

I disturbi del sonno nell'anziano

Angelo Bianchetti

Dipartimento Medicina e Riabilitazione – ICSA Gruppo San Donato – Brescia
Società Italiana di Geriatria e Gerontologia
Associazione Italiana di Psicogeriatria
Università di Brescia – SS di Geriatria

Outline

- I disturbi del sonno nell'anziano: elementi caratteristici
- L'approccio al trattamento dei disturbi del sonno
- I trattamenti non farmacologici
- I trattamenti farmacologici: approccio tradizionale e elementi innovativi
- I disturbi del sonno nella demenza

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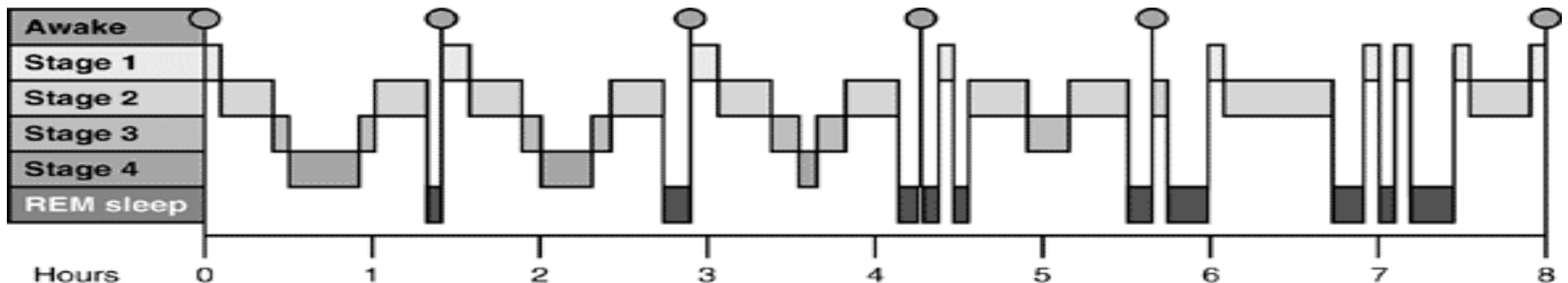
Cosa è il sonno?



- Il sonno è uno stato normale, reversibile e ricorrente di ridotta reattività agli stimoli esterni, accompagnato da complessi e prevedibili cambiamenti fisiologici.
- Questi cambiamenti includono una attività cerebrale coordinata, spontanea e generata internamente, e fluttuazioni nei livelli ormonali e nel rilassamento della muscolatura.
- Il sonno di solito richiede la presenza di muscoli scheletrici rilassati e l'assenza del comportamento apertamente orientato agli obiettivi di cui l'organismo sveglio è capace

