Melatonin for Sleep Onset Latency Outcome, Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD)

National Drug Monograph

March 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Description/Mechanism of Action	Melatonin is marketed as a "dietary supplement." It can be purchased without a prescription. However, the mechanism of action of exogenous melatonin is similar to that of endogenous melatonin, which is a pineal gland hormone that regulates circadian rhythm, endocrine secretions, and sleep patterns.[1] Based on expert opinion and clinical/observational trials, melatonin has been used for an assortment of indications including sleep disorders, jet lag, shift work, cognitive dysfunction, ADHD, migraines, depression, irritable bowel syndrome, and pain.
Indication(s) Under Review in this document (may include off label)	Melatonin is not FDA approved for any indications. Unless supplement regulations change, it is unlikely that melatonin will be FDA approved for any indication. For this review, melatonin will be evaluated for effectiveness and safety for the treatment of insomnia, and specifically for sleep onset latency as that outcome was the most frequently studied. In addition, using melatonin for the treatment of Delayed Sleep-Wake Disorder (DSWPD), Non-24 Hour Sleep-Wake Rhythm Disorder (N24SWD), and Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD) have been included.
Dosage Form(s) Under Review	A variety of dosage strength and formulations of melatonin are available.
REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Pregnancy category unknown

Executive Summary	
Efficacy: • Sleep Onset Latency	• Sleep onset latency was the most frequently recorded primary outcome measure included in the meta-analyses reviewed for primary and secondary insomnia. • Three of the four meta-analyses[2-4] reported a statistically significant mean reduction in sleep latency compared to placebo (range: -4 to -13.2 minutes) in a population of primary and secondary insomnia. The fourth meta-analysis[5] with patients with secondary sleep disorders favored melatonin but was not significant until one outlier study was removed resulting in a point estimate of -17.4 minutes compared to placebo in the post hoc analysis. • The effect on sleep onset latency with melatonin compared to placebo was more pronounced in a subgroup of primary insomniac patients with delayed sleep-phase syndrome (-38.8 minutes) which was statistically significant and clinically

	important.[3] • Sleep duration (total sleep time) increased statistically significantly ranging from 8.25-15.6 minutes compared to placebo. • Sleep efficiency was reported to be improved however it was not consistently statistically significant.
• DSWPD	• For DSWPD, administering strategically timed melatonin versus no treatment may be helpful in adults with DSWPD with or without depression. A meta-analysis[13] evaluating melatonin 5 mg for about one month in a subset of depressed patients (n=28, all < 50 years of age) reported a significant increase in polysomnography determined total sleep time (TST) of 41 minutes compared to placebo. In the subset patients without depression (n=12), the TST was 56 minutes higher (95% CI 48.51, 63.49) compared to placebo. In another meta-analysis[12] using studies in which the timing of melatonin treatment in relationship to the circadian clock was included (5 trials, n=91 adults, age <61 years), melatonin doses of 0.3 mg, 3 mg and 5 mg for 2-4 weeks resulted in significant results in adults for the following two outcomes: advanced dim light melatonin onset (DLMO): mean -1.69 hours, (95% CI -2.31 to -1.07) and sleep onset latency of -0.70 hours (95 % CI -1.04, -0.36), both p<0.0001. In these studies, melatonin was administered between 1500-2130 (mean 1715).
• N24SWPD	• For N24SWD, administering appropriately timed oral melatonin using doses between 0.3-3 mg about 5 hours before the desired bedtime and ideally at the correct circadian phase (i.e. at a circadian time that would shift the biological clock to an earlier hour) is recommended to achieve entrainment for the majority of N24SWD patients versus no treatment. The majority of patients will achieve entrainment with melatonin 0.5 mg dose. Chronic therapy is required to maintain entrainment in totally blind patients with N24SWD. See posted Tasimelteon Drug Monograph and CFU for more details.
• RBD	• For RBD, there is supporting literature that melatonin is a reasonable option for patients with RBD over clonazepam due to a favorable adverse-effect profile especially in elderly individuals with neurodegenerative disorders, and those with comorbid conditions including dementia, gait disorders, or concomitant obstructive sleep apnea. However, to date, no head-to-head trials have been conducted comparing melatonin to clonazepam. The most commonly used dose in RBD trials has been 3 mg nightly before bedtime. Higher doses of melatonin (i.e., 6 mg-15 mg) have also been used with success.
Safety	• For short term use, melatonin is relatively safe with the most common side effects being headaches, dizziness, nausea, and drowsiness. • Use should be avoided in patients who are pregnant/lactating. • Caution is advised for patients with seizure disorders.
Potential Impact	• For Fiscal Years 2010-2014, there were 898,321 unique Veterans with insomnia diagnoses based on ICD 9 codes (780.52; 780.50; 307.49; 307.48; 307.47; 307.46; 307.41; 307.42; 307.40; 327.0; 327.01; 327.02; 327.09). The numbers of unique Veterans diagnosed with insomnia have increased from 246,422 in FY 10 to 343,228 in FY 14. • Despite good median Jadad score and Down and Black quality index on the meta-analyses included in this review for sleep onset latency, the studies did not adequately report details on the melatonin formulations used, interventions, and methods of allocations. • The duration of melatonin evaluated in the sleep onset latency studies included in the meta-analyses varied highly, ranging from 1 day to 12 months. • Results from the "fair" rated meta-analysis indicate that melatonin may be an agent to consider for reducing sleep onset latency short term (< 4 weeks) in patients with primary insomnia. However, larger and better designed trials would need to be conducted to determine its full clinical impact.

	• Some indication that melatonin may offer some effectiveness in the areas of Delayed Sleep-Wake Phase, Non-24-Hour Sleep Wake Rhythm Disorders, and Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD). Again, larger and better designed trials need to be conducted. • Melatonin does appear to offer a benign side effect profile, reasonable cost acquisition and limited evidence of habituation and tolerance. • ProClarity Review of Uniques Prescribed melatonin: FY 10: 214; FY 11:448; FY12: 877; FY13: 1381; FY14: 2034 ; VAADERS Reported AEs with melatonin: FY 10-14; 12

Background

Purpose for review

Melatonin is an over-the-counter medication available in a variety of doses and formulations. It is not FDA approved for any indications; however it has been historically used to treat sleep disorders among other indications. The National Sleep Foundation estimated 30% of the general population has sleep disruption and 10-22% experience symptoms related to insomnia.[6] In 2010, 3.4% of Veterans receiving care had insomnia diagnosis associated with an average of 4 additional psychotropic agents over the year.[7] A study published in 2013 noted that OEF/OIF/OND Veterans had a higher incidence of insomnia of 24-54%.[8]

Issues to be determined:

- ✔ Evidence of need
- ✔ Does melatonin offer advantages to currently available alternatives?
- ✔ Does melatonin offer advantages over current VANF agents?
- ✔ What safety issues need to be considered?

Other therapeutic options

Formulary Alternatives for Sleep Onset	Issues for Consideration
*Benzodiazepines (e.g., lorazepam, temazepam)	BEERS criteria, ADE profile, potential for misuse and abuse
zolpidem IR¶	BEERS criteria, ADE profile, potential for misuse and abuse
*Antidepressants (e.g., mirtazapine, trazodone, doxepin)	BEERS criteria, ADE profile
*Antihistamines (e.g., diphenhydramine, hydroxyzine, cyproheptadine)	BEERS criteria, ADE profile
VA Non-formulary Alternative for Sleep Onset	
eszopiclone (Lunesta) ramelteon (Rozerem) zolpidem SL zolpidem spray zolpidem SA	
VA Non-formulary Alternative for Sleep Maintenance	
doxepin (Silenor) eszopiclone (Lunesta)	
* Off-labeled use; ¶=not FDA approved for sleep maintenance; ADE=Adverse Drug Events	

Efficacy

Literature Search Summary

A literature search was performed on PubMed/Medline (2000 to August 2014) using the search term melatonin for sleep latency. The search was expanded to October 2015 to include a brief overview of melatonin for DSWPD and N24SWD and then in November, 2015, rapid eye movement sleep behavior disorder (RBD) was included. The monograph does not include a review of the use of melatonin for other circadian rhythm sleep-wake disorders (e.g., jet lag). An in-depth review of melatonin in neurodegenerative conditions or in conjunction with cancer treatment was not included. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. All meta-analyses were included.

