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PSYCHIATRICS • REVIEW

Excessive sleepiness in shift work disorder: a narrative review of the last 5 years

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Abstract

Introduction Shift work sleep disorder (SWSD), also known as shift work disorder (SWD), is a circadian rhythm sleep disorder characterized by insomnia and/or excessive sleepiness, associated with a recurring work schedule that overlaps the usual time designated for sleeping.

Purpose This article aims to provide a narrative review of the pharmacological trials conducted on SWD in the last 5 years, to better address safety and health issues inherent to this disorder.

Methods An electronic literature search was conducted using PubMed. All eligible randomized controlled trials (RCTs) and cross-over RCTs with employees undertaking shift work (including night shifts) were considered, yielding three articles.

Results All three studies showed the efficacy of armodafinil in improving subjective and objective sleepiness, clinical conditions, and global functioning regardless of shift duration. Both performance and driving simulator performance tests administered during the night shift bore better results following armodafinil administration than after placebo. However, armodafinil only reduced subjective disability in individuals working more than 9 h; furthermore, even after armodafinil, alertness was reduced but not normalized.

Conclusion These studies underscore the importance of preventing and/or minimizing disturbances due to shift work. This may be achieved through various strategies, such as the employer's commitment to adopt ergonomic criteria in shift design and to implement work-environment interventions like controlled bright light. Health personnel is of pivotal importance to detect potential factors of intolerance to shift work or early symptoms of SWD. Additional and improved studies are needed to further evaluate the effectiveness and safety of both pharmacological and non-pharmacological interventions.

Keywords Shift work disorder; excessive sleepiness · Insomnia · Performance · Alertness · Stimulants · Armodafinil

Introduction

Sleep and wakefulness alternate in a 24-h behavioral cycle. Sleep is an integral component of a functional complex called the "sleep-wake system," wherein it is regulated by the circadian process. The latter dictates the daily rhythm of sleep and sleep-wake homeostasis, provoking sleep through the accumulation of sleep-inducing substances in the brain.

Campbell and Zulley performed a temporal isolation study, minimizing activities of subjects in an isolation chamber and encouraging them "to sleep whenever they wanted to sleep" [1]. In this so-called "disentrainment" situation, the longest episodes of spontaneous sleep occurred just prior to the minimum body temperature (Tmin), which is at night, when sleep usually occurs. In contrast to the Tmin, which is associated with the maximum circadian propensity to sleep, the maximum body temperature (Tmax), occurring in the afternoon/evening (7 p.m.-1 a.m.; "evening wakefulness"), is associated with the minimum circadian drive to sleep and the maximum physiological alertness [2].

The persistence and constancy of daily rhythms suggest that these are internally generated in living beings and are

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not merely passive responses to environmental stimuli [3]. In fact, a circadian pacemaker exists in the hypothalamus of mammals and is localized in the suprachiasmatic nucleus (SCN) [4]. The molecular basis for the generation of circadian rhythms is an intracellular feedback loop that needs 24 h to unfold completely; it is the result of the opposing actions of activators and repressors of the transcription of the so-called core circadian genes [5] or "clock genes."

The SCN can be influenced by so-called environmental synchronizers or zeitgebers that serve to entrain endogenous circadian rhythms.

Light is the main zeitgeber for the circadian rhythms of most living beings; it allows to correct the displacement between the internal clock (a little over 24 h) and the clock imposed by the rotation of the earth (24 h).

The SCN, activated by light via the retinohypothalamic tract (RHT), suppresses the pineal gland and its production of melatonin via a complex polysynaptic pathway known as the "eye-pineal" neural pathway. The production of melatonin is allowed to begin only at dusk; its onset occurs approximately 2 h before the individual's usual bedtime. Melatonin, in turn, is the hormone most able to influence the activity of the SCN, inhibiting the firing of its neurons. In this way, melatonin is intrinsically involved in promoting sleep by lowering body temperature and regulating circadian rhythms [6].

Several non-photic stimuli may entrain circadian rhythms, such as food, temperature, and social cues. The influence of social cues on the suprachiasmatic nucleus may be mediated by serotoninergic fibers arising from the mesencephalic raphe and not from the visual domain: these fibers inhibit the effect of light on the circadian phase in the SCN [7]. The latter may thus exempt itself from the mandatory entrainment to the light-dark cycle, making it possible to stay awake at night to work, as in jobs involving night shifts or simply for recreational activities, and to recover the lost night's sleep the following day (Fig. 1).

Modern-day pressure to continuously increase efficiency and productivity, coupled with the very nature of our 24/7 lifestyles call for work shifts outside of the typical "09.00-to-05.00" business day: thus, our new "24-h society" has increased night work and work-hour patterns. While shift work allows corporate enterprises to operate around the clock, create jobs, and provide cheaper products and services, it often presents serious health consequences for its workers. Staying awake at night and trying to sleep during the day is not a physiological condition for diurnal creatures such as humans, creating significant stress for the SCN that must renounce the corrective effects of light, its main environmental synchronizer. These negative consequences, in turn, perturb the endogenous regulation of the "circadian" rhythms of biological functions, which are driven by the endogenous "master clock," that is, the SCN. There are substantial individual differences in the ability to adjust to shift work and many subjects fall prey to shift work sleep disorder (SWSD), also known as shift-work disorder (SWD), a circadian rhythm sleep disorder characterized by excessive sleepiness during the working period and insomnia when sleep is allowed.

This article aims to provide a narrative review of the pharmacological trials conducted on SWD in the last 5 years. First, however, available evidence regarding SWD from clinical perspectives will be summarized, and the general characteristics, etiology, and consequences of SWD will be presented. Lastly, shift-work organizational methods aimed at mitigating the consequences of work schedules will be considered.

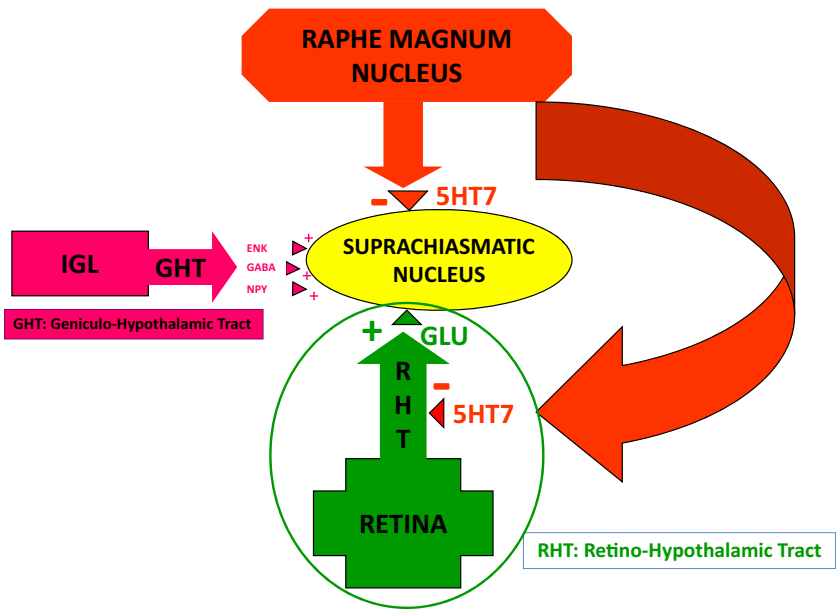

Fig. 1 Mesencephalic raphe and effects on photic stimulation: serotoninergic fibers arising from the mesencephalic raphe and not from the visual domain. The 5HT1A/7 receptors, most likely located on the soma and dendritic processes of SCN neurons, can attenuate several aspects of the photic response of the SCN, inhibiting photic responses in its cells. The 5HT1B receptors located on RHT axon terminals can regulate RHT glutamatergic neurotransmission in the SCN, inhibiting the effect of light on circadian phase in the SCN; Legend: + stimulates, − inhibits

General characteristics, physiopathology, and complications of SWD

The actual prevalence of SWD is unknown, but an estimated prevalence of 10% to 38% in rotating- and night-shift workers is thought to be reasonable among experts. When considering that approximately 20% of the workforce in industrialized countries is employed in a job that requires shift work, the weight of the problem becomes evident.

