Online Supplementary File 2

Table 1A: Summary of studies on non-pharmacological interventions to manage travel fatigue and jet lag in athletes

Level of evidence OCEBM*	Author (publication year) Title	Study design / Type of study	Study duration	Sex	Participant(s)	Age	Study groups control/ no control	Actual / Simulated phase-shift	Aim of Study	Intervention used	Measurements used (outcome variables)	Main outcomes (primary, secondary)
Exercise												
Level 3B	**Montaruli, et al.[29]** **(2009)** The sportsman readjustment after transcontinental flight: a study on marathon runners	Non-Randomised control trial	5 days (3 days baseline; 2 days intervention)	Male	Mixed population healthy, physically fit n=18 (marathon athletes n=12, physically active healthy controls n=6)	Across three groups (Mean age: control 39±6 yrs; morning training 42±4 yrs; evening training 40±6 yrs)	Yes, n=6	5h phase-delay, Milan to New York	Evaluate the synchronising effect of physical activity on the rest- and sleep-activity cycle after a flight (Milan to New York)	Exercise: running sessions 3x/week, Morning group: 7h00 – 9h00, Evening group 19h00 – 21h00	• Wristwatch actigraphy to determine sleep and activity levels (3d before, 2d after flight) • Sleep diary to confirm findings • Subjective Waterhouse jet lag questionnaire.	• Exercise pre-flight showed better adaptation for resynchronisation after flight (evening 4h, morning 1h) • Aerobic activity in the evening improved sleep parameters • No differences with respect to the nocturnal sleep • Physical activity planned at definite times of day before & after a transcontinental flight with crossing of 6 time-zones represents a tool that may help to adapt to the new arrival time-zone
Level 3B	**Cardinali, et al.[30]** **(2012)** A multifactorial approach employing melatonin to accelerate resynchronization of sleep-wake cycle after a 12 time-zone westerly transmeridian flight in elite soccer athletes	Single-group, one condition Multifactorial approach – exercise, melatonin, light)	8 days	Male	Professional soccer players n=22	Mean age 29.7±8.7 yrs	No control group	12h phase-advance, Buenos Aires to Tokyo	Effect of a combined intervention (3mg melatonin, sunlight exposure/avoidance, physical exercise exposure/avoidance) in facilitating circadian adaptation after a rapid time-zone shift of 12h East/West (Buenos Aires to Tokyo).	Scheduled training sessions set at Tokyo time-zone	• 3mg melatonin daily at expected bedtime • daily physical exercise routine outdoors (08:00-11:00am & 13:00-16:00pm). • Exposure to sunlight or physical exercise at other times of the day was avoided • Routine kept until day 6, game on day 7 • Subjective sleep logs were collected the day before travel and for 8d following travel. • Sleep onset time was used as a marker of circadian phase. • Urinary melatonin metabolite (6-Sulphatoxymelatonin) measured by radioimmunoassay	• On average, sleep onset time returned to normal after 2.13±0.88days. However, sleep onset is more likely to be an indicator of behavioural adaptation as distinct from physiological adaptation. • Mean resynchronization rate was 2.13±0.88days compared with an expected minimal resynchronization rate of 6d after a 12h flight eastward w/o any treatment
Level 2B	**Barger, et al.[31]** **(2004)** Daily exercise facilitates phase delays of circadian melatonin rhythm in very dim light	Randomised control trial	15 days	Male	Mixed population healthy, physically fit n=18; (recreational athletes n=9, healthy controls n=9)	Mean age 23.0±3.6 yrs	Yes, n=9	Simulated shift, 9h phase-delay	Test the effectiveness of moderate exercise to phase delay the human circadian pacemaker under very dim light conditions	Exercise 3x 45 min cycling daily; day 7-13	• Subjective sleep diaries, • Wrist actigraphy (objective sleep parameters), • Plasma melatonin	• Subjects who completed three 45-min bouts of cycle ergometry each night showed a significantly greater shift in the dim light melatonin onset (DLMO25%), dim light melatonin offset, and midpoint of the melatonin profile compared with non-exercising controls • Magnitude of phase delay induced by the exercise intervention was significantly dependent on the relative timing of the exercise • Exercise may help to facilitate circadian adaptation to schedules requiring a delay in the sleep-wake cycle.

