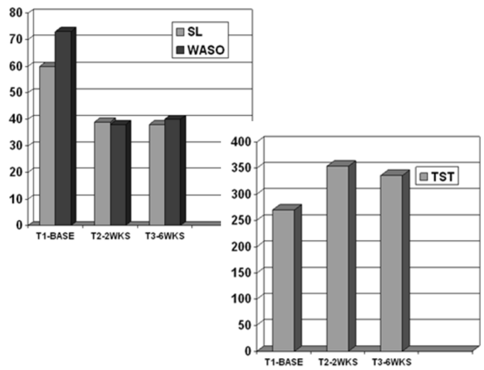
	MON	TUES	WED	THUR	FRI	SAT	SUN		MEAN
TYPICAL DAY? (YES/NO) *									
FATIGUE (NONE 0—1—2—3—4—5 A LOT)									
STRESS (NONE 0—1—2—3—4—5 A LOT)									
ALERT (NOT VERY 0—1—2—3—4—5 VERY)									
CONCENTRATION (GOOD 0—1—2—3—4—5 BAD)									
MOOD (BAD 0—1—2—3—4—5 GOOD)									
TIME SPENT EXERCISING (MIN.)									
TIME SPENT OUTSIDE TODAY (MIN.)									
NUMBER OF ALCOHOLIC BEVERAGES									
PRESCRIPTIONS TODAY (YES/NO)									
OTC MEDS TODAY (YES/NO)									
PAIN TODAY (NONE 0—1—2—3—4—5 A LOT)									
HEALTH (FELT FINE 0—1—2—3—4—5 BAD)									
MENSTRUATE TODAY (YES/NO)									
MENSTRUAL PAIN (NONE 0—1—2—3—4—5 BAD)									

* PLEASE INDICATE ON THE BACK OF THIS SHEET WHY ANY GIVEN DAY WAS NOT TYPICAL AND/OR WHAT MEDICATIONS YOU TOOK ON ANY GIVEN DAY.

COMPLETE IMMEDIATELY ON AWAKENING

	MON	TUES	WED	THURS	FRI	SAT	SUN		MEAN
TIME TO BED (CLOCK TIME)									
TIME OUT OF BED (CLOCK TIME)									
TIME TO BED (DEV FRM 11)									
TIME OUT OF BED (DEV FRM 7)									
(SL) TIME TO FALL ASLEEP									
(NUMA) NUMBER TIMES AWAKENED									
(WASO) WAKE AFTER SLEEP ONSET									
(TTOB) TOTAL AMOUNT TIME OUT OF BED									
(TST) TOTAL SLEEP TIME (MIN.)									
SLEEP QUALITY (GOOD 0—1—2—3—4—5 POOR)									
FATIGUE (NONE 0—1—2—3—4—5 A LOT)									

SE AND TIB TO BE AUTOCALCULATE



Quetiapine for Primary Insomnia: A Double Blind, Randomized Controlled Trial

Kanida Tassniyom MD*, Suchat Paholpak MD*, Somporn Tassniyom MD**, Jiraporn Khiewyoo PhD***

*Department of Psychiatry, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
**Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
***Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand

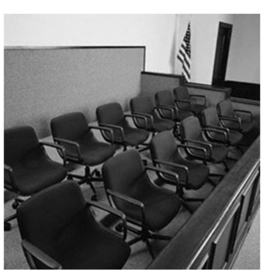
Objective: To evaluate the clinical efficacy of Quetiapine 25 mg for the treatment of primary insomnia.
Material and Method: A randomized, double-blind, placebo-controlled clinical trial was conducted. Patients with DSM-IV-TR defined primary insomnia were asked to record a sleep diary one week prior to treatment, followed by 2 weeks of nightly treatment with either Quetiapine 25 mg or placebo. The primary outcomes were total sleep time (TST), sleep latency (SL), daytime alertness and functioning and sleep satisfaction; side effects were recorded as secondary outcome. Data were collected between January 2007 and December 2007, at Srinagarind Hospital of Khon Kaen University.
Results: Thirteen patients completed the present study (mean age 45.93 years old, range 25-62). Quetiapine group increased mean TST by 124.92 minutes and 72.24 minutes in the placebo group. Mean SL was reduced by 96.16 minutes in the Quetiapine group and 23.72 minutes in the placebo group. Statistical significance was not reached between both groups. In the Quetiapine group two patients reported side effects of dry lips, dry tongue and morning drowsiness.
Conclusion: The present study is the first study to evaluate the effect of Quetiapine in primary insomnia in a randomized controlled trial. Quetiapine at 25 mg at night did show a trend for improvement of TST and reduced SL in primary insomnia with few side effects but not reaching statistical significance. A study with a larger sample size is needed to demonstrate its efficacy.