The Diagnostic Criteria for SWD, according to the third edition of the International Classification of Sleep Disorders (ICSD-3), are reported in Table 1 [8].

This disorder is common among people who work night shifts, sacrificing the hours usually dedicated to sleep.

Several types of shift-work schedules include work hours at night. The most frequently associated with sleep disorders are:

- Night shifts, resulting in difficulty falling asleep late in the morning or in the afternoon (recovery sleep), as well as severe sleepiness in the last half of the shift and when returning home (car accidents);
- Morning shifts starting in the early morning hours between 4 and 7 a.m., leading to difficulty falling asleep (anxiety for awakening) and waking up; morning shifts also produce notable REM sleep caused by the advanced awakening time, usually not compensated by a corresponding advanced bedtime the night before, due to social habits and activities [9].

Sleep is reduced by 1 to 4 h in night and morning shifts and patients complain of unsatisfactory sleep and decreased vigilance during work, generating lower productivity and higher safety risks due to sleepiness-related errors and accidents, occurring especially in the early morning hours.

With regard to the physiopathology of sleepiness that characterized this disorder, excessive sleepiness in SWD is due both to cumulative sleep loss and to circadian misalignment, resulting in reduced alertness during night work hours. At present, the data available in the literature do not allow professionals to distinguish the effects of short sleep duration from those of atypical working hours in SWD [10]. Sleep deprivation accumulates when multiple night shifts occur, especially if sufficient time is not allowed for recovery of sleep. The negative effects of sleep deprivation on alertness and performance are stable in a given individual but vary greatly from one individual to another [10].

Regarding circadian misalignment, polysomnogram (PSG) sleep parameters, such as sleep duration, sleep onset latency, sleep efficiency, and REM sleep latency, have been shown to vary with the circadian phase and to depend on the subject's body temperature and melatonin rhythms during sleep [10]. When a subject goes to bed at a time near the Tmin, which occurs early in the morning, a few hours before the usual wake time, s/he falls asleep quickly and sleeps more efficiently. The reverse occurs when s/he goes to bed at a time close to the Tmax, in the evening, a few hours before the usual bedtime [10]: indeed, at this time, there is the so-called "evening wakefulness" which prevents sleep. Thus, the shift worker is not always able to attain satisfying recovery sleep in the late morning or in the afternoon, following the night shift.

Sleepiness reduces cognitive performance and increases the number of attention errors on psychomotor alertness tests. Just as the duration and quality of sleep depend on the circadian phase during which the sleeping occurs, so too psychomotor performance correlates with the circadian phase in which it is called upon. Partial or total re-entrainment by phase delays can produce substantial performance improvements in night-shift workers, especially if they are young: in fact, in adapted patrol officers in which the salivary melatonin peak was observed to shift from the night to their daytime sleep period, levels of performance appeared stable along 7 consecutive nights of night work. On the contrary, when no adjustment is achieved, a drop in alertness and performance levels occurs in the early morning hours, at the end of the night shift: in non-adapted subjects, a sleep latency of less than 5 min, indicating severe sleepiness, was observed when they went to bed, independently of diurnal or nocturnal bedtime. Thus, non-adapted night-shift workers may be affected by excessive sleepiness throughout the 24-h cycle [10]. On the other hand, a complete adaptation occurs in less than 3% of night-shift workers, even if they always work night shifts; a partial adjustment takes place in less than 25%, while the majority of these workers (more than 72%) do not show any circadian adaptation.

Table 1 Diagnostic criteria of shift work disorder according to the third edition of the International Classification of Sleep Disorders (ICSD-3)

Criteria A–D must be met:
A. There is a report of insomnia and/or excessive sleepiness, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps the usual time for sleep.
B. The symptoms have been present and associated with the shift-work schedule for at least 3 months.
C. Sleep log and actigraphy monitoring (whenever possible and preferably with concurrent light exposure measurement) for at least 14 days (work and free days) demonstrate a disturbed sleep and wake pattern.
D. The sleep and/or wake disturbance are not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

Based on these observations, an increase in the risk of accidents is not surprising. Sleepiness is also responsible for road accidents in shift workers returning home by car after a night shift [10].

Several complications may occur during the course of SWD: an increasing amount of epidemiological studies carried out in the last decades show that shift and night work may cause severe long-term effects with regard to health, with consequentially high economic and social costs for both the individual and society [9].

After sleep disorders, gastrointestinal disorders are most frequently lamented by shift workers due to phase displacements between mealtimes (important synchronizers in human beings) and normal circadian phases of gastrointestinal functions [9]. Metabolic disorders, such as obesity and dyslipidemia, well-known risk factors for cardiovascular diseases, have been reported especially in night workers due to higher stress levels, mismatch of circadian rhythms, and changes in daily lifestyle (lower-quality meals with elevated fat and carbohydrate intake). Counter-clockwise shift rotation seems to be the most hazardous [9].

The relationship between cardiovascular disorders and shift work is not explained merely by metabolic disorders but may also be due to a combination of factors such as the stress produced by an inverted sleep-wake cycle and resulting circadian disruption with disturbed cardiac autonomic control, sleep deprivation, and lifestyle changes [9].

Women's reproductive functions may also be impaired: the menstrual cycle is the most well-known monthly ("circatrigintan") hormonal rhythm in humans and may be disrupted, in association with circadian rhythms, in rotating shift workers [9]. In 2007, the International Agency for Research on Cancer (IARC) classified "shift-work that involves circadian disruption" as "probably carcinogenic to humans" (group 2A) on the basis of "limited evidence in humans for the carcinogenicity of shift work that involves night work", and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)" [11]. This classification specifically regarded breast cancer in women. In fact, a new line of research focusing on circadian gene functions and their relationship to the risk of breast cancer has developed over the past decade. The so-called LAN effect (exposure to light at night) can induce epigenetic modifications at the level of circadian genes and an association has been found between "clock genes" and breast cancer development in humans [10].

Finally, psychological and mental health may be damaged as a result of SWD: since free time must be largely dedicated to the recovery of sleep, shift work significantly interferes with family and social life. Said interference may result in irritability related not only to lack of sleep but also to conflicting demands for sleep and social activities, potentially producing psychological stress and/or psychosomatic disorders. Disruption of circadian rhythms and sleep deficits may also lead to mood disorders, as well as to chronic anxiety; addiction to drugs or alcohol, taken as an attempt to improve sleep or vigilance, or to treat mental disorders, has also been observed in these patients [9].

