Executive Summary

Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). An Update for 2015.

An American Academy of Sleep Medicine Clinical Practice Guideline

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INTRODUCTION

The two-process model for sleep regulation delineates two principle mechanisms for the governance of sleep and wakefulness: "Process S" and "Process C".[1] The homeostatic drive to sleep (Process S) is proportional to the duration of wakefulness. In contrast, Process C creates a drive for wakefulness that variably opposes Process S and is dependent upon circadian ("approximately daily") rhythms intrinsic to the individual. Master coordination of this sleep/wake rhythm is provided by the neurons of the suprachiasmatic nuclei located within the hypothalamus.[2-5] As this intrinsic period is typically slightly longer than 24 hours in humans, synchronization to the 24-hour day[6] (entrainment) is accomplished by various environmental inputs, the most important of which is light and dark exposure.[7] Failure to synchronize can alter the phase relationships between internal rhythms and the light/dark cycle, which may manifest in the form of circadian rhythm sleep-wake disorders (CRSWDs). The endogenous CRSWDs refer to those conditions that are thought to exist predominantly due to innate phenomena, although exogenous components contribute to varying degrees in all of these disorders.

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Glossary of Terms and Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
aMT6s	6-sulfatoxymelatonin (urinary metabolite of melatonin)
CBT_{Min}	Core body temperature minimum
DLMO	Dim light melatonin onset
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ISL	Initial sleep latency
PSG	Polysomnography
SOT	Sleep onset time
SOffT	Sleep offset time
TF	Task Force
TST	Total sleep time

METHODS

Expert Task Force

In order to develop these Clinical Practice Guidelines, the AASM commissioned a task force (TF) of 4 members with expertise in the field of CRSWDs, assigned an AASM BOD liaison, and an AASM Science and Research Department staff member to manage the project. None of the TF members declared any conflicts of interest. The present paper was approved by the AASM BOD and replaces the previous Practice Parameters.[8] The AASM expects these guidelines to have a positive impact on clinical decision-making and patient outcomes. These recommendations reflect the state of knowledge at the time of publication and will be revised when the availability of new information necessitates.

PICO Questions

Eight PICO (**P**atient, **P**opulation or **P**roblem, **I**ntervention, **C**omparison, and **O**utcomes) questions were developed based on both the questions raised in the previous AASM publication[8, 9] and an investigation of systematic reviews, meta-analyses, and guidelines published subsequently. The AASM Board of Directors ultimately approved these questions.

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Table 1-PICO Question Parameters

Population	**I**ntervention	**C**omparison	**O**utcomes
Patients diagnosed with intrinsic CRSWDs (ASWPD, DSWPD, N24SWD, ISWRD)	1. Prescribed sleep-wake scheduling 2. Timed physical activity/exercise 3. Strategic avoidance of light (e.g., with the use of eyewear) 4. Light therapy 5. Sleep-promoting medications (hypnotics/sedatives/neuroleptics/other novel agents) 6. Timed oral administration of melatonin or agonists 7. Wakefulness-promoting medications (e.g. modafinil, traditional stimulants) 8. Other somatic interventions	Control group, those treated with placebo or, where a comparison group was not available, measurements performed "before" (baseline) and "after" treatment	*Physiologic circadian phase markers* *Total sleep time* (TST) *Initial sleep latency* (ISL) *Sleep onset time* (SOT) *Sleep offset time* (SOffT)

Literature Searches

Literature search #1 was performed in PubMed using broad terms (see Appendix) in order to identify systematic reviews, meta-analyses or practice guidelines published subsequent to availability of the previous AASM Practice Parameters. Examination of discovered papers (n=93) enabled elucidation of Practice Parameter recommendations requiring revisions, and also assisted with further refinement of the PICO questions. The next literature search (#2) targeted treatment trials involving intrinsic CRSWDs that addressed at least one PICO question. This search utilized PubMed, Embase and PsycInfo databases. At least two TF members carefully assessed the abstract of each retrieved article (n=2063), to determine whether the publication should be included for further consideration. The same search terms, databases and inclusion/exclusion criteria were also used for literature search #3, although new date limitations were applied. The aim of this last search was to capture new articles published since the previous

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search (June 2012 - March 2014). Four hundred fifty-three additional publications were retrieved.

Since new inclusion/exclusion criteria were used in this project, investigations cited in the previous Practice Parameters[8] were not necessarily incorporated into the current analysis. Studies that did not meet inclusion criteria were selectively used for discussion purposes, but were neither included in the GRADE reports nor used as a basis for recommendations. The TF made a particular effort to discuss those studies (containing either patients or healthy subjects) that might spur and/or improve future clinical research for the reviewed CRSWDs.

A final PubMed search was conducted to identify harms or adverse effects attributed to the relevant interventions: light therapy (PICO 4), hypnotics (PICO 5), and melatonin (PICO 6) (see Appendix). Limitations were imposed to select for English-language "meta-analyses" and "systematic reviews" pertaining to human subjects. The titles and abstracts of articles produced by these searches were reviewed for relevance, and pertinent publications were examined. Other cited articles from the "Harms and Adverse Effects" section were culled from prior searches (but deemed ineligible for quantitative analysis) or were provided via TF members' preemptive awareness and consensus regarding relevancy. Adverse effects of combined treatments were addressed based on the singular components of combinations.

Treatment Efficacy Outcomes

During the process of data extraction, the TF developed a list of patient-oriented clinically relevant outcomes and rated their relative importance. Physiologic circadian phase markers, total sleep time (TST), initial sleep latency (ISL), sleep onset time (SOT), and sleep offset time (SOffT) were deemed CRITICAL for making recommendations, and a significance threshold was defined for each outcome based upon consensus (see **Table 2**). An exception was made for N24SWD, for which entrainment status was uniquely (and solely) utilized as a CRITICAL outcome measure, as it physiologically defines this CRSWD (See section 5.3).

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Table 2-Critical Outcomes and Their Clinical Significance Thresholds Defined by the TF

	Clinical Significance Thresholds					
Diagnosis	**Circadian Phase (change in minutes)**	**TST (change in minutes)**	**ISL (change in minutes)**	**SOT (change in minutes)**	**SOffT (change in minutes)**	**Entrainment Status**
ASWPD	30	30	15	15	15	N/A
DSWPD	30	30	15	15	15	N/A
ISWRD	30	30	15	15	15	N/A
N24SWD	N/A	N/A	N/A	N/A	N/A	Yes/No

Extraction of Evidence

Quantitative data pertaining to the outcomes of interest as well as information necessary for systematic evaluation and grading of the evidence were extracted from accepted articles using a dedicated spreadsheet. Studies that did not meet inclusion criteria for this review but were felt to be of potential relevance for clinicians and/or future research are also discussed, but were not graded, and did not serve as a basis for recommendations. Extracted data were pooled across the studies for each outcome measure in accordance with PICO questions and based on diagnosis, study design, patient population, clinical outcome of interest, and method of derivation (e.g., PSG-derived data were analyzed separately from data derived from actigraphy or sleep diaries).

Statistical Analyses

Meta-analyses were completed (in the few instances possible) using the random effects model. All computations were performed using the Review Manager software[10], and included calculations of the mean difference (MD) ± standard deviation (SD) for CRITICAL outcomes. The results of meta-analyses are depicted in figures within the text, in association with a "forest plot." Summary of Findings tables for all investigations are presented in the Appendix.

When studies contained placebo/control groups, the evaluation of the effect of treatment was performed by comparison of averaged post-treatment and averaged post-placebo/control group values, regardless of the authors' approaches. In studies with crossover or "before-after" designs where there was no placebo/control group, post-treatment values were compared to

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baseline values. Our use of this methodology occasionally produced results that differed from those reported in the original publications (e.g.[11-13]).

Interpretation of Clinical Significance of Results

Interpretation of clinical significance was ascertained via comparisons with pre-defined thresholds (see **Table 2**).

Quality of Evidence

The GRADE approach (recently adopted by the AASM) was used for the assessment of quality of evidence.[14-21]

Also see: {http://www.gradeworkinggroup.org/publications/JCE_series.htm}.

In GRADE, there are 4 specific categories for assessing the quality of a body of evidence:

High: corresponds to a high level of certainty that the true effect lies close to that of the estimate of the effect.

Moderate: corresponds to a moderate level of certainty in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: corresponds to a low level of certainty in the effect estimate; the true effect may be substantially different from the estimate of the effect..

Very low: corresponds to very little certainty in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

A summary of the GRADE approach to rating quality of evidence is presented in **Table 3**.

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Table 3-Summary of GRADE Approach to Rating Quality of Evidence[14]

Study design	Initial quality of a body of evidence	Downgrade if	Upgrade if	Quality of a body of evidence
Randomized trials	High →	**Risk of bias**	Large effect	**HIGH** (four plus: ⊕⊕⊕⊕)
		−1 Serious	+1 Large	
		−2 Very serious	+2 Very large	
		Inconsistency	Dose response	**MODERATE** (three plus: ⊕⊕⊕◯)
		−1 Serious	+1 Evidence of a gradient	
		−2 Very serious	All plausible residual confounding	
Observational studies	Low →	**Indirectness**	+1 Would reduce a demonstrated effect	**LOW** (two plus: ⊕⊕◯◯)
		-1 Serious	+1 Would suggest a spurious effect if no effect was observed	
		-2 Very serious		
		Imprecision		**VERY LOW** (one plus: ⊕◯◯◯)
		-1 Serious		
		-2 Very serious		
		Publication bias		
		-1 Serious		
		-2 Very serious		

The body of evidence for each outcome was assessed and graded, taking into account quality considerations based on the quantitative analysis and other major factors described above. CRITICAL outcome results are presented as summary of findings tables organized by PICO question and patient population (see **Appendix, Tables 1-12**).

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Strength of Recommendations

The TF developed recommendation statements and determined the direction and strengths of these recommendations based on the balance of the following major factors:

1. Level of evidence
2. Benefits vs. Harms
3. Patient values and preferences – based on the clinical expertise of the TF and relevant published data.

Taking these major factors into consideration, each recommendation statement is given a "strength value" of Strong For, Weak For, Weak Against or Strong Against (see **Table 4**).

Table 4-Definitions of AASM Strengths of Recommendations

AASM Strength of Recommendation	Characteristics Guiding Recommendation
STRONG FOR	• There is a high degree of clinical certainty in the net benefits of this patient-care strategy. • The **vast majority** of well-informed patients would most likely choose this patient-care strategy, compared to alternative patient-care strategies or no treatment.
WEAK FOR	• There is a lower degree of clinical certainty in the balance between benefits vs. harms (i.e., net benefits) of this patient-care strategy. • The **majority** of well-informed patients would most likely choose this patient-care strategy, compared to alternative patient-care strategies or no treatment.
WEAK AGAINST	• There is a lower degree of clinical certainty in the balance between benefits vs. harms (i.e., net harms) of this patient-care strategy. • The **majority** of well-informed patients would most likely not choose this patient-care strategy, compared to alternative patient-care strategies or no treatment.
STRONG AGAINST	• There is a high degree of clinical certainty in the net harms of this patient-care strategy. • The **vast majority** of well-informed patients would most likely not choose this patient-care strategy, compared to alternative patient-care strategies or no treatment.

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There were multiple cases when the TF chose to make "NO RECOMMENDATION," which reflects either a complete lack of available evidence (no studies were published) or situations when evidence was available but either did not meet review inclusion criteria or was considered insufficient to support a recommendation (See **Appendix, Tables 5-6**). At the step of review of the extracted evidence, the TF made a decision to exclude studies with fewer than 10 subjects if the study constituted a single source of evidence, as it was felt that affiliated data were insufficient to support a recommendation.

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196 **Table 5-**Overview of AASM Recommendation Status for Intrinsic CRSWD Treatments

Treatment	ASWPD	DSWPD	N24SWD	ISWRD
Prescribed sleep-wake scheduling	No Recommendation	No Recommendation	**No Recommendation**	No Recommendation
Timed physical activity/exercise	No Recommendation	No Recommendation	No Recommendation	No Recommendation
Strategic avoidance of light	No Recommendation	No Recommendation	**No Recommendation**	No Recommendation
Light therapy	**5.1.4a WEAK FOR** (adults)	No Recommendation	No Recommendation	**5.4.4a WEAK FOR** (elderly with dementia)
Sleep-promoting medications	No Recommendation	No Recommendation	No Recommendation	**5.4.5a STRONG AGAINST** (elderly with dementia)
Timed oral administration of melatonin or agonists	No Recommendation	**5.2.6.1a WEAK FOR** (adults with and without depression) **5.2.6.2.1a WEAK FOR** (children/adolescents without comorbidities) **5.2.6.2.2a WEAK FOR** (children/adolescents with psychiatric comorbidities)	**5.3.6a WEAK FOR** (blind adults) No Recommendation (sighted)	**5.4.6.1a WEAK AGAINST** (elderly with dementia) **5.4.6.2a WEAK FOR** (children/adolescents with neurologic disorders)
Wakefulness-promoting medications	No Recommendation	No Recommendation	No Recommendation	No Recommendation
Other somatic interventions	No Recommendation	No recommendation	**No Recommendation**	No Recommendation
Combination treatments	No Recommendation	No Recommendation (adults) **5.2.9.2a WEAK FOR** light therapy + multicomponent behavioral interventions for children/adolescents)	No Recommendation	**5.4.9.1a WEAK AGAINST** (combination treatment of light and melatonin for demented, elderly patients

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RECOMMENDATIONS

Recommendations for the treatment of ASWPD

5.1.4a We suggest that clinicians treat adult ASWPD patients with evening light therapy (versus no treatment). [WEAK FOR]

Summary: No treatment trials of light therapy in ASWPD have been published since the 2007 Practice Parameters, which recommended this therapy as an OPTION. The largest effects were seen after a 12 day treatment of 2 hours of bright white broad spectrum light (~4,000 lux) from 2 light boxes (proximity to source not specified), timed to occur daily between 20:00 and 23:00, and ending before habitual bedtime. Nevertheless, the overall quality of evidence derived from the analyses of two publications[22, 23] is VERY LOW (**Appendix, Table 1**), with potential benefits of light therapy closely balanced with the harm/burden. Associated risks are minimal, as detailed separately in the "Harms and Adverse Effects" section. Patients report reasonable compliance and high satisfaction with this treatment[22] and light boxes are available over-the-counter in the U.S., at relatively affordable prices. Thus, the majority of well-informed patients would choose light therapy versus no treatment.

Recommendations for the treatment of DSWPD

5.2.6.1a We suggest that clinicians treat DSWPD in adults with and without depression with strategically-timed melatonin (versus no treatment). [WEAK FOR]

Summary: The previously published recommendation was designated as a GUIDELINE. The overall quality of evidence from the analyses of the three accepted/reviewed studies[11, 24, 25] was LOW (**Figures 2, 3** and **Appendix, Table 2**), and data regarding the sleep/circadian-related effects of melatonin were contradictory. Positive results were obtained with a 5 mg dose timed between 19:00-21:00 (no circadian-based timing), for a period of 28 days.[24, 25] The Rahman study[24] was the sole study identified subsequent to publication of the previous Practice Parameters. Taking into account the discussion regarding potential safety/adverse effects of melatonin (see separate "Harms and Adverse Effects" section), the benefits/harms ratio remains uncertain, but clinical experience suggests frequent acceptance of this treatment among adults versus no treatment.

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5.2.6.2.1a We suggest that clinicians treat children and adolescents with DSWPD (and no comorbidities) with strategically-timed melatonin (versus no treatment). [WEAK FOR]

Summary: This is a new recommendation in comparison to the prior Practice Parameter, as no studies were previously reviewed which directly addressed the pediatric/adolescent population. The level of reviewed evidence from a singular study[13] was MODERATE (**Appendix, Table 3**). Optimal results were obtained with a dose of 0.15 mg/kg, taken 1.5-2.0 hours prior to habitual bedtime, for 6 nights. Although no serious adverse reactions have been described in relation to melatonin use to date, relevant concerns have been raised by select studies with respect to the pediatric/adolescent population,[26] and rigorous long-term data are lacking (see separate "Harms and Adverse Effects" section). As such, the benefits/harms assessment is uncertain. Clinical experience nevertheless supports frequent acceptance of this therapy versus no treatment, with appropriate informed consent from the patient and caregiver.

5.2.6.2.2a We suggest that clinicians treat children and adolescents with DSWPD comorbid with psychiatric conditions with strategically-timed melatonin (versus no treatment). [WEAK FOR]

Summary: This is a new recommendation in comparison to the previous Practice Parameters, as no studies specifically addressed this patient population. The overall quality of evidence from the analyses of the two reviewed studies[27, 28] was LOW (see **Figures 4, 5** and **Appendix, Table 4**). A fast-release formulation of melatonin was utilized, with dosages ranging from 3-5 mg, taken between 18:00-19:00 (no circadian-based timing), for 4 weeks. In the pooled analysis, actigraphically-assessed sleep onset time advanced in conjunction with an advance in the circadian phase marker (DLMO). Although no serious adverse reactions have been described in relation to melatonin use to date, relevant concerns have been raised by select studies with respect to the pediatric/adolescent population, and rigorous long-term data are lacking (see separate "Harms and Adverse Effects" section). As such, the benefits/harms assessment is uncertain. Clinical experience nevertheless supports frequent acceptance of this therapy versus no treatment, with appropriate informed consent from the patient and caregiver.

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5.2.9.2a We suggest that clinicians treat children and adolescents with DSWPD with post-awakening light therapy in conjunction with behavioral treatments (versus no treatment). [WEAK FOR]

Summary: This is a new recommendation, based both upon the novel cohort (solely children/adolescents) and light/behavioral multicomponent interventions. The level of reviewed evidence[29] was LOW (**Appendix, Table 7**), and solely weekday data were considered with respect to determination of the recommendation, as this information is presumably most relevant in the clinical setting. Light therapy occurred via exposure to natural sunlight (when available), or with use of a white broad spectrum lamp (~1000 lux, proximity to source not specified), for ≥ 0.5 hours (2 hours maximum), with the time of administration advanced by 0.5 hours daily from "natural" wake time, until a target time of 06:00 was reached. Light therapy was subsequently discontinued, and behavioral interventions ensued. Follow-up data are promising. Overall, a benefits/harms ratio analysis favors a trial of treatment, as children/adolescents with DSWPD represent a particularly challenging patient population (for a multitude of reasons), and the suggested interventions pose no apparent safety concerns (see separate "Harms and Adverse Effects" section)**.** Clinical experience suggests that motivated patients would accept this treatment option versus no treatment, particularly with active caregiver support.

Recommendations for the treatment of N24SWD

5.3.6.1a We suggest that clinicians use strategically - timed administration of melatonin for the treatment of N24SWD in blind adults (versus no treatment). [WEAK FOR]

***Summary*:** This recommendation was designated at the GUIDELINE level (for the blind) in the previous Practice Parameters.[8] Only 3 studies[30-32] met inclusion criteria for the present analysis and the level of evidence from these small trials is LOW (**Figure 6** and **Appendix, Table 8**). Doses ranged between 0.5-10.0 mg, and were administered either 1 hour prior to preferred bedtime, or at a fixed clock hour (21:00), for a period of 26-81 days. Patient preference would be expected to favor the use of easily obtained and inexpensive melatonin that requires once daily dosing. No serious adverse reactions to melatonin have been described to date (see separate "Harms and Adverse Effects"

section) and therefore the benefits of use appear to outweigh any potential harms. A majority of well-informed patients and caregivers would therefore accept this treatment option versus no treatment.

Recommendations for the treatment of ISWRD

5.4.4a We suggest that clinicians treat ISWRD in elderly patients with dementia with light therapy (versus no treatment). [WEAK FOR]

Summary: This recommendation was designated as an OPTION in the 2007 Practice Parameters, and only one subsequent study has been published that met inclusion criteria for the current document.[33] The cumulative level of reviewed evidence (2 studies)[33, 34] was VERY LOW (**Appendix, Table 9**), and none of the TF-defined CRITICAL outcomes showed improvement. Behavioral symptoms nevertheless improved in the sole study that measured this outcome.[34] The interventions consisted of white broad spectrum light therapy, 2500-5000 lux (~1 meter from participants), and 1-2 hours in duration, between 09:00-11:00, for a period of 4-10 weeks.[33, 34] Benefits of treatment are closely balanced with harm/burden. In addition to the general side effects reported in the "Harms and Adverse Effects" section, other side effects in this population range from complaints of eye irritation[35] to agitation and confusion,[36] and these potential drawbacks should be considered when recommending treatment. Furthermore, depending on the method and setting of light delivery, treatment may be labor intensive, and modest improvements in outcomes may not justify associated costs. Nevertheless, clinical experience suggests that the majority of well-informed patients and/or caregivers of elderly, demented patients with ISWRD would choose light therapy in comparison to no intervention.

5.4.5a We do NOT recommend that clinicians use sleep-promoting medications to treat demented elderly patients with ISWRD (versus no treatment). [STRONG AGAINST]

Summary: This is a new recommendation in comparison to the previous Practice Parameters, which did not address the use of sleep-promoting medications (other than melatonin) for ISWRD. Although no relevant subsequent studies have been published, other extant literature indicates that administration of hypnotics to demented elderly

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patients increases risks of falls and other untoward outcomes Altered pharmacokinetics observed with aging may be one mechanism by which hypnotics increase adverse events in older adults.[37] Risk appears to be increased even further in elderly patients with dementia,[38] particularly when used in combination with other medications[39] (also see separate "Harms and Adverse Effects" section). Thus, the risk of harm from use of hypnotics in demented elderly patients with ISWRD outweighs potential positive effects. As such, the vast majority of well-informed patients and/or caregivers would not select this treatment.