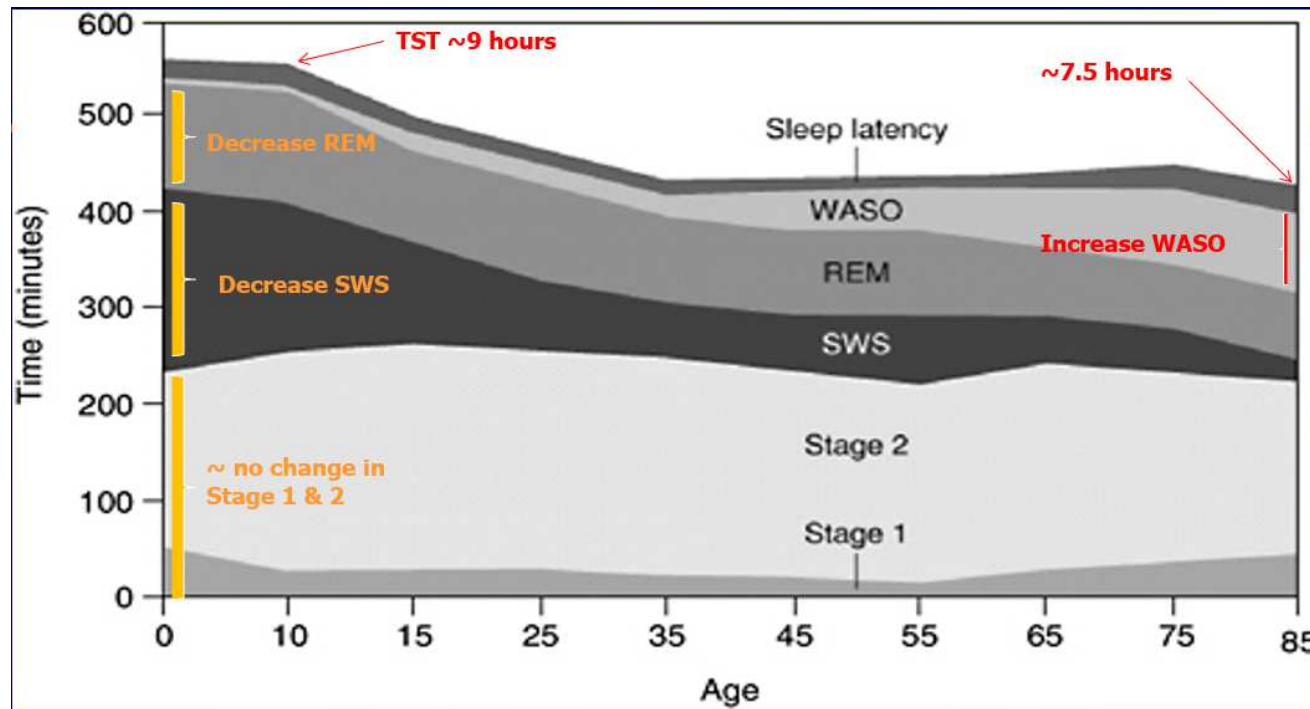
Gli stadi del sonno

- Stadio W *veglia tranquilla (onde α)*
- Stadio 1 NREM *sospensione (floating) (onde a bassa ampiezza, onde β ; Fast Wave Sleep)*
- Stadio 2 NREM *sonno vero e proprio (fusi sigma, onde β , complessi k; Fast Wave Sleep)*
- Stadio 3 NREM *sonno profondo (onde lente tipo delta; Slow Wave Sleep)*
- Stadio 4 NREM *sonno profondo (onde delta ultralente; Slow Wave Sleep)*
- Fase REM *rapid eye movements, Lowest muscular tone (bassa ampiezza, simile stadio 2)*



- Il sonno **REM** compare ciclicamente durante la notte ogni 90-120 minuti.
- Lo **stadio 1** occupa il 2-5% del tempo; lo **stadio 2** il 45- 55%; lo **stadio 3** il 10-15%; e il sonno **REM** il 20-25%.
- Brevi risvegli sono possibili normalmente durante la notte, specialmente alla fine di ogni ciclo del sonno.

Changes in Sleep in the Elderly



Time (in minutes) for sleep latency, amount of time spent awake after initially falling asleep (WASO), rapid eye movement (REM), non-rapid eye movement (NREM), stages 1, 2, and slow-wave sleep (SWS – stages 3, 4).

Carskadon & Rechtschaffen 2005

- Earlier wake times (~1.3 hours)
- Go to bed earlier (~1.1 hours)
 - ? Secondary to advanced circadian pacemaker, increased sensitivity to light
- Modified circadian rhythm:
 - body temperature changes, misaligned melatonin, cortisol and other hormone secretion
- More nocturnal awakenings
 - Loss of ? protective measure, decline in homeostatic sleep pressure & circadian pacemaker
- Reduction in total sleep time, slow-wave sleep and REM sleep
- Decrease ability to maintain sleep

Classification of sleep disorders

DSM-5 CLASSIFICATION

- Insomnia Disorder
- Hypersomnolence Disorder
- Narcolepsy
- Breathing-Related Sleep Disorders
 - Obstructive Sleep Apnea Hypopnea
 - Central Sleep Apnea
 - Sleep Related Hypoventilation
- Circadian Rhythm Sleep–Wake Disorders
- Parasomnias
 - Non-REM Sleep Arousal Disorders
 - Nightmare Disorder and REM Sleep Behavior Disorder
- Restless Legs Syndrome
- Substance/Medication-Induced Sleep Disorder

ICD 10 CLASSIFICATION

- G47 Sleep disorders
 - G47.0 Disorders of initiating and maintaining sleep [insomnias]
 - G47.1 Disorders of excessive somnolence [hypersomnias]
 - G47.2 Disorders of the sleep-wake schedule
 - G47.3 Sleep apnoea
 - G47.4 Narcolepsy and cataplexy
 - G47.8 Other sleep disorders
 - G47.9 Sleep disorder, unspecified

Prevalence of Primary Sleeps Disorders

<u>Condition</u>	<u>All Adults</u>	<u>Elderly</u>
Insomnia	10-20%	40-50%
Sleep Apnea	1%-25%	24%-40%
Periodic Limb Movements	2-5%	30%-45%
Restless Leg Syndrome	2%-15%	12%-30%
REM Sleep Behavior	0.5%	0.5%-2%

Young T, et al., Ancoli-Israel S, et al., Sleep 2001; Mant E, et al., Age and Ageing 1992; Ancoli-Israel S, et al. Sleep 1993; Phillips BA, et al., Sleep 1994; Hoch CC, et al., Sleep 1994; O'Keefe ST, et al., Age and Ageing 1994; Phillips B, et al., Arch Int Med 2000; Allen R, et al. Arch Int Med 2005