In light of these staggering data, safety and health issues raised by shift work cannot be neglected. Different strategies have been purposed to counterbalance the impairment of sleep and alertness due to shift work. Among these are changes in the shift system guided by ergonomic criteria and respect for the individual vulnerability of the worker, as well as pharmacological and/or non-pharmacological interventions.

Non-pharmacological interventions for SWD

Non-pharmacological interventions aim to improve health and well-being without the use of drugs and include, among others, education on sleep hygiene, changes in light exposure, strategic naps, and cognitive-behavioral techniques. Exposure to bright light between 1000 and 10,000 lx, both in blocks of 3–6 h and in blocks of 20 min or 1 h (ending 2 h before the end of the shift), can accelerate adaptation to the night shift and improve alertness and performance at work. A recent study emphasized the effectiveness of blue-enriched light in promoting alertness and performance in night-shift workers [12], probably owing to this particular spectrum of light's ability to inhibit melatonin. However, controlled bright light exposure at night cannot be considered devoid of adverse effects: a study on healthy volunteers showed that after 8 days of exposure to bright light for 8 h during the night, the expression of these genes shifted in relationship with the shifted sleep-wake schedule, reaching its peak at the end of the afternoon [13]. This study suggests that the light-dark cycle can influence the expression of "clock" genes in humans, but the circadian molecular perturbations could lead to adverse health consequences, as reported above. Avoiding exposure to bright light in the morning or limiting its action with sunglasses has also been proven useful [10]. Another easy and inexpensive measure consists in maintaining stable dark conditions during the daytime sleep episode following the night shift, thus facilitating adaptation to night shifts and allowing adequate nighttime sleep on rest days. Strategic napping, prophylactic naps (in the evening before the night shift) as well as recovery naps (during the night shift for temporary relief of sleepiness), increase total sleep time during the day and can improve alertness and performances at work [10]. However, the workers should be cognizant of the potential risk of "sleep inertia" following a recovery nap, possibly resulting in errors and accidents due to confusion when waking from a nap during night work; moreover, naps during the night shift may reduce sleep pressure, resulting in worse adaption to the shifted sleep-wake cycle.

A review of non-pharmacological interventions [14] for sleepiness at work and sleep disturbance in shift workers found several limits, such as methodological diversity of the included studies in terms of interventions, settings, and assessment tools, as well as limited reporting and very low to low-quality evidence. The review included 17 relevant trials (with 556 review-relevant participants) categorized into three types

of interventions: (1) various exposures to bright light ($n = 10$); (2) various opportunities for napping ($n = 4$); and (3) other interventions, such as physical exercise or sleep education ($n = 3$). In light of the aforementioned limits, the authors concluded that "it is not possible to determine whether shift workers' sleepiness can be reduced or if their sleep length or quality can be improved with these interventions". Perfected and adequately structured RCTs on the effectiveness of non-pharmacological interventions are thus warranted.

Pharmacological interventions for SWD

Pharmacological interventions may attenuate the negative effects of shift work on sleep: therapies can be aimed at decreasing daytime insomnia (i.e., hypnotics facilitating recovery daytime sleep) or at increasing alertness during work shifts (i.e., stimulants). Hypnotics with a short half-life only slightly improve the maintenance of sleep, which is the main problem afflicting the daytime sleep of night workers. However, treatment with triazolam resulted in an improvement of both the sleep disorder and quality of life in a trial on Air Force radar controllers affected by SWD. In fact, after triazolam, the parameter "time devoted to recreational activities" of the Sickness Impact Questionnaire showed a higher score than at baseline; moreover, the selective alertness tests failed to demonstrate any "sedative carry-over" in the treated patients [15] (Fig. 2).

While hypnotics with a long half-life may further aggravate sleepiness during night work, psychostimulants, instead, can enhance wakefulness during shift work, improve alertness, and facilitate normal levels of attention and energy throughout the nocturnal work period. Prophylactic and strategic use of caffeine during night work can also improve alertness [10]. Wakefulness-promoting medication prior to the shift, like modafinil and armodafinil, may be useful but they are associated with adverse effects. Unfortunately, modafinil is not approved for the treatment of adults with excessive sleepiness associated with SWD in some countries, including Italy, and armodafinil is licensed only in the USA where it is approved for the treatment of SWD. The ideal drug should promote wakefulness at work and restorative sleep at the end of the work-shift.

Melatonin has little effect if taken when endogenous levels are high or rising; nevertheless, it possesses circadian phase-dependent hypnotic properties. It can attenuate the wake-promoting drive from the circadian system, reduce sleep latency, and allow consolidation of sleep occurring out-of-phase with endogenous melatonin secretion.

Exogenous melatonin has been shown to have some beneficial effects on circadian rhythm sleep disorders. In fact, strategically timed melatonin has been recommended for a variety of disorders, including delayed sleep-wake phase disorder in adults with and without depression and in children/adolescents even if affected by psychiatric disorders, non-24-hour sleep-wake rhythm disorder in blind adults, and in irregular sleep-wake rhythm disorder in children/adolescents with neurologic disorders and in demented, elderly patients [16].

Liira et al. [17] performed a Cochrane review of pharmacological interventions for sleepiness and sleep disturbances caused by shift work up to September 20, 2013. The authors included all eligible RCTs and cross-over RCTs with workers undertaking shift work (including night shifts) in their present job. They emphasized the following noteworthy points:

1. There is only low-quality evidence that melatonin lengthens daytime sleep duration following a night shift
2. Modafinil and armodafinil increase alertness and reduce sleepiness to some extent but are associated with adverse effects
3. There is only low-quality evidence that caffeine and naps reduce sleepiness during night shifts
4. One low-quality trial showed that hypnotics did not improve sleep length and quality after a night shift.

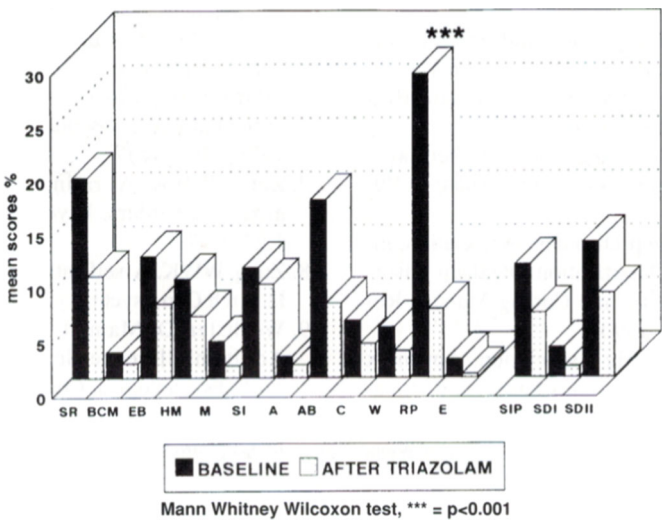

Fig. 2 Sickness impact profile: improvement of recreational pastime (RP) after treatment with triazolam. [Reproduced from Puca F, Perrucci S, Prudenzano M et al. (1996) Quality of life in shift work syndrome. Functional Neurology 11:261–8]

Comprehensively, these conclusions warranted further and better-quality trials not only to probe the effectiveness of all pharmacological agents that induce sleep or promote alertness in shift workers but also to examine their adverse effects [17].