Level 2B	**Yamanaka, et al.[32]** **(2010)** Physical exercise accelerates re-entrainment of human sleep-wake cycle but not of plasma melatonin rhythm to 8-h phase-advanced sleep schedule	Randomised control trial	12 days	Male	Mixed population healthy, physically fit n=17; (recreational athletes n=9, healthy controls n=8)	Age range 20-24 yrs	Yes, n=8	Simulated shift, 8h phase-advance	Examine the effects of timed physical exercise on the re-entrainment of sleep-wake cycle and circadian rhythms to an 8h phase-advanced sleep schedule	Exercise (2h interval cycling session of 15min cycle, 15min rest from day 2-5)	• Sleep-wake cycle through bed sensors (weight sensor and bed lamp), • Polysomnography • Wrist actigraphy • Plasma melatonin, • Core body temperature	• The sleep-onset on the first day of free-run in the exercise group was significantly phase-advanced from that in the control and from the baseline • Circadian melatonin rhythm was significantly phase-delayed in the both groups, showing internal desynchronization of the circadian rhythms
Sleep												
Level 2B	**Petit, et al.[33]** **(2014)** A 20-min nap in athletes changes subsequent sleep architecture but does not alter physical performances after normal sleep or 5-h phase-advance conditions.	Randomised crossover counter balanced design	9 nights	Male	Highly trained male athletes n=16	Mean age 22.2±1.7 yrs	Own control	Simulated shift, 5h phase-advance	Examine the effects of a post-prandial 20-min nap on subsequent sleep, short-term physical exercise after simulated jet lag.	20min nap post-lunch after a simulated 5h phase advance	• Overnight polysomnography, • Wingate test, • Blood lactate, • Core body temperature	• Significant increase in sleep onset latency on night following the nap • Significant decrease in number of awakenings • Increase in REM sleep not significant, but suggesting a good quality of daytime sleep. • No change in any other sleep measurements • No change in any physical performance measures • No change in blood lactate concentrations • A significant change (delay) in acrophase and batyphase of core body temperature • No change in all other core body temperature measurements • A short post-lunch nap may induce difficulties falling asleep after crossing time-zones. • Napping had no beneficial effect on physical performance or to facilitate readjustment of core body temperature
Level 2B	**Petit, et al.[34]** **(2018)** Effects of a 20-Min Nap Post Normal and Jet Lag Conditions on P300 Components in Athletes	Randomised cross over design	5 nights	Male	Highly trained male athletes n=16	Mean age 22.2±1.7 yrs	Own control	Simulated shift, 5h phase-advance	Investigate whether a 20-min nap may have different effects on cognitive performance as measured by event-related potentials (ERP), subjective alertness and psychomotor performance in highly physically trained subjects after simulated jet lag	20min nap between 08:00 and 09:00h after a simulated 5h phase advance	• Polysomnography, • Auditory event related potentials, • Visual Analogue Scale (VAS), • Attentional performance (TAP-M)	• A nap which took place between 08:00 and 09:00h after a night simulating 5h jet lag sig. increased P300amplitudes in frontal and central derivations • No sig. difference in P300 latencies or mean reaction times (psychomotor performance) in attentional tests. • A significant change in acrophase and batyphase of core body temperature • A 20 min nap has beneficial effects on alertness and cognitive processing. • The timing of the nap closer to the afternoon circadian dip in alertness would be ideal for athletes whose cognitive performance is normally required immediately upon wakening.

Level 2B	**Straub, et al.[35]** **(2008)** The effects of diaphragmatic breathing and sleep training on sleep, jet lag and swimming performance.	Randomised control trial	21 days	Male & Female	Elite swimmers n=16; (Males n=6, Female n=10)	Mean age 21.1 yrs (Age range 15-26yrs)	Yes, Treatment group n=8; Control group n=8	10h phase-advance, (Stockholm to Hobart)	Evaluate the effect of a combined intervention (diaphragmatic breathing & listening to sleep training CD) to improve sleep, mood, and performance, and to reduce jet lag after a rapid time-zone shift of 10h east (Stockholm to Hobart).	diaphragmatic breathing, sleep training	• Sleep was assessed each night before and after travel using wrist activity monitors for a total of 21 days. • Mood (POMS) was assessed each day (except during competition) after travel. • Swimming performance was assessed using official FINA points during competition in Hobart. • Subjective jet lag was assessed each day for four days after travel using an 11-point Likert-scale.	• Sleep training and diaphragmatic breathing did not affect sleep, mood, jet lag, or swimming performance. • Combined intervention → unable to determine the independent effect of sleep training on outcome measures.
