

Management of Shift Work Disorder

an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment.

INTRODUCTION

This systematic review is intended to provide supporting evidence for a clinical practice guideline on the treatment of shiftwork disorder (SWD), and update the evidence review conducted for the previously published American Academy of Sleep Medicine (AASM) guidelines. Primary critical outcomes examined include excessive sleepiness/alertness, accident risk, sleep quality, and cognitive performance/work performance. Secondary important outcomes examined include circadian alignment, quality of life, mental health, sleep outcomes other than quality (sleep latency, total sleep time, sleep efficiency, wakefulness after sleep onset), as well as disease severity.

BACKGROUND

In our current society, shift work is a common phenomenon, whether out of necessity in fields such as healthcare, transportation, and public safety, or for economic reasons in manufacturing and consumer businesses. Shift work can be defined broadly as being required to regularly work during times when an individual would normally be sleeping. Shift work schedules can range from requirements to work fixed early morning, evening or overnight shifts or can consist of a schedule of rotating, split or irregular shifts. Based on those definitions, according to the US Bureau of Labor Statistics, approximately 16% of the US work force is engaged in shift work with some occupations having more than 33% engaged in shift work¹. As a result of working on a shift work schedule, individuals can develop symptoms of insomnia from attempting to sleep when due to their circadian biology they would normally be awake and/or symptoms of excessive sleepiness from working during times they would normally be sleeping. To be diagnosed with shift work disorder (SWD), an individual must have clinically meaningful symptoms associated with working a shift work schedule that have been present for at least 3 months. It is important to note that not all individuals who engage in shift work develop symptoms of SWD. A recent meta-analysis determined the overall prevalence of SWD among shift workers to be ~26.5%, but with a range of 2.3% to 84% depending on the study². Not all individuals with SWD will experience the same constellation of symptoms. As such, the International Classification of Sleep Disorders³ has proposed three distinct phenotypes of SWD: 1) insomnia 2) sleepy and 3) mixed. When determining the appropriate treatments for a patient with SWD, it is important to evaluate which symptoms a patient is experiencing, as not all treatments recommended will be appropriate for all patients.

In addition to symptoms of insomnia and sleepiness, leading to impairment in cognitive and work performance and safety, there are also health consequences associated with shift work and SWD, stemming primarily from a combination of insufficient sleep (i.e., <7 hours per 24 hour day³) and circadian misalignment (e.g., wakefulness, food intake, and activity occurring when the endogenous circadian system is promoting sleep and sleep occurring when the endogenous circadian system is promoting wakefulness^{4,5}). Whether from difficulty sleeping, or from competing demands of nighttime work and daytime familial or social responsibilities, shift workers experience an average weekly reduction in total sleep time of 10 hours or more. Even when on a fixed shift schedule, individuals engaged in shift work often do not align their circadian system with the shift work schedule⁶, with alignment being a near impossible goal while on rotating shifts. As a result, shift workers may be in a state of circadian misalignment with the environment (wakefulness occurring during the solar night and sleep occurring during the solar day), as well as in a state of internal circadian misalignment between components of the internal circadian system, resulting in symptoms that extend beyond difficulties with sleep and alertness.

The daily production of melatonin occurs with a circadian rhythm and represents the timing of the brain's endogenous master circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus. For a day worker, melatonin levels typically increase in the evening before bedtime, representing the beginning of the biological night, and levels typically decrease in the morning after waketime⁷, representing the beginning of the biological day. Exposure to light at night can acutely reduce melatonin levels as well as shift the timing of the circadian rhythm of melatonin^{8,9}. The melatonin rhythm in some night shift workers remains similarly timed to that of day workers (i.e., high levels at night), whereas in others the melatonin rhythm is shifted/timed earlier or later⁵. In humans, the rise of melatonin levels is a circadian signal to prepare for sleep and associated functions that occur preferentially during the biological night. High melatonin levels are incompatible with behaviors associated with shift work schedules such as wakefulness, food intake, and being physically active. The endogenous circadian system also includes local clocks in brain and body tissues outside of the SCN^{10,11,12,13,14,15}. These local clocks are important components of the internal circadian system that time cellular and tissue physiology to prepare the body for time-of-day relevant behaviors and environmental exposures (e.g., metabolic tissues are prepared for nutrient intake, cardiovascular and neuromuscular systems are prepared for physical activity, the immune system is prepared for exposure to pathogens).

Shift work is associated with an increased risk for adverse health outcomes, including cardiovascular disease, diabetes, hypertension, obesity, gastrointestinal disease, depression, negative reproductive outcomes, and cancer^{16,17,18,19,20,21,22,23}. For example, findings from several large cohort studies have demonstrated that exposure to shift work is associated with increased risk for the development of cancer, leading to the International Agency for Research on Cancer to declare it a probable carcinogen in 2007. These adverse health effects are thought to be due to a combination of the impact of sleep disruption, circadian misalignment, and internal circadian desynchrony (i.e., misalignment among internal circadian clocks). Patients with SWD often have a higher medical burden than shift workers without SWD^{24,25,26,27,28}.

Based on the available evidence, the current treatment guidelines focus primarily on the impact of treatments on the more acute outcomes of excessive sleepiness/alertness, accident risk, sleep quality, and cognitive performance/work performance. Future studies are needed to address the impact of interventions for shift work and SWD on well-being and the long-term health consequences of shift work exposure.

METHODOLOGY

Expert Task Force

The AASM commissioned a task force (TF) of sleep and circadian medicine researchers and clinicians with expertise in circadian rhythm disorders and shift work, and the treatment of SWD, along with guideline methodologists. The TF was required to disclose all potential conflicts of interest (COI), per the AASM's COI policy, prior to being appointed to the TF and throughout the research and writing of these documents. In accordance with the AASM's conflicts of interest policy, TF members with a Level 1 conflict were not allowed to participate. TF members with a Level 2 conflict were required to recuse themselves from any related discussion or writing responsibilities. All relevant conflicts of interest are listed in the Disclosures section.

Patient, Intervention, Comparison, and Outcomes (PICO) Questions

PICO questions were developed by the TF based on a review of the existing AASM practice parameters on the Clinical Evaluation and Treatment of CRSWDs and a review of systematic reviews, meta-analyses, and guidelines published since 2007. The AASM Board of Directors approved the final list of questions presented in **Table 1** before the literature searches were performed. Through consensus, the TF then developed a list of patient-oriented, clinically relevant outcomes to determine the efficacy of the interventions. Input on interventions, outcomes, and

adverse events from interest holders (formerly known as stakeholders, e.g., patients, caregivers, and health care providers) was collected using electronic surveys. The TF rated the relative importance of each outcome to determine which outcomes were critical versus important for decision-making. A summary of these outcomes by PICO is presented in **Table 2**.

The TF set a clinically meaningful threshold (CMT) for outcome measures to determine whether the mean differences between treatment and control or the mean differences between before and after treatment were clinically meaningful. The CMT was defined as the minimum level of improvement in the outcome of interest that would be considered clinically important to clinicians and patients. CMTs were determined based on a TF literature review of commonly used thresholds. When no clearly established threshold values were available, the TF used their clinical judgment and experience to establish a CMT based on consensus; yet CMTs were not determined for all outcomes as some outcomes were not used clinically and/or were not used widely in research. A summary of the CMTs for the clinical outcome measures is presented in **Table 3**.

Table 1 - PICO Questions

1	POPULATION: Adults with Shift Work Disorder (Patients with SWD, no diagnosis, healthy participants) INTERVENTION: - planned sleep schedules/naps - timed light and or dark exposure - timed melatonin/melatonin agonist administration or other chronobiotic administration - sleep promoting medications (e.g., benzodiazepines, benzodiazepine receptor agonists), or substances; stimulant medications/wake promoting medications, or substances - caffeine - timed physical activity/exercise - diet and meal timing - combination treatments - CBT-I or sleep hygiene - planned work schedule (shifts $\leq$ 12 hours) COMPARISON: Placebo, usual care, baseline other intervention, or no treatment OUTCOMES: Excessive sleepiness/alertness, accident risk, sleep quality, and cognitive performance/work performance, circadian adaptation
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Table 2 – Summary of Clinically Meaningful Thresholds for Outcome Measures

Outcome Measure	Clinically Meaningful Threshold*†
Excessive sleepiness/Alertness (Critical outcomes)	
Karolinska Sleepiness Scale (KSS)	-1 point
Stanford Sleepiness Scale (SSS)	-1 point
Epworth Sleepiness Scale (ESS)	-2 points
Maintenance of Wakefulness Test (MWT)	+2 minutes
Repeated Test of Sustained Wakefulness (RTSW)	+2 minutes
Multiple Sleep Latency Test (MSLT)	+1 minute
Visual Analogue Scale (VAS)	No CMT
Clinical Global Impression of Change (CGI-C)	-1 point
Fatigue rating scale	No CMT

Johns Drowsiness Scale	No CMT
Seven-point scale	No CMT
Electroencephalography (EEG), alpha/beta/theta power	No CMT
Samn-Perelli Fatigue Scale	No CMT
Correct responses during Bakan Vigilance Task	No CMT
Morning questionnaire	No CMT
Accident Risk (Critical outcomes)	
Standard deviation of lane position	Any improvement
Steering wheel movements	Any improvement
Injury rates	Any improvement
Inappropriate lane crossings	Any improvement
Off road deviations	Any improvement
Accidents, near misses	Any improvement
Time spent in safe zone	Any improvement
Average number and size of steering wheel movements	Any improvement
Medical Errors	Any improvement
Visual Analogue Scale (VAS; difficulty driving home)	Any improvement
Sleep quality (Critical outcomes)	
Pittsburgh Sleep Quality Index (PSQI)	-3 points
Sleep Diary	+10%
Visual Analog Scale (VAS)	No CMT
Sleep quality index	No CMT
Sleep Sufficiency Index (SSI)	No CMT
Actigraphy	No CMT
General Sleep Disturbance Scale (GSDS; Sleep Quality)	-10%
9-point scale	No CMT
Post-Sleep Questionnaire	No CMT
Shift Work Survey Questionnaire	No CMT
World Health Organization Quality of Life Brief Version (WHOQOL-BREF)	No CMT
Cognitive/ Work Performance (Critical outcomes)	
Psychomotor Vigilance Task (PVT) Lapses	-1 lapse
Other performance tests**	No CMT
Sleep latency (Important outcomes)	
Sleep Diary/subjective reporting	-20 minutes
Polysomnography (PSG)/ Electroencephalography (EEG)	-20 minutes
Actigraphy	-15 minutes
Wakefulness After Sleep Onset (WASO) (Important outcomes)	
Sleep Diary/subjective reporting	-20 minutes
Polysomnography (PSG)/ Electroencephalography (EEG)	-20 minutes
Actigraphy	-20 minutes
Total Sleep Time (Important outcomes)	

Sleep Diary/subjective reporting	+15 minutes
Polysomnography (PSG)/ Electroencephalography (EEG)	+15 minutes
Actigraphy	+15 minutes
Sleep Efficiency (Important outcomes)	
Sleep Diary/subjective reporting	10%
Polysomnography (PSG)/ Electroencephalography (EEG)	10%
Actigraphy	10%
Circadian Adaptation (Important outcomes)	
Melatonin phase shift (Dim Light Melatonin Onset [DLMO] phase shift, Midpoint of the Melatonin Secretion Episode [MMSE], MEL25%up phase shift, MEL25%down phase shift, Midpoint Melatonin Secretion, 6-Sulfatoxymelatonin (aMT6s) phase shift, Melatonin [midpoint])).	No CMT
Body temperature phase shift. Core body temperature (tmin)	No CMT
Melatonin (phase angle)	No CMT
Core body temperature (phase angle)	No CMT
Overlap melatonin-sleep (hours)	No CMT
Quality of Life (Important outcomes)	
modified Sheehan Disability Scale	No CMT
Functional Outcomes of Sleep Questionnaire short version (FOSQ-10)	-1 point
Karolinska sleep diary	No CMT
The World Health Organization-Five Well-Being Index (WHO-5)	No CMT
RAND health survey Physical Component Summary (RAND-PCS)	No CMT
Mental Health (Important outcomes)	
Global Assessment of Functioning (GAF)	No CMT
Hospital Anxiety and Depression Scale (HADS)	No CMT
Scale for shift-work complaints	No CMT
Subjective questionnaire with seven-point scale	No CMT
General health questionnaire	No CMT
Stress scale	No CMT
Depression-like Mood	No CMT
Anxiety-like Mood	No CMT
Center for Epidemiologic Studies- Depression scale	No CMT
Standard Shiftwork Index (SSI): Anxiety	No CMT
Beck Depression Inventory (BDI)-II	-5 points
Montgomery-Åsberg Depression Rating Scale (MARDS)	No CMT
SCI-90: Global Index	No CMT
Profile of Mood States (POMS;tension/anxiety)	No CMT
Profile of Mood States (POMS; depression)	No CMT
Profile of Mood States (POMS ;anger)	No CMT
Center for Epidemiologic Studies Depression Scale	No CMT

(CES-D)	
General health questionnaire	No CMT
Disease Severity (Important outcomes)	
Clinical Global Impression Scale (CGI)	-1 point
Insomnia Severity Index (ISI)	-8 points
Adverse effects	
Number of adverse events	No CMT
Number of serious adverse events	No CMT
*References used to inform task force consensus **Complete list of cognitive performance tests can be found in the supplemental material † The clinical meaningful thresholds are for comparison of pre- versus post-treatment effects as well as between intervention and control.	

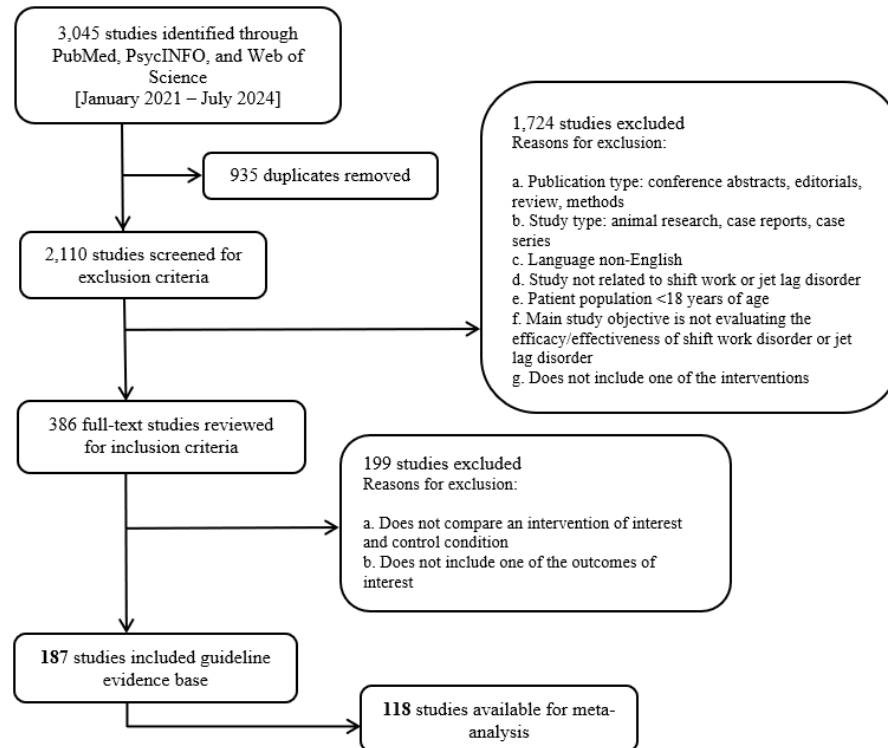
Literature Searches, Evidence Review and Data Extraction

The TF performed an extensive review of the scientific literature using PubMed, Web of Science, and PsycINFO databases (see **Figure 1**) to retrieve articles that addressed the PICO questions. Articles that met inclusion criteria but did not report outcomes of interest were rejected from the final evidence base. The key terms, search limits, and inclusion/exclusion criteria specified by the TF are detailed in the supplemental material.

The initial literature search was performed in January 2021. Subsequent literature searches were conducted in April 2023 and July 2024 to identify studies published since the initial search, updating the body of evidence for the review. These searches identified a total of 3,045 articles. Lastly, the TF reviewed previously published guidelines, systematic reviews, and meta-analyses to spot check for references that may have been missed during the prior searches.

The TF set inclusion and exclusion criteria, which are presented in the supplemental material. All studies were reviewed based on inclusion/exclusion criteria by two TF members. Any discrepancies between the reviewers were discussed and resolved by the two reviewers or a third TF member. A total of 118 studies were determined to be suitable for meta-analysis and/or grading.

Figure 1 – PRISMA DIAGRAM



Statistical and Meta-analysis and Interpretation of Clinical Meaningfulness

Meta-analysis was performed on outcomes of interest, when possible, for each PICO question (see **Table 1**). Comparisons of interventions to controls and/or assessment of efficacy before and after treatment of shiftwork disorder were performed. The analyses were performed using Review Manager 5.3 software by pooling data across studies for each outcome measure. Data was separated into three separate groups based on the patient population/participants studied. The first group included individuals with a formal diagnosis of SWD. The second group included studies with participants who were shift workers without a formal diagnosis of SWD. The final group included healthy participants who did not participate in shift work and were most often studied in a lab simulated shift work setting. Both the second and third groups were judged to provide indirect evidence as these individuals lacked the long-term symptoms seen in SWD. The evidence was further divided into lab and field subgroupings based on the setting in which the SWD or shift work participants were observed.

Clinical meaningfulness of treatments was determined by critical or important outcomes crossing the predetermined CMTs. Outcomes that did not meet the CMT are described by the magnitude and direction of change. As noted, reasons for not establishing CMTs for outcomes included the test not being used clinically and/or not being used widely in research. Further, for some outcomes used in research where there was no agreed upon threshold for clinical meaningfulness, the TF did not want to establish clinical cutoffs that could not be justified by current scientific evidence. Outcomes without a CMT are described by the magnitude and direction of change.

Post-treatment data from each arm were used for meta-analysis of Randomized Control Trials (RCTs) when change values were not reported and baseline values between the two study groups were statistically similar. Pre-and post-treatment data were used for meta-analyses of observational studies. The pooled results for each continuous outcome measure were usually expressed as the mean difference between the intervention and control for RCTs or pre-treatment versus post-treatment for observational studies; however, for some outcomes where individual component scales were pooled, a standardized mean difference (SMD) or effect size was determined. The pooled results for dichotomous outcome measures were expressed as the risk ratio or risk difference between the

intervention and comparator or pre- versus posttreatment. The relative risk data were converted to an absolute risk estimate expressed as the number of events/1000 patients treated. All analyses were performed using either a random effect model for pooled results or a fixed effect model for single studies, with results displayed as a forest plot. Interpretation of clinical meaningfulness for the outcomes of interest was conducted by comparing the mean difference in effect size, or the risk difference for dichotomous outcomes, of each treatment approach to the CMT (see **Table 3**)

GRADE Assessment for Developing Recommendations

The evidence was assessed according to the GRADE process for the purposes of making clinical practice recommendations. The TF considered the following four GRADE domains: quality of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use, as described below:

1. **Certainty of evidence:** Based on an assessment of the overall risk of bias (randomization, blinding, allocation concealment, selective reporting), imprecision (95% confidence interval crosses the CMT and/or sample size < 200 participants), inconsistency ($I^2 \geq 50\%$), indirectness (study population vs target patient population), and risk of publication bias, the TF determined their overall confidence that the estimated effect found in the body of evidence was representative of the true treatment effect that typical hospitalized patients with sleep-disordered breathing would see. The certainty of the evidence (CoE) was based on outcomes that the TF deemed critical for decision making; important outcomes were only considered when critical outcomes were limited or unavailable. Otherwise, important outcomes were not considered when determining the overall certainty of evidence.
2. **Benefits vs harms:** Based on the meta-analysis of adverse effects reported within the accepted literature and on the clinical expertise of the TF, the TF determined whether the beneficial outcomes of using each intervention outweighed any harms.
3. **Patient values and preferences:** Based on the clinical expertise of the TF members and any data published on the topic relevant to patient preferences, the TF determined if patient values and preferences would be generally consistent across most patients, and if patients would use the intervention based on the relative harms and benefits identified.
4. **Resource use:** Based on the clinical expertise of the TF members and any data published on the topic relevant to resource use, the TF determined whether the accessibility and costs associated with each intervention compared favorably to those associated with alternative interventions. Information on costs to both patients and the health care system, impact on health equity, acceptability and feasibility to implement the interventions were considered.

TF members voted on the strength and direction of each recommendation using the GRADE framework. A threshold of $\geq 70\%$ agreement was required to achieve consensus. Where consensus was not initially achieved, further discussion and re-voting were conducted until a decision was reached. A summary of each GRADE domain is provided after the detailed evidence review for each PICO question.

Public Comment and Final Approval

Drafts of the systematic review and accompanying guideline were made available for public comment for a four-week period on the AASM website. AASM members, the general public and other relevant interest holders were invited to provide feedback on the drafts. The TF also invited subject matter experts as external reviewers to provide additional feedback on the drafts. The TF took into consideration all the comments received and made decisions about whether to revise the draft based on the scope and feasibility of comments. The public comments and revised documents were submitted to the AASM Board of Directors who subsequently approved the final documents for publication. The AGREE II tool was used to assess the quality and rigor of the methodology used to develop the guideline and ensure the methodology is transparently described.

The AASM expects this systematic review to have an impact on professional behavior, patient outcomes, and, possibly, health care costs. This review reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available. The AASM reviews existing guidelines at least every 2 years. Updates to existing guidelines are based on advancements in the field of sleep medicine and the availability of scientific literature.

RESULTS

The aims of the current systematic reviews and data analyses were to address PICO questions pertaining to the treatment of excessive sleepiness and/or sleep disturbance/insomnia associated with SWD, and for circadian adaptation to shift work schedules. Primary critical outcomes examined include excessive sleepiness/alertness, accident risk, sleep quality, and cognitive performance/work performance

Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the task force. Each evidence summary is accompanied by a discussion of the quality of evidence, balance of benefits and harms, patient values and preferences, and resource use considerations that contributed to the development of the clinical practice recommendations, which are provided in the accompanying clinical practice guideline. A summary of the language used for interpretation of clinical meaningfulness based on findings from the meta-analysis is detailed in the supplemental material of the accompanying systematic review (Figure S0).

ADULTS WITH SHIFTWORK DISORDER (SWD)

Symptoms of excessive sleepiness

Armodafinil

A total of five RCTs²⁹⁻³³ and 2 non-randomized studies^{34, 35} investigated the use of armodafinil in adults with SWD to improve one or more of the following outcomes: excessive sleepiness/alertness, accident risk, cognitive performance, and serious adverse events. Participants in the RCTs had a mean age of 38 years (48% female) and were diagnosed with shiftwork disorder. Participants received dosages of 150 mg armodafinil or placebo. Two RCTs^{30, 31} used a crossover design, with participants serving as their own controls, and a washout period of 1-week. The non-randomized studies^{34, 35} were before-and-after, open-label treatment design investigating participants receiving a dosage of 50 mg – 300 mg of armodafinil for a duration of 3-12 months. Meta-analyses were performed to assess the efficacy of armodafinil as a treatment for adults with SWD. The meta-analyses are provided in the supplemental material, Figure S1 through Figure S25. A summary of findings table is provided in the supplemental material, Table S2. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of armodafinil to treat adults with SWD: Excessive sleepiness/alertness, accident risk, and cognitive performance.

EXCESSIVE SLEEPINESS/ALERTNESS: Three RCTs²⁹⁻³¹ (N = 280 SWD participants) demonstrated that armodafinil had a clinically meaningful increase in alertness as measured by MSLT compared to no treatment (MD = 4.50 minutes; 95% CI: 1.83 to 7.17; [CMT = 1 min]; CoE is high). Participants received 150 mg of armodafinil with a follow-up duration ranging from one night to 12 weeks (see supplemental material, Figure S1).

Three RCTs^{29, 30, 32} (N = 612 SWD participants) demonstrated that, while not clinically meaningful, armodafinil reduced excessive sleepiness when measured using the KSS compared to no treatment (MD = -0.99 points; 95% CI: -1.32 to -0.65; [CMT=1.0 pt]; CoE is moderate due to imprecision). Participants received 150 mg of armodafinil with a follow-up duration ranging from one night to 12 weeks (see supplemental material, Figure S2)

Two RCTs^{29, 32} (N = 510 SWD participants) demonstrated armodafinil may improve CGI-C rating of sleepiness compared to no treatment (risk ratio of 1.36; 95% CI: 1.15 to 1.61 and an absolute risk improvement of 204 more per 1,000 (ranging from 85 to 346 more); [CMT= Not Established]; CoE is high). Participants received 150 mg of armodafinil with a follow-up duration ranging from 6-12 weeks. In addition, two observational studies^{34, 35} demonstrated a reduction in excessive sleepiness as reported by the CGI-C rating of sleepiness (see supplemental material, Figure S3 and Table S2).

ACCIDENT RISK: One RCT³⁰ (N = 40 SWD participants) demonstrated that armodafinil, when compared to no treatment, may have a clinically meaningful decrease in accident risk when measured by the deviation of lane position (MD= -0.50 meters; 95% CI: -1.02 to 0.02; [CMT = Any change]; CoE is low due to imprecision) and the number of off-road deviations on a driving simulator (MD = -5.19 off-road deviations; 95% CI: -14.29 to 3.91; [CMT = Any change]; CoE is low due to imprecision). Participants were given 150 mg of armodafinil with a single night follow-up (see supplemental material, Figure S4-S5).

One RCT²⁹ (N = 150 SWD participants) demonstrated that armodafinil had a clinically meaningful decrease in accidents when subjectively reporting the number of mistakes, near misses, or accidents during the drive home compared to no treatment (risk ratio of 0.62; 95% CI: 0.40 to 0.96; and absolute risk of 205 fewer per 1,000 (from 324 fewer to 22 fewer); [CMT = Any change], CoE is moderate due to imprecision and risk of reporting bias). Participants received 150 mg of armodafinil and were followed for a duration of 12 weeks and (see supplemental material, Figure S6).

One RCT²⁹ (N = 150 SWD participants) demonstrated that armodafinil resulted in a clinically meaningful reduction in the number of accidents when subjectively reporting the number of mistakes, near misses, or accidents during the night shift compared to no treatment (risk ratio of 0.64; 95% CI: 0.45 to 0.91; and absolute risk of 202 fewer per 1,000 (from 308 fewer to 50 fewer); [CMT = Any change], CoE is moderate due to imprecision and risk of reporting bias). Participants were followed for a duration of 12 weeks and received 150 mg of armodafinil (see supplemental material, Figure S7).

COGNITIVE PERFORMANCE: One RCT³⁰ (N = 40 SWD participants) demonstrated that armodafinil may improve cognitive performance when measuring the number of correct responses on the Digit Symbol Substitution Test (DSST) compared to no treatment (MD = 3.27 correct responses; 95% CI: 1.64 to 4.90; [CMT = Not Established], CoE is moderate due to imprecision). Additionally, the study³⁰ demonstrated that armodafinil may increase cognitive performance when using the remote associate's test (MD = 2.50 correct responses; 95% CI: -0.90 to 5.90; [CMT = Not Established]; CoE is moderate due to imprecision). Participants were given 150 mg of armodafinil or placebo with a single night follow-up (see supplemental material, Figure S8-S9).

One RCT³¹ (N = 24 SWD participants) demonstrated that armodafinil may improve cognitive performance when measured by free memory recall compared to no treatment (MD = 1.75 correct responses; 95% CI: -0.85 to 4.35; [CMT = Not Established]; CoE is moderate due to imprecision). Additionally, the study³¹ demonstrated that armodafinil may improve cognitive performance when measuring central and peripheral reaction time on the divided attention test compared to no treatment (central reaction time MD = -139.00 ms; 95% CI: -258.55 to -19.45; peripheral reaction time MD = -72.00 ms; 95% CI: -165.86 to 21.86; [CMT = Not Established], CoE is moderate due to imprecision). Participants were given 150 mg of armodafinil for 1 night (see supplemental material, Figure S10-12).