Keywords: Insomnia, Primary insomnia, Quetiapine, Sleep

J Med Assoc Thai 2010; 93 (6): 729-34
Full text. e-Journal: http://www.mat.or.th/journal

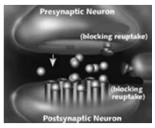
BOTTOM LINE

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"

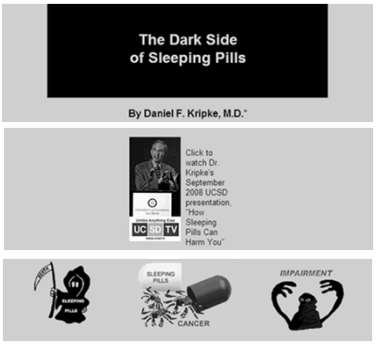
ANTIPSYCHOTICS
"THE JURRY IS OUT"

SO WHAT ABOUT

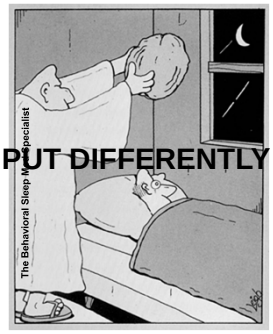
COMPARATIVE EFFICACY IN GENERAL (ZOLP)
COMPARATIVE EFFICACY BY TYPE / SUBTYPE

	NIH – 1983	NIH – 2005
Definition	Insomnia is a symptom, not a primary disorder	Insomnia is a disorder, typically comorbid with other disorders
Treatment	Treat the primary disorder (insomnia symptoms are sometimes addressed, sometimes ignored)	Chronic insomnia exists and merits treatment
	Hypnotics should generally be used only for short-term treatment	Treat insomnia as well as other disorder(s): improvements in insomnia may result in improvements in other disorder(s)
Other	Chronic insomnia occurs in the context of medical/psychiatric disorders	Insomnia is associated with significant impairment in function and quality of life

NOT EVERYONE, HOWEVER, IS KEEN ON BZRAs



AND NOW A WORD FROM OUR SPONSOR



PUT DIFFERENTLY

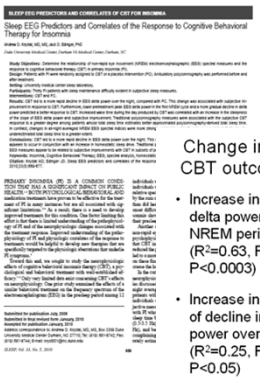
When proven ineffective, the sandman is replaced by the boulder guy

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

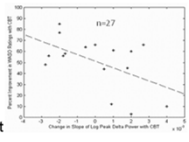
- Takes between 3 - 8 weeks
- Transient worsening of symptoms (1-2 weeks)
- Requires substantial patient compliance
- Only effective as practiced by specialists (?)



Sleep EEG Predictors and Correlates of the Response to Cognitive Behavioral Therapy for Insomnia

Change in SWA indices correlate with CBT outcome: patient-reported WASO

- Increase in peak delta power for first NREM period (R^2=0.63, F=24, P<0.0003)
- Increase in the rate of decline in delta power over the night (R^2=0.25, F=4.7, P<0.05)



Effect of cognitive behavioural therapy for insomnia on sleep architecture and sleep EEG power spectra in psychophysiological insomnia

KATERINA CERVENA[1,2], YVES DAUVILLIERS[1,2], FABRICE ESPA[1,2], JACQUES TOUCHON[1,2], MILOS MATOUSEK[3], MICHEL BILLIARD[1] and ALAIN BESSET[1,2]