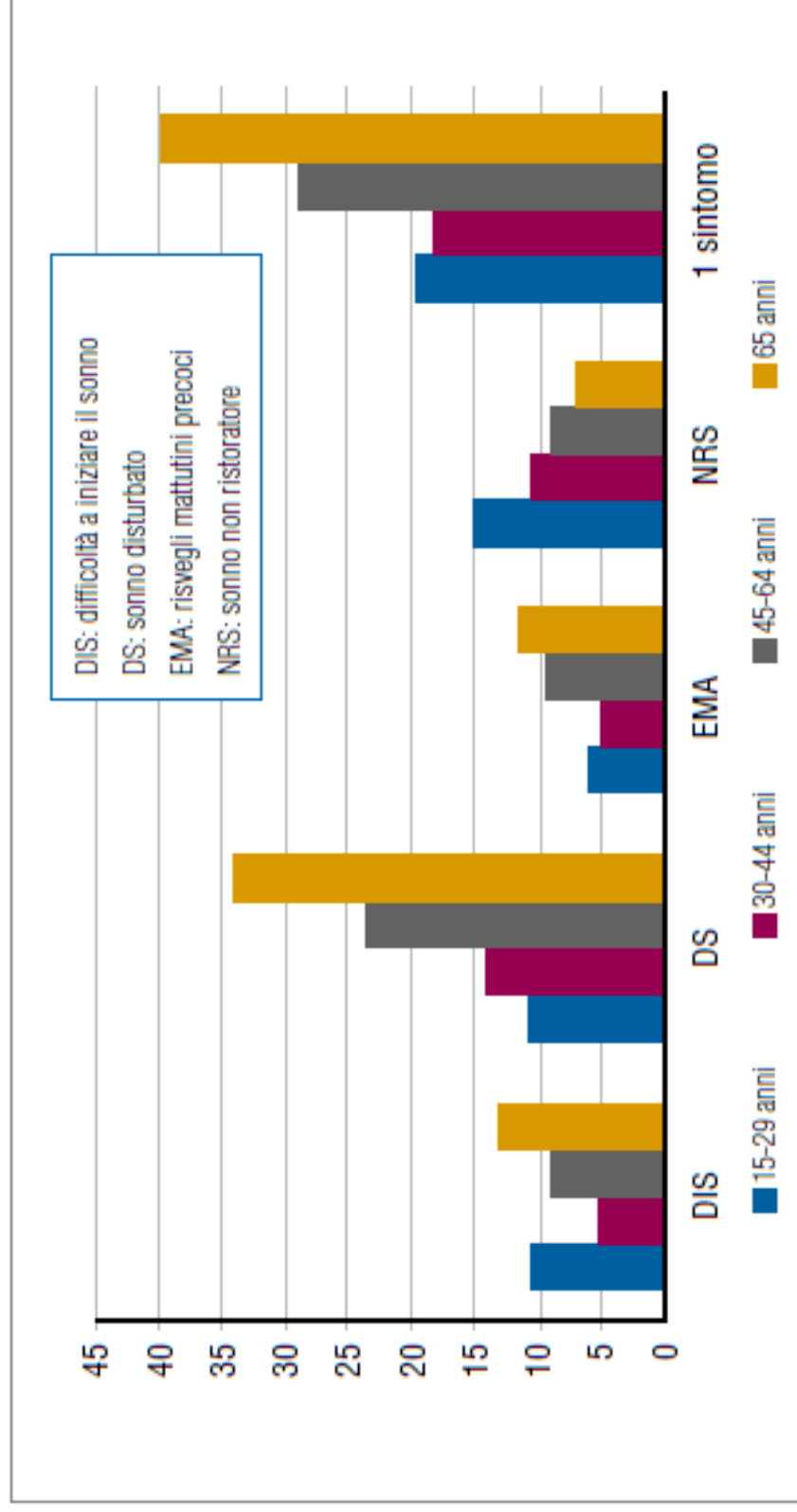


Figura 2. Prevalenza dei sintomi di insonnia per gruppi di età nella popolazione generale in Italia (da Ohayon, Smirne, 2002, mod.)⁶.