One RCT²⁹ (N = 216 SWD participants) demonstrated that armodafinil may improve cognitive performance, compared to no treatment, when measured by the following composite factors from the computerized Cognitive Drug Research (CDR) system: decrease of power of attention test (MD = -179.33 ms; 95% CI: -304.22 to -54.44, [CMT = Not Established]), an increase in the quality of episodic memory (MD = 24.24 units; 95% CI: 7.69 to

40.79; [CMT = Not Established]), an increase in the percent correct on the delayed word recall test (MD = 4.37 percent correct; 95% CI: 1.07 to 7.67; [CMT = Not Established]), and a decrease in simple reaction time of (MD = -53.19 ms; 95% CI: -91.77 to -14.61; [CMT = Not Established]) all CoE was moderate due to imprecision. Participants received 150 mg of armodafinil and were followed for 12 weeks (see supplemental material, Figure S13-16)

Important Outcomes

TOTAL SLEEP TIME: One RCT²⁹ (N = 193 SWD participants) demonstrated that armodafinil may have a clinically meaningful decrease in total sleep time as measured by PSG when compared to no treatment (MD = -16.60 minutes; 95% CI: -41.26 to 8.06; [CMT = 15 min]). Participants received 150 mg of armodafinil and were followed for 12 weeks (see supplemental material, Figure S17).

MENTAL HEALTH: One RCT³² (N = 359 SWD participants) demonstrated that armodafinil may improve mental health when measured using the Global Assessment of Function (GAF) compared to no treatment (MD = 4.70 points; 95% CI: 3.00 to 6.40; [CMT = Not Established]). Participants received 150 mg of armodafinil and were followed for six weeks (see supplemental material, Figure S18).

QUALITY OF LIFE: One RCT³³ (N = 383 SWD participants) demonstrated that armodafinil may improve quality of life when measured using the modified Sheehan Disability Scale compared to no treatment (MD = -3.5 points; 95% CI: -4.92 to -2.08; [CMT = Not Established]). Participants received 150 mg of armodafinil and were followed for six weeks (see supplemental material, Figure S19).

One RCT³³ (N = 383 SWD participants), demonstrated that armodafinil may improve quality of life when measured by the functional outcomes of sleep questionnaire (FOSQ-10) compared to no treatment (MD = 0.70 points; 95% CI: -0.12 to 1.52; [CMT = Not Established]). Participants received 150 mg of armodafinil and were followed for six weeks (see supplemental material, Figure S20).

WASO: One RCT²⁹ (N = 193 SWD participants) demonstrated that, while not clinically significant, armodafinil may decrease WASO when measured by PSG compared to no treatment (MD = 13.50 minutes; 95% CI: -9.71 to 36.71; [CMT = 20 min]). Participants received 150 mg of armodafinil and were followed for 12 weeks (see supplemental material, Figure S21).

SLEEP LATENCY: One RCT²⁹ (N = 193 SWD participants) demonstrated little to no difference in sleep latency when measured by PSG between armodafinil and no treatment (MD = 3.10 minutes; 95% CI: -0.43 to 6.63; [CMT = 20 min]). Participants received 150 mg of armodafinil and were followed for 12 weeks (see supplemental material, Figure S22).

SLEEP EFFICIENCY: One RCT²⁹ (N = 193 SWD participants) demonstrated little to no difference in sleep efficiency when measured by PSG between armodafinil and no treatment (MD = -3.40 percent; 95% CI: -8.47 to 1.67; [CMT = 10%]). Participants received 150 mg of armodafinil and were followed for 12 weeks (see supplemental material, Figure S23).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of armodafinil in adults with SWD was moderate based on the critical outcomes and downgrading of the evidence due to imprecision (see supplemental material, Table S2).

BENEFITS VS HARMS: The potential benefits of armodafinil in adults with SWD include a clinically meaningful improvement in excessive sleepiness and accident risk. Potential harms were noted in a few studies, including a serious adverse event of suicidal ideation in a patient with a history of depression, with an absolute risk of 3 fewer

per 1,000 (from 6 fewer to 23 more)^{29, 32}. There were also a number of reported adverse events leading to withdrawal, including headaches, nausea, nasopharyngitis, and anxiety with an absolute risk of 27 more per 1,000 (from 1 fewer to 105 more)^{29, 32}. Other side effects including nasopharyngitis, anxiety, diarrhea, dermatitis, hypertension, and dyspepsia have been reported. The TF judged that the potential benefits of armodafinil in adults with SWD outweigh the potential harms. (see supplemental materials, Figure S24 and Figure S25)

RESOURCE USE: The current unit cost for armodafinil is \$0.91 for a 150 mg tablet and \$0.88 for a 250 mg tablet. The TF judged these costs are moderate.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically meaningful improvement in excessive sleepiness measured by MSLT, the TF judged that most with SWD would generally be accepting of treatment with armodafinil.

Modafinil

A total of five RCTs³⁶⁻⁴⁰ investigated the use of modafinil in adults with SWD to improve one or more of the following outcomes: excessive sleepiness/alertness, accident risk, and cognitive performance. Participants in the RCTs had an age range 18-65 years (33% female). Participants received dosages of 200-300 mg modafinil. Three RCTs³⁷⁻³⁹ used a crossover design, with participants serving as their own controls, and a washout period of 2-7 weeks. One study³⁶ included SWD participants in a lab setting, one study³⁸ included shift workers without a diagnosis of SWD, and three studies^{37, 39, 40} included healthy participants in a simulated night shift setting. Meta-analyses were performed to assess the efficacy of modafinil as a treatment for adults with SWD. The meta-analyses are provided in the supplemental material, Figure S26 through Figure S46. A summary of findings table is provided in the supplemental material, Table S5. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of modafinil to treat adults with SWD: Excessive sleepiness/alertness, accident risk, and cognitive performance

EXCESSIVE SLEEPINESS/ALERTNESS: One RCT³⁶ (N = 182 SWD participants) demonstrated that modafinil may have a clinically meaningful increase in alertness as measured by MSLT compared to no treatment (MD = 1.40 minutes; 95% CI: 0.42 to 2.38; [CMT = 1 min]; CoE is low due to imprecision). Participants received 200 mg of modafinil and were followed for three months (see supplemental material, Figure S26).

One RCT³⁶ (N = 183 SWD participants) demonstrated that modafinil may have a clinically meaningful reduction in excessive sleepiness as measured by KSS when compared to no treatment (MD = -1.10 points; 95% CI: -1.69 to -0.51 points; [CMT = 1 pt]; CoE is low due to imprecision). Additionally, modafinil may reduce sleepiness when measured by CGI-C when compared to no treatment (risk ratio of 2.08; 95% CI: 1.57 to 2.78 and an absolute risk of 387 more per 1,000 (from 204 more to 637 more); [CMT = Not Established]; CoE is moderate due to imprecision). Patients received 200 mg of modafinil and were followed for three months (see supplemental material, Figure S27-S28).

One RCT³⁷ (N = 48 healthy participants) demonstrated little to no difference in excessive sleepiness as measured by the SSS between modafinil and no treatment (MD = -0.70 points; 95% CI: -0.86 to -0.54; [CMT = 1 pt]; CoE is low due to imprecision and indirectness). Participants were in a lab-simulated shift work setting and received 200 mg of modafinil and were followed for one month (see supplemental material, Figure S29).

One RCT⁴⁰ (N = 32 healthy participants) demonstrated that modafinil may have a clinically meaningful increase in alertness as measured by MWT compared to no treatment (MD = 5.20 minutes; 95% CI: -0.67 to 11.07; [CMT = 2 min]; CoE is very low due to imprecision and indirectness). Participants were in a lab-simulated shift work setting and received 200 mg of modafinil with a follow-up of four days (see supplemental material, Figure S30).

One RCT³⁸ (N = 50 shift workers without a diagnosis of SWD) demonstrated that modafinil may reduce excessive sleepiness as measured using VAS of the difficulty attending lecture after taking the pill compared to no treatment (MD = -23.64 mm; 95% CI: -40.40 to -6.88; [CMT = Not Established]; CoE is moderate due to imprecision and indirectness). Participants received 200 mg of modafinil with a follow-up of one night (see supplemental material, Figure S31).

ACCIDENT RISK: One RCT³⁶ (N = 204 SWD participants) demonstrated that modafinil had a clinically meaningful reduction in accident risk as measured by subjective reports of the number of accidents or near accidents in sleep diaries when compared to no treatment (risk ratio of 0.54; 95% CI: 0.38 to 0.78; and an absolute risk of 247 fewer per 1,000 (from 333 fewer to 118 fewer); [CMT = Any decrease]; CoE is high). Participants received 200 mg of modafinil and were followed for three months (see supplemental material, Figure S32).

One RCT³⁶ (N = 50 SWD participants) demonstrated that modafinil may have a clinically meaningful reduction in accident risk as measured using the VAS reporting difficulty driving home compared to no treatment (MD = -10.29 mm; 95% CI: -25.52 to 4.94; [CMT = Any improvement]; CoE is low due to imprecision). Participants received 200 mg of modafinil and were followed for three months (see supplemental material, Figure S33).

COGNITIVE PERFORMANCE: One RCT³⁶ (N = 135 SWD participants) demonstrated that modafinil had a clinically meaningful improvement in cognitive performance when measured using change from baseline data of PVT lapses compared to no treatment (MD = -6.38 lapses; 95% CI: -11.65 to -1.11; [CMT = 1 pt]; CoE is low due to imprecision). Participants received 200 mg of modafinil and were followed for three months (see supplemental material, Figure S34).

One RCT⁴⁰ (N = 32 healthy participants) also demonstrated that modafinil had a clinically meaningful improvement in cognitive performance when measured using PVT lapses compared to no treatment (MD = -12.12 lapses; 95% CI: -22.44 to -1.80; [CMT = 1 pt]; CoE is low due to imprecision and indirectness). Participants were monitored in a lab-simulated night shift (see supplemental material, Figure S35).

One RCT³⁸ (N = 50 shift workers without a diagnosis of SWD) demonstrated little to no difference on cognitive performance when measured by the number of correct substitutions during the coding task between modafinil and no treatment (MD = 0.84 correct substitutions; 95% CI: -5.59 to 7.27; [CMT = Not Established]; CoE is low due to imprecision and indirectness). Participants received 200 mg of modafinil and were followed for one night (see supplemental material, Figure S36).

One RCT³⁹ (N = 16 healthy participants) demonstrated that modafinil may improve cognitive performance as measured by percentage change from baseline scores of the grammatical reasoning test response time when compared to no treatment (MD = -13.75 percent; 95% CI: -27.11 to -0.39; [CMT = Not Established]; CoE is low due to imprecision and indirectness). Participants were in a lab-simulated night shift and received 300 mg of modafinil with a follow-up of two nights (see supplemental material, Figure S37).

One RCT³⁷ (N = 48 healthy participants) demonstrated that, when compared to no treatment, modafinil may improve cognitive performance as measured by the deviation of altitude (MD = -64.50 km; 95% CI: -92.09 to -36.91; [CMT = Not Established]; CoE low due to imprecision and indirectness) and flight velocity envelope in a flight simulator (MD = -9.83 km/h; 95% CI: -11.81 to -7.85; [CMT = Not Established]; CoE is low due to imprecision and indirectness). Participants were in a lab-simulated night shift and received 200 mg of modafinil with a follow-up of one night (see supplemental material, Figure S38-S39).

Important Outcomes

TOTAL SLEEP TIME: One RCT³⁶ (N = 150 SWD participants) had results that failed to show, or to exclude, that modafinil had a clinically meaningful benefit or harm regarding total sleep time as measured by PSG when compared to no treatment (MD = -3.20 minutes (95% CI: -30.50 to 24.10; [CMT = 15 minutes])). Participants received 200 mg of modafinil and were followed for three months (see supplemental material, Figure S40).

Another RCT⁴⁰ (N = 32 healthy participants) demonstrated that modafinil may have a clinically meaningful increase in total sleep time when measured by PSG compared to no treatment (MD = 32.90 minutes; 95% CI: -15.96 to 81.76; [CMT = 15 minutes])). Participants were in a lab-simulated night shift and received 200 mg of modafinil with a follow-up period of four days modafinil (see supplemental material, Figure S41).

SLEEP LATENCY: One RCT³⁶ (N = 150 SWD participants) demonstrated little to no difference on sleep latency when measured by PSG between modafinil and no treatment (MD = 1.60 minutes; 95% CI: -3.37 to 6.57; [CMT = 20 minutes])). Participants received 200 mg of modafinil and were followed for three months (see supplemental material, Figures S42).

Another RCT⁴⁰ (N = 32 healthy participants) demonstrated little to no difference on sleep latency when measured by PSG between modafinil and no treatment (MD = 4.70 minutes; 95% CI: -0.08 to 9.48; [CMT = 20 minutes])). Participants were in a lab-simulated night shift and received 200 mg of modafinil with a follow-up period of four days (see supplemental material, Figures S43).

SLEEP EFFICIENCY: One RCT³⁶ (N = 150 SWD participants) demonstrated little to no difference on sleep efficiency as measured by PSG between modafinil and no treatment (MD = 0.20 percent; 95% CI: -5.20 to 5.60; [CMT = 10%])). Participants received 200 mg of modafinil and were followed for three months (see supplemental material, S44).

Another RCT⁴⁰ (N = 32 healthy participants) demonstrated that, while not clinically meaningful, modafinil may increase sleep efficiency as measured by PSG compared to no treatment (MD = 4.50 percent; 95% CI: -5.00 to 14.00; [CMT = 10%])). Participants were in a lab-simulated night shift and received 200 mg of modafinil with a follow-up period of four days (see supplemental material, S45).

One RCT³⁶ (N = 162 SWD participants) demonstrated little to no difference in sleep efficiency as measured by subjective reports in sleep diaries between modafinil and no treatment (MD = -2.20 percent; 95% CI: -7.87 to 3.47; [CMT = 10%])). Participants received 200 mg of modafinil and were followed for three months (see supplemental material, S46).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of modafinil in adults with SWD was low based on the critical outcomes and downgrading of the evidence due to imprecision, indirectness, and risk of bias (see supplemental material, Table S5).

BENEFITS VS HARMS: The potential benefits of modafinil in adults with SWD include a clinically meaningful improvement in excessive sleepiness and accident risk. The potential harms include a risk of headache, nausea, and insomnia/sleep disturbance. Other side effects including abdominal pain, vasodilation, kidney calculus, nervousness, and dry mouth have been reported. The TF judged that the potential benefits of modafinil in adults with SWD outweigh the potential harms.

RESOURCE USE: The current unit costs for modafinil are \$0.84 for a 200 mg tablet and \$0.35 for a 100 mg tablet. The TF judged these costs as moderate.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically meaningful improvement in excessive sleepiness measured by MSLT, the TF judged that most patients with SWD would generally accept treatment with modafinil.

Bright Light (acute)

A total of 24 RCTs⁴¹⁻⁶⁵ investigated the use of acute exposure to bright light in adults with SWD to improve one or more of the following outcomes: excessive sleepiness/alertness, accident risk, cognitive performance, and sleep quality. Eleven studies^{41-49, 61, 64} included shift workers without a diagnosis of SWD and thirteen studies^{50-60, 62, 65} included healthy participants in a simulated night shift setting. The healthy participants in the lab-based night shift studies had an age of 18-55 years (24% female). Meta-analyses were performed to assess the efficacy of acute exposure to bright light as a treatment for adults with SWD. The meta-analyses are provided in the supplemental material, Figure S47 through Figure S120. A summary of findings table is provided in the supplemental material, Table S7. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of acute exposure of bright light to treat adults with SWD: Excessive sleepiness/alertness, accident risk, cognitive performance and sleep quality.

EXCESSIVE SLEEPINESS/ALERTNESS: Two RCTs^{42, 45} (N = 104 shift workers without a diagnosis of SWD) demonstrated little to no difference on excessive sleepiness as measured using KSS between bright light and no bright light (MD = 0.02 points; 95% CI: -0.40 to 0.43; [CMT = 2 pts]; CoE is low due to risk of bias, indirectness and imprecision). Participants were exposed to 20-45 minutes of bright light with an intensity of light of 2500-4500 lux (see supplemental material, Figure S47).

Two non-randomized studies^{43, 44} (N = 37 shift workers without a diagnosis of SWD) demonstrated little to no difference on excessive sleepiness as measured using KSS between bright light and no bright light (MD = -0.22 points; 95% CI: -0.48 to 0.04; [CMT = 2 pts]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were exposed to 20-45 minutes of bright light with an intensity of light of 2500-4500 lux (see supplemental material, Figure S48).

Two RCTs^{55, 56} (N = 62 healthy participants) demonstrated little to no difference on excessive sleepiness as measured using KSS between bright light and no bright light (MD = -0.73 points; 95% CI: -1.43 to -0.02); [CMT = 2 pts]; (CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift (see supplemental materials, Figure S49).

One study⁴⁴ (N = 86 shift workers without a diagnosis of SWD) demonstrated little to no difference on excessive sleepiness as measured using SSS between bright light and no bright light (MD = -0.42 points; 95% CI: -0.92 to 0.08; [CMT = 1 pt]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were exposed to 10 hours of bright light with an intensity of light of 1,500-5,000 lux (see supplemental material, Figure S50).

Two RCTs^{54, 57} (N = 47 healthy participants) demonstrated little to no difference on excessive sleepiness as measured using SSS between bright light and no bright light (MD = -0.04 points; 95% CI: -0.53 to 0.45; [CMT = 1 pt]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift and the duration of exposure to bright light ranged from 3-10 hours with an intensity of light of 2,500-5,000 lux (see supplemental material, Figure S51).

One RCT⁴⁶ (N = 36 shift workers without a diagnosis of SWD) demonstrated that bright light may improve excessive sleepiness as measured using a VAS compared to no bright light (MD = 28.13 mm; 95% CI: 14.71 to 41.55; [CMT = Not Established; CoE is low due to risk of bias and indirectness). The VAS ranged from 0-100 mm, denoting the “most alert state” as 100 mm and the “most sleepy state” as 0. Participants were exposed to 4-hours of bright light with an intensity of light ranging from 4,000-6,000 lux (see supplemental material, Figure S52).

One RCT⁶⁵ (N = 27 healthy participants) demonstrated bright light may improve excessive sleepiness as measured using a VAS compared to no bright light (MD = 5.51; 95% CI: -7.33, 18.35; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). The study used a scale of 0-100 mm with 100 mm denoting most alert. Participants were followed in a lab-simulated night shift and were exposed to bright light with an intensity of light of 2,500 lux (supplemental material, Figure S53).

One RCT⁴⁷ (N = 22 shift workers without a diagnosis of SWD) demonstrated that bright light may worsen excessive sleepiness as measured using a VAS compared to no bright light (MD = -7.70 mm; 95% CI: -21.64 to 6.24; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). The VAS ranged from 0-100 mm with higher values representing more arousal. Participants were followed for three days and were exposed to 1-hour of bright light with an intensity of light of 3,000 lux (see supplemental material, Figure S54).

One RCT⁵⁵ (N = 24 healthy participants) demonstrated that bright light may improve excessive sleepiness as measured using a VAS for Fatigue compared to no bright light (MD = 1.00 units; 95% CI: -0.38 to 2.38; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). The study used an 18-item scale relating to the subjective experience of fatigue. Participants were followed in a lab-simulated night shift and were exposed to bright light with an intensity of light of 5,000 lux (see supplemental material, Figure S55).

One non-randomized study⁴⁸ (N = 30 shift workers without a diagnosis of SWD) demonstrated that bright light may worsen excessive sleepiness as measured using a fatigue rating scale compared to no bright light (MD = 0.90 units; 95% CI: -3.14 to 4.94; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed for one day and were exposed to four 20-minute sessions of bright light with an intensity of light of 2,350 lux (see supplemental materials, Figure S56).

One RCT⁴⁹ (N = 30 shift workers without a diagnosis of SWD) demonstrated that after one night, bright light may worsen excessive sleepiness as measured using a seven-point scale of sleepiness compared to dim light (MD = 0.50 units; 95% CI: -0.57 to 1.57 units; [CMT = Not Established]), however, after the second night bright light may improve excessive sleepiness as measured the same scale compared to dim light (MD = -0.40 units; 95% CI: -1.63 to 0.83 units; [CMT = Not Established]). The CoE for this study was very low due to risk of bias, indirectness, and imprecision. The seven-point scale measured sleepiness with a score of one being the minimum level of sleepiness and seven being the maximum. Participants were followed for two days and were exposed to four 20-minute sessions of bright light with an intensity of light of 2,350 lux (see supplemental materials, Figure S57 and Figure S58).

Two RCTs^{50, 54} (N = 39 healthy participants) demonstrated that bright light may have a clinically meaningful increase in alertness as measured using the MWT compared to no bright light (MD = 2.58 minutes; 95% CI: 0.35 to 4.81; [CMT = 2 minutes]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift for one day and were exposed to 9-12 hours of bright light with an intensity of light ranging from 2,500-5,000 lux (see supplemental material, Figure S59).

Two RCTs^{51, 52} (N = 76 healthy participants) demonstrated that bright light had a clinically meaningful improvement in excessive sleepiness as measured using RTSW compared to dim light (MD = 5.09; 95% CI: 2.70 to 7.47; [CMT = 2 minutes]; CoE is low due to indirectness and imprecision). Participants were followed for two

to three days in a lab-simulated night shift. In one study, participants were exposed to four hours of bright light with an intensity of light of 5,000 lux in the first half of night shift 1, and in the other study, participants were exposed to eight hours of dim light with an intensity of light ranging from 10 to 20 lux. On night shift 2, in both studies, participants were exposed to eight hours of bright light with an intensity of light of 1,000 lux (see supplemental material, Figure S60).

One RCT⁵⁸ (N = 34 healthy participants) demonstrated that bright light, compared to no bright light, may improve alertness as measured using EEG alpha waves (MD = -0.18 units; 95% CI: -0.36 to 0.0; [CMT = Not Established]), beta waves (MD = 0.02 units; 95% CI: -0.08 to 0.11; [CMT = Not Established]), and theta waves (MD = 0.03 units; 95% CI: -0.13 to 0.18; [CMT = Not Established]). The CoE for these studies was very low due to indirectness and imprecision. Participants were followed in a lab-simulated night shift and were exposed to two hours of bright light with an intensity of 361 lux (see supplemental material, Figure S61, Figure S62 and Figure S63).

Two RCTs^{59, 60} (N = 16 healthy participants) demonstrated little to no difference on excessive sleepiness as measured using the general activation/deactivation sleepiness index (GADS) between bright light and dim light (MD = -0.02 units; 95% CI: -0.12 to 0.08; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift for one night and were exposed to 4-8 hours of bright light with an intensity of light ranging from 1,000-2,000 lux (see supplemental material, Figure S64).

ACCIDENT RISK: One crossover RCT⁵⁶ (N = 19 healthy participants) demonstrated little to no difference on accident risk as measured using the variability of lane position in a driving simulation between bright light and dim light (MD = 0.00 meters; 95% CI: -0.05 to 0.05; [CMT = Any Change]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulation of the drive home after a night shift and were exposed to 45 minutes of bright light with an intensity of light of 5,600 lux (see supplemental material, Figure S65).

One crossover RCT⁵⁶ (N = 19 healthy participants) demonstrated that bright light, compared to dim light, may result in a clinically meaningful decrease in accident risk as measured using the number of accidents driving simulation (MD of -8.98 accidents; 95% CI: -22.39 to 4.43; [CMT = Any Change]), and using steering wheel movement (MD = -4.09 movements; 95% CI: -9.14 to 0.96; [CMT = Any Change]). The CoE for these studies is very low due to risk of bias, indirectness, and imprecision. Participants were followed in a lab-simulation of the drive home after a night shift and were exposed to 45 minutes of bright light with an intensity of light of 5,600 lux (see supplemental material, Figure S66 and Figure S67).

SLEEP QUALITY: One non-randomized study⁴¹ (N = 36 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep quality as measured using a sleep quality index between bright light and dim light (MD = 0.00 units; 95% CI: -0.28 to 0.28; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed for four nights and were exposed to two hours of bright light exposure with an intensity of light of 10,000 lux (see supplemental material, Figure S68).

COGNITIVE PERFORMANCE: One RCT⁶² (N = 17 healthy participants) demonstrated that bright light may have a clinically meaningful improvement on cognitive performance as measured using PVT lapses compared to no bright light (MD = -2.50 lapses; 95% CI: -6.31 to 1.31; [CMT = 1 lapse]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed for four weeks in a lab-simulated night shift and were exposed to 30 minutes of intermittent bright light with intensities of light of ~8,000 lux, ~2,500 lux and ~1,250 lux followed by 30-minutes of indoor light with an intensity of light of 103 lux (see supplemental material, Figures S69).

One RCT⁵⁸ (N = 34 healthy participants) demonstrated that bright light, compared to no bright light, may improve cognitive performance as measured by the following domains of a GO/NOGO performance test: normalized reaction time (MD = -27.72 seconds; 95% CI: -38.50 to -16.94; [CMT = Not Established]), 10% best throughput (MD = 0.02 seconds; 95% CI: 0.01 to 0.02; [CMT = Not Established]), and worst throughput (MD = 0.01 seconds; 95% CI: 0.00 to 0.01; [CMT = Not Established]). The CoE for these studies is very low due to risk of bias, indirectness, and imprecision. Participants were followed in a lab-simulated night shift for one day and were exposed to 120 minutes of bright light with an intensity of light of 361 lux (see supplemental material, Figure S70, Figure S70 to S72).

One RCT⁴⁴ (N = 86 shift workers without a diagnosis of SWD) demonstrated little to no difference on cognitive performance as measured using PVT mean reaction time between bright light and no bright light (MD = -2.28 ms; 95% CI: -36.25 to 31.69; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were exposed to 8-10 hours of bright light with an intensity of light of 1,500-2,000 lux (see supplemental material, Figure S73).

Three RCTs^{54, 56, 62} (N = 74 healthy participants) demonstrated that bright light may improve cognitive performance as measured by PVT mean reaction time compared to dim light (MD = -15.28 ms; 95% CI: -46.29 to 15.73; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift and were exposed to 45 minutes to 10 hours of bright light with an intensity of light of 1,250-8,000 lux (see supplemental material, Figure S74).

One RCT⁴⁷ (N = 22 shift workers without a diagnosis of SWD) demonstrated that bright light may improve cognitive function as measured using reaction time of a five-choice performance test compared to no bright light (MD = -127.70 ms; 95% CI: -303.74 to 48.34; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were exposed to one hour of bright light with an intensity of light of 3,000 lux (see supplemental material, Figure S75).

One RCT⁵⁴ (N = 42 healthy participants) demonstrated that bright light may improve cognitive performance when measured by the Wilkinson four choice reaction time test compared to no bright light (MD = 10.10; 95% CI: -5.54 to 25.74; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift and were exposed to 4-10 hours of bright light with an intensity of light of 2,500-4,000 lux (see supplemental material, Figure S76).

One RCT⁵² (N = 42 healthy participants) demonstrated that bright light may worsen cognitive performance when measured by the percent improvement on the Wilkinson four choice reaction time test compared to dim light (MD = -5.90%; 95% CI: -28.63 to 16.83; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift and were exposed to 4-10 hours of bright light with an intensity of light of 2,500-4,000 lux (see supplemental material, Figure S77).

One RCT⁴⁷ (N = 22 shift workers without a diagnosis of SWD) demonstrated that bright light may worsen cognitive performance as measured using the response time to MORE difficult visuospatial discrimination compared to dim light (MD = 0.24 ms; 95% CI: -0.60 to 1.08; [CMT = Not Established], CoE is very low due to risk of bias, indirectness, and imprecision). Participants were exposed to one hour of bright light with an intensity of light of 3,000 lux (see supplemental material, Figure S78).