Sleep parameters	Before CBT-I	After CBT-I	Z	P	ES
Sleep architecture					
Total sleep time (min)	323.67 (37.32)	415.39 (41.35)	−2.67	0.008	−2.22
Stage 1 (min)	37.50 (15.96)	39.50 (12.68)	−0.77	0.441	−0.13
Stage 1 (%)	11.67 (4.92)	9.59 (3.15)	−1.95	0.051	0.48
Stage 2 (min)	168.39 (33.35)	206.06 (46.60)	−2.67	0.008	−0.89
Stage 2 (%)	52.37 (11.26)	49.36 (8.99)	−2.67	0.008	0.28
Slow wave sleep (min)	62.56 (33.30)	86.50 (23.77)	−2.55	0.01	−0.79
Slow wave sleep (%)	19.09 (9.21)	21.21 (7.13)	−1.24	0.214	−0.24
REM sleep (min)	55.22 (20.33)	83.33 (23.63)	−2.24	0.025*	−1.21
REM sleep (%)	16.87 (5.11)	19.85 (4.97)	−1.60	0.110	−0.56

Values in parenthesis represent SD. ES, effect size.

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)

EFFICACY

Author	Year	Title	Journal
Morin et al.	1994	Nonpharmacological interventions for insom-nia: a meta-analysis of treatment efficacy	Am J Psychiatry, 151, 1172-1180
Murtagh & Greenwood	1995	Identifying effective psychological treatments for insomnia: a meta-analysis	J Consult Clin Psychol, 1995, 79-89
Pallesen et al.	1998	Nonpharmacological interventions for insom-nia in older adults: a meta-analysis of treat-ment efficacy	Psychotherapy, 35, 472-481
Montgomery & Dennis	2003	Cognitive behavioral interventions for sleep problems in adults aged 60+	Cochrane Library, 1, 1-39/ Sleep Med Rev,8, 47-62
Irwin et al.	2006	Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age	Health Psychology, 25,3-14.
Okajima et al.	2011	A meta-analysis on the treatment effective-ness of cognitive behavioral therapy for primary insomnia	Sleep & Biol Rhythms, 9,24-34
Mitchell et al	2012	Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review	BMC Family Practice, 13, 40-51
Miller et al.	2014	The evidence base of sleep restriction therapy for treating insomnia disorder	Sleep Med Rev, 18, 415-424
Koffel et al.	2015	A meta-analysis of group cognitive behaviorla therapy for insomnia	Sleep Med Rev, 19 epub

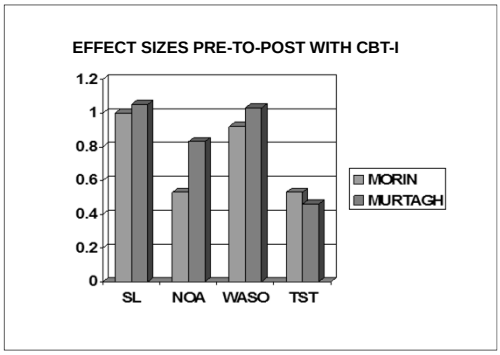
Compiled by Dieter Riemann

EFFICACY

Morin et al.
Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy.
Am J Psychiatry 1994; 151(8):1172-1180.

Murtagh et al.
Identifying effective psychological treatments for insomnia: a meta-analysis.
J Consult Clin Psychol 1995; 63(1):79-89.

EFFICACY



RCT DATA AIN'T THE REAL WORLD !