Nevertheless, a pharmacologic treatment may be of crucial importance for SWD patients. To verify whether other trials were performed subsequent to the abovementioned Cochrane review, we performed a narrative review, searching for trials on this topic published between September 20, 2013 and May 2, 2019.

Materials and methods

An electronic literature search was conducted using PubMed with the following keywords in different combinations: shift work, shift work disorder, shift workers, work schedule, shift rosters, rotating shifts, night shifts, *and* insomnia, sleep quality, sleepiness, drowsiness, hypersomnolence, alertness, wakefulness, cognitive performance, psychomotor performance, concentration difficulties, *and* pharmacological treatment, pharmacological intervention, stimulants, caffeine, modafinil, armodafinil, melatonin, hypnotic(s), drugs. We selected articles reporting research conducted on human subjects and published in peer-reviewed journals in the English language. Non-pharmacological studies were excluded. In addition, we checked the references of the selected articles to identify studies that had potentially not resulted in our database search.

We followed the same search criteria employed by Liira et al. [17], considering RCTs and cross-over RCTs with workers who undertook shift work (including night shifts) in their present job. We excluded all trials that used healthy volunteers undergoing simulated shift work because, in agreement with Liira [17], the results of these trials may not apply to shift workers "in a real-life working environment". We admitted trials comparing drugs to placebo or to an alternative drug. Trial outcomes had to include sleep length while off work and sleepiness at work. Sleep quality parameters, like sleep latency or the number of awakenings, could be reported by diary or actigraphy, and subjective sleep quality could be described in diary entries. Accepted measures for sleepiness during the night shift were subjective tests and/or objective tests, whereas alertness had to be evaluated through measures of objective functioning or performance decrease, like clinical assessment of global functioning and psychomotor performance tasks.

A total of 6180 articles were found. After removing duplicates and irrelevant material based on the screening of titles, we identified 71 eligible articles on shift work interventions. Of the latter, we decided to retrieve the full-text studies of 42 articles, eliminating the rest on the basis of their abstracts. The references of these articles were reviewed to include any additional study deemed pertinent, but none were found. A full-text screening of these 42 articles investigating pharmacological interventions resulted in the elimination of 39 studies, yielding only three that met the inclusion criteria, i.e., RCTs field-based on actual shift workers with sleepiness at work or reduced sleep quality/total sleep time following a night shift [18,19,20].

Characteristics including title, authors, year of publication, study design, sample size, baseline demographics of the sample, type of pharmacological intervention, outcome measures, and results were summarized (Table 2).

All three articles were published in the same year (2014) and two of these shared three authors. All three investigated the efficacy of armodafinil on shift workers.

Armodafinil is a longer-lasting R-isomer of modafinil, as shown by the improvement in alertness in healthy subjects 6–8 h post-administration of 200 mg during simulated night shifts [21]. It is licensed only in the USA where it is approved for the treatment of SWD, but not in Europe.

The three trials evaluated the effects of armodafinil on night-shift sleepiness and performance or global functioning in actual shift workers with a diagnosis of SWD and subjective sleepiness as measured by the Karolinska Sleepiness Scale (KSS) [22] or Epworth Sleepiness Scale [23]. However, the objectives were different:

- Harsh et al. examined the impact of night shift duration on efficacy and tolerability of armodafinil
- Howard et al. investigated whether armodafinil could normalize objective nocturnal sleepiness
- Drake et al. tested whether armodafinil could improve driving performance late in the shift when workers typically drive home

Study design of selected trials

The study by Harsh and colleagues was a post hoc analysis based on prospectively collected data of a 6-week treatment with armodafinil or placebo; it used a multicenter, randomized, double-blind, placebo-controlled, parallel-group design; the other two were randomized, double-blind, placebo-controlled, crossover studies.

In all three studies, exclusion criteria included the presence of any history of psychiatric disorders and pregnancy; Harsh et al. [18] and Drake et al. [20] also excluded patients using any medication that acts on the central nervous system; Harsh et al. [18] and Howard et al. [19] ascertained the absence of sleep disorders by standard PSG, whereas Drake used the STOP questionnaire to screen outpatients with a likelihood of sleep apnea [24], as well as a careful sleep history, a routine physical examination, and a 2-week sleep diary.