One RCT⁴⁷ (N = 22 shift workers without a diagnosis of SWD) demonstrated that bright light may improve cognitive performance as measured using the response time to LESS difficult visuospatial discrimination compared to dim light (MD = -0.05 ms; 95% CI: -0.81 to 0.71; [CMT = Not Established], CoE is very low due to risk of bias, indirectness, and imprecision). Participants were exposed to one hour of bright light with an intensity of light of 3,000 lux (see supplemental material, Figure S79).

One RCT⁴⁷ (N = 22 shift workers without a diagnosis of SWD) demonstrated that dim light may improve cognitive performance when measured using the number of trials without a false alarm on a letter cancellation performance test compared to bright light (MD = -0.50 trials; 95% CI: -0.70 to -0.30; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were exposed to 1 hour of bright light with an intensity of light of 3,000 lux (see supplemental material, Figure S80).

One RCT⁴⁹ (N 30 shift workers without a diagnosis of SWD) demonstrated that bright light may improve cognitive performance when measured using the reaction time on the search and memory test compared to dim light on night one (MD = -7.30 ms; 95% CI: -22.23 to 7.63 ms; [CMT = Not Established]) and on night two (MD = -8.00 ms; 95% CI: -22.98 to 6.98 ms; [CMT = Not Established]). Additionally, bright light may improve cognitive performance when measured using the score of the search and memory test compared to dim light on night one (MD = 0.75 % correct/square root of time; 95% CI: 0.27 to 1.22; [CMT = Not Established]) and on night two (MD = 0.32% correct/square root of time;; 95% CI: -0.34 to 0.98; [CMT = Not Established]). The CoE for these studies is very low due to risk of bias, indirectness, and imprecision. Participants were followed for two days and were exposed to four 20-minute sessions of bright light with an intensity of light of 2,350 lux (see supplemental material, Figure S81 to Figure S84).

One RCT⁶⁰ (N = 8 healthy participants) demonstrated that bright light, compared to dim light, had little to no difference on cognitive performance when measure by either the SAM 3 (MD = 0.00; 95% CI -0.15 to 0.15; [CMT = Not Established]) or the SAM 5 (MD = -0.01; 95% CI -0.16 to 0.14; [CMT = Not Established]). The CoE for this study is very low due to risk of bias, indirectness, and imprecision. Participants were followed in a lab-simulated shift work environment and were exposed to 4-hours of bright light with an intensity of light of 700 lux (see supplemental material, Figure S85 and Figure S86).

One non-randomized study⁴¹ (N = 36 shift workers without a diagnosis of SWD) demonstrated that bright light may improve cognitive performance when measured using a subject rating of the percentage of time with reduced performance compared to dim light (MD = -10.40%; 95% CI: -18.14 to -2.66; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed for four nightshifts and exposed to 30 minutes of bright light with an intensity of light of 10,000 lux (see supplemental material, Figure S87).

One RCT⁵⁴ (N = 20 healthy participants) demonstrated that bright light may improve cognitive performance when measured using the dual task performance test compared to dim light (MD = -4.27 losses; 95% CI: -14.80 to 6.26; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift for one day and were exposed to 10 hours of bright light with an intensity of light of 2,000 lux (see supplemental material, Figure S88).

One RCT⁵² (N = 24 healthy participants) demonstrated that bright light may improve cognitive performance when measured using the percentage improvement on the Manikin performance test compared to dim light (MD = 17.30%; 95% CI: 8.90 to 25.70; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift for three days and were exposed to 8 hours of bright light with an intensity of light of 1,000 lux (see supplemental material, Figure S89).

One RCT⁵⁴ (N = 20 healthy participants) demonstrated that bright light may improve cognitive performance when measured using the Mannequin throughput on the switching task performance test compared to dim light (MD = 0.51 units; 95% CI: -2.86 to 3.88; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift for one night and were exposed to 10 hours of bright light with an intensity of light of 2,000 lux (see supplemental material, Figure S90).

One RCT⁵⁴ (N = 20 healthy participants) demonstrated that dim light may improve cognitive performance when measured using the math throughput on the switching task performance test compared to bright light (MD = -1.02

units; 95% CI: -4.98 to 2.94; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift for one night and were exposed to 10 hours of bright light with an intensity of light of 2,000 lux (see supplemental material, Figure S91).

One RCT⁵⁸ (N = 26 healthy participants) demonstrated that bright light improved cognitive performance when measured using the average tracking score in the MAT tracking task compared to dim light (MD = 4.20 units; 95% CI: 1.15 to 7.25; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift for one day and were exposed to 120 minutes of bright light with an intensity of light of 361 lux (see supplemental material, Figure S92).

One RCT⁵¹ (N = 26 healthy participants) demonstrated that dim light may improve cognitive performance as measured using the Night 1 percent correct on the Simulate Assembly Line Test (SALT) compared to bright light (MD = -1.71% correct; 95% CI: -11.50 to 8.08; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift for one day and Participants were exposed to 4 hours of bright light with an intensity of 5,000 lux (see supplemental material, Figure S93).

One RCT⁵¹ (N = 26 healthy participants) demonstrated little to no difference on cognitive performance as measured using the Night 1 response time in the SALT between bright light and dim light (MD = -0.06 sec; 95% CI: -2.16 to 2.04; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift for one day and Participants were exposed to 4 hours of bright light with an intensity of 5,000 lux (see supplemental material, Figure S94).

One RCT⁵¹ (N = 26 healthy participants) demonstrated that bright light may improve cognitive performance as measured by the percentage of improvement on the logical reasoning test compared to dim light (MD = 12.30% (95% CI: 6.98 to 17.62; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift for one day and Participants were exposed to 4 hours of bright light with an intensity of 5,000 lux (see supplemental material, Figure S95).

One RCT⁶³ (N = 16 healthy participants) demonstrated that bright light, compared to dim light, may improve cognitive performance when measured using the following domains of the Posner same-different letter presentation test and the manikin test: Posner S-D AT reaction time (MD = -93.00 ms; 95% CI: -179.64 to -6.36; [CMT = Not Established]), the Posner response time variability (MD = -102.20; 95% CI: -254.30 to 49.90; [CMT = Not Established]), the Manikin reaction time (MD = -144.89 ms; 95% CI: -449.78 to 160.00; [CMT = Not Established]), and the Manikin throughput (MD = -246.15 ms; 95% CI: -754.82 to 262.52; [CMT = Not Established]). The CoE for these findings is very low due to risk of bias, indirectness, and imprecision. Participants were followed in a lab-simulated night shift and were exposed to 4-hours of bright light with an intensity of light of 4,000-7,000 lux (see supplemental material, Figures S96-S99).

One RCT⁶⁶ (N = 24 healthy participants) demonstrated that bright light may improve cognitive performance when measured using simple reaction time compared to dim light (MD = -21.21 ms; 95% CI: -48.83 to 6.41; [CMT = Not Established, CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift and were exposed to five 15-minute sessions of bright light with an intensity of light of 4,100 lux. Participants wore sunglasses when they were outside during the day (see supplemental material, Figure S100).

Important Outcomes

TOTAL SLEEP TIME: Two non-randomized studies^{41, 48} (N = 44 shift workers without a diagnosis of SWD) demonstrated that, while not clinically meaningful, bright light, when compared to dim light, decreased total sleep time as measured using subjective reports in sleep diaries (MD = -10.07 minutes; 95% CI: -32.19 to 12.05; [CMT

= 15 minutes]). Participants were exposed to either 30 minutes of bright light daily or four 20-minute sessions of bright light with an intensity of light of 2,350 to 10,000 lux (see supplemental material, Figure S101).

Two RCTs^{45, 46} (N = 52 shift workers without a diagnosis of SWD) demonstrated that bright light may have a clinically meaningful improvement in total sleep time as measured using actigraphy compared to dim light (MD = 25.12 minutes; 95% CI: -13.87 to 64.11; [CMT = 15 minutes]). Participants were exposed to two 20-minute sessions up to 8 hours of bright light with an intensity of light of 650 to 6,000 lux (see supplemental material, Figure S102).

One non-randomized study⁴³ (N = 23 shift workers without a diagnosis of SWD) failed to show, or to exclude, that bright light had a clinically meaningful benefit or harm regarding total sleep time as measured using actigraphy compared to dim light (MD = -17.80 minutes; 95% CI: -87.59 to 51.99; [CMT = 15 minutes]). Participants were exposed to two 20-minute sessions up to 8 hours of bright light with an intensity of light of 650 to 6,000 lux (see supplemental material, Figure S103).

MENTAL HEALTH: One RCT⁶¹ (N = 92 shift workers without a diagnosis of SWD) demonstrated that bright light may improve mental health as measured using the hospital anxiety depression scale (HADS) compared to dim light (MD = -7.00 points; 95% CI: -9.04 to -4.96; [CMT = Not Established]). Participants were followed for two weeks and were exposed to 30 minutes of bright light with an intensity of light of 7,000-10,000 lux (see supplemental material, Figure S104).

One RCT⁶⁴ (N = 87 shift workers without a diagnosis of SWD) demonstrated that bright light may improve mental health as measured using the scale for shift-work complaints (SSC) compared to dim light (MD = -5.80 complaints; 95% CI: -8.61 to -2.99; [CMT = Not Established]). Participants were followed for two weeks and were exposed to four 20-minute sessions of bright light with an intensity of light of 5,000 lux (see supplemental material, Figure S105).

One RCT⁴⁹ (N = 30 shift workers without a diagnosis of SWD) demonstrated that bright light, compared to dim light, may improve mental health as measured using a seven-point scale of mood on both the first night (MD = 0.12 units; 95% CI: -0.96 to 1.20 units; [CMT = Not Established]), and on the second night (MD = 0.30 units (95% CI: -0.67 to 1.27 units; [CMT = Not Established])). The scale measured mood with a score of 1 indicating a worsened mood and 7 indicating an improved mood. Participants were followed for two nights and were exposed to four 20-minute sessions of bright light with an intensity of light of 2,350 (see supplemental material, Figure S106 and S107).

CIRCADIAN ADAPTATION: One RCT⁶⁵ (N = 27 healthy participants) demonstrated that bright light may improve circadian adaptation as measured using MMSE compared to dim light (MD = 4.13; 95% CI: 1.63 to 6.63; [CMT = Not Established]). Participants were followed in a lab-simulated night shift and were exposed to acute bright light for 4 hours at an intensity ranging from 2,500-7,000 lux (see supplemental material, Figure S108).

One RCT⁶² (N = 25 healthy participants) demonstrated that bright light, compared to dim light, may improve circadian adaptation using the following metrics: phase shift MEL_{25%up} (MD = 0.73 hr; 95% CI: -1.96 to 3.42 hr; [CMT = Not Established]), phase shift (MD = 1.71 hr; 95% CI: -1.04 to 4.46 hr; [CMT = Not Established]), and phase shift (MD = 2.28 hr; 95% CI: 0.08 to 4.48 hr; [CMT = Not Established]). Participants were followed in a lab-simulated night shift for four weeks and were exposed to 30 minutes of ~8,000, ~2,500 and ~1,250 lux followed by 30-minutes of indoor light (see supplemental material, Figures S109-S111).

QUALITY OF LIFE: One non-randomized study⁴¹ (N = 36 shift workers without a diagnosis of SWD) demonstrated that bright light may improve quality of life when measured using subject ratings in Karolinska sleep diary compared to dim light (MD = -0.30 units; 95% CI: -0.47 to -0.13 units; [CMT = Not Established]).

Individuals rated the quality of their day on a scale of 1-9 with 1 indicating a very good day and 9 a very bad day. Participants were exposed to acute bright light for 30 minutes daily during the first four nights of the night-shift period at an intensity of 10,000 lux (see supplemental material, Figure S112).

DISEASE SEVERITY: One RCT⁶¹ (N = 92 shift workers without a diagnosis of SWD) demonstrated that bright light had a clinically meaningful improvement in disease severity as measured using the insomnia severity index (ISI) compared to dim light (MD = -11.20 points; 95% CI: -12.92 to -9.48; [CMT = 8 points]). Participants were followed for two weeks and the duration of acute bright light exposure ranged from >30 minutes at an intensity 7,000-10,000 lux (see supplemental material, Figure S113).

WASO: One non-randomized study⁴¹ (N = 36 shift workers without a diagnosis of SWD) demonstrated that bright light may improve WASO when measured using subject ratings in Karolinska sleep diary compared to dim light (MD = 0.10 units; 95% CI: 0.0 to 0.20 units; [CMT = Not Established]). The following rating scale was given to the participants: 1=many hours awake after initially falling asleep; 4=a few minutes awake; 5= not awake at all after falling asleep. Participants were exposed to acute bright light for 30 minutes daily during the first four nights of the night-shift period at an intensity of 10,000 lux (see supplemental material, Figure S114).

Two RCTs^{51, 53} (N = 39 healthy participants) demonstrated that bright light had a clinically meaningful improvement on WASO when measured using a sleep electroencephalogram (EEG) compared to dim light (MD = -46.64 minutes; 95% CI: -63.14 to -30.14; [CMT = 20 minutes]). Participants were followed in a lab-simulated night shift and were exposed to a 4-hour pulse of acute bright light at an intensity ranging from 4,000-6,000 lux (see supplemental material, Figure S115).

SLEEP LATENCY: One non-randomized study⁴¹ (N = 36 shift workers without a diagnosis of SWD) demonstrated that little to no difference in sleep latency when measured using subject ratings in Karolinska sleep diary between bright light and dim light; MD = 1.20 minutes (95% CI: -0.24 to 2.64; [CMT = 20 minutes]). Participants were exposed to acute bright light for 30 minutes daily during the first four nights of the night-shift period at an intensity of 10,000 lux (see supplemental material, Figure S116).

One RCT⁴⁶ (N = 24 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep latency when measured using actigraphy between bright light and dim light (MD = 0.50 minutes; 95% CI: -6.71 to 7.71; [CMT = 15 minutes]). Participants were exposed to acute bright light for 4 hours at an intensity of 10,000 lux (see supplemental material, Figure S117).

One RCT (N = 21 healthy participants) demonstrated that bright light had a clinically meaningful worsening of sleep latency as measured using PSG/EEG compared to dim light (MD = 54.00; 95% CI: 32.15 to 75.85; [CMT = 20 minutes]). Participants were followed in a lab simulated night shift and were exposed to acute bright light for 4 hours at an intensity ranging from 2,500-7,000 lux (see supplemental material, Figure S118).

SLEEP EFFICIENCY: Two RCTs^{45, 46} (N = 54 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep efficiency when measured using actigraphy between bright light and dim light (MD = 1.21%; 95% CI: -0.10 to 2.53; [CMT = 10%]). Participants were exposed to acute bright light for a duration ranging from 20 minutes to 4 hours at an intensity of 2,500-10,000 lux (see supplemental material, Figure S119).

Two RCTs^{51, 53} (N = 39 healthy participants) demonstrated that bright light may have a clinically meaningful increase in sleep efficiency when measured using EEG compared to dim light (MD = 10.45%; 95% CI: 6.63 to 14.28; [CMT = 10%]). Participants were followed in a lab-simulated night shift and were exposed to a 4-hour pulse of acute bright light at an intensity ranging from 4,000-6,000 lux (see supplemental material, Figure S120).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of acute bright light in adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to imprecision, indirectness of the patient population, and risk of bias. (see supplemental material, Table S7).

BENEFITS VS HARMS: The potential benefits of acute bright light in adults with SWD include a clinically meaningful improvement in sleep quality as measured by ISI, excessive sleepiness as measured by MWT, and improvements in cognitive performance as measured by PVT lapses. The potential harms include a risk of headaches in individuals with a history of migraines, temporary eye strain, and may be contraindicated in individuals with bipolar disorder. The TF judged that the potential benefits of exposure to acute bright light in adults with SWD outweigh the potential harms.

RESOURCE USE: The current costs for a bright light lamp ranges from \$25-100. The TF judged these costs are negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically meaningful improvement in excessive sleepiness measured by MWT, sleep quality as measured by ISI, and cognitive performance as measured by PVT lapses, the TF judged that most with SWD would generally be accepting of treatment with acute bright light.

Caffeine

A total of 8 RCTs^{37, 47, 54, 67-71} investigated the use of caffeine in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness/alertness, accident risk, and cognitive performance. Participants in the RCTs had an age range 18-62 years (18% female). Participants received dosages of 98-250 mg caffeine. Four RCTs^{37, 47, 70, 71} used a crossover design, with participants serving as their own controls, and a washout period ranging from 1- 2-weeks. Two studies^{47, 70} included shift workers without a diagnosis of SWD and 5 studies^{37, 54, 67-69} included healthy participants in a simulated night shift setting. Meta-analyses were performed to assess the efficacy of caffeine as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S121 through Figure S151. A summary of findings table is provided in the supplemental material, Table S9. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of caffeine to treat adults with SWD: Excessive sleepiness/alertness, and cognitive performance.

EXCESSIVE SLEEPINESS/ALERTNESS: Two RCTs^{54, 67} (N = 53 healthy participants) demonstrated that, while not clinically meaningful, caffeine may increase alertness as measured by MWT compared to no treatment (MD = 1.81 minutes; 95% CI: 0.13 to 3.50; [CMT = 2 minutes]; CoE is very low due to imprecision and indirectness). Participants were followed for 2-4 nights in a lab-simulated night shift and received 200 mg or 4 mg/kg of caffeine (see supplemental material, Figure S121).

Two RCTs^{37, 54} (N = 68 healthy participants) demonstrated little to no difference in excessive sleepiness as measured by SSS between caffeine and no treatment (MD = -0.82 points; 95% CI: -0.97 to -0.66; [CMT = 1 pt]; CoE is low due to imprecision and indirectness). Participants were followed for 1-4 nights in a lab-simulated night shift and received 200 mg of caffeine (see supplemental material, Figure S122).

One RCT⁶⁷ (N = 33 healthy participants) demonstrated that caffeine may have a clinically meaningful decrease in excessive sleepiness as measured by KSS compared to no treatment (MD = -1.40 points; 95% CI: -2.60 to -0.20;

[CMT = 1 pt]: CoE is very low due to imprecision and indirectness). Participants were followed for 1-4 nights in a lab-simulated night shift and received 4 mg/kg of caffeine (see supplemental material, Figure S123).

One RCT⁶⁸ (N = 30 healthy participants) demonstrated that caffeine may have a clinically meaningful increase in alertness as measured by MSLT compared to no treatment (MD = 3.25 minutes; 95% CI: 0.37 to 6.13; [CMT = 1 minute]; CoE is very low due to imprecision and indirectness). Participants were followed for five nights in a lab-simulated night shift and received 98-197 mg of caffeine (see supplemental material, Figure S124).

One RCT⁴⁷ (N = 22 shift workers without a diagnosis of SWD) failed to show, or to exclude, that caffeine had a benefit or harm on arousal as measured using a VAS compared to no treatment (MD = 0.35 cm; 95% CI: -13.51 to 14.21; [CMT = Not Established]; CoE is low due to imprecision and indirectness). Participants received 200 mg of caffeine and were followed for one night (see supplemental material, Figure S125).

Two RCTs^{68, 69} (N = 60 healthy participants) demonstrated that caffeine may increase subjective measures of alertness as measured using a VAS compared to no treatment (MD = 14.12 mm; 95% CI: 6.58 to 21.65; [CMT = Not Established]; CoE is low due to imprecision and indirectness). Participants were followed for 1-5 nights in a lab-simulated night shift and received 98-200 mg of caffeine (see supplemental material, Figure S126).

One RCT⁷¹ (N = 12 healthy participants) demonstrated that caffeine and a nap may decrease excessive sleepiness as measured by the Samn Perelli Fatigue Scale compared to placebo and a nap (MD = -1.62 points; 95% CI: -3.13 to -0.11; [CMT = Not Established]; CoE is low due to imprecision and indirectness). Participants were followed for one night in a lab-simulated night shift and received 200 mg of caffeine (see supplemental material, Figure S127).

COGNITIVE PERFORMANCE: Two RCTs^{67, 71} (N = 45 healthy participants) demonstrated that caffeine may have a clinically meaningful improvement in cognitive function as measured by PVT lapses (MD = -3.20 lapses; 95% CI: -5.53 to -0.88; [CMT = 1 lapse]; CoE is very low due to imprecision and indirectness). Participants were followed for 1-4 nights in a lab-simulated night shift and received 300 mg or 4 mg/kg of caffeine (see supplemental material, Figure S128).

One RCT⁶⁷ (N = 33 healthy participants) demonstrated that caffeine may improve cognitive performance as measured by the change of standard score in the Torrance test of creative thinking compared to no treatment (MD = 3.79 change score; 95% CI: -2.95 to 10.53; [CMT = Not Established]; CoE is low due to imprecision and indirectness). Participants were followed for four nights in a lab-simulated night shift and received 300 mg of caffeine (see supplemental material, Figure S129).

One RCT⁵⁴ (N = 19 healthy participants) demonstrated that caffeine may improve cognitive performance based on the following measures when compared to no treatment: reaction time on the PVT (MD = -32.17 ms; 95% CI: -65.94 to 1.60; [CMT = Not Established]), the number of control losses on the dual task (MD = -9.13 control losses; 95% CI: -20.91 to 2.65; [CMT = Not Established]), the mannequin throughput on the switch task (MD = 2.45 units; 95% CI: -1.31 to 6.21; [CMT = Not Established]), the Wilkinson four-choice reaction time throughput (MD = 10.64 units; 95% CI: -8.10 to 29.38; [CMT = Not Established]), and the math throughput on the switching task (MD = 3.83 units; 95% CI: -1.71 to 9.37; [CMT = Not Established]). All measures had low CoE due to imprecision and indirectness. Participants were followed for two nights of sleep deprivation in a lab-simulated shift work setting and received 200 mg of caffeine (data from the first night were analyzed) (see supplemental materials, Figure S130-S134).

One RCT⁶⁸ (N = 30 healthy participants) demonstrated that caffeine, compared to no treatment, may improve cognitive performance when measured using the following domains on the SALT: the percent correct responses (MD = 4.00 percent; 95% CI: -0.78 to 8.78; [CMT = Not Established]), correction time (MD = -0.90 seconds; 95% CI: -2.69 to 0.89; [CMT = Not Established]), percentage of non-faulty items (MD = -0.50 percent; 95% CI: -1.02

to 0.02; [CMT = Not Established]), and percentage of empty items (MD = -0.20 percent; 95% CI: -0.38 to -0.02; [CMT = Not Established]). All measures had low CoE due to imprecision and indirectness. Participants were followed for five nights and received 97-198 mg of caffeine (see supplemental material, Figures S135-S138).

One RCT³⁷ (N = 48 healthy participants) demonstrated that caffeine, compared to no treatment, may improve cognitive performance as measured by the deviation of altitude in a flight simulator (MD = -80.20 km; 95% CI: -106.57 to -53.83; [CMT = Not Established]) and deviation in velocity envelope in a flight simulator (MD = -6.93 km/h; 95% CI: -9.20 to -4.66; [CMT = Not Established]). Both measures had low CoE due to imprecision and indirectness. Participants were followed for one night in a lab-simulated night shift and received 200 mg of caffeine (see supplemental material, Figures S14-S140).

One RCT⁴⁷ (N = 22 shift workers without a diagnosis of SWD) demonstrated that caffeine, compared to no treatment, may improve cognitive performance as measured using the choice reaction time (MD = -107.17 ms; 95% CI: -292.50 to 78.16; [CMT = Not Established]) and improved cognitive performance as measured using the number of trials without false alarms during the letter cancellation task (MD = 0.29 trials; 95% CI: 0.09 to 0.49; [CMT = Not Established]). Both measures had low CoE due to imprecision and indirectness. Participants were followed for one night and received 200 mg of caffeine (see supplemental material, Figures S141-S142).

Important Outcomes

TOTAL SLEEP TIME: Two RCTs^{67, 68} (N = 63 healthy participants) failed to show, or to exclude, that caffeine had a benefit or harm on total sleep time as measured by PSG compared to no treatment (MD = -24.44 minutes; 95% CI: -66.03 to 17.16; [CMT = 15 minutes]). Participants were followed for 4-5 nights in a lab-simulated night shift and received either 4 mg/kg or 97-198 mg of caffeine (see supplemental material, Figure S143).

One RCT⁷⁰ (N = 34 shift workers without a diagnosis of SWD) demonstrated that caffeine had a clinically meaningful reduction in total sleep time as measured by PSG compared to no treatment (MD = -81.7 minutes; 95% CI: -136.47 to -26.93; [CMT = 15 minutes]). Participants were followed for two nights and received 200 mg of caffeine (see supplemental material, Figure S144).

One RCT⁶⁸ (N = 30 healthy participants) demonstrated that caffeine may have a clinically meaningful decrease in total sleep time as measured using a subject questionnaire compared to no treatment (MD = -67.00 minutes; 95% CI: -130.18 to -3.82 minutes; [CMT = 15 minutes]). Participants were followed for five nights in a lab-simulated night shift and received 98-197 mg of caffeine (see supplemental material, Figure S145).

WASO: One RCT⁶⁸ (N = 30 healthy participants) failed to show, or to exclude, that caffeine had a benefit or harm regarding WASO as measured by a subjective questionnaire compared to no treatment (MD = 36.20 minutes; 95% CI: -26.88 to 99.28; [CMT = 20 minutes]). Participants were followed for five nights in a lab-simulated night shift and received 98-197 mg of caffeine (see supplemental material, Figure S146).

SLEEP LATENCY: One RCT⁶⁸ (N = 30 healthy participants) demonstrated little to no difference in sleep latency as measured by PSG between caffeine and no treatment (MD = -1.50 minutes, 95% CI: -7.63 to 4.63; [CMT = 20 minutes]). Participants were followed for 5 nights in a lab-simulated night shift and received 98-197 mg of caffeine (see supplemental material, Figure S147).

One RCT⁷⁰ (N = 34 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep latency as measured by PSG between caffeine and no treatment (MD = 2.80 minutes; 95% CI: -1.23 to 6.83; [CMT = 20 minutes]). Participants were followed for two nights and received 200 mg of caffeine (see supplemental material, Figure S148).

One RCT⁶⁸ (N = 30 healthy participants) failed to show, or to exclude, that caffeine had an effect on sleep latency as measured by a subjective questionnaire between compared to no treatment (MD = 34.70 minutes; 95% CI: -26.05 to 95.45; [CMT = 20 minutes]). Participants were followed for five nights in a lab-simulated night shift and received 98-197 mg of caffeine (see supplemental material, Figure S159).9).

SLEEP EFFICIENCY: One RCT⁷² (N = 16 healthy participants) demonstrated that, while not clinically meaningful, caffeine may reduce sleep efficiency as measured by PSG compared to no treatment (MD = -8.00 percent; 95% CI: -19.08 to 3.08; [CMT = 10%]). Participants were followed for one night in a lab-simulated night shift and received 300 mg of caffeine (see supplemental material, Figure S150).

One RCT⁷⁰ (N = 34 shift workers without a diagnosis of SWD) demonstrated that caffeine may result in a clinically meaningful reduction in sleep efficiency as measured by PSG compared to no treatment (MD = -18.00 percent; 95% CI: -31.22 to -4.78; [CMT = 10%]). Participants were followed for two nights and received 200 mg of caffeine (see supplemental material, Figure S151).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of caffeine in adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to imprecision and indirectness. (see supplemental material, Table S9).

BENEFITS VS HARMS: The potential benefits of caffeine in adults with SWD include a clinically meaningful improvement in excessive sleepiness. The potential harms include a risk of anxiety and trouble sleeping. The TF judged that the potential benefits of caffeine in adults with SWD outweigh the potential harms.

RESOURCE USE: The current unit costs for caffeine is \$0.08 for a 200 mg tablet. The TF judged these costs are negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically meaningful improvement in excessive sleepiness measured by MWT, the TF judged that most with SWD would generally be accepting of treatment with caffeine.