RCT

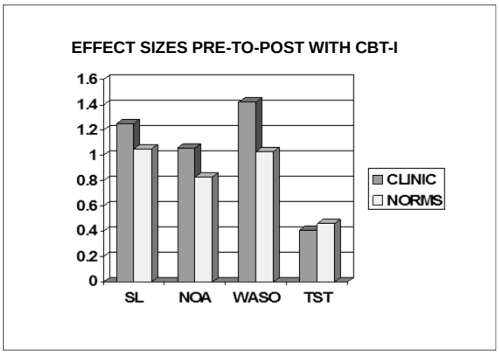
CLINIC

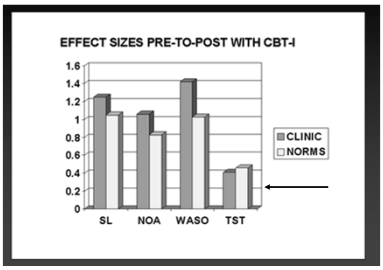
EFFECTIVENESS

AN EXAMPLE

Perlis, M, Aloia M, Boehmler J, Millikan A, Greenblatt D, Giles D. Behavior treatment of insomnia: a clinical case series study. The Journal of Behavioral Medicine,23(2)149-161, 2000.

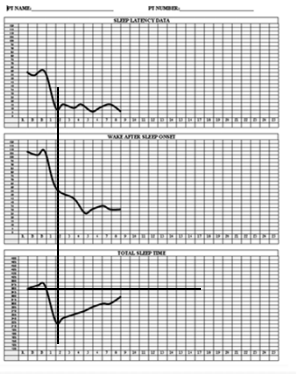
EFFECTIVENESS





WHY ARE THE TST EFFECTS SO POOR ?

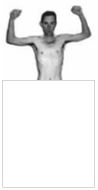
HERE'S WHY



HOW DOES PHARMACOTHERAPY WITH BZRAs 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 ?

Studies comparing CBT-I to pharmacological therapies

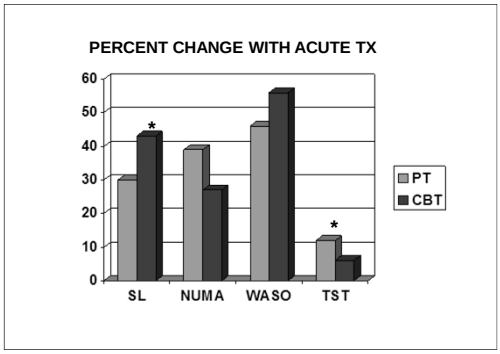
Study Location	Design Quality	Patients Longest follow-up	Intervention and duration	Comparison	Sleep measurements reported	Comment
CBT-I vs. zopiclone						
Siewtsen 2006 (26) Norway	RCT 5	46 patients, age 55 and up 12 months	Individual CBT-I, 6 weekly sessions	Zopiclone, 7.5 mg nightly	Sleep diaries, polysomnography	Study also included placebo group Daytime outcomes reported in (36)
CBT-I vs. zolpidem						
Jacobs 2004 (27) USA	RCT 5	63 patients, age 25-64 12 months	Individual CBT-I, 5 sessions, 6 weeks; plus 1 telephone session	Zolpidem, see comment	Sleep diaries, sleep monitor	Dose 10 mg→5 mg→5 mg q2d
CBT-I vs. temazepam						
Wu 2006 (29) China	RCT 2	77 patients 8 months	Individual CBT-I 2 per week, 8 weeks	Temazepam, see comment	Sleep diaries, polysomnography	Dose 7.5 mg→10 mg→15 mg Study also included placebo and combined therapy groups
Morin 1999 (28) Canada	RCT 6	70 patients, age 55 and up 24 months	Group CBT-I 8 weekly sessions	Temazepam, see comment	Sleep diaries, polysomnography	Dose 7.5 mg→30 mg as needed Study also included placebo and combined therapy groups. Adverse effects reported in (37) Attitudes reported in (38)
CBT-I vs. triazolam						
McCluskey 1991 (30) USA	RCT 4	30 patients 9 weeks	Group CBT-I 2 per week, 3 weeks	triazolam, 0.5 mg then tapered to 0	Sleep diaries	triazolam group also had weekly group meetings but no CBT-I

RELATIVE EFFICACY

HOW DO MEDICAL AND BEHAVIORAL INTERVENTIONS COMPARE ?