5.4.6.1a We suggest that clinicians avoid the use of melatonin as a treatment for ISWRD in older people with dementia (compared to no treatment). [WEAK AGAINST]

***Summary*:** Melatonin was deemed "not indicated" for the treatment of ISWRD in older people with dementia (OPTION) in the previous Practice Parameters. The present recommendation against melatonin treatment is based on one reviewed study that failed to show benefit with respect to the CRITICAL outcome of TST.[40] Level of evidence: LOW (**Appendix, Table 10**). Furthermore, there is evidence that melatonin could be harmful in this population.[41] Thus, the risk-benefit ratio suggests that the potential for harms outweighs the possibility for benefits. Clinical experience therefore dictates that the majority of older patients with dementia and/or their caregivers would not favorably accept a trial of melatonin.

5.4.6.2a We suggest that clinicians use strategically-timed melatonin as a treatment for ISWRD (versus no treatment) in children/adolescents with neurologic disorders. [WEAK FOR]

***Summary*:** This recommendation was designated as an OPTION in the 2007 Practice Parameters, but none of the reviewed studies were eligible for the current analysis. One subsequently published eligible study was identified, with a MODERATE level of evidence[42] (**Appendix, Table 11**). The data indicate that melatonin administration of 2-10 mg during the hour before planned bedtime may improve CRITICAL sleep outcomes in children/adolescents with neurologic disorders and ISWRD, although confidence intervals associated with positive values crossed the threshold of the pre-determined

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clinically significant minimal change (see **Table 2**). Another caveat is that this recommendation is culled from a small sample of patients with a range of developmental disorders. As such, it may not generalize to all children/adolescents with ISWRD/neurologic disorders. Although no serious adverse reactions have been described in relation to melatonin use to date, relevant concerns have been raised by select studies with respect to the pediatric/adolescent population,[26] and rigorous long-term data are lacking (see separate "Harms and Adverse Effects" section). Nevertheless, clinical experience suggests that a majority of patients and caregivers would accept this treatment option (versus no treatment), particularly taking into account significant burdens associated with the neurologic disabilities and severe associated sleep disturbances.

5.4.9.1a We suggest that clinicians do NOT use combined treatments consisting of light therapy in combination with melatonin in demented, elderly patients with ISWRD (versus no treatment). [WEAK AGAINST]

***Summary*:** This recommendation was designated as a GUIDELINE in the previous Practice Parameters. One relevant randomized controlled trial[33] was published subsequent to 2007. The level of reviewed evidence from this single study was VERY LOW (**Appendix, Table 12**). Including melatonin as part of a combination treatment with light therapy does not appear to confer additional benefit[33] and may increase the potential for harms.[41] Clinical experience suggests that patients/caregivers would carefully consider the risks of depression and withdrawn behaviors with treatments that include melatonin. Thus, the majority of patients/caregivers would not accept combination treatments consisting of melatonin and bright light (versus no treatment). Other combination treatments (e.g., bright light, scheduled sleep-wake, and physical activity) are worthy of further investigation.

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386 **Table 6-**Summary of Recommendation Statements for Treatment of Patients with CRSWDs
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Treatment (PICO question)	Recommendation Statement	Direction and Strength of Recommendation	Quality of Evidence	Benefits/Harms Assessment	Patients' Values and Preferences
Advanced Sleep-Wake Phase Disorder (ASWPD)					
5.1.4 Light therapy (PICO Question 4)	**5.1.4a** We suggest that clinicians treat adult ASWPD patients with evening light therapy (versus no treatment)	WEAK FOR	VERY LOW	Benefits closely balanced with harms	The majority of patients would use this treatment.
Delayed Sleep-Wake Phase Disorder (DSWPD)					
5.2.6 Timed oral administration of melatonin or agonists (PICO Question 6)	**5.2.6.1a** We suggest that clinicians treat DSWPD in adults with and without depression with strategically-timed melatonin (versus no treatment)	WEAK FOR	LOW	Uncertainty in the estimates of benefits/harms	The majority of patients would use this treatment.
	5.2.6.2.1a We suggest that clinicians treat children and adolescents with DSWPD (and no comorbidities) with strategically-timed melatonin (versus no treatment)	WEAK FOR	MODERATE	Uncertainty in the estimates of benefits/harms	The majority of patients would use this treatment, with appropriate informed consent from the patient and caregiver.
	5.2.6.2.2a We suggest that clinicians treat children and adolescents with DSWPD comorbid with psychiatric conditions with strategically-timed melatonin (versus no treatment)	WEAK FOR	LOW	Uncertainty in the estimates of benefits/harms	The majority of patients would use this treatment, with appropriate informed consent from the patient and caregiver.
5.2.9 Combination Treatments	**5.2.9.2a** We suggest that clinicians treat children/adolescents with DSWPD with post-awakening light therapy in conjunction with behavioral treatments (versus no treatment)	WEAK FOR	LOW	Benefits clearly outweigh harms	The majority of patients would use this treatment, particularly with active caregiver support.
Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD)					
5.3.6 Timed oral administration of melatonin or agonists (PICO Question 6)	**5.3.6a** We suggest that clinicians use strategically- timed administration of melatonin for the treatment of N24SWD in blind adults (versus no treatment)	WEAK FOR	LOW	Benefits clearly outweigh harms	The majority of patients would use this treatment.

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Irregular Sleep-Wake Rhythm Disorder (ISWRD)					
5.4.4 Light Therapy (PICO Question 4)	**5.4.4.1a** We suggest that clinicians treat ISWRD in elderly patients with dementia with light therapy (versus no treatment)	WEAK FOR	VERY LOW	Benefits closely balanced with harms	The majority of well-informed patients and/or caregivers of would elect to use this treatment.
5.4.5 Sleep-promoting medications (PICO Question 5)	**5.4.5.1a** We do **NOT** recommend that clinicians use sleep-promoting medications to treat demented elderly patients with ISWRD	STRONG AGAINST	NONE*****	Harms clearly outweigh benefits	The vast majority of well-informed patients and/or caregivers would NOT elect to use this treatment.
5.4.6 Timed oral administration of melatonin or agonists (PICO Question 6)	**5.4.6.1a** We suggest that clinicians avoid the use of melatonin as a treatment for ISWRD in older people with dementia (compared to no treatment)	WEAK AGAINST	LOW	Harms outweigh benefits	The majority of patients and/or caregivers would NOT elect to use this treatment.
	5.4.6.2a We suggest that clinicians use strategically-timed melatonin as a treatment for ISWRD (versus no treatment) in children/adolescents with neurologic disorders	WEAK FOR	MODERATE	Benefits clearly outweigh harms	The majority of patients and/or caregivers would elect to use this treatment.
5.4.9 Combination treatments	**5.4.9.1a** We suggest that clinicians avoid the use of light therapy combined with melatonin in demented, elderly patients with ISWRD (versus no treatment)	WEAK AGAINST	VERY LOW	Harms outweigh benefits	The majority of patients and/or caregivers would NOT elect to use this treatment.

*Although no randomized controlled trials have examined sleep-promoting medications for the treatment of ISWRD, other extant literature indicates that administration of hypnotics to demented elderly patients increases risks of falls and other untoward outcomes (see separate "Harms and Adverse Effects" section).

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1.0 INTRODUCTION

The American Academy of Sleep Medicine (AASM) produced the first Practice Parameters (and associated reviews) for the evaluation and treatment of circadian rhythm sleep-wake disorders (CRSWDs) in 2007.[8, 9, 43] The purpose of the present publication is to provide an evidence-based update of existing recommendations for the treatment of the *intrinsic* CRSWDs: advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD). The *extrinsic* or predominantly environmentally-influenced CRSWDs, namely shift work and jet lag disorder, are not addressed in this paper.

2.0 BACKGROUND

Reviewed studies that included patients with an explicitly-stated CRSWD predominantly utilized the International Classification of Sleep Disorders second edition (ICSD-2)[44] diagnostic criteria, despite the fact that ICSD-3[45] nomenclature is referenced throughout the manuscript. Important modifications to the ICSD include incorporation of the word "wake" (the ICSD-2 referred solely to circadian rhythm *sleep* disorders), to highlight the significant impairment that these conditions exert on daytime functioning. Caregiver input is also emphasized in the ICSD-3, particularly with respect to diagnostic assessments among cognitively impaired and pediatric patients. Other major changes include the recommendation that CRSWD diagnoses are ascertained via actigraphy-derived data when possible (with inclusion of both work/school and

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free days), to provide objective longitudinal documentation of sleep-wake patterns. Consistent with this emphasis on objective measures, circadian phase assessments (e.g., dim light melatonin onset, or DLMO) are also recommended, if feasible. Other changes include a de-emphasis on "conventional" and "socially acceptable" clock times (recognizing the relative nature of these terms, and instead highlighting patients' subjective concerns), extensive additions to the "Pathology and Pathophysiology" and "Polysomnographic and Other Objective Findings" sections, and new descriptions of "Developmental Issues" and "Clinical and Pathophysiologic Subtypes".[45]

In many instances, this review incorporated trials with participants who were not recruited in strict accordance with ICSD criteria, but who nonetheless described symptoms consistent with a CRSWD (based upon Task Force consensus). Examples include pediatric/adolescent patients with "idiopathic sleep-onset insomnia," whose symptoms were consistent with DSWPD, as well as institutionalized elderly patients, among whom varied descriptions of insomnia, nighttime wakefulness, and daytime napping appeared to be representative of ISWRD, despite the fact that this condition was not named explicitly. A similar approach was taken for this latter group of patients during literature review and development of the previous Practice Parameters.[8, 9]

The intrinsic CRSWDs are briefly characterized as follows. DSWPD manifests as a delay of the major sleep episode with respect to the patient's desired timing or the timing required to attend to social, educational, and/or occupational demands. Patients report extreme difficulty both with falling asleep at bedtimes considered typical among their peers, and with waking at the required or desired times, but sleep quality is typically reported as normal when the individual sleeps at the delayed times. In contrast, an advance of the major sleep episode with respect to the patient's desired or required sleep-wake times characterizes ASWPD. ASWPD patients report extreme difficulty staying awake during evening hours and frequently note falling asleep before completion of pertinent work, social, or family obligations. In addition, wake time is undesirably early, and considered atypical in comparison to peers. For both conditions, symptoms must be present for at least 3 months and schedules need to be documented with sleep diaries and/or wrist actigraphy for a period of at least 7 days.

N24SWD is diagnosed when patients fail to entrain to the 24-hour light-dark cycle and clock times. Thus, patients exhibit sleep-wake patterns that show a progressive delay (usually)

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or advance, depending upon the period length (tau) of their endogenous circadian rhythms. During a symptomatic period, the time of high sleep propensity gradually shifts, such that patients experience daytime hypersomnolence and nighttime insomnia. Most patients with N24SWD are totally blind, but this disorder also occurs among sighted individuals. In contrast to the other CRSWDs, an N24SWD diagnosis requires at least 14 days of documentation of progressively shifting sleep-wake times with sleep diaries and/or actigraphy.

Patients with ISWRD lack a clear circadian pattern of sleep-wake behavior. Thus, afflicted individuals experience prolonged periods of wakefulness during the typical nocturnal sleep episode in addition to excessive sleepiness and prolonged sleep bouts during daytime hours. Sleep is fragmented and frequently insufficient. ISWRD is observed more commonly among patients with neurodevelopmental or neurodegenerative disorders, and can pose particular challenges for caregivers. Documentation (sleep diaries and/or actigraphy) of multiple non-circadian sleep-wake bouts for a period of at least 7 days is required for diagnosis.

Interventions for CRSWDs can be broadly categorized as follows: 1) prescribed timing of sleep-wake and/or physical activity/exercise 2) strategic receipt and/or avoidance of light 3) use of medications and/or supplements to phase shift and/or to promote sleep or wakefulness and 4) alternate interventions that exert effects by altering bodily functions to impact sleep/wake behaviors (i.e., somatic interventions).

Light is strategically-timed according to phase response curves (PRCs).[43] In brief, light can suppress melatonin secretion[46] and phase shift circadian timing in humans,[47] leading to the use of timed light exposure as a treatment for CRSWDs. Light timed in the evening and before the core body temperature minimum (CBT_{min}) leads to phase delays, and light timed after the CBT_{min} in the morning leads to phase advances.[47] Larger effects are observed with greater intensities of light and longer durations of light, but the increases are nonlinear.[48, 49] Additionally, the response to light is modified by prior exposure to light or "light history",[50, 51] such that a history of less light exposure leads to a greater response to light. Just as light exposure can shift circadian timing, so too can the strategic avoidance or reduction of light.[52, 53] Finally, the human circadian system is most sensitive to short wavelength blue light (~480 nm),[54, 55] although at bright intensities phase shifts to white broad spectrum light and blue enriched light are similar, presumably due to a saturation of photoreceptors.[56, 57]

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Less is known about the variables contributing to melatonin response (reviewed in[43]). The melatonin PRC is approximately 180 degrees out of phase with the light PRC, such that dosing in the evening shifts rhythms earlier and dosing in the morning shifts rhythms later. As the CBT_{min} serves as the "inflection point" between delaying and advancing effects for light, the DLMO serves as the inflection point for advancing and delaying effects of melatonin. Optimal dosing of melatonin for circadian effects remains unclear, and studies suggest that timing is more important than dose (PRCs for doses above 5 mg have not been published). In addition to phase shifting effects, melatonin may also have direct soporific effects, particularly at higher doses.

3.0 METHODS

3.1 Expert Task Force

In order to develop this clinical practice guideline, the AASM commissioned a Task Force (TF) of four members with expertise in the field of CRSWDs, assigned a Board of Directors (BOD) liaison and appointed a Science and Research Department staff member to manage the project. Prior to appointment, the content experts were required to disclose all potential conflicts of interest according to AASM policy. None were declared. The TF performed an extensive review of the scientific literature and assessed the available evidence employing the methodology of evidence-based medicine (specifically, meta-analysis and the Grading of Recommendations Assessment, Development and Evaluation system, or GRADE) to draft recommendations. The present paper was approved by the AASM BOD and replaces the previous Practice Parameters.[8] The AASM expects these guidelines to have a positive impact on clinical decision-making and patient outcomes. These recommendations reflect the state of knowledge at the time of publication and will be revised when the availability of new information necessitates.

3.2 PICO Questions

Eight PICO (**P**atient, **P**opulation or **P**roblem, **I**ntervention, **C**omparison, and **O**utcomes) questions were developed, based on both the inquiries raised in the previous AASM publications[8,9] and an investigation of systematic reviews, meta-analyses, and guidelines published subsequently. The AASM BOD ultimately approved these questions.

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Table 1-PICO Question Parameters

Population	**I**ntervention	**C**omparison	**O**utcomes
Patients diagnosed with intrinsic CRSWDs (ASWPD, DSWPD, N24SWD, ISWRD)	1. Prescribed sleep-wake scheduling 2. Timed physical activity/exercise 3. Strategic avoidance of light (e.g., with the use of eyewear) 4. Light therapy 5. Sleep-promoting medications (hypnotics/sedatives/neuroleptics/other novel agents) 6. Timed oral administration of melatonin or agonists 7. Wakefulness-promoting medications (e.g. modafinil, traditional stimulants) 8. Other somatic interventions	Control group, those treated with placebo or, where a comparison group was not available, measurements performed "before" (baseline) and "after" treatment	*Physiologic circadian phase markers* *Total sleep time* (TST) *Initial sleep latency* (ISL) *Sleep onset time* (SOT) *Sleep offset time* (SOffT)

3.3 Literature Searches

Literature search #1 was performed in PubMed using broad terms (see Appendix), in order to identify systematic reviews, meta-analyses or relevant practice guidelines published subsequent to availability of the previous AASM Practice Parameters. Examination of discovered papers (n=93) enabled elucidation of Practice Parameter recommendations requiring revisions, and also assisted with further refinement of the PICO questions. The next literature search (#2) targeted treatment trials involving intrinsic CRSWDs that addressed at least one PICO question. This search utilized PubMed, Embase and PsycInfo databases.

At least two TF members carefully assessed the abstract of each retrieved article (n=2063), to determine whether the publication should be included for further consideration. The following list of general exclusion criteria was used:

1. Diagnosis or not treatment
2. Not CRSWD

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3. Not intrinsic CRSWD (shift work or jet-lag disorder)
4. Wrong publication type (review, editorial, etc.)
5. Not human subjects
6. Mechanistic or methodological study
7. Study was published before October 2006

When there were questions or disagreements, the full text of the article was reviewed in detail until consensus was reached. The same search terms, databases and inclusion/exclusion criteria were used for literature search #3, although new date limitations were applied (June, 2012 - March, 2014), with the intention to capture articles published after completion of search #2. Four hundred and fifty-three additional publications were retrieved, and TF assessments occurred in the same manner described above. Finally, TF members selected several literature reviews (by consensus), and screened reference lists to identify other articles of potential interest. This "pearling" process served as a "spot control" for the previous searches, and ensured that important articles were not missed. All duplicate references were eliminated.

Since new inclusion/exclusion criteria were used in this project, investigations cited in the previous Practice Parameters[8] were not necessarily incorporated into the current analysis. Studies that did not meet inclusion criteria were selectively used for discussion purposes, but were neither included in the GRADE reports nor used as a basis for recommendations. The TF made a particular effort to discuss those studies (containing either patients or healthy subjects) that might spur and/or improve future clinical research for the reviewed CRSWDs.

A final PubMed search was conducted to identify harms or adverse effects attributed to the relevant interventions: light therapy (PICO 4), hypnotics (PICO 5), and melatonin (PICO 6) (see Appendix). Limitations were imposed to select for English-language "meta-analyses" and "systematic reviews" pertaining to human subjects. The titles and abstracts of articles produced by these searches were reviewed for relevance, and pertinent publications were examined. Other cited articles from the "Harms and Adverse Effects" section were culled from prior searches (but deemed ineligible for quantitative analysis) or were provided via TF members' preemptive awareness and consensus regarding relevancy. Adverse effects of combined treatments were addressed based on the singular components of combinations.

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3.4 Treatment Efficacy Outcomes

During the process of data extraction, the TF developed a list of patient-oriented clinically relevant outcomes and rated their relative importance. Physiologic circadian phase markers, total sleep time (TST), initial sleep latency (ISL), sleep onset time (SOT), and sleep offset time (SOffT) were deemed CRITICAL for making recommendations, and a significance threshold was defined for each outcome based upon consensus (**Table 2**). Sleep parameters were alternately evaluated with polysomnography (PSG), wrist actigraphy, or sleep diaries. Although both wakefulness after sleep onset and sleep efficiency were also commonly reported, the two variables were rated as IMPORTANT (but not CRITICAL) by the TF. As such, related data did not factor into clinical recommendations. A unique scenario arose for N24SWD, for which entrainment status (i.e., whether the biological clock is synchronized to the 24-hour day) was solely utilized as a CRITICAL outcome measure, as it defines this CRSWD physiologically (see section 5.3).

Table 2-CRITICAL Outcomes and Their TF-Defined Clinical Significance Thresholds

	Clinical Significance Thresholds					
Diagnosis	**Circadian Phase (change in minutes)**	**TST (change in minutes)**	**ISL (change in minutes)**	**SOT (change in minutes)**	**SOffT (change in minutes)**	**Entrainment Status**
ASWPD	30	30	15	15	15	N/A
DSWPD	30	30	15	15	15	N/A
ISWRD	30	30	15	15	15	N/A
N24SWD	N/A	N/A	N/A	N/A	N/A	Yes/No

3.5 Extraction of Evidence

Quantitative data pertaining to the outcomes of interest as well as information necessary for systematic evaluation and grading of the evidence were extracted from accepted articles using a dedicated spreadsheet. Articles determined to lack quantitative data or with data presented in a format incompatible with desired statistical analyses were rejected at this stage, but used selectively for further discussion. In instances where desired data were available (but not presented in the desired format), the authors were contacted, and raw data were acquired if possible. Data were pooled across the studies for each outcome measure in accordance with PICO questions and based on diagnosis, study design, patient population, clinical outcome of

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interest, and method of derivation (e.g., PSG-derived data were analyzed separately from data derived from actigraphy or sleep diaries).

3.6 Statistical Analyses

Meta-analyses were completed (in the few instances possible) using the random effects model. All computations were performed using the Review Manager software,[10] and included calculations of the mean difference (MD) ± standard deviation (SD) for CRITICAL outcomes. Values analyzed in this manner are displayed to the hundredths place. Age demographics and information regarding melatonin doses are presented in the format provided by the associated study (mean ± SD if available) but, in an effort to maintain consistency, are displayed only to the tenths place in instances where the authors provided values with numerical place values of lower hierarchy. The results of meta-analyses are depicted in figures within the text, in association with a "forest plot." Summary of Findings tables for all investigations are presented in the Appendix.

When studies contained placebo/control groups, the evaluation of the effect of treatment was performed by comparison of averaged post-treatment and averaged post-placebo/control group values, regardless of the authors' approaches. In studies with crossover or "before-after" designs where there was no placebo/control group, post-treatment values were compared to baseline values. Our use of this methodology occasionally produced results that differed from those reported in the original publications (e.g.[11-13]).