Clockwise Rotating Shift Schedule

A total of 10 non-randomized trials⁷³⁻⁸² investigated the use of a clockwise rotating shift schedule compared to a counterclockwise rotating shift schedule in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness/alertness, sleep quality, and cognitive performance. Participants in the studies had a mean age of 35 years (54.5% female) and were shift workers without a diagnosis of SWD⁷³⁻⁸⁰ or healthy participants in a lab-simulated shift schedule^{81, 82}. The follow-up duration ranged from 5 days-3 years. Meta-analyses were performed to assess the efficacy of a clockwise rotating shift schedule as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S152 through Figure S172. A summary of findings table is provided in the supplemental material, Table S11. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of clockwise shift rotation to treat adults with SWD: Excessive sleepiness/alertness, sleep quality, and cognitive performance.

EXCESSIVE SLEEPINESS/ALERTNESS: Two non-randomized studies^{76, 78} (N = 170 shift workers without a diagnosis of SWD) demonstrated that a clockwise rotating schedule may have a clinically meaningful decrease in excessive sleepiness as measured using KSS compared to a counterclockwise rotating schedule (MD = -1.45 (95%

CI: -2.08 to -0.83; [CMT = 1 pt]; CoE is very low due to inconsistency, indirectness, and imprecision) (see supplemental material, Figure S152).

Two non-randomized studies^{73, 74} (N = 166 shift workers without a diagnosis of SWD) demonstrated that, while not clinically meaningful, a clockwise rotating schedule may decrease excessive sleepiness as measured using ESS compared to a counterclockwise rotating schedule (MD = -0.85 (95% CI: -1.93 to 0.23; [CMT = 2 pt]; CoE is very low due to imprecision, indirectness, and risk of bias) (see supplemental material, Figure S153).

One non-randomized study⁸² (N = 23 healthy participants) demonstrated that a clockwise rotation schedule may have a clinically meaningful decrease in excessive sleepiness as measured using SSS compared to a counterclockwise rotation schedule (MD = -1.20 points (95% CI: -2.43 to 0.03; [CMT = 1 pt]; CoE is very low due to imprecision and indirectness). Participants were followed for two weeks in a lab-simulated night shift (see supplemental material, Figure S154).

One non-randomized study⁷⁹ (N = 23 shift workers without a diagnosis of SWD) demonstrated that a clockwise rotation schedule may decrease excessive sleepiness as measured by a subjective morning questionnaire compared to a counterclockwise rotation schedule (MD = 17.30 units (95% CI: 2.37 to 32.23; [CMT = Not Established]; CoE is very low due to imprecision and indirectness). The questionnaire reported sleepiness as a measure from 1 to 100, with 1 being very sleepy and 100 being very alert. Participants were followed for five days (see supplemental material, Figure 155).

SLEEP QUALITY: One non-randomized study⁷⁶ (N = 25 shift workers without a diagnosis of SWD) demonstrated that a clockwise rotating schedule may improve sleep quality as measured by the sleep quality index compared to a counterclockwise rotating schedule (MD = 0.58 units (95% CI: -0.01 to 1.17; [CMT = Not Established]; CoE is very low due to imprecision, indirectness). The sleep quality index is a scale from 1-5, with 1 representing poor sleep and 5 representing no problems with sleep (see supplemental material, Figure S156).

One non-randomized study⁷⁷ (N = 4,750 shift workers without a diagnosis of SWD) demonstrated that a clockwise rotating schedule may improve sleep quality as measured using the PSQI compared to a counterclockwise rotating schedule (MD = -0.60 points (95% CI: -0.84 to -0.36; [CMT = Not Established]; CoE is low due to indirectness). Participants were followed for one year (see supplemental material, Figure S157).

One non-randomized study⁷⁵ (N = 611 shift workers without a diagnosis of SWD) demonstrated that a clockwise rotating schedule had little to no effect on sleep quality as measured using a modified SSI compared to a counterclockwise rotating schedule (MD = 0.00 points (95% CI: -0.15 to 0.15; [CMT = Not Established]; CoE is very low due to imprecision and indirectness). Higher scores on the modified SSI were associated with experiencing more sleep disturbances (see supplemental material, Figure S158).

COGNITIVE PERFORMANCE: One non-randomized study⁷⁸ (N = 145 shift workers without a diagnosis of SWD) demonstrated that a clockwise rotating schedule, compared to a counterclockwise rotating schedule, may improve cognitive performance as measured by the following metrics of the PVT: mean reaction time (MD = -66.30 ms; 95% CI: -93.31 to -39.29; [CMT = Not Established]), speed (MD = 0.60 1/ms; 95% CI: 0.32 to 0.88; [CMT = Not Established]), fastest 10% reaction times (MD = -54.50 ms; 95% CI: -71.46 to -37.54; [CMT = Not Established]), and slowest 10% reaction time (MD = -201.50 ms; 95% CI: -472.22 to 69.22 ms; [CMT = Not Established]). All metrics had very low CoE due to imprecision and indirectness. Participants were followed for five days (see supplemental materials, Figures S159-S162).

One non-randomized study⁸⁰ (N = 100 shift workers without a diagnosis of SWD) demonstrated that a clockwise rotating schedule may improve cognitive performance as measured by a subjective questionnaire reporting the number of individuals having difficulty concentrating at work compared to a counterclockwise rotating schedule (risk ratio of 0.31; 95% CI: 0.17 to 0.56; and an absolute risk of 442 fewer per 1,000 (531 fewer to 282 fewer);

[CMT = Not Established]; CoE is very low due to imprecision and indirectness). Participants were followed for six days (see supplemental material, Figure S163).

One non-randomized study⁸¹ (N = 28 healthy participants) demonstrated that a clockwise rotating schedule may worsen cognitive performance as measured by the number of correct responses during the Bakan vigilance test compared to a counterclockwise rotating schedule (MD = -8.56 correct responses; 95% CI: -28.02 to 10.90; [CMT = Not Established]; CoE is very low due to imprecision). Participants were followed for two weeks in a lab-simulated night shift (see supplemental material, Figure S164).

Important Outcomes

TOTAL SLEEP TIME: One non-randomized study⁷⁵ (N = 611 shift workers without a diagnosis of SWD) demonstrated that a clockwise rotating schedule may decrease total sleep time as measured using a revised SSI compared to a counterclockwise rotating schedule (MD = -6.06 minutes; 95% CI: -22.63 to 10.52; [CMT = Not Established]) (see supplemental material, Figure S165).

Three non-randomized studies^{74, 76, 80} (N = 229 shift workers without a diagnosis of SWD) demonstrated that a clockwise rotating schedule may have a clinically meaningful increase in total sleep time as measured using subject reports compared to a counterclockwise rotating schedule (MD = 22.8 minutes; 95% CI: -12.68 to 58.28; [CMT = 15 minutes]). Participants were followed for a duration ranging from 5 days to 2.5 years (see supplemental material, Figure S166).

One non-randomized study⁸² (N = 23 healthy participants) demonstrated little to no difference in total sleep time as measured by actigraphy between a clockwise rotating schedule and a counterclockwise rotating schedule (MD = -0.20 minutes; 95% CI: -1.43 to 1.03; [CMT = 15 minutes]). Participants were followed for two weeks (see supplemental material, Figure S167).

One non-randomized study (N = 33 shift workers without a diagnosis of SWD) failed to show, or to exclude, that a clockwise rotating schedule had a benefit or harm on total sleep time as measured by actigraphy compared to a counterclockwise rotating schedule (MD = -54.0 minutes; 95% CI: -227.32 to 119.32; [CMT = 15 minutes]). Participants were followed for five days (see supplemental material, Figure S168).

MENTAL HEALTH: One non-randomized study⁷⁵ (N = 611 shift workers without a diagnosis of SWD) demonstrated little to no difference on mental health as measured using the general health questionnaire between a clockwise rotating schedule and a counterclockwise rotating schedule (MD = -0.52 units; 95% CI: -1.58 to 0.54; [CMT = Not Established]) (see supplemental material, Figure S169).

One non-randomized study⁷⁶ (N = 25 shift workers without a diagnosis of SWD) demonstrated little to no difference on mental health as measured by a subjective stress scale between a clockwise rotating schedule and a counterclockwise rotating schedule (MD = 0.28 points; 95% CI: -0.52 to 1.08; [CMT = Not Established]). A score of 1 indicated very low stress and a score of 9 indicated very high stress (see supplemental material, Figure S170).

SLEEP LATENCY: One non-randomized study⁷⁹ (N = 33 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep latency as measured by actigraphy between a clockwise rotating schedule and a counterclockwise rotating schedule (MD = -3.49 minutes; 95% CI: -4.91 to -2.07; [CMT = 15 minutes]). Participants were followed for five days (see supplemental material, Figure S171).

SLEEP EFFICIENCY: One non-randomized study⁷⁹ (N = 33 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep efficiency as measured by actigraphy between a clockwise rotating schedule and a counterclockwise rotating schedule (MD = -0.73 percent; 95% CI: -4.59 to 3.13; [CMT = 10%]). Participants were followed for five days (see supplemental material, Figure S172).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of clockwise rotating shift schedules in adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to imprecision, risk of bias, and indirectness. (see supplemental material, Table S11).

BENEFITS VS HARMS: The potential benefits of clockwise rotating shift schedules in adults with SWD includes a clinically meaningful improvement in excessive sleepiness. No potential harm or adverse events were presented in the included studies. The TF judged that the potential benefits of clockwise rotating shift schedules in adults with SWD outweigh the potential harms.

RESOURCE USE: The TF estimated the resources required to implement clockwise rotating shift schedule were negligible to adults with SWD at an individual level, though may require increased resources to implement at an institutional level.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the improvement in excessive sleepiness, sleep quality, and cognitive performance, the TF judged that most with SWD would generally be accepting of working a clockwise rotating shift schedule.

Naps prior to the night of shift

A total of 1 RCT⁶⁷ and 2 non-randomized studies^{83, 84} investigated the use of naps taken prior to the night shift in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness/alertness, cognitive performance, sleep quality, and TST. Participants in the RCT had an age range of 18-65 years (38% female) and the nap duration in the studies ranged from 1.6-3 hours prior to the start of the shift. The studies included healthy participants in a simulated night shift setting. Meta-analyses were performed to assess the efficacy of naps taken prior to the night shift as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S177 through Figure S185. A summary of findings table is provided in the supplemental material, Table S13. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of naps prior to the first night of the shift to treat adults with SWD: Excessive sleepiness/alertness, accident risk, cognitive performance, sleep quality.

EXCESSIVE SLEEPINESS/ALERTNESS: One RCT⁶⁷ (N = 33 healthy participants) demonstrated that naps prior to the first night shift may have a clinically meaningful decrease in excessive sleepiness as measured by MWT compared to no naps prior to the first shift (MD = 5.24 minutes; 95% CI: -1.13 to 11.61; [CMT = 2 minutes]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed for two days in a lab-simulated night shift and given 2.5-hour nap opportunity (see supplemental material, Figure S177).

One non-randomized study⁸³ (N = 16 healthy participants) demonstrated that naps prior to the first night shift may decrease excessive sleepiness as measured by a VAS compared to no naps prior to the first night shift (MD = -0.63 cm; 95% CI: -1.35 to 0.09; [CMT = Not Established]; CoE is very low due to imprecision). Participants were followed for one day in a lab-simulated night shift and were given a 3-hour nap opportunity (see supplemental material, Figure S178).

SLEEP QUALITY: One non-randomized study⁸⁴ (N = 18 shift workers without a diagnosis of SWD) demonstrated that naps prior to the first night shift may decrease sleep quality as measured by a 9-point Likert scale compared

to no naps prior to the first night shift (MD = -0.55 points; 95% CI: -2.25 to 1.15; [CMT = Not Established]; CoE is very low due to imprecision and indirectness). Participants were followed for one day and slept at least 15 minutes during their nap opportunity, which occurred more than 60 minutes prior to their main sleep period (see supplemental material, Figure S179).

COGNITIVE PERFORMANCE: One RCT⁶⁷ (N = 33 healthy participants) demonstrated that naps prior to the first night shift may have a clinically meaningful increase in cognitive performance as measured by lapses on the PVT compared to no naps prior to the first night shift (MD = -2.44 lapses; 95% CI: -4.63 to -0.25; [CMT = 1 lapse]; CoE is very low due to imprecision). There was little to no difference on cognitive performance when measured by the change from baseline data on the Torrance test of creative thinking between naps prior to the first night shift and no naps prior to the first night shift (MD = -0.65 units; 95% CI: -7.86 to 6.56; [CMT = Not Established]; CoE is very low due to imprecision). Participants were followed for two days in a lab-simulated night shift and were given a 2.5-hour nap opportunity (see supplemental material, Figures S180-S181).

One non-randomized study⁸³ (N = 16 healthy participants) demonstrated that naps prior to the first night shift, compared to no naps prior to the first night shift, may improve cognitive performance as measured by the four-choice serial reaction time (MD = -1.06 sec; 95% CI: -4.23 to 2.12; [CMT = Not Established]; CoE is very low due to imprecision) and by the two-letter memory and search test (MD = -0.04 sec; 95% CI: -0.21 to 0.13; [CMT = Not Established]; CoE is very low due to imprecision). Participants were followed for one day in a lab-simulated night shift and were given a 3-hour nap opportunity (see supplemental material, Figures S182-S183).

One non-randomized study⁸⁴ (N = 18 healthy participants) demonstrated that naps prior to the night shift may decrease cognitive performance as measured by the percent time off target on the hand steadiness test compared to no naps prior to the first night shift (MD = 1.79 percent (95% CI: -7.56 to 11.14; [CMT = Not Established]; CoE is very low due to imprecision and indirectness). Participants were followed for one day in a lab-simulated night shift and slept at least 15 minutes during their nap opportunity, which occurred more than 60 minutes prior to their main sleep period (see supplemental material, Figure S184).

Important Outcomes

TOTAL SLEEP TIME: One non-randomized study⁸⁴ (N = 18 healthy participants) failed to show, or to exclude, that naps prior to the first night shift had a benefit or harm regarding total sleep time as measured by a subjective report compared to no naps prior to the first night shift (MD = 57.0 minutes (95% CI: -52.93 to 166.93; [CMT = 15 minutes])). Participants were followed for one day in a lab-simulated night shift and slept at least 15 minutes during their nap opportunity, which occurred more than 60 minutes prior to their main sleep period (see supplemental material, Figure S185).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of naps taken prior to the night shift in adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to imprecision and indirectness. (see supplemental material, Table S13).

BENEFITS VS HARMS: The potential benefits of naps during the shift in adults with SWD include a clinically meaningful improvement in excessive sleepiness and cognitive performance. The potential harms include a risk of worsened fatigue, cognitive performance, driving simulator performance, and sleep inertia if the individual is not given sufficient time to recover from the nap. The TF judged that the potential benefits of naps taken prior to the night shift in adults with SWD outweigh the potential harms.

RESOURCE USE: The costs associated with naps are minimal but may require upfront expenses for an employer to provide a space for employees to nap. The TF judged these costs are negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the improvements in excessive sleepiness and cognitive performance, the TF judged that most with SWD would generally be accepting of treatment with naps taken prior to the night shift.

Diet and Meal-timing

A total of 4 RCTs⁸⁵⁻⁸⁸ investigated the use meal timing in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness/alertness, accident risk, and cognitive performance. Participants in the RCTs had a mean age of 25 years (25% female). Participants either did not eat or only ate a snack during the night shift and were compared to participants that ate a full meal during the night shift. All studies included healthy participants in a simulated night shift setting with a follow-up duration ranging from 6-7 days. Meta-analyses were performed to assess the efficacy of meal timing as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S186 through Figure S205. A summary of findings table is provided in the supplemental material, Table S15. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of diet and meal timing to treat adults with SWD: Excessive sleepiness/alertness, accident risk, and cognitive performance.

EXCESSIVE SLEEPINESS/ALERTNESS: One RCT⁸⁸ (N = 10 healthy participants) demonstrated that eating a snack/not eating may have a clinically meaningful decrease in excessive sleepiness as measured using KSS compared to eating a full meal (MD = -3.24 points; 95% CI: -5.68 to -0.80; [CMT = 1 pt]; CoE is very low due to imprecision and indirectness). Participants were followed for four nights in a lab-simulated night shift and either ate a full meal at night or did not eat (see supplemental material, Figure S186).

One RCT⁸⁵ (N = 39 healthy participants) demonstrated that, while not clinically meaningful, eating a snack/not eating decreased excessive sleepiness as measured using SSS compared to eating a full meal (MD = -0.79 points; 95% CI: -1.30 to -0.27; [CMT = 1 pt]; CoE is very low due to imprecision and indirectness). Participants were followed for four nights in a lab-simulated night shift and received either a full meal, a snack, or no food during the night shift (see supplemental material, Figure S187).

ACCIDENT RISK: Two RCTs^{85, 86} (N = 49 healthy participants) demonstrated that eating a snack/not eating, compared to eating a full meal, may have a clinically meaningful improvement in accident risk as measured by the following metrics on a driving simulator: percentage of time spent in the safe zone (MD = 5.49 percent; 95% CI: -0.34 to 11.32; [CMT = Any change]; CoE is very low due to imprecision, indirectness, and inconsistency), speed variability (MD = -1.92 km/h; 95% CI: -3.92 to 0.08; [CMT = Any change]; CoE is very low due to imprecision, indirectness, and inconsistency), and lane variability (MD = -0.06 m; 95% CI: -0.11 to -0.01; [CMT = Any change]; CoE is low due to imprecision and indirectness). Participants were followed for 6-7 nights in a lab-simulated night shift and received either a full meal, a snack, or no food during the night shift (see supplemental material, Figures S188-S190).

COGNITIVE PERFORMANCE: Two RCTs^{85, 86} (N = 49 healthy participants) demonstrated that eating a snack/not eating, compared to eating a full meal, resulted in a clinically meaningful improvement in cognitive performance as measured by the following metrics: PVT lapses (MD = -3.07 lapses; 95% CI: -4.21 to -1.93; [CMT = 1 lapse]; CoE is low due to imprecision and indirectness) and reciprocal reaction time on PVT (MD = 0.23 ms; 95% CI: 0.04 to 0.42; [CMT = Not Established]; CoE is low due to imprecision and indirectness). Participants were followed for 6-7 nights in a lab-simulated night shift and received either a full meal, a snack, or no food during the night shift (see supplemental material, Figures S191-S192).

One RCT⁸⁸ (N = 10 healthy participants) demonstrated that eating a snack/not eating, compared to eating a full meal, may improve cognitive performance as measured by the following metrics: the number correct on the DSST (MD = 3.89 correct responses; 95% CI: -12.97 to 20.75; [CMT = Not Established]; CoE is low due to imprecision and indirectness) and the number of errors on the PVT (MD = -7.92 errors; 95% CI: -18.28 to 2.44; [CMT = Not Established]; CoE is low due to imprecision and indirectness). Participants were followed for six nights in a lab-simulated night shift and received either a full meal or no food during the night shift (see supplemental material, Figures S193-S194).

One RCT⁸⁵ (N = 39 healthy participants) demonstrated that eating a snack/not eating, compared to eating a full meal, may improve cognitive performance as measured using the following metrics: the throughput on the choice reaction time task (MD = 12.38 correct responses/minute; 95% CI: 6.90 to 17.86; [CMT = Not Established]; CoE is low due to imprecision and indirectness) and the running memory continuous performance task (MD = 15.56 correct responses/minute (95% CI: 9.01 to 22.10; [CMT = Not Established]; CoE is low due to imprecision and indirectness). Participants were followed for seven days in a lab-simulated night shift and received either a full meal, a snack, or no food during the night shift (see supplemental material, Figures S195-S196).

Important Outcomes

TOTAL SLEEP TIME: Two RCTs^{85, 86} (N = 49 healthy participants) demonstrated that, while not clinically meaningful, eating a snack/not eating may increase total sleep time as measured by PSG or EEG compared to eating a full meal (MD = 1.62 minutes; 95% CI: -12.15 to 15.38; [CMT = 15 minutes]). Participants were followed for 6-7 nights in a lab-simulated night shift and received either a full meal, a snack, or no food during the night shift (see supplemental material, Figure S197).

One RCT⁸⁵ (N = 32 healthy participants) demonstrated little to no difference in total sleep time as measured by actigraphy between eating a snack/not eating and eating a full meal (MD = -0.59 minutes; 95% CI: -6.06 to 4.88; [CMT = 15 minutes]). Participants were followed for seven nights in a lab-simulated night shift and received either a full meal, a snack, or no food during the night shift (see supplemental material, Figure S198).

MENTAL HEALTH: One RCT⁸⁷ (N = 19 healthy participants) demonstrated that eating a snack/not eating, compared to eating a full meal, may improve mental as measured using a VAS of depression (MD = 13.20 percent; 95% CI: 10.01 to 16.39; [CMT = Not Established]) and a VAS of anxiety (MD = 6.0 percent; 95% CI: 2.41 to 9.59 percent; [CMT = Not Established]). The data was presented as a percent change from baseline, with the higher numbers representing less depression or less anxiety. Participants were followed for four nights in a lab-simulated night shift and received a full meal during the night shift (see supplemental material, Figure S199-S200).

WASO: Two RCTs^{85, 86} (N = 49 healthy participants) demonstrated little to no difference in WASO as measured by PSG or EEG between eating a snack/not eating and eating a full meal (MD = -0.08 minutes; 95% CI: -13.77 to 13.61; [CMT = 20 minutes]). Participants were followed for 6-7 nights in a lab-simulated night shift and received either a full meal, a snack, or no food during the night shift (see supplemental material, Figure S201).

SLEEP LATENCY: Two RCTs^{85, 86} (N = 49 healthy participants) demonstrated little to no difference on sleep latency as measured by PSG or EEG between eating a snack/not eating and eating a full meal (MD = 1.05 minutes; 95% CI: 0.01 to 2.09; [CMT = 20 minutes]). Participants were followed for 6-7 nights in a lab-simulated night shift and received either a full meal, a snack, or no food during the night shift (see supplemental material, Figure S202).

One RCT⁸⁵ (N = 32 healthy participants) demonstrated little to no difference on sleep latency as measured by PSG or EEG between eating a snack/not eating and eating a full meal (MD = 0.93 minutes; 95% CI: -1.00 to 2.86; [CMT = 15 minutes]). Participants were followed for seven nights in a lab-simulated night shift and received either a full meal, a snack, or no food during the night shift (see supplemental material, Figure S203).

SLEEP EFFICIENCY: Two RCTs^{85, 86} (N = 44 healthy participants) demonstrated little to no difference on sleep efficiency as measured by PSG or EEG between eating a snack/not eating and eating a full meal (MD = -0.23 percent; 95% CI: -3.96 to 3.50; [CMT = 10%]) Participants were followed for 6-7 nights in a lab-simulated night shift and received either a full meal, a snack, or no food during the night shift (see supplemental material, Figure S204).

One RCT⁸⁵ (N = 32 healthy participants) demonstrated that, while not clinically meaningful, eating a snack/not eating may increase sleep efficiency as measured by actigraphy compared to eating a full meal (MD = 4.66 percent; 95% CI: -4.41 to 13.72; [CMT = 10%]) Participants were followed for seven nights in a lab-simulated night shift and received either a full meal, a snack, or no food during the night shift (see supplemental material, Figure S205).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of diet and meal timing in adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to inconsistency, imprecision, and indirectness (see supplemental material, Table S15).

BENEFITS VS HARMS: The potential benefits of diet and meal timing in adults with SWD include clinically meaningful improvements in excessive sleepiness, cognitive performance, and accident risk favoring eating a snack or not eating during the night shift. No adverse events were reported in the included studies, however, there may be patients who do not wish to feel hungry during their shift. Avoiding meals during the shift may be contraindicated in individuals with diabetes. The TF judged that the potential benefits of eating a snack or not eating during the night shift in adults with SWD outweigh the potential harms.

RESOURCE USE: Minimal resources are needed to shift the majority of food consumption to the daytime. The TF judged these costs to be negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the improvement in excessive sleepiness and accident risk, the TF judged that most people with SWD would generally be accepting of treatment with eating a snack or not eating during the night shift.

Bright Light and Caffeine

A total of 2 RCTs^{47, 54} investigated the use of the combination of bright light and caffeine in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness/alertness and cognitive performance. Participants in the RCTs had an age range 19-36 years (9% female). In 1 RCT⁴⁷, participants were exposed to bright light with an intensity of light of 3000 lux for 1 hr or dim light with an intensity of light of ~20-50 lux in combination with either 200 mg of caffeine or placebo for 1 night. Participants in this study were shift workers without a diagnosis of SWD. The other RCT⁵⁴ exposed participants to bright light with an intensity of light of 2500 lux for 4 hrs and of 2000 lux during testing times or dim light with an intensity of light at <100 lux in combination with either 200 mg caffeine or placebo for 2 nights. Participants in this study were healthy individuals in a simulated lab setting. Meta-analyses were performed to assess the efficacy of the combination of bright light and caffeine as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S206 through Figure S221. A summary of findings table is provided in the supplemental material, Table S17. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of the combination of bright light and caffeine to treat adults with SWD: Excessive sleepiness/alertness and cognitive performance.

EXCESSIVE SLEEPINESS/ALERTNESS: One RCT⁴⁷ (N = 22 shift workers without a diagnosis of SWD) demonstrated that bright light and caffeine may improve alertness as measured by a VAS compared to dim light and no caffeine (MD = 6.71 cm; 95% CI: -7.43 to 20.85; [CMT = Not Established]; CoE is very low due to imprecision, indirectness, and risk of bias). Participants were followed for 1 night and received 200 mg of caffeine with exposure to 3000 lux of bright light for 1 hour. Higher numbers on the VAS indicated more arousal. Additional information on the effectiveness of the combination treatment against individual treatments can be found in the supplemental materials (see supplemental material, Figures S206-S208).

One RCT⁵⁴ (N = 19 healthy participants) demonstrated that bright light and caffeine, compared to dim light and no caffeine, may have a clinically meaningful improvement on excessive sleepiness when measured using both the SSS (MD = -1.77 points; 95% CI: -2.87 to -0.67; [CMT = 1 pt]; CoE is very low due to imprecision, indirectness, and risk of bias) and the MWT (MD = 2.02 minutes; 95% CI: 1.48 to 2.56, [CMT = 2 minutes]; CoE is very low due to imprecision, indirectness, and risk of bias). Participants were followed for 2 nights in a lab-simulated shift work setting and received 200 mg of caffeine with exposure to 2500 lux of bright light for 10 hours. Additional information on the effectiveness of the combination treatment against individual treatments can be found in the supplemental materials (see supplemental material, Figures S209-S211 and Figures S212-S214).

COGNITIVE PERFORMANCE: One RCT⁴⁷ (N = 22 shift workers without a diagnosis of SWD) demonstrated that bright light and caffeine, when compared to dim light and no caffeine, may improve cognitive performance as measured by the following metrics: the choice reaction time (MD = -108.06 ms; 95% CI: -280.77 to 64.65; [CMT = Not Established]; CoE is very low due to imprecision, indirectness and risk of bias) and the number of trials without a false alarm on the letter cancellation test (MD = 0.51 trials; 95% CI: 0.09 to 0.93; [CMT = Not Established]; CoE is very low due to imprecision, indirectness and risk of bias). Participants were followed for 1 night and received 200 mg of caffeine with exposure to 3000 lux of bright light for 1 hour (see supplemental material, Figures S215-S216).

One RCT⁵⁴ (N = 19 healthy participants) demonstrated the bright light and caffeine, compared to dim light and no caffeine, may improve cognitive performance as measured by the following metrics: PVT reaction time (MD = -61.55 ms; 95% CI: -91.41 to -31.69; [CMT = Not Established]), number of losses on the dual task (MD = -16.98 losses; 95% CI: -27.81 to -6.15; [CMT = Not Established]), the mannequin throughput on the switching task (MD = 3.16 units; 95% CI: -0.75 to 7.07; [CMT = Not Established]), the Wilkinson four-choice reaction time throughput (MD = 27.20 units; 95% CI: 14.68 to 39.72; [CMT = Not Established]), and the math throughput on the switching task (MD = 6.28 units; 95% CI: 1.03 to 11.53; [CMT = Not Established]). For all measures, CoE was very low due to imprecision, indirectness, and risk of bias. Participants were followed for 2 nights in a lab-simulated shift work setting and received 200 mg of caffeine with exposure to 2500 lux of bright light for 10 hours (see supplemental material, Figures S217-S221).