Table 1: Review of Efficacy for Melatonin in Sleep Latency

	Brzezinski (2005) Meta-Analysis	Buscemi (2005) Systematic Review	Buscemi (2006) Systematic Review	Ferracioli-oda (2013) Meta-Analysis
Number of Studies (number of participants)	17 (N=284)	14 (N=279)	9 (N=279)	19 (N=1683)
Number of studies (types of patients)	7 – healthy normal 6- insomniacs 1-artificially induced insomnia 1-combination institutionalized and independently living insomniacs 1-patients with schizophrenia 1-Alzheimer's disease patients	All primary sleep disorders 12-insomnia 2-delayed sleep-phase syndrome	All secondary sleep disorders 2- developmental disability 2-schizophrenia 1-neurological impairment 1-mild cognitive impairment 1-Rett syndrome 1-Tuberous sclerosis 1-dementia 1-major depressive disorder 1-Alzheimer's disease 1-chronic whiplash syndrome	All primary sleep disorders
Dose (Range) and Formulation	0.1mg-80mg IR 0.5mg-2mg CR 2mg-2.5mg SR 50mg IV	<1mg -5mg IR/SR	0.5mg-7.5mg IR 2.5mg SR	0.1mg-5mg 0.05mg/kg-0.15mg/kg IV
Duration of Study (Range)	1 day – 2 months	4 weeks or less	10 days-12 months	7 days -182 days
Age (Range)	18-93 years	Not specified: included children and adults	8.8-84.2 (average)	Not specified: included children and adults
Sleep Latency (95% CI)	↓ 4 min (-5.4, -2.5) [13 studies] Heterogeneity: Q=52 Q=34.1 (when 2 outlier studies were removed)	↓ 11.7 min (-18.24, -5.2); p=0.00001 [14 studies] Heterogeneity:I^2=81.6% Sub analysis: • Patients with delayed sleep phase: ↓ 38.8min (-50.3, -27.3) (2 studies) • Patients with diagnosis of insomnia: ↓7.2 min(-12.0, -2.4) (12 studies) • Adequate concealment: ↓16.4min (-24.3, -8.5) (3 studies) • Elderly: (≥ 66): ↓10.3min (-20.1, -0.6) (5 studies) • Jadad quality score: High ↓14.2 min (-26.2, -1.7) (10 studies)	↓ 13.2 min (-27.3, 0.89); p=0.07 [6 studies] Heterogeneity:I^2=79.2% Sub-analysis: • ↓17.4min (-26.4 , -8.4) (when one outlier study removed): • Adequate concealment: 5.8 min (2.5 -9.1) (one study) • Adults: (19-65): ↓6.6min (-24.6, 11.4) (3 studies)	↓ 7.06 min (-9.75, -4.37); p<0.001 Heterogeneity: I^2=56% Sub-analysis: • Objective measures -↓ 5.50 min (-8.71, -2.29) (unknown studies) • Subjective measures : ↓ 10.68min (-15.58, -5.78) (unknown studies)-
Sleep Duration (95% CI)	↑12.8 min (2.9, 22.8) Heterogeneity: Q=4.3	↑9.6 min (-4.7, 23.9)	↑15.6 min (7.2, 24)	↑8.25 min (1.74, 14.75) p=0.013 Heterogeneity:I^2=44%
Sleep Efficiency (95% CI)	↑2.2% (0.2, 4.2)	↑2.5% (-0.2, 5.2)	↑1.9% (0.5, 3.3)	↑0.22% (0.12-0.32)

		Heterogeneity: Q=7.5	Heterogeneity:I^2=80.7%	Heterogeneity:I^2=0%	p<0.001 Heterogeneity:I^2=0%
Assessment of Methodological Quality	Efficacy: Jadad scale	None	Moderate (Jadad score 2-3): 4 studies High (Jadad score 4-5): 10 studies	Moderate (Jadad score 2-3): (4 studies) High (Jadad score 4-5): (5 studies) (includes subgroup and sensitivity analyses of sleep onset latency)	None
	Safety: Downs and Black Checklist	None	Median quality index score 21.5 (out of 29) IQR: 12-25 (10 studies of which 9 were RCTs, N=222 with melatonin duration of < 3 months	Median quality index 21 (out of 29) (10 studies of which 9 were RCT; n= 487 with melatonin duration of up to 12 months IQR: 20-22	None
Reviewer's Quality Assessment*		Poor	Fair	Fair	Fair

IR=Immediate Release, CR+ Controlled Release; SR= Sustained Release; IV=Intravenous; IQR= Interquartile range
*= screened independently by 3 reviewers using criteria based on USPSTF Methodology.

Melatonin in Adults with Delayed Sleep-Wake Phase Disorder: [12-13]

It is estimated that Delayed Sleep-Wake Phase Disorder (DSWPD) affects approximately 10% of the patients with chronic insomnia. Delayed Sleep-Wake Phase Disorder is characterized by a delayed sleep-wake timing usually greater than two hours. The primary complaint of individuals with DSWPD is the difficulty falling asleep at a time desired contributing to an insufficient total sleep time leading to difficulties getting up at the expected time to participate in next day's activities. Discontinuation of melatonin therapy in adults with DSWPD will result in the delay of sleep onset and a return to pretreatment values within a few days to 1 year. The role of melatonin in this sleep disorder is dependent on when the drug is administered in relation to the correct timing to the individual's circadian clock, as well as the melatonin dose. If the dose is too low, no results will be observed. If the dose is higher than required, the chronobiologic effects of melatonin may be lost and instead, somnolence may be observed. In addition, when the timing of melatonin is earlier compared to the dim-light melatonin onset (DLMO), greater phase advances occurs. (Refer to Table 2)

Recently, the American Academy of Sleep Medicine released Clinical Practice Guideline (CPG) for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders. The CPG included a meta-analysis of 3 studies in adults with DSWPD with the critical outcomes of change in minutes for the following thresholds: circadian phase, total sleep time (TST), initial sleep latency (ISL), sleep onset time (SOT), and sleep offset time (SOffT). The dose of melatonin studied included 0.3 mg, 3 mg, and 5 mg. The duration of melatonin treatment was ~ 30 days in all studies. The polysomnography (PSG) determined TST resulted in an increase of 41 minutes (95% CI 13.19, 69.70) in a subgroup with comorbid depression (n=28) and 56.0 minutes higher (95% CI 48.41, 63.49) in a subgroup with no depression (n=12) with melatonin versus placebo, respectively. The PSG determined ISL was very similar in both subgroups with and without depression treated with melatonin. (Refer to Table 3). Two of the studies had positive results for TST, ISL with 5mg time administered between 1900-2100 for a period of 28 days. Although the overall level of evidence was low, and the results regarding the sleep/circadian-related effects of melatonin were inconsistent, the recommendation to use strategically timed melatonin was made based on the assessment of evidence, unknown benefits/harms ratio, and accepted patient values and preferences versus no treatment at all.

Table 2: Review of Efficacy for Melatonin in Adults with Delayed Sleep-Wake Sleep Phase Disorder

	vanGeijlswijk et. al (2010) Meta-Analysis
Number of Studies (number of participants)	5 (N=91 adults)
Type of placebo-controlled studies	4/5 crossover; 1/5 parallel group All included information about timing of melatonin administration
Dose (Range) and Formulation	0.3, 3mg, 5 mg
Duration of Study (Range)	2-4 weeks
Age (Range)	Unknown

Sleep Onset Latency (95% CI)		↓ 30.28 minutes (-63.29, 2.74); [4 studies, n=111] Z score=1.80
Total Sleep Time (95% CI)		↑ 0.77 minutes (-33.87, 35.42); [3 studies, n=67] Z score=0.04
DLMO (95% CI)		Mean ↓1.69 hours (2,31, -1.07); p<0.0001 [3 studies, n=82] Z score = 5.34
SOT		↓0.70 hours (-1.04, -0.336); p<0.0001 [5 studies, n=111] Z score=4.08
WUT		-0.95 hours (-3.25 1.36); [2 studies, n=27] Z score =0.8
Assessment of Methodological Quality	Efficacy: Jadad scale	Mean score was 4 out of 5 (9 trials)
	Safety: Downs and Black Checklist	26 out of 32 (range 19-31) (9 trials)
Reviewer's Quality Assessment		Fair

DLMO=dim-light melatonin onset; SOT=Sleep-onset time; WUT=wake-up time

Table 3: PSG Measured TST and ISL Outcomes with Melatonin in Adults with DSWPD with and without Depression

Outcomes	# of subjects/ (# studies)	Quality of Study	Absolute effect [95% CI
TST*	28 (2)	Low	↑ 41.44 [13.19, 69.70], p=0.004
ISL*	28 (2)	High	↓ 43.52, [- 52.60, -34.45], p<0.00001
TST¶	12 (1)	High	↑ 56.0 [48.51 63.49]
ISL¶	12 (1)	High	↓ 37.70 [-43.65, -31.75]

TST=Total Sleep Time, ISL= Initial Sleep Latency; *Subgroup with depression;¶ Subgroup without depression; PSG= Polysomnography

Melatonin in Adults with Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD) [13-25]

The optimal dose of melatonin to produce the desired phase advance shifts or phase delay shifts has been conducted using doses as low as 0.3 mg in N24SWD patients to 3 mg in normal healthy adults. It is usually accepted that low oral dose of 0.5 mg melatonin daily is effective at entraining the free-running circadian systems in most studies with blind patients. It is hypothesized that using high dose melatonin will cause a supraphysiologic concentration which will be difficult to recognize at the receptor level and may also produce numerous biological effects including daytime sleepiness, impaired mental and physical performance, hypothermia, and hyperprolactinemia. Findings from a variety of studies using melatonin for N24SWD indicate that treatment is optimal when melatonin is administered at the correct circadian phase. When melatonin is administered in the phase advance portion of the phase response curve, most free-running subjects will entrain, whereas when melatonin is initially given in the phase delay portion, the majority of these patients will not entrain. Taking melatonin at bedtime, as a sleep aid, will have a relatively minor effect on circadian phase so administering melatonin about 5 hours before the desired bedtime is recommended to achieve entrainment for the majority of N24SWD patients.