Light												
Level 2B	**Thompson, et al.[36]** **(2012)** The practicality and effectiveness of supplementary bright light for reducing jet lag in elite female athletes	Randomised control trial	4 days	Female	Elite soccer players from a national team n=22	Mean Age 26±4 yrs	Yes, Intervention n=11, Control n=9	5h phase-advance (East-coast USA to Portugal; n=12) 8hphase-advance (West-coast USA to Portugal, n=10)	Assess efficacy of intervention to minimise jet lag after air travel with time-zone shift of 5h east (East-coast USA to Portugal) or 8h east (West-coast USA to Portugal). Light intervention intended to facilitate a phase advance – 45-60min of exposure to 2,500 lux polychromatic light at 15:30–16:30 on day 1, 14:30–15:30 on day 2, 10:30–11:30 on day 3, 09:45–10:45 on day 4	Light treatment	• Subjective Liverpool jet lag questionnaire, • Intra-aural temperature, • Grip strength, • Function, • Diet, • Sleep, • Bowel movement	• Subjective jet lag did not differ between the groups on days 1, 3, and 4 after travel, but it was higher for the treatment group than the control group on day 2. • The light treatment did not reduce subjective jet lag
Level 3B	**Cardinali, et al.[30]** **(2012)** A multifactorial approach employing melatonin to accelerate resynchronization of sleep-wake cycle after a 12 time-zone westerly transmeridian flight in elite soccer athletes	Single-group, one condition Multifactorial approach – exercise, melatonin, light)	8 days	Male	Professional soccer players n=22	Mean age 29.7±8.7 yrs	No control group	12h phase-delay, Buenos Aires to Tokyo	Effect of a combined intervention (3mg melatonin, sunlight exposure/avoidance, physical exercise exposure/avoidance) in facilitating circadian adaptation after a rapid time-zone shift of 12h East/West (Buenos Aires to Tokyo).	Lighting conditions of aircraft and inflight meal schedule set at Tokyo time-zone	• 3mg melatonin daily at expected bedtime -daily physical exercise routine outdoors (08:00-11:00am and 13:00-16:00pm). • Exposure to sunlight or physical exercise at other times of the day was avoided • Routine kept until day 6, game on day 7 • Subjective sleep logs were collected the day before travel & 8 days following travel. • Sleep onset time was used as a marker of circadian phase. • Urinary melatonin metabolite (6-Sulphatoxymelatonin) measured by radioimmunoassay (RIA)	• On average, sleep onset time returned to normal after 2.13±0.88 days. However, sleep onset is more likely to be an indicator of behavioural adaptation rather than physiological adaptation. • Mean resynchronization rate was 2.13±0.88 days compared with an expected minimal resynchronization rate of 6 days after a 12h flight eastward w/o any treatment
Nutrition (meal timing / composition)												
Level 4	**Reynolds & Montgomery.[37]** **(2002)** Using the Argonne Diet in Jet Lag Prevention: Deployment of Troops across nine time-zones	Case control	4 day pre-deployment, 4 days on return home.	Male & Female	Healthy Soldiers n=186; (used diet on deployment n=95; used diet on return n=39)	Mean age 33 yrs (Age range 19-58 yrs)	Yes, pseudo control n=91 on deployment, n=147 on return	9h phase advance, USA to South Korea	Assess the frequency of jet lag symptoms and the effect of the Argonne diet (AD) in preventing jet lag among soldiers deployed from the USA to South Korea.	Argonne diet	• During pre-deployment briefings soldiers were told about the Argonne diet and written instructions provided. – They could choose to use the diet for either or both directions of travel or not at all. • All soldiers given questionnaires about diet, activities, and symptoms and history of jet lag, collected by commanders and sent to higher headquarters for tabulation.	• Argonne diet (AD) users reported fewer symptoms of jet lag vs those who did not use the diet. • n=95 used the AD before deployment (n=91 did not) and n=39 before the return flight (n=127 did not). • Past history of jet lag and a sedentary lifestyle increased the odds of jet lag after return.