Important Outcomes

NONE

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of the combination of bright light and caffeine in adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to risk of bias, imprecision, and indirectness. (see supplemental material, Table S17).

BENEFITS VS HARMS: The potential benefits of the combination of bright light and caffeine in adults with SWD include a clinically meaningful improvement in excessive sleepiness. The potential harms include a risk of headaches in individuals with a history of migraines, anxiety, trouble sleeping, and developing tolerance to

caffeine. The TF judged that the potential benefits of the combination of bright light and caffeine in adults with SWD outweigh the potential harms.

RESOURCE USE: The current unit costs for caffeine is \$0.08 for a 200 mg tablet. The cost of a bright light device can range from \$25-100. The TF judged these costs are negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically meaningful improvement in excessive sleepiness, the TF judged that most with SWD would generally be accepting of treatment with the combination of bright light and caffeine.

Nap and Caffeine

One RCT⁶⁷ investigated the use of the combination of caffeine and naps in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness/alertness, cognitive performance, and total sleep time. Participants in the RCT had an age range 18-65 years (44% female). Participants received dosages of 300 mg of caffeine over 4 nights. The RCT⁶⁷ included two experimental conditions: a field setting with shift workers without a diagnosis of SWD and a simulated night shift setting with healthy participants. Meta-analyses were performed to assess the efficacy of caffeine in combination with naps as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S222 through Figure S238. A summary of findings table is provided in the supplemental material, Table S19. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of the combination of naps and caffeine to treat adults with SWD: Excessive sleepiness/alertness and cognitive performance.

EXCESSIVE SLEEPINESS/ALERTNESS: One RCT⁶⁷ (N = 111 healthy participants) demonstrated that a nap and caffeine may have a clinically meaningful improvement on excessive sleepiness as measured using KSS compared to no nap and no caffeine (MD = -1.96 points; 95% CI: -3.06 to -0.85; [CMT = 1pt]; CoE is very low due to imprecision, indirectness, and risk of bias). Participants were followed for four nights and received 300 mg of caffeine and were given a 2.5-hour nap opportunity. Additional information on the effectiveness of the combination treatment against individual treatments can be found in the supplemental materials (see supplemental material, Figures S222-S224).

One RCT⁶⁷ (N = 33 healthy participants) demonstrated that a nap and caffeine may have a clinically meaningful improvement on excessive sleepiness as measured using MWT compared to no nap and no caffeine (MD = 7.12 minutes; 95% CI: 0.45 to 13.79; [CMT = 2 minutes]; CoE is very low due to imprecision, indirectness, and risk of bias). Participants were followed for four nights and received 300 mg of caffeine. Additional information on the effectiveness of the combination treatment against individual treatments can be found in the supplemental materials (see supplemental material, Figures S225-S227).

COGNITIVE PERFORMANCE: One RCT⁶⁷ (N = 33 healthy participants) demonstrated that a nap and caffeine may have a clinically meaningful improvement on cognitive performance as measured by PVT lapses compared to no nap and no caffeine (MD = -2.23 lapses; 95% CI: -4.53 to 0.07; [CMT = 1 lapse]; CoE is very low due to imprecision, indirectness, and risk of bias). Participants were followed for four nights and received 300 mg of caffeine. Additional information on the effectiveness of the combination treatment against individual treatments can be found in the supplemental materials (see supplemental material, Figures S228-S230).

One RCT⁶⁷ (N = 78 healthy participants) demonstrated that a nap and caffeine may improve cognitive performance as measured by the mean reaction time of the slowest 10% in the PVT compared to no nap and no caffeine (MD = 0.10 sec; 95% CI: -0.23 to 0.43; [CMT = Not Established]; CoE is very low due to imprecision, indirectness, and risk of bias). Participants were followed for four nights and received 300 mg of caffeine (see supplemental material, Figure S231).

One RCT⁶⁷ (N = 33 healthy participants) demonstrated that a nap and caffeine may improve cognitive performance as measured using the Torrance test of creative thinking of verbal and figural fluency compared to no nap and no caffeine (MD = 9.75 units; 95% CI: 1.86 to 17.64; [CMT = Not Established]; CoE is very low due to imprecision, indirectness, and risk of bias). Participants were followed for four nights and received 300 mg of caffeine. Additional information on the effectiveness of the combination treatment against individual treatments can be found in the supplemental materials (see supplemental material, Figures S232-S234).

Important Outcomes

TOTAL SLEEP TIME: One RCT⁶⁷ (N = 99 healthy participants) demonstrated that a nap and caffeine had a clinically meaningful increase in total sleep time as measured using PSG compared to no nap and no caffeine (MD = 56.61 minutes; 95% CI: 23.66 to 89.56 minutes; [CMT = 15 minutes]). Participants were followed for four nights and received 300 mg of caffeine. Additional information on the effectiveness of the combination treatment against individual treatments can be found in the supplemental materials (see supplemental material, Figures S235-S237).

One RCT⁶⁷ (N = 78 healthy participants) demonstrated that, while not clinically meaningful, a nap and caffeine may increase total sleep time as measured using subjective sleep diary reports compared to no nap and no caffeine (MD = 14.0 minutes; 95% CI: -18.92 to 46.92 minutes; [CMT = 15 minutes]). Participants were followed for four nights and received 300 mg of caffeine (see supplemental material, Figure S238).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of the combination of caffeine and naps in adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to risk of bias, imprecision, and indirectness. (see supplemental material, Table S19).

BENEFITS VS HARMS: The potential benefits of the combination of caffeine and naps in adults with SWD include a clinically meaningful improvement in excessive sleepiness, cognitive performance, and TST. The potential harms include a risk of anxiety, trouble sleeping, and developing tolerance to caffeine. The TF judged that the potential benefits of the combination of caffeine and naps in adults with SWD outweigh the potential harms.

RESOURCE USE: The current unit costs for caffeine is \$0.08 for a 200 mg tablet. The TF judged these costs are negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically meaningful improvement in excessive sleepiness, cognitive performance, and TST the TF judged that most with SWD would generally be accepting of treatment with the combination of caffeine and naps.

Symptoms of insomnia

Cognitive Behavioral Therapy-Insomnia

A total of 1 RCT⁸⁹ and 3 non-randomized studies⁹⁰⁻⁹² investigated the use of CBT-I in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness/alertness and sleep quality. Participants

had a mean age of 44 years (58% female). Participants were shift workers who were either diagnosed with SWD^{89, 91, 92} or worked on a night shift without a formal diagnosis.⁹⁰ Participants in the RCT⁸⁹ received either group-based CBT-I, self-guided CBT-I, or sleep hygiene education with a 6-month follow-up. The non-randomized studies were before-and-after treatment design investigating participants receiving online CBT-I,⁹¹ outpatient CBT-I,^{90, 91} or home-based CBT-I⁹² for a duration of 1-24 months. Meta-analyses were performed to assess the efficacy of CBT-I as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S239 through Figure S274. A summary of findings table is provided in the supplemental material, Table S21. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of CBT-I to treat adults with SWD: Excessive sleepiness/alertness, sleep quality.

EXCESSIVE SLEEPINESS/ALERTNESS: One non-randomized study⁹¹ (N = 66 SWD participants) demonstrated that, while not clinically meaningful, CBT-I may reduce excessive sleepiness as measured by the ESS compared to pre-CBT-I (MD = -1.17 points; 95% CI: -3.04 to 0.70; [CMT = 2 pts]; CoE is very low due to imprecision). Participants were followed for four weeks (see supplemental material, Figure S239).

SLEEP QUALITY: One non-randomized study⁹¹ (N = 66 SWD participants) demonstrated that, while not clinically meaningful, CBT-I improved sleep quality [as measured using PSQI compared to pre-CBT-I (MD = -1.84 points; 95% CI: -3.38 to -0.31; [CMT = 3 pts]; CoE is very low due to imprecision). Participants were followed for four weeks (see supplemental material, Figure S240)

One non-randomized study⁹² (N = 50 SWD participants) demonstrated that CBT-I may improve sleep quality as measured by the SSI sleep disturbance questionnaire compared to pre-CBT-I (MD = -1.80 points; 95% CI: -3.46 to -0.14; [CMT = Not Established]; CoE is very low due to imprecision). Participants were followed for four weeks (see supplemental material, Figure S241).

One non-randomized study⁹² (N = 50 SWD participants) demonstrated that CBT-I may improve sleep quality as measured by the sleep quality domain on the GSDS compared to pre-CBT-I (MD = -0.89 points; 95% CI: -1.51 to -0.27; [CMT = Not Established]; CoE is very low due to imprecision). Participants were followed for four weeks (see supplemental material, Figure S242).

One RCT⁸⁹ (N = 54 SWD participants) demonstrated that CBT-I may improve sleep quality as measured by the subjective reports of sleep quality-restedness in sleep diaries compared to no CBT-I (MD = -0.15 units (95% CI: -0.48 to 0.18; [CMT = Not Established]; CoE is very low due to imprecision). The sleep diary measured the rating of restedness after the sleep period on a scale of 1 to 5, with 1 representing good restedness and 5 representing poor restedness. Participants were followed for six months (see supplemental material, Figure S243).

One non-randomized study⁹⁰ (N = 86 shift workers without a diagnosis of SWD) demonstrated that CBT-I had little to no effects on sleep quality as measured by subjective reports of sleep quality in sleep diaries compared to pre-CBT-I (MD = 0.0 units (95% CI: -0.21 to 0.21 units; [CMT = Not Established]; CoE is very low due to imprecision, indirectness, and risk of bias). The sleep diary measured the rating of sleep quality after the sleep period on a scale of 1 to 5, with 1 representing bad sleep quality and 5 representing good sleep quality. Participants were followed for 24 months (see supplemental material, Figure S244).

Important Outcomes

TOTAL SLEEP TIME: Two non-randomized studies^{90, 91} (N = 152 [66] SWD participants and [86] shift workers with a diagnosis of SWD) demonstrated that, while not clinically meaningful, CBT-I decreased total sleep time as

measured by subject reports in sleep diaries compared to pre-CTB-I (MD = -3.51 minutes; 95% CI: -17.23 to 10.2; [CMT = 15 minutes]). Participants were followed for 4 weeks to 24 months (see supplemental material, Figure S245).

One non-randomized study⁹² (N = 50 SWD participants) failed to show, or to exclude, that CBT-I had a benefit or harm on total sleep time as measured by actigraphy compared to pre-CBT-I (MD = -2.0 minutes; 95% CI: -49.25 to 45.25; [CMT = 15 minutes]). Participants were followed for four weeks (see supplemental material, Figure S246).

One RCT⁸⁹ (N = 52 SWD participants) failed to show, or to exclude, that CBT-I had a benefit or harm on total sleep time as measured by both actigraphy (MD = 5.80 minutes; 95% CI: -28.93 to 40.52; [CMT = 15 minutes]) and subjective reporting in sleep diaries (MD = 8.66 minutes; 95% CI: -32.16 to 49.49; [CMT = 15 minutes]). Participants were followed for six months (see supplemental material, Figures S247-S248).

MENTAL HEALTH: One non-randomized study⁹² (N = 50 SWD participants) demonstrated that CBT-I, compared to pre-CBT-I, may improve mental health as measured by the Center for Epidemiologic Studies depression scale (CES-D) (MD = -0.60 units; 95% CI: -5.51 to 4.31; [CMT = Not Established]) and the anxiety domain on the SSI (MD = -1.30 units; 95% CI: -4.87 to 2.27; [CMT = Not Established]). Participants were followed for four weeks (see supplemental material, Figures S249-S250).

One non-randomized study⁹¹ (N = 24 SWD participants) demonstrated that CBT-I may improve mental health as measured by the Beck depression inventory (BDI) II compared to pre-CTB-I (MD = -7.10 units; 95% CI: -14.38 to 0.18; [CMT = Not Established]). Participants were followed for four weeks (see supplemental material, Figure S251).

One RCT⁸⁹ (N = 59 SWD participants) demonstrated that CTB-I may improve mental health as measured by the BDI compared to no CBT-I (MD = -0.42 units; 95% CI: -3.14 to 2.3; [CMT = Not Established]). Participants were followed for six months (see supplemental material, Figure S252).

One non-randomized study⁹¹ (N = 24 SWD participants) demonstrated that CBT-I may improve mental health as measured by the Montgomery-Åsberg depression rating scale (MADRS) compared to pre-CBT-I (MD = -11.0 units; 95% CI: -15.85 to -6.15; [CMT = Not Established]). Participants were followed for four weeks (see supplemental material, Figure S253).

One non-randomized study⁹⁰ (N = 82 shift workers without a diagnosis of SWD) demonstrated that CBT-I, compared to pre-CB-I, may improve mental health as measured by the following metrics on the symptom checklist 90 (SCI 90): the Global Index (MD = -0.20 units; 95% CI: -0.37 to -0.03 units; [CMT = Not Established]), the Depression Index (M = -0.20 units; 95% CI: -0.50 to 0.10 units; [CMT = Not Established]), and the Anxiety Index (MD = -0.10 units; 95% CI: -0.30 to 0.10 units; [CMT = Not Established]). Participants were followed for 24 months (see supplemental material, Figures S254-256).

CIRCADIAN ADAPTATION: One non-randomized (N = 50 SWD participants) demonstrated that CBT-I may improve circadian adaptation as measured by actigraphy compared to pre-CBT-I (MD = -0.20 units; 95% CI: -4.54 to 4.14; [CMT = Not Established]). The study reported circadian disruption as mesor, defined as the 24-hr adjusted mean activity level fitted to a cosinusoidal wave form, with higher values indicating more activity. Participants were followed for four weeks (see supplemental material, Figure S257).

QUALITY OF LIFE: One non-randomized study⁹¹ (N = 24 SWD participants) demonstrated the CBT-I may improve quality of life as measured by the World Health Organization – five well-being index (WHO-5) compared

to pre-CBT-I (MD = 3.0 units; 95% CI: 0.58 to 5.42; [CMT = Not Established]). Participants were followed for four weeks (see supplemental material, Figure S258).

One RCT⁸⁹ (N = 59 SWD participants) demonstrated that CBT-I may improve quality of life as measured by the RAND-PCS compared to no CBT-I (MD = 2.81 units; 95% CI: -5.47 to 11.10; [CMT = Not Established]). Participants were followed for six months (see supplemental material, Figure S259).

One non-randomized study⁹⁰ (N = 82 shift workers without a diagnosis of SWD) demonstrated that CBT-I may decrease quality of life as measured by RAND-PCS compared to pre-CBT-I (MD = -0.90 units; 95% CI: -8.42 to 6.62; [CMT = Not Established]). Participants were followed for 24 months (see supplemental material, Figure S260).

WASO: One RCT⁸⁹ (N = 54 SWD participants) demonstrated, while not clinically meaningful, that CBT-I may improve WASO as measured by subjective reporting in sleep diaries compared to no CBT-I (MD = -7.66 minutes; 95% CI: -21.35 to 6.02); [CMT = 20 minutes]). Participants were followed for six months (see supplemental material, Figure S261).

One RCT⁸⁹ (N = 52 SWD participants) demonstrated little to no difference in WASO as measured using actigraphy to between CBT-I and no CBT-I (MD = 7.39 minutes; 95% CI: 0.53 to 14.25 minutes; [CMT = 20 minutes]). Participants were followed for six months (see supplemental material, Figure S262).

One non-randomized study⁹⁰ (N = 86 shift workers without a diagnosis of SWD) demonstrated little to no difference in WASO as measured by subject reporting in sleep diaries between CBT-I and pre-CBT-I (MD = -1.0 minute; 95% CI: -10.48 to 8.48; [CMT = 20 minutes]). Participants were followed for 24 months (see supplemental material, Figure S263).

SLEEP LATENCY: One non-randomized study⁹² (N = 50 SWD participants) demonstrated little to no difference in sleep latency as measured by the sleep onset latency domain on the PSQI between CBT-I pre-CBT-I (MD = -0.10 points; 95% CI: -0.50 to 0.30; [CMT = 20 minutes]). Participants were followed for four weeks (see supplemental material, Figure S264).

One non-randomized study⁹² (N = 40 SWD participants) demonstrated little to no difference in sleep latency as measured by the sleep onset latency domain on the GSDS between CBT-I and pre-CBT-I (MD = -1.05 points; 95% CI: -1.86 to -0.24; [CMT = 20 minutes]). Participants were followed for 24 months (see supplemental material, Figure S265).

One RCT⁸⁹ (N = 54 SWD participants) demonstrated little to no difference in sleep latency as measured by subjective reporting in sleep diaries between CBT-I no CBT-I (MD = 0.04 minutes; 95% CI: -9.49 to 9.58; [CMT = 20 minutes]). Participants were followed for six months (see supplemental material, Figure S266).

One RCT⁸⁹ (N = 52 SWD participants) demonstrated little to no difference in sleep latency as measured by actigraphy between CBT-I and no CBT-I (MD = -1.28 minutes; (95% CI: -7.30 to 4.74; [CMT = 20 minutes]). Participants were followed for six months (see supplemental material, Figure S267).

One non-randomized study⁹⁰ (N = 86 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep latency as measured by subjective reporting in sleep diaries between CBT-I and pre-CBT-I (MD = -1.0 minute; 95% CI: -6.28 to 4.28; [CMT = 20 minutes]). Participants were followed for 24 months (see supplemental material, Figure S268).

SLEEP EFFICIENCY: One non-randomized study⁹² (N = 50 SWD participants) demonstrated that CBT-I may improve sleep efficiency as measured by the sleep efficiency domain on the PSQI compared to pre-CBT-I (MD = -0.50 points; 95% CI: -1.09 to 0.09; [CMT = Not Established]). Participants were followed for four weeks (see supplemental material, Figure S269).

One non-randomized study⁹¹ (N = 66 SWD participants) demonstrated that, while not clinically meaningful, CBT-I improved sleep efficiency as measured by the subjective reporting in sleep diaries compared to pre-CBT-I (MD = 7.31 percent; 95% CI: 1.43 to 13.18; [CMT = 10%]). Participants were followed for 24 months (see supplemental material, Figure S270).

One RCT⁸⁹ (N = 54 SWD participants) demonstrated little to no difference in sleep efficiency as measured by the subjective reporting in sleep diaries between CBT-I and no CBT-I (MD = 2.85 percent; 95% CI: -0.97 to 6.67; [CMT = 10%]). Participants were followed for six months (see supplemental material, Figure S271).

One RCT⁸⁹ (N = 52 SWD participants) demonstrated little to no difference in sleep efficiency as measured by actigraphy between CBT-I and no CBT-I (MD = -2.16 percent; 95% CI: -4.84 to 0.52; [CMT = 10%]). Participants were followed for six months (see supplemental material, Figure S272).

One non-randomized study⁹⁰ (N = 86 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep efficiency as measured by subject reporting in sleep diaries between CBT-I and pre-CBT-I (MD = 0.2 percent; 95% CI: -2.14 to 2.54; [CMT = 10%]). Participants were followed for 24 months (see supplemental material, Figure S273).

DISEASE SEVERITY: One non-randomized study⁹¹ (N = 24 SWD participants) demonstrated little to no difference in disease severity when measured using the quality of life ISI between CBT-I and pre-CBT-I (MD = -3.30 points (95% CI: -6.19 to -0.14; [CMT = 8 points])). Participants were followed for four weeks (see supplemental material, Figure S274).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of CBT-I in adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to imprecision, indirectness, and risk of bias. (see supplemental material, Table S21).

BENEFITS VS HARMS: The potential benefits of CBT-I in adults with SWD include a non-clinically meaningful improvements in excessive sleepiness and sleep quality. No adverse events were reported in the included studies. There is an acute risk of a reduction in sleep due to sleep restriction during CBT-I. The TF judged that the potential benefits of CBT-I in adults with SWD outweigh the potential harms.

RESOURCE USE: The current costs for internet-delivered CBT-I program is estimated at \$245 per person. The TF judged these costs are moderate.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Patients who do not wish to take medication for SWD may prefer CBT-I as a treatment option. Given the improvement in excessive sleepiness and sleep quality, the TF judged that most with SWD would generally be accepting of treatment with CBT-I.

Melatonin for daytime sleep

A total of 10 RCTs⁹³⁻¹⁰² investigated the use of melatonin in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness or alertness, sleep quality, cognitive performance, and adverse events. Participants in the RCTs had a mean age of 26.4 years (39% female). Participants received dosages of 0.18-

9 mg melatonin prior to a daytime sleep opportunity while working on the night shift for a duration of 1-21 days. 8 RCTs^{93, 95-100, 102} used a crossover design, with participants serving as their own controls, and a washout period of 4-16 days. Participants in 4 RCTs^{94-96, 102} were shift workers who did not have a diagnosis of SWD. Participants in 6 RCTs^{93, 97-101} were healthy individuals in a lab simulated night shift. Meta-analyses were performed to assess the efficacy of melatonin as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S275 through Figure S305. A summary of findings table is provided in the supplemental material, Table S23. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of melatonin to treat adults with SWD: Excessive sleepiness or alertness, sleep quality, and cognitive performance.

EXCESSIVE SLEEPINESS/ALERTNESS: One RCT⁹³ (N = 16 healthy participants) demonstrated that, while not clinically meaningful, melatonin, when taken for daytime sleep, may improve excessive sleepiness as measured by KSS compared to no treatment (MD = 0.45 points; 95% CI: -0.30 to 1.20; [CMT = 1 pt]; CoE is very low due to indirectness and imprecision). Participants were followed for 2 days in a lab-simulated shift work environment and received 2.1 mg melatonin via skin patch (see supplemental material, Figure S275).

One RCT⁹⁴ (N = 14 shift workers without a diagnosis of SWD) demonstrated that melatonin, when taken for daytime sleep, may increase alertness as measured by a VAS compared to no treatment (MD = 11.9 cm; 95% CI: -0.58 to 24.38; [CMT = Not Established]; CoE is very low due to imprecision and indirectness). Higher numbers on VAS indicated an increase in alertness. Participants were followed for 7 days and received 5 mg of melatonin (see supplemental materials, Figure S276).

One RCT⁹⁵ (N = 44 shift workers without a diagnosis of SWD) demonstrated that melatonin, when taken for daytime sleep, may decrease excessive sleepiness as measured by a VAS compared to no treatment (MD = -0.5 cm; 95% CI: -1.38 to 0.38; [CMT = Not Established]; CoE is very low due to imprecision and indirectness). The VAS ranged from 0-10 cm, with 0 representing the most alert and 10 representing the most tired. Participants were followed for 4 to 6 days and received 6 mg of melatonin (see supplemental material, Figure S277).

One RCT⁹⁶ (N = 44 shift workers without a diagnosis of SWD) demonstrated that melatonin, when taken for daytime sleep, may decrease excessive sleepiness as measured by subject reports of adverse events compared to no treatment (risk ratio of 0.18; 95% CI: 0.02 to 1.44; [CMT = Not Established]; CoE is very low due to imprecision and indirectness). Participants were followed for 2 weeks and received 3 mg of melatonin (see supplemental material, Figure S278).

One RCT¹⁰⁰ (N = 42 healthy participants) failed to show, or to exclude, that melatonin, when taken for daytime sleep, had a benefit or harm on excessive sleepiness as measured by MSLT compared to no treatment (MD = 0.53 minutes; 95% CI: -2.16 to 3.22; [CMT = 1 minute]; CoE is very low due to imprecision and indirectness). Participants were followed for 2 days in a lab-simulated night shift and received 1.8 mg of sustained-release melatonin (see supplemental material, Figure S279).

One RCT¹⁰⁰ (N = 42 healthy participants) demonstrated that, while not clinically meaningful, melatonin, when taken for daytime sleep, may decrease excessive sleepiness as measured by the SSS compared to no treatment (MD = -0.19 points; 95% CI: -1.05 to 0.67; [CMT = 1 point]; CoE is very low due to imprecision and indirectness). Participants were followed for 2 days in a lab-simulated night shift and received 1.8 mg of sustained-release melatonin (see supplemental material, Figure S280).

SLEEP QUALITY: One RCT¹⁰¹ (N = 36 healthy participants) demonstrated that melatonin, when taken for daytime sleep, may improve sleep quality as measured by movement minutes compared to no treatment (MD = -1.54

minutes; 95% CI: -11.12 to 8.04; [CMT = Not Established]; CoE is very low due to imprecision and indirectness). Participants were followed for 5 days in a lab-simulated night shift and received 1.8 mg of melatonin (see supplemental material, Figure S281).

One RCT⁹⁴ (N = 14 shift workers without a diagnosis of SWD) demonstrated that melatonin, when taken for daytime sleep, may improve sleep quality as measured by a VAS compared to no treatment (MD = 10.60 cm; 95% CI: 2.51 to 18.69; [CMT = Not Established]; CoE is very low due to incomplete outcome data and indirectness). Higher numbers on the VAS indicated better sleep quality. Participants were followed for 7 days and received 5 mg of melatonin (see supplemental material, Figure S282).

COGNITIVE PERFORMANCE: Two RCTs^{93, 100} (N = 58 healthy participants) demonstrated little to no difference on cognitive performance as measured by lapses on the PVT between melatonin when taken for daytime sleep and no treatment (MD = -0.04 lapses (95% CI: -0.8 to 0.72 lapses; [CMT = 1 lapse]; CoE is very low due to imprecision and indirectness). Participants were followed for 6 to 16 days and received between 1.8-2.1 mg of melatonin (see supplemental material, Figure S283).

One RCT⁹⁶ (N = 44 shift workers without a diagnosis of SWD) demonstrated that melatonin, when taken for daytime sleep, had little to no difference on cognitive performance as measured by the following domains of the Conner's continuous performance test compared to no treatment: reaction time (MD = -6.30 ms; 95% CI: -32.11 to 19.51; [CMT = Not Established]), hit reaction time block change (MD = 0 ms; 95% CI: -0.01 to 0.01 ms; [CMT = Not Established]), attentiveness (MD = 0.10 units; 95% CI: -0.33 to 0.53; [CMT = Not Established]), risk-taking (MD = 0 units; 95% CI: -0.66 to 0.66 units; [CMT = Not Established]), and commission errors (MD = 0.20 errors; 95% CI: -2.98 to 3.38; [CMT = Not Established]). The CoE for all these measures is very low due to imprecision and indirectness. Participants were followed for 2 weeks and received 3 mg of melatonin (see supplemental material, Figures S284-S288).

Important Outcomes

TOTAL SLEEP TIME: Four RCTs^{93, 99-101} (N = 124 healthy participants) demonstrated that melatonin, when taken for daytime sleep, may have a clinically meaningful increase in total sleep time as measured by PSG compared to no treatment (MD = 18.54 minutes; 95% CI: 3.88 to 33.19; [CMT = 15 minutes]). Participants were followed for 2 to 6 days in a lab-simulated night shift and received 1.8 to 3 mg of melatonin (see supplemental material, Figure S289).

Three RCTs⁹⁹⁻¹⁰¹ (N = 124 healthy participants) demonstrated that melatonin, when taken for daytime sleep, may have a clinically meaningful increase in total sleep time as measured by subjective reporting in sleep diaries compared to no treatment (MD = 15.67 minutes; 95% CI: 2.55 to 28.80; [CMT = 15 minutes]). Participants were followed for 5 to 6 days in a lab-simulated night shift and received 1.8 to 3 mg of melatonin (see supplemental material, Figure S290).

