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R E V I E W

# Ready for takeoff? A critical review of armodafinil and modafinil for the treatment of sleepiness associated with jet lag

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**Abstract:** Jet lag syndrome (JLS) is a clinical syndrome of disrupted nocturnal sleep and daytime neurocognitive impairment which occurs in the context of rapid transmeridian travel. Many strategies for treatment of JLS exist, and include hypnotics to enhance nocturnal sleep, chronotherapeutic approaches (eg, light therapy, melatonin, or gradual schedule shifting), and alerting agents to counter daytime sleepiness. Safety concerns have prompted renewed interest in managing JLS-associated excessive daytime sleepiness (JLSAEDS). Off-label use of the newer alerting agents modafinil and armodafinil is increasing for this indication, often at the specific request of patients. In order to better evaluate the potential risks and benefits of these medications for the management of JLSAEDS, clinicians must be aware of what is known – and still not known. In this article, the pharmacology and pharmacokinetics of modafinil and armodafinil are reviewed, along with evidence for their efficacy in treating sleepiness associated with narcolepsy, obstructive sleep apnea and shift work sleep disorder. Clinical trial data for use of alerting agents in the management of JLSAEDS are limited to one three-day trial involving armodafinil, dosed in the morning to treat JLSAEDS in the setting of eastbound transmeridian travel. This study showed improvement in objective measures of daytime sleepiness at doses of 50 and 150 mg per day. However, global impression of clinical severity of symptom scores only improved on day 1 for those patients receiving 150 mg, and were otherwise not superior to placebo. Consideration for the use of modafinil or armodafinil for the treatment of sleepiness associated with JLS involves careful integration of patient-reported goals, a review of medical contraindications, and an awareness of rare adverse events. More research is needed in order to identify those who are most likely to benefit from this intervention and better define the risk-benefit ratio for this indication.

**Keywords:** jet lag syndrome, modafinil, armodafinil

## Management issues in the treatment of jet lag syndrome

Jet lag syndrome (JLS) is a clinical disorder characterized by patient complaints of disrupted nocturnal sleep and/or daytime impairment symptoms of fatigue, poor concentration, or daytime sleepiness, precipitated acutely by rapid transmeridian travel.[1] Physical symptoms of gastrointestinal discomfort, somatic pain, or headaches may accompany the syndrome, but are not required for the diagnosis.

Symptoms are believed to arise from three main sources – circadian misalignment, partial sleep deprivation and physical discomforts associated with travel. With rapid travel across time zones, a patient's internal rhythm-generating system will remain synchronized to the light-dark cycle at the point of origin, thus leading to improper

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alignment at the travel destination. For those traveling in the eastern direction, this misalignment leads to a delayed sleep phase – travelers often find it difficult to achieve sleep at their usual bedtimes and experience next-day morning drowsiness – while westward travelers typically experience an apparent advance in their usual sleep phase, with symptoms of excessive sleepiness earlier than their clock-directed bedtimes, accompanied by early-morning awakening. In addition, the circadian phase-shifting can lead to inappropriate timing of normal autonomic functions such as defecation, pancreatic and metabolic activity, and may cause disruption of the menstrual cycle.[2]

Next, for a transmeridian traveler, circadian misalignment symptoms typically mingle with symptoms of acute partial sleep deprivation. Factors that contribute to sleep deprivation in this population are listed in Box 1.

Lastly, some of the symptoms of JLS may simply arise from the physical discomforts associated with travel – poor quality food or unusual mealtimes, dehydration, musculoskeletal discomfort from prolonged sitting or standing, and bladder/bowel complaints associated with use of public facilities – all may contribute to the overall presentation. While these symptoms are not specific to transmeridian travelers, they are important to recognize as potential targets for intervention, and as potential pitfalls which can limit the success of specific pharmacologic management strategies.