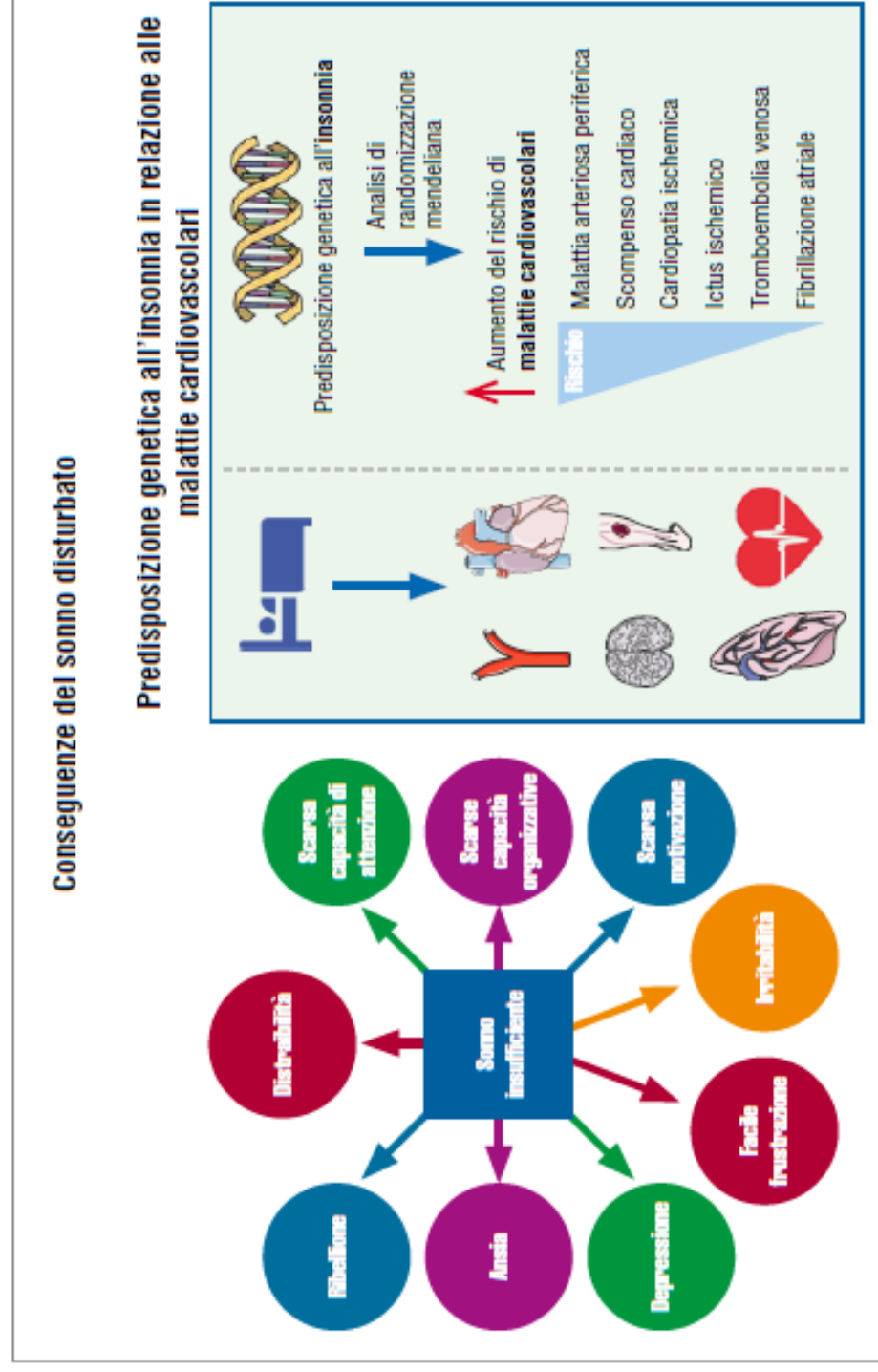


Figura 4. Conseguenze dei disturbi del sonno (da Yuan et al., 2021, mod.)¹⁶.

PRINCIPALI CAUSE DI DISTURBI CRONICI DEL SONNO NEL SOGGETTO ANZIANO

Disturbi primari del sonno

- sindrome delle apnee ostruttive del sonno
- sindrome delle gambe senza riposo e movimenti periodici degli arti
- disturbi comportamentali del sonno REM (REM Behavior Disorders, RBD)
- disordini del ritmo circadiano sonno-veglia

Malattie acute e croniche

- dolore
- malattie cardiovascolari, polmonari, metaboliche, gastrointestinali, urinarie
- malattie psichiatriche (depressione, ansia, delirium, alcolismo)
- malattie neurologiche (malattia di Alzheimer, malattia a corpi di Lewy, malattia di Parkinson, malattie cerebrovascolari)

Abitudini e situazioni stressanti di tipo psicologico o fisico

- "sonnellino" diurno
- andare a letto troppo presto
- utilizzare il letto per leggere o guardare la TV
- scarsità di esercizio fisico durante la giornata
- solitudine
- lutto
- ospedalizzazione o istituzionalizzazione

Cause ambientali

- luminosità o rumorosità eccessiva degli ambienti
- umidità o temperatura eccessiva
- letto poco confortevole
- scarsa esposizione alla luce durante la giornata

Farmaci o sostanze

Angelo Bianchetti^{1,2}, Chiara Ruffolo³, Laura Vernuccio³, Fabio Guerini^{1,2}, Mario Barbagallo³

1. Dipartimento di Medicina e Riabilitazione, Istituto Clinico S. Anna, Brescia | 2. Gruppo di Ricerca Geriatrica, Brescia e Associazione Italiana di Psicogeriatrica | 3. Cattedra di Geriatria, Università degli Studi di Palermo

Tabella 22.2 Farmaci come causa di ipersonnolenza

- Antidepressivi: triciclici e IMAO
- SSRI: fluvoxamina, paroxetina, trazodone, nefazodone, maprotilina, amoxapina e venlafaxina. Tranne la mirtazapina, riducono la durata del sonno, specie REM
- Litio e antipsicotici
- Benzodiazepine: effetto funzione anche dell'emivita
- Pramipexolo e benzotropine (antiACH)
- Anticonvulsivanti, specie tradizionali
- Antistaminici lipofili e ceterizina
- CV: clonidina, CH3dopa, reserpina, β -bloccanti, labetalolo, spirinolattone, gemfibrozil, clofibrato
- Vari: miorilassanti, FANS, tramadolo, sumatriptan, bechidi

Tabella 22.3 Farmaci come causa di insonnia

- Stimolanti: caffeina, xantine (latenza di addormentamento e I stadio +, REM-), modafinil
- Decongestionanti: pseudoefedrina, fenilpropanolamina
- Antidepressivi: effetto sospensione o primario (MAO, citalopram, venlafaxina, bupropione)
- Ipnotici e sedativi: effetto rebound
- Antiparkinson
- Antiepilettici: felbamato, lamotrigina
- CV: β -bloccanti (atenololo e metoprololo), metildopa, ipolipemizzanti, losartan, diltiazem, mexiletina, flecainide, amiodarone
- Corticosteroidi: sonno profondo e REM-, II stadio +
- Vari: chindoloni, salmeterolo, anfotericina B, aloperidolo (effetto paradosso)

REM- = riduzione del sonno REM.