Three RCTs⁹⁴⁻⁹⁶ (N = 148 shift workers without a diagnosis of SWD) demonstrated that melatonin, when taken for daytime sleep, may have a clinically meaningful increase in total sleep time as measured by subjective reporting in sleep diaries compared to no treatment (MD = 17.67 minutes; 95% CI: -2.45 to 37.78; [CMT = 15 minutes]). Participants were followed for 4 days to 2 weeks and received 3 to 6 mg of melatonin (see supplemental material, Figure S291).

MENTAL HEALTH: One RCT⁹⁶ (N = 44 shift workers without a diagnosis of SWD) demonstrated that melatonin compared to no treatment, when taken for daytime sleep, had little to no difference on mental health as measured by the following POMS: tension/anxiety (MD = 0.10 units; 95% CI: -5.33 to 5.13; [CMT = Not Established]), depression (MD = 0.10 units; 95% CI: -8.13 to 8.33; [CMT = Not Established]), and anger (MD = 0 units; 95%

CI: -6.53 to 6.53; [CMT = Not Established]). Participants were followed for 2 weeks and received 3 mg of melatonin (see supplemental material, Figure S292-S294).

WASO: Two RCTs^{93, 100} (N = 68 healthy participants) failed to show, or to exclude, that melatonin, when taken for daytime sleep, had a benefit or harm regarding WASO as measured by PSG compared to no treatment (MD = -13.72 minutes; 95% CI: -88.46 to 61.02; [CMT = 20 minutes]). Participants were followed for 2 to 6 days in a lab-simulated night shift and received 1.8 to 2.1 mg of melatonin (see supplemental material, Figure S295).

SLEEP LATENCY: One RCT¹⁰² (N = 28 shift workers without a diagnosis of SWD) demonstrated little to no effect on sleep latency as measured by PSG between melatonin when taken for daytime sleep and to no treatment (MD = 0.79 minutes; 95% CI: -2.83 to 4.41; [CMT = 20 minutes]). Participants were followed for 3 days and received 1 mg of melatonin (see supplemental material, Figure S296).

Five RCTs^{93, 97, 98, 100, 101} (N = 150 healthy participants) demonstrated little to no difference on sleep latency as measured by PSG between melatonin taken for daytime sleep and no treatment (MD = -1.47 minutes; 95% CI: -4.08 to 1.14 minutes; [CMT = 20 minutes]). Participants were followed for 2 to 6 days in a lab-simulated night shift and received 1.8 to 9 mg of melatonin (see supplemental material, Figure S297).

One RCT⁹⁴ (N = 14 shift workers without a diagnosis of SWD) demonstrated little to no difference on sleep latency as measured by subject reporting in sleep diaries between melatonin taken for daytime sleep and no treatment (MD = -1.05 minutes; 95% CI: -4.95 to 2.85; [CMT = 20 minutes]). Participants were followed for 7 days and received 5 mg of melatonin (see supplemental material, Figure S298).

SLEEP EFFICIENCY: One RCT¹⁰² (N = 38 shift workers without a diagnosis of SWD) failed to show, or to exclude, that melatonin, when taken for daytime sleep, had a benefit or harm on sleep efficiency as measured by PSG compared to no treatment (MD = 0.18 percent; 95% CI: -17.82 to 18.18; [CMT = 10%]). Participants were followed for 3 days and received 1 mg of melatonin (see supplemental material, Figure S299).

Two RCTs^{93, 100} (N = 56 healthy participants) demonstrated that, while not clinically meaningful, melatonin, when taken for daytime sleep, may improve sleep efficiency as measured by PSG compared to no treatment (MD = 5.10 percent; 95% CI: -4.22 to 14.42; [CMT = 10%]). Participants were followed for 2 to 6 days in a lab-simulated night shift and received 1.8 to 2.1 mg of melatonin (see supplemental material, Figure S300).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of melatonin for daytime sleep in adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to imprecision, risk of bias, and indirectness. (see supplemental material, Table S23).

BENEFITS VS HARMS: The potential benefits of melatonin in adults with SWD include a clinically meaningful improvement in TST and WASO. The potential harms were noted in a single study and included a risk of headaches with an absolute risk of 110 fewer per 1,000 (from 300 fewer to 184 more); abdominal pain with an absolute risk of 82 more per 1,000 (from 50 fewer to 584 more); vomiting with an absolute risk 0 fewer per 1,000; nausea with an absolute risk of 156 more per 1,000 (from 32 fewer to 717 more); dizziness with an absolute risk of 4 more per 1,000 (from 30 fewer to 512 more). The TF judged that the potential benefits of melatonin in adults with SWD outweigh the potential harms. (see supplemental materials, Figures S310-S314).

RESOURCE USE: The current unit cost for melatonin is \$0.04 for a 3 mg tablet and \$0.18 for a 5 mg gummy. The TF judged these costs are negligible

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the improvement in TST and WASO, the TF judged that most with SWD would generally be accepting of treatment with melatonin.

Melatonin for transition from daytime to nighttime sleep following the night shift

A total of 3 RCTs¹⁰³⁻¹⁰⁵ investigated the use of melatonin in adults with shiftwork disorder to improve one or more of the following outcomes: sleep quality, TST, mental health, sleep latency, WASO, and sleep efficiency. Participants in the RCTs had a mean age of 30.6 years (72% female). Participants received dosages of 5 mg melatonin taken 30 minutes before nighttime sleep,¹⁰³ 3 mg of melatonin 30 minutes before nighttime sleep,¹⁰⁴ or 3 mg one hour before nighttime sleep [Farahmand 2018] on the first night off. The RCTs used a crossover design, with participants serving as their own controls, and a washout period of 4-6 days. Participants in all studies were shift workers without a diagnosis of SWD. Meta-analyses were performed to assess the efficacy of melatonin as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S306 through Figure S313. A summary of findings table is provided in the supplemental material, Table S27. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of melatonin to treat adults with SWD: Sleep quality.

SLEEP QUALITY: One RCT¹⁰³ (N = 172 shift workers without a diagnosis of SWD) demonstrated that melatonin, when taken for recovery from the night shift, may improve sleep quality as measured by a subjective questionnaire, compared to no treatment (MD = -0.11 units; 95% CI: -0.32 to 0.10; [CMT = Not Established]; CoE is low due to imprecision and indirectness). Participants were followed for 1 night and received 5 mg of melatonin (see supplemental material, S306).

Important Outcomes

TOTAL SLEEP TIME: One RCT¹⁰³ (N = 172 shift workers without a diagnosis of SWD) demonstrated that melatonin, when taken for recovery from the night shift, may have a clinically meaning increase in total sleep time as measured by subject reports in sleep diaries compared to no treatment (MD = 20.10 minutes; 95% CI: 4.88 to 35.32 minutes; [CMT = 15 minutes]; CoE is low due to imprecision and indirectness). Participants were followed for 1 night and received 5 mg of melatonin (see supplemental material, Figure S307).

One RCT¹⁰⁴ (N = 56 shift workers without a diagnosis of SWD) demonstrated that melatonin, when taken for recovery from the night shift, may have a clinically meaningful increase total sleep time as measured by actigraphy compared to no treatment (MD = 18 minutes; 95% CI: -12.49 to 48.49; [CMT = 15 minutes]; CoE is low due to imprecision and indirectness). Participants were followed for 1 night and received 3 mg of melatonin (see supplemental material, Figure S308).

MENTAL HEALTH: One RCT¹⁰⁵ (N = 48 shift workers without a diagnosis of SWD) demonstrated little to no difference on mental health as measured using POMS between melatonin when taken for recovery from the night shift and no treatment (MD = 1.25 points; 95% CI: -24.15 to 26.65; [CMT = Not Established]; CoE is low due to imprecision and indirectness). Participants were followed for 1 night and received 3 mg of melatonin (see supplemental material, Figure S309).

WASO: One RCT¹⁰⁴ (N = 56 shift workers without a diagnosis of SWD) demonstrated that, while not clinically meaningful, melatonin, when taken for recovery from the night shift, may improve WASO as measured by actigraphy compared to no treatment (MD = -5.40 minutes; 95% CI: -19.85 to 9.05; [CMT = 20 minutes]; CoE is

low due to imprecision and indirectness). Participants were followed for 1 night and received 3 mg of melatonin (see supplemental material, Figure S310).

SLEEP LATENCY: One RCT¹⁰³ (N = 172 shift workers without a diagnosis of SWD) demonstrated that melatonin, when taken for recovery from the night shift, had a clinically meaningful improvement in sleep latency as measured by subject reports in sleep diaries compared to no treatment (MD = -28.20 minutes; 95% CI: -35.62 to -20.78; [CMT = 20 minutes]; CoE is moderate due to imprecision and indirectness). Participants were followed for 1 night and received 5 mg of melatonin (see supplemental material, Figure S311).

One RCT¹⁰⁴ (N = 56 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep latency as measured by actigraphy between melatonin when taken for recovery from the night shift and no treatment (MD = -6.60 minutes; 95% CI: -11.47 to -1.73; [CMT = 20 minutes]; CoE was low due to imprecision and indirectness). Participants were followed for 1 night and received 3 mg of melatonin (see supplemental material, Figure S312).

SLEEP EFFICIENCY: One RCT¹⁰⁴ (N = 56 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep efficiency as measured by actigraphy melatonin taken for recovery from the night shift and no treatment (MD = 2.96 percent; 95% CI: -0.84 to 6.76; [CMT = 10%]; CoE is low due to imprecision and indirectness). Participants were followed for 1 night and received 3 mg of melatonin (see supplemental material, Figure S313).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of melatonin at night following shiftwork in adults with SWD was low based on the critical outcomes and downgrading of the evidence due to imprecision and indirectness. (see supplemental material, Table S25).

BENEFITS VS HARMS: The potential benefits of melatonin in adults with SWD include a clinically meaningful improvement in TST and SOL. The potential harms include a risk of headaches, drowsiness, dizziness, and nausea. The TF judged that the potential benefits of melatonin in adults with SWD outweigh the potential harms.

RESOURCE USE: The current unit cost for melatonin is \$0.04 for a 3 mg tablet and \$0.18 for a 5 mg gummy. The TF judged these costs are negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the improvement in TST and SOL, the TF judged that most with SWD would generally be accepting of treatment with melatonin.

Melatonin for naps prior to first night shift

A total of 4 RCTs¹⁰⁶⁻¹⁰⁹ investigated the use of melatonin in adults with shiftwork disorder to improve one or more of the following outcomes: TST, sleep latency, WASO, and sleep efficiency. Participants in the RCTs had an age range of 18-26 years (100% male). Participants received dosages of 0.1-40 mg melatonin prior to a daytime sleep opportunity on the first day before the night shift. All 4 RCTs used a crossover design, with participants serving as their own controls, and a washout period of 3-5 days. Participants in the studies were healthy individuals in a lab-simulated night shift. Meta-analyses were performed to assess the efficacy of melatonin as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S314 through Figure S319. A summary of findings table is provided in the supplemental material, Table S27. A summary of the evidence for each outcome is provided below.

Critical Outcomes

NONE

Important Outcomes

The following outcomes were determined by the TF to be important for evaluating the efficacy of melatonin to treat adults with SWD: Total sleep time, sleep latency, sleep efficiency, and WASO.

TOTAL SLEEP TIME: Three RCTs¹⁰⁶⁻¹⁰⁸ (N = 76 healthy participants) demonstrated that melatonin, when taken for daytime sleep prior to the first night shift, may have a clinically meaningful increase in total sleep time as measured by PSG compared to no treatment (MD = 15.70 minutes (95% CI: 6.06 to 25.34; [CMT = 15 minutes]; CoE is very low due to imprecision and indirectness). Participants were followed for 1 to 4 days in a lab-simulated night shift and received 1 to 40 mg of melatonin (see supplemental material, Figure S314).

WASO: Two RCTs^{106, 107} (N = 60 healthy participants) demonstrated that melatonin, when taken for daytime sleep prior to the first night shift, may have a clinically meaningful impact on WASO as measured by PSG compared to no treatment (MD = -20.06 minutes (95% CI: -29.69 to -10.43; [CMT = 20 minutes]; CoE is very low due to imprecision and indirectness). Participants were followed for 1 day in a lab-simulated night shift and received 1 to 40 mg of melatonin (see supplemental material, Figure S315).

SLEEP LATENCY: Three RCTs¹⁰⁶⁻¹⁰⁸ (N = 76 healthy participants) demonstrated little to no difference in sleep latency as measured by PSG melatonin taken for daytime sleep prior to the first night shift no treatment (MD = -1.97 minutes (95% CI: -2.55 to -1.39; [CMT = 20 minutes]; CoE is low due to imprecision and indirectness). Participants were followed for 1 to 4 days in a lab-simulated night shift and received 1 to 40 mg of melatonin (see supplemental material, Figure S316).

One RCT¹⁰⁹ (N = 100 healthy participants) demonstrated little to no difference in sleep latency as measured by sleep test. melatonin taken for daytime sleep prior to the first night shift and no treatment (MD = -9.52 minutes (95% CI: -12.36 to -6.68; [CMT = 20 minutes]; CoE is low due to imprecision and indirectness). Participants were followed for 1 day in a lab-simulated night shift and received 0.1 to 10 mg of melatonin (see supplemental material, Figure S317).

One RCT¹⁰⁹ (N = 100 healthy participants) demonstrated little to no difference in sleep latency as measured by self-report melatonin taken for daytime sleep prior to the first night shift and no treatment (MD = -10.76 minutes (95% CI: -13.55 to -7.96 minutes; [CMT = 20 minutes]; CoE is low due to imprecision and indirectness). Participants were followed for 1 day in a lab-simulated night shift and received 0.1 to 10 mg of melatonin (see supplemental material, Figure S318).

SLEEP EFFICIENCY: Two RCTs^{107, 108} (N = 44 healthy participants) demonstrated that, while not clinically meaningful, melatonin, when taken for daytime sleep prior to the first night shift, may improve sleep efficiency as measured by PSG compared to no treatment (MD = 7.22 percent (95% CI: -1.68 to 16.12; [CMT = 10%]; CoE is very low due to imprecision and indirectness). Participants were followed for 1 to 4 days in a lab-simulated night shift and received 1 to 40 mg of melatonin (see supplemental material, Figure S319).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of melatonin for daytime sleep prior to the first night shift in adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to imprecision and indirectness. (see supplemental material, Table S27).

BENEFITS VS HARMS: The potential benefits of melatonin in adults with SWD include a clinically meaningful improvement in TST and WASO. The potential harms include a risk of headaches, drowsiness, dizziness, and nausea. The TF judged that the potential benefits of melatonin in adults with SWD outweigh the potential harms.

RESOURCE USE: The current unit cost for melatonin is \$0.04 for a 3 mg tablet and \$0.18 for a 5 mg gummy. The TF judged these costs are negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the improvement in TST and WASO, the TF judged that most with SWD would generally be accepting of treatment with melatonin.

Ramelteon

One RCT¹¹⁰ investigated the use of ramelteon in adults with shiftwork disorder to improve one or more of the following outcomes: sleep quality, TST, and SOL. Participants in the RCT had a mean age of 23.2 years (36% female). This study was a crossover RCT during which participants received ramelteon at 8 mg or placebo for 1 day with a 1-week washout period. Participants in this study were healthy individuals in a lab-simulated night shift. Meta-analyses were performed to assess the efficacy of ramelteon as a treatment for adults with shiftwork disorder. The analyses are provided in the supplemental material, Figure S320 through Figure S324. A summary of findings table is provided in the supplemental material, Table S29. A summary of the evidence for each outcome is provided below.

Critical Outcomes

None

Important Outcomes

The following outcomes were determined by the TF to be important for evaluating the efficacy of ramelteon to treat adults with SWD: total sleep time, WASO, sleep efficiency, and sleep latency.

TOTAL SLEEP TIME: One RCT¹¹⁰ (N = 28 healthy participants) demonstrated that ramelteon may have a clinically meaningful increase in total sleep time as measured by EEG compared to no treatment (MD = 43.20 minutes; 95% CI: 5.05 to 81.35; [CMT = 15 minutes]; CoE is low due to imprecision and indirectness). Participants were followed for 1 day in a lab-simulated night shift and received 8 mg of ramelteon (see supplemental material, Figure S320).

One RCT¹¹⁰ (N = 28 healthy participants) demonstrated that ramelteon had a clinically meaningful increase in total sleep time as measured using subject reporting in sleep diaries compared to no treatment (MD = 76 minutes; 95% CI: 25.75 to 126.25; [CMT = 15 minutes]; CoE is low due to imprecision and indirectness). Participants were followed for 1 day in a lab-simulated night shift and received 8 mg of ramelteon (see supplemental material, Figure S321).

WASO: One RCT¹¹⁰ (N = 28 healthy participants) demonstrated that ramelteon may have a clinically meaningful effect on WASO as measured by EEG compared to no treatment (MD = -36.50 minutes; 95% CI: -72.54 to -0.46; [CMT = 20 minutes]; CoE is low due to imprecision and indirectness). Participants were followed for 1 day in a lab-simulated night shift and received 8 mg of ramelteon (see supplemental material, Figure S322).

SLEEP EFFICIENCY: One RCT¹¹⁰ (N = 28 healthy participants) demonstrated that ramelteon may have a clinically meaningful improvement in sleep efficiency as measured using the percent wakefulness compared to no treatment (MD = -16.20 percent (95% CI: -31.95 to -0.45; [CMT = 10%]; CoE is low due to imprecision and indirectness). The percentage wakefulness was expressed relative to the 240-minute sleep opportunity recording time. Participants were followed for 1 day in a lab-simulated night shift and received 8 mg of ramelteon (see supplemental material, Figure S323).

SLEEP LATENCY: One RCT¹¹⁰ (N = 28 healthy participants) demonstrated little to no difference on sleep latency as measured by EEG between ramelteon and no treatment (MD = -1.60 minutes; 95% CI: -4.66 to 1.46; [CMT = 20 minutes]; CoE is low due to imprecision and indirectness). Participants were followed for 1 day in a lab-simulated night shift and received 8 mg of ramelteon (see supplemental material, Figure S324).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of ramelteon in adults with SWD was low based on the important outcomes and downgrading of the evidence due to imprecision and indirectness. (see supplemental material, Table S29).

BENEFITS VS HARMS: The potential benefits of ramelteon in adults with SWD include a clinically meaningful improvement in sleep efficiency and TST. The potential harms include a risk of drowsiness, dizziness, and nausea. The TF judged that the potential benefits of ramelteon in adults with SWD outweigh the potential harms.

RESOURCE USE: The current unit cost for ramelteon is \$0.85 for an 8 mg tablet. The TF judged these costs are moderate.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the improvement in sleep efficiency and TST, the TF judged that most with SWD would generally be accepting of treatment with ramelteon.

Suvorexant

One RCT¹¹¹ investigated the use of suvorexant in adults with shiftwork disorder to improve one or more of the following outcomes: sleep quality, TST, SOL, disease severity and mental health. Participants in the RCT had a mean age of 37.7 years (32% female). Participants received suvorexant at either 10 or 20 mg for 21 days. Participants in this study were shift workers without a diagnosis of SWD. Meta-analyses were performed to assess the efficacy of suvorexant as a treatment for adults with shiftwork disorder. The analyses are provided in the supplemental material, Figure S325 through Figure S330. A summary of findings table is provided in the supplemental material, Table S31. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of suvorexant to treat adults with SWD: Sleep quality, total sleep time.

SLEEP QUALITY: One RCT¹¹¹ (N = 44 shift workers without a diagnosis of SWD) demonstrated that suvorexant may improve sleep quality as measured by subjective sleep quality scores compared to no treatment (MD = 0.48 units; 95% CI: 0.12 to 0.83; [CMT = Not Established]; CoE is moderate due to imprecision and indirectness). The subjective sleep quality score was a 5-point Likert scale with a score of 1 indicating very poor sleep quality and a score of 5 indicating very good sleep quality. Participants were followed for 21 days and received either 10 or 20 mg of suvorexant (see supplemental material, Figure S325).

Important Outcomes

TOTAL SLEEP TIME: One RCT¹¹¹ (N = 44 shift workers without a diagnosis of SWD) demonstrated that suvorexant had a clinically meaningful increase in total sleep time as measured by actigraphy compared to no treatment (MD = 176.59 minutes; 95% CI: 130.23 to 222.95; [CMT = 15 minutes]; CoE is moderate due to imprecision and indirectness). Participants were followed for 21 days and received either 10 or 20 mg of suvorexant (see supplemental material, Figure S326).

One RCT¹¹¹ (N = 44 shift workers without a diagnosis of SWD) demonstrated that suvorexant had a clinically meaningful increase in total sleep time as measured using subject reports in sleep logs compared to no treatment

(MD = 155.91 minutes; 95% CI: 101.51 to 210.31; [CMT = 15 minutes]; CoE is moderate due to imprecision and indirectness). Participants were followed for 21 days and received either 10 or 20 mg of suvorexant (see supplemental material, Figure S327).

DISEASE SEVERITY: One RCT¹¹¹ (N = 44 shift workers without a diagnosis of SWD) demonstrated that, while not clinically meaningful, suvorexant may improve disease severity as measured by the CGI-S compared to no treatment (MD = -0.57 points; 95% CI: -1.26 to 0.13; [CMT = 1 point]; CoE is low due to imprecision and indirectness). Participants were followed for 21 days and received either 10 or 20 mg of suvorexant (see supplemental material, Figure S328).

MENTAL HEALTH: One RCT¹¹¹ (N = 44 shift workers without a diagnosis of SWD) demonstrated that suvorexant may improve mental health as measured by the CES-D compared to no treatment (MD = -5.47; 95% CI: -8.02 to -2.93; [CMT = Not Established]). Participants were followed for 21 days and received either 10 or 20 mg of suvorexant (see supplemental material, Figure S329).

SLEEP LATENCY: One RCT¹¹¹ (N = 44 shift workers without a diagnosis of SWD) demonstrated that suvorexant may have a clinically meaningful improvement on sleep latency as measured by subjective reporting in sleep logs compared to no treatment (MD = -20 minutes; 95% CI: -29.87 to -10.12; [CMT = 20 minutes]; CoE is low due to imprecision and indirectness). Participants were followed for 21 days and received either 10 or 20 mg of suvorexant (see supplemental material, Figure S330).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of suvorexant in adults with SWD was low based on the critical outcomes and downgrading of the evidence due to imprecision and indirectness. (see supplemental material, Table S31).

BENEFITS VS HARMS: The potential benefits of suvorexant in adults with SWD include a clinically meaningful improvement in TST and SOL. The potential harms include a risk of drowsiness, dizziness, headache, unusual dreams, dry mouth, cough, and diarrhea. Doses 30 mg and higher are not approved for use due to suicide ideation. The TF judged that the potential benefits of suvorexant in adults with SWD outweigh the potential harms.

RESOURCE USE: The current unit cost for suvorexant is \$13.50 for a 15 mg tablet and \$13.49 for a 20 mg tablet. The TF judged these costs are moderate.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the improvement in TST and SOL, the TF judged that most with SWD would generally be accepting of treatment with suvorexant.

Triazolam

Four RCTs^{107, 112-114} investigated the use of triazolam in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness/alertness and sleep quality. Four RCTs^{107, 112-114} investigated the use of triazolam in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness/alertness and sleep quality. Participants in the RCTs had a mean age of 23.2 years (36% female). The studies were crossover RCTs during which participants received a dose of triazolam ranging from 0.25-0.5 mg or placebo for 2-5 days. Participants were healthy individuals in a lab simulated night shift. Meta-analyses were performed to assess the efficacy of triazolam as a treatment for adults with shiftwork disorder. The analyses are provided in the supplemental material, Figure S331 through Figure S339. A summary of findings table is provided in the supplemental material, Table S33. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of triazolam to treat adults with SWD: Excessive sleepiness/alertness, and accident risk.

EXCESSIVE SLEEPINESS/ALERTNESS: Three RCTs¹¹²⁻¹¹⁴ (N = 240 healthy participants) demonstrated that triazolam may have a clinically meaningful improvement on nighttime alertness as measured by MSLT compared to no treatment (MD = 1.01 minutes (95% CI: 0.44 to 1.58; [CMT = 1 minute]; CoE is moderate due to imprecision and indirectness). Participants were followed for 2 to 5 days in a lab-simulated night shift and received 0.25 to 0.5 mg of triazolam (see supplemental material, Figure S331).

One RCT¹¹³ (N = 12 healthy participants) failed to show, or to exclude, that triazolam had a benefit or harm on nighttime alertness as measured by MWT compared to no treatment (MD = 1.19 minutes (95% CI: -4.82 to 7.21; [CMT = 2 minutes]; CoE is very low due to imprecision and indirectness). Participants were followed for 5 days in a lab-simulated night shift and received 0.25 to 0.5 mg of triazolam (see supplemental material, Figure 332).

SLEEP QUALITY: One RCT¹¹³ (N = 12 healthy participants) demonstrated that triazolam may improve sleep quality as measured by subjective questionnaire responses compared to no treatment (MD = 0.80 units (95% CI: -0.24 to 1.84; [CMT = Not Established]; CoE is very low due to imprecision, indirectness and risk of bias). The subjective questionnaire rated a value of 2 as “extremely bad” and a value of 7 as “extremely good”. Participants were followed for 5 days in a lab-simulated night shift and received 0.25 to 0.5 mg of triazolam (see supplemental material, Figure S333).

Important Outcomes

TOTAL SLEEP TIME: One RCT¹¹³ (N = 12 healthy participants) demonstrated that triazolam may have a clinically meaningful increase in total sleep time as measured by subjective reports compared to no treatment (MD = 57.9 minutes (95% CI: 7.47 to 108.33; [CMT = 15 minutes])). The analysis investigated the total sleep time across 4 daytime home sleep periods. Participants were followed for 5 days in a lab-simulated night shift and received 0.25 to 0.5 mg of triazolam (see supplemental material, Figure S334).

Two RCTs^{107, 114} (N = 50 healthy participants) demonstrated that triazolam had a clinically meaningful increase on total sleep time as measured by PSG compared to no treatment (MD = 35.85 minutes (95% CI: 16.25 to 55.45; [CMT = 15 minutes])). Participants were followed for 4 to 7 days in a lab-simulated night shift and received 0.125 to 0.5 mg of triazolam (see supplemental material, Figure S335).

WASO: One RCT¹⁰⁷ (N = 14 healthy participants) demonstrated that, while not clinically meaningful, triazolam may improve WASO as measured by PSG compared to no treatment (MD = -19.6 minutes (95% CI: -45.47 to 6.27 minutes; [CMT = 20 minutes])). Participants were followed for 7 days in a lab-simulated night shift and received 0.125 mg of triazolam (see supplemental material, Figure S336).

SLEEP LATENCY: One RCT¹⁰⁷ (N = 14 healthy participants) demonstrated that triazolam may improve sleep latency as measured by PSG compared to no treatment (MD = -7.20 minutes (95% CI: -11.35 to -3.05; [CMT = Not Established])). Participants were followed for 7 days in a lab-simulated night shift and received 0.125 mg of triazolam (see supplemental material, Figure S337).

One RCT¹¹³ (N = 12 healthy participants) demonstrated that, while not clinically meaningful, triazolam may improve sleep latency as measured by subjective reports compared to no treatment (MD = -10.50 minutes (95% CI: -36.82 to 15.82; [CMT = 20 minutes])). Participants were followed for 5 days in a lab-simulated night shift and received 0.25 to 0.5 mg of triazolam (see supplemental material, Figure S338).

SLEEP EFFICIENCY: Two RCTs^{107, 114} (N = 50 healthy participants) demonstrated that, while not clinically meaningful, triazolam improved sleep efficiency as measured by PSG compared to no treatment (MD = 8.44 percent (95% CI: 3.55 to 13.33; [CMT = 10%]). Participants were followed for 4 to 7 days in a lab-simulated night shift and received 0.125 to 0.5 mg of triazolam (see supplemental material, Figure S339).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of triazolam for adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to imprecision, indirectness, and issues with risk of bias (see supplemental material, Table S33).