Level 2B	**Ruscitto & Ogden.[38]** **(2017)** The impact of an implementation intention to improve mealtime and reduce jet lag in long-haul cabin crew	Randomised control trial	3 days	Male & Female	Healthy long-haul cabin crew n=61; (Male n=11; Female n=50)	Mean age 41.9±9.8 yrs (Age range 20-60 yrs)	Yes, Intervention n=31, Control n=30	Different travel directions (min ≥4h time change; duration of layover ≥48h	Evaluate whether an implementation intention intervention [to eat regular meals on the day following a long-haul flight] can be used to reduce the degree of jet lag and improve alertness in cabin crew of long-haul flights.	Regular meals on days off	• MEQ to assess chronotype • Rating statements (1-never to 5-always) relating to sleep (9 items) and eating strategies (5 items) • Unidimentional jet lag: Liverpool Jet lag Questionnaire (LJLQ) • Multidimentional jet lag: amended version of LJLQ. • 3min Psychomotor Vigilance Task (PVT), a reaction time test, for objective alertness –via iPhone app., ('sleep-2-Peak')	• Forming an implementation intention to consume regular meals the day after long-haul flight reduced subjective levels of jet lag (based on LJLQ unidimentional measure); • Eating meals at the appropriate times with the LD cycle helps with synchronisation of the master clock and peripheral oscillators, improving jet lag and resetting the body clock • Implementation intentions were an effective means through which to bring about this dietary eating behaviour change; • No impact of the intervention on either multidimensional jet lag or PVT i.e. objective measure of alertness.

Author project groups on non-pharmacological interventions: Exercise [HF, PF]; Sleep [GV, AB, SH, ML, CS, ID]; Light [DS, GR]; Nutrition (meal timing/composition) [AC]; Nutrition (hydration/fluids) [AC]; All [CJvR, AJvR, TC]

Table 1B: Summary of studies on pharmacological interventions to manage travel fatigue in athletes

Level of evidence OCEBM*	Author (publication year) Title	Study design / Type of study	Study duration	Sex	Participant(s)	Age	Study groups control/ no control	Actual / Simulated phase-shift	Aim of Study	Intervention used	Measurements used (outcome variables)	Main outcomes (primary, secondary)
Melatonin												
Level 3B	**Cardinali, et al.[30]** **(2012)** A multifactorial approach employing Melatonin to accelerate resynchronization of sleep-wake cycle after a 12 time-zone westerly transmeridian flight in elite soccer athletes	Single-group, one condition Multifactorial approach – exercise, melatonin, light)	8 days	Male	Professional soccer players n=22	Mean age 29.7±8.7 yrs	No control group	12h phase-delay, Buenos Aires to Tokyo	Effect of a combined intervention (3mg melatonin, sunlight exposure/avoidance, physical exercise exposure/avoidance) in facilitating circadian adaptation after a rapid time-zone shift of 12h East/West (Buenos Aires to Tokyo).	3mg melatonin p.o. daily at expected bedtime at Tokyo immediately after leaving Buenos Aires	• 3mg melatonin daily at expected bedtime • Daily physical exercise routine outdoors (08:00-11:00am and 13:00-16:00pm). • Exposure to sunlight or physical exercise at other times of the day was avoided • Routine kept until day 6, game on day 7 • Subjective sleep logs were collected the day before travel and for 8d following travel. • Sleep onset time was used as a marker of circadian phase. • Urinary melatonin metabolite (6-Sulphatoxymelatonin) measured by radioimmunoassay (RIA)	• On average, sleep onset time returned to normal after 2.13±0.88 days. However, sleep onset is more likely to be an indicator of behavioural adaptation rather than physiological adaptation. • Mean resynchronization rate was 2.13±0.88 days compared with an expected minimal resynchronization rate of 6d after a 12h flight eastward w/o any treatment
Level 3B	**Manfredini, et al.[39]** **(2000)** Standard Melatonin intake and circadian rhythms of elite athletes after a transmeridian flight	Single-group, one condition	6 days	Male & Female	Elite biathletes n=12	Mean age 25.9 yrs (Males n=8) Mean age 22.5 yrs (Female n=4)	No control group.	8h phase-advance, Milan to Tokyo	Evaluate the effect of a standard dose of melatonin (5mg for males; 3mg for females) in facilitating circadian adaptation after a rapid time-zone shift of 8h East (Milan to Tokyo).	melatonin	• Oral body temperature was recorded every 2-3h from 0700h-2200h) before and after travel and was used as a marker of circadian phase. • Daily questionnaire reporting subjective impressions of quality of sleep (scored 1=poor to 5=excellent) and the presence or absence of undesired effects.	• standardized melatonin administration had different effects on computed body temperature rhythms of athletes. Extreme paucity of studies in literature probably derives from difficulty in obtaining data from elite athletes engaged in their usual activity, their willingness to comply or to participate as 'controls', and difficulties of devising chronobiological protocols with a reasonably limited number of daily measurements. • present results show the generic intake of melatonin at standardized times & dosages, although in the presence of a good sleep and in the absence of undesired side-effects, may have widely differing effects on biological rhythms & the resynchronizing effect is not always fully obtained