Table 2 Characteristics of included studies meeting search criteria

Study: title and authors	Trial design	Sample size	Sample	Recruitment	Intervention	Outcome measures	Results
The impact of shift duration on the efficacy and tolerability of armodafinil in patients with excessive sleepiness associated with shift-work disorder Harsh, Yang and Hull, 2014	Post hoc analysis of a 6-week treatment: multicenter, randomized, double-blind, placebo--controlled, parallel-group, not prospective trial	383, Placebo: 190 Armodafinil: 193 stratification into one of two treatment groups based on the duration of their night shift: ≤9 h or > 9 h. After the period here, can the following sentence start on the next line below, so that the data is more leggible? ≤9 h Armodafinil = 147; >9 h Armodafinil = 61; Placebo = 43	Baseline demographics ≤9 h: Armodafinil = 71 M and 61 F, mean age 36.9 ± 10.8 Placebo = 75 M and 72 F, mean age 35.6 ± 10.7 years. >9 h: Armodafinil = 37 M and 24 F, mean age 36.4 ± 10.5 Placebo = 25 M and 18 F, mean age 37.9 ± 10.9 years	Subjects working 5 or more 6-to-12-h night shifts between 10 p.m. and 8 a.m., per month Having diagnosis of SWD Having mild to severe impairment in outcome measure evaluation Having no other medical conditions, or psychiatric disorders, or sleep disorders	Trial intervention: Armodafinil titrated from 50 mg (1 tablet) to 150 mg (3 tablets) over the first 4 nights; thereafter took 3 tablets orally once nightly, 30 to 60 min before the start of the night shift Comparison intervention: placebo	Clinician assessments of: excessive sleepiness late-in-shift: Clinical Global Impression Change (CGI-C) rating and Functioning: Global Assessment of Functioning (GAF) scale; Patient assessment of: sleepiness late-in shift: Karolinska Sleepiness Scale (KSS) at 04:00, 06:00, and 08:00 a.m. Self-reported overall functioning: modified Sheehan Disability Scale (SDS.M) Scale: KSS	In patients treated with armodafinil for both shift duration compared with placebo patients: At least minimal improvement in late-in-shift CGI-C in a greater proportion of subjects A greater improvement in GAF score A greater improvement in mean late-in shift-KSS score Mean improvement in SDS-M: not different between the armodafinil and placebo groups among patients working shifts ≤9 h; greater among patients working shifts > 9 h
The effects of armodafinil on objective sleepiness and performance in a shift-work disorder sample unselected for objective sleepiness Howard, Roth and Drake, 2014	Randomized, double-blind, placebo--controlled, crossover design	12	Baseline demographics: 5 M and 7 F, mean age 33.75 ± 8.57 years Store stockers (3) Cab driver (1) Crane repair person (1) Nurse (3) Police officer (1) Pharmacist (1) Surgical tech (1) Nurse's aid (1)	Subjects working at least 5 night shifts for 12 h or less in the past month, with 6 h or more worked between 10:00 p.m. and 08:00 a.m. Having diagnosis of SWD Having excessive sleepiness (> 10 on the Epworth Sleepiness Scale)	Trial intervention: Armodafinil 150 mg at 10:30 p.m. Comparison intervention: Placebo at 10:30 p.m. Drug nights separated by 1 week	Objective sleepiness: Mean MSLT latency with naps performed at 01:30 a.m., 03:30 a.m., 05:30 a.m., and 07:30 a.m. Subjective alertness: 100-mm Visual Analogic Scale (VAS) anchored from "sleepy" to "alert" at the beginning of the study session (8:00 p.m.), before each MSLT nap, and at the end of the study session (8:00 a.m.) Performance: 2 computer-based measures at 2:15 a.m.: A divided attention test, consisting of tracking and reaction time tasks A memory test in which the patient was presented a series of 4 images of common things, given 20 s to view each item, and asked to recall as many items as they could	On MSLT, sleep latency was lower with armodafinil than with placebo in the first 2 nap sessions The first 2 VAS sessions showed higher scores after armodafinil administration than after placebo On the divided attention test, peripheral and central reaction times were lower with armodafinil than with placebo On the free recall memory test, the number of correct answers was higher with armodafinil than with placebo
Effects of armodafinil on simulated driving and alertness in shift-work disorder Drake, Gumenyuk, Roth and Howard, 2014	Randomized, double-blind, placebo--controlled, crossover study	20	3 M and 17 F, mean age 42.7 ± 8.7 years	Subjects working at least 5 night shifts each month with 6 h or more between 10:00 p.m. and 08:00 a.m. Having diagnosis of SWD Having excessive sleepiness (> 10 on the Epworth Sleepiness Scale) Having no other medical conditions, or psychiatric disorders, or sleep disorders	Trial intervention: Armodafinil 150 mg at 11:45 p.m. Comparison intervention: Placebo at 11:45 p.m. On counterbalanced nights separated by 7–14 days	Subjective sleepiness: KSS administered six times thorough the night at 00:30 a.m., 02:30 a.m., 04:40 a.m., 06:30 a.m., and 08:30 a.m. Objective sleepiness: mean MSLT latency with naps performed at 01:30 a.m., 03:30 a.m., 05:30 a.m., and 07:30 a.m. Performance driving simulator test at 03.00 a.m., 05.00 a.m., 07:00 a.m., and 09.00 a.m. Endpoints: standard deviation of lateral position (SDLP), and off-road deviations Cognitive performance: Digit Symbol Substitution Task (DSST), given twice at baseline prior to drug or placebo administration (10:30 p.m., 11:00 p.m.) and in four other sessions: 11.25, 4.9, 6.25, and 8.75 h after drug or placebo administration Creativity by the Remote Associates Test (RAT) administered prior to drug or placebo administration and at 04:00 a.m.; endpoint: number of corrected answers	Compared with placebo, armodafinil improved: Subjective sleepiness at 02:30 a.m., 04:40 a.m., 06:30 a.m., and 08:30 a.m. Objective sleepiness on each session Performance ability to drive: decrease in SDLP at 05:30 a.m., 07:30 a.m., 09:30 a.m., and in off-road deviations at 07:30 and 09:30 on driving simulator test Cognitive performance: increase in DSST score at 06:00 a.m. and in creativity expressed by RAT mean score

In all three studies, the eligible subjects were actual shift workers affected by SWD with subjective sleepiness.

Unlike the other two studies, Harsh et al. used a subjective measure of sleepiness [KSS, scale from 1 (very alert) to 9 (very sleepy)] [22] and regarded the change in sleepiness as an additional secondary endpoint. Sleepiness represented a primary endpoint in the other two studies and was objectively evaluated by the Multiple Sleep Latency Test (MSLT) [25], starting 3 h and 1.75 h after drug or placebo administration in the studies of Howard et al. [19] and Drake et al. [20], respectively.

The Harsh et al. study conducted patient assessments, i.e., modified Sheehan Disability Scale (SDS-M) [26] and KSS [22]), and clinical assessments, i.e., Clinical Global Impressions-Change (CGI-C) [27], and the Global Assessment of Functioning (GAF) [28]. The assessments were made at the study site, at baseline as well as at weeks 3 and 6. CGI-C used a clinician-rated measure assessing symptom severity, ranging from "very much improved" to "very much worse" and was performed immediately after the last night shift [27]. The primary efficacy measure was the proportion of treated patients with at least minimal improvement on CGI-C compared to placebo patients [27]. Secondary efficacy assessments included an improvement in overall psychological, social, and occupational functioning (GAF) with higher scores indicating better functioning [28]. Additional secondary measures included mean change from baseline to final visit in KSS scores [22] on the last night worked at 04:00 a.m., 06:00 a.m., and 08:00 a.m. (more or less than 15 min), and assessment of disability by SDS-M [26] with higher scores indicating higher disability. The SDS-M explores the three domains of work, social life, and family life, and the modified version specifically assesses the impact of work on a scale of 0 ("not at all") to 10 ("extremely") [26]. So, both CGI-C [27] and KSS [22] investigated late-in-shift conditions including the commute home (04:00 a.m. to 08:00 a.m.).

Howard et al. [19] considered other outcome measures besides objective sleepiness. A subjective sleepiness-alertness visual analog scale (endpoints: "sleepy" and "alert") [19] was administered before each MSLT nap and at the end of the study session. Two computer-based performance tests evaluating attention and memory were conducted 3.75 h after armodafinil or placebo administration on the experimental nights: a divided attention test [29] and a free recall memory test [30] were chosen because they are sensitive to both pharmacologically improved wakefulness and decreased alertness from experimental sleep deprivation.

Drake et al. used other primary endpoints besides objective sleepiness. They evaluated driving simulator performance using the standard deviation of lateral position (SDLP) and off-road deviations as endpoints, both of which are indicative of drug effects on driving [31]. Cognitive performance was also investigated using the Digit Symbol Substitution Task (DSST) and the Remote Associates Test (RAT), which is a well-established measure of creativity [32]. Patients completed a 30-min driving task at 3.25, 5.25, 7.25, and 9.25 h after administration, whereas the RAT [32] was given at 4.25 h post-drugs, at a time that coincides with the estimated circadian nadir in alertness. Drake et al. also evaluated subjective sleepiness through the KSS [22], administered six times during the experimental night: at 10 p.m., before drug administration, as a baseline measure, and at 12:30, 02:30, 04:40, 06:30, and 08:30 a.m.

Participants

Regarding sample size, Harsh et al. randomly assigned 193 patients to receive armodafinil (55.95% males) and 190 to the placebo group (52.63% males). Instead, Drake et al. and Howard et al. had much smaller sample sizes, respectively 20 (15% males) and 12 (41.6% males) participants. For their post hoc analysis, Harsh et al. stratified the patients in each group into two subgroups, depending on the duration of their night shift ($\leq$ 9 h or >9 h). The mean age of these patients was 36.9 and 36.4 in the two armodafinil groups ($\leq$ 9 h >9 h respectively) and 35.6 and 37.9 in the two placebo groups ($\leq$ 9 h or >9 h respectively) [18]. The mean age of the patients enrolled by Drake et al. was 42.7 and the proportion of males-to-females was 3:17 [20], whereas those included in the study by Howard et al. presented a lower mean age (33.75) and a more balanced male-to-female proportion (5:7) [19].