3.7 Interpretation of Clinical Significance of Results

Interpretation of clinical significance was ascertained via comparisons with pre-defined thresholds (see **Table 2** and **Figure 1**). For meta-analyses, the pooled MD (black diamond) on "forest plots" depicts the average response or magnitude of effect across all studies, the width of the diamond represents the associated 95% confidence interval (C.I.), and the "no effect" line represents nil benefit from the intervention. The dotted lines on the left and right sides (equidistant from the "no effect" line) represent clinical decision thresholds defined by the TF (**Figures 1A, B, and C**). The right side represents an increase in the outcome measure, while the left represents a decrease. An increase in some outcome measures, such as TST, represents improvement. If the black diamond of TST data lies beyond the clinical significance threshold on

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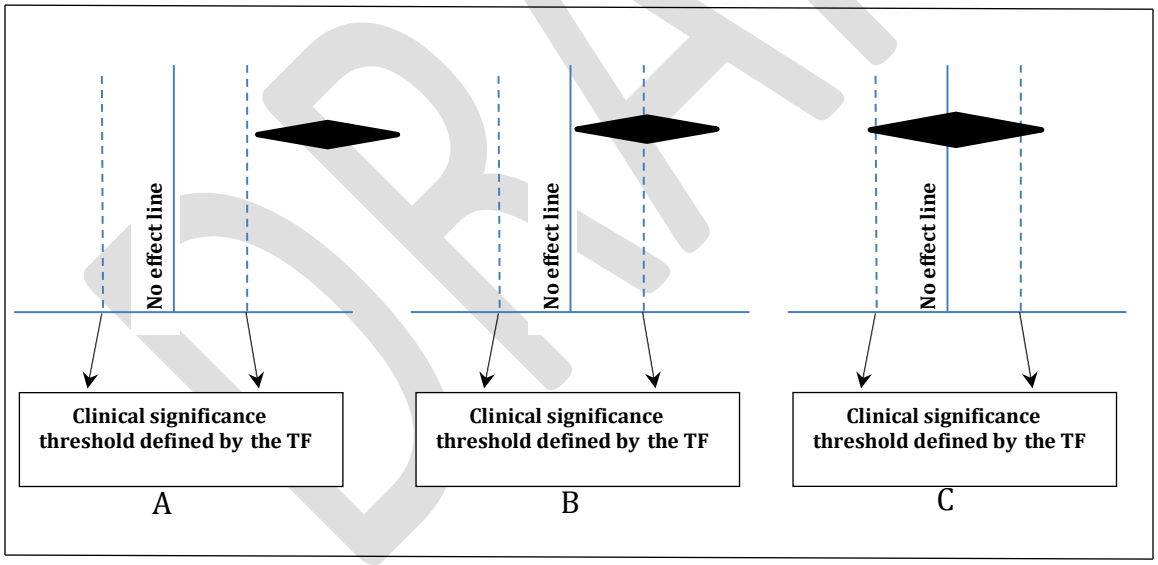
the right side, the result of a treatment is interpreted as a clinically significant improvement (**Figure 1A**). If, however, the diamond lies to the left of the "clinical significance" line, the decrease is regarded as a clinically significant undesired outcome, and the treatment is deemed contraindicated. When improvement is signified by a decrease in the outcome measure (e.g., ISL), the interpretation is reversed.

When the confidence interval crosses the clinical significance threshold on one side, the evidence is graded one level down (**Figure 1B**) for "serious imprecision." When the confidence interval crosses the clinical significance threshold on both sides of the no effect line, the evidence is graded two levels down for "very serious imprecision" (**Figure 1C**). Since the Review Manager software does not operate with clinical significance thresholds, these dotted lines are not depicted in the figures associated with the actual data. The interpretation of clinical significance from results of individual studies was accomplished in the same manner, but forest plots were not created.

Figure 1-Guide for Interpretation of Clinical Significance of the Results



3.8 Quality of Evidence

The GRADE approach was used for the assessment of quality of evidence[14-21] (also see: {http://www.gradeworkinggroup.org/publications/JCE_series.htm}). In contrast to other methods, an estimate of effect is generated for critical outcomes across studies, as opposed to an

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evaluation of individual studies. Multiple aspects of quality of evidence are assessed, with downgrading of evidence as applicable (see **Table 3**).

GRADE assigns high quality to evidence from randomized controlled trials while evidence from observational studies is considered low quality. However, high quality evidence can be graded down, and low quality evidence can be graded up, based upon the factors described below (see **Table 3**). The analysis of risk of bias includes review of the presence/absence of blinding, allocation concealment, loss to follow up, or selective outcome reporting. Indirectness occurs when the question being addressed is different than the available evidence in terms of population, intervention, comparator, or outcome. There is inconsistency when there is unexplained heterogeneity of the results. Imprecision is described in section 3.7.

In GRADE, there are 4 specific categories for assessing the quality of a body of evidence (a cumulative quality grade for a particular PICO question and patient population is predicated upon the lowest level of evidence assigned to one of the CRITICAL outcomes):

High: corresponds to a high level of certainty that the true effect lies close to that of the estimate of the effect.

Moderate: corresponds to a moderate level of certainty in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: corresponds to a low level of certainty in the effect estimate; the true effect may be substantially different from the estimate of the effect.

Very low: corresponds to very little certainty in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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Table 3-Summary of GRADE Approach to Rating Quality of Evidence (from[14])

Study design	Initial quality of a body of evidence	Downgrade if	Upgrade if	Quality of a body of evidence
Randomized trials	High →	**Risk of bias**	Large effect	**HIGH** (four plus: ⊕⊕⊕⊕)
		−1 Serious	+1 Large	
		−2 Very serious	+2 Very large	
		Inconsistency	Dose response	**MODERATE** (three plus: ⊕⊕⊕◯)
		−1 Serious	+1 Evidence of a gradient	
		−2 Very serious	All plausible residual confounding	
Observational studies	Low →	**Indirectness**	+1 Would reduce a demonstrated effect	**LOW** (two plus: ⊕⊕◯◯)
		-1 Serious	+1 Would suggest a spurious effect if no effect was observed	
		-2 Very serious		
		Imprecision		**VERY LOW** (one plus: ⊕◯◯◯)
		-1 Serious		
		-2 Very serious		
		Publication bias		
		-1 Serious		
		-2 Very serious		

The body of evidence for each outcome was assessed and graded, taking into account quality considerations based on the quantitative analysis and other major factors described above. CRITICAL outcome results are presented as summary of findings tables organized by PICO question and patient population (see **Appendix Tables 1-12**).

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3.9 Strength of Recommendations

The TF developed recommendation statements and determined the strengths of these recommendations based on the balance of the following major factors:

1. Level of evidence – based on an assessment of the quality of evidence using GRADE criteria (see **Table 3**), the TF categorized the evidence as:
    a. High
    b. Moderate
    c. Low
    d. Very Low
2. Benefits vs. Harms – based upon CRITICAL outcomes and analysis of any harms/side effects, the TF determined if:
    a. Benefits outweighed harms
    b. Benefits equaled harms
    c. Harms outweighed benefits
    d. The balance between benefits and harms was unclear
3. Patient values and preferences – based on the clinical expertise of the TF and relevant published data, the TF determined if:
    a. The **vast majority** of well-informed patients (>90%) would most likely use this patient-care strategy, compared to alternative patient-care strategies or no treatment
    b. The **majority** of well-informed patients would most likely use this patient-care strategy, compared to alternative patient-care strategies or no treatment
    c. The **majority** of well-informed patients would most likely NOT use this patient-care strategy, compared to alternative patient-care strategies or no treatment
    d. The **vast majority** of patients (>90%) would most likely NOT use this patient-care strategy, compared to alternative patient-care strategies or no treatment

Taking these variables into consideration, each recommendation statement was given a "strength value" of Strong For, Weak For, Weak Against or Strong Against (see **Table 4**).

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Table 4-Definitions of AASM Strengths of Recommendations

AASM Strength of Recommendation	Characteristics Guiding Recommendation
STRONG FOR	• There is a high degree of clinical certainty in the net benefits of this patient-care strategy. • The **vast majority** of well-informed patients would most likely choose this patient-care strategy, compared to alternative patient-care strategies or no treatment.
WEAK FOR	• There is a lower degree of clinical certainty in the balance between benefits vs. harms (i.e., net benefits) of this patient-care strategy. • The **majority** of well-informed patients would most likely choose this patient-care strategy, compared to alternative patient-care strategies or no treatment.
WEAK AGAINST	• There is a lower degree of clinical certainty in the balance between benefits vs. harms (i.e., net harms) of this patient-care strategy. • The **majority** of well-informed patients would most likely not choose this patient-care strategy, compared to alternative patient-care strategies or no treatment.
STRONG AGAINST	• There is a high degree of clinical certainty in the net harms of this patient-care strategy. • The **vast majority** of well-informed patients would most likely not choose this patient-care strategy, compared to alternative patient-care strategies or no treatment.

There were multiple cases when the TF chose to make "No Recommendation," which reflects either a complete lack of available evidence (no studies were published) or situations when evidence was available but either did not meet review inclusion criteria or was considered insufficient to support a recommendation (See **Appendix Tables 5-6**). At the step of review of the extracted evidence, the TF made a decision to exclude studies with fewer than 10 subjects if the study constituted a single source of evidence, as it was felt that affiliated data were insufficient to support a recommendation.

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4.0 HARMS AND ADVERSE EFFECTS

4.1 Light Therapy

No studies/reviews were identified that specifically addressed potential harms among patients with CRSWDs. In their Cochrane Systematic Review for the treatment of non-seasonal depression, Tuunainen and colleagues[58] found that hypomania was the sole side effect that was more common among patients receiving light therapy versus controls (Relative Risk 4.91 [C.I. 1.66-4.46]). Nevertheless, light treatment has been safely used for the treatment of bipolar depression, with careful monitoring.[59]

Other commonly described side effects include eyestrain, nausea, and agitation, albeit with predominant spontaneous remission. Treatment-emergent headaches also commonly remit, [60] but light therapy can induce migraines in approximately one-third of those susceptible.[61]

Finally, although commercially available products do not emit ultraviolet light, patients with eye disease and/or those using photosensitizing medications should only use light therapy with periodic ophthalmological and/or dermatological monitoring of the underlying condition.[60, 62, 63] Reassuringly, one study reported no changes in extensive ophthalmologic examinations among seasonal affective disorder patients without preexisting conditions after up to 6 years of daily use in the fall and winter months.[62]

4.2 Melatonin

Melatonin is considered a dietary supplement, and is therefore not subject to the scrutiny afforded to United States Food and Drug Administration (FDA)-approved medications. Concerns have been raised about the purity of available preparations, as well as the reliability of stated doses. Formulations that are United States Pharmacopeial Convention Verified can be considered most reliable in this regard.

Few identified papers addressed risks or side effects specifically among patients with CRSWDs. In general, melatonin is associated with a lack of reported serious adverse effects.[64-68] A review by the National Academy of Sciences stated that short-term use of ≤10 mg/daily (well within the range of typical chronobiotic doses) appears to be safe in healthy adults but recommended caution in children/adolescents and women of reproductive age (see further below). Adverse effects such as headaches, somnolence, hypotension, hypertension,

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gastrointestinal upset, and exacerbation of *alopecia areata* have been reported at higher melatonin doses in healthy adults, and the same effects have been reported at lower doses among those with relevant preexisting conditions. Melatonin has also been associated with an increase in depressive symptoms,[69] and caution is advised when prescribing to patients taking warfarin and to patients with epilepsy, as a result of various case reports submitted to the World Health Organization.[65]

Studies that address long-term effects are scarce, as are studies that specifically involve pediatric/adolescent populations. A randomized, placebo-controlled trial that investigated the toxicology of a 28-day treatment with 10 mg melatonin (solely comprised of healthy male adult participants) revealed no group differences with respect to adverse effects on polysomnographically-recorded sleep, subjective sleepiness, numerous clinical laboratory examinations, or other subjectively recorded events.[70] Similarly, in a meta-analysis that reviewed controlled trials with melatonin (n=10 studies, over 200 subjects) used for ≤3 months, there were few reports of adverse events.[68]

A long-term follow-up study of pediatric patients with DSWPD + attention deficit hyperactivity disorder (ADHD) who utilized melatonin doses up to 10 mg (mean follow-up time of approximately 4 years) detected no serious adverse events as a result of serial interviews with the children's parents, and 65% of participants continued to use the medication daily.[71] A follow-up open-label prospective study of subjects with neurodevelopmental disabilities comorbid with DSWPD who received controlled-release melatonin (max dosage 15 mg) up to 3.8 years similarly described no adverse events.[72, 73] Patients and caregivers are nevertheless frequently wary to use this supplement, due to concerns related to potential adverse effects on growth hormone regulation (10 mg dose),[74] and on reproductive function/development (3 mg dose).[75] Possibly relevant to the latter concern, Tanner stages were assessed serially in a questionnaire-based study involving children/adolescents (mean duration ~3 years), in an effort to compare pubertal development among those using melatonin (mean dose ~3 mg) during pre-puberty to non-melatonin users in the general Dutch population (controls).[76] No significant group differences were detected.

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4.3 Hypnotics

General adversities attributed to sedative-hypnotics (though not specifically among patients with CRSWDs) include increased risks for falls, headaches, nausea, medication-medication interactions, and drug dependence,[77, 78] with elderly patients at specific high risk.[79-81] Data regarding the use of hypnotics specifically among demented older adults (a population of interest for this review, see section 5.4) are scarce,[82] but their cognitive and other vulnerabilities would appear to place them at even greater risk than non-demented elderly adults.

Benzodiazepines in particular are associated with an increased incidence of confusion, impaired motor performance, anterograde amnesia, daytime sleepiness, and physiologic dependence.[82, 83] The newer generation nonbenzodiazepine benzodiazepine receptor agonists (e.g., zolpidem, zaleplon, eszopiclone) have shorter half-lives and fewer overall side effects, but high quality data to support their use with demented older adults are nonexistent.[82, 84] Commonly used over-the-counter antihistamines have very high rates of side effects, including cognitive impairment, daytime somnolence, and anticholinergic responses.[82] Trazodone, a sedating antidepressant, is widely used off-label as a hypnotic, despite the fact that there is virtually no evidence-based data to support its efficacy with older adults.[82] Moreover, it is associated with significant risks, including priapism, orthostatic hypotension, and cardiac arrhythmias.[85] Finally, the off-label use of neuroleptics for dementia-related behavioral disturbances (including sleep disturbances) is associated with a "black box" warning, due to increased mortality risks (approximately twofold higher than that associated with placebo-treated patients), mostly due to cardiovascular or infectious causes.[86]

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5.0 RECOMMENDATIONS FOR TREATMENTS OF INTRINSIC CRSWDs

Table 5-Overview of AASM Recommendation Status for Intrinsic CRSWD Treatments

Treatment	ASWPD	DSWPD	N24SWD	ISWRD
Prescribed sleep-wake scheduling	No Recommendation	No Recommendation	No Recommendation	No Recommendation
Timed physical activity/exercise	No Recommendation	No Recommendation	No Recommendation	No Recommendation
Strategic avoidance of light	No Recommendation	No Recommendation	No Recommendation	No Recommendation
Light therapy	**5.1.4a WEAK FOR** (adults)	No Recommendation	No Recommendation	**5.4.4a WEAK FOR** (elderly with dementia)
Sleep-promoting medications	No Recommendation	No Recommendation	No Recommendation	**5.4.5a STRONG AGAINST** (elderly with dementia)
Timed oral administration of melatonin or agonists	No Recommendation	**5.2.6.1a WEAK FOR** (adults with and without depression) **5.2.6.2.1a WEAK FOR** (children/adolescents without comorbidities) **5.2.6.2.2a WEAK FOR** (children/adolescents with psychiatric comorbidities)	**5.3.6a WEAK FOR** (blind adults) No Recommendation (sighted)	**5.4.6.1a WEAK AGAINST** (elderly with dementia) **5.4.6.2a WEAK FOR** (children/adolescents with neurologic disorders)
Wakefulness-promoting medications	No Recommendation	No Recommendation	No Recommendation	No Recommendation
Other somatic interventions	No Recommendation	No recommendation	No Recommendation	No Recommendation
Combination treatments	No Recommendation	No Recommendation (adults) **5.2.9.2a WEAK FOR** (light therapy + multicomponent behavioral interventions for children/adolescents)	No Recommendation	**5.4.9.1a WEAK AGAINST** (combination treatment of light and melatonin for demented, elderly patients)

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5.1 RECOMMENDATIONS FOR THE TREATMENT OF ASWPD

ASWPD is characterized by a stable advance (earlier timing) of the major sleep episode, such that habitual sleep onset and offset typically occur two or more hours prior to required or desired sleep times. Affected individuals complain of early morning or maintenance insomnia and excessive evening sleepiness. When allowed to maintain an advanced schedule, sleep quality and quantity are improved.[45]

5.1.1 Prescribed Sleep-Wake Scheduling

Sleep-wake scheduling has only been described in one case report, but favorably affected the pre-defined CRITICAL outcomes (SOT and SOffT, both subjective) in ASWPD.[87] No new studies were identified.

In the report of a 62-year-old male, sleep times were advanced 3 hours every 2 days for 2 weeks and then stabilized at the desired times, which were maintained at 5 months follow up. This treatment was designated as an OPTION in the 2007 Practice Parameters, but the current TF did not regard a single case report as sufficient evidence for a recommendation.

There is insufficient evidence to support the use of prescribed sleep-wake scheduling as a treatment for patients with ASWPD (versus no treatment). No recommendation.

5.1.2 Timed Physical Activity/Exercise

No recommendation was made in the 2007 Practice Parameters, and no new studies were identified.

There is no evidence to support the use of timed physical activity or exercise as a treatment for patients with ASWPD. No recommendation.

5.1.3 Strategic Avoidance of Light

No recommendation was made in the 2007 Practice Parameters, and no new studies were identified.

There is no evidence to support the use of strategic avoidance of light as a treatment for patients with ASWPD. No recommendation.

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5.1.4 Light Therapy

No treatment trials of light therapy in ASWPD have been published since the 2007 Practice Parameters, which recommended this therapy as an OPTION. Most of the previously referenced studies[88-91] were not included for the current analysis, as participants were not clearly diagnosed with ASWPD. Discrete benefits from this treatment are difficult to ascertain given methodological limitations within the two reviewed studies[22, 23] (discussed further below), and the cumulative level of evidence was VERY LOW (**Appendix, Table 1**).

Only one randomized Advanced Sleep Phase Disorder (ASPD)/ASWPD treatment trial was identified (also referenced in the previously published Practice Parameters).[22] A parallel group design was used to test 28 days of a daily evening exposure to a white broad spectrum light (~265 lux) versus a dim red light control (~2 lux) among 47 patients (mean age 70.0 ± 6.4 years). The light source consisted of a rice paper shade over a vertical light tube, and the protocol instructed subjects to sit within 1 meter of the light source, for 2-3 hours in duration, ending 1 hour before habitual bedtime. There were no significant post-treatment group differences with respect to most pre-defined CRITICAL outcomes, namely circadian phase (urinary 6-sulfatoxymelatonin [aMT6s] acrophase), ISL (actigraphy and subjective), SOT (actigraphy and subjective), SOffT (actigraphy and subjective), and TST (subjective). Total sleep time (actigraphy) actually significantly decreased post-treatment within the active treatment group (mean difference 34.62 minutes [C.I. -0.96 to -68.28]), possibly due to a non-significant delay in SOT. Importantly, while photosensors attached to the light source indicated good compliance to the scheduled light therapy on and off times, light exposure data on wrist worn photometers suggested that, on average, patients were only adjacent to the light source for about half of the scheduled treatment duration. Nonetheless, the treatment was well-tolerated, and the majority of the patients who received the white broad spectrum light source asked to keep it for long-term personal use.

Given the low intensity of light used in this study, the TF questioned the validity of the results, and elected to expand the GRADE analysis to include a non-randomized trial (**Appendix, Table 1**). A parallel group design study by Campbell and colleagues[23]

(also referenced in the previous Practice Parameters) tested 12 days of a daily evening exposure to bright white light (4,000 lux) versus a dim red light (~50 lux) control in 16 patients with ASWPD (mean age 70.4 ± 4.9 years). The light source consisted of two light boxes (proximity to source not specified), and therapy was for 2 hours in duration, between 20:00 and 23:00 (ending before habitual bedtime). The treatment significantly delayed circadian phase (CBT_{Min}, mean difference 141.00 minutes [C.I. 26.10-255.90]), and increased TST (PSG, mean difference 51.30 minutes [C.I. 2.69-99.91]), but both values crossed the threshold of the pre-determined clinically significant minimal change (see **Table 2** and **Appendix, Table 1**). There were no significant changes in ISL, SOT, or SOffT (PSG) post-treatment relative to the control condition (**Appendix, Table 1**).

The results of studies that tested evening light therapy in patients complaining of insomnia (not eligible for the current review, as subjects were not discreetly diagnosed with ASWPD) are generally favorable. For example, in studies of patients with early-morning awakenings, evening light delayed circadian timing,[90, 91] delayed SOffT[91] and increased TST,[90, 91] although positive effects were not always observed.[89] Evening light therapy also phase delayed circadian timing and SOT in patients with sleep maintenance insomnia.[88] In otherwise healthy older adults with sleep complaints, evening light therapy delayed the DLMO, but there was no observed effect on ISL and TST, while sleep timing remained fixed by the study protocol.[92]

5.1.4a We suggest that clinicians treat adult ASWPD patients with evening light therapy (versus no treatment). [WEAK FOR]

Summary: No treatment trials of light therapy in ASWPD have been published since the 2007 Practice Parameters, which recommended this therapy as an OPTION. The largest effects were seen after a 12 day treatment of 2 hours of bright white broad spectrum light (~4,000 lux) from 2 light boxes (proximity to source not specified), timed to occur daily between 20:00 and 23:00, and ending before habitual bedtime. Nevertheless, the overall quality of evidence derived from the analyses of two publications[22, 23] is VERY LOW (**Appendix, Table 1**), with potential benefits of light therapy closely balanced with the harm/burden. Associated risks are minimal, as detailed separately in the "Harms and Adverse

Effects" section. Patients report reasonable compliance and high satisfaction with this treatment[22] and light boxes are available over-the-counter in the U.S., at relatively affordable prices. Thus, the majority of well-informed patients would choose light therapy versus no treatment.