A meta-analysis with the critical outcome of entrainment using melatonin was included in the recent American Academy of Sleep Medicine Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders. Three placebo-controlled, crossover studies using timed oral melatonin for patients with N24SWD (n=36) were included in the meta-analysis. The dose of melatonin studied included 0.5 mg, 5 mg, and 10 mg and the duration of melatonin treatment ranged from 26-81 days. The odds ratio for entrainment was 21.18 (95% CI 3.22-139.17) in favor of melatonin. Although the quality of evidence was low and the strength of the recommendation was weak for, the recommendation that clinicians use strategically timed melatonin for the treatment of N24SWD in blind adults (versus no treatment) was made based on the assessment of evidence, benefits versus harms analyses, and patient values and preferences.

Melatonin in Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD) [26-31]

Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD) occurs when the loss of muscle tone usually seen in REM sleep is incomplete or absent. In RBD, α-synuclein abnormalities in the brainstem disinhibit the rapid eye movement sleep motor activity, leading to dream enactment. As a result, people with RBD will physically "act out' dreams that can be characterized by simple limb twitches to more intense and violent behavior. Dream enactment

behaviors can include loud vocalization, sudden violent arm and leg actions such as jumping out of bed, flailing arms, kicking, and grabbing resulting in injuries to the patients themselves or to bed partners. It has been reported that between 33% and 65% of RBD patients report sleep related injury to self or bed partner. These actions may occur occasionally or several times per night. Dream enactment behaviors typically start during the fifth or sixth decade of life and often worsen over time. Various degenerative neurological conditions such as dementia, Alzheimer's disease (AD), multiple system atrophy, Parkinson's disease are seen in patients with RBD. Although many types of insomnia can occur in neurodegenerative diseases, it is believed that RBD is seen as a precursor to PD. It has been reported that 50% of patients with RBD will convert to a parkinsonian disorder within a decade and nearly all (80-90%) patients with RBD will develop a neurodegenerative disorder. Sedative-hypnotic withdrawal and the acute administration of antidepressants have also been associated with RBD.

Studies have suggested that melatonin's neuroprotective role of preventing oxidative damage is useful in treating RBD in neurodegenerative disorders. Melatonin's exact neuroprotective mechanism of action against RBD is unknown although it has been postulated that it could be a combination of influences including a direct impact on REM sleep atonia, modulation of gamma-aminobutyric acid inhibition, stabilizing circadian clock variability and desynchronization, increasing sleep efficiency, and decreasing calmodulin which may modulate the cytoskeletal structure and nicotinic acetylcholine receptor expression in the skeletal muscle cells. The most commonly cited RBD treatment strategies based on case series and small clinical trials have included low dose clonazepam (0.5-1.0 mg) or high-dose melatonin (6-15 mg) taken orally at bedtime. A naturalistic survey of patient-reported clinical outcomes in patient with RBD (n=133) conducted between 2008-2010 reported effective daily doses of melatonin in patients with RBD ranged from $\leq$ 6 mg to 25 mg. A combination therapy of clonazepam 0.5 mg -1 mg and melatonin 6 mg was used in a published retrospective case series (n=28). At 6 months, the combination therapy resulted in statistically significant reductions of nights with dream enactment and vocalization compared to baseline, ($p \leq 0.001$). In 2010, the Standards of Practice Committee of the American Academy of Sleep Medicine suggested melatonin for the treatment of RBD due to the advantage that there are few side effects. (Level B).

Appendix A: Review of Melatonin Meta-Analyses: In Patients with Primary and Secondary Insomnia

<table>
<tr><th>References</th><th>Purpose, Design, Study Population</th><th></th><th>Findings</th></tr>
<tr><td>Brzezinski (2005)</td><td>
Purpose: To identify directional effects of melatonin

The studies were identified from MEDLINE search (1980 to December 2003), supplemented by personal files of authors.
Criteria for study inclusion: English-language, peer-reviewed scientific journals; ≥ 6 adult subjects with no severe disabling systemic disease; randomized and double-blinded; involved placebo-controlled clinical trials; evaluated sleep using objective measurements. Crossover and parallel group designs were included.

Summary of trials included:
17 studies involving 284 subjects

<table>
<tr><th># of studies</th><th>Types of Patients</th></tr>
<tr><td>7</td><td>healthy normal volunteers</td></tr>
<tr><td>6</td><td>insomniacs</td></tr>
<tr><td>1</td><td>artificially induced insomnia</td></tr>
<tr><td>1</td><td>combination of institutionalized and independently living insomniacs</td></tr>
<tr><td>1</td><td>schizophrenics</td></tr>
<tr><td>1</td><td>Alzheimer's</td></tr>
</table>
<table>
<tr><th># of studies</th><th>Type of objective measurement</th></tr>
<tr><td>4</td><td>Actigraphy</td></tr>
<tr><td>10</td><td>Polysomnography (PSG)</td></tr>
<tr><td>1</td><td>Index finger switch depression</td></tr>
<tr><td>1</td><td>PSG and actigraphy</td></tr>
<tr><td>1</td><td>unknown</td></tr>
</table>
Pre-Determined Outcomes (at least 1 of the three outcomes had to be included)
<table>
<tr><th># of studies</th><th>Recorded Pre-Determined Outcome</th></tr>
<tr><td>13</td><td>Sleep onset latency: (time between lights out and PSG or actigraphic evidence of sleep onset)</td></tr>
<tr><td>9</td><td>Total sleep duration: (total time spent asleep subsequent</td></tr>
</table>
</td><td></td><td>
<u>Efficacy: Sleep Latency</u> <u>compared to placebo</u>
• Evaluated by 13 studies
• Mean reduction of 4 min (95% CI -5.4, -2.5)
Heterogeneity: Q=52 (significant)
  ◦ Q=34.1 (when outliers were removed, significant)
• Post-Hoc:
  ◦ Two studies (with healthy normals) were excluded due to outliers in data
    ▪ Mean Reduction of 7.5 min (95% CI -9.9, -5.2)
  ◦ One study with schizophrenia patients and one study with Alzheimer's patients were excluded
    ▪ Mean reduction of 3.9 min (95% CI -5.4, -2.5)
  ◦ Two above outlier studies plus patients with schizophrenia were omitted
    ▪ Mean reduction by 7.4 (95% CI -9.8, -5.1)

<u>Total Sleep Duration</u> <u>compared to placebo</u>
• Evaluated by 8 studies
  ◦ Mean increase of 12.8 min (95% CI 2.9, 22.8)
  ◦ Heterogeneity: Q=4.3 (insignificant)
• Post-Hoc
  ◦ Two outlier studies plus trials with schizophrenic and Alzheimer's patients were omitted
    ▪ Mean increase of 13.7 min (95% CI 3.1, 24.3)

<u>Sleep Efficiency</u> <u>compared to placebo</u>
• Evaluated by 7 studies
  ◦ Mean increase of 2.2% (95% CI 0.2, 4.2)
  ◦ Heterogeneity: Q=7.5 (insignificant)
• Post-Hoc
  ◦ Omitted two outlier studies plus trials that included patients with schizophrenia and Alzheimer's
    ▪ Mean increase of 3.1% (95% CI 0.7, 5.5)

Discussion:
• Studies included were of crossover and parallel design utilizing melatonin of various formulations ranging from 1 day to 2 months in duration.
• Melatonin statistically improved sleep onset latency by 4 minutes; sleep duration by 12.8 minutes, and sleep efficiency by 2.2%.
• When 2 outlier studies were omitted, sleep latency onset improved to 7.5 minutes, also statistically significant.
• Some concerns with the study methodology are apparent. (A discrepancy between the N reported for study participants (284 subjects) vs. that reported in Table 1 of the study (total of 337
</td></tr>
</table>