To combat the symptoms of JLS, numerous treatment recommendations have been proposed, with varying degrees of success. A summary of basic treatment strategies, including rationale and evidence for their use, is provided in Table 1. Though a detailed analysis of these different approaches is beyond the scope of this paper, several excellent reviews of the pathophysiology and treatment for JLS have recently been published, and are recommended for the interested reader.[3–5]

Notably, most research on the treatment of JLS involves attempts to correct circadian misalignment, to pharmaceutically improve nocturnal sleep, or both. Interventions such

as pharmaceutical melatonin administration,[6] timed bright light exposure and light avoidance,[7,8] and nocturnal hypnotic agents[9–13] therefore make up the majority of what has been studied. Though the basic concept of JLS management is relatively simple – the goal is essentially to adapt the patient's inner rhythms as quickly as possible to the new environment – the practical application of this concept is complicated by many factors, including the direction and distance of travel, the patient's inherent circadian phase and personal tendency towards "morningness" or "eveningness".[4] Such factors play an important role in the design of a chronotherapy regimen, simply because the direction of phase-shift induced by melatonin or light exposure is determined by the patient's circadian phase and personal tendency towards "drift". If the timing of such interventions is not properly planned, phase-shifting in the direction opposite to the desired effect can result, and JLS symptoms can be unintentionally prolonged.[8] In addition, bright light exposure and light avoidance techniques may involve the use of specialized equipment such as lightboxes,[14] welder's goggles[15] or "blue-blocker" glasses,[16] which can limit the widespread acceptance of these recommendations. In fact, given the time and effort required for phase-adaptation, in some situations – such as short trips with expected return within 48 hours – adaptation to the new environment is not a practical expectation, and maintaining a schedule based on the clock-time of the point of origin is recommended.[17]

Given the complexity associated with circadian realignment, the potential for specific treatment of daytime impairment – without regard for the patient's circadian phase, direction of travel, or personal sensitivity towards phase shift, and without need for special equipment – has obvious allure. Nonetheless, although the specific targeting of daytime sleepiness with stimulant medications is an obvious clinical solution to the daytime impairment problem in JLS, there are little published data on this subject. Based on the results from two small trials,[18,19] the American Academy of Sleep Medicine (AASM) lists caffeine as an "option" for the treatment of excessive sleepiness associated with JLS, but cautions that disturbed nocturnal sleep may result.[20] As for other stimulant medications, including modafinil, armodafinil, and traditional sympathomimetic stimulants, no mention is made, a testament to the lack of evidence on the subject. In the same practice parameters paper, the AASM specifies modafinil as a "guideline" for treating sleepiness associated with shift-work sleep disorder (SWSD), a circadian misalignment syndrome involving excessive sleepiness and fatigue during desired wakefulness in the nocturnal timeframe, a problem mechanistically similar to sleepiness associated with JLS

**Box 1** Factors contributing to sleep deprivation in transmeridian travelers

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Disrupted/shortened sleep on travel days
    Early rise time on day of journey
    "Red eye" flights
    Late arrival time at destination

Disrupted or shortened nocturnal sleep at destination
    Unfamiliar or uncomfortable accommodations
    Physical symptoms (eg, pain, nocturnal defecation)
    Social or work responsibilities

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**Table 1** Treatment strategies for management of jet lag syndrome (JLS)

| Strategy | Desired outcomes | Interventions used | Summary of evidence | Selected references |
|---|---|---|---|---|
| Enable better quality nocturnal sleep to prevent symptoms of sleep deprivation | Improve quality of nocturnal sleep; improve quality of daytime alertness | Benzodiazepines, benzodiazepine receptor agonists, melatonin | May improve sleep quality and duration. No convincing data to suggest improved daytime functioning. Potential benefits must be balanced with potential for harm | Paul[27] Suhner[28] |
| Shift circadian phase | Speed transition to destination circadian cycle; improve quality of nocturnal sleep; improve quality of daytime alertness | Chronobiotic agents (eg, melatonin); light therapy; pre-travel chronotherapy | Melatonin improves sleep quality and may help accelerate phase-shifting in both eastward and westward travel. Optimum dose not known, but 0.5–5 mg has been used and immediate-release likely better than slow release; risk of treatment low. Care must be taken in timing of the dose, as phase advance or phase delay may result. Gradual pre-travel adjustment of the sleep–wake cycle using a combination of bright light exposure and gradual advancement of bedtime may be of benefit for phase shifting and may decrease daytime JLS symptoms in eastbound travelers | Petrie[29] Petrie[30] Suhner[31] Burgess[7] Boulos[32] Paul[33] |
| Maintain circadian phase to point of origin | Allow continuation of innate rhythms to avoid discomfort of rhythm changes | Maintain schedule and sleeping habits on "home clock" | Keeping home based hours may decrease sleepiness and daytime JLS symptoms. Recommended trips lasting ≤2 days | Lowden[17] |
| Alerting agents | Improve quality of daytime alertness, preventing daytime naps may allow better nocturnal sleep consolidation | Over the counter stimulants (caffeine); traditional prescription stimulants: (methylphenidate, dextroamphetamine, others); non-traditional prescription stimulants (modafinil, armodafinil) | Caffeine 300 mg taken as a slow-release formulation may decrease daytime sleepiness, but nocturnal sleep may suffer. No peer-reviewed data are available for other alerting agents in managing daytime sleepiness in JLS | Beaumont[18] Pierard[19] |
| Supportive measures and behavioral counseling | Decrease physical discomfort, thus improving nighttime sleep and daytime functioning | Avoid excessive alcohol or nocturnal caffeine, avoid large high-fat meals during atypical eating times, drink plenty of water, wear comfortable traveling clothes, avoid nocturnal travel if possible | No rigorous controlled studies. Because these elements may play a role in JLS symptoms, all patients should be counseled appropriately | Arendt[34] |