5.1.5 Sleep-Promoting Medications

No recommendation was made in the 2007 Practice Parameters, and no new studies were identified.

There is no evidence to support the use of sleep-promoting medications as a treatment for patients with ASWPD. No recommendation.

5.1.6 Timed Oral Administration of Melatonin or Agonists

The administration of a low dose of melatonin after early morning awakenings and upon final arising in the morning was indicated as an OPTION for ASWPD in the 2007 Practice Parameters, based on expert consensus alone. No new studies were identified.

There is no evidence to support the use of melatonin or agonists as a treatment for patients with ASWPD. No recommendation.

5.1.7 Wakefulness-Promoting Medications

No recommendation was made in the 2007 Practice Parameters, and no new studies were identified.

There is no evidence to support the use of wakefulness-promoting medications as a treatment for patients with ASWPD. No recommendation.

5.1.8 Other Somatic Interventions

No recommendation was made in the 2007 Practice Parameters, and no new studies were identified.

There is no evidence to support the use of other somatic interventions as a treatment for patients with ASWPD. No recommendation.

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5.1.9 Combination Treatments

No recommendation was made in the 2007 Practice Parameters, and no new studies were identified.

There is no evidence to support the use of combination treatments for patients with ASWPD. No recommendation.

5.2 RECOMMENDATIONS FOR THE TREATMENT OF DSWPD

DSWPD is characterized by habitual sleep-wake timing that is delayed, usually greater than two hours, relative to conventional or socially acceptable timing. Affected individuals complain of difficulty falling asleep at a time required to obtain sufficient sleep duration on a school or work night, and experience concomitant difficulties arising at the required times. When allowed to follow his or her preferred schedule, sleep quality and quantity are typically reported as normal.[45]

5.2.1 Prescribed Sleep-Wake Scheduling

The previous recommendation was designated as an OPTION, based upon two studies with adult participants.[93, 94] The 1993 study by Ito and colleagues,[93] reviewed previously, was not included in the current analysis, as it did not investigate discrete sleep outcomes, but instead incorporated subjective assessments of global functioning. The 1981 study by Czeisler and colleagues[94] was excluded due to a low number of subjects (n=5).

Although ineligible for current analyses, 3 studies were published subsequent to availability of the previous Practice Parameters that may bear relevance to the use of prescribed sleep-wake scheduling as a therapy for adolescent patients.[95-97] Two groups[96, 97] described potentially meaningful outcomes, but the parameters of interest were different from those specifically defined by the TF and, in the case the of the de Sousa study[97], all participants were healthy adolescents (i.e., not afflicted with DSWPD). Similarly, the Sharkey group (2011) studied a cohort with subthreshold DSWPD (the general CRSWD social/occupational impairment criterion was not applied), such that participants did not meet inclusion criteria for this review.[95] While a 6 day prescribed

advanced sleep schedule (with adjunctive strategic avoidance of evening light) resulted in concomitant advances in DLMO, the majority of participants exhibited decreased TST.

There is insufficient evidence to support prescribed sleep-wake scheduling as a stand-alone treatment (versus no treatment) for patients with DSWPD. No recommendation.

5.2.2 Timed Physical Activity/Exercise

No recommendation was made in the 2007 Practice Parameters, and no new studies were identified.

There is no evidence to support the use of timed physical activity or exercise as a treatment for patients with DSWPD. No recommendation.

5.2.3 Strategic Avoidance of Light

No recommendation was made in the 2007 Practice Parameters.

A relevant open-label study was published subsequently, but data were not presented in a fashion compatible with the data interpretation used for other studies.[98] Adult subjects with DSWPD + ADHD were instructed to wear amber glasses that blocked wavelengths ≤530 nm "…from sundown until bedtime every evening," for a minimum of 3 hours, and for a period of 2 weeks. Concomitant instructions included the use of only floor and table lamps (i.e. avoidance of overhead lights) during the evening. If a participant awoke during the night, he/she was instructed to don the glasses prior to light exposure. In addition, subjects were given specific instructions to avoid/minimize caffeine, nicotine, and alcohol. Outcomes were compared to a weeklong baseline assessment period. As determined by the Pittsburgh Sleep Quality Index, significant improvements in TST, ISL, and sleep quality were noted. In a separate study potentially related to the treatment of DSWPD, adult insomnia patients who wore "blue blocker" (<550 nm) glasses during the 3 hours prior to habitual bedtime demonstrated improved subjective sleep quality[99] compared with the placebo intervention (yellow-tinted glasses that blocked only ultraviolet light). Importantly, there are no tangible risks associated with these interventions.

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There is insufficient evidence to support the use of strategic avoidance of light as a treatment for patients with DSWPD (versus no treatment). No recommendation.

5.2.4 Light Therapy

The previously published recommendation was designated as a GUIDELINE and was based on two studies.[12, 100] The Rosenthal study was not analyzed for current purposes due to a lack of rigorously reported sleep-related outcomes.[100] The Cole study[12] is included in a separate section (see Combination Treatments, below). A separate open-label light therapy trial was identified[101], but ultimately rejected due to a small number of subjects (n=6). Only one study pertaining to adult DSWPD populations has been published subsequent to the release of the previous CRSWD Practice Parameters in 2007 [102] (also reviewed in the Combination Treatments section below).

There is insufficient evidence to support efficacy of post-awakening light therapy (monotherapy) as a treatment for DSWPD (versus no treatment). No recommendation.

5.2.5 Sleep-Promoting Medications

No recommendation was made in the 2007 Practice Parameters.

There are isolated reports regarding the use of hypnotics in DSWPD (typically as an adjunctive treatment with chronotherapy), but there is insufficient rigor in methodology for purposes of evidence analysis.[93, 103] Two reports describe DSWPD patients' resistance to the effects of traditional hypnotics.[104, 105] Nevertheless, a laboratory-based study that imposed a 4-hour phase advance on healthy subjects described sleep-related benefits (PSG and subjective measures) with zolpidem.[106]

There is insufficient evidence to support the use of sleep-promoting medications as a treatment for patients with DSWPD (versus no treatment). No recommendation.

5.2.6 Timed Oral Administration of Melatonin or Agonists

5.2.6.1 Melatonin for adult patients with DSWPD

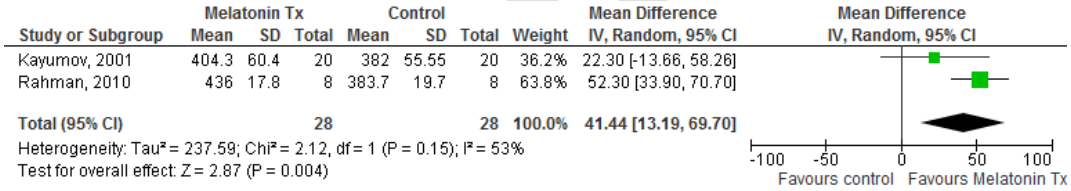
The previously published recommendation was designated as a GUIDELINE, and was supported by four studies.[11, 25, 107, 108] Two of these publications[107, 108] did not meet inclusion criteria for the present review, due to an insufficient number of subjects,[107] or due to design and reporting limitations[108] that hindered comparisons with the included investigations. One study was published subsequent to availability of the previous Practice Parameters.[24] The three reviewed investigations provide contradictory information regarding sleep/circadian-related effects of melatonin among adults with DSWPD. Level of reviewed evidence: LOW (**Appendix, Table 2**).

In a randomized double-blinded placebo-controlled study (parallel design, n=11, mean age 28.2 ± 5.7 years[11]), Mundey and colleagues utilized either 0.3 or 3.0 mg melatonin between 15:00-21:30 (1.5-6.5 hours before baseline DLMO), with an advance in timing of 1 hour after 2 weeks, for a total treatment duration of 29 days. No improvements in actigraphically-determined sleep parameters were observed, and our analysis demonstrated no group difference with respect to the timing of DLMO[11] (**Appendix, Table 2**). As the present review did not analyze outcomes relative to the timing of melatonin administration, however, it is important to note that the authors reported an inverse relationship between the timing of melatonin administration (irrespective of dose) and the magnitude of DLMO phase advance, such that earlier timing of the former (in relation to DLMO) resulted in greater phase advances. No such correlation was identified with respect to CBT_{Min} (assessed only within the active treatment group).

The Kayumov and Rahman studies (same investigative group) demonstrated substantial select PSG-measured benefits in sleep parameters (TST, ISL), but an affiliated circadian phase marker was not employed[24, 25] (solely the Mundey group included such a measure). The Rahman study[24] (n=20, randomized, double-blind, placebo-controlled, crossover design, mean age 30.8 ± 12.4 and 35.6 ± 14.0 years for females and males, respectively [editor's note: the authors provided age demographics according to gender]) utilized 5 mg melatonin administered between 19:00-21:00, for a period of 28 days. The Kayumov study[25] (n=20, same design/age distribution) used the same dose, but scheduled it at 19:00 the first week, between 19:00-21:00 during the second and third weeks (according to subjects' preferences), and at a consistent time during the fourth week

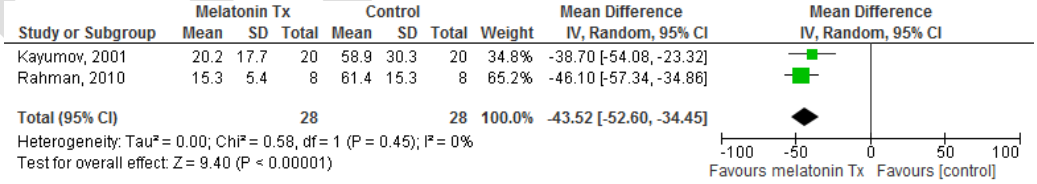
(average chosen time 21:00). Analyses among a subset of depressed patients from both studies (n=28) demonstrated a statistically significant increase in TST (mean difference 41.44 minutes, [C.I. 13.19-69.70]), but the level of evidence was downgraded due to inconsistency and imprecision (see **Figure 2** and **Tables 2-3**). More definitive results were obtained from an analysis of a subset of non-depressed patients from the Rahman study (**Appendix, Table 2**) (n=12, TST= 56.00 minutes [C.I. 48.51-63.49]).

Figure 2-Meta-Analysis of Data for PSG-determined TST in Response to Melatonin Treatment of Adult Patients with DSWPD and Comorbid Depression.



ISL was polysomnographically assessed with the same subcategorization of groups. Among the depressed subgroup (n=28), sleep latency decreased by 43.52 minutes [C.I. -34.45 to -52.60] (see **Figure 3** and **Appendix, Table 2**). Among the non-depressed subjects from the Rahman study (n=12), sleep latency decreased by 37.70 minutes [C.I. -31.75 to -43.65] (**Appendix, Table 2**).

Figure 3-Meta-Analysis of Data for ISL in Response to Melatonin Treatment of Adult Patients with DSWPD and Comorbid Depression.



5.2.6.1a We suggest that clinicians treat DSWPD in adults with and without depression with strategically-timed melatonin (versus no treatment). [WEAK FOR]

Summary: The previously published recommendation was designated as a GUIDELINE. The overall quality of evidence from the analyses of the three accepted/reviewed studies[11, 24, 25] was LOW (**Figures 2, 3** and **Appendix, Table 2**), and data regarding the sleep/circadian-related effects of melatonin were

contradictory. Positive results were obtained with a 5 mg dose timed between 19:00-21:00 (no circadian-based timing), for a period of 28 days.[24, 25] The Rahman study[24] was the sole study identified subsequent to publication of the previous Practice Parameters. Taking into account the discussion regarding potential safety/adverse effects of melatonin (see separate "Harms and Adverse Effects" section), the benefits/harms ratio remains uncertain, but clinical experience suggests frequent acceptance of this treatment among adults versus no treatment.

5.2.6.2. Melatonin for children/adolescents with DSWPD

5.2.6.2.1 Melatonin for children/adolescents with DSWPD and no comorbidities

No studies were previously reviewed which directly addressed the pediatric/adolescent population. Strategically-timed melatonin at the dose specified below is effective for children/adolescents with DSWPD. Level of reviewed evidence: MODERATE (**Appendix, Table 3**).

One randomized, placebo-controlled double-blinded study was reviewed (unpublished raw data provided courtesy of author).[13] Participants ranged in age from 6-12 years. The 3 active treatment groups received melatonin at dosages of 0.05 mg/kg, 0.1 mg/kg and 0.15 mg/kg, with respective mean doses of 1.6±0.4 mg (n=16), 2.9±0.9 mg (n=19) and 4.4±1.0 mg (n=18). Seventeen participants were allocated to the placebo group. The duration of treatment was 6 nights, with instructions to take melatonin 1.5-2.0 hours prior to habitual bedtime (unclear if equivalent to habitual sleep onset time), with consistent nightly timing.

The data of 64 participants were utilized for actigraphy/sleep-related analyses. With respect to CRITICAL outcomes, sleep onset time favorably advanced in comparison to placebo among the 0.1 and 0.15 mg/kg groups (mean difference -33.70 minutes [C.I. -10.95 to -56.46] and mean difference -42.77 minutes [C.I. -21.77 to -63.78], respectively), but the confidence interval of the value associated with the lower dose crossed the threshold of the pre-determined clinically significant minimal change (see **Table 2** and **Appendix, Table 3**). Statistical differences were not observed with the .05 mg/kg group. Nevertheless, sleep latency improved among all three groups (statistical

and clinically significant differences) in comparison to placebo (mean difference -38.39 minutes [C.I -18.24 to -58.53], mean difference -44.24 minutes [C.I. -24.04 to -64.44], and mean difference -43.80 minutes [C.I. -24.06 to -63.54], respectively, in order of ascending dosage).

With respect to DLMO analyses, no significant differences were noted among any of the three treatment groups in comparison to placebo. However, the authors separately calculated individualized outcomes based upon melatonin use in relation to both DLMO (circadian) and clock time of administration (TOA). These analyses were not compatible with the Review Manager software used in this project. Data were depicted solely within figures (i.e. no raw representation). As with the previously discussed Mundey study,[11] a positive relationship between DLMO phase advances and an earlier circadian TOA were described (no relationship observed with respect to clock TOA), but no differences were observed between the various melatonin dosage groups. On the contrary, no advantages between clock versus circadian TOA were demonstrated in relation to sleep onset and initial sleep latency times.

5.2.6.2.1a We suggest that clinicians treat children and adolescents with DSWPD (and no comorbidities) with strategically-timed melatonin (versus no treatment). [WEAK FOR]

Summary: This is a new recommendation in comparison to the prior Practice Parameter, as no studies were previously reviewed which directly addressed the pediatric/adolescent population. The level of reviewed evidence from a singular study[13] was MODERATE (**Appendix, Table 3**). Optimal results were obtained with a dose of 0.15 mg/kg, taken 1.5-2.0 hours prior to habitual bedtime, for 6 nights. Although no serious adverse reactions have been described in relation to melatonin use to date, relevant concerns have been raised by select studies with respect to the pediatric/adolescent population[26], and rigorous long-term data are lacking (see separate "Harms and Adverse Effects" section). As such, the benefits/harms assessment is uncertain. Clinical experience nevertheless supports frequent acceptance of this therapy versus no treatment, with appropriate informed consent from the patient and caregiver.

5.2.6.2.2 Melatonin for children/adolescents with DSWPD and psychiatric comorbidities

This is a new recommendation in comparison to the previous Practice Parameters, as no studies specifically addressed this patient population. Strategically-timed fast-release melatonin at dosages ranging from 3-5 mg may be effective for children/adolescents with DSWPD and psychiatric comorbidities. Level of reviewed evidence: LOW (**Appendix, Table 4**)

Two randomized, placebo-controlled studies by the same group examined the use of melatonin for DSWPD among children/adolescents with various psychiatric comorbidities (all were diagnosed with ADHD).[27, 28] Participants aged 6-12 years received fast-release melatonin (one of several instances where melatonin formulation was specified) for 4 weeks at dosages of 3 or 5 mg, at either 18:00 or 19:00. The more recent study[27] based dosage on weight (3 mg if <40 kg; 5 mg if >40 kg, taken at 19:00), while the earlier protocol[28] uniformly provided 5 mg at 18:00. Combined analyses (n=132) revealed an advance in DLMO of nearly 1 hour in comparison to placebo (mean difference -54.22 minutes [C.I. -31.67 to -76.78]) (see **Figure 5**). Actigraphically-assessed sleep-onset time (n=130) also advanced (mean difference -36.57 minutes [C.I. -16.96 to -56.18]) (see **Figure 4**). Other actigraphically-derived sleep parameters were obtained only in the more recent study (n=105). A significant decrease in ISL was detected (mean difference -18.70 minutes [C.I. -7.01 to -30.39], but the confidence interval crossed the threshold of the pre-determined clinically significant minimal change (see **Table 2** and **Appendix, Table 4**). No significant group differences were noted with respect to TST.[27] Previously published subjective assessments failed to demonstrate significant group differences in TST (n=31), ISL (n=33), or sleep-onset (n=33) and offset (n=32) times.[28]

Although not accepted for analysis for this review due to concerns regarding patient heterogeneity, a randomized placebo-controlled study by Wasdell and colleagues (which contained an admixture of DSWPD and insomnia patients) explored the effects of 5 mg controlled-release melatonin (10 days) among approximately 50 children with neurodevelopmental disabilities (ages 2-18, mean 7.4 years).[72] Melatonin was

administered 20-30 minutes prior to the caregiver-determined desired time of sleep onset. Significant improvements were observed in subjectively and actigraphically recorded TST, ISL, and clinician- and caregiver-assessed overall sleep disorder severity and other functional and health dimensions. During the 3-month open-label phase of the trial, escalation of the melatonin dosage provided no definitive benefits. A separate follow-up open-label prospective study (duration up to 3.8 years) demonstrated continued caregiver-reported benefits on sleep, overall health, behavior, education, and learning.[73]

Figure 4-Meta-Analysis of Data for SOT in Response to Melatonin Treatment of Children/Adolescents with DSWPD and Comorbid Psychiatric Conditions.

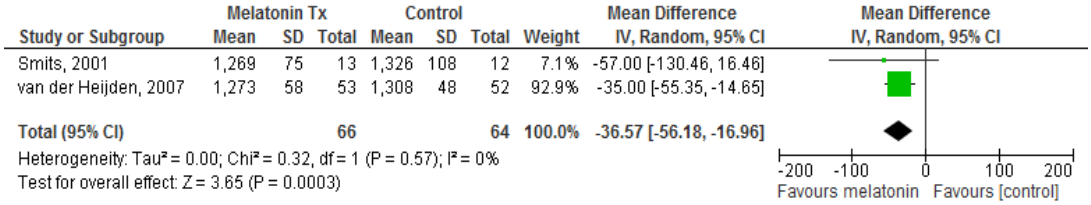
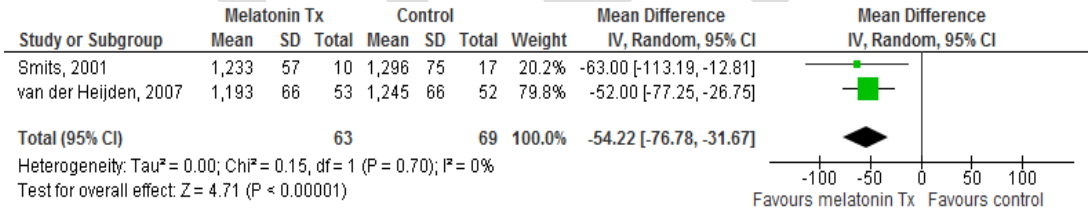


Figure 5-Meta-Analysis of Data for DLMO in Response to Melatonin Treatment of Children/Adolescents with DSWPD and Comorbid Psychiatric Conditions.



5.2.6.2.2a We suggest that clinicians treat children and adolescents with DSWPD comorbid with psychiatric conditions with strategically-timed melatonin (versus no treatment). [WEAK FOR]

Summary: This is a new recommendation in comparison to the previous Practice Parameters, as no studies specifically addressed this patient population. The overall quality of evidence from the analyses of the two reviewed studies[27, 28] was LOW (see **Figures 4, 5** and **Appendix, Table 4**). A fast-release formulation of melatonin was utilized, with dosages ranging from 3-5 mg, taken between 18:00-19:00 (no circadian-based timing), for 4 weeks. In the pooled analysis, actigraphically-assessed sleep onset time advanced in conjunction with an

advance in the circadian phase marker (DLMO). Although no serious adverse reactions have been described in relation to melatonin use to date, relevant concerns have been raised by select studies with respect to the pediatric/adolescent population, and rigorous long-term data are lacking (see separate "Harms and Adverse Effects" section). As such, the benefits/harms assessment is uncertain. Clinical experience nevertheless supports frequent acceptance of this therapy versus no treatment, with appropriate informed consent from the patient and caregiver.

5.2.7 Wakefulness-Promoting Medications

No recommendation was made in the 2007 Practice Parameters, and no new studies were identified.

There is no evidence to support the use of wakefulness-promoting medications as a treatment for patients with DSWPD. No recommendation.

5.2.8 Other Somatic Interventions

In the previous Practice Parameters, oral vitamin B12 therapy was described as "not indicated," designated at the GUIDELINE level. No subsequent relevant studies (involving B12 or separate somatic interventions) have been published. There is no clear evidence of benefit from oral vitamin B12 among adults with DSWPD. Level of reviewed evidence: VERY LOW (**Appendix, Table 5**).

In a multicenter study[109] that contained predominantly adult DSWPD patients (n=50, mean age 26.8 ± 1.3 years), participants received 3 mg total daily dose of vitamin B12 (three times daily divided dosing) versus placebo (double-blinded) for a period of 4 weeks. No clinically significant differences were observed with respect to subjectively assessed TST and SOT (see **Table 2** and **Appendix, Table 5**). Remaining sleep parameters were not compatible with the TF's pre-defined clinical outcomes (ISL was evaluated according to a 5-point Likert scale).