	<table><tr><td></td><td>to sleep onset)</td></tr><tr><td>8</td><td>Sleep efficiency: (ratio of total sleep time to total time in bed)</td></tr></table> Duration of Trials: (N trials) <table><tr><td># of studies</td><td>Duration</td></tr><tr><td>6</td><td>1 day</td></tr><tr><td>2</td><td>3 nights</td></tr><tr><td>3</td><td>1 week</td></tr><tr><td>4</td><td>3-4 weeks</td></tr><tr><td>1</td><td>2 months</td></tr></table> <u>Summary of Drug Formulations:</u> Orally: 0.1mg, 0.3mg, 0.5mg CR, 1mg, 2mg CR, 2mg Sustained and fast release, 2.5mg SR, 5mg, 10mg, 40mg, 80mg IV: 50 mg injection <u>Summary of Patient Characteristics:</u> Age range: 18-93 years Average 47.5 years (12 trials) Average: 49.9 years (10 trials-removed trials with patients with Alzheimer's and schizophrenia)		subjects; 231 when healthy subjects and artificially induced insomnia were removed) • Proper chi-square reference value/test statistic was not used. (See Figure 1: reference should have been to X_{10} test statistic, not X_{12}) • The study effect size was determined by using the highest dose versus placebo and all results reported were based on that comparison. • All studies were heterogeneous with regard to sleep onset latency including when outlier studies were omitted. • Unable to rule out the possibility that studies were homogenous with regard to total sleep duration. • Homogeneity cannot be rejected for sleep efficiency. **Conclusions:** • The duration of the studies and types of patients differed. Of the 17 studies included, 7 involved healthy volunteers without a diagnosis of insomnia. • A variety of melatonin dosages and formulations were used and the results of placebo arms were not included. • The efficacy of melatonin for sleep latency of 4 minutes was statistically significant but questionably clinically important. Other outcomes including sleep efficiency and sleep duration statistically improved with melatonin compared to placebo. • Limited efficacy data available for the use of melatonin for sleep latency onset. Quality: Poor (typos; discrepancy in total number of patients included and analyzed; questionable depiction of data, incorrect statistical test, allocation concealment not provided, no assessment of methodological quality provided) Although results are not generalizable to the Veteran population, as most of the study population was healthy volunteers without insomnia, there was evidence that the use of melatonin decreased sleep onset latency, increased in sleep efficiency and increased total sleep duration. Funding: Study was supported by in part of NIH Grants and The National Institutes of Health, Center for Brain Sciences and Metabolism Charitable Trust and the Women' Health Center, Hadassah-Hebrew University Medical Center.
Buscemi (2005)	Purpose: Systematic review of the efficacy and safety of melatonin in the management of primary sleep disorders. Studies were identified from 13 electronic databases dates ranging from 1966-2003, published and unpublished literature, abstracts from Associated Professional Sleep Society meeting 1999-2003, reference lists of relevant reviews and MEDLINE and EMBASE from		**Primary Sleep Disorders:** **<u>Efficacy: Sleep Onset Latency</u>** <u>compared to placebo</u> • Evaluated by 14 studies ◦ Weighted Mean Difference (WMD): -11.7 min (95% CI -18.2, -5.2); p=0.00001 ◦ Heterogeneity: I^2=81.6% (substantial) • 12/14 studies favored melatonin • Sub-analysis by age ◦ 0-18 yrs: -16.7 min (95%CI -29.4, -4); p=0.008;I^2=0 (2 studies) ◦ 19-65 yrs: -11.2 min (95% CI -27.7, 5.4); I^2=84% (7 studies) ◦ > 66 yrs: -10.3 min (95% CI -20.1, -0.6);

	early 2004. Summary of study retrieval and selection: 1,884 studies screened; 935 potential inclusion, 919 excluded, 16 studies were included Allocation concealment: • 11 unclear; 3 adequate Efficacy Criteria of Study Inclusion: English-language; RCT, human participants with primary sleep disorder, melatonin vs. placebo, included either sleep onset latency; sleep efficiency; sleep quality; wakefulness after sleep onset; total sleep time; or percent time in REM sleep. Safety Criteria for Study inclusion: English-language, RCTs and non-RCTs with human participants with primary sleep disorders and compared melatonin with placebo, reporting on adverse events and/or adverse effects. Summary of Efficacy trials included: • 14 studies (279 subjects) Assessment of Methodological Quality: • Jadad mean quality score: 4 moderate (score 2-3); 10 high (4-5) Study Design: 11 crossover, 3 parallel; • 11/14 studies were designed to minimize and/or eliminate comorbid medical and psychiatric conditions Funding: • 7 reported public (half of the studies did not report funding source) • 4 studies had a discrepancy in the number of participants enrolled and the number analyzed (type of analysis was not specified or unclear in these studies) Summary of Safety Trials included: • 10 studies (222 subjects) Study Design: 9 RCTs and 1 non-RCT) for safety for primary sleep disorders. Duration of melatonin administration was 3 months or less. Using modified Downs and Black Checklist, with maximum quality		I^2=79% (5 studies) • Sub-analysis by dose ○ <1mg: -0.9 min (95% CI -5.4,3.6); I^2=0% (2 studies) ○ 1-3mg: -9.6 min (95% CI -17.5, -1.7); I^2=54.6% (6 studies) ○ 4-5mg: -13.8 min (95% CI -28.9, 1.3); I^2=88.6% (7 studies) • Sub-analysis by study duration ○ <1wk: -9.7 min (95% CI -20.5, 1.1); (1 study) ○ 1-2 wks: -7.9min (95% CI -17.5, 1.6); I^2=0% (5 studies) ○ 3-4 wks: -13.6min (95% CI -22, -5.1); I^2=88.9% (8 studies) • Sub-analysis by primary diagnosis ○ Insomnia :WMD -7.2 min (95% CI -12, -2.4); p<.00001; I^2=60.5% (12 studies) ○ Delayed sleep-phase syndrome: WMD -38.8 min (95% CI -50.3, -27.3); I^2=0% (2 studies) • Sub-analysis by Jadad quality score ○ Moderate: -5.4 (95% CI -11.8, 0.9) I^2=37.2% (4 studies) ○ High: -14.2 (95% CI -26.6, -1.7 I^2=85.9% (10 studies) • Sub-analysis Allocation concealment ○ Unclear: -10.1 (-17.4, -2.8) I^2=81.7% (11 studies) ○ Adequate -16.4 (-24.3, -8.5); I^2=0% (3 studies) **Sleep** efficiency compared to placebo • Evaluated by 10 studies ○ WMD: 2.5% (95% CI -0.2, 5.2) ○ Heterogeneity: I^2=80.7% • Elderly population: WMD 5.3(95% CI 0.7, 9.8) compared to the adult population: WMD -0.0; 95% CI: -1.6, 1.5) **Sleep Quality** compared to placebo • Evaluated by 2 studies ○ Standardized Mean Difference: 0.5 (95% CI -0.1, 1.1) **Wakefulness after sleep onset** compared to placebo • Evaluated by 6 studies ○ WMD: -8.2 (95% CI -28.2, 11.9) **Total sleep time** compared to placebo • Evaluated by 13 studies ○ WMD: 9.6 (95% CI -4.7, 23.9) **Percentage time in REM sleep** compared to placebo • Evaluated by 3 studies ○ WMD: 0.4 (95% CI -1.2, 2.0) **Safety:** compared to placebo (10 studies of which 9 were RCTs) Most common adverse events reported were headaches, dizziness, nausea, and drowsiness. Headache: (13 events) • Evaluated by 9 studies ○ Risk Difference: 0 (95% CI -0.05, 0.06) Dizziness (10 events) • Evaluated by 8 studies ○ Risk Difference: 0.01 (95% CI -0.04, 0.06) Nausea (3 events)

index of 29) for safety the score was 21.5 out of 29; IQR 12 to 25

Recorded Pre-Determined Outcome(at least 1 of the outcome had to be included)
• Sleep onset latency: (amount of time spent asleep as a percentage of the total time spent in bed)-primary most important
• Sleep efficiency: (amount of time spent asleep as a percentage of the total time spent in bed)
• Sleep quality: perceived quality of sleep
• Wakefulness after sleep onset: amount of time spent awake in bed following the first attainment of sleep)
• Total sleep time (total time spent asleep while in bed • % in REM sleep (Percent time spent dreaming

Duration of Trials: All <4 weeks

Duration of Trials: (N trials)

# of studies	Duration (weeks)
1	<1
5	1-2
8	3-4

Summary of dosing formulations: Slow to fast release

Summary of dosing strategies:

# of studies	Dosing Strategies
2	<1 mg
6	1-3 mg
7	4 to 5 mg

Summary of Patient' Ages

# of studies	Patient's Age (yrs)
2	Children (≤18)
7	Adult (19-65)
5	Elderly (≥ 66)

- Evaluated by 8 studies
  - Risk Difference: -0.02 (95% CI -0.06, 0.03)

Drowsiness (3 events)
- Evaluated by 8 studies
  - Risk Difference: 0.01 (95% CI -0.04, 0.05)

Discussion:
- Average sleep onset latency reduction was 11.7 minutes for patients with primary sleep disorders which the authors conclude is of little clinical significance.
- Secondary analysis on delayed sleep-phase syndrome noted average reduction of 38.8 minutes which was both clinically and statistically significant (2 studies involved <30 participants; n=12).
- Sensitivity analyses conducted on 3 studies with adequate allocation concealment had negligible heterogeneity with statistically significant results favoring melatonin over placebo for sleep onset latency.
- When stratified by age, the reduction of sleep onset latency was 11.2 minutes for those 19-65 years (trend towards favoring melatonin) and 10.3 minutes for >65 years (statistically significant).
- Sleep quality (2 trials), wakefulness after sleep onset (6 trials), total sleep time (13 trials), and percentage time in REM sleep (3 trials) favored melatonin over placebo, however results were not statistically significant.
- Ten studies of which 9 were RTCs with ~222 participants were included in the safety review. The most common adverse events reported were headaches, dizziness, nausea, and drowsiness. In all cases, there were no significant differences between melatonin d placebo for safety measures.

Conclusion:
- Details of content, quality of melatonin formulation and verification of doses were not adequately described.
- Efficacy and safety data is reported for less than 4 weeks.
- Some evidence to support that melatonin is decreases sleep onset latency in patients with primary sleep disorders with short-term use (i.e., < 4 weeks) but it may not be of clinically important. Larger trials would need to be conducted to determine the clinically usefulness of melatonin in this setting.
- Some evidence to support that melatonin is safe in the management of primary sleep disorders with short-term use (i.e., < 3 months).
- Results may be generalizable to Veteran population as the majority of the studies included were for those >18 years of age diagnosed with primary sleep disorders.

Quality: Fair (see discussion)

Funding: Study was conducted under contract to the Agency for Healthcare Research and Quality and support from the National Center for Complementary and Alternative Medicine, National Institute for Health, Bethesda, Md

<table>
<tr>
<td>Buscemi (2006)</td>
<td>Purpose: Systematic review of the efficacy and safety of exogenous melatonin in managing secondary sleep disorders and sleep disorders accompanying sleep restriction, such as jet lag and shift worker disorders.

The studies were identified from 13 electronic databases dates ranging from 1999-2003, reference lists of relevant reviews, random sample of included studies, abstracts from Associated Professional Sleep Society meeting 1999-2003, and MEDLINE and EMBASE from early 2004

<u>Summary of study retrieval and selection:</u>
1,884 studies screened; 935 potential inclusion, 910 excluded, 25 studies were included

<u>Summary of study retrieval and selection:</u>

<u>Allocation Concealment:</u>
• unclear in all studies except one

<u>Funding Source:</u>
• 5 studies from public sponsors

Summary of Studies Included:
<table>
<tr><td colspan="2">Secondary Sleep Disorders: (defined by a specific chronic medical or psychiatric disorders)</td></tr>
<tr><td>Efficacy</td><td>9 studies
270 subjects</td></tr>
<tr><td>Safety</td><td>7 studies
164 subjects</td></tr>
<tr><td colspan="2">Sleep Accompanying Sleep Restriction (exposed to transmeridian air travel, shiftwork, or other forms of sleep schedule alteration)</td></tr>
<tr><td>Efficacy</td><td>9 studies
427 subjects</td></tr>
<tr><td>Safety</td><td>10 studies
487 subjects</td></tr>
</table>
<u>Efficacy Criteria for Study Inclusion:</u>
(English-language; RCT, human participants who had a secondary sleep disorder or a sleep disorder accompanying sleep restriction; compared melatonin to placebo and reported on one or more of sleep onset latency, sleep efficiency, sleep quality, wakefulness after sleep onset , total sleep time or percentage of time in rapid eye movement (REM) sleep including adverse events
<u>Assessment of Methodological Quality:</u>
• Jadad mean quality score:</td>
<td></td>
<td>Secondary Sleep Disorders: Efficacy
<u>Sleep Onset Latency</u> <u>compared to placebo</u>
• Evaluated by 6 studies (n=163)
• Weighted Mean difference (WMD): -13.2 min (95% CI -27.3, 0.89); I^2=79.2%; p=0.07
• Post-Hoc
◦ One study omitted
◦ WMD -17.4 (95% CI -26.4, -8.4)
• Sub-analysis by age; p<0.001
◦ 0-18 yrs: WMD: -18.1 min (95% CI -29.4, -6.8);
◦ 19-65 yrs: WMD: -6.6 min (95% CI -24.6, 11.4)
• Sub-analysis by co-morbidity; p<0.001
◦ Rett syndrome: WMD: -12.9 min (95% CI -27.6, 1.8) (1 study)
◦ Tuberous sclerosis: WMD: -23.4 min (-45.2, -1.6) (1 study)
◦ Developmental disabilities: WMD: -30 min (95% CI -60.2, 0.2) (1 study)
◦ Depression: WMD: -13.5 min (95% CI -32.5, 5.5) (1 study)
◦ Schizophrenia: WMD: -4.6 min (95(CI -29.8, 20.6) (2 studies)
• Sub-analysis by dose (95% CI)
◦ 1-3 mg: WMD: -4.6 min (-29.8, 20.6) (2 studies)
◦ 4-5 mg: WMD: -23.4 min (-45.2, -1.6) (1 study)
◦ 6-10 mg: WMD: -13.5 min (-32.5, 5.5) (1 study)
• Sub-analysis by study duration (95% CI); p<0.001
◦ 1-2 weeks: WMD: -25.7 min (-43.3, -8) (2 studies)
◦ 3-4 weeks: WMD: -4.6 min (-29.8, 20.6) (2 studies)
◦ >4 weeks: WMD: -13.1 min (-24.8, -1.5) (2 studies)
• Sub-analysis by measurement method (95% CI); p<0.001
◦ Polysomnography: WMD: 5.8 min (2.5, 9.1) (1 study)
◦ Actigraphy: WMD: -14.5 min (-25, -4.1) (3 studies)
◦ Questionnaire: WMD: -25.7 min (-43.3, -8) (2 studies)
<u>Sleep Efficiency (%)</u> <u>compared to placebo</u>
• Evaluated by 6 studies (n=316)
• Weighted Mean difference: 1.9% (95% CI 0.5, 3.3); I^2=0%
<u>Wakefulness after sleep onset</u> <u>compared to placebo</u>
• Evaluated by 3 studies (n=217)
• Weighted Mean difference: -6.3 min (95% CI -16.6, 3.9)
<u>Total Sleep Time</u> <u>compared to placebo</u>
• Evaluated by 9 studies (n=382)
• Weighted Mean difference: 15.6 min (95% CI 7.2, 24)
<u>REM sleep</u> <u>compared to placebo</u>
• Evaluated by 1 study (n=28)
• Weighted Mean difference: -1.5 min (95% CI -4.4, 1.4)</td>
</tr>
</table>

4 out of 5 (interquartile range 2-4)

Safety Criteria for Study Inclusion: (using modified Downs and Black Checklist, with maximum quality index of 29) : English-language, RCTs and non-RCTs with human participants with secondary sleep disorder or a sleep disorder accompanying sleep restriction and reporting on adverse events

Types of Study Designs Included: 3 RCT; parallel; 6 RCT, cross over; 2 N-of-1 RCT, 1 Non-RCT, crossover

Summary of co-morbidities for secondary sleep disorders

# Trials	Co-morbidities
2	developmental disability
2	schizophrenia
1	neurological impairment
1	mild cognitive impairment
1	Rett syndrome
1	Tuberous sclerosis
1	dementia
1	major depressive disorder
1	Alzheimer's disease
1	chronic whiplash syndrome

Recorded Pre-Determined Outcomes in order of importance(at least 1 of the outcome had to be included)
• Sleep onset latency: *PRIMARY OUTCOME* (amount of time between lying down to sleep and onset of sleep)
• Sleep efficiency: (amount of time spent asleep as a percentage of the total time spent in bed)
• Sleep quality: perceived quality of sleep
• Wakefulness after sleep onset: amount of time spent awake in bed following the first attainment of sleep)
• Total sleep time (total time spent asleep while in bed)
• % in REM sleep (Percent time spent dreaming

Range of duration of Trials 10 days-12 months (weeks)