(see later). Of note, though the AASM lists methamphetamine as an efficacious choice for use in sleepiness associated with SWSD, overt precautionary statements are made regarding "significant abuse liability",[20] a warning that would logically carry over for its use in JLS as well.

With the now-widespread availability of modafinil, a drug often touted as having fewer unfavorable side effects and less potential for abuse than its older predecessors,

many patients are now requesting prescriptions for alerting medications for off-label indications such as JLS.[21,22] Moreover, increasing concern over flight-safety among aviators has sparked increased interest in specific pharmacologic management of daytime impairment in the setting of transmeridian travel, with particular interest being paid to armodafinil.[23] This is likely due to armodafinil's longer half-life with single-dosing, as well as initial trials suggest-

ing possible improved alertness and reaction parameters compared with modafinil.[24] Recently, media interest in armodafinil has intensified, fueled at least in part by the manufacturer's attempt to win FDA approval for the jet lag indication.[25,26] Arguably, even if the FDA finally rejects the bid for the new indication, elevated media coverage may rouse enough interest to increase patient-initiated requests for modafinil and armodafinil as an "off-label" treatment for sleepiness associated with JLS. As a result, this paper was undertaken to critically evaluate these drugs, with particular attention to what is known – and not known – about them with regard to this issue, to prepare clinicians to effectively weigh the risks and potential benefits of these medications prior to reaching for the pen and prescription pad.

Therefore, this paper will review the pharmacologic and pharmacokinetic characteristics of modafinil and armodafinil, efficacy data for the use of these drugs in the treatment of sleepiness associated with other disorders (obstructive sleep apnea, narcolepsy, and SWSD), preliminary evidence for clinical efficacy in the treatment of JLS, and safety and tolerability data. Finally, the paper will conclude with a commentary on the place of these drugs within the context of other available therapeutic options.

## Modafinil and armodafinil: pharmacology, mode of action and pharmacokinetics

Armodafinil is the R-enantiomer of modafinil (which is an equal mixture of R- and S-enantiomers). Both drugs are orally administered, wakefulness-promoting agents, approved by the US Food and Drug Administration (FDA) for the treatment of sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder.[35,36] Though the pharmacologic activities of the two enantiomers are roughly equivalent, their individual pharmacokinetics are not. The half-life of the S-enantiomer of modafinil is relatively short – roughly 3–4 hours – while the half life of the R-enantiomer is much longer at approximately 12 to 14 hours.[37] In the setting of chronic modafinil administration, the plasma concentration of the R-enantiomer is roughly three times that of the S-enantiomer, an observation which has led to speculation that the R-enantiomer is responsible for much of the clinical benefit.[38]

The precise mechanism by which modafinil and armodafinil exert their wake-enhancing effects is incompletely understood. Traditional sympathomimetic stimulants promote diffuse enhancement of synaptic dopaminergic and noradrenergic transmission, including activation of the dopaminergic pathways associated with pleasure and reward, primarily via blockade of dopamine transporters. Such diffuse activation is felt to contribute to a worse cardiovascular risk profile as well as elevation in potential for abuse and dependency. Modafinil was originally thought to exert its effects independent of dopaminergic signaling, due to initial data showing that the wake-promoting effects of modafinil were unaffected by haloperidol, a powerful dopamine receptor antagonist.[39] Amphetamine-induced wakefulness, by contrast, is blocked by haloperidol.