There is insufficient evidence to support the use of oral vitamin B12 (and no evidence to support alternate somatic interventions) among patients with DSWPD (versus no treatment). No recommendation.

5.2.9 Combination Treatments

Combination treatments for DSWPD were not addressed separately in the previous Practice Parameters and associated review papers, but one of the reviewed studies [12] was addressed in the singular light therapy category. The combination treatments sections throughout the paper contain studies that explicitly denote dual treatment interventions, although the TF acknowledges that other reviewed studies may have also employed multicomponent treatment strategies, but failed to mention or emphasize their nature in the published methodologies or to include proper controls for all components of the treatment.

5.2.9.1. Light/combination treatments for adults

There is no evidence to support efficacy of light therapy (provided by means other than a "light box") in association with concomitant behavioral instructions among adults. Level of reviewed evidence: VERY LOW (**Appendix, Table 6**).

In a randomized parallel clinical trial (n=54) involving adults (mean age 25 ± 6 years) with DSWPD, Cole and colleagues (2002)[12] used a light mask that exposed participants to 2700 lux of white broad spectrum light on closed eyelids (about 57 lux at the cornea) for a period of 26 days, and compared it to an inactive condition (0.1 lux of red light, estimated corneal illuminance = 0.007 lux). Light therapy commenced (<0.01 lux) 4 hours before the scheduled rise time, proceeded with ramped intensity for 1 hour, and remained at full brightness until arising. Volunteers were not informed of the hypotheses of the study and were blinded to the treatment received by the other group. The study personnel who interacted with participants and scored data were also blind to treatment assignments.

Both groups received concomitant behavioral instructions. Subsequent to the first 2 treatment days, subjects were asked to advance both bedtime and time of arising (in equal measure) on a daily basis, to achieve a cumulative advance of at least 1 hour per week (≤15 minutes daily, unless he/she experienced spontaneous awakening >15 minutes ahead of schedule 2 days in a row). Subjects were also asked to stop advancing sleep if he/she achieved a preselected target wakeup time, but were allowed to change the target time if he/she wished. Participants were urged to avoid naps during the treatment

interval, and were provided specific instructions to minimize late-afternoon and evening light exposure on all treatment days. Specific interventions included shading of windows between 17:00 and dusk and utilization of dark wraparound form-fitting goggles (2% transmittance) if necessary to go outdoors during this time interval. Subjects were also instructed to use the minimum practical amount of artificial room light from 17:00 to bedtime.

As determined by the acrophase of aMT6s excretion, there were no group phase differences. Similarly, there were no differences in (predominantly actigraphically-measured, n=2 sleep logs) sleep onset or offset times. When the group was subdivided according to whether the baseline acrophase was later or earlier than 06:00 (n=23 and n=22, respectively, used as a measure to divide groups by the degree to which they were physiologically delayed), significant differences were noted solely for the former group, but the confidence interval crossed the threshold of the pre-determined clinically significant minimal change (mean difference -83.00 minutes in comparison to the inactive condition [C.I. -8.09 to -157.91]) (see **Table 2** and **Appendix, Table 6**). No significant differences were noted with respect to actigraphically-determined sleep onset and offset times among either subgroup. The light mask was nevertheless described as well-tolerated, with little (actigraphically-measured) sleep disturbance.

A separate group[102] performed a randomized controlled trial of 7 days duration (n=18, mean age 28.2 ± 10.6 years) using post-awakening morning blue light in association with a gradually advancing sleep/wake schedule. The portable source contained light-emitting diodes (LEDs; 470 nm peak wavelength with irradiance of 65 $\mu W/cm^2$) attached to the lower rims of spectacle frames, approximately 15 mm from the cornea, for duration of 2 hours, immediately after arising. While a bedtime was not prescribed, subjects were instructed to advance wake times by 30 minutes daily. The presence or absence of blinding procedures was not specified. As compared to the control group (lighting exposure unspecified), DLMO advanced by 2.53 hours (reported verbally and depicted in a figure). However, there were no group differences in subjectively assessed TST, SOT, or SOffT. Among other design limitations, many details were missing with respect to methodology, and there was high imprecision in the reported results.

Despite the present uncertainty as to benefits, there are few major risks associated with a trial of one of these "non-light box" interventions. A review of adverse effects associated with light interventions in general is addressed elsewhere (see "Harms and Adverse Effects" section). It is interesting that the light mask worn during the sleep episode in the Cole protocol[12] was well-tolerated, with little (actigraphically-measured) sleep disturbance, as compliance with post-awakening light therapy can be poor.[110]

A laboratory-based study from Figueiro and Rea shows promise for future "light masks" in the treatment of CRSWDs, based upon optimal eyelid transmittance using green LEDs (max wavelength of 527 nm) and individualized dose assessments to predict optimal circadian benefit[111] Particularly relevant to the discussion of combination therapies, at least three laboratory-based studies among healthy adults describe a synergistic effect (with respect to circadian phase advances) when strategically-timed light and melatonin therapy are used together.[112-114] In addition, although physiologic phase assessments were not employed, a separate case series described success with this treatment combination among DSWPD patients in the field (age range 15-60 years). Three milligrams melatonin was taken 2 hours prior to desired bedtime in conjunction with either outdoor or 5000 lux white broad spectrum light exposure, for a minimum of 30 minutes, between 06:00-08:00. During a median follow-up period of 6.4 weeks, 82% reported improvements of sleep patterns, with a mean sleep phase advance of approximately 2 hours.[115] Reported outcomes were unfortunately not compatible with those selected by the TF for this review.

There is insufficient evidence to support the use of novel forms of light therapy (i.e., via means other than a "light box"), in association with concomitant behavioral instructions among adults with DSWPD (versus no treatment). No recommendation.

5.2.9.2 Light/combination treatments for children/adolescents

Post-awakening light therapy in conjunction with behavioral instructions is effective among adolescents with DSWPD, but a physiologic circadian correlate is lacking. Level of reviewed evidence: LOW (**Appendix, Table 7**). This is a new

recommendation, based both upon the novel cohort (solely children/adolescents) and light/behavioral multicomponent interventions.

One non-blinded randomized controlled trial[29] was identified (n=40), comprised of adolescents aged 13-18 (mean ages 14.7 ± 1.7 and 14.7 ± 1.8 years in the active and control groups, respectively). The minority of participants (20%) had mental health comorbidities and were spread evenly across the two groups. Over a period of 8 weeks, active subjects (n=23) were exposed to either post-awakening natural sunlight (when available) or a broad spectrum lamp (~1000 lux, proximity to source not specified) for ≥ 30 minutes (2 hours maximum), with the time of administration advanced 30 minutes daily from "natural" wake time, until a target time of 06:00 was reached (3-5 weeks). Light therapy was subsequently discontinued and a regular rise time between 06:30-07:30 was advised. Concomitant multicomponent behavioral education/interventions (including instructions to "reduce evening light") were provided in six 45-60 minute sessions (with parental involvement), either weekly (first 4 sessions) or biweekly (last 2 sessions). Compliance was monitored with sleep diaries, but affiliated data were not provided. An objective measure was not employed to measure light therapy compliance specifically. The control group was designated to a waitlist (n=17).

Solely completed participants' data were analyzed (i.e. an intention-to-treat analysis was not undertaken). With respect to CRITICAL outcomes during weekday assessments, significant differences were detected with respect to subjective TST (mean difference 72.00 minutes [C.I. 37.35 - 106.65]), and ISL (mean difference -43.10 minutes [C.I. -22.46 to -63.74]). Sleep onset and offset times also demonstrated significant group differences, but the confidence interval crossed the threshold of the pre-determined clinically significant minimal change (mean difference -42.00 minutes [C.I. -2.74 to -81.26] and -23.00 minutes [C.I. -0.87 to -45.13], respectively) (see **Table 2** and **Appendix, Table 7**). Weekend assessments demonstrated beneficial significant differences for sleep onset times (mean difference -93.9 minutes [C.I. -49.09 to -138.71]). Significant favorable differences were also noted with respect to ISL and sleep offset times, but the confidence interval again overlapped the threshold of the pre-determined clinically significant minimal change (mean difference -26.5 minutes [C.I. -4.37 to -48.63] and -51.0 minutes [C.I. -10.82 to -91.18], respectively). No weekend differences

were noted for TST. With the exception of weekday sleep offset times, 6-month follow-up assessments (n=15) revealed no significant differences in comparison to the values observed immediately post-treatment.

5.2.9.2a We suggest that clinicians treat children and adolescents with DSWPD with post-awakening light therapy in conjunction with behavioral treatments (versus no treatment). [WEAK FOR]

Summary: This is a new recommendation, based both upon the novel cohort (solely children/adolescents) and light/behavioral multicomponent interventions. The level of reviewed evidence[29] was LOW (**Appendix, Table 7**), and solely weekday data were considered with respect to determination of the recommendation, as this information is presumably most relevant in the clinical setting. Light therapy occurred via exposure to natural sunlight (when available), or with use of a white broad spectrum lamp (~1000 lux, proximity to source not specified), for ≥ 0.5 hours (2 hours maximum), with the time of administration advanced by 0.5 hours daily from "natural" wake time, until a target time of 06:00 was reached. Light therapy was subsequently discontinued, and behavioral interventions ensued. Follow-up data are promising. Overall, a benefits/harms ratio analysis favors a trial of treatment, as children/adolescents with DSWPD represent a particularly challenging patient population (for a multitude of reasons), and the suggested interventions pose no apparent safety concerns (see separate "Harms and Adverse Effects" section)**.** Clinical experience suggests that motivated patients would accept this treatment option versus no treatment, particularly with active caregiver support.

5.3 RECOMMENDATIONS FOR THE TREATMENT OF N24SWD

N24SWD occurs when the hypothalamic circadian pacemaker fails to entrain (synchronize) to the 24-hour day. As a result, individuals can suffer from periodic nighttime insomnia and daytime somnolence as the circadian rhythms in sleep propensity and alertness drift in and out of synchrony with the 24-hour day.[45] The condition primarily occurs in blind individuals, and at least 50% of the totally blind (i.e., those with

no light perception) are thought to suffer from the disorder.[116] While the etiology in the blind is a loss of photic input to the pacemaker,[117] the pathophysiology among sighted individuals is unknown.

As stated above, entrainment status was uniquely utilized as an outcome measure, as it physiologically defines this disorder (just as elevated blood pressures characterize essential hypertension). This was the sole outcome variable rated as CRITICAL for N24SWD.

5.3.1 Prescribed Sleep-Wake Scheduling

The previously published Practice Parameters[8] recommended prescribed sleep-wake scheduling at an OPTION level, noting that it may be a useful method to improve the entrainment of circadian rhythms among sighted patients with N24SWD. However, this guideline was created in the absence of discrete evidence, as there have been no published trials among sighted or blind patients.

There is some evidence that *sleep* timing (independent of the timing of light exposure) is able to reset the circadian pacemaker in humans,[52, 118-120] and prescribed sleep-wake scheduling therefore represents a *potential* therapeutic intervention for N24SWD. However, this evidence is indirect, as data were culled from basic science experiments conducted among non-clinical populations.

There is no evidence to support the use of prescribed sleep-wake scheduling in patients with N24SWD. No recommendation.

5.3.2 Timed Physical Activity/Exercise

There was no recommendation in the previous Practice Parameters[8] regarding timed physical activity/exercise as a treatment for patients with N24SWD. Physical activity has been demonstrated to reset the timing of the circadian pacemaker among healthy subjects[121] and therefore represents another *potential* therapy. Indeed, the circadian pacemaker can be entrained in blind individuals in the absence of circadian photoreception.[122] As with prescribed sleep-wake scheduling, however, there have not been any published trials. The evidence is therefore indirect and insufficient to serve as the basis of a recommendation.

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There is no evidence to support the use of timed physical activity or exercise in patients with N24SWD. No recommendation.

5.3.3 Strategic Avoidance of Light

There is one case report that includes strategic avoidance of light, and it is included below in the combination treatments section.[123] The previous Practice Parameters[8] provided no pertinent recommendations.

There is no evidence to support the use of strategic avoidance of light (as monotherapy) in patients with N24SWD. No recommendation.

5.3.4 Light Therapy

The previous Practice Parameters recommended this treatment at an OPTION level (for sighted individuals), based on 5 case series/reports,[123-127] all comprised of 1-2 subjects. The small numbers of study participants prevented inclusion for the present report, and no studies have been published subsequently.

There is some experimental evidence that light is capable of resetting the circadian pacemaker in the absence of conscious light perception[128], and most blind individuals who retain such photic input to the circadian pacemaker would not be expected to have N24SWD. However, some such individuals may have insufficient *exposure* to light to maintain entrainment and therefore timed light exposure may be a *potential* therapeutic intervention in a subset of blind individuals with N24SWD. However, as noted, there have been no studies that examined this question.

There is insufficient evidence to support the use of light therapy in patients with N24SWD (versus no treatment). No recommendation.

5.3.5 Sleep-Promoting Medications

The previous Practice Parameters did not make any recommendation for the use of sleep-promoting medications in N24SWD, and no new studies were identified.

There is no evidence to support the use of sleep-promoting medications in patients with N24SWD. No recommendation.

DRAFT

5.3.6 Timed Oral Administration of Melatonin or Agonists

5.3.6.1 Melatonin for blind adult patients with N24SWD

The previously published recommendation was designated at the GUIDELINE level[8], based upon 4 case reports[129-132] and 5 small observational studies.[30-32, 133, 134] Some of these studies, and others, have examined important treatment parameters and outcomes, including dose,[133, 135, 136] phase angle of entrainment,[134] and circadian time of administration,[137] but many were small, often uncontrolled trials. Three placebo-controlled, crossover studies from the previous Practice Parameters were eligible for the current review[30-32] and the overall level of evidence for the CRITICAL outcome (circadian entrainment) was LOW (**Appendix, Table 8**).

Sack and colleagues (n=7, mean age 47.3 ± 5.0 years) administered 10 mg of melatonin 1 hour prior to bedtime[30] while Lockley et al. (n=7, mean age 44.6 ± 8.4 years)[31] and Hack et al. (n=10, mean age 48.2 ± 12.5 years)[32] administered 5 mg and 0.5 mg of melatonin, respectively, at 21:00. The duration of treatment for these studies was 26-81 days. Results (excluding subjects without placebo control or complete CRITICAL outcome data) were combined for meta-analysis of entrainment as a dichotomous outcome (Yes/No), using the Mantel-Haezel test (see **Figure 6** and **Appendix, Table 8**). The odds ratio for entrainment was 21.18 [3.22, 139.17]. In other words, the likelihood of entrainment with melatonin was ~21 times higher in comparison to placebo. Although the evidence level can only be graded as LOW due to the fact that these are small observational studies, this is the best evidence to date that melatonin is an effective treatment for N24SWD. Taken together, these placebo-controlled studies represent the largest number of N24SWD patients whose entrainment status was assessed subsequent to melatonin treatment.

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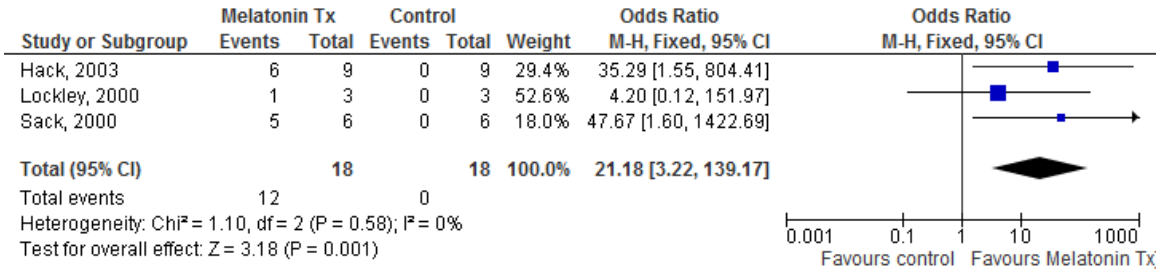
Figure 6-Meta-Analysis of Evidence for Entrainment as a Result of Melatonin Treatment of Blind Adult Patients with N24SWD.



5.3.6.1a We suggest that clinicians use strategically-timed administration of melatonin for the treatment of N24SWD in blind adults (versus no treatment). [WEAK FOR]

***Summary*:** This recommendation was designated at the GUIDELINE level (for the blind) in the previous Practice Parameters.[8] Only 3 studies[30-32] met inclusion criteria for the present analysis and the level of evidence from these small trials is LOW (**Figure 6** and **Appendix, Table 8**). Doses ranged between 0.5-10.0 mg, and were administered either 1 hour prior to preferred bedtime, or at a fixed clock hour (21:00), for a period of 26-81 days. Patient preference would be expected to favor the use of easily obtained and inexpensive melatonin that requires once daily dosing. No serious adverse reactions to melatonin have been described to date (see separate "Harms and Adverse Effects" section) and therefore the benefits of use appear to outweigh any potential harms. A majority of well-informed patients and caregivers would therefore accept this treatment option versus no treatment.

5.3.6.1 Melatonin for sighted patients with N24SWD

The recommendation for sighted individuals was provided at an OPTION level in the previous Practice Parameters,[8] based upon 4 case series.[126, 138-140] None of these studies were eligible for the current review, based upon insufficient numbers of subjects.

There is insufficient evidence to support the use of melatonin among sighted patients with N24SWD (versus no treatment). No recommendation.

DRAFT

5.3.7 Wakefulness-Promoting Medications

The previous Practice Parameters did not make any pertinent recommendations regarding the use of wakefulness-promoting medications in N24SWD, and no new studies were identified.

As noted above, both sleep and activity have the potential to reset the circadian pacemaker and therefore it is reasonable to think that medications that promote either sleep or wakefulness might be useful in the treatment of this disorder, either by entrainment of the biological clock or by improving alertness and sleep when individuals are sleeping out of synchrony with the circadian pacemaker. Similar to sleep-wake scheduling and physical activity however, there have not been any studies of either of these approaches in N24SWD.

There is no evidence to support the use of wakefulness-promoting medications in patients with N24SWD. No recommendation.

5.3.8 Other Somatic Interventions

The previous Practice Parameters cited "insufficient evidence" to support the use of oral vitamin B12 for use in sighted individuals with N24SWD (OPTION), based on 2 open-label case reports.[141, 142] No studies have since been published pertaining to the use of vitamin B12 (or other alternate somatic interventions) for N24SWD.

There is insufficient evidence to support the use of oral vitamin B12 (and no evidence to support alternate somatic interventions) among patients with N24SWD (versus no treatment). No recommendation.

5.3.9 Combination Treatments

The previous Practice Parameters did not discuss the use of combination treatments in N24SWD. There are 4 uncontrolled case reports involving a combination of treatments in sighted individuals with N24SWD.[123, 127, 143, 144] However, these studies did not meet inclusion criteria for the present review.

There is insufficient evidence to support the use of combination treatments in patients with N24SWD (versus no treatment). No recommendation.

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5.4 RECOMMENDATIONS FOR THE TREATMENT OF ISWRD

ISWRD is diagnosed when patients exhibit no clear circadian pattern of sleep-wake behavior. Afflicted individuals demonstrate wakefulness during conventional sleeping hours and bouts of sleep during the day.[45] The condition is observed most commonly among patients with neurodevelopmental or neurodegenerative disorders, and can pose particular challenges for caregivers.

5.4.1 Prescribed Sleep-Wake Scheduling

There was no recommendation in the previous Practice Parameters regarding prescribed sleep-wake scheduling as a stand-alone treatment for patients with ISWRD, and no new studies were identified. However, prescribed schedules have been tested in combination with other modalities (see section 5.4.9, Combination Treatments).

There is no evidence to support the use of prescribed sleep-wake scheduling as a stand-alone treatment for patients with ISWRD. No recommendation.

5.4.2 Timed Physical Activity/Exercise

There was no recommendation in the previous Practice Parameters regarding timed physical activity/exercise as a sole treatment for patients with ISWRD, and no new studies were identified. However, scheduled activity has been used in combination with other modalities (see section 5.4.9, "Combination Treatments").

There is no evidence to support the use of timed physical activity or exercise as a stand-alone treatment for patients with ISWRD. No recommendation.

5.4.3 Strategic Avoidance of Light

There was no recommendation in the previous Practice Parameters regarding strategic avoidance of light as a treatment for patients with ISWRD, and no new studies were identified.

There is no evidence to support the use of strategic avoidance of light as a treatment for patients with ISWRD. No recommendation.

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5.4.4 Light Therapy for ISWRD in elderly patients with dementia

In contrast to the present review, the 2007 Practice Parameters[8] did not separate ISWRD treatment recommendations by patient subgroup. The section that follows (and other sections) are subcategorized as warranted.

The recommendation in the 2007 Practice Parameters was designated as an OPTION, but only one[34] of the previously reviewed studies[35, 36, 145-150] and one new study[33] met inclusion criteria for the current document. Although neither demonstrated improvements in CRITICAL outcomes, one[34] showed that light therapy improved behavioral symptoms, an area of significant clinical importance. The cumulative level of analyzed evidence was VERY LOW (**Appendix, Table 9**).