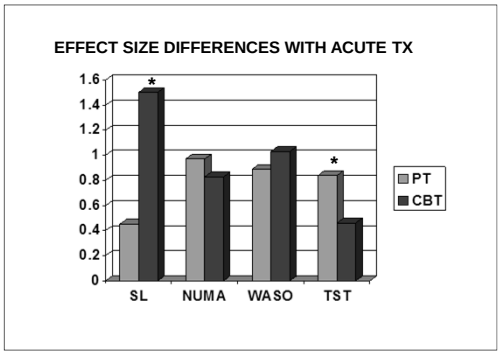
Smith MT, Perlis, ML, Park A, Giles DE, Pennington JA, Buysse, D. Behavioral treatment vs pharmacotherapy for Insomnia - A comparative meta-analyses. American Journal of Psychiatry. 159: 5-11. 2002.

COMPARATIVE EFFICACY



SMITH, PERLIS, ET AL., 2002

COMPARATIVE EFFICACY



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 ?

ON-LINE TREATMENT OF INSOMNIA

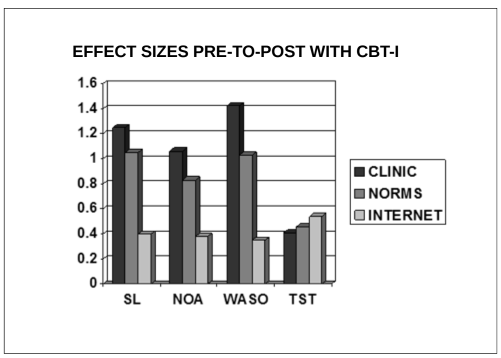
Logging on for Better Sleep: RCT of the Effectiveness of Online Treatment for Insomnia

Norah Vincent, PhD; Samantha Lewycky, MA

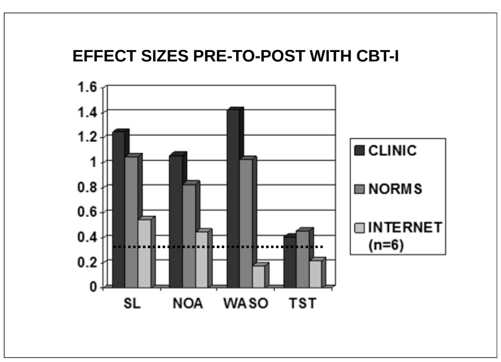
Department of Clinical Health Psychology, University of Manitoba, Manitoba, Canada

Study Objectives: Despite effective cognitive behavioral treatments for chronic insomnia, such treatments are underutilized. This study evaluated the impact of a 5-week, online treatment for insomnia.
Design: This was a randomized controlled trial with online treatment and waiting list control conditions.
Participants: Participants were 118 adults with chronic insomnia.
Setting: Participants received online treatment from their homes.
Intervention: Online treatment consisted of psychoeducation, sleep hygiene, and stimulus control instruction, sleep restriction treatment, relaxation training, cognitive therapy, and help with medication tapering.
Measurement and Results: From pre- to post-treatment, there was a 33% attrition rate, and attrition was related to referral status (i.e., drop-outs were more likely to have been referred for treatment rather than recruited from the community). Using a mixed model analysis of variance procedure (ANOVA), results showed that online treatment produced statistically significant improvements in the primary end points of sleep quality, insomnia severity, and daytime fatigue. Online treatment also produced significant changes in process variables of pre-sleep cognitive arousal and dysfunctional beliefs about sleep.
Conclusions: Implications of these findings are that identification of who most benefits from online treatment is a worthy area of future study.
Keywords: Online treatment, insomnia, self-administered treatment
Citation: Vincent N; Lewycky S. Logging on for better sleep: RCT of the effectiveness of online treatment for insomnia. SLEEP 2009;32(6):807-815.