More recent investigations, however, suggest that modafinil may not be as mechanistically different from amphetamines as originally believed. Madras and colleagues recently demonstrated that modafinil occupies dopamine and norepinephrine transporters in monkeys.[40] Moreover, mice lacking the dopamine transporter did not experience any increase in wakefulness with modafinil.[41] The same was observed for mice lacking $D_1$ and $D_2$ receptors.[42] Recently, Volkow and colleagues published positron emission tomography imaging data in human men showing that modafinil acutely increases central nervous system (CNS) dopamine, apparently by blocking dopamine transporters at a site overlapping with and competitive for that of cocaine.[43] These data also show that modafinil specifically promotes dopaminergic stimulation in the nucleus accumbens, an area felt to be important in the neurophysiology of addiction.[44] Of interest, these findings may help explain some recent observations regarding the potential benefit of modafinil in the treatment of cocaine addiction.[45] More importantly, in total, these data suggest a mechanism for modafinil that involves dopaminergic signaling, and which may be, in fact, quite similar to that of older stimulants. How the clinician should interpret these data as pertinent to any potential for addiction and abuse will be discussed in more detail later, in the section covering tolerability.

Modafinil's actions appear to rely on other CNS mono-aminergic compounds in addition to dopamine. Modafinil has been shown to improve cognitive performance in human subjects.[46] Such cognitive enhancement can be attenuated *in vivo* by the α1 adrenergic antagonist prazosin, suggesting that α1 adrenergic transmission is an important component of this effect.[47]

Ishizuka and colleagues demonstrated that modafinil-induced locomotor activity was associated with increased CNS histamine signaling, and that depletion of CNS histamine abolished this effect. By contrast, increased locomotor activity caused by methylphenidate was not associated with increased CNS histamine.[48] The regional activity of modafinil

also appears to differ from than that of amphetamines. Engber and colleagues used *c*-Fos immunohistochemistry to demonstrate that while modafinil increased activity in the hypothalamus, suprachiasmatic nucleus, and amygdyla, it caused no increase in activity in the frontal cortex, striatum, lateral habenula, or the superoptic nucleus – all areas that were stimulated by amphetamine.[49] Functional MRI imaging data suggest that modafinil functions to increase phasic activity in the locus coeruleus, a factor linked to improved task-specific cognitive performance.[50]

The oral bioavailabilies of modafinil and armodafinil have not been directly determined, due to low aqueous solubility which precludes intravenous administration of these drugs. Indirect evidence, relying on urinary recovery of the drug and its metabolites, suggest at least 60% of modafinil is absorbed orally.[51] At clinically relevant doses, the pharmacokinetics of modafinil and armodafinil are essentially linear. After oral administration, both modafinil and armodafinil reach peak plasma concentration in roughly two hours in the fasting state. Food may slow absorption time by as much 1 to 4 hours, but does not reduce the bioavailability.[39,52]

Modafinil has been shown *in vitro* to reduce expression of CYP2C9, suggesting a potential for an interaction between modafinil and warfarin or phenytoin.[52] An *in vivo* evaluation of warfarin in healthy subjects taking chronic therapeutic doses of modafinil, however, showed no significant change in the pharmacokinetics of warfarin, compared with subjects taking warfarin plus placebo.[52] Modafinil has been shown to induce CYP3A4, and one report indicates potential to decrease cyclosporine blood levels by 50%.[52] Armodafinil is metabolized by multiple pathways, primarily in the liver. Not surprisingly, like modafinil, it too has potential for mild CYP3A induction, and chronic administration can reduce the bioexposure of drugs metabolized by this pathway, such as midazolam and cyclosporine.[39] Inducers of CYP3A (carbamezapine, phenobarbital, rifampin) may lead to decreased plasma levels of armodafinil while CYP3A inhibitors (ketoconazole, erythromycin) have potential to lead to higher-than-intended levels.[39] Armodafinil is also a moderate inhibitor of CYP2C19, which has potential to increase bioexposure to drugs metabolized by this pathway, such as omeprazole, diazepam, phenytoin, and propranolol.[39]