# of studies	Duration (weeks)
1	0.7
2	2
2	3
3	4
1	6

Safety

Evaluated by 7 studies (N=164*);Point estimate (95% CI)

- Headache: 0.02 (-0.03 to 0.07)
- Dizziness: 0 (-0.03 to 0.03)
- Nausea: 0 (-0.03 to 0.03)
- Drowsiness: 0 (-0.03 to 0.03)

**Due to many of the studies were cross-over design, the N reported in the safety section captured unique patients verses the N of 253 initially reported.*

Discussion:

- The sleep onset latency was reduced by mean of 13.2 minutes in patients with secondary sleep disorders but was not statistical significant.
- The secondary analysis noted significant improvement in sleep latency for patients aged 0-18 years, with a diagnosis of tuberous sclerosis, with melatonin doses of 4-5 mg, in study duration of 1-2 weeks, and with actigraphy or questionnaire as measurement tool for sleep onset latency.
- The effect of melatonin on sleep efficiency in patients with secondary sleep disorders was small and questionable clinically significant. Other remaining outcomes including sleep quality, wakefulness after sleep onset, and % REM sleep were not statistical significant with melatonin compared to placebo.
- A mean of 15.6 minutes increase was seen with melatonin for total sleep duration compared to placebo. (95% CI 7.2 to 24.0)
- The most commonly reported ADEs were headache, dizziness, nausea, and drowsiness which did not differ significantly between melatonin and placebo. 17 RCT (secondary sleep disorders with and without sleep restriction) with 651 participants using melatonin short term use (< 3 months or less) showed no evidence of adverse effects.
- One study with adequate allocation concealment had an increase in sleep onset latency of 5.8 min (95% CI 2.5, 9.1).
- Results of melatonin on sleep onset latency sleep efficiency, sleep quality, wakefulness after sleep onset, and total sleep time in sleep disorders accompanying sleep restriction (data not shown here) were not clinically important or statistically significant compared to placebo.
- The study which evaluated melatonin for 12 months included 15 subjects between the ages of 0.5-14 years therefore is not applicable to the Veteran population.

Conclusion:

- The studies included in the review were of short duration, with inadequate intervention, and design details. Substantial heterogeneity; failure to conceal treatment allocations, formulations vary in quality, or not known, and duration of therapy were additional limitations.
- As reported in this meta-analysis with the known

	1 | 8 1 | 10 1 | 48 Summary of Drug Formulations: # of studies | Formulations 1 | Immediate release 2 | Slow release 1 | Slow and immediate release 6 | Not specified Summary of dosing strategies: # of studies | Dosing Strategies 1 | 0.5mg or 1 mg 6 | 2.5 mg 1 | 2.5mg SR 1 | 2.5-7.5 mg 3 | 6 mg Average Age (range): 45.8 (8.8-84.2)# of studies | Age of Patients (years) 4 | Children (0-18) 4 | Adult (19-65) 3 | Elderly (≥ 66)		limitations as stated above, melatonin appeared safe in the population, using the doses and the duration studied. Melatonin as reported in this analysis did not improve sleep latency until one outlier study was omitted. • The results may be generalizable to the Veteran population as the majority of the studies included were those >18 years of age diagnosed with secondary sleep disorders for the specific co-morbidities identified. Assessment of Methodological Quality: Using validated Jadad scale 0-5, with 5 being highest quality) for efficacy, the Jadad mean score was 4. Using Downs and Black Checklist, with maximum quality index of 29) for safety the median quality index score was 21. Quality: Fair (see discussion) Funding: The study was conducted under contract to the Agency for Healthcare Research and Quality and support from the National Center for Complementary and Alternative Medicine, National Institute for Health, Bethesda, Md

Ferracioli-Oda (2013)	Purpose: Meta-analysis to investigate the efficacy of melatonin compared to placebo in improving sleep parameters in primary sleep disorders.
	
	Two reviewers conducted a PubMed search using the terms “Melatonin” and “sleep disorder”. Randomized controlled trials and meta-analyses were reviewed including references of related reviews, meta-analyses, and included articles were searched for additional citations. All studies were published before or on March 2012.
	
	Criteria for study inclusion:
	Included primary sleep disorders as defined by DSM-IV; randomized placebo controlled, at least 10 participants for parallel design or 5 participants for crossover; and published in English.
	
	Summary of study retrieval and selection:
	268 studies screened; 249 studies excluded; 19 studies were included (n=1683)
	
	Primary Outcome measures
			Primary Sleep Disorders: Efficacy
			Sleep onset latency compared to placebo
			• Weighted Mean Difference (WMD): -7.06 min (95% CI -9.75, -4.37); p<0.001
			  • Heterogeneity: I^2=56%-Significant
			• Random effects model: WMD: -10.18 min (95% CI -14.27, -6.1); p<0.001
			• Sub-analysis on objective measures
			  ○ WMD: -5.5 min (95% CI -8.71, -2.29); p<0.001
			• Sub-analysis on subjective measures
			  ○ WMD: -10.68 min (95% CI -15.58, -5.78); p<0.001
			• Meta-regression of longer duration trials: parameter estimate (PE)=0.53 (95%CI 0.21, 0.86); p=0.001
			• Meta-regression using trials of higher doses: PE=1.95 (95%CI 0, 3.91); p=0.05
			
			Total sleep time compared to placebo
			• WMD: Improved by 8.25 min (95% CI 1.74, 14.75); p=0.013
			  • Heterogeneity: I^2=44%
			• Random effects model: WMD: 8.48 min (95% CI -4.02, 20.98); p=0.184
			• Sub-analysis on objective measures
			  ○ WMD: 0.33 min (95% CI -11.19, 11.87); p=0.95
			• Sub-analysis on subjective measures
			  ○ WMD: 11.93 min (95% CI 4.06, 19.81); p=0.002
			• Meta-regression trials of longer duration: PE=1.6 (95%CI 0.5, 2.69); p=0.004

• mean improvement in sleep onset latency
• total sleep time
• sleep quality (considered the same as sleep efficiency

Summary of trials included:

# of Trials	Types
14	insomnia
4	delayed sleep-phase syndrome
1	REM sleep behavior disorder

9/19-parallel design
10/19-cross-over

Duration of trials (weeks):
Range: 7 days-182 days

# of studies	Duration (weeks)
4	1
1	2
3	3
8	4
1	8
1	18
1	26

Summary of dosing strategies:

# Studies	Dosing Strategies
4	0.1mg or 0.3mg:
4	0.5mg or 1mg
5	2mg
1	3mg
7	5mg
1	Weight based (mg/kg) (0.05; 0.1; 0.15)

Drug formulations not specified in study.

Summary of patient characteristics:
Total N=1683

# of studies	Age of Patients (years)
3	Children (0-18)
16	Adult (>18)

- Meta-regression trials using higher doses: PE=7.52 (95% CI 1.94, 12.54); p=0.007

Sleep quality compared to placebo

- Standardized Mean Difference (SMD): 0.22 (95% CI 0.12, 0.32); p<0.001
- Heterogeneity: I^2=0%
- Random effects model provided same overall effect
- Sub-analysis on objective measures
  - SMD: 0.2 (95% CI -0.04, 0.44); p=0.1
- Sub-analysis on subjective measures
  - SMD: 0.23 (95%CI 0.12, 0.34); p<0.001
- Meta-regression on trial duration: PE 0.005 (95% CI -0.0006, 0.012); p=0.08
- Meta-regression on dose: PE 0.01 (95% CI -0.114, 0.09); p=0.81

Discussion:

- Statistically significant decrease in sleep onset latency of 7 minutes in patients with primary sleep disorders with melatonin compared to placebo.
- Sleep onset latency improved with melatonin when measured by both subjective and objective measurements.
- Total sleep time and sleep quality statistically improved by 8.25 minutes and 0.22% respectively, with melatonin compared to placebo.
- Sub-analysis between age groups was not performed due to lack of studies included for those ≤18 years.
- The meta-regression demonstrated trials of longer duration reported greater effects on sleep latency. The longest trial include was 182 days in duration.[7] However, long vs. short duration of melatonin studies in sub-analysis were not defined.
- High vs. low doses of melatonin in sub-analysis were not defined
- Melatonin formulations used in the trials were not provided.
- Significant heterogeneity was noted for sleep onset latency and sleep latency via random effects model.
- Safety of melatonin was not evaluated.
- There is no evidence of publication bias based on Egger's test for all outcome measures evaluated.

Conclusions:

- Small number of trials included therefore may have limited power, however it is the largest meta-analysis comparing melatonin and placebo for sleep disorders
- Results of the meta-analysis may be generalizable to the Veteran population as many trials included were for ages >18 with primary insomnia.