Sedatives												
Level 4	**Reilly, et al.[40]** **(2001)** Effect of low-dose temazepam on physiological variables and performance tests following a westerly flight across five time-zones	Case control observational study	7 days	Male & Female	Mixed population British men's gymnastics squad (n=8; 7 Males); Support staff control (n=9; 4 Females, 5 Males) *pair-matched for age, sex & athleticism, & assigned to Treatment n=9 (7 Males); Placebo n=8 (6 Males)	Mean age 30.2±10.8 yrs (18-55 yrs) Mean age: treatment group 30.2±10.8 yrs placebo group 28.5±9.2 yrs	Yes, n=8	8h phase delay from UK to Atlanta, Florida; and 1h onwards to Tallahassee, Florida	i) Monitor a selection of subjective, physiological and performance variables in elite athletes and sedentary subjects following a westerly flight across five time-zones ii) Examine whether the promotion of sleep by means of a low-dose Benzodiazepine drug influences responses to transmeridian travel	On days 1, 2 & 3, either 10mg of Temazepam or placebo	• Subjective measurements (sleep quality, sleep length, subjective jet lag), • Thermometer (tympanic temperature), • Choice reaction time, • Grip strength, • Leg and back strength	• Mean subjective jet lag significantly reduced compared to baseline, and mean sleep quality improved from day 1 to day 5 • Subjective jet lag, left and right grip strength and choice reaction time all showed post-flight day x time of day interactions • Trend for the reduction in subjective jet lag over the post-flight days to be more rapid following ingestion of a low dose of Temazepam (although possible type 1 error may be present) • A nightly administration of a low dose (10mg) of Temazepam has little influence on the recovery of subjective, physiological and performance measures following a westward flight across five time-zones

												Important to monitor jet lag symptoms and performance variables at different times of day following a flight to a new time-zone
Stimulants												
Level 2B	**Rosenberg, et al.[41]** **(2010)** A phase 3, double-blind, randomized, placebo-controlled study of armodafinil for excessive sleepiness associated with jet lag disorder.	Randomised, double-blind, placebo-controlled, parallel-group study	3 day laboratory-based	Male & Female	Healthy adults n=427; (Armodafinil @ 50mg/d n=142; 150mg/d n=143; placebo n=142) * Participants had symptoms of jet lag disorder	Age 18–65 yrs (50mg/d = 36.7±12.01 yrs); (150mg/d = 34.6±10.38 yrs); (placebo = 36.0±10.06 yrs)	Yes, n=142	6h phase-advance, USA to France	Evaluate Armodafinil (50 & 150mg/d) for treatment of excessive sleepiness associated with jet lag disorder due to eastbound travel in a population of travellers with a history of jet lag symptoms	Armodafinil 50mg/d and 150mg/d	• Wakefulness (efficacy) Multiple Sleep Latency Test (MSLT), Patient Global Impression of Severity (PGI-S), Karolinska Sleepiness Scale (KSS) • Safety & Tolerability: Mini International Neuropsychiatric Interview, Columbia Suicide History Scale, monitor adverse events	• Efficacy against placebo: −MSLT: 50 & 150mg/d significantly different −PGI-S: 150mg/d significantly different −KSS: 50 & 150mg/d significantly different • Safety and Tolerability: −Most frequently reported: headache (27%), nausea (13%), diarrhoea (5%), circadian rhythm sleep disorder (5%), palpitations (5%) −Grade: Mild to moderate, no serious adverse events • 150mg/d increases wakefulness after eastbound travel through 6 time-zones in those with a history of symptoms of jet lag and is generally well tolerated.
Level 3	**Lagarde, et al.[42]** **(2001)** Evaluation of pharmacological aids on physical performance after a transmeridian flight	Randomised double-blind placebo controlled	10 days	Male & Female	Healthy U.S. Air Force reservists n=27; (Male n=19; Female n=8)	Age 20-48 yrs	Yes, n=9	7h phase-advance	Assess physical performance after an eastbound across 7 time-zones based on conditions of slow-release caffeine (300mg), melatonin (5mg), and placebo (lactose capsules)	300mg Slow release Caffeine, 5mg Exogenous melatonin	• Hand grip strength test (static) • Squat jump test (dynamic) • Multiple jump test (dynamic) 15sec 2x/d (morning and afternoon), started 2d before and up to 10d after travel.	• Morning static performance (grip strength) in dominant hand decreased for first 3d for placebo, increased for caffeine, and was maintained for melatonin. • Caffeine and melatonin may be useful at improving static performance (handgrip) after eastbound travel, not on dynamic performance.