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Caregiver reported sleep disturbance

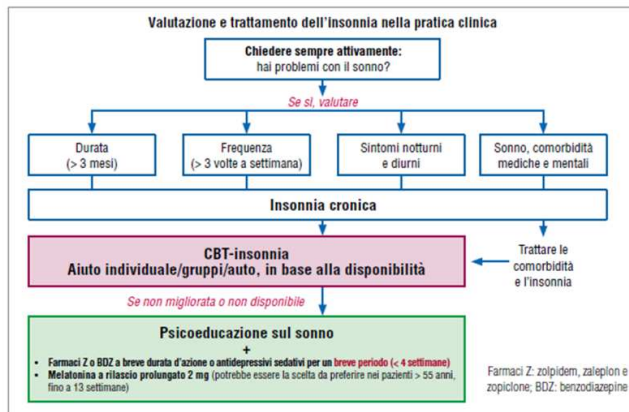
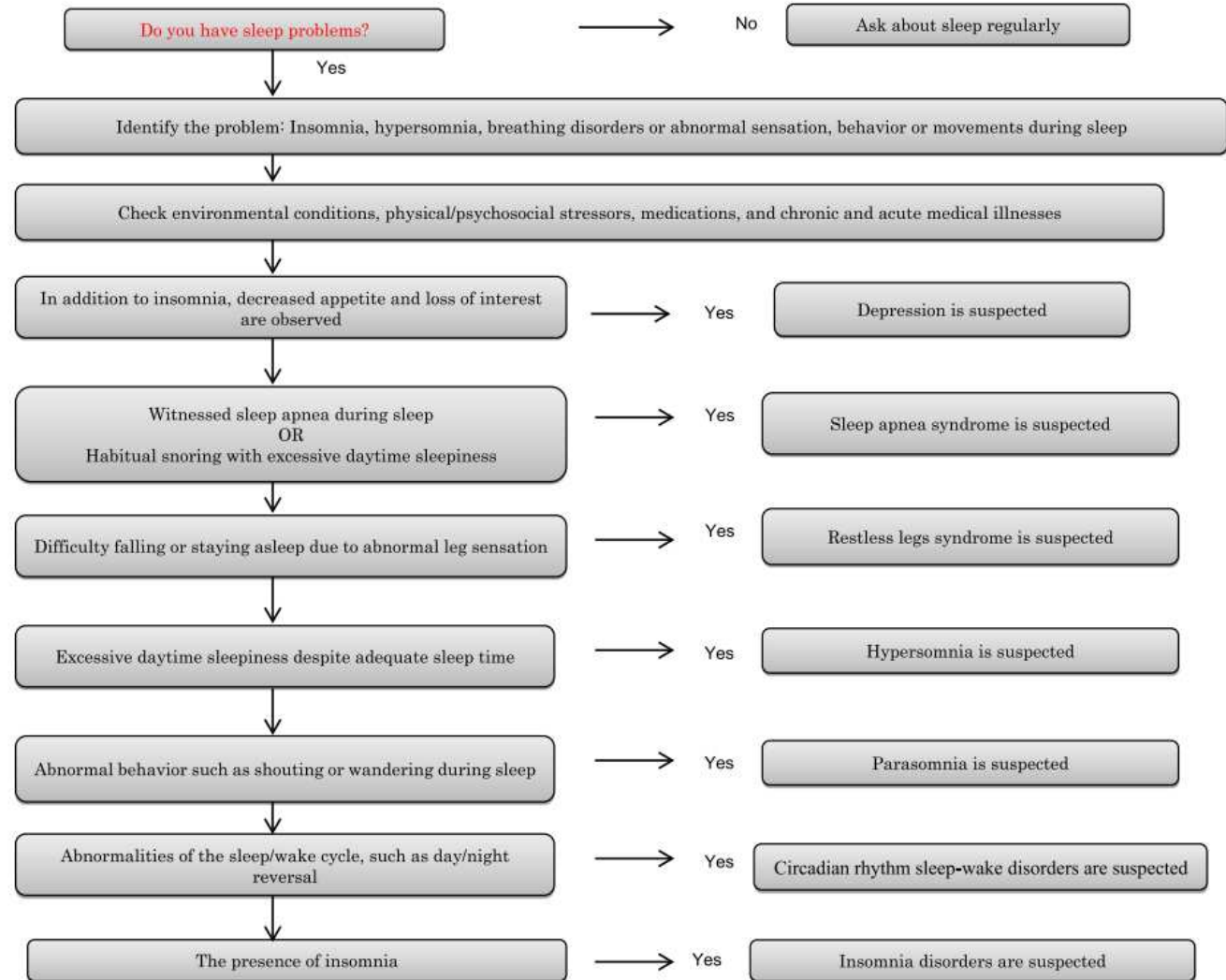


Figura 5. Opinioni di esperti e raccomandazioni di consenso per la valutazione e la gestione dell'insonnia nella pratica clinica: dichiarazioni congiunte di cinque Società scientifiche italiane (da Palagini et al., 2020, mod.)²¹.