Quality: Fair (see discussion)

Funding: National Institute of Mental Health support of the Yale Child Study Center Research Training program, National Institutes of Health, the APIRE/Eli Lilly Psychiatric Research Fellowship, the AACAP/Eli Lilly Pilot Research Award, Trichotillomania Learning Center, National Alliance for Research on Schizophrenia and

			Depression, National center for Research Resources, Department and Institute of Psychiatry of the University of Sao Paulo School of Medicine Hospital, Brazil National Counsel of Technological and Scientific Development, Science without Borders Program.

Appendix B: Review of Melatonin Meta-Analyses: In Adults with Delayed Sleep-Wake Phase

References	Purpose, Design, Study Population	Findings
van Geijlswijk (2010)	Purpose: To review the efficacy and safety of exogenous melatonin in advancing sleep-wake rhythm in patients with delayed sleep phase disorder. A PubMed, Embase and abstracts of sleep and chronobiologic societies were searched between Jan. 1990 and Sept. 2009. Randomized placebo-controlled, double-blind, clinical trials that used melatonin in (circadian rhythm) sleep (onset) disorders were included. Two reviewers assessed the methodologic quality of the studies. Criteria for study inclusion: English-language, randomized controlled trials including individuals with DSWPD (individuals with ADHD were included), melatonin vs. placebo; and had to report 1 or more of the following: dim light melatonin onset (DLMO), sleep onset time (SOT), wake-up time (WUT), SOL (amount of time between lying down to sleep and onset of sleep), and TST (amount of time between SOT and WUT); Jadad scaled ≥3 Summary of study retrieval and selection: 182 studies screened; 173 studies excluded; 9 studies were included (n=284) of which 5 were adults (n= 91) 4/5 trials cross-over in design 1/5-parallel in design Summary of Dosing Strategies for Adults Studies | # Studies | Dosing Strategies | | 4 | 5mg | | 1 | 0.3mg/3 mg |	**Efficacy: DLMO** compared to placebo • Evaluated by 3 studies • Mean reduction of 1.69 hours (95% CI -2.31, --1.07); p<0.0001 • Z score=5.34 **Efficacy: SOT compared to placebo** • Evaluated by 5 studies • Mean reduction of -0.70 (95% CI -1.04, --0.36); p<0.0001 • Z score=4.08 **Efficacy: WUT compared to placebo** • Evaluated by 2 studies • Mean reduction of -0.95 (95% CI -3.25, 1.36); • Z score=0.8 **Efficacy: SOL compared to placebo** • Evaluated by 4 studies • Mean reduction of -30.28 (95% CI -63.29, 2.74) • Heterogeneity: Z=1.80 **Efficacy: TST compared to placebo** • Evaluated by 3 studies • Mean reduction of 0.77 (95% CI -33.87, 35.42) • Z score=0.04 **Safety:** 4/5 trials reported no adverse events 1 trial reported headache in one patient out of 8 **Discussion:** • Due to broad range of timing administration and small placebo group size, the relationship between the mean time of melatonin administration and the mean difference in after-treatment DLMO between melatonin and placebo group could not be statistically confirmed, p=0.307. • Mean difference in DLMO was -1.69 hours and -0.70 hours for SOL in trials with DSWPD adults taking melatonin doses 0.3 -5mg for 2-4 weeks. • Melatonin did not extend the TST in adults. • WUT in adults was not influenced by melatonin. • Appropriately timed administration of exogenous melatonin does advance DLMO and sleep onset in adults. • Several methods of outcome measurements were used including polysomnography, actigraphy, and diary. • Melatonin was safe for short-term use (i.e., 1 month)

			Conclusion: • The lack of melatonin efficacy in SOL and TST could be attributed to adults not having a scheduled time for bed. • Although DLMO may not be a common endpoint and not widely available to measure, however, determining when the appropriate time to administer melatonin may be useful in achieving higher efficacy of the treatment. • The optimal dose and timing of melatonin for DSWPD is not known. Authors suggested that melatonin administration should be 3 to 6 hours before DLMO which is normally between 19:30 and 21:30 in adults (circadian time 8-11). Authors reported that the greatest advancement observed from other studies is when melatonin is administered 5 hours prior to DLMO. Quality: Fair (see discussion) Funding: None

Appendix C: Review of Melatonin Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD)

References	Purpose, Design, Study Population	Findings
Zhang (2015)	Purpose: To review the efficacy of melatonin in the treatment of sleep problems in persons with neurodegenerative disorders, particularly Alzheimer's Diseases (AD) and Parkinson's Disease (PD) A PubMed, Cochrane Library, and ClinicalTrials.gov were searched (last search July, 2015). Bibliographies of included trials and related reviews were manually searched. Criteria for study inclusion: Randomized controlled trials with patients with neurodegenerative diseases, melatonin or melatonin receptor agonists vs. placebo therapy; any or all sleep outcomes reported including: subjective sleep quality (evaluated by the Pittsburgh Sleep Quality Index, PSQI), objective sleep outcomes (evaluated by polysomnography or with actigraphy for dementia patients); total nocturnal sleep time (TNST); sleep efficiency (TNST/time in bed); nocturnal time awake (after sleep onset and before final awakening) (WASO); number of nocturnal awakenings; sleep latency; ratio of day-time sleep to total sleep over 24 h; and RBD measured by improvement in clinical global impression (CGI) change scores. Two reviewers extracted the data independently and assessed the methodological quality of the trials. Summary of study retrieval and selection: 610 studies identified; 32 studies screened; 20 studies excluded; 9 studies were included 3/9 trials were cross-over in design; 2/9-3 parallel treatment groups design; 4/9 were RCTs. Summary of trials included: # of Trials / Types 6 / Alzheimer's Disease 2 / Parkinson's Disease 1 / RBD	**Melatonin in Alzheimer's Disease (AD)** **Efficacy:** • Evaluated by 4 studies • No significant effect of melatonin on TNST, sleep efficiency, WASO, number of night-time awakenings, or on the ratio of day-time sleep to night-time sleep compared to placebo. • AD patients treated with 24-weeks of 2 mg prolonged release melatonin compared to placebo had significantly better sleep quality, as assessed by changes in the PSQI component 4 (Median: 0.67, 95% CI 0.04-1.30; p=0.04). Z score = 2.09 • In the comorbid insomnia (PSQI=6) subgroup, prolonged melatonin resulted in significant and clinically meaningful effects versus placebo in sleep quality (data not shown) **Melatonin in Parkinson's Disease** **Efficacy:** • Evaluated by 1 study • Melatonin 3 mg improved sleep quality significantly compared to placebo as assessed by PSQI component 6 (Median: 4.20, 95% CI 0.92-7.48; p = 0.01) Z score = 2.51 • No significant effect of melatonin on TNST, sleep efficiency, or on number of night-time awakenings compared to placebo. • One study reported melatonin 50mg increased TNST (10 minutes) versus placebo (p < 0.05). Melatonin 5 mg significantly improved overall sleep quality compared to placebo (p<0.05) but not with melatonin 50 mg. • **Melatonin in RBD** • **Efficacy:** • Evaluated by 1 study, n=8, mean age 54 ○ (idiopathic insomnia (n=2);periodic limb movement disorder (n=2), PD (n=1) narcolepsy (n=7) • Melatonin 3 mg x 4 weeks improved RBD symptoms as indicated in an average decrease in CGI score severity of 1.5 points (p=0.024) compared to baseline : 7/8 subjects had complete resolution, 4/8 had marked improvement; 2/8 had little improvement, 1/8 had no change. Symptom improvement were reported within the first week of treatment and continued to improve over the 4-week study period. • Melatonin decreased the percentage of REM sleep without atonia from 39.2% to 26.8% (p=0.012) and sleep-onset latency by 1.96 min (p=0.05) compared to baseline; however a statistically significant change was not found when compared to placebo.[30]

Duration of Trials (weeks):
Range: 10 days-168 days

# of studies	Duration (weeks)
1	1.4
2	2
3	4
1	8
1	10
1	24

Summary of dosing strategies:

# Studies	Dosing Strategies
1	2.mg
1	2.5mg
3	3 mg
2	5mg
1	6 mg
1	10 mg
1	50 mg in comparison with 5mg)

Summary of patient characteristics:
Total N=400. Age range 26-86 years; 193 Males/246 Females

Safety:
Assessed by 1 PD trial. No significant difference in the number of AD or in the seriousness or relatedness scores for adverse events was seen with melatonin.

Discussion:

- For both AD and PD patients, melatonin has positive effects on sleep quality as assessed by PSQI, but not for objective sleep outcomes.
- Treatment with melatonin improved the clinical and neurophysiological aspects of RBD as a sole or add-on therapy based on 1 trial with 8 subjects.
- .Several methods of subjective and objective outcome measurements were used in this meta-analysis.
- A variety of melatonin strengths for different duration were used.
- Small number of studies and small patient population included in this meta-analysis may increase bias
- Not all included studies reported an outcome measure of interest.