In the study of Harsh et al., the patients in the treatment group received armodafinil orally once nightly before each night shift (taking place five or more times a month and lasting from 6 to 12 h) over 6 weeks; the drug was titrated from 50 mg (1 tablet) to 150 mg (3 tablets) over the first four nights. The two treatment groups were compared to the two placebo groups. In the other two studies, armodafinil 150 mg was administered at 10:30 p.m. [19] or 11:45 p.m. [20] in a randomized, double-blind, placebo-controlled, crossover design only on experimental nights separated by 1 week in the first study and 7–14 days in the latter one.

Results

Harsh et al. [18] found that for both shift durations:

- A greater proportion of patients treated with armodafinil showed at least minimal improvement in late-in-shift CGI-C compared to placebo (78 vs 60%; $p = 0.0017$ in shifts $\leq$ 9 h; 77 vs 46%; $p = 0.0020$ in shifts > 9 h);
- A greater improvement in the armodafinil groups compared with placebo groups on clinical assessment of global

functioning by GAF from baseline to final visit (in shifts ≤ 9 h: + 9.5 vs + 5.4; $p < 0.0001$; 95% confidence interval [CI] 2.15, 6.02; in shifts > 9 h: + 9.6 vs + 4.3; $p = 0.0019$; 95% CI 2.01, 8.56);

- A greater improvement on the changes from baseline to final visit in mean late-in-shift KSS scores (in shifts ≤ 9 h: mean decrease 2.9 vs 1.9; $p = 0.0002$; 95% CI − 1.50, − 0.48; in shifts > 9 h: 2.8 vs 1.6; $p = 0.0028$; 95% CI − 1.99, − 0.42);
- A greater decrease on SDM composite score, meaning a greater improvement in disability, only in armodafinil patients working > 9 h compared with placebo (− 6.8 vs − 2.7; $p = 0.0086$; 95% CI − 7.15, − 1.07) [18].

Howard et al. found higher values of mean MSLT scores when shift workers were treated with armodafinil than with placebo (11.1 ± 4.79 min vs 5.3 ± 3.25 min; $F_{1,11} = 11.50$; $p = 0.0006$). Armodafinil improved sleepiness on the first two naps compared to placebo (13.8 ± 7.0 vs 6.1 ± 5.2, $p = 0.003$ on nap 1; 12.7 ± 7.6 vs 3.6 ± 3.3 min, $p = 0.003$ on nap 2), whereas no armodafinil effects were found on the last two naps, respectively 7 h and 9 h following drug administration. Mean VAS scores also showed greater values on armodafinil nights compared with placebo nights ($F_{1,11} = 10.99$; $p = 0.0008$). Like MSLT, VAS scores improved 3 h and 5 h after armodafinil administration compared with placebo (59.5 ± 25.7 mm vs 37.8 ± 22.1 mm, $p = 0.02$ and 53.4 ± 21.7 mm vs 35.8 ± 23.9 mm, $p = 0.02$ respectively), but there was no difference between armodafinil and placebo effects at 7 and 9 h following their administration. The divided attention test showed lower mean values, indicative of better performance, on armodafinil nights than on placebo nights for both peripheral (526 ± 86 vs 665 ± 193 ms; $F_{1,11}$, $p = 0.006$) and central reaction time (472 ± .95 vs 544 ± 13.6 ms; $F_{1,11} = 14.74$, $p = 0.006$). The free recall memory test also exhibited better results (higher number of correct answers) after armodafinil with respect to placebo (12.08 ± 2.75 vs 10.33 ± 3.68; $F_{1,11} = -4.69$; $p = 0.05$) [19].

Drake et al. found that armodafinil administration provided better results across the night on simulated driving performance compared with placebo on both SLDP [$F(1, 19) = 18.02$; $p < 0.001$] and off-road deviations [$F(1, 19) = 8.18$; $p = 0.01$]. Additional comparisons demonstrated that both SLDP and off-road deviations presented lower values following armodafinil administration than after placebo on the last two sessions, respectively 5.75 and 7.75 h, after the administration (at 07:30 a.m.: $p < 0.01$ and $p = 0.05$ respectively; at 09:30 a.m.: $p = 0.001$ and $p = 0.03$ respectively). SLDP also showed lower values in the third session, at 05:30 a.m., in patients belonging to the treatment group compared to the control group ($p < 0.01$). Mean overall MSLT scores presented higher latency in patients taking armodafinil than in those placebo-treated, with a gain of 5.97 ± 5.0 min (9.7 ± 5.2 min vs 3.7 ± 0.6 min; $p < 0.001$). According to subsequent post hoc comparisons, armodafinil induced greater sleep latencies during each nap compared to placebo ($p < 0.01$). Change of subjective sleepiness (KSS score) from baseline measurement to the mean of the five measurements obtained post-drug administration was better on drug nights (lower scores) than on placebo nights (higher scores); there was no difference in KSS scores between armodafinil and placebo-treated patients 45 min post-administration (3.6 ± 1–5 vs 3.8 ± 2.2; $p = 0.69$). Regarding cognitive performance tasks, only creativity resulted better when patients took armodafinil rather than a placebo (RAT scores: 11.25 ± 6.0 vs 8.75 ± 4.9; $p = 0.001$), whereas DSST revealed higher scores with armodafinil only in the measurement recorded 6.25 h post-administration [20].

Discussion

Given the diverse nature of these three studies, it is difficult to evaluate their results comprehensively.

With respect to inclusion criteria, Drake et al. were the only authors not to perform a PSG in the screening of the patients [20]; thus, some patients with sleepiness also caused by a sleep apnea syndrome may have been included, despite the use of the STOP questionnaire.

Design-wise, Harsh et al. employed parallel groups [18], thus differing from the crossover design of the other two studies [19; 20].

Sleepiness was subjectively investigated by KSS [22] only in two studies and at different times: Harsh et al. [18] considered its change from baseline to final visit only in the critical circadian nadir period (every 2 h between 4 a.m. and 8 a.m.) on the last night worked, whereas Drake et al. [20] took into account the change of subjective sleepiness from baseline measurement to the mean of the five measurements throughout the whole experimental night.

The MSLT was used in two studies [19; 20] but nap sessions occurred at different times in relation to the time of armodafinil or placebo administration: 1.75, 3.75, 5.75, and 7.75 h after drug/placebo administration in the study of Drake et al. [20], whereas Howard et al. conducted the sessions at 3, 5, 7, and 9 h following drug/placebo administration, thus having the possibility of evaluating even later effects of the drug [19].

Furthermore, the outcome measures of the three studies were different. Performance was evaluated on experimental nights via different tests in the two studies of Howard et al. [19] and Drake et al. [20], as well as at different times in relation to the time of armodafinil or placebo administration, whereas Harsh only evaluated subjective investigator-rated (clinical condition and global functioning) and patient-rated (disability) measures of efficacy [18].