## Efficacy of modafinil and armodafinil in the treatment of sleepiness associated with narcolepsy

The efficacy of modafinil in the treatment of sleepiness associated with narcolepsy is well-established.[53–57] As for armodafinil, Harsh and colleagues demonstrated in adult narcoleptic patients that 150 mg or 250 mg taken once daily prolongs maintenance of wakefulness test (MWT) times in a dose-dependent manner.[58] This study also showed an improvement in clinical global impression of change (CGI-C), fatigue scores, memory and attention in the patients receiving armodafinil, compared with placebo. Although direct comparisons with modafinil are unavailable in the published literature, rough comparison indicates that the effect size seen on this study is similar, and not clearly superior to that seen with modafinil (Table 2).

## Efficacy of modafinil and armodafinil in the treatment of residual sleepiness associated with CPAP-treated obstructive sleep apnea

Several studies have shown modafinil and armodafinil to be effective treatments to reduce residual symptoms of daytime sleepiness in continuous positive airway pressure (CPAP)-compliant patients with obstructive sleep apnea.[38,59–62] As

**Table 2** Comparison of efficacy of modafinil vs armodafinil for treatment of excessive daytime sleepiness associated with narcolepsy

| Trial | Intervention | Mean MWT | Δ from Placebo | Notes |
|---|---|---|---|---|
| US Modafinil in narcolepsy multicenter group[56] | Placebo | 5.1 min | n/a | 20 minute MWT test done. |
| | Modafinil 200 mg | 8.1 min | +3 min | Data reported are from |
| | Modafinil 400 mg | 8.9 min | +3.8 min | 9 week follow-up testing |
| Broughton et al[57] | Placebo | 11.2 min | n/a | 40 minute MWT test done. |
| | Modafinil 200 mg | 15.7 min | +4.5 min | Data reported are following |
| | Modafinil 400 mg | 17.2 min | +6 min | 2 weeks on medication |
| Harsh et al[58] | Placebo | 10.6 min | n/a | 20 minute MWT test done. |
| | Armodafinil 150 mg | 13.4 min | +2.8 min | Data reported are from |
| | Armodafinil 250 mg | 12.1 min | +1.5 min | 12-week follow up testing |

**Abbreviation:** MWT, maintenance of wakefulness test.

an example, in a 1-month, randomized, placebo-controlled trial, Pack and colleagues demonstrated efficacy of modafinil (200 mg per day for 1 week, followed by 400mg per day) in reducing daytime sleepiness, as measured by Epworth Sleepiness Scale (ESS) scores, and MWT. CGI-C scores also significantly favored the modafinil group, with improvement in 71% of those receiving active drug and only in 35% of those receiving placebo.[59] In a modafinil dose-comparison study, Black and Hirshkowitz found that modafinil at a dose of 200 mg or 400 mg per day were superior to placebo in improving sleepiness as measured by MWT, ESS, and CGI-C in sleepy CPAP-compliant adults, though there was no significant difference between the two doses.[62] More recently, Hirshkowitz and colleagues found in a 12-week trial that, compared with placebo,150 mg of armodafinil improved maintenance of wakefulness times, CGI-C, episodic secondary memory, and patient-estimated wakefulness.

Once again, a rough comparison with a similar study involving modafinil shows that the two drugs have similar effects, though comparison is somewhat skewed by the fact that patients in the modafinil trial appeared to have more severe sleepiness at baseline (Table 3).

## Efficacy of modafinil and armodafinil in the treatment of sleepiness associated with SWSD

The treatment of sleepiness associated with SWSD has clear implications for sleepiness associated with JLS – both problems are impacted by a misalignment of the patient's intrinsic circadian phase with the environment. For patients with professional responsibilities in travel-related fields (eg, airline pilots, flight attendants), the two syndromes may share a considerable degree of overlap. Czeisler and colleagues found, in patients with shift work sleep disorder, modafinil 200 mg at the beginning of a night shift led to improvements in objective wakefulness, subjective sleepiness symptoms, and vigilance-dependent performance tasks, with a decrease in reported near accidents on the trip home.[35] Though

armodafinil also has won FDA approval for the treatment of shift work sleep disorder, as of the time of this writing, these data remain on file with the pharmaceutical company and have not been published in a peer-reviewed journal.