Both reviewed light therapy studies examined institutionalized elderly subjects with dementia.[33, 34] In their randomized clinical trial of 50 nursing home patients (mean age 86 ± 8 years), Dowling and colleagues compared 60 minutes of light therapy scheduled from 09:30-10:30 (1.5 hours after the nursing home's set rise time) 5 days per week for a period of 10 weeks, to a dim-light control condition consisting of indoor light of 150-200 lux.[33] Bright light was delivered via white broad spectrum light boxes, positioned on tables and located approximately 30 to 34 inches from participants' eyes. Light levels in the direction of gaze were monitored for each participant during each treatment session to maintain levels > 2500 lux. At the end of the intervention, average actigraphically-measured TST did not differ between active and control groups. A second open-label study tested light therapy of 2 hours duration between 09:00-11:00 among 14 patients (mean age 75 years, range 61-83) with sleep disturbances. Patients were treated for 4 weeks with white broad spectrum tabletop light boxes that produced 3000-5000 lux and were positioned at a distance of 1 meter from the participants. As with the Dowling study, no improvements in TST (subjective) were demonstrated, but the study did show improvement of caregiver-rated behavioral symptoms, including decreases in wandering, violent behavior, restlessness, and symptoms of delirium.[34]

Other research that was ineligible for this review may nonetheless inform clinicians' decision-making regarding the use of light therapy among demented elderly patients with ISWRD. Riemersma-van der Lek and colleagues[41] randomized twelve assisted-living facilities in the Netherlands to common areas that were lit with ceiling

fixtures that emitted either bright white broad spectrum (1000 lux) or dim light (300 lux). Participants in the bright light facilities had *lower* TST compared to participants living in a dim light facility at two follow-up assessments (6 weeks and 6 months after the change in facility light levels). Other outcomes, including cognitive deficits and depression, were improved in association with the light intervention, however. Additional studies cited in the previous Practice Parameters and associated review[8, 9] treated subjects with white broad spectrum artificial light or outdoor light at levels ranging from 1000- 8000 lux. Durations of daily light exposure ranged from 45-120 minutes and treatment durations lasted from 10 days to 11 weeks.[35, 36, 145-150] Although presently defined CRITICAL sleep outcomes were not analyzed, some of these studies showed positive effects of light exposure on 24-hour rest-activity rhythms, with more consolidated rest periods at night and more activity and fewer naps during the day.

5.4.4a We suggest that clinicians treat ISWRD in elderly patients with dementia with light therapy (versus no treatment). [WEAK FOR]

Summary: This recommendation was designated as an OPTION in the 2007 Practice Parameters, and only one subsequent study has been published that met inclusion criteria for the current document.[33] The cumulative level of reviewed evidence (2 studies)[33, 34] was VERY LOW (**Appendix, Table 9**), and none of the TF-defined CRITICAL outcomes showed improvement. Behavioral symptoms nevertheless improved in the sole study that measured this outcome.[34] The interventions consisted of white broad spectrum light therapy, 2500-5000 lux (~1 meter from participants), 1-2 hours in duration, between 09:00-11:00, for a period of 4-10 weeks.[33, 34] Benefits of treatment are closely balanced with harm/burden. In addition to the general side effects reported in the "Harms and Adverse Effects" section, other side effects in this population range from complaints of eye irritation[35] to agitation and confusion,[36] and these potential drawbacks should be considered when recommending treatment. Furthermore, depending on the method and setting of light delivery, treatment may be labor intensive, and modest improvements in outcomes may not justify associated costs. Nevertheless, clinical experience suggests that the majority of well-informed patients and/or caregivers

of elderly, demented patients with ISWRD would choose light therapy in comparison to no intervention.

5.4.5 Sleep-Promoting Medications for ISWRD in elderly patients with dementia

There was no recommendation in the previous Practice Parameters regarding sleep-promoting medications for patients with ISWRD, and no new studies have been published. Various investigations have concluded, however, that hypnotic medications increase risks of adverse events within this population (see "Harms and Adverse Effects" section).

5.4.5a We do NOT recommend that clinicians use sleep-promoting medications to treat demented elderly patients with ISWRD. [STRONG AGAINST]

Summary: This is a new recommendation in comparison to the previous Practice Parameters, which did not address the use of sleep-promoting medications (other than melatonin) for ISWRD. Although no relevant subsequent studies have been published, other extant literature indicates that administration of hypnotics to demented elderly patients increases risks of falls and other untoward outcomes Altered pharmacokinetics observed with aging may be one mechanism by which hypnotics increase adverse events in older adults.[37] Risk appears to be increased even further in elderly patients with dementia[38], particularly when used in combination with other medications[39] (also see separate "Harms and Adverse Effects" section). Thus, the risk of harm from use of hypnotics in demented elderly patients with ISWRD outweighs potential positive effects. As such, the vast majority of well-informed patients and/or caregivers would not select this treatment.

5.4.6 Timed Oral Administration of Melatonin or Agonists

5.4.6.1 Melatonin for elderly patients with dementia and ISWRD

In the 2007 Practice Parameters, melatonin was deemed "not indicated" for this specific population, based upon two studies,[40, 130] only one of which was eligible for the current review.[40] No subsequently published relevant studies were identified. Melatonin

administration did not significantly improve the pre-defined CRITICAL outcome of TST. Level of evidence: LOW (**Appendix, Table 10**).

Twenty-five patients with dementia and ISWRD (mean age 84.2±7.6 years) were enrolled in a double-blind crossover trial of 6 mg slow-release melatonin versus placebo.[40] Participants were studied for a 2 week baseline period and were then randomized to receive either 6 mg slow-release melatonin or placebo for 2 weeks at their usual bedtimes, followed by a 1-week washout period and cross-over to the second study period. Mean TST estimated with actigraphy did not differ between the two groups.

Other research may inform clinical decision-making in this area. Singer and colleagues examined the effects of treatment with 2.5 mg slow-release or 10 mg immediate-release melatonin administered 1 hour before bedtime (versus placebo) on actigraphically-estimated TST in patients with Alzheimer's disease and sleep disturbance.[151] The patients in this study did not have discreet diagnoses of ISWRD and data were therefore not eligible for inclusion in the present review. Nevertheless, in keeping with the results of Serfaty and colleagues,[40] this large, well-designed trial also failed to show an improvement in TST with either dose of melatonin compared to placebo. Riemersma-van der Lek and colleagues[41] published another potentially relevant combination study among dementia patients in assisted living in whom ISWRD was not specifically identified. In contrast to the other studies, the melatonin-only arm (2.5 mg immediate-release formulation administered approximately one hour before bedtime) demonstrated decreased actigraphic ISL and increased TST compared to placebo. However, detrimental effects of melatonin on mood and daytime functioning were also observed.

5.4.6.1a We suggest that clinicians avoid the use of melatonin as a treatment for ISWRD in older people with dementia (compared to no treatment). [WEAK AGAINST]

***Summary*:** Melatonin was deemed "not indicated" for the treatment of ISWRD in older people with dementia (OPTION) in the previous Practice Parameters. The present recommendation against melatonin treatment is based on one reviewed study that failed to show benefit with respect to the CRITICAL outcome of

TST.[40] Level of evidence: LOW (**Appendix, Table 10**). Furthermore, there is evidence that melatonin could be harmful in this population.[41] Thus, the risk-benefit ratio suggests that the potential for harms outweighs the possibility for benefits. Clinical experience therefore dictates that the majority of older patients with dementia and/or their caregivers would not favorably accept a trial of melatonin.

5.4.6.2 Melatonin in children/adolescents with neurologic disorders

Melatonin was recommended at the OPTION level in the previous Practice Parameters for children with various neurologic disorders,[8] based upon four studies,[152-155] none of which was eligible for the current review, due to an insufficient number of participants or grouping of participants with different CRSWDs. One new eligible study was identified[42], and melatonin was shown to improve select pre-defined CRITICAL outcomes (TST, ISL), although the confidence interval associated with both values crosses the threshold of the pre-determined clinically significant minimal change (see **Table 2**). The level of reviewed evidence was MODERATE (**Appendix, Table 11**).

Wright and colleagues[42] performed a double-blind, randomized, controlled, crossover trial in 16 children (mean age 9±2.9 years) with autism spectrum disorder. The protocol consisted of 1-month baseline, 3 months melatonin vs. placebo, 1-month washout, 3 months melatonin vs. placebo (crossover), and 1-month medication free. Melatonin dosing (using a "standard release" formulation administered 30-40 minutes before planned bedtime) started at 2 mg, and parents were given the option of increasing the dose by 2mg every 3 days, until 50% or more improvement in sleep was observed, up to 10 mg. The average final dose during the melatonin arm was 7±3.0 mg (range 2-10 mg). Parents' subjective reports of ISL and TST were improved, although both values crossed the threshold of the pre-determined clinically significant minimal change (mean difference -51.71 minutes [C.I. -13.49 to -89.93] and 48.45 minutes [C.I. 6.29 to 90.61 minutes], respectively) (see **Table 2**).

Studies that were not eligible for analysis may nonetheless provide additional relevant clinical information. In an open-label observational trial in five children with severe developmental disabilities and disrupted sleep-wake patterns, Pillar and colleagues

[152] found that 3 mg melatonin administered at 18:30 increased actigraphically-recorded TST. Other trials have tested the effects of melatonin for nocturnal sleep disturbance in children with a range of neurodevelopmental difficulties.[153-155] Many of the children included in these studies had at least one comorbid disability (e.g., epilepsy, blindness), and all had disturbed sleep-wake patterns. Although considerable inter-individual variability was observed in the response to melatonin, all of the studies showed significant improvements in at least one sleep measure. Another important finding from these studies is the relative safety of melatonin in this population as no significant side effects were observed in these trials.

5.4.6.2a We suggest that clinicians use strategically-timed melatonin as a treatment for ISWRD (versus no treatment) in children/adolescents with neurologic disorders. [WEAK FOR]

***Summary*:** This recommendation was designated as an OPTION in the 2007 Practice Parameters, but none of the reviewed studies were eligible for the current analysis. One subsequently published eligible study was identified, with a MODERATE level of evidence[42] (**Appendix, Table 11**). The data indicate that melatonin administration of 2-10 mg during the hour before planned bedtime may improve CRITICAL sleep outcomes in children/adolescents with neurologic disorders and ISWRD; although confidence intervals associated with positive values crossed the threshold of the pre-determined clinically significant minimal change (see **Table 2**). Another caveat is that this recommendation is culled from a small sample of patients with a range of developmental disorders. As such, it may not generalize to all children/adolescents with ISWRD/neurologic disorders. Although no serious adverse reactions have been described in relation to melatonin use to date, relevant concerns have been raised by select studies with respect to the pediatric/adolescent population[26], and rigorous long-term data are lacking (see separate "Harms and Adverse Effects" section). Nevertheless, clinical experience suggests that a majority of patients and caregivers would accept this treatment option (versus no treatment), particularly taking into account

significant burdens associated with the neurologic disabilities and severe associated sleep disturbances.

5.4.7 Wakefulness-Promoting Medications

There was no recommendation in the previous Practice Parameters regarding wakefulness-promoting medications as a treatment for patients with ISWRD, and no new studies were published.

There is no evidence to support the use of wakefulness-promoting medications as a treatment for patients with ISWRD. No recommendation.

5.4.8 Other Somatic Interventions

There was no recommendation in the previous Practice Parameters regarding other somatic interventions as a treatment for patients with ISWRD, and no subsequent relevant studies have been published.

There is no evidence to support the use of other somatic interventions for the treatment of patients with ISWRD. No recommendation.

5.4.9 Combination Treatments in demented elderly adults with ISWRD

This recommendation was designated as a GUIDELINE in the previous Practice Parameters[8], based upon two studies, neither of which were included in the present analysis, either because participants clearly did not have a diagnosis of ISWRD[156] or because pre-defined CRITICAL outcomes were not measured.[157] One randomized controlled trial pertaining to the treatment of demented elderly patients with ISWRD[33] was published subsequent to 2007, and did not demonstrate benefit with respect to predefined CRITICAL outcomes. The level of reviewed evidence was VERY LOW (**Appendix, Table 12**).

Dowling and colleagues[33] examined sleep-related outcomes from the combination of light treatment (>2500 lux white broad spectrum light delivered by light boxes at a distance of 30-34 inches from the eye between 09:30-10:30 AM for 10 weeks) and either melatonin (5 mg immediate-release between 17:00-18:00) or placebo among 32 nursing home patients with Alzheimer's disease (mean age 86±8 years). The dim-light control

condition was exposed to indoor light of 150-200 lux (see additional study details in section 5.4.4.1). The intervention did not significantly improve actigraphically-estimated TST, the sole investigated CRITICAL outcome.

Various other studies were ineligible for the current analysis, but nonetheless bear potential relevance to clinicians. Two non-blinded, randomized trials examined multimodal treatments that included daytime activity, bright light exposure, and sleep scheduling in *community-dwelling* elderly patients with dementia.[156, 158] The results demonstrated significant decreases in nighttime wakefulness, and greater adherence to the intervention was associated with more improvement. Combination treatments involving prescribed sleep-wake scheduling, light exposure and increased daytime activity have also been examined in two 5-day studies among demented, elderly nursing home residents.[157, 159] Participants were required to be out of bed from 08:00 to 20:00, had scheduled low-intensity physical activity 3 times per day, and exposure to at least 30 minutes of outdoor sunlight daily. Other intervention procedures included caregivers imposing a structured nighttime routine and minimizing nighttime noise and interventions. Although these studies did not measure outcomes defined by the TF, the multimodal interventions significantly improved daytime functioning and amplitude of rest-activity rhythms. The investigations were restricted by constraints inherent to the nursing home environment (e.g., high dropout rate, inability to blind raters to condition), yet both had relatively large sample sizes. An additional caveat is that many more participants were screened than were eligible for participation, such that the results may not generalize to all patients with dementia.

5.4.9.1a We suggest that clinicians do NOT use combined treatments consisting of light therapy in combination with melatonin in demented, elderly patients with ISWRD (versus no treatment). [WEAK AGAINST]

***Summary*:** This recommendation was designated as a GUIDELINE in the previous Practice Parameters. One relevant randomized controlled trial[33] was published subsequent to 2007. The level of reviewed evidence from this single study was VERY LOW (**Appendix, Table 12**). Including melatonin as part of a combination treatment with light therapy does not appear to confer additional

benefit[33] and may increase the potential for harms.[41] Clinical experience suggests that patients/caregivers would carefully consider the risks of depression and withdrawn behaviors with treatments that include melatonin. Thus, the majority of patients/caregivers would not accept combination treatments consisting of melatonin and bright light (versus no treatment). Other combination treatments (e.g., bright light, scheduled sleep-wake, and physical activity) are worthy of further investigation.

5.4.9.2 Combination treatments in children/adolescents with ISWRD

The previous Practice Parameters recommendation was designated at the OPTION level, based upon the results of one study.[160] No new studies were identified. The previously cited investigation was an open trial in children with moderate-to-severe mental retardation and associated nocturnal sleep disturbances, and employed combination treatment with light therapy, prescribed sleep-wake schedules, and timed daytime activity.[160] Five out of 14 patients showed improvements in TST measured on sleep diaries (completed by parents). However, as it was not clear that these patients met diagnostic criteria for ISWRD, this study was not eligible for analysis in the present review.

There is insufficient evidence to support the use of combination treatments in children/adolescents with ISWRD (versus no treatment). No recommendation.

Table 6-Recommendation Statements for Treatment of Patients with Intrinsic CRSWDs

Treatment (PICO question)	Recommendation Statement	Direction and Strength of Recommendation	Quality of Evidence	Benefits/Harms Assessment	Patients' values and Preferences
Advanced Sleep-Wake Phase Disorder (ASWPD)					
5.1.4 Light therapy (PICO Question 4)	5.1.4a We suggest that clinicians treat adult ASWPD patients with evening light therapy (versus no treatment)	WEAK FOR	VERY LOW	Benefits closely balanced with harms	The majority of patients would use this treatment.
Delayed Sleep-Wake Phase Disorder (DSWPD)					
5.2.6 Timed oral administration of melatonin or agonists (PICO Question 6)	**5.2.6.1a** We suggest that clinicians treat DSWPD in adults with and without depression with strategically-timed melatonin (versus no treatment)	WEAK FOR	LOW	Uncertainty in the estimates of benefits/harms	The majority of patients would use this treatment.

	5.2.6.2.1a We suggest that clinicians treat children and adolescents with DSWPD (and no comorbidities) with strategically-timed melatonin (versus no treatment)	WEAK FOR	MODERATE	Uncertainty in the estimates of benefits/harms	The majority of patients would use this treatment, with appropriate informed consent from the patient and caregiver.
	5.2.6.2.2a We suggest that clinicians treat children and adolescents with DSWPD comorbid with psychiatric conditions with strategically-timed melatonin (versus no treatment)	WEAK FOR	LOW	Uncertainty in the estimates of benefits/harms	The majority of patients would use this treatment, with appropriate informed consent from the patient and caregiver.
5.2.9 Combination Treatments	**5.2.9.2a** We suggest that clinicians treat children/adolescents with DSWPD with post-awakening light therapy in conjunction with behavioral treatments (versus no treatment)	WEAK FOR	LOW	Benefits clearly outweigh harms	The majority of patients would use this treatment, particularly with active caregiver support.
Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD)					
5.3.6 Timed oral administration of melatonin or agonists (PICO Question 6)	**5.3.6a** We suggest that clinicians use strategically- timed administration of melatonin for the treatment of N24SWD in blind adults (versus no treatment)	WEAK FOR	LOW	Benefits clearly outweigh harms	The majority of patients would use this treatment.
Irregular Sleep-Wake Rhythm Disorder (ISWRD)					
5.4.4 Light Therapy (PICO Question 4)	**5.4.4.1a** We suggest that clinicians treat ISWRD in elderly patients with dementia with light therapy (versus no treatment)	WEAK FOR	VERY LOW	Benefits closely balanced with harms	The majority of well-informed patients and/or caregivers of would elect to use this treatment.
5.4.5 Sleep-promoting medications (PICO Question 5)	**5.4.5.1a** We do **NOT** recommend that clinicians use sleep-promoting medications to treat demented elderly patients with ISWRD	STRONG AGAINST	NONE*	Harms clearly outweigh benefits	The vast majority of well-informed patients and/or caregivers would NOT elect to use this treatment.

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5.4.6 Timed oral administration of melatonin or agonists (PICO Question 6)	**5.4.6.1a** We suggest that clinicians avoid the use of melatonin as a treatment for ISWRD in older people with dementia	WEAK AGAINST	LOW	Harms outweigh benefits	The majority of patients and/or caregivers would NOT elect to use this treatment.
	5.4.6.2a We suggest that clinicians use strategically-timed melatonin as a treatment for ISWRD (versus no treatment) in children/adolescents with neurologic disorders	WEAK FOR	MODERATE	Benefits clearly outweigh harms	The majority of patients and/or caregivers would elect to use this treatment.
5.4.9 Combination treatments	**5.4.9.1a** We suggest that clinicians avoid the use of light therapy combined with melatonin in demented, elderly patients with ISWRD (versus no treatment)	WEAK AGAINST	VERY LOW	Harms outweigh benefits	The majority of patients and/or caregivers would NOT elect to use this treatment.

*Although no randomized controlled trials have examined sleep-promoting medications for the treatment of ISWRD, other extant literature indicates that administration of hypnotics to demented elderly patients increases risks of falls and other untoward outcomes (see separate "Harms and Adverse Effects" section).

4.0 CONCLUSIONS AND FUTURE DIRECTIONS

Circadian-based basic science developments continue to outpace clinical research pertaining to CRSWDs. Since publication of the prior Practice Parameters,[8] relatively few new studies have emerged, although it is encouraging that investigations specifically oriented to the pediatric/adolescent and other "special" populations have been published. The major change with the present review is the use of the GRADE system of analysis. While more rigorous in many respects than the previously employed evidence-based assessment, derived data is designed to be more clinically relevant, as the GRADE system requires a combined consideration of strength of evidence, in conjunction with risk/benefit analyses and determination of patient values and preferences. As such, many previously endorsed practice recommendations have been negated, and numerous PICO questions remain unanswered. While this certainly points out the significant gaps with respect to the clinical CRSWD research (highlighted by the prior Standards of Practice

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group),[8] these updated Practice Parameters are intended to provide clinicians with heightened confidence in prescribing treatments and, equally importantly, they should serve as a roadmap for future studies that will propel higher quality, more sophisticated CRSWD therapies.

Generally speaking, larger more rigorously designed studies (randomized placebo-controlled trials) with ICSD-3 defined CRSWDs[45] are required, and replication of results from separate centers is essential. Clinical research pertaining to ASWPD and ISWRD in particular has suffered significantly due to a lack of adherence to ICSD diagnostic criteria. In the specific case of ASWPD, one can only conjecture that the results of light therapy studies that address sleep maintenance/early-morning awakening difficulties are applicable to the treatment of ASWPD, and uncertainty will remain unless strict terminology are used. Others have raised concerns about the frequency at which one actually encounters patients with this condition in the clinical arena,[161] a topic that is beyond the scope of this discussion. As for ISWRD, the term is rarely used in the medical literature, presumably because the comorbid disorders that frequently overlap (e.g., dementia, developmental disabilities) tend to overshadow the CRSWD. Nevertheless, sleep disturbances are among the most onerous of difficulties for caregivers of these patients. Thus, lack of consideration of the formal diagnosis of ISWRD in studies of sleep in these populations makes it difficult to identify effective treatments for this important clinical problem.

More specifically, future studies could advance the field by including detailed therapeutic information, such as the method and means of treatment delivery (e.g., protective eyewear vs. volitional avoidance of light, light therapy intensity/wavelength/proximity/continuous versus pulsed administration, melatonin formulation, etc.), relationship of treatment timing with respect to a defined physiologic circadian phase marker or other sleep parameter, inclusion/exclusion of prescribed sleep/wake schedules or other behavioral interventions, and study environment (laboratory vs. non-laboratory). Regarding the latter factor, field-based studies are sorely needed, and one must be cautious not to let tightly controlled bench research prematurely dictate clinical treatment. As a prime example, there are currently no data to support devices that solely deliver blue short wavelength light in the treatment of CRSWDs, and

two laboratory-based studies that describe no additional benefit with blue-enriched bright light,[56, 57] despite the fact that these wavelengths have been identified as especially important for circadian phase resetting in non-clinical experiments (reviewed in [43]). More importantly, compliance with post-awakening "light boxes" in the field is very poor,[110] and studies that examine the bypassing of this compliance barrier are particularly intriguing.[12, 111, 162] Future research should address "dose" of light including lux level and duration,[49] and should also consider season[163] and other environmental factors that affect overall light exposure history.[51] Finally, more such studies specifically targeting CRSWD populations are desired.