Level 3	**Piérard, et al.[43]** **(2001)** Resynchronizatio n of hormonal rhythms after an eastbound flight in humans: effects of slow-release caffeine and Melatonin	Randomised double-blind placebo controlled	10 days	Male & Female	Healthy U.S. Air Force reservists n=27; (Male n=18; Female n=9)	Mean age 35.3±8.1 yrs (19-47 yrs)	Yes, n=9	7h phase-advance	Investigate the effects of slow-release caffeine compared to melatonin and placebo on endogenous melatonin and cortisol after eastbound air travel with a time change of 7h in military personnel.	300mg Slow release Caffeine, 5mg Exogenous melatonin	• Salivary melatonin, cortisol and caffeine samples as well as overnight urinary and plasma 6-sulphatoxymelatonin were collected before (3d) and following (10d) the flight	• 300mg administered at 8am in the destination time for 5d following the flight resulted in lower cortisol concentrations when compared to control from days 2-5. • Slow release caffeine (as well as melatonin) allows a faster resynchronisation of hormone rhythms in the 4d following an eastbound flight incurring a time-loss of 7h.
Level 2	**Beaumont, et al.[44]** **(2004)** Caffeine or Melatonin effects on sleep and sleepiness after rapid eastward transmeridian travel.	Randomised double-blind placebo controlled	10 days	Male & Female	Healthy U.S. Air Force reservists n=27; (Male n=18; Female n=9)	Mean age 35.3±8.1 yrs (19–47 yrs)	Yes, n=9	7h phase-advance	Compare the effects of slow release caffeine with those of melatonin on recovery sleep and daytime sleepiness after a 7h time-zone eastbound flight, by using subjective and objective methods	300mg slow release Caffeine, 5mg Exogenous melatonin	• Polysomnography, • Wrist actigraphy, • Subjective sleep measures (daytime sleepiness), • Oral temperature, • Subjective vigilance. • 300mg slow release caffeine on recovery day 1 to day 5 (08:00) or 5mg melatonin on pre-flight day 1 (17:00), flight day 0 (16:00), and from day 1 to day 3 (23:00), or placebo at the same times.	• Both drugs have positive effects on some jet lag symptoms after an eastbound flight: slow release caffeine on daytime sleepiness and melatonin on sleep. • Slow release caffeine and melatonin may be of value for alleviating some symptoms related to conditions, including an eastbound jet lag combined with sleep deprivation. • melatonin decreases sleepiness subjectively, but not objectively, and improves recovery sleep. • Slow release caffeine reduces sleepiness for a few days with unwanted effects on recovery sleep
Melatonin Analogues												
Level 3B	**Nickelsen, et al.[45]** **(2002)**	Non-Randomised double-blind 3 period cross over	13 day trial; separated by 22 days wash-out	Male	Healthy male volunteers n=8	Mean age 27.9±3.1 yrs (25-35 yrs)	Own control	Simulated shift, 9h phase advance	- 1st Clinical trial of compound to allow prelim efficacy assessment in simulated shift lag setting	LY 156735	• Degree of shift lag & daytime fatigue: −Fatigue Questionnaire, −Stanford Sleepiness Scale −Two 100 mm visual analogue scales of alertness and tenseness −Visual analogue scales of jet lag	• All subjective = negative • HD significantly blunted the post-shift deterioration of performance in those tests that were sensitive to shift lag • Capable of significantly advancing several key circadian rhythms when given

	Chronobiotic effects of the Melatonin agonist LY 156735 following a simulated 9h time shift: results of a placebo controlled trial (TIK301)								- Each subject received 5mg (HD); 0.5mg (LD) of LY 156735 as well as placebo in randomised order		• Physiological markers of CR: −Core body temperature - continuously throughout each trial (rectal probe) −Wrist actigraphy entire study, start 14d before trial −Urine: cortisol, calcium, potassium, sodium, & chloride concentrations • Performance tests battery @ 3h intervals 09:00 - 21:00 −Single reaction time, −Memory search test, −Unstable tracking task, −Grammatical reasoning test Each test = duration of 3min, except single reaction time = 10min • Polysomnographic (PSG) night-time, every night • Safety (days 1 & 13): −lab assessment (complete blood count, fasting chemistry screen, urinalysis) −complete physical examination −EKG (during screening & at end of study)	at the appropriate time of day (5mg) whilst in contrast, the 0.5mg has no consistent effects • Ability to enhance quality of post-shift daytime performance & to hasten shift of circadian rhythms, therefore can be acknowledged as a chronobiologically active melatonin analogue