Nevertheless, each of the three studies provides new and useful data on the effect of armodafinil on the symptoms of shift workers.

Prior to the trial of Harsh et al. [18], a previous study [33] had already examined the effect of armodafinil on late-in-shift clinical conditions and overall functioning in SWD patients with excessive subjective sleepiness. The peculiarity of Harsh et al.'s study [18] consists of investigating drug efficacy in two different night work schedules depending on their extension, albeit the two shift-worker populations were not balanced due to the post hoc design. It is well known that there is an association between extended duration of work shifts and motor vehicle crashes or work-related accidents [34] which increases exponentially after 8 or 9 h at work [35]. Harsh et al. demonstrated that armodafinil does not merely improve late-in-shift clinical condition, sleepiness, and overall global functioning compared to placebo regardless of shift duration, but also that shift workers that endured longer shifts (> 9 h) were the only ones to improve on the SDS-M, which specifically assesses the impact of work, compared to placebo. This suggests a specific clinical benefit of armodafinil in SWD patients working longer shifts, an encouraging finding in light of the aforementioned risks associated with shift work, especially when considering that one-third of the sample worked longer shifts (> 9 h). Another strength of this study compared to the other two is represented by the 6-week duration of the parallel-group design, with patients taking armodafinil before the start of each night shift [18].

Unlike a previous parallel-group trial on the efficacy of armodafinil [36], the study by Howard et al. [19], and that of Drake et al. [20] were not limited to preselected SWD patients with a basal level of sleepiness of $\leq$ 6 min. The baseline MSLT score was 2.3 ± 1.6 min in the previous study, whereas the mean sleep latency through the placebo experimental nights was 5.3 $\pm$ 3.25 min in Howard et al.'s cohort [19]. The authors [19] consider these values more indicative of the actual levels of sleepiness in shift workers, based on similar data from individual melatonin profiles [37]. The lack of initial sleepiness criteria in the selected participants likely explains the highest difference (+ 5.8 min) between the mean sleep latency on the placebo experimental nights and the mean sleep latency during the armodafinil nights [19], compared to the value of improvement (+ 3 min) in the previous study, which failed to demonstrate a normalization of sleepiness in SWD patients [36]. However, a similar comparison may be unsound given the difference in the design of the two trials. Moreover, Howard et al. found no difference in the effect of armodafinil from placebo in the last two nap sessions at 7 and 9 h after drug administration, as if the efficacy of the drug had subsided [19]. A limitation of this study consists in the administration of both the attention and memory performance tests at 2:15 a.m. [19], preventing any conclusions regarding later morning performance. In fact, while it is true that the circadian nadir of alertness is maximal in the middle of the night, it is also true that the drug's efficacy has been shown to attenuate with time after its administration, hence performance tests closer to the end of the shift, near the time of commuting home, would have been useful.

Drake et al. confirmed the increase of about 5 min in the mean MSLTs conducted on armodafinil nights compared with placebo nights [20]. They also showed that the improvement was present in all four sessions, thus demonstrating the persistence of the drug's efficacy at least up to 7.75 h following armodafinil administration [20]. Similarly to the Howard et al. trial [19], this study was also conducted on patients without screening for a minimal level of basal sleepiness, in order to allow the generalization of the results to the larger SWD population. However, the significance of Drake et al.'s study is that it is the first to investigate the efficacy of a stimulant on simulated driving performance in SWD, so as to assess the level of risk in the commute home. The analysis revealed an improvement in driving simulator performance for both "weaving" from the center of the right-hand lane (SDLP) and off-road deviations during the last two sessions, occurring at 7:30 and 9:30 a.m., which represent common commute times in the SWD population [20]. It must, however, be outlined that this trial, as well as that of Howard et al., found two disquieting results:

1. First, even after armodafinil administration, sleep latencies were not normalized (shorter than 8 min) between 5 and 8 a.m., a span of time during which most night workers' drive home
2. Secondly, at 7:30 a.m., shift workers exhibited an average of more than five off-road deviations [19; 20]

It is well established that excessive sleepiness impairs global functioning as well as performance on several tasks including those involving psychomotor performance and cognitive functions such as attention and memory [38]. Hence, it is not surprising that stimulants, as wake-promoting agents, can also improve performance levels due to better vigilance. Unfortunately, this improved vigilance still fails to guarantee shift workers a normal and safe performance level.

Furthermore, stimulant drugs are not without adverse effects, the most common being headache, nausea, insomnia, and dry mouth in the study of Harsh et al. [18]; these events caused discontinuation in nine patients receiving armodafinil and in one receiving a placebo. The highest incidence of these effects resulted in patients taking armodafinil with working shifts > 9 h: in fact, 60% of shift workers with night shift $\geq$ 9 h taking armodafinil reported > 1 adverse event vs 27% of the placebo group. Only two separate reports of headaches of mild severity (one occurring during the placebo condition and one occurring during the armodafinil condition) were

mentioned by Howard et al. [19], whereas adverse events were not investigated by Drake et al. [20].

The most significant limit of the two crossover studies consists in the employment of a single dose with a single administration. Since SWD is a chronic disorder, the use of stimulants is also chronic. Therefore, these trials prevent any conclusions regarding potential tolerance that may both reduce the chronic efficacy of these drugs on alertness and performance, and their tolerability, given that adverse effects can be fully evaluated only with more chronic use. Moreover, a limitation common to all three trials is the lack of objective (PSG) or subjective assessment of daytime sleep on the following day, precluding researchers from emphasizing an important potential adverse effect of armodafinil: this drug may actually disrupt recovery sleep, thus increasing sleep pressure and reducing alertness during the subsequent night shifts. However, a previous study using similar doses of armodafinil at similar times did not observe adverse effects on daytime sleep variables (sleep latency, sleep duration, and sleep-stage distribution) compared with placebo [36].

Lastly, all three studies were supported by Teva Pharmaceuticals, and one of the authors of the Harsh et al. trial was an employee of Teva Pharmaceuticals.

Conclusion

The present review confirms that stimulants are an important tool for shift workers and, in absence of circadian phase adjustment, they can "attenuate negative consequences at critical points in the circadian cycle including common commute times in the early morning" [20], though "they do not restore alertness to the levels observed in well-rested day workers" [39]. Moreover, stimulants do not improve the alignment between internal circadian rhythms and the work-sleep schedule because they do not affect circadian adaptation to night work shifts; they must be regarded only as symptomatic drugs. Indeed, even if SWD patients taking armodafinil may not be as sleepy during their work shift or driving home as non-treated patients, disruption of circadian rhythm remains, inducing some somnolence or insomnia during non-working hours, consequently impairing their social and family relations and their quality of life [40].

It is recommended that pharmacotherapy with agents such as armodafinil be part of a comprehensive treatment program to improve the patient's overall burden of symptoms. This program should involve proper sleep hygiene, sleep education, appropriate diet and exercise, and non-pharmacological interventions such as planned napping and increasing bright light exposure at night combined with reducing exposure to bright light in the morning.