Conclusion:

- Longer melatonin trials may be needed in AD patients to show benefit in sleep quality.
- Prospective, long-term, controlled trials using melatonin in a larger number of patients with RBD needs to be conducted.
- The most effective dose and duration with melatonin in treatment of RBD has yet to be determined.

Quality: Fair (see discussion)
Funding: None

Safety	Comments
Boxed Warning	• None noted
Contraindications	• Allergic reactions associated to pineal hormones and/or melatonin
Warnings/Precautions	• No data

Safety Considerations
Safety

- Safety profile of melatonin has not been established with long term use
- For short term use, melatonin is relatively safe
- Use should be avoided in patients who are pregnant/lactating[9]
- Caution is advised for patients with psychiatric comorbidities and history of seizures (literature in children/adolescents) [9]

Post-marketing Safety Experience

- No data

Sentinel Events

- No data

Adverse Reactions

Common adverse reactions	• Headache, dizziness, nausea, drowsiness[2]
Death/Serious adverse reactions	• None noted
Discontinuations due to adverse reactions	• Well tolerated at physiologic and pharmacologic doses

Other Adverse Events

- Nasopharyngitis, arthralgia, lower and upper respiratory tract infections , vivid dreams , transient depressive symptoms, increased anxiety, irritability, confusion, abdominal cramps [3,5,10]

	Buscemi (2005) RD (95%CI)	Buscemi (2006) Point Estimate (95% CI)
Headache	9 studies (13 events) 0 (-0.05,0.06)	7 studies 0.02 (-0.33, 0.03)
Dizziness	8 studies (10 events) 0.01 (-0.04, 0.06)	7 studies 0 (-0.03, 0.03)
Nausea	8 studies (3 events) -0.02 (-0.06, 0.03)	7 studies 0 (-0.03, 0.03)
Drowsiness	8 studies (3 events) 0.01 (-0.04, 0.05)	7 studies 0 (-0.03, 0.03)

RD = risk difference

Drug Interactions

Drug-Drug Interactions[9]

- Warfarin: increased risk of bleed
  - Monitor INR closely
- Anticoagulant/antiplatelet medications: may increase risk of bleed
  - Monitor closely
- Medications for hypertension: melatonin may decrease blood pressure
  - Monitor closely and adjust dosing as needed
- Fluvoxamine: increased CNS depression
  - Monitor closely and consider lower dose of melatonin
- Medications for diabetes: may increase or decrease blood glucose levels
  - Monitor blood glucose closely
- Immunosuppressants: may have decreased effectiveness
  - Avoid use
- CNS depressants: may increase somnolence
- Oral contraceptives: may increase serum levels of melatonin
- Caffeine, verapamil, flumazenil: may decrease effectiveness of melatonin

Risk Evaluation*

	Comments
Sentinel event advisories	• None noted • Sources: Institute for Medication Safe Practices, Food and Drug Administration, The Joint Commission
Look-alike/sound-alike error potentials	See table below • Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Melatonin, MEL, MLT	None	None	None	Melathion Memantine Metolazone

*As of 2/26/2015

Dosing and Administration

- Available in numerous dosage forms, formulations, and strengths over-the-counter.
- Sleep Onset Latency: Melatonin 0.3-5mg [10] commonly administered in the evening about 30-60 minutes before bedtime.
- DSWPD: The dose of melatonin should be as low as possible and administered as early as tolerable. Studies incorporated in the American Academy of Sleep Medicine Clinical Practice Guidelines for this use included melatonin ≤ 5 mg for approximately one month in duration. Strategically timed melatonin is recommended. If melatonin is administered too late with respect to endogenous melatonin onset, melatonin levels may persist through the early morning resulting in delaying the DLMO instead of advancing it.
- N24SWD: Strategically timed oral melatonin using doses between 0.3-3 mg about 5 hours before the desired bedtime and ideally at the correct circadian phase (i.e. at a circadian time that would shift the biological clock to an earlier hour) is recommended to achieve entrainment for the majority of N24SWD patients. The majority of patients will achieve entrainment with melatonin 0.5 mg dose.
- RBD: There is supporting literature that melatonin is a reasonable option for patients with RBD over clonazepam due to a favorable adverse-effect profile especially in elderly individuals with neurodegenerative disorders, and those with comorbid conditions. However, to date, no head-to-head trials have been conducted comparing melatonin to clonazepam. The most commonly used dose in RBD trials has been 3 mg nightly before bedtime, with no adverse events reported at this dose. However, higher doses of melatonin (i.e., 6 mg-15 mg) have been also been used.

Special Populations (Adults) [9]

Pregnant and lactating females: avoid use

- Patients with depression: may worsen depression symptoms
- Children and adolescents with seizures: risk of seizures may increase (literature in children and adolescents)

Projected Place in Therapy (this section may be edited prior to final approval of document and web posting)

Diagnosis and Prevalence of Insomnia

- For Fiscal Years 2010-2014, there were 898,321 unique Veterans with insomnia diagnoses based on ICD 9 codes (780.52; 780.50; 307.49; 307.48; 307.47; 307.46; 307.41; 307.42; 307.40; 327.0; 327.01; 327.02; 327.09) with the numbers of unique Veterans diagnosed increasing from 246,422 in FY 10 to 343,228 in FY 14.
- In a study published in 2013, it was noted that OEF/OIF/OND Veterans had a higher incidence of insomnia of up to 54%. [8]

Melatonin Studies Reviewed for Sleep Latency

- The duration of studies included in the meta-analyses reviewed varied highly, ranging from 1 day to up to 12 months.
- The heterogeneity of studies was significant for sleep onset latency across the four meta-analyses.
- Studies included in each meta-analysis for this review differed considerably in terms of subjects examined, melatonin doses, preparations, indication for use, study design, and duration of therapy.
- Sleep onset latency was the most frequently outcome recorded in the studies and considered to be the primary outcome measure in all meta-analyses reviewed.

Melatonin Effect on Sleep Latency

- Three of four meta-analyses[2-4] included in this review reported a statistically significant mean reduction in sleep latency compared to placebo (range: -4 min to -13.2). The fourth meta-analysis[5] favored melatonin but was not significant until one outlier study was removed in a post-hoc analysis.
- Melatonin may be appropriate for short-term use for sleep latency; however the exact length of therapy is unknown. Only 3 of the 59 studies evaluated in the meta-analyses were longer than 3 months in duration.

Comparison of other melatonin receptor agent

- Another melatonin receptor agent, ramelteon is FDA approved for the treatment of insomnia characterized by difficulty with sleep onset. According to the product information, ramelteon 8mg vs.

placebo in adults with chronic insomnia showed statistically significant reduction in sleep onset latency of 9.5 minutes based on polysomnography after 6 months of treatment. [11] Ramelteon Monograph

- No direct comparison between melatonin and ramelteon has been conducted.

Expense

- The cost associated with branded ramelteon is almost 120% more expensive than melatonin per dose. The patent for ramelteon expires in 2017.

Use in VA and Veteran population

- The results of three of the melatonin meta-analyses [3-5] evaluated may be generalizable to the Veteran population as a majority of the trials included were conducted in adults with primary or secondary sleep disorders. The majority of the studies included in Brzezinski et al.[2] meta-analysis evaluated melatonin efficacy in healthy patients.
- The use of melatonin is cautioned in patients with history of seizures, uncontrolled hypertension or diabetes, and pregnant and lactating females.
- Melatonin has shown moderate benefit in reducing sleep onset latency as well as low incidence of serious short term effects.
- Strategically timed melatonin has shown some benefit compared to no treatment in adults with DSWPD with or without depression and in N24SWD.
- Melatonin has shown benefit in reducing clinical behavioral outcomes during REM sleep in patients with RBD. Larger clinical trials are needed to establish melatonin as the first-line treatment option over clonazepam therapy. However, melatonin with a more favorable safety profile compared to clonazepam is being recognized as a reasonable option to use especially in the elderly with neurodegenerative disorders.

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Prepared March, 2015, Revised with addition of Non-24- Hour Sleep-Wake Rhythm Disorder (N24SWD), Delayed Sleep-Wake Phase Disorder (DSWPD), and REM Sleep Behavior Disorder (RBD) in November, 2015. Angela Hwang, PharmD (PGY-1 Pharmacy Resident); Rebecca Riley Brothers, PharmD, BCPS (Assistant chief of Pharmacy, Clinical Programs)-Cincinnati VAMC. Contact person: Janet H. Dailey, PharmD, VA PBM Services