## Efficacy of armodafinil in the treatment of sleepiness associated with JLS

Modafinil has not been systematically studied for the treatment of sleepiness associated with JLS. Recently, Bogan and colleagues presented preliminary data from a three-day treatment trial comparing armodafinil 50 mg and 150 mg to placebo in the treatment of excessive sleepiness associated with JLS in eastbound travelers with a 6-hour time change.[63] Objective sleepiness, as measured by multiple sleep latency testing (MSLT) improved in a dose-dependent manner on all three days, compared with placebo. Subjective sleepiness, as estimated by the Karolinska Sleepiness Scale – a sleepiness scale that tracks nicely with other physiologic and behavioral markers of sleep, including performance variables[64] – also showed dose-dependent improvement. Notably, however, though the mean patient global impression of clinical severity of illness (PGI-S) was improved on day 1 in the group receiving 150 mg armodafinil (compared with placebo), this effect was lost by days 2 and 3. The 50 mg armodafinil group had PGI-S scores similar to those of the placebo group across the 3-day study. This finding is arguably important for clinicians to discuss with their patients, for whom the global impression of severity of illness may be the most important endpoint. Also notable is the absence of data on subjective nocturnal sleep quality in this initial report. Therefore, the question of how armodafinil affects nocturnal sleep in this population remains unsettled.

## Safety and tolerability issues

Though modafinil and armodafinil are typically well-tolerated in clinical trials, rare, but important complications are known

**Table 3** Comparison of efficacy of modafinil vs armodafinil for the treatment of residual excessive daytime somnolence in continuous positive airway pressure-compliant patients with obstructive sleep apnea

| Trial | Intervention | Mean MWT | Δ from Placebo | Notes |
|---|---|---|---|---|
| Black et al[62] | Placebo | 12.65 min[a] | n/a | 20 minute MWT test done. Data reported |
| | Modafinil 200 mg | 14.85 min[a] | +2.2 min | are from 12 week follow up testing |
| | Modafinil 400 mg | 15.1 min[a] | +2.45 min | |
| Hirshkowitz et al[38] | Placebo | 21.7 min[a] | n/a | 40 minute MWT test done. Data reported |
| | Armodafinil 150 mg | 26.4 min[a] | +4.7 min | are from 12 week follow up testing |

**Abbreviation:** MWT, maintenance of wakefulness test.
[a]Calculated from values estimated from graphic.

to occur. In the counseling of patients regarding risks and expected benefits of a pharmacologic intervention for an arguably self-limited problem such as JLS, clinicians should maintain an awareness of these rare events, and assist patients to make decisions respectful of their values and concerns. All data on adverse events are taken from modafinil and armodafinil prescriber's information,[39,52] except where indicated.

In clinical trials involving patients with narcolepsy, obstructive sleep apnea, and shift-work sleep disorder, modafinil and armodafinil are generally reported to be well-tolerated. The most common adverse effect reported is headache, occurring in approximately one in six patients. Headaches were severe enough to require discontinuation of the drug in ~1% of patients. Nausea, dizziness, and insomnia are also reported, occurring in approximately 1 in 20 patients. Overall, according to product labeling, approximately 7% of patients receiving armodafinil in clinical trials discontinued the drug due to perception of adverse events.

## Dermatologic events
Modafinil has been linked to development of Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms (DRESS) and there is no reason to suspect that the same problem would not be caused by armodafinil. In pooled analysis of clinical trials, rash is noted as a treatment-emergent problem in ~2% of patients taking armodafinil.

## Cardiovascular safety
Neither modafinil nor armodafinil have been studied in patients with unstable cardiac disease, and both drugs have been linked to chest pain and ischemic ECG changes in patients with left ventricular hypertrophy and mitral valve prolapse. In retrospective postmarketing analysis, both drugs have also been shown to be associated with a 1% to 2% increase in requirement for new antihypertensive medication.

## Psychiatric events
Though modafinil has been associated with mania, delusions, hallucinations, suicidal ideation, and aggression, these events are most often observed in patients with a prior psychiatric history or with higher-than-recommended doses. Self-reported irritibility and nervousness are cited by ~1% of patients taking armodafinil as a reason for discontinuation.