Flowchart of screening for sleep disturbances in elderly

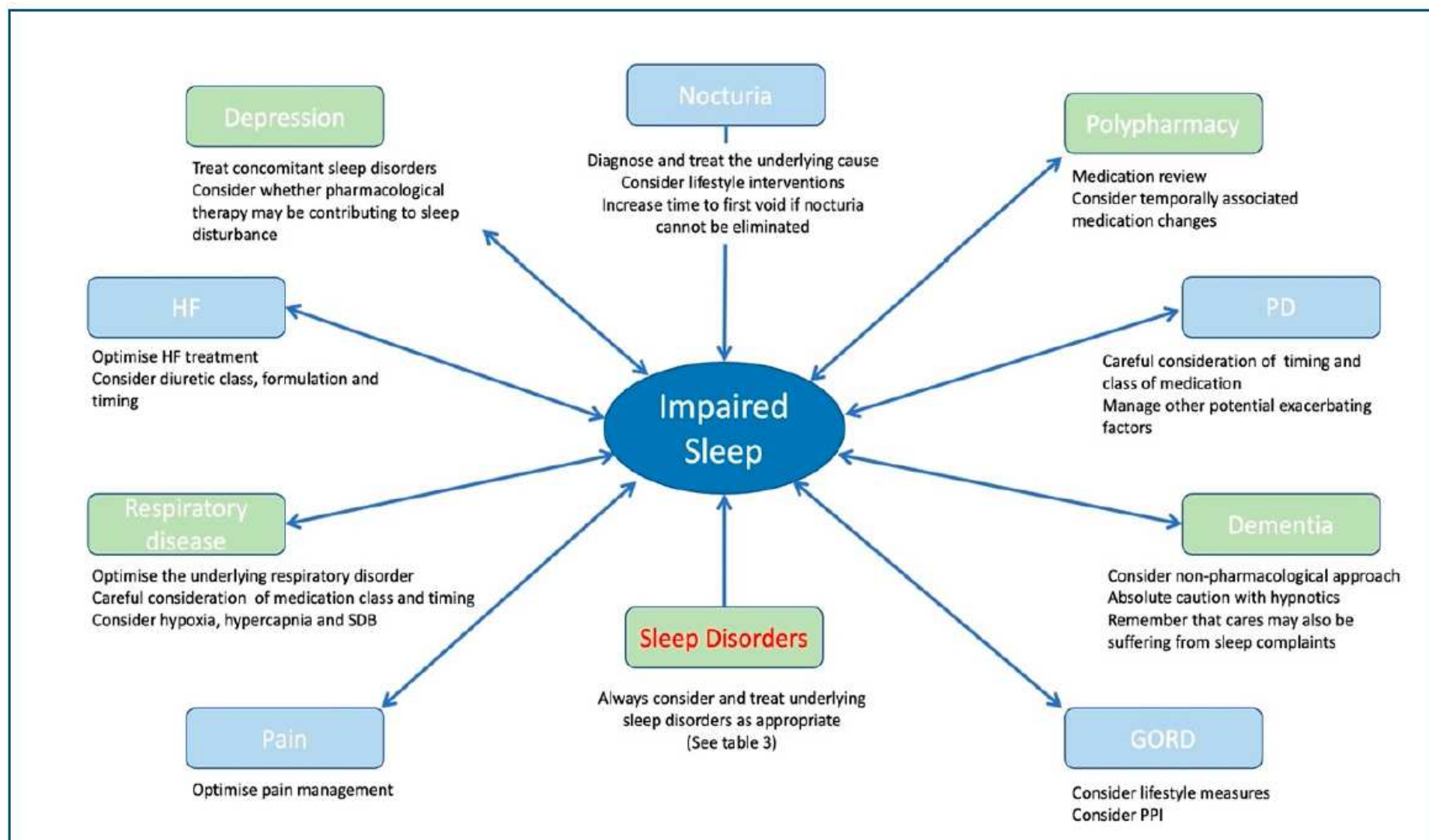


Figure 1. Summary of co-morbidities and considerations in the context of sleep complaints. HF = heart failure, GORD = gastro-oesophageal reflux disease, PD = Parkinson's disease, SDB = sleep disordered breathing.

Table 2. Examples of sleep assessment/screening tools and their utility in older patients.

