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.

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.

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

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).

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

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**.

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**).

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.

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.

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

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.

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.

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

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

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.

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.

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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