### Potential for abuse and addiction
Data for the abuse potential of modafinil – and by extension, armodafinil – are conflicting.[65,66] Myrick and colleagues

summarize much of these data to conclude that, though the abuse potential for modafinil is not zero, it appears to be a much lower risk compared with traditional stimulants such as cocaine and amphetamine.[44] Nonetheless, modafinil was shown in one study to function as a reinforcer, if behavioral demands requiring attention and performance were placed on the patient.[67] Recent imaging data also shows that modafinil leads to acute increases in dopaminergic activity in the nucleus accumbens, an area which has been implicated as central to neurobiological addiction.[43] With greater availability of modafinil and armodafinil and increased patient-initiated requests for treatment of lifestyle-related clinical syndromes such as JLS, the clinician should be aware of the potential for abuse, and exercise appropriate caution.

## Pediatric patients
Initial pediatric trials involving modafinil were associated with a 0.8% incidence of rash resulting in discontinuation of the drug. Clinicians should be aware that armodafinil has not been studied in pediatric patients, and neither drug is FDA approved for use in patients under the age of 18.

## Pregnancy
Both modafinil and armodafinil are classified as pregnancy category C, and neither has been systematically studied in pregnant women. Animal studies at clinically relevant doses show potential for visceral and skeletal malformations. Intruterine growth retardation and spontaneous abortion have been described in association with armodafinil and modafinil. Due to potential for induction of increased clearance of ethinyl estradiol, both drugs also carry warnings for potential increased risk of oral contraception failure.

## Patient-focused perspectives such as quality of life, patient satisfaction and acceptability
Interestingly, these drugs may have different overall effects in patients who do not suffer from sleepiness compared with those who do. One study in normal, non sleep-deprived volunteers showed an increase in anxiety, aggression, and somatic tension resulting from modafinil use.[68] By contrast, another study involving modafinil 400 mg per day in narcoleptic patients showed significant improvements in health-related quality of life compared with placebo, with improved energy, psychological well-being, and self-esteem.[54] Recently, a study involving armodafinil in narcoleptic subjects showed that patients were over three times

as likely to rate themselves as "much improved" or "very much improved" when taking the active drug, compared with placebo.[58] This disparity highlights the importance of a good clinical understanding of each patient's unique sense of suffering and relief whenever a condition is diagnosed and a treatment recommended. This would appear to be particularly true for circumstantial conditions with protean manifestations, such as JLS.

## Conclusions, place in therapy

JLS is a clinical syndrome of disrupted nocturnal sleep and daytime neurocognitive impairment which occurs in the context of transmeridian travel. Optimum treatment of JLS requires a multidimensional understanding of each patient's specific symptoms, with efforts made to integrate the management plan with the patient's perception of risk, personal goals of therapy, and previous medical history, including prior knowledge of treatment response to specific interventions. Conservative measures, including counseling to decrease physical discomforts associated with travel, and pre-travel efforts to acclimate to a new time zone are low-risk and should be considered for all patients.

In patients for whom excessive daytime sleepiness or lack of vigilance represents an unacceptable condition – pilots, surgeons, and performers are examples – the short-term use of an alerting agent such as modafinil or armodafinil to decrease daytime sleepiness symptoms may be a reasonable option, though cheaper and more readily available options (such as caffeine) may have just as much to offer. Based on the current available data, it would be prudent to conclude that newer agents would be best offered to patients who have a history of proven ineffectiveness or intolerance to caffeine used for this indication.

The decision to prescribe modafinil or armodafinil must also be balanced with a thorough knowledge of potential rare adverse events, medical contraindications, and the apparently low but nonetheless non-zero potential for abuse. More research is needed to determine if modafinil or armodafinil improve functional measures of vigilance and alertness in patients with JLS, though data from shift work studies are encouraging in this regard. Furthermore, future studies may illuminate whether these agents impact nocturnal sleep quality in patients with JLS – for better or for worse – an important element in helping patients understand the risk-benefit ratio of this intervention.

Perhaps most importantly, it remains to be seen whether JLS patients treated with these drugs truly "feel better", as this is the endpoint that is arguably most important to many patients. Given the fact that initial data show no improvement in second and third-day PGI-S scores despite an improvement in objective and subjective sleepiness,[63] the answer to this question is likely to be very important, indeed.

## Disclosure

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