The role of health personnel is also crucial. A general practitioner can catch the early symptoms of SWD thanks to his or her extended data on the patient and establish a temporal association between the onset of the disturbances and the initiation of the shift work. Ideally, the general practitioner should advise the patient to consult a sleep expert that, once a diagnosis of SWD has been ascertained, can decide to discuss the case with the occupational health physician (OHP). The latter has the responsibility to communicate the patient's diagnosis and related health risks to the employer. The sleep expert can also differentiate "tolerable" troubles (compatible with transitory perturbation of the sleep-wake cycle) from severe troubles or pathological disorders that require prompt interventions at work (transfer to day work) and personal treatment (therapy, rehabilitation). Hence, OHPs rely on the help and support of sleep experts in order to obtain certified diagnoses and expert guidance for the treatment of SWD [9] and other potentially comorbid sleep disorders affecting the productivity and well-being of shift workers.

Factors affecting vulnerability and tolerance to shift work

As stated by ILO Convention (International Labour Office, 1990) No. 171 on night work, as well as by the European Directive No. 104/1993, workers should be entitled "…to undergo a free health assessment before their assignment to night work and thereafter at regular intervals and in case they experience health problems because of it" [41]. Health surveillance aims to investigate factors affecting the worker's tolerance prior to the shift-work assignment and to detect early signs of intolerance. Individual vulnerability to SWD symptoms may be influenced by various factors, including physiological and physiopathological changes in sleep duration and quality occurring in older adults, as well as proneness to advanced phase or even desynchronization of biological rhythms [42]. Workers with cognitive impairment are less able to implement the countermeasures that facilitate adapting to the sleep-wake rhythm alterations imposed by shift work. A reduced tolerance to shift work has been observed in women due to greater family burden and commitments (especially in women with small children and/or larger families), which hinder a satisfactory recovery from sleep deprivation and fatigue [9].

Individual hypnotypes should also be taken into account. Long sleepers generally require a longer interval between two consecutive shifts [9] and "morningness"/"eveningness" should also be investigated in a worker prior to assigning shift schedules. Evening types, i.e., "owls" that go to bed and wake up late, tolerate better night work than morning types, i.e., "larks" that go to bed and wake up early, due to delayed phase position of their circadian rhythms towards evening hours; on the contrary, morning types cope quite well with early morning shifts, due to early activation of their biological rhythms. Thus, night shifts and early morning shifts would be more advantageously assigned to evening types and morning types

respectively, in the cases of fixed or slowly rotating shift systems [9].

Circadian rhythm stability (flexible/rigid) is likewise imperative: flexibility is associated with better sleep quality in a recent systematic review on individual vulnerability to sleep disturbances in shift workers [43]. The ability to overcome drowsiness and thus to sustain alertness during shift work, as well as the ability to obtain adequate sleep during non-working hours, considerably influence the vulnerability to SWD, but seem to depend on complex and not fully understood mechanisms [44].

Physical fitness augments tolerability to shift work by reducing fatigue and improving recovery mechanisms. Comorbid sleep disorders and other health problems such as severe gastrointestinal disorders, cardiovascular diseases, psychiatric disorders, neurological syndromes, metabolic disorders, hormonal disorders, chronic renal impairment, and cancer may reduce tolerance to shift work [9].

Current pharmacological therapy taken by patients should also be considered in order to evaluate the timing of treatment, as well as possible interference with alertness and sleep; in particular, the use of potentially sedative pharmacological treatments in progress must be investigated [9]. Lastly, social and environmental factors such as social support from co-workers and supervisors at work, as well as from family members, are of great relevance in the worker's ability to improve adaptation and tolerance to shift work. In fact, shift workers that are very susceptible to social pressures often experience difficulties maintaining a daytime sleep schedule on days off, hindering circadian adjustment [9].

In addition to the measures presented above, collaborative consultations between the employer and the company medical staff are necessary to design suitable work shifts. Shift schedules should be designed according to ergonomic criteria, which has been demonstrated to limit adverse effects on health and well-being by avoiding or minimizing circadian disruption and the accumulation of sleep deficits and fatigue (Table 3). Moreover, employers can assist with alleviating their workers' symptoms by providing appropriately timed light exposure to encourage circadian rhythm adjustment [40].

Table 3 Ergonomic criteria for shift design and evaluation

1. Limit night work as much as possible to minimize potential long-term health effects.
2. A large number of consecutive night shifts should be avoided, since fewer consecutive night shifts have been shown to cause no significant accumulation of sleep deficits and less disturbance of the physiological functions [45].
3. Quickly rotating (every 1–3 days) shift systems are preferable to slowly rotating (i.e., weekly or longer) ones because fast rotation, favored in Europe, lets the worker escape the consequences of partial temporal adaptation [46] and has been associated with improved outcomes such as better sleep quality and reduced fatigue [44].
4. Clockwise rotation (morning/afternoon/night) seems to be most compatible with the properties of the human circadian system, given that forward rotations are consistent with the tendency of the circadian clock to delay sleep, in addition to allowing for an extended time between each rotation [46].
5. Work-shift duration should be defined according to psycho-physical demands and to potential toxic exposure [47; 48].
6. Adequate time-off between shifts must be allowed (> 11 h), based on the finding that shorter rest periods may reduce sleep duration to 3 or 5 h [49].
7. An adequate number of rest days between shifts, particularly after night shifts, must be allowed: at least 2 days off after the last night shift to minimize the reduction of sleep before undertaking a morning shift [47].
8. Early start times should be avoided, given that they may reduce REM sleep and, above all, shorten sleep before the morning shift, thereby increasing fatigue as well as the risk of errors and accidents during the shift [50].
9. Daytime shifts should be adopted periodically to reduce the negative consequences of shift work.
10. A regular shift system should be established, allowing workers easier and earlier planning of their activities.
11. Each shift worker should enjoy certain flexibility in their work schedule according to his/her needs and preferences and shift swapping should be allowed [47].

These criteria for the organization of shift schedules serve as salient preventive and corrective measures for the well-being of shift workers

Conclusive remarks and future directions

In conclusion, our 24-h society compels humans to work around the clock, to the point of encouraging "sleep loss and circadian disruption as a sign of strength" that allows them "to remain awake and still perform". Consequentially, it has been conveniently ignored that staying awake to work during biologically sleepy hours will almost inevitably result in sleepiness and impaired performance during work hours. More importantly, modern society neglects the consequences of sleep deprivation and its repercussions not only on the health of the individual worker, but also on the safety of the whole community and, ultimately, on productivity itself [51]. In fact, while it is true that "shift work represents for employers an opportunity to increase production and customer service", it is also true that SWD "involves significant costs related to productivity loss" [52] due to poor work performance, work errors, or absenteeism.

The extant data suggest that further epidemiological research is needed to assess the prevalence of SWD, as well as its pervasiveness and severity. Moreover, since circadian misalignment is associated with multiple health morbidities, additional studies are warranted to develop "the best diagnostic tools for health surveillance and assessing the 'risk-benefit' ratio for the worker, and if it is acceptable or not" [53]. Interventions must

endorse a multivariate approach involving the participation of various actors, among these, ergonomists and managers that should cooperate to identify work schedules meeting ergonomic criteria (Table 3) and personalized management plans aimed at addressing symptoms and circadian misalignment.

Lastly, social and political attention should be granted to this disorder in an effort to inform the public of the difficulties and dangers associated with shift work and to promote the establishment of more sensible regulations conducive to protecting shift workers from developing SWD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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