EFFECTIVENESS



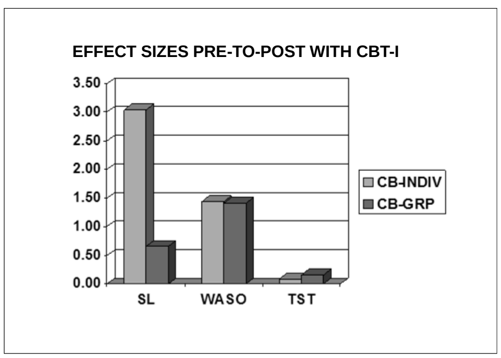
EFFECTIVENESS



Cognitive–Behavioral Therapy for Insomnia: Comparison of Individual Therapy, Group Therapy, and Telephone Consultations

Célyne H. Bastien, Charles M. Morin, Marie-Christine Ouellet, France C. Blais, and Sébastien Bouchard
Université Laval, Québec

EFFECTIVENESS



Célyne Bastien – JCCP 2004, Vol. 72, No. 4, 653–659

SLEEP AND BIOLOGICAL RHYTHMS

ORIGINAL ARTICLE

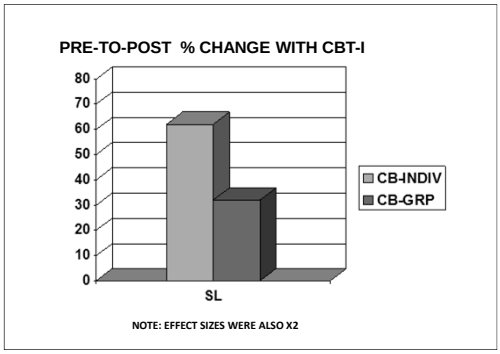
Comparisons of short-term efficacy between individual and group cognitive behavioral therapy for primary insomnia

Wataru YAMADERA, Miki SATO, Daisuke HARADA, Masayuki IWASHITA, Ryo AOKI, Keita OBUCHI, Motohiro OZONE, Hiroshi ITOH and Kazuhiko NAKAYAMA
Department of Psychiatry, Jikei University School of Medicine, Tokyo, Japan

Abstract

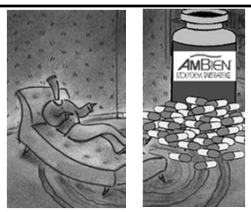
The purpose of this study was to compare the efficacy of individual and group cognitive behavioral therapy for insomnia (CBT-I) in outpatients with primary insomnia diagnosed by DSM-IV-TR. The participants were 20 individually treated (I-CBT-I) and 25 treated in a group therapy format (three to five patients per group) (G-CBT-I), which showed no significant difference regarding demographic variables between groups. The same components of CBT-I stimulus control therapy, sleep restriction therapy, cognitive therapy, and sleep hygiene education were applied on both groups. The short-term outcome (4 weeks after treatment) was measured by sleep logs, actigraphy, the Pittsburgh Sleep Quality Index (PSQI), and the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS), and was compared between I-CBT-I and G-CBT-I. The results indicated that CBT-I was effective in improving subjective and objective sleep parameters and subjective sleep evaluations for both individual and group treatment. However, I-CBT-I resulted in significantly better improvements over G-CBT-I, in (i) objective and subjective sleep onset latency time, (ii) objective sleep efficacy and moving time during sleeping, (iii) overall sleep quality and duration of actual sleep time in PSQI, (iv) consequences of insomnia, control and predictability of sleep, sleep requirement expectation, and sleep-promoting practices in DBAS. The present study suggested the superiority of I-CBT-I over G-CBT-I in clinical settings, and further evaluations are necessary.

EFFICACY



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 jet lag, 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.

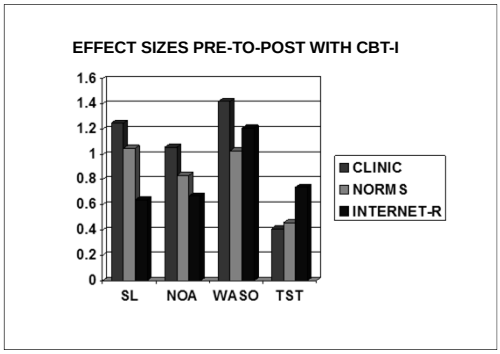
Journal of Psychosomatic Research, 54 (1): 51-59, 2003.

FOR A SURPRISINGLY GOOD 30K VIEW OF TX

BREAK

Michael Perlis PhD
Director, Upenn Behavioral Sleep Medicine Program
mperlis@upenn.edu

EFFECTIVENESS



Arch Gen Psychiatry. 2009 Jul;66(7):692-8