BENEFITS VS HARMS: The potential benefits of triazolam in adults with SWD include a clinically meaningful improvement in excessive sleepiness and improvement in sleep quality for which there was no clinically meaningful threshold. The potential harms include a risk of medication abuse, dependence, and withdrawal symptoms as well as a safety concern about falls. The TF judged that the potential harms of triazolam in adults with SWD outweigh the potential benefits.

RESOURCE USE: The current cost of triazolam is \$0.80 per 0.125 mg tablet and \$0.74 per 0.25 mg tablet. The TF determined these costs to be negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the moderate level of harm and small beneficial effect on excessive sleepiness and sleep quality, the TF judged that most with SWD would generally not be accepting of treatment with triazolam.

Circadian Adaptation

Bright Light (phase shift)

A total of 8 RCTs^{51, 53, 63, 65, 66, 115-119} and 3 non-randomized studies^{41, 48, 66} investigated the use of bright light in adults with shiftwork disorder seeking circadian adaptation to improve one or more of the following outcomes: excessive sleepiness/alertness, accident risk, cognitive performance, and sleep quality. Participants in the RCTs had a mean age of 30 years (40% female). In the RCTs^{26, 41, 43, 84-8}, participants were exposed to bright light with an intensity of light of 379 – 10,000 lux for a duration ranging from 1 night – 12 weeks. Participants in the RCTs were either shift workers without a diagnosis of SWD^{116, 119} or healthy individuals in a lab simulated night shift.^{51, 53, 63, 65, 66, 115, 117, 118} The non-randomized studies^{41, 48, 66} exposed participants to bright light with an intensity of light of 2,350-10,000 lux for 1-7 days. Participants in these studies were shift workers without a diagnosis of SWD. Meta-analyses were performed to assess the efficacy of the combination of bright light as a treatment for adults with shiftwork disorder seeking circadian adaptation. The meta-analyses are provided in the supplemental material, Figure S340 through Figure S371. A summary of findings table is provided in the supplemental material, Table S35. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of bright light to treat adults with SWD seeking circadian adaptation: Excessive sleepiness/alertness, cognitive performance, and sleep quality.

EXCESSIVE SLEEPINESS/ALERTNESS: One RCT¹¹⁶ (N = 34 shift workers without a diagnosis of SWD) demonstrated that, while not clinically meaningful, bright light may improve excessive sleepiness as measured using KSS compared to dim light (MD = -0.32 points; 95% CI: -1.00 to 0.35; [CMT = 1 point]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed for seven days and were exposed bright light with an intensity of light of 10,000 lux for 30 minutes a day (see supplemental material, Figure S340).

One non-RCT⁴¹ (N = 14 shift workers without a diagnosis of SWD) demonstrated that, while not clinically meaningful, bright light may improve excessive sleepiness as measured using KSS compared to dim light (MD = -0.62 points; 95% CI: -1.71 to 0.46; [CMT = 1 point]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were exposed to acute bright light for 30 minutes daily during the first four nights of the night-shift period with an intensity of light of 10,000 lux (see supplemental material, Figure S341).

One RCT⁶⁵ (N = 27 healthy participants) demonstrated that bright light may improve excessive sleepiness as measured using VAS compared to dim light (MD = 5.51 mm; 95% CI: -7.33 to 18.35; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants rated their level of alertness on a VAS with values 1–100, with 100 representing alertness. Participants were followed in a lab-simulated work setting and were exposed to bright light with an intensity of light of 2,500 lux for 2 hours (see supplemental material, Figure S342).

Two RCTs^{51, 53} (N = 51 healthy participants) demonstrated that bright light may have a clinically meaningful improvement on excessive sleepiness as measured using the repeated test of sustained wakefulness (RTSW) compared to dim light (MD = 2.25 minutes; 95% CI: -0.28 to 4.79; [CMT = 2 minutes]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated work setting and were exposed to bright light with an intensity of light of 1,000–6,000 lux for 4-hours (see supplemental material, Figure S343).

One non-randomized study⁴⁸ (N = 30 shift workers without a diagnosis of SWD) demonstrated that bright light may worsen excessive sleepiness as measured using a fatigue rating scale compared to dim light (MD = 0.90 units; 95% CI: -3.14 to 4.94 units; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed for one day and the duration of exposure to acute bright light was four 20-minute sessions with an intensity of light of 2,350 lux (see supplemental material, Figure S344).

SLEEP QUALITY: One RCT¹¹⁶ (N = 32 shift workers without a diagnosis of SWD) demonstrated that bright light had little to no effect on sleep quality as measured using subjective reports in sleep diaries compared to no bright light (MD = 0.0; 95% CI: -0.49 to 0.49; [CMT = Not Established]). Participants were exposed to bright light with an intensity of 10,000 lux for 30 minutes a day for 7 days (see supplemental material, Figure S345).

One non-randomized study⁴¹ (N = 14 shift workers without a diagnosis of SWD) demonstrated that bright light had little to no effect on sleep quality as measured using subjective reports in sleep diaries compared to no bright light (MD = 0.0 points; 95% CI: -0.31 to 0.31; [CMT = Not Established]). Participants were exposed to acute bright light for 30 minutes daily during the first four nights of the night-shift period with an intensity of light of 10,000 lux (see supplemental material, Figure 346).

One RCT¹¹⁹ (N = 22 shift workers without a diagnosis of SWD) demonstrated that bright light had little to no effect on sleep quality as measured using the following domains on the Pittsburgh Sleep Quality Index (PSQI) compared to no bright light. Participants with a PSQI score of 1–4 demonstrated a risk ratio of 1.04 (95% CI: 0.22 to 5.01) and an absolute risk of 9 more per 1,000 (from 173 fewer to 891 more). The analysis of the number of participants with a PSQI score of 5–21 demonstrated a risk ratio of 1.15 (95% CI: 0.67 to 2.00) and an absolute risk of 100 more per 1,000 (from 220 fewer to 667 more). There were no CMTs established for these measures (see supplemental material, Figures S347–S348).

COGNITIVE PERFORMANCE: One RCT⁵¹ (N = 26 healthy participants) demonstrated that bright light may worsen cognitive performance as measured using night three percentage correct on the SALT compared to dim light (MD = -0.81% correct; 95% CI: -7.41 to 5.79; [CMT = Not Established]; CoE is very low due to indirectness and imprecision). Participants were followed in a lab-simulated night shift and were exposed to bright light with an intensity of light of 5,000 lux for 4 hours (see supplemental material, Figure S349).

One RCT⁵¹ (N = 26 healthy participants) demonstrated that bright light may improve cognitive performance as measured using night three time to respond on the SALT compared to dim light (MD -0.52 sec; 95% CI: -2.03 to 0.99; [CMT = Not Established]; CoE is very low due to indirectness, and imprecision). Participants were followed in a lab-simulated night shift and were exposed to bright light with an intensity of light of 5,000 lux for 4 hours (see supplemental material, Figure S350).

One RCT⁶⁶ (N = 24 healthy participants) demonstrated that bright light may improve cognitive performance as measured using the simple reaction time test compared to dim light (MD = -21.21 ms; 95% CI: -48.83 to 6.41; [CMT = Not Established]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift and were exposed to bright light with an intensity of light of 4,100 lux for five 15-minute sessions. Participants wore sunglasses when they were outside during the day (see supplemental material, Figure S351).

One non-randomized study⁴¹ (N = 34 shift workers without a diagnosis of SWD) demonstrated that bright light may improve cognitive performance as measured by subjective reports of the percentage of time with reduced performance compared to dim light (MD = -10.40%; 95% CI: -18.12 to -2.68; [CMT = Not Established]; CoE is low due to indirectness and imprecision). Participants were exposed to bright light with an intensity of light of 10,000 lux for 30 minutes daily during the first four nights of the night-shift (see supplemental material, Figure S352).

Important Outcomes

TOTAL SLEEP TIME: One RCT⁵¹ (N = 26 healthy participants) failed to show, or to exclude, that bright light had a benefit or harm on total sleep time as measured using EEG compared to dim light (MD = -10.17 minutes; 95% CI: -69.39 to 49.05; [CMT = 15 minutes]). Participants were followed in a lab-simulated night shift and were exposed to bright light with an intensity of light of 5,000 lux for 4 hours during the night shift (see supplemental material, Figure S353).

One RCT¹¹⁶ (N = 30 shift workers without a diagnosis if SWD) failed to show, or to exclude, that bright light had a benefit or harm on total sleep time when measured using actigraphy compared to dim light (MD = 16.00 minutes; 95% CI: -28.03 to 60.03; [CMT = 15 minutes]). Participants were followed for seven days and exposed to bright light with an intensity of light of 10,000 lux for 30 minutes a day (see supplemental material, Figure S354).

One RCT¹¹⁶ (N = 32 shift workers without a diagnosis of SWD) failed to show, or to exclude, that bright light had a benefit or harm on total sleep time as measured using sleep diaries compared to dim light (MD = 6.00 minutes; 95% CI: -31.78 to 43.78; [CMT = 15 minutes]). Participants were followed for seven days and exposed to bright light with an intensity of light of 10,000 lux for 30 minutes a day (see supplemental material, Figure S355).

Two non-randomized studies^{41, 48} (N = 44 shift workers without a diagnosis of SWD) demonstrated that, while not clinically meaningful, bright light may decrease total sleep time as measured by subject reports in sleep diaries compared to dim light (MD = -10.07 minutes; 95% CI: -32.19 to 12.05; [CMT = 15 minutes]). Participants were exposed to bright light with an intensity of light of 10,000 lux for either 30 minutes daily⁴¹ or of 2,350 lux for four 20-minute sessions⁴⁸ (see supplemental material, Figure S356).

Two non-randomized studies^{41, 48} (N = 44 shift workers without a diagnosis of SWD) demonstrated that bright light had a clinically meaningful increase in total sleep time when measured using PSG compared to dim light (MD = 54.94; 95% CI: 36.41 to 73.46; [CMT = 15 minutes]). Participants were exposed to either 30 minutes daily or four 20-minute sessions of bright light with an intensity of light of 2,350 to 10,000 lux (see supplemental material, Figure S357).

MENTAL HEALTH: One RCT¹¹⁶ (N = 32 shift workers without a diagnosis of SWD) demonstrated that bright light, compared to dim light, may worsen mental health as measured using the following measure of HADS: anxiety (MD = 0.40 units; 95% CI: -1.44 to 2.24; [CMT = Not Established]), and depression (MD = 0.60 units; 95% CI: -1.10 to 2.30; [CMT = Not Established]). Participants were followed for seven days and exposed to bright light with an intensity of light of 10,000 lux for 30 minutes a day (see supplemental material Figures S358 and S359).

CIRCADIAN ADAPTATION: Two RCTs^{65, 117} (N = 41 healthy participants) demonstrated that bright light may worsen circadian adaptation when measured using DLMO compared to dim light (MD = 2.48 hr; 95% CI: 1.37 to 3.59; [CMT = Not Established]). Participants were followed in a lab-simulated night shift and were exposed to bright light for 4-6 hours with an intensity of light of 2,500-7,000 lux (see supplemental material, Figure S360).

One RCT⁶⁵ (N = 27 healthy participants) demonstrated that bright light may worsen circadian adaptation when measured using midpoint of melatonin secretion compared to dim light (MD = 4.13 hr; 95% CI: 1.63 to 6.63; [CMT = Not Established]). Participants were followed in a lab-simulated night shift and were exposed to bright light with an intensity of light of 2,500 lux for 6 hours (see supplemental material S361).

Two RCTs^{51, 65} (N = 93 healthy participants) demonstrated that bright light may improve circadian adaptation when measured using body temperature compared to dim light (MD = 3.26 hr; 95% CI: 1.59 to 4.92; [CMT = Not Established]). Participants were followed in a lab-simulated night shift and were exposed to bright light with an intensity of light of 1,000-2,500 lux for 4-6 hours (see supplemental material Figure S362).

QUALITY OF LIFE: One non-randomized study⁴¹ (N = 14 shift workers without a diagnosis of SWD) demonstrated that bright light may improve quality of life when measured using subjective reports compared to dim light (MD = -0.30 units; 95% CI: -0.74 to 0.14; [CMT = Not Established]). Individuals rated the quality of their day on a scale of 1-9 with 1 indicating a very good day and 9 a very bad day. Participants were exposed to bright light with an intensity of light of 10,000 lux for 30 minutes daily during the first four night shifts (see supplemental material, Figure S363).

WASO: One RCT⁵¹ (N = 26 healthy participants) failed to show, or to exclude, that bright light had a benefit or harm regarding WASO when measured using EEG compared to dim light (MD = 4.54 minutes; 95% CI: -49.07 to 58.15; [CMT = 20 minutes]). Participants were followed in a lab-simulated night shift and were exposed to bright light with an intensity of light of 5,000 lux for 4 hours during the night shift (see supplemental material, Figure S364).

One non-randomized study⁴¹ (N = 14 shift workers without a diagnosis of SWD) demonstrated little to no difference on WASO when measured using subjective reports in sleep diaries between bright light and dim light (MD = 0.10 units; 95% CI: -0.18 to 0.38; [CMT = 20 minutes]). The following rating scale was given to the participants: 1=many hours awake after initially falling asleep; 4=a few minutes awake; 5= not awake at all after falling asleep. Participants were exposed to acute bright light with an intensity of light of 10,000 lux for 30 minutes daily during the first four night shifts (see supplemental material, Figure S365).

SLEEP LATENCY: One RCT⁵¹ (N = 26 healthy participants) demonstrated little to no difference in sleep latency as measured using EEG between bright light and dim light (MD = 10.38 minutes; 95% CI: 3.72 to 17.04; [CMT = 20 minutes]). Participants were followed in a lab-simulated night shift and were exposed to bright light with an intensity of light of 5,000 lux for 4 hours (see supplemental material, Figure S366).

One RCT¹¹⁶ (N = 32 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep latency when measured using subject reports in sleep diaries between bright light and dim light (MD = -5.00 minutes; 95%

CI: -10.04 to 0.04; [CMT = 20 minutes]). Participants were followed for seven days and were exposed to bright light with an intensity of light of 10,000 lux for 30 minutes a day (see supplemental material, Figure S367).

One non-randomized study⁴¹ (N = 14 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep latency as measured using subject reports in sleep diaries bright light and dim light (MD = 1.20 minutes; 95% CI: -4.90 to 7.30; [CMT = 20 minutes]). Participants were exposed to bright light with an intensity of light of 10,000 lux for 30 minutes daily during the first four night shifts (see supplemental material, Figure S368).

SLEEP EFFICIENCY: One RCT⁵¹ (N = 26 healthy participants) failed to show, or to exclude, that bright light had a benefit or harm on sleep efficiency as measured using EEG compared to dim light (MD = -0.97%; 95% CI: -13.15 to 11.21; [CMT = 10%]). Participants were followed in a lab-simulated night shift and were exposed to bright light with an intensity of light of 5,000 lux for 4 hours (see supplemental material, Figure S369).

One RCT¹¹⁶ (N = 32 shift workers without a diagnosis of SWD) demonstrated little to no difference on sleep efficiency as measured using subject reports in sleep diaries between bright light and dim light (MD = 0.00%; 95% CI: -5.30 to 5.30; [CMT = 10%]). Participants were followed for seven days and were exposed to bright light with an intensity of light of 10,000 lux for 30 minutes a day (see supplemental material, Figure S370).

One RCT¹¹⁶ (N = 32 shift workers without a diagnosis of SWD) demonstrated little to no difference in sleep efficiency as measured using actigraphy between bright light and dim light (MD = 2%; 95% CI: -4.09 to 8.09; [CMT = 10%]). Participants were followed for seven days and were exposed to bright light with an intensity of light of 10,000 lux for 30 minutes a day (see supplemental material, Figure S371).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of bright light in adults with SWD seeking circadian adaptation was very low based on the critical outcomes and downgrading of the evidence due to imprecision, indirectness, and risk of bias (see supplemental material, Table S35).

BENEFITS VS HARMS: The potential benefits of acute bright light in adults with SWD include a clinically meaningful improvement in excessive sleepiness as measured by RTSW and improvements in cognitive performance and circadian adaptation on measures for which there were no prespecified CMTs. The potential harms include a risk of headaches in individuals with a history of migraines, temporary eye strain, and may be contraindicated in individuals with bipolar disorder. The TF judged that the potential benefits of exposure to acute bright light in adults with SWD outweigh the potential harms.

RESOURCE USE: The current costs for a bright light lamp ranges from \$25-100. The TF judged these costs are negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically meaningful improvement in excessive sleepiness measured by RTSW, the TF judged that most with SWD seeking circadian adaptation would generally be accepting of treatment with bright light.

Bright Light and Fixed sleep timing

A RCT⁶⁵ investigated the use of the combination of bright light and fixed sleep timing in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness/alertness and circadian adaptation. Participants in the RCT were healthy individuals with an age range of 20-40 years (50% female) in a simulated lab setting. Participants received bright light at approximately 2500 lux for 6 hours or dim light at 105 lux in

combination with either a fixed sleep period or free sleep opportunity. Meta-analyses were performed to assess the efficacy of the combination of bright light and fixed sleep timing as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S372 through Figure S375. A summary of findings table is provided in the supplemental material, Table S37. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of the combination of bright light and fixed sleep timing to treat adults with SWD: Excessive sleepiness/alertness.

EXCESSIVE SLEEPINESS/ALERTNESS: One RCT⁶⁵ (N = 27 healthy participants) demonstrated that bright light and a fixed sleep schedule may improve alertness as measured using a VAS compared to dim light and free sleep (MD = 19.80 mm; 95% CI: 5.49 to 34.11; [CMT = Not Established] CoE is very low due to risk of bias, indirectness, and imprecision). Higher numbers on the VAS indicated more alertness. Participants were followed in a lab-simulated night shift for one night and were exposed to 2500 lux of bright light (see supplemental material, Figure S372).

Important Outcomes

CIRCADIAN ADAPTATION: One RCT⁶⁵ (N = 22 healthy participants) demonstrated that bright light and fixed sleep schedule may improve circadian alignment when measured using DLMO compared to dim light and free sleep (MD = -5.52 hours; 95% CI: -7.04 to -4.00; [CMT = Not Established], CoE is low due to risk of bias, indirectness and imprecision). Participants were followed in a lab-simulated night shift for one night and exposed to 2500 lux of bright light (see supplemental material, Figure S373).

One RCT⁶⁵ (N = 22 healthy participants) demonstrated that bright light and fixed sleep schedule may improve circadian alignment when measured using midpoint melatonin secretion compared to dim light and free sleep (MD = 7.31 clock hours; 95% CI: 5.97 to 8.65 clock hours; [CMT = Not Established], CoE is low due to risk of bias, indirectness and imprecision). Participants were followed in a lab-simulated night shift for one night and exposed to 2500 lux of bright light (see supplemental material, Figure S374).

One RCT⁶⁵ (N = 22 healthy participants) demonstrated that bright light and fixed sleep schedule may improve circadian alignment when measured using core body temperature phase compared to dim light and free sleep (MD = 7.19 clock hours; 95% CI: 5.26 to 9.12 clock hours; [CMT = Not Established], CoE is low due to risk of bias, indirectness and imprecision). Participants were followed in a lab-simulated night shift for one night and exposed to 2500 lux of bright light (see supplemental material, Figure S375).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of the combination of bright light and fixed sleep timing in adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to risk of bias, imprecision, and indirectness. (see supplemental material, Table S37).

BENEFITS VS HARMS: The potential benefits of the combination of bright light and fixed sleep timing in adults with SWD include a clinically meaningful improvement in excessive sleepiness along with improvement in circadian adaptation on measures for which no CMT was prespecified. The potential harms include a risk of headaches in individuals with a history of migraines, temporary eye strain, and may be contraindicated in individuals with bipolar disorder. The TF judged that the potential benefits of the combination of bright light and fixed sleep timing in adults with SWD outweigh the potential harms.

RESOURCE USE: The cost of a bright light device can range from \$25-100. The TF judged these costs are negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the improvement in excessive sleepiness and the circadian adaptation shift measured by DLMO, the TF judged that most with SWD would generally be accepting of treatment with the combination of bright light and fixed sleep timing.

Bright Light, Fixed sleep timing, and Reduced light-transmittance glasses

A total of 4 RCTs^{115, 120-122} and 1 non-randomized study¹²³ investigated the use of the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness/alertness, accident risk, cognitive performance, and sleep quality. Participants in the RCTs had a mean age of 36.8 years (52% female). In the RCTs,^{115, 120-122} participants were exposure to bright light at a range of 3000 - 5910 lux in combination with reduced light-transmittance glasses and fixed sleep timing for a duration ranging from 2 nights – 2 weeks. Participants in the RCTs were either shift workers without a diagnosis of SWD^{121, 122} or healthy individuals in a lab simulated night shift.^{115, 120} The non-randomized study¹²³ exposed participants to bright light at approximately 5,500 lux in combination with reduced light-transmittance glasses and fixed sleep timing for 1 week. Participants in this study were shift workers without a diagnosis of SWD. Meta-analyses were performed to assess the efficacy of the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S385 through Figure S402. A summary of findings table is provided in the supplemental material, Table S39. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses to treat adults with SWD: Excessive sleepiness/alertness, accident risk, cognitive performance, and sleep quality.

EXCESSIVE SLEEPINESS/ALERTNESS: One non-randomized study¹²³ (N = 66 shift workers without a diagnosis of SWD) demonstrated that, while not clinically meaningful, the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses may improve excessive sleepiness as measured by KSS compared to no combination (MD = -0.39 points; 95% CI: -1.47 to 0.69; [CMT = 1 point]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed for one week and were exposed to 5,500 lux of bright light (see supplemental material, Figure S385).

ACCIDENT RISK: One non-randomized study¹²³ (N = 66 shift workers without a diagnosis of SWD) demonstrated that the combination of bright light, fixed sleep timing and reduced light-transmittance had a clinically meaningful improvement in accident risk when measured by the number of errors compared to no combination a risk ratio of 0.38; 95% CI: 0.15 to 0.96) and an absolute risk of 244 fewer per 1,000 (from 335 fewer to 16 fewer); [CMT = Any Change]; CoE is very low due to indirectness and imprecision). Participants were followed for one week and were exposed to 5,500 lux of bright light (see supplemental material, Figure S386).

SLEEP QUALITY: One non-randomized study¹²³ (N = 66 shift workers without a diagnosis of SWD) demonstrated that the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses may improve sleep quality as measured using the sleep quality scale compared to no combination (MD = 0.41 points; 95% CI: -0.27 to 1.09; [CMT = Not Established]; CoE is very low due to indirectness and imprecision). Participants were followed for one week and were exposed to 5,500 lux of bright light (see supplemental material, Figure S387).

COGNITIVE PERFORMANCE: One RCT¹²² (N = 17 shift workers without a diagnosis of SWD) demonstrated that the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses may improve cognitive

performance as measured using PVT mean reaction time compared to no combination (MD = -16.20 ms; 95% CI: -44.75 to 12.35; [CMT = Not Established]; CoE is low due to indirectness and imprecision). Participants were followed for one week and exposed to 2,500 lux of bright light (see supplemental material, Figure S388).

One RCT¹²² (N = 17 shift workers without a diagnosis of SWD) demonstrated that the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses may improve cognitive performance as measured using PVT reaction speed compared to no combination (MD = 0.24 1/ sec; 95% CI: -0.22 to 0.70 1/sec; [CMT = Not Established]; CoE is low due to indirectness and imprecision). Participants were followed for one week and exposed to 2,500 lux of bright light (see supplemental material, Figure S389).

Important Outcomes

TOTAL SLEEP TIME: One RCT¹²¹ (N = 17 shift workers without a diagnosis of SWD) demonstrated that the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses may have a clinically meaningful increase in total sleep time when measured using PSG compared to no combination (MD = 30 minutes; 95% CI: 3.34 to 56.66; [CMT = 15 minutes]; CoE is low due to indirectness and imprecision). Participants were followed for one week and exposed to 3,200 lux of bright light (see supplemental material, Figure S390).

One non-randomized study¹²³ (N = 66 shift workers without a diagnosis of SWD) failed to show, or to exclude, that the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses had a benefit or harm on total sleep time when measured by self-report compared to no combination (MD = 15.0 minutes; 95% CI: -74.36 to 104.36; [CMT = 15 minutes]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed for one week and were exposed to 5,500 lux of bright light (see supplemental material, Figure S391).

One RCT¹²⁰ (N = 23 healthy participants) demonstrated that the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses had a clinically meaningful increase in total sleep time when measured using self-reports compared to no combination (MD = 117.0 minutes; 95% CI: 54.49 to 179.51; [CMT = 15 minutes]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift for two nights and were exposed to approximately 3,500 lux of bright light (see supplemental material, Figure S392).

MENTAL HEALTH: One non-randomized study¹²³ (N = 66 shift workers without a diagnosis of SWD) demonstrated that the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses, compared to no combination, may improve mental health as measured by the following measure on the I-PANAS-SF: positive mood (MD = 1.28 points; 95% CI: -0.88 to 3.44; [CMT = Not Established]), and negative mood (MD = -0.15 points; 95% CI: -1.02 to 0.72; [CMT = Not Established]). Participants were followed for one week and were exposed to 5,500 lux of bright light (see supplemental material, Figure S393 and S394).

CIRCADIAN ADAPTATION: Two RCTs^{115, 120} (N = 45 healthy participants) demonstrated that, while not clinically meaningful the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses, compared to no combination, improved circadian adaptation when measured by DLMO compared to no combination (MD = 2.82 hours; 95% CI: 1.97 to 3.68; [CMT = 3 hours]; CoE is very low due to risk of bias, indirectness, and imprecision). Participants were followed in a lab-simulated night shift for two nights and were exposed to approximately 3,500-5,000 lux of bright light (see supplemental material, Figure S395).

One RCT¹¹⁸ (N = 17 shift workers without a diagnosis of SWD) demonstrated that bright light may improve circadian adaptation when measured using the midpoint of plasma melatonin compared to dim light (MD = 6.10 h; 95% CI: 0.88 to 11.32; [CMT = Not Established]). Participants were exposed to bright light with an intensity of light of 3243 lux for 6 hours during shifts and used tinted goggles (15% light transmission) to shield from morning light (see supplemental material, Figure S396).

One RCT¹¹⁸ (N = 17 shift workers without a diagnosis of SWD) demonstrated that bright light may improve circadian adaptation when measured using the phase angle of plasma melatonin compared to dim light (MD = -6.16 h; 95% CI: -11.44 to -0.88; [CMT = Not Established]). Participants were exposed to bright light with an intensity of light of 3243 lux for 6 hours during shifts and used tinted goggles (15% light transmission) to shield from morning light (see supplemental material, Figure S397).

One RCT¹¹⁸ (N = 17 shift workers without a diagnosis of SWD) demonstrated that bright light may improve circadian adaptation when measured using core body temperature compared to dim light (MD = 6.56 h; 95% CI: 1.82 to 11.30; [CMT = Not Established]). Participants were exposed to bright light with an intensity of light of 3243 lux for 6 hours during shifts and used tinted goggles (15% light transmission) to shield from morning light (see supplemental material, Figure S398).

One RCT¹¹⁸ (N = 17 shift workers without a diagnosis of SWD) demonstrated that bright light may improve circadian adaptation when measured using the phase angle of core body temperature compared to dim light (MD = -6.64 h; 95% CI: -11.43 to -1.85; [CMT = Not Established]). Participants were exposed to bright light with an intensity of light of 3243 lux for 6 hours during shifts and used tinted goggles (15% light transmission) to shield from morning light (see supplemental material, Figure S399).

SLEEP LATENCY: One RCT¹²¹ (N = 17 shift workers without a diagnosis of SWD) demonstrated that the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses had little to no difference in sleep latency as measured by PSG compared to no combination (MD = 2.0 minutes; 95% CI: -3.54 to 7.54; [CMT = 15 minutes]). Participants were followed for one week and exposed to 3,200 lux of bright light (see supplemental material, Figure S400).