Tool:	Purpose:	Studied in Older Populations:	Comments/Limitations:
Pittsburgh Sleep Quality Index (PSQI) [276]	Investigates sleep quality and disturbance.	Yes, with reasonable validity [276,277,278].	Can take ≥30 min to complete and requires recollections from the previous month, so it may not be appropriate for a geriatric clinic where sleep is one of many issues being addressed, or where patients suffer short-term memory problems [279].
Epworth Sleepiness Scale (ESS) [280]	A tool to profile excessive daytime sleepiness. High scores of >10 are less common in insomnia and should trigger further interrogation for another sleep disorder [279].	Yes, with reasonable validity [278].	Some geriatric populations may find the scale difficult to complete [281].
Insomnia Severity Index (ISI) [282]	Instrument to assess insomnia severity.	Some evidence to suggest validity in the older population [283,284].	Applies to insomnia only and does not assess sleep generally or symptoms that may be relevant to other sleep disorders [285].
Patient-Reported Outcomes Information System (PROMIS) Sleep Disturbance Scale [286]	The six-item scale assesses perceptions of sleep quality, restfulness, sleep problems and difficulty falling asleep.	Some evidence to suggest validity of the six-item scale in the older population [285].	Requires recollections from the past 7 days and does not assess symptoms of specific sleep disorders, but the overall severity of sleep problems.
The Essener Questionnaire on Age and Sleepiness (EQAS) [287]	Assessment of observed daytime sleepiness.	Some evidence to suggest validity, with low participant numbers [287].	Can be filled out by carers following patient observation, and may be an option in patients with cognitive impairment or communication difficulties, although it does not assess for multiple sleep disorders.
Berlin Questionnaire (BQ) [288]	Identify patients at risk of OSA.	Studied in an exclusively older population, and was found to have reduced accuracy to discriminate between those with and without OSA [289].	May have limited discriminative utility in older patients, and screens for OSA alone.
STOP-BANG questionnaire [290]	Identify patients at risk of OSA.	Recently studied in an exclusively older population found to be of limited utility [291]. A very high proportion met OSA criteria, and an argument against screening in this population was made, with further research needed.	May have limited discriminative utility in older patients, and screens for OSA alone.
Sleep Apnoea Clinical Score (SACS) [292]	Identify patients at risk of OSA.	Studied in a cohort of COPD patients where mean age was >65, with reasonable predictive ability in comparison to ESS and BQ [293].	May be an option in older patients with COPD, although further studies are needed.

For restless leg syndrome and REM sleep behaviour disorder, single screening questions should be considered (see dedicated sections). BQ = Berlin Questionnaire, ESS = Epworth Sleepiness Scale, EQAS = The Essener Questionnaire on Age and Sleepiness, ISI = Insomnia Severity Index, OSA = obstructive sleep apnoea, PSQI = Pittsburgh Sleep Quality Index, PROMIS = Patient-Reported Outcomes Information System, SACS = Sleep Apnoea Clinical Score.

Table 1 Questions to ask the patient and caregiver

1. Consistency of sleep schedule
2. Bedtime and wake-up time during the week and on the weekends
3. Time to fall asleep after bedtime
4. Frequency and causes of nighttime awakenings
5. Time to return to sleep after a nighttime awakening
6. Frequency and duration of daytime naps
7. Caffeine and alcohol use
8. Medical and psychiatric factors that may be associated with insomnia, e.g., pain, nocturia
9. Environmental factors that may be associated with insomnia
10. Symptoms of other sleep disorders, e.g., snoring, dream enactment behavior