Level 2B	**Rajaratnam, et al.[46]** **(2009)** Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials	Two randomised, double-blind, placebo-controlled, parallel-groups (2 USA sites) = • Phase II: 10mg (n=9), 20mg (n=8), 50mg (n=7), 100mg (n=7) Placebo (n=8) • Phase III: 20mg (n=100), 50mg (n=102), 100mg (n=106) Placebo (n=103) • Phase II & Phase III 30min before bedtime, for 3 days	• Phase II: 7 nights • Phase III: unconfirmed	Male & Female	Healthy adults • Phase II: n=39 • Phase III: n=411	• Phase II: Age 18-50 yrs • Phase III: Age 21-50 yrs	Yes, • Phase II: n=8 • Phase III: n=103	Simulated shift. 5h phase-advance	Treatment of transient insomnia • Phase II: to establish efficacy & physiological mechanism; measure plasma melatonin for circadian phase assessment • Phase III: to confirm sleep efficacy	Tasimelteon	• Polysomnography: −Sleep efficiency (%) −Total sleep time (min) −Wake after sleep onset (min) −Latency to sleep onset (min) −Latency to persistent sleep (min) • Self-reported questionnaire: −Latency to sleep onset (min) −Total sleep time (min) • Melatonin: −Circadian phase measurements	• Phase II vs placebo: −Significant higher sleep efficiency = 50mg (85.5%, p=0.02) &100mg (89.3%, p=0.02) −Significant greater total sleep time = 20mg (+71.4min, p=0.03), 50mg (+85.7min, p=0.013) & 100mg (+104.2min, p=0.01) −Significant decreased mean latency to sleep onset = 10mg (-11.6min, p=0.025), 20mg (-11.8min, p=0.023), 50mg (-10.2min, p=0.018) & 100mg (-15.0min, p=0.01) −Significant decreased mean latency to persistent sleep = 10mg (-13.7min, p=0.03), 50mg (-13.9min, p=0.019) & 100mg (-19.1min, p=0.021) −Significant earlier dim light melatonin onset = 100mg (2–3h, p=0.01) • Phase III vs placebo: −Significant higher sleep efficiency = 20mg (73.2%, p=0.002), 50mg (76.0%, p<0.001) & 100mg (72.3%, p=0.005) −Significant greater total sleep time = 20mg (+33.5min, p=0.002), 50mg (+47.9min, p<0.001) & 100mg (+30.0min, p=0.005) −Significant decreased wake after sleep onset = 20mg (-24.1min, p=0.002) & 50mg (-34.0min, p<0.001) −Significant decreased mean sleep onset latency = 20mg (-11.9min, p<0.006), 50mg (-14.1min, p<0.001) & 100mg (-12.2min, p=0.002) −Significant decreased mean latency to persistent sleep = 20mg (-21.4min, p<0.001), 50mg (-26.1min, p<0.001) & 100mg (-22.6min, p<0.001) • Simultaneously improve sleep latency & sleep maintenance with a shift in circadian rhythms

												• Has potential for treatment of transient insomnia associated with jet lag • Efficacy in entraining circadian rhythm significantly when measuring cortisol • Significantly improve night-time & daytime sleep variables, timing of sleep
Level 2B	**Richardson, et al.[47]** **(2008)** Circadian Phase-Shifting Effects of Repeated Ramelteon Administration in Healthy Adults	Randomised, double-blind, multi centre placebo-controlled	6 days	Male & Female	Healthy adult volunteers n=75; (Males n=38; Females n=37)	Age 18–45 yrs	Yes, n=15	Simulated shift., 5h phase-advance	▪ Efficacy of Ramelteon (1, 2, 4, or 8mg) administered 30min before bedtime, for 4 consecutive days - to facilitate re-synchronization following an acute 5h phase advance shift of sleep-wake cycle, & determine optimal dose ▪ Bedtime = 5h before habitual bedtime to induce a 5h advance in sleep-wake cycle ▪ Ramelteon administered during phase-advance portion of melatonin phase-response curve	Ramelteon	▪ Objective sleep parameters: Impact on sleep quantified as polysomnography recordings: −latency to persistent sleep −total sleep time −sleep efficiency −wake time after sleep onset −number of awakenings after persistent sleep −% of sleep time in different sleep stages −latency to REM sleep ▪ Subjective