One non-randomized study¹²³ (N = 66 shift workers without a diagnosis of SWD) demonstrated that the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses had little to no difference in sleep latency when measured by self-report compared to no combination (MD = -1.97 minutes; 95% CI: -7.42 to 3.48; [CMT = 15 minutes]). Participants were followed for one week and were exposed to 5,500 lux of bright light (see supplemental material, Figure S401).

SLEEP EFFICIENCY: One RCT¹²¹ (N = 17 shift workers without a diagnosis of SWD) demonstrated that, while not clinically meaningful, the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses may improve sleep latency as measured by PSG compared to no combination (MD = 4.0 percent; 95% CI: -2.20 to 10.20; [CMT = 10%]). Participants were followed for one week and exposed to 3,200 lux of bright light (see supplemental material, Figure S402).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses in adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to indirectness, imprecision, and risk of bias. (see supplemental material, Table S39).

BENEFITS VS HARMS: The potential benefits of the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses in adults with SWD include clinically meaningful improvements in accident risk and TST, and improvements in circadian adaptation for which no CMT was prespecified. The potential harms from the use of bright light include a risk of headaches in individuals with a history of migraines, temporary eye strain, and may be contraindicated in individuals with bipolar disorder. Additional safety concerns were considered with the use of light-filtering glasses during the commute home. The TF judged that the potential benefits of the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses in adults with SWD outweigh the potential harms.

RESOURCE USE: The cost of a bright light device can range from \$25-100. The TF judged these costs are negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically meaningful improvement in TST and the circadian adaptation shift measured by DLMO, the TF judged that most with SWD would generally be accepting of treatment with the combination of bright light, fixed sleep timing, and reduced light-transmittance glasses.

Other Considerations for Adults with SWD

8-hour or 12-hour work shift

A total of 5 non-randomized studies¹²⁴⁻¹²⁸ investigated the use of an 8-hour work shift compared to a 12-hour work shift in adults with shiftwork disorder to improve one or more of the following outcomes: excessive sleepiness/alertness, accident risk, and cognitive performance. Participants in the studies had a mean age of 33 years (8.8% female) and were shift workers without a diagnosis of SWD. Participants worked either an 8-hour shift or a 12-hour shift with a total number of hours worked per week ranging from 36-52 hours. The follow-up duration ranged from 2-42 days. Meta-analyses were performed to assess the efficacy of an 8-hour work shift vs. A 12-hour work shift as a treatment for adults with shiftwork disorder. The meta-analyses are provided in the supplemental material, Figure S403 through Figure S411. A summary of findings table is provided in the supplemental material, Table S41. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The following outcomes were determined by the TF to be critical for evaluating the efficacy of working an 8-hour shift compared to a 12-hour shift to treat adults with SWD: Excessive sleepiness/alertness, sleep quality, cognitive performance.

EXCESSIVE SLEEPINESS/ALERTNESS: One non-randomized study¹²⁴ (N = 162 shift workers without a diagnosis of SWD) demonstrated that 12-hour shifts may improve excessive sleepiness as measured by modified SSI compared to 8-hour shifts (MD = 0.20 points; 95% CI: -0.30 to 0.7; [CMT = Not Established]; CoE is very low due to imprecision and indirectness) (see supplemental material, Figure S403).

One non-randomized study¹²⁷ (N = 31 shift workers without a diagnosis of SWD) demonstrated little to no difference in excessive sleepiness as measured by KSS between 8-hour shifts and 12-hour shifts (MD = -0.6 points; 95% CI: -0.88 to -0.32; [CMT = 1 point]; CoE is very low due to imprecision and indirectness) (see supplemental material, Figure S404).

SLEEP QUALITY: One non-randomized study¹²⁷ (N = 31 shift workers without a diagnosis of SWD) demonstrated that 8-hour shifts may improve sleep quality as measured by sleep questionnaire reports compared to 12-hour shifts (MD = 0.10 points; 95% CI: -0.18 to 0.38; [CMT = Not Established]; CoE is very low due to imprecision and indirectness). The questionnaire reported a sleep quality index from 1 to 5, with 5 indicating good sleep quality. (see supplemental material, Figure S405).

One non-randomized study¹²⁶ (N = 120 shift workers without a diagnosis of SWD) demonstrated that 12-hour shifts may improve sleep quality as measured by sleep quality index reports compared to 8-hour shifts (MD = -0.15 points; 95% CI: -0.69 to 0.39; [CMT = Not Established]; CoE is very low due to imprecision and indirectness). The sleep quality index ranged from 1 to 9, with 9 indicating good sleep quality (see supplemental material, Figure S406).

One non-randomized study¹²⁸ (N = 214 shift workers without a diagnosis of SWD) demonstrated that 12-hour shifts may improve sleep quality as measured by shift work survey questionnaire reports compared to 8-hour shifts (MD = 0.70; 95% CI: -0.83 to 2.23; [CMT = Not Established]; CoE is very low due to imprecision and indirectness) (see supplemental material, Figure S407).

COGNITIVE PERFORMANCE: One non-randomized study¹²⁷ (N = 31 shift workers without a diagnosis of SWD) demonstrated that 8-hour shifts may improve cognitive performance as measured by serial simple reaction time compared to 12-hour shifts (MD = -15.0 ms; 95% CI: -43.52 to 13.52 ms; [CMT = Not Established]; CoE is very low due to imprecision and indirectness) (see supplemental material, Figure S408).

Important Outcomes

TOTAL SLEEP TIME: Two non-randomized studies^{126, 127} (N = 182 shift workers without a diagnosis of SWD) demonstrated that, while not clinically meaningful, 12-hour shifts may improve total sleep time as measured by sleep questionnaire reports compared to 8-hour shifts (MD = -8.23 minutes; 95% CI: -24.52 to 8.07; [CMT = 15 minutes]) (see supplemental material, Figure S409).

MENTAL HEALTH: One non-randomized study¹²⁵ (N = 36 shift workers without a diagnosis of SWD) demonstrated that 12-hour shifts may improve mental health as measured by general health questionnaire reports compared to 8-hour shifts (MD = 4.27; 95% CI: -0.5 to 9.04; [CMT = Not Established]) (see supplemental material, Figure S410).

SLEEP LATENCY: Two non-randomized studies^{126, 127} (N = 182 shift workers without a diagnosis of SWD) demonstrated little to no difference on sleep latency as measured by sleep questionnaire reports between 8-hour shifts and 12-hour shifts (MD = 0.17 minutes; 95% CI: -2.45 to 2.79; [CMT = 20 minutes]) (see supplemental material, Figure S411).

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of 8-hour shifts over 12-hour shifts for adults with SWD was very low based on the critical outcomes and downgrading of the evidence due to indirectness and imprecision in the non-randomized trials. (see supplemental material, Table S41).

BENEFITS VS HARMS: The results of the analysis showed no potential benefits of working 8-hour shifts over 12-hour shifts in adults with SWD. No potential harm or adverse events were presented in the included studies. The TF judged that the balance of effects does not favor either an 8-hour shift or a 12-hour shift in adults with SWD.

RESOURCE USE: The TF was unable to estimate the resources required to implement either an 8-hour shift or a 12-hour shift.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. The TF judged that for most with SWD, there would be variability in accepting an 8-hour shift compared to a 12-hour shift, depending on whether greater value is placed on working more days with shorter hours or fewer days with longer hours.

DISCUSSION & FUTURE DIRECTIONS

Shift work disorder (SWD) is a complex and heterogeneous condition that can present in a variety of different ways, depending on the required shift schedule, non-work activities of the patient and the resultant symptoms. As such, there is rarely a single treatment that will be effective or appropriate for all patients. In addition, studies looking at interventions to address SWD are not always representative of the clinical population, and include a heterogeneous mix of intervention types, doses and timing that are not always easily pooled in the context of a systematic review. Shift work schedules in general are a challenge for human circadian biology and available treatment strategies do not result in nighttime alertness levels and daytime sleep quality in patients with SWD that are comparable to those seen in healthy dayworkers. This discussion will touch on additional aspects of the recommended treatments reviewed above and will also highlight the many gaps and areas for future research identified by the TF.

Overall, the evidence for the majority of treatments reviewed was downgraded due to imprecision and indirectness related to: 1) few studies tested patients with a diagnosis of SWD; 2) when shift workers were tested, it was often not determined how many participants may have met the criteria for SWD; 3) the majority of in-laboratory shift work simulation studies tested healthy participants; 4) the majority of studies included small sample sizes (< 200 participants)--large sample sizes are a challenge for shift work studies given the need to assess outcomes frequently across the shift and over many shifts; 5) 95% confidence intervals were often wide and crossed the clinically meaningful thresholds (CMTs) and/or crossed the null.

CMTs were Not Established by the TF for many outcomes. Reasons for not establishing CMTs for outcomes included the test not being used clinically and/or not being used widely in research; for outcomes used widely in research where there was no agreed upon threshold for clinical meaningfulness, the TF did not want to establish clinical cutoffs that could not be justified by current scientific evidence. Regarding accidents, the TF reasoned that any decrease would be clinically meaningful, and this is a limitation as this value judgement may overestimate the actual clinical meaningfulness of accident outcomes.

Patients with Excessive Sleepiness

Armodafinil/Modafinil

Modafinil and armodafinil are the only FDA approved medications for the treatment of excessive sleepiness in patients with SWD. Their use in the treatment of excessive sleepiness in SWD is supported by randomized clinical trials of patients with SWD. One RCT head-to-head trial compared 105 patients randomized to armodafinil (150 mg) and 106 patients randomized to modafinil (200 mg) across 12 weeks. This trial was not included in the SR as there was no placebo condition. Findings showed similar effectiveness in reducing sleepiness on the Stanford Sleepiness Scale assessed in the morning hours at the end of three consecutive night shifts at each of 4, 8 and 12 weeks compared to baseline¹²⁹. In the SR, when compared to placebo, armodafinil showed higher certainty of evidence for reducing objective, subjective, and physician ratings of sleepiness than modafinil. In the primary RCTs, armodafinil increased latency to sleep on the MSLT compared to placebo across the entire nightshift whereas modafinil increased latency to sleep over the first, but not the second half of the nightshift. The apparent longer duration of effect during the night shift for armodafinil may be related to its longer duration of action. Additional research is needed to examine the influence of modafinil and armodafinil on other critical outcomes such as actual accident rates. Armodafinil and modafinil have also not been tested in other shift work schedules such as early morning shift work. There is also opportunity for the development and testing of additional wakefulness promoting therapeutics for the treatment of excessive sleepiness in patients with SWD (e.g., orexin receptor agonists).

The side effects to modafinil/armodafinil are generally mild, and most frequently include headache, nausea and dry mouth. Additional consideration should be made for women using hormonal contraceptives as their primary method of birth control, as both modafinil and armodafinil can decrease serum hormone concentrations and thus decrease effectiveness of this method of contraception. Overall, patients need to balance armodafinil and modafinil use to promote wakefulness and potential negative side effects.

Caffeine

Caffeine is among the most used drugs in the world to improve alertness and performance. Individual differences in the wakefulness promoting and sleep disturbing effects of caffeine are known to have a genetic component^{130, 131}. In the context of shift work, caffeine helps reduce sleepiness and improve cognitive performance during the night shift. The optimal dose and timing of caffeine prior to and/or during the night shift to improve alertness is unknown. Additional research is needed to assess whether caffeine use reduces accidents and work-related injuries in patients with SWD and to determine if caffeine improves alertness and performance in early morning shift workers (e.g., on the commute to work and in the early morning hours of the shift). Regarding caffeine use and daytime sleep, the available evidence indicates that caffeine is more disruptive to daytime than nighttime sleep. Generally, it is recommended to avoid caffeine close to bedtime (e.g., within six hours). However, it is unknown when patients with SWD and shift workers in general should stop caffeine use prior to daytime sleep. Overall, patients need to balance caffeine use to promote wakefulness and the potential negative impact on sleep.

Clockwise vs Counterclockwise

For patients on a rotating rather than fixed shift schedule, a clockwise rotation may improve alertness and performance. It should be noted that one of the original studies that examined the implementation of clockwise vs. counterclockwise rotations was not included in the SR because it did not include any of the pre-specified critical or important outcomes. In Czeisler et al¹³², 85 rotating shift workers on a counterclockwise schedule were switched to a clockwise schedule, either rotating weekly or every 21 days. Overall, the participants reported greater satisfaction and showed greater productivity with the clockwise rotating schedule compared to the counterclockwise rotation schedule. Based on circadian biology, most shift workers would be expected to better tolerate clockwise over counterclockwise rotating shift schedules as most people have a circadian period that is longer than 24 hours^{133, 134, 135, 136, 137}. However, some people (~20%) have circadian periods that are shorter than 24 hours and they would be expected to better tolerate counterclockwise over clockwise rotating shift schedules.

Naps

Naps on the transition to the first night shift (~2-3h naps) have been tested as treatments to reduce excessive sleepiness. The optimal duration and timing of a nap to improve alertness is unknown and requires further study. A nap in the late afternoon/early evening has the benefit of reducing the time that patients are awake prior to starting a nightshift. Most day workers are awake for a few hours before starting their working day whereas night shift workers will often be awake for many hours before a night shift increasing the risk of sleepiness on the night shift. While naps can be effective for reducing homeostatic sleep drive, there are safety concerns associated with sleep inertia^{138, 139} especially in the context of napping immediately prior to the commute to and from work requiring that the risk is managed¹⁴⁰. The effect of sleep inertia on alertness and cognition is greatest within 10 minutes after awakening from a nap and thus patients should avoid safety critical activities immediately after awakening (>20 minutes) and/or decisions should be checked by another person. The magnitude of sleep inertia after a nap is worst when awakening from deep slow wave sleep (N3) and brief naps (e.g., 10 min nap) have been tested to reduce the likelihood of awakening from N3 sleep. It should also be noted that there are significant interindividual differences in the magnitude of sleep inertia experienced by individuals¹⁴¹. Considering these factors, some patients may place more value on the use of naps than others, depending upon the amount of sleep inertia they personally experience, and how quickly they would need to engage in safety critical activities following a nap.

Acute Bright Light

Bright light exposure may be used to acutely to improve nighttime alertness and performance. Much of the evidence in support of the latter comes from controlled in-laboratory research studies. The impact of light on human

physiology and behavior is influenced by the intensity, biological timing, duration and spectral composition of light exposure. Light intensity is most often measured in lux, which is an international unit primarily based on the sensitivity of human cone photoreceptors. More recently, light intensity for non-visual effects of light^{8, 142} has been more appropriately measured using Melanopic Equivalent Daylight Illuminance (Melanopic EDI lux), a new international unit based on the sensitivity of the human melanopsin photoreceptor. Future studies should consider recommended guidelines for reporting on light exposure^{143, 144}. The light exposure treatments tested to acutely increase alertness and performance at night and reported in this SR vary widely in intensity ranging from 361 lux to 10,000 lux, duration ranging from 20 minutes to 9 hours of continuous or intermittent exposure, and in spectral composition due to the light sources used (e.g., fluorescent, LED, broad spectrum and blue-enriched white light). The optimal intensity, timing, duration (continuous or intermittent), and spectral composition of bright light exposure to acutely improve alertness at night in patients with SWD and in shift workers is unknown and requires further study. No studies on the effects of morning bright light to improve alertness and performance in early morning shift work are available and future research is needed. Implementation studies of bright light exposure under real shift work conditions in patients with SWD are needed to determine feasibility (e.g., light treatment is likely not feasible in all circumstances) and remove barriers to improve the effectiveness of light interventions.

Bright light exposure can acutely reduce or entirely suppress endogenous melatonin levels. The TF did not include melatonin suppression as an outcome and thus the impact of reducing melatonin levels in patients with SWD and shift workers in general on the critical and important outcomes examined here as well as for any long-term health and well-being outcomes requires additional research.

Diet and Meal Timing

The circadian system times metabolic physiology to be prepared for food intake during biological daytime and for fasting and related metabolic processes during the biological nighttime. This circadian biology represents a challenge for patients with SWD and shift workers whose circadian systems are not adapted to the work schedule. In the context of excessive sleepiness during the night shift, not eating or eating a snack compared to eating a meal improves alertness. Higher sleepiness when eating a meal at night has been proposed to be associated with post-meal difficulties digesting food at inappropriate circadian times, shifts in energy resources from performance to digestion, as well as post-meal mood changes⁸⁵. The time course of post-meal effects on sleepiness and performance is unknown and requires future study. Additional research is also needed to determine if meal content (e.g., macronutrients, calories, with or without caffeine) impacts any post-meal responses^{145, 146, 147}. It is also possible that arousal is higher at night when fasting versus eating due to fasting related impacts on wakefulness centers in the brain such as orexin in the lateral hypothalamus¹⁴⁸. Additional research is also needed to determine if adapting meal intake to match the timing of circadian metabolic physiology, rather than the sleep-wake schedule imposed by shift work, may provide long-term cardiometabolic health benefits in this population.

Combination Treatments

The premise behind combination treatments is that they work on multiple physiological mechanisms to promote alertness and performance. Although this review focused on combination treatments (e.g. bright light plus caffeine, naps plus caffeine) compared to no treatment, combination treatments have some evidence to be more effective than either treatment alone. Additional research is needed to examine these, evaluating different doses, intensities and timing of combination treatments, testing other combination treatments, and testing their effectiveness for the treatment of patients with SWD.

In addition to the studies included in the SR, there is additional data looking at the use of hypnotics to aid with sleep during a 6 hour pre-work nap opportunity, followed by the use of either caffeine or modafinil to assist with alertness during the shift⁷². While both combinations did result in both improvements in sleep during the nap opportunity,

and improvements in alertness during the work shift, the study was excluded from the SR because it was evaluating work shifts that were 18 hours in duration. For the purposes of this SR, only studies looking at shift durations of ≤ 12 hours were included. Further, one study not included in this review reported that performance during sleep deprivation was improved by the combination of modafinil and a nap compared to a nap alone¹⁴⁹.

Other combinations evaluated included a study using bright light glasses and the option of napping during the shift, however was not included in the analysis because use of the napping facility was optional, so this was not considered to be a true intervention¹⁵⁰. It should be noted that the participants chose to make use of the napping facility 77% of the time when the option was offered, but only fell asleep 39.5% of the time and averaged only 5.7 minutes spent in the napping facility (despite a 20 minute opportunity). This suggests that there may be practical limitations to implementing this combination during the work shift.

Patients with Symptoms of Sleep Disturbance/Insomnia

Medications

Several medications, including the melatonin agonist ramelteon, and the orexin antagonist suvorexant were identified as being beneficial for addressing insomnia associated with shift work disorder. However, while triazolam shows some benefit with respect to treating insomnia, the TF was concerned about the increased risk for long term side effects, including cognitive impairment, along with the potential for tolerance and dependence associated with the use of benzodiazepines. In this case, the potential harms outweighed the potential benefit, so the TF recommended against the use of triazolam for the treatment of insomnia in SWD.

Cognitive Behavioral Therapy for Insomnia

Cognitive behavioral therapy for insomnia (CBT-I) has been identified as the first line treatment for patients with traditional chronic insomnia and also shows evidence for improving insomnia in patients with SWD. Several components of CBT-I, such as maintaining a regular bedtime and wake time, are not practical or appropriate to implement in a patient who is working rotating shifts, so adaptations need to be made to standard CBT-I protocols to address the unique needs of shift workers. Further study is needed to determine how best to optimize CBT-I for the unique needs of SWD. In addition, at baseline there is a significant shortage of qualified CBT-I providers, with even fewer comfortable with adapting protocols for SWD. Also, given the atypical work schedule, this is a population who would benefit from more flexible timing, whether this is through digital self-guided programs, or providers with flexible hours.

Melatonin and melatonin agonists

Melatonin is widely available over the counter in many countries (e.g., USA, Canada, Mexico, Singapore), whereas in others it requires a prescription (e.g., the UK, many European Union members, Australasia). Some melatonin agonists are FDA approved for the treatment of insomnia and circadian rhythm disorders other than SWD. In the context of SWD, melatonin and melatonin agonists may help to improve daytime sleep as well as nap sleep prior to the first night shift. Research is needed to determine if late afternoon/early evening melatonin and melatonin agonists improve sleep prior to early morning shifts. The optimal dose and timing of melatonin and melatonin agonists prior to daytime sleep to improve insomnia symptoms in patients with SWD and in shift workers in general, are unknown. Immediate release doses from 0.1 to 40 mg, and sustained release doses have been examined. In general doses ~ 0.3 mg or lower produce plasma melatonin levels that are similar to those produced endogenously and higher doses produce supraphysiological levels. There is some evidence for dose dependent effects for daytime sleep maintenance. Regarding timing, most doses are administered close to and 30-60 min prior to bedtime. Endogenous melatonin levels rise about two hours prior to typical bedtime in people who sleep ~ 8 h at night and current dosing strategies have largely not considered this physiology. Additional research is needed to assess whether melatonin and melatonin agonists used to improve daytime sleep also improve subsequent alertness and performance during work shift. Head-to-head comparisons of melatonin and melatonin agonists for the treatment

of SWD are unavailable. Approved melatonin agonists to date bind to both MT1 and MT2 membrane bound melatonin receptors and development and testing of specific melatonin receptor agonists are needed to determine if they have better effectiveness in the treatment of SWD and other circadian disorders, Melatonin can improve nighttime sleep after a series of nightshifts (e.g., recovery from night shift work). Yet findings from one RCT, not included in the SR, of emergency medical physicians without SWD given 5 mg of melatonin 30 min prior to nighttime sleep for three days after the transition from nightshift work, indicated little benefit of melatonin for nighttime sleep duration¹⁵¹, although the participants on average obtained more than 7h of sleep under melatonin and placebo.

Patients Seeking Circadian Adaptation

Theoretically, circadian adaptation to shift work schedules would treat the excessive sleepiness and sleep disturbance/insomnia symptoms seen in SWD. Practically, however, this is not often a goal of treatment as then patients would experience excessive sleepiness and sleep disturbance/insomnia symptoms on days off from work unless they maintain their work-related wakefulness and sleep schedule. Timed light exposure during the night shift, with and without fixed sleep/darkness exposure, and with and without reduced light transmittance glasses on the commute home has been shown to partially or fully adapt the circadian melatonin and body temperature rhythms to simulated night shift work. Partial circadian adaptation with a circadian phase delay has benefits for reducing sleepiness and accident risk and for improving performance and sleep. Additional research is needed to determine if reduced light transmittance glasses in isolation is effective for partial or full circadian adaptation. Partial circadian adaptation with a circadian phase advance induced by afternoon bright light has also been tested in one study¹¹⁷, and future research is needed to assess for any potential benefits in patients with SWD. Further, research is also needed to test if circadian adaptation to early morning shift work schedules has benefits for sleep, sleepiness, performance, accident risk and health outcomes in early morning shift workers that have SWD.

Other Considerations

Anchor sleep and pre-shift nap

A split sleep strategy, combining a primary “anchor” daytime sleep after a night shift with a nap later in the day before the next night shift is a strategy often recommended to increase total daily sleep duration¹⁵². At least 7 hours of sleep each day is recommended to promote health, well-being and performance³ and many shift workers obtain insufficient sleep during their work schedules. Patients with SWD show shorter total daily sleep duration compared to shift workers without SWD²⁴. Yet the effectiveness of such a split sleep^{153, 154} schedule has not been systematically tested to treat sleepiness and insufficient sleep in patients with SWD. Total 24h sleep time was reported to be significantly higher in 2^{83, 84} of the 3 RCTs^{67, 83, 84}. Additional research is needed to test the anchor sleep strategy.

Split shift - no recommendation

The TF was unable to make recommendations regarding the use of split shifts (i.e., working two shorter shifts per 24h) for SWD, due to a lack of available studies meeting inclusion criteria for the SR. In an observational study¹⁵⁵ that did not meet the requirements to be included in the SR, data was obtained from 4042 individuals comparing work injury related absences in individuals working rotating shifts, compared to those working split shifts. This study found a higher rate of work injury related absences in split shift workers when compared to rotating shift workers. However, this study broadly included any individual who worked at least 2 shifts within a single day, with at least 4 hours of unpaid time between shifts, across any profession. No information was available comparing total work hours or sleep timing/duration between groups.

Planned work – no recommendation

In addition to shift duration and direction of rotation, the TF identified several studies that examined different strategies for scheduling blocks of shifts, examining aspects such as the speed of rotation, and duration of time off between shifts. Due to the significant amount of heterogeneity between studies, the TF was not able to make a specific recommendation for shift scheduling.

Many studies attempted to address the impact of different shift types (morning, evening and overnight) on individuals. One study looked at the impact of delaying work start time by one hour¹⁵⁶. While this improved sleep and fatigue associated with the morning shift, this change resulted in worse outcomes when working evening and overnight shifts. Observational studies have identified that, as expected, individuals working mixed shift schedules report poorer sleep quality than those working fixed shifts, while among those working fixed shifts, those working evening shifts report the worst sleep quality¹⁵⁷. A novel strategy to try to address the impact of different shift types recognized the amount of heterogeneity present in shift workers, so adapted the work schedule based on chronotype¹⁵⁸. Individuals who were extreme morning types were scheduled to work more early morning, and evening shifts, but did not work overnight shifts, while extreme evening types worked evening and overnight shifts, but did not work early morning shifts. With this adjustment, participants reported an improvement in self-reported sleep duration and quality. While somewhat more challenging to coordinate, this suggests a promising strategy if implemented at a company level.

Gaps and Additional Areas for Future Research

There are many limitations in the current available evidence in the study of the treatment of shift work disorder. Of note, the majority of the available data comes either from controlled laboratory studies using healthy control participants subjected to a shift work model, or are observational studies looking at individuals who are shift workers, but who haven't necessarily been diagnosed with shift work disorder. As such, many of the recommendations in these guidelines are based on indirect evidence. On the one hand, this may make these recommendations more generalizable, as they have been studied in individuals who are considered 'at risk' for shift work disorder, but have not actually been diagnosed with the disorder, but it does decrease the specificity of the recommendations. It is important for future treatment-based studies to specifically identify individuals who have SWD, rather than including all shift workers, regardless of whether they have SWD.

It should also be noted that the majority of treatments discussed in these guidelines address the acute symptoms of SWD. However, in addition to the commonly recognized symptoms of insomnia and excessive sleepiness, shift work and SWD have also been associated with an increased long-term risk for multiple adverse health outcomes (e.g., including malignancy, cardiometabolic disease, and depression)²⁴. Further studies are needed to determine whether current interventions impact health outcomes (e.g., sick days, health biomarkers, prevention, diagnosis and/or management of chronic disease) and also to develop future interventions for shift work disorder that can effectively target the long-term negative health consequences of shift work (e.g., timed physical activity, how much time is needed for recovery from shift work and what needs to be recovered, what are the health benefits of reducing quick returns [i.e., 11 hours or less time off between consecutive shifts]^{159, 160}. There is also a need to develop biomarkers of circadian phase to assist with the timing of interventions and the impact of interventions on circadian rhythms in patients with shift work disorder.

In addition, the population of individuals with SWD are quite heterogeneous. Individuals may have symptoms of only insomnia, only excessive sleepiness, or both. Shift work schedules can be quite variable, with individuals working fixed shifts that are outside of standard working hours, split shifts, rotating shifts which can be rapid, slow, clockwise or counterclockwise, or they can work a combination of all of these. As such, adaptation strategies may also be quite variable, with some individuals seeking circadian alignment, while others may simply want temporary

symptom relief. It should also be noted that the type of duties performed during shift work can be quite variable, depending on the occupation. For the purposes of this review, the task force combined all studies on shift work, without considering occupation, though at an individual level, there may be occupation specific details that will need to be factored in when making treatment recommendations. For example, recommendations regarding bright light therapy during the work shift may not be practical to implement for individuals who are spending the majority of their shift behind the wheel. Furthermore, the taskforce did not address long duration shifts >24h seen in some occupations¹⁶¹.

On review of the available data, the task force also recognized that most interventions focus on individuals working overnight or rotating shifts. However, very few interventions address the symptoms of individuals working early morning shifts.

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