From the standpoint of outcomes, similar *clinically relevant sleep-related* measures will be required for inter-study comparative purposes (PSG vs. actigraphy vs. subjective reports, physiologic or non-physiologic circadian marker), along with systematic measures of treatment compliance, to accurately inform clinical practice. In the instance of ISWRD, it should be determined whether separate outcome measures (e.g., circadian amplitude, rest-activity cycle variations) may be superior indicators of treatment efficacy. Optimal inter-study medication comparisons will require equivalent dosing (analyzed melatonin study doses ranged from 0.3-10.0 mg), timing (with respect to clock time, typical sleep onset time or other physiologic/non-physiologic circadian marker), and treatment durations, to accurately gauge benefit. The issue of formulation may also be relevant in melatonin studies (regular- vs. sustained-release vs. sublingual etc.), and one group suggested that slow exogenous melatonin metabolism could be responsible for a lack of sustained effect in select instances.[164]

Taking into account melatonin safety concerns (particularly among children and those of reproductive age), future properly powered studies should be performed to identity the lowest effective melatonin dosage and duration of treatment (acute and maintenance). Long-term physiologic studies are needed to accurately ascertain any serious chronic risks, particularly as melatonin supplements are not subject to FDA oversight (reviewed in [26]). In January of 2014 the FDA approved the melatonin agonist Hetlioz™ (tasimelteon) for the treatment of N24SWD among the blind. This is the first FDA-approved drug for any CRSWD, but no peer-reviewed trials have been published.

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At least two other investigations (involving ramelteon) suggest a potential future CRSWD role for these agents.[165, 166]

Related to long-term risks of circadian-based interventions in general**,** research is needed to determine the minimum required duration of specific treatments (or to determine that they are required indefinitely), and/or to determine maintenance treatment schedules. Studies that extricate independent effects of treatment modalities utilized in multicomponent interventions, so that relative successes and failures can be exploited for differing clinical scenarios (including those with dementia or other cognitive dysfunction) are needed. For instance, in the previously cited Gradisar study (involving adolescents with DSWPD),[29] light therapy was discontinued (and apparently not required) once a target wake time was reached, at which time solely behavioral interventions ensued. It is not clear to what degree this treatment could be generalized to all DSWPD populations.

Demonstration of superiority (or lack thereof) of circadian versus clock-hour TOA for interventions should engender studies that aim to explore demonstrable benefits of phase assessments in the clinical setting. Some of the reviewed interventions demonstrated successful sleep-related outcomes without changes in the circadian phase marker and vice versa. In the instance that the importance of circadian TOA *is* demonstrated, it will be necessary to determine light and melatonin phase PRCs for adult populations afflicted with CRSWDs (as they may differ from normal populations[47, 167] and to determine the same for both afflicted and healthy pediatric/adolescent populations. Complicating matters, alterations in phase relationships between the circadian timing system and the timing of sleep among those with CRSWDs could impact the ability of interventions to exert benefits, even with knowledge of the PRC. For example, longer intervals from various endogenous melatonin parameters[168] and CBT_{min}[169-171] to sleep offset have frequently been described among adult patients with DSWPD as compared to controls. However, this finding has not been demonstrated among protocols in which subjects are forced to maintain a more conventional sleep/wake schedule[11, 172, 173] suggesting that this observation may simply be a consequence of longer habitual TST. Greater elucidation is required. On a separate note, effective treatments may need to address concomitant impairment of homeostatic sleep processes in CRSWDs, as has been

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demonstrated in DSWPD and among adolescents in general.[174, 175] Whether hypnotics have a role in this setting deserves to be further explored.[106]

Present guidelines predominantly reflect biological underpinnings associated with CRSWDs. Studies are needed to investigate and understand predominant exogenous and endogenous contributors to the development and perpetuation of CRSWDs, so that different subtypes (and possibly different treatment/prophylactic regimens) can be identified. In the case of adolescents/young adults (and, to a lesser degree, other adults[176]), numerous exogenous factors, such as increased autonomy with respect to sleep time, employment, and involvement in extracurricular activities have been identified as variables contributing to the generally observed delay in sleep/wake patterns[177], but have not been studied among adolescent DSWPD cohorts specifically.[178, 179] Additionally, repeated exposure to frustrations at not being able to fall asleep at a desired time can lead to the development of a concomitant conditioned insomnia, which can perpetuate sleep difficulties. Exposure to indoor lighting during evening hours [180-183] and/or delays in weekend wake times[184-186] have also been implicated as contributors to persistently delayed sleep/wake times, but have not been specifically implicated in adolescent DSWPD.[187] Some have urged that school lighting environments be optimized for maximal circadian benefits.[188] **In the case of N24SWD, it may be that the exogenous and endogenous contributors to the disorder differ between blind and sighted individuals and that this may similarly necessitate different treatment regimens.** Identification and manipulation of exogenous variables in trials of CRSWDs may prove fruitful.

The associated development of clinical profiles would enable clinicians to better ascertain which patients might respond to suggested treatments, and related research is encouraged. In the Gradisar study involving adolescents with DSWPD,[29] school non-attendance, unrestricted sleep during vacation periods, and (not surprisingly) amotivation were all noted to be barriers to successful outcomes with light therapy. Patients fitting this profile are perhaps better suited to less complex interventions. In a separate study involving young adult subjects with DSWPD and N24SWD receiving melatonin, a higher response rate correlated indirectly with shorter habitual TST, as well as a later age of

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onset.[139] Information such as this may eventually allow clinicians to optimally tailor treatment.

In select cases, accommodation to a CRSWD patient's circadian preference may be most practical, and further studies examining implementation of such schedules are desirable. Believing that some CRSWD cases are refractory to treatment, Dagan and Abadi (2001)[189] recommended foregoing therapy (specifically among DSWPD patients), and instead urged implementation of rehabilitation and accommodation to the preferred sleep/wake schedule in select instances, including support for disability from duties that require strict sleep/wake schedules, and encouragement to pursue endeavors with more flexible scheduling. The benefits of such accommodation were demonstrated in a separate military-based study, with evidence of superior performance and mood among those enabled to adapt a relatively delayed sleep/wake schedule, which correlated with increased TST.[190] A later school start time may be sought for adolescents, if practical and available. This intervention alone can significantly increase TST and mitigate associated impairments.[191-194] Unfortunately, the implementation of this policy change frequently encounters staunch political resistance and is presently available in select regions only.[192]

In sum, although much work remains, significant progress has been made in the recognition/treatment of CRSWDs since the inception of Sleep Medicine as a distinct medical discipline. Our aim with the present guidelines is to provide clinicians with immediate access to up-to-date information in order to make properly informed treatment decisions. In addition, this publication should serve as an impetus to address clinical research deficiencies and to promote novel inquiries for treatments of these challenging and interesting conditions.

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REFERENCES

1. Borbely AA A two process model of sleep regulation. *Human neurobiology* 1982;1:195-204.
2. Moore RY, Eichler VB Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. *Brain research* 1972;42:201-6.
3. Stephan FK, Zucker I Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *Proceedings of the National Academy of Sciences of the United States of America* 1972;69:1583-6.
4. Ralph MR, Foster RG, Davis FC, Menaker M Transplanted suprachiasmatic nucleus determines circadian period. *Science* 1990;247:975-8.
5. Welsh DK, Logothetis DE, Meister M, Reppert SM Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. *Neuron* 1995;14:697-706.
6. Czeisler CA, Duffy JF, Shanahan TL et al. Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science* 1999;284:2177-81.
7. Waterhouse JaD, P.J. Chronobiology: Biological Timekeeping. Sinauer Associates, Inc., 2004.
8. Morgenthaler TI, Lee-Chiong T, Alessi C et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine report. *Sleep* 2007;30:1445-59.
9. Sack RL, Auckley D, Auger RR et al. Circadian rhythm sleep disorders: part II, advanced sleep phase disorder, delayed sleep phase disorder, free-running disorder, and irregular sleep-wake rhythm. An American Academy of Sleep Medicine review. *Sleep* 2007;30:1484-501.
10. 5.2 RM. RevMan 5.2 In: Editor, ed.^eds. RevMan 5.2. City, 2012.
11. Mundey K, Benloucif S, Harsanyi K, Dubocovich ML, Zee PC Phase-dependent treatment of delayed sleep phase syndrome with melatonin. *Sleep* 2005;28:1271-8.
12. Cole RJ, Smith JS, Alcala YC, Elliott JA, Kripke DF Bright-light mask treatment of delayed sleep phase syndrome. *Journal of biological rhythms* 2002;17:89-101.
13. van Geijlswijk IM, van der Heijden KB, Egberts AC, Korzilius HP, Smits MG Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT. *Psychopharmacology* 2010;212:379-91.
14. Guyatt G, Oxman AD, Akl EA et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of clinical epidemiology* 2011;64:383-94.
15. Balshem H, Helfand M, Schunemann HJ et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of clinical epidemiology* 2011;64:401-6.
16. Guyatt GH, Oxman AD, Vist G et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *Journal of clinical epidemiology* 2011;64:407-15.
17. Guyatt GH, Oxman AD, Montori V et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *Journal of clinical epidemiology* 2011;64:1277-82.

DRAFT

18. Guyatt GH, Oxman AD, Kunz R et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *Journal of clinical epidemiology* 2011;64:1283-93.
19. Guyatt GH, Oxman AD, Kunz R et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *Journal of clinical epidemiology* 2011;64:1294-302.
20. Guyatt GH, Oxman AD, Kunz R et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *Journal of clinical epidemiology* 2011;64:1303-10.
21. Guyatt GH, Oxman AD, Sultan S et al. GRADE guidelines: 9. Rating up the quality of evidence. *Journal of clinical epidemiology* 2011;64:1311-6.
22. Palmer CR, Kripke DF, Savage HC, Jr., Cindrich LA, Loving RT, Elliott JA Efficacy of enhanced evening light for advanced sleep phase syndrome. *Behavioral sleep medicine* 2003;1:213-26.
23. Campbell SS, Dawson D, Anderson MW Alleviation of sleep maintenance insomnia with timed exposure to bright light. *Journal of the American Geriatrics Society* 1993;41:829-36.
24. Rahman SA, Kayumov L, Shapiro CM Antidepressant action of melatonin in the treatment of Delayed Sleep Phase Syndrome. *Sleep medicine* 2010;11:131-6.
25. Kayumov L, Brown G, Jindal R, Buttoo K, Shapiro CM A randomized, double-blind, placebo-controlled crossover study of the effect of exogenous melatonin on delayed sleep phase syndrome. *Psychosomatic medicine* 2001;63:40-8.
26. Kennaway DJ Potential safety issues in the use of the hormone melatonin in paediatrics. *Journal of paediatrics and child health* 2015.
27. Van der Heijden KB, Smits MG, Van Someren EJ, Ridderinkhof KR, Gunning WB Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *Journal of the American Academy of Child and Adolescent Psychiatry* 2007;46:233-41.
28. Smits MG, Nagtegaal EE, van der Heijden J, Coenen AM, Kerkhof GA Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. *Journal of child neurology* 2001;16:86-92.
29. Gradisar M, Dohnt H, Gardner G et al. A randomized controlled trial of cognitive-behavior therapy plus bright light therapy for adolescent delayed sleep phase disorder. *Sleep* 2011;34:1671-80.
30. Sack RL, Brandes RW, Kendall AR, Lewy AJ Entrainment of free-running circadian rhythms by melatonin in blind people. *The New England journal of medicine* 2000;343:1070-7.
31. Lockley SW, Skene DJ, James K, Thapan K, Wright J, Arendt J Melatonin administration can entrain the free-running circadian system of blind subjects. *The Journal of endocrinology* 2000;164:R1-6.
32. Hack LM, Lockley SW, Arendt J, Skene DJ The effects of low-dose 0.5-mg melatonin on the free-running circadian rhythms of blind subjects. *Journal of biological rhythms* 2003;18:420-9.
33. Dowling GA, Burr RL, Van Someren EJ et al. Melatonin and bright-light treatment for rest-activity disruption in institutionalized patients with Alzheimer's disease. *Journal of the American Geriatrics Society* 2008;56:239-46.
34. Mishima K, Okawa M, Hishikawa Y, Hozumi S, Hori H, Takahashi K Morning bright light therapy for sleep and behavior disorders in elderly patients with dementia. *Acta psychiatrica Scandinavica* 1994;89:1-7.

35. Fetveit A, Bjorvatn B The effects of bright-light therapy on actigraphical measured sleep last for several weeks post-treatment. A study in a nursing home population. *Journal of sleep research* 2004;13:153-8.
36. Skjerve A, Holsten F, Aarsland D, Bjorvatn B, Nygaard HA, Johansen IM Improvement in behavioral symptoms and advance of activity acrophase after short-term bright light treatment in severe dementia. *Psychiatry and clinical neurosciences* 2004;58:343-7.
37. Greenblatt DJ, Harmatz JS, Singh NN et al. Pharmacokinetics of zolpidem from sublingual zolpidem tartrate tablets in healthy elderly versus non-elderly subjects. *Drugs & aging* 2014;31:731-6.
38. Berry SD, Lee Y, Cai S, Dore DD Nonbenzodiazepine sleep medication use and hip fractures in nursing home residents. *JAMA internal medicine* 2013;173:754-61.
39. Hartikainen S, Rahkonen T, Kautiainen H, Sulkava R The use of psychotropics and survival in demented elderly individuals. *International clinical psychopharmacology* 2005;20:227-31.
40. Serfaty M, Kennell-Webb S, Warner J, Blizard R, Raven P Double blind randomised placebo controlled trial of low dose melatonin for sleep disorders in dementia. *International journal of geriatric psychiatry* 2002;17:1120-7.
41. Riemersma-van der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJ, Van Someren EJ Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *JAMA : the journal of the American Medical Association* 2008;299:2642-55.
42. Wright B, Sims D, Smart S et al. Melatonin versus placebo in children with autism spectrum conditions and severe sleep problems not amenable to behaviour management strategies: a randomised controlled crossover trial. *Journal of autism and developmental disorders* 2011;41:175-84.
43. Sack RL, Auckley D, Auger RR et al. Circadian rhythm sleep disorders: part I, basic principles, shift work and jet lag disorders. An American Academy of Sleep Medicine review. *Sleep* 2007;30:1460-83.
44. Medicine AAoS. International Classification of Sleep Disorders. Westchester, Illinois: American Academy of Sleep medicine, 2005.
45. Medicine AAoS. International Classification of Sleep Disorders. Darien, IL: American Academy of Sleep Medicine, 2014.
46. Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP Light suppresses melatonin secretion in humans. *Science* 1980;210:1267-9.
47. St Hilaire MA, Gooley JJ, Khalsa SB, Kronauer RE, Czeisler CA, Lockley SW Human phase response curve to a 1 h pulse of bright white light. *The Journal of physiology* 2012;590:3035-45.
48. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *The Journal of physiology* 2000;526 Pt 3:695-702.
49. Chang AM, Santhi N, St Hilaire M et al. Human responses to bright light of different durations. *The Journal of physiology* 2012;590:3103-12.

DRAFT

50. Hebert M, Martin SK, Lee C, Eastman CI The effects of prior light history on the suppression of melatonin by light in humans. *Journal of pineal research* 2002;33:198-203.
51. Chang AM, Scheer FA, Czeisler CA The human circadian system adapts to prior photic history. *The Journal of physiology* 2011;589:1095-102.
52. Buxton OM, L'Hermite-Baleriaux M, Turek FW, van Cauter E Daytime naps in darkness phase shift the human circadian rhythms of melatonin and thyrotropin secretion. *American journal of physiology. Regulatory, integrative and comparative physiology* 2000;278:R373-82.
53. Burgess HJ, Molina TA Home lighting before usual bedtime impacts circadian timing: a field study. *Photochemistry and photobiology* 2014;90:723-6.
54. Thapan K, Arendt J, Skene DJ An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. *The Journal of physiology* 2001;535:261-7.
55. Brainard GC, Hanifin JP, Greeson JM et al. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2001;21:6405-12.
56. Smith MR, Eastman CI Phase delaying the human circadian clock with blue-enriched polychromatic light. *Chronobiology international* 2009;26:709-25.
57. Smith MR, Revell VL, Eastman CI Phase advancing the human circadian clock with blue-enriched polychromatic light. *Sleep medicine* 2009;10:287-94.
58. Tuunainen A, Kripke DF, Endo T Light therapy for non-seasonal depression. *The Cochrane database of systematic reviews* 2004:CD004050.
59. Dauphinais DR, Rosenthal JZ, Terman M, DiFebo HM, Tuggle C, Rosenthal NE Controlled trial of safety and efficacy of bright light therapy vs. negative air ions in patients with bipolar depression. *Psychiatry research* 2012;196:57-61.
60. Terman M, Terman JS Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. *CNS spectrums* 2005;10:647-63; quiz 72.
61. Ulrich V, Olesen J, Gervil M, Russell MB Possible risk factors and precipitants for migraine with aura in discordant twin-pairs: a population-based study. *Cephalalgia : an international journal of headache* 2000;20:821-5.
62. Gallin PF, Terman M, Reme CE, Rafferty B, Terman JS, Burde RM Ophthalmologic examination of patients with seasonal affective disorder, before and after bright light therapy. *American journal of ophthalmology* 1995;119:202-10.
63. Reme CE, Rol P, Grothmann K, Kaase H, Terman M Bright light therapy in focus: lamp emission spectra and ocular safety. *Technology and health care : official journal of the European Society for Engineering and Medicine* 1996;4:403-13.
64. Ferracioli-Oda E, Qawasmi A, Bloch MH Meta-analysis: melatonin for the treatment of primary sleep disorders. *PloS one* 2013;8:e63773.
65. Herxheimer A, Petrie KJ Melatonin for the prevention and treatment of jet lag. *The Cochrane database of systematic reviews* 2002:CD001520.

DRAFT

66. Spadoni G, Bedini A, Rivara S, Mor M Melatonin receptor agonists: new options for insomnia and depression treatment. *CNS neuroscience & therapeutics* 2011;17:733-41.
67. Committee on the Framework for Evaluating the Safety of the Dietary Supplements FaNB, Board on Life Sciences, Institute of Medicine and national Research Council of the National Academies. Dietary Supplements: A Framework for Evaluating safety. Washington, DC: The National Academies Press, 2005.
68. Buscemi N, Vandermeer B, Hooton N et al. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. *Journal of general internal medicine* 2005;20:1151-8.
69. Werneke U, Turner T, Priebe S Complementary medicines in psychiatry: review of effectiveness and safety. *The British journal of psychiatry : the journal of mental science* 2006;188:109-21.
70. Seabra ML, Bignotto M, Pinto LR, Jr., Tufik S Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment. *Journal of pineal research* 2000;29:193-200.
71. Hoebert M, van der Heijden KB, van Geijlswijk IM, Smits MG Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. *Journal of pineal research* 2009;47:1-7.
72. Wasdell MB, Jan JE, Bomben MM et al. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. *Journal of pineal research* 2008;44:57-64.
73. Carr R, Wasdell MB, Hamilton D et al. Long-term effectiveness outcome of melatonin therapy in children with treatment-resistant circadian rhythm sleep disorders. *Journal of pineal research* 2007;43:351-9.
74. Valcavi R, Zini M, Maestroni GJ, Conti A, Portioli I Melatonin stimulates growth hormone secretion through pathways other than the growth hormone-releasing hormone. *Clinical endocrinology* 1993;39:193-9.
75. Luboshitzky R, Shen-Orr Z, Nave R, Lavi S, Lavie P Melatonin administration alters semen quality in healthy men. *Journal of andrology* 2002;23:572-8.
76. van Geijlswijk IM, Mol RH, Egberts TC, Smits MG Evaluation of sleep, puberty and mental health in children with long-term melatonin treatment for chronic idiopathic childhood sleep onset insomnia. *Psychopharmacology* 2011;216:111-20.
77. Ilomaki J, Paljarvi T, Korhonen MJ et al. Prevalence of concomitant use of alcohol and sedative-hypnotic drugs in middle and older aged persons: a systematic review. *The Annals of pharmacotherapy* 2013;47:257-68.
78. Buscemi N, Vandermeer B, Friesen C et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *Journal of general internal medicine* 2007;22:1335-50.
79. Peron EP, Gray SL, Hanlon JT Medication use and functional status decline in older adults: a narrative review. *The American journal of geriatric pharmacotherapy* 2011;9:378-91.