sleep parameters: −post-sleep questionnaire ▪ Dim-light melatonin offset time (DLMoff): −salivary samples within 5min of awakening −saliva samples obtained every 60min (±5min) during all waking hours ▪ Next-morning residual effects: −post-sleep questionnaire −assessments of vital signs, −adverse events	▪ No significant differences in any objective sleep parameters (i.e. % of sleep time spent in any sleep stage = stages 1, 2, 3 or 4 REM sleep), or latency to REM sleep vs placebo groups ▪ No significant differences in subjective measures of sleep vs placebo ▪ Endogenous melatonin rhythm significantly shifted (DLMoff) = 1mg (-88min, p=0.002), 2mg (-80.5min, p=0.003) & 4mg (-90.5min, p=0.01) vs placebo ▪ melatonin shifts occurred as early as day 1 (4mg) & day 2 (1mg & 4mg) after the light shift ▪ Ramelteon 1, 2, or 4mg day administered 30min before bedtime significantly advanced circadian rhythm phase in persons subjected to a 5h phase advance in the sleep-wake cycle (equal to eastward jet-travel across 5 time-zones) ▪ Low-dose has potential as a specific therapy for circadian rhythm sleep disorders ▪ Higher dose (8mg) did not result in significant phase-shift compared to placebo
Level 2B	**Zee, et al.[48]** **(2010)** Effects of ramelteon on insomnia symptoms induced by rapid, eastward travel	Randomised, double-blind, placebo-controlled, parallel-group	4 nights	Male & Female *History of jet lag induced sleep difficulty	Healthy adults n=110; (Males n=58; Females n=52)	Age 18–50 yrs	Yes, n=29	5h phase-advance (Hawaii to East USA coast)	▪ Evaluate ability of Ramelteon to alleviate sleep-onset difficulties associated with jet lag following eastward jet travel across 5 time-zones ▪ Ramelteon 1, 4, or 8mg or placebo administered for 5 days, 5min before lights out (based on each participant's habitual sleep time)	Ramelteon	▪ Objective sleep parameters: −latency to persistent sleep −total sleep time −wake after sleep onset time −number of awakenings [Using polysomnography (EEG, EMG, EOG, ECG) & Actigraphy recordings] ▪ Subjective sleep parameters: −sleep latency −total sleep time −wake after sleep onset time −number of awakenings −sleep quality −ease of awakening [using post sleep Q's each morning] ▪ Dim light melatonin offset time (DLMoff): −Salivary samples within 5min of awakening ▪Next-morning residual effects: −Digit symbol substitution test −Immediate and delayed memory recall test −Visual Analog Scale (mood & feelings) ▪Daytime sleepiness and functioning: Daytime ability to function, alertness, concentrate, quality of sleep, ease of awakening using: −Karolinska Sleepiness Scale −Daytime Function Q	• After a 5h phase advance due to eastward jet travel: - Mean latency to persistent sleep reduced significantly with 1mg (-10.64min, p=0.030) vs placebo - No significant changes in sleep parameters with 4, 8mg vs placebo - Significantly lower performance (p≤0.05) with 1mg, 4mg & 8mg on immediate memory recall tasks following jet lag (day 4) vs placebo ▪No significant differences with any dose vs placebo for any other measures of objective and subjective sleep ▪ No significant differences in melatonin phase measured by DLMoff i.e. no significant phase advance between any dose vs placebo ▪ No significant difference between any dose vs placebo in next-morning residual effects ▪ Significant improvements in daytime ability to function, alertness, concentrate, quality of sleep, ease of awakening with 4mg vs placebo (suggests possible improvement in daytime impairments associated with jet lag ▪ 1mg reduced mean latency to persistent sleep (p=0.030) ▪ 4mg improve daytime ability to function, alertness, concentrate, quality of sleep, ease of awakening

												▪ Immediate memory recall test – significantly affected for all dosages on day 4 ($p<0.05$) ▪ Delayed memory recall test – no significant differences

Author project groups on pharmacological interventions: Melatonin [GV, ML, CS, GR]; Sedatives [HF, DS, PF]; Stimulants [AB, SH, ID]; Melatonin analogues [CJvR, AJvR]; Supplements [AC]; Antihistamines [DS]; Glucocorticoids [DS]; All [CJvR, AJvR, TC]