80. Woolcott JC, Richardson KJ, Wiens MO et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Archives of internal medicine* 2009;169:1952-60.
81. Bakken MS, Engeland A, Engesaeter LB, Ranhoff AH, Hunskaar S, Ruths S Risk of hip fracture among older people using anxiolytic and hypnotic drugs: a nationwide prospective cohort study. *European journal of clinical pharmacology* 2014;70:873-80.
82. Deschenes CL, McCurry SM Current treatments for sleep disturbances in individuals with dementia. *Current psychiatry reports* 2009;11:20-6.
83. Sateia MJ, Kirby-Long P, Taylor JL Efficacy and clinical safety of ramelteon: an evidence-based review. *Sleep medicine reviews* 2008;12:319-32.
84. Hajak G, Muller WE, Wittchen HU, Pittrow D, Kirch W Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addiction* 2003;98:1371-8.
85. James SP, Mendelson WB The use of trazodone as a hypnotic: a critical review. *The Journal of clinical psychiatry* 2004;65:752-5.
86. Stone M. Mortality and antipsychotic drug use in dementia-related behavioral disorders. In: Editor, ed.^eds. Mortality and antipsychotic drug use in dementia-related behavioral disorders. . City, 2005.
87. Moldofsky H, Musisi S, Phillipson EA Treatment of a case of advanced sleep phase syndrome by phase advance chronotherapy. *Sleep* 1986;9:61-5.
88. Suhner AG, Murphy PJ, Campbell SS Failure of timed bright light exposure to alleviate age-related sleep maintenance insomnia. *Journal of the American Geriatrics Society* 2002;50:617-23.
89. Pallesen S, Nordhus IH, Skelton SH, Bjorvatn B, Skjerve A Bright light treatment has limited effect in subjects over 55 years with mild early morning awakening. *Perceptual and motor skills* 2005;101:759-70.
90. Lack L, Wright H, Kemp K, Gibbon S The treatment of early-morning awakening insomnia with 2 evenings of bright light. *Sleep* 2005;28:616-23.
91. Lack L, Wright H The effect of evening bright light in delaying the circadian rhythms and lengthening the sleep of early morning awakening insomniacs. *Sleep* 1993;16:436-43.
92. Munch M, Scheuermaier KD, Zhang R et al. Effects on subjective and objective alertness and sleep in response to evening light exposure in older subjects. *Behavioural brain research* 2011;224:272-8.
93. Ito A, Ando K, Hayakawa T et al. Long-term course of adult patients with delayed sleep phase syndrome. *The Japanese journal of psychiatry and neurology* 1993;47:563-7.
94. Czeisler CA, Richardson GS, Coleman RM et al. Chronotherapy: resetting the circadian clocks of patients with delayed sleep phase insomnia. *Sleep* 1981;4:1-21.
95. Sharkey KM, Carskadon MA, Figueiro MG, Zhu Y, Rea MS Effects of an advanced sleep schedule and morning short wavelength light exposure on circadian phase in young adults with late sleep schedules. *Sleep medicine* 2011;12:685-92.

96. Iwamitsu Y, Ozeki, Y., Konishi, M., Murakami, J., Kimura, S., Okawa, M. Psychological characteristics and the efiicacy of hospitalization treatment on delayed sleep phase syndrome patients with school refusal. *Sleep and Biological Rhythms, 2007, 5, 15-22* 2007;5:15-22.
97. de Sousa IC, Araújo, I.C., de Azevedo, C.V.M. The effect of a sleep hygiene education program on the sleep-wake cycle of Brazilian adolescent students. *Sleep and Biological Rhythms* 2007;5:251-58.
98. Fargason RE, Preston, T., Hammond, E., May, R., Gamble, K.L. Treatment of attention deficit hyperactivity disorder insomnia with blue wavelength light-blocking glasses. *ChronoPhysiology and Therapy* 2013:1-8.
99. Burkhart K, Phelps JR Amber lenses to block blue light and improve sleep: a randomized trial. *Chronobiology international* 2009;26:1602-12.
100. Rosenthal NE, Joseph-Vanderpool JR, Levendosky AA et al. Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. *Sleep* 1990;13:354-61.
101. Watanabe T, Kajimura N, Kato M, Sekimoto M, Takahashi K Effects of phototherapy in patients with delayed sleep phase syndrome. *Psychiatry and clinical neurosciences* 1999;53:231-3.
102. Lack L, Bramwell, T., Wright, H., Kemp, K. Morning blue light can advance the melatonin rhythm in mild
delayed sleep phase syndrome. *Sleep and Biological Rhythms* 2007:78-80.
103. Ohta T, Iwata T, Kayukawa Y, Okada T Daily activity and persistent sleep-wake schedule disorders. *Progress in neuro-psychopharmacology & biological psychiatry* 1992;16:529-37.
104. Mizuma H, Miyahara, Y., Sakamoto, T., Kotorii, T., Nakazawa, Y. Two cases of delayed sleep phase syndrome (DSPS). *Japanese Journal of Psychiatry ans Neurology* 1991;45:163-64.
105. Yamadera H, Takahashi K, Okawa M A multicenter study of sleep-wake rhythm disorders: therapeutic effects of vitamin B12, bright light therapy, chronotherapy and hypnotics. *Psychiatry and clinical neurosciences* 1996;50:203-9.
106. Walsh JK, Deacon S, Dijk DJ, Lundahl J The selective extrasynaptic GABAA agonist, gaboxadol, improves traditional hypnotic efficacy measures and enhances slow wave activity in a model of transient insomnia. *Sleep* 2007;30:593-602.
107. Dahlitz M, Alvarez B, Vignau J, English J, Arendt J, Parkes JD Delayed sleep phase syndrome response to melatonin. *Lancet* 1991;337:1121-4.
108. Dagan Y, Yovel I, Hallis D, Eisenstein M, Raichik I Evaluating the role of melatonin in the long-term treatment of delayed sleep phase syndrome (DSPS). *Chronobiology international* 1998;15:181-90.
109. Okawa M, Takahashi K, Egashira K et al. Vitamin B12 treatment for delayed sleep phase syndrome: a multi-center double-blind study. *Psychiatry and clinical neurosciences* 1997;51:275-9.
110. Bjorvatn B, Pallesen S A practical approach to circadian rhythm sleep disorders. *Sleep medicine reviews* 2009;13:47-60.
111. Figueiro MG, Rea MS Preliminary evidence that light through the eyelids can suppress melatonin and phase shift dim light melatonin onset. *BMC research notes* 2012;5:221.

DRAFT

112. Revell VL, Burgess HJ, Gazda CJ, Smith MR, Fogg LF, Eastman CI Advancing human circadian rhythms with afternoon melatonin and morning intermittent bright light. *The Journal of clinical endocrinology and metabolism* 2006;91:54-9.
113. Burke TM, Markwald RR, Chinoy ED et al. Combination of light and melatonin time cues for phase advancing the human circadian clock. *Sleep* 2013;36:1617-24.
114. Paul MA, Gray GW, Lieberman HR et al. Phase advance with separate and combined melatonin and light treatment. *Psychopharmacology* 2011;214:515-23.
115. Samaranayake CB, Fernando, A., Warman, G. Otcome of combined melatonin and bright light treatments for delayed sleep phase disorder. *The Royal Aust NZ J Psychiatry* 2010;44:676.
116. Sack RL, Lewy AJ, Blood ML, Keith LD, Nakagawa H Circadian rhythm abnormalities in totally blind people: incidence and clinical significance. *The Journal of clinical endocrinology and metabolism* 1992;75:127-34.
117. Czeisler CA, Shanahan TL, Klerman EB et al. Suppression of melatonin secretion in some blind patients by exposure to bright light. *The New England journal of medicine* 1995;332:6-11.
118. Danilenko KV, Cajochen C, Wirz-Justice A Is sleep per se a zeitgeber in humans? *Journal of biological rhythms* 2003;18:170-8.
119. Gordijn MC, Beersma DG, Korte HJ, van den Hoofdakker RH Effects of light exposure and sleep displacement on dim light melatonin onset. *Journal of sleep research* 1999;8:163-74.
120. Hoban TM, Lewy AJ, Sack RL, Singer CM The effects of shifting sleep two hours within a fixed photoperiod. *Journal of neural transmission. General section* 1991;85:61-8.
121. Buxton OM, Lee CW, L'Hermite-Baleriaux M, Turek FW, Van Cauter E Exercise elicits phase shifts and acute alterations of melatonin that vary with circadian phase. *American journal of physiology. Regulatory, integrative and comparative physiology* 2003;284:R714-24.
122. Klerman EB, Rimmer DW, Dijk DJ, Kronauer RE, Rizzo JF, 3rd, Czeisler CA Nonphotic entrainment of the human circadian pacemaker. *The American journal of physiology* 1998;274:R991-6.
123. Oren DA, Giesen HA, Wehr TA Restoration of detectable melatonin after entrainment to a 24-hour schedule in a 'free-running' man. *Psychoneuroendocrinology* 1997;22:39-52.
124. Hoban TM, Sack RL, Lewy AJ, Miller LS, Singer CM Entrainment of a free-running human with bright light? *Chronobiology international* 1989;6:347-53.
125. Watanabe T, Kajimura N, Kato M, Sekimoto M, Hori T, Takahashi K Case of a non-24 h sleep-wake syndrome patient improved by phototherapy. *Psychiatry and clinical neurosciences* 2000;54:369-70.
126. Okawa M, Uchiyama M, Ozaki S et al. Melatonin treatment for circadian rhythm sleep disorders. *Psychiatry and clinical neurosciences* 1998;52:259-60.
127. Hayakawa T, Kamei Y, Urata J et al. Trials of bright light exposure and melatonin administration in a patient with non-24 hour sleep-wake syndrome. *Psychiatry and clinical neurosciences* 1998;52:261-2.

DRAFT

128. Klerman EB, Shanahan TL, Brotman DJ et al. Photic resetting of the human circadian pacemaker in the absence of conscious vision. *Journal of biological rhythms* 2002;17:548-55.
129. Arendt J, Aldhous M, Wright J Synchronisation of a disturbed sleep-wake cycle in a blind man by melatonin treatment. *Lancet* 1988;1:772-3.
130. Folkard S, Arendt J, Aldhous M, Kennett H Melatonin stabilises sleep onset time in a blind man without entrainment of cortisol or temperature rhythms. *Neuroscience letters* 1990;113:193-8.
131. Lapierre O, Dumont M Melatonin treatment of a non-24-hour sleep-wake cycle in a blind retarded child. *Biological psychiatry* 1995;38:119-22.
132. Tzischinsky O, Pal I, Epstein R, Dagan Y, Lavie P The importance of timing in melatonin administration in a blind man. *Journal of pineal research* 1992;12:105-8.
133. Lewy AJ, Bauer VK, Hasler BP, Kendall AR, Pires ML, Sack RL Capturing the circadian rhythms of free-running blind people with 0.5 mg melatonin. *Brain research* 2001;918:96-100.
134. Lewy AJ, Hasler BP, Emens JS, Sack RL Pretreatment circadian period in free-running blind people may predict the phase angle of entrainment to melatonin. *Neuroscience letters* 2001;313:158-60.
135. Lewy AJ, Emens JS, Sack RL, Hasler BP, Bernert RA Low, but not high, doses of melatonin entrained a free-running blind person with a long circadian period. *Chronobiology international* 2002;19:649-58.
136. Lewy AJ, Emens JS, Lefler BJ, Yuhas K, Jackman AR Melatonin entrains free-running blind people according to a physiological dose-response curve. *Chronobiology international* 2005;22:1093-106.
137. Lewy AJ, Emens JS, Bernert RA, Lefler BJ Eventual entrainment of the human circadian pacemaker by melatonin is independent of the circadian phase of treatment initiation: clinical implications. *Journal of biological rhythms* 2004;19:68-75.
138. Siebler M, Steinmetz H, Freund HJ Therapeutic entrainment of circadian rhythm disorder by melatonin in a non-blind patient. *Journal of neurology* 1998;245:327-8.
139. Kamei Y, Hayakawa T, Urata J et al. Melatonin treatment for circadian rhythm sleep disorders. *Psychiatry and clinical neurosciences* 2000;54:381-2.
140. McArthur AJ, Lewy AJ, Sack RL Non-24-hour sleep-wake syndrome in a sighted man: circadian rhythm studies and efficacy of melatonin treatment. *Sleep* 1996;19:544-53.
141. Okawa M, Mishima K, Nanami T et al. Vitamin B12 treatment for sleep-wake rhythm disorders. *Sleep* 1990;13:15-23.
142. Ohta T, Ando K, Iwata T et al. Treatment of persistent sleep-wake schedule disorders in adolescents with methylcobalamin (vitamin B12). *Sleep* 1991;14:414-8.
143. Kamgar-Parsi B, Wehr TA, Gillin JC Successful treatment of human non-24-hour sleep-wake syndrome. *Sleep* 1983;6:257-64.

DRAFT

144. Sugita Y, Ishikawa, H., Mikami, A., Teshima, Y., Tsutsumi, T., Tachibana, N., Inatani, K., Uruha, S., Honda, H., Terashima, K., Egawa, I. Successful treatment for a patient with hypernychthermal syndrome. *Sleep Research* 1987:642.
145. Ancoli-Israel S, Gehrman P, Martin JL et al. Increased light exposure consolidates sleep and strengthens circadian rhythms in severe Alzheimer's disease patients. *Behavioral sleep medicine* 2003;1:22-36.
146. Ancoli-Israel S, Martin JL, Kripke DF, Marler M, Klauber MR Effect of light treatment on sleep and circadian rhythms in demented nursing home patients. *Journal of the American Geriatrics Society* 2002;50:282-9.
147. Dowling GA, Hubbard EM, Mastick J, Luxenberg JS, Burr RL, Van Someren EJ Effect of morning bright light treatment for rest-activity disruption in institutionalized patients with severe Alzheimer's disease. *International psychogeriatrics / IPA* 2005;17:221-36.
148. Van Someren EJ, Kessler A, Mirmiran M, Swaab DF Indirect bright light improves circadian rest-activity rhythm disturbances in demented patients. *Biological psychiatry* 1997;41:955-63.
149. Fetveit A, Skjerve A, Bjorvatn B Bright light treatment improves sleep in institutionalised elderly--an open trial. *International journal of geriatric psychiatry* 2003;18:520-6.
150. Satlin A, Volicer L, Ross V, Herz L, Campbell S Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. *The American journal of psychiatry* 1992;149:1028-32.
151. Singer C, Tractenberg RE, Kaye J et al. A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease. *Sleep* 2003;26:893-901.
152. Pillar G, Shahar E, Peled N, Ravid S, Lavie P, Etzioni A Melatonin improves sleep-wake patterns in psychomotor retarded children. *Pediatric neurology* 2000;23:225-8.
153. Jan JE, Espezel H, Appleton RE The treatment of sleep disorders with melatonin. *Developmental medicine and child neurology* 1994;36:97-107.
154. Jan JE, Hamilton D, Seward N, Fast DK, Freeman RD, Laudon M Clinical trials of controlled-release melatonin in children with sleep-wake cycle disorders. *Journal of pineal research* 2000;29:34-9.
155. McArthur AJ, Budden SS Sleep dysfunction in Rett syndrome: a trial of exogenous melatonin treatment. *Developmental medicine and child neurology* 1998;40:186-92.
156. McCurry SM, Gibbons LE, Logsdon RG, Vitiello MV, Teri L Nighttime insomnia treatment and education for Alzheimer's disease: a randomized, controlled trial. *Journal of the American Geriatrics Society* 2005;53:793-802.
157. Alessi CA, Martin JL, Webber AP, Cynthia Kim E, Harker JO, Josephson KR Randomized, controlled trial of a nonpharmacological intervention to improve abnormal sleep/wake patterns in nursing home residents. *Journal of the American Geriatrics Society* 2005;53:803-10.
158. McCurry SM, Pike KC, Vitiello MV, Logsdon RG, Larson EB, Teri L Increasing walking and bright light exposure to improve sleep in community-dwelling persons with Alzheimer's disease: results of a randomized, controlled trial. *Journal of the American Geriatrics Society* 2011;59:1393-402.

DRAFT

159. Martin JL, Marler MR, Harker JO, Josephson KR, Alessi CA A multicomponent nonpharmacological intervention improves activity rhythms among nursing home residents with disrupted sleep/wake patterns. *The journals of gerontology. Series A, Biological sciences and medical sciences* 2007;62:67-72.
160. Guilleminault C, McCann CC, Quera-Salva M, Cetel M Light therapy as treatment of dyschronosis in brain impaired children. *European journal of pediatrics* 1993;152:754-9.
161. Auger RR Advance-Related Sleep Complaints and Advanced Sleep Phase Disorder. *Sleep Medicine Clinics* 2009;4:219-27.
162. Fromm E, Horlebein, C., Meergans, A., Niesner, M., Randler, C. Evaluation of a dawn simulator in children and adolescents. *Biological Rhythm Research* 2011;42:417-25.
163. Higuchi S, Motohashi Y, Ishibashi K, Maeda T Less exposure to daily ambient light in winter increases sensitivity of melatonin to light suppression. *Chronobiology international* 2007;24:31-43.
164. Braam W, van Geijlswijk I, Keijzer H, Smits MG, Didden R, Curfs LM Loss of response to melatonin treatment is associated with slow melatonin metabolism. *Journal of intellectual disability research : JIDR* 2010;54:547-55.
165. Richardson GS, Zee PC, Wang-Weigand S, Rodriguez L, Peng X Circadian phase-shifting effects of repeated ramelteon administration in healthy adults. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2008;4:456-61.
166. Rajaratnam SM, Polymeropoulos MH, Fisher DM et al. Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials. *Lancet* 2009;373:482-91.
167. Burgess HJ, Revell VL, Molina TA, Eastman CI Human phase response curves to three days of daily melatonin: 0.5 mg versus 3.0 mg. *The Journal of clinical endocrinology and metabolism* 2010;95:3325-31.
168. Shibui K, Uchiyama M, Okawa M Melatonin rhythms in delayed sleep phase syndrome. *Journal of biological rhythms* 1999;14:72-6.
169. Ozaki S, Uchiyama M, Shirakawa S, Okawa M Prolonged interval from body temperature nadir to sleep offset in patients with delayed sleep phase syndrome. *Sleep* 1996;19:36-40.
170. Watanabe T, Kajimura N, Kato M et al. Sleep and circadian rhythm disturbances in patients with delayed sleep phase syndrome. *Sleep* 2003;26:657-61.
171. Uchiyama M, Okawa M, Shibui K et al. Altered phase relation between sleep timing and core body temperature rhythm in delayed sleep phase syndrome and non-24-hour sleep-wake syndrome in humans. *Neuroscience letters* 2000;294:101-4.
172. Wyatt JK, Stepanski EJ, Kirkby J Circadian phase in delayed sleep phase syndrome: predictors and temporal stability across multiple assessments. *Sleep* 2006;29:1075-80.
173. Chang AM, Reid KJ, Gourineni R, Zee PC Sleep timing and circadian phase in delayed sleep phase syndrome. *Journal of biological rhythms* 2009;24:313-21.
174. Jenni OG, Achermann P, Carskadon MA Homeostatic sleep regulation in adolescents. *Sleep* 2005;28:1446-54.

DRAFT

175. Uchiyama M, Okawa M, Shibui K et al. Poor compensatory function for sleep loss as a pathogenic factor in patients with delayed sleep phase syndrome. *Sleep* 2000;23:553-8.
176. Asaoka A, Fukuda, K., Tsutsui, Y., Yamazaki, K. Does television viewing cause delayed and/or irregularsleep–wake patterns? *Sleep and Biological Rhythms* 2007;5:23-27.
177. Crowley SJ, Acebo C, Carskadon MA Sleep, circadian rhythms, and delayed phase in adolescence. *Sleep medicine* 2007;8:602-12.
178. Carskadon MA Patterns of sleep and sleepiness in adolescents. *Pediatrician* 1990;17:5-12.
179. Wyatt JK Delayed sleep phase syndrome: pathophysiology and treatment options. *Sleep* 2004;27:1195-203.
180. Peixoto CA, da Silva AG, Carskadon MA, Louzada FM Adolescents living in homes without electric lighting have earlier sleep times. *Behavioral sleep medicine* 2009;7:73-80.
181. Vollmer C, Michel U, Randler C Outdoor light at night (LAN) is correlated with eveningness in adolescents. *Chronobiology international* 2012;29:502-8.
182. Cajochen C, Frey S, Anders D et al. Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance. *Journal of applied physiology* 2011;110:1432-8.
183. Figueiro MG, Rea MS Evening daylight may cause adolescents to sleep less in spring than in winter. *Chronobiology international* 2010;27:1242-58.
184. Taylor A, Wright, H. R., Lack, L.C. Sleeping-in on the weekend delays circadian phase and increases sleepiness the following week. *Slep and Biological Rhythms* 2008;6:172-79.
185. Burgess HJ, Eastman CI A late wake time phase delays the human dim light melatonin rhythm. *Neuroscience letters* 2006;395:191-5.
186. Crowley SJ, Carskadon MA Modifications to weekend recovery sleep delay circadian phase in older adolescents. *Chronobiology international* 2010;27:1469-92.
187. Auger RR, Burgess HJ, Dierkhising RA, Sharma RG, Slocumb NL Light exposure among adolescents with delayed sleep phase disorder: a prospective cohort study. *Chronobiology international* 2011;28:911-20.
188. Figueiro MG, Rea MS Lack of short-wavelength light during the school day delays dim light melatonin onset (DLMO) in middle school students. *Neuro endocrinology letters* 2010;31:92-6.
189. Dagan Y, Abadi J Sleep-wake schedule disorder disability: a lifelong untreatable pathology of the circadian time structure. *Chronobiology international* 2001;18:1019-27.
190. Miller NL, Tvaryanas AP, Shattuck LG Accommodating adolescent sleep-wake patterns: the effects of shifting the timing of sleep on training effectiveness. *Sleep* 2012;35:1123-36.
191. (2006) NSF. 2006 Sleep in America Poll Summary Findings In: Editor, ed.^eds. 2006 Sleep in America Poll Summary Findings. City, 2006.
192. Wahlstrom K Changing times: findings from the first longitudinal study of later school start times. . *NAASP Bulletin* 2002;86:3-21.

DRAFT

193. Danner F, Phillips B Adolescent sleep, school start times, and teen motor vehicle crashes. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2008;4:533-5.
194. Owens JA, Belon K, Moss P Impact of delaying school start time on adolescent sleep, mood, and behavior. *Archives of pediatrics & adolescent medicine* 2010;164:608-14.

DRAFT