Algoritmo clinico per il trattamento dell'insonnia cronica

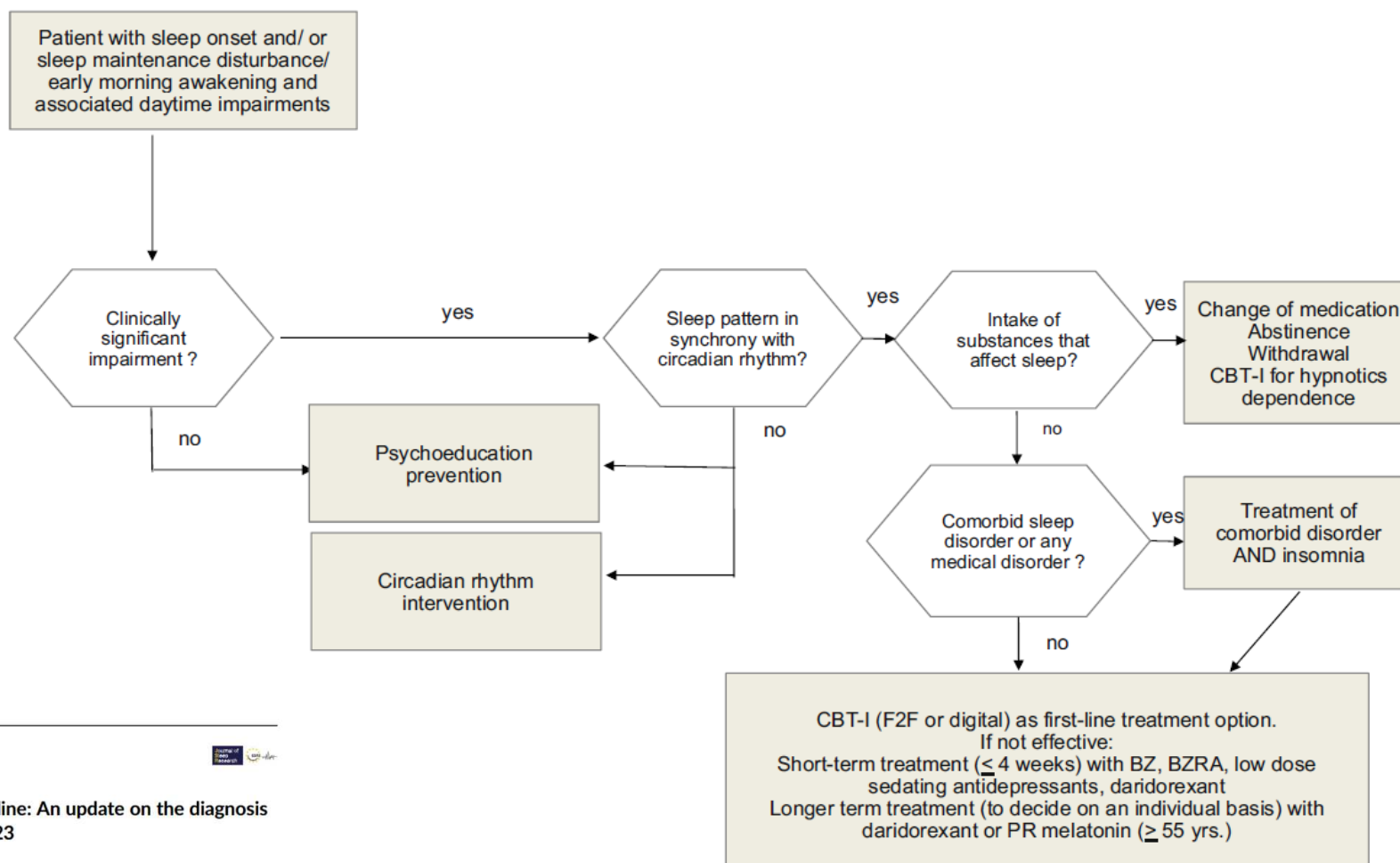
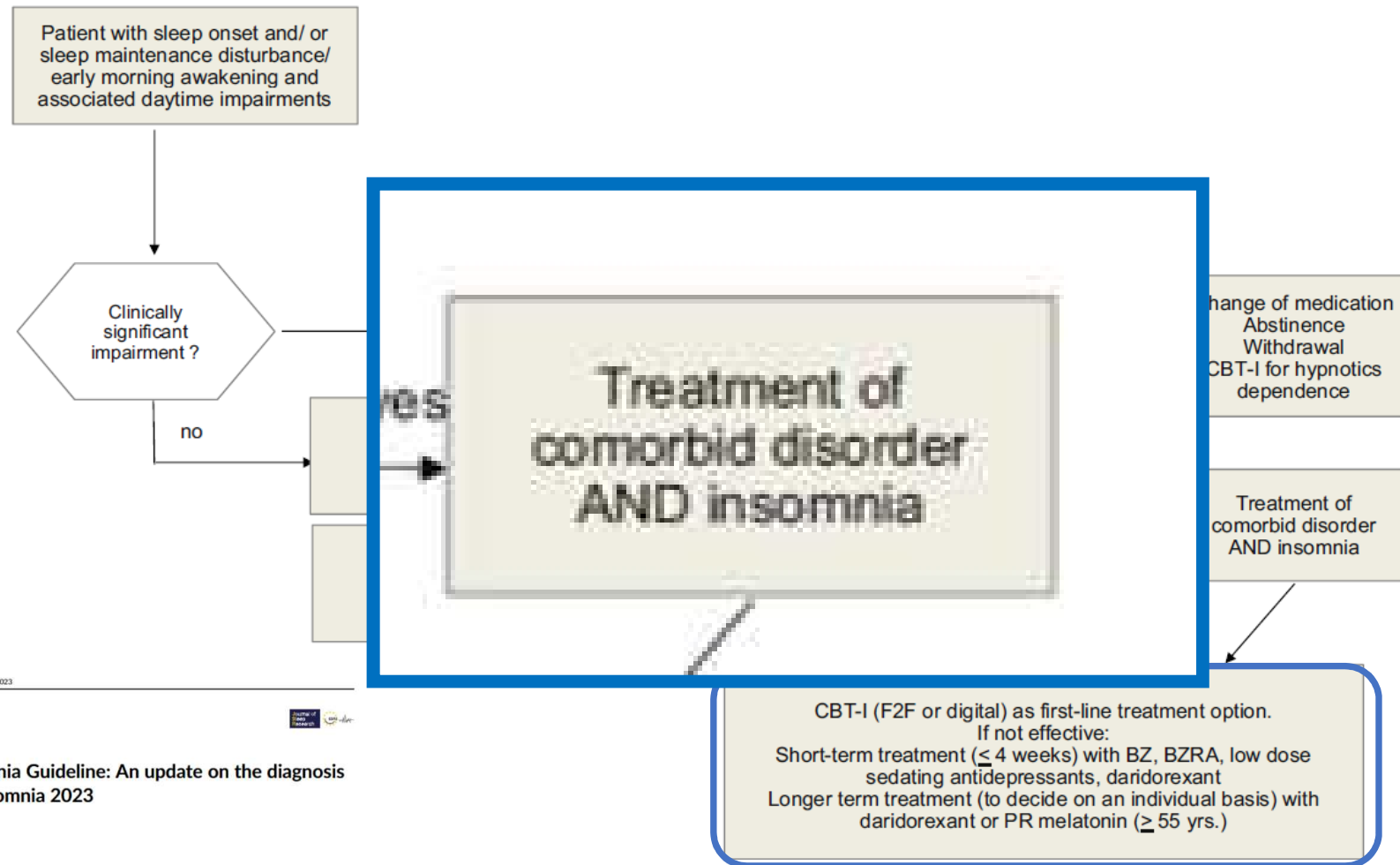


FIGURE 1 Clinical algorithm. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

Algoritmo clinico per il trattamento dell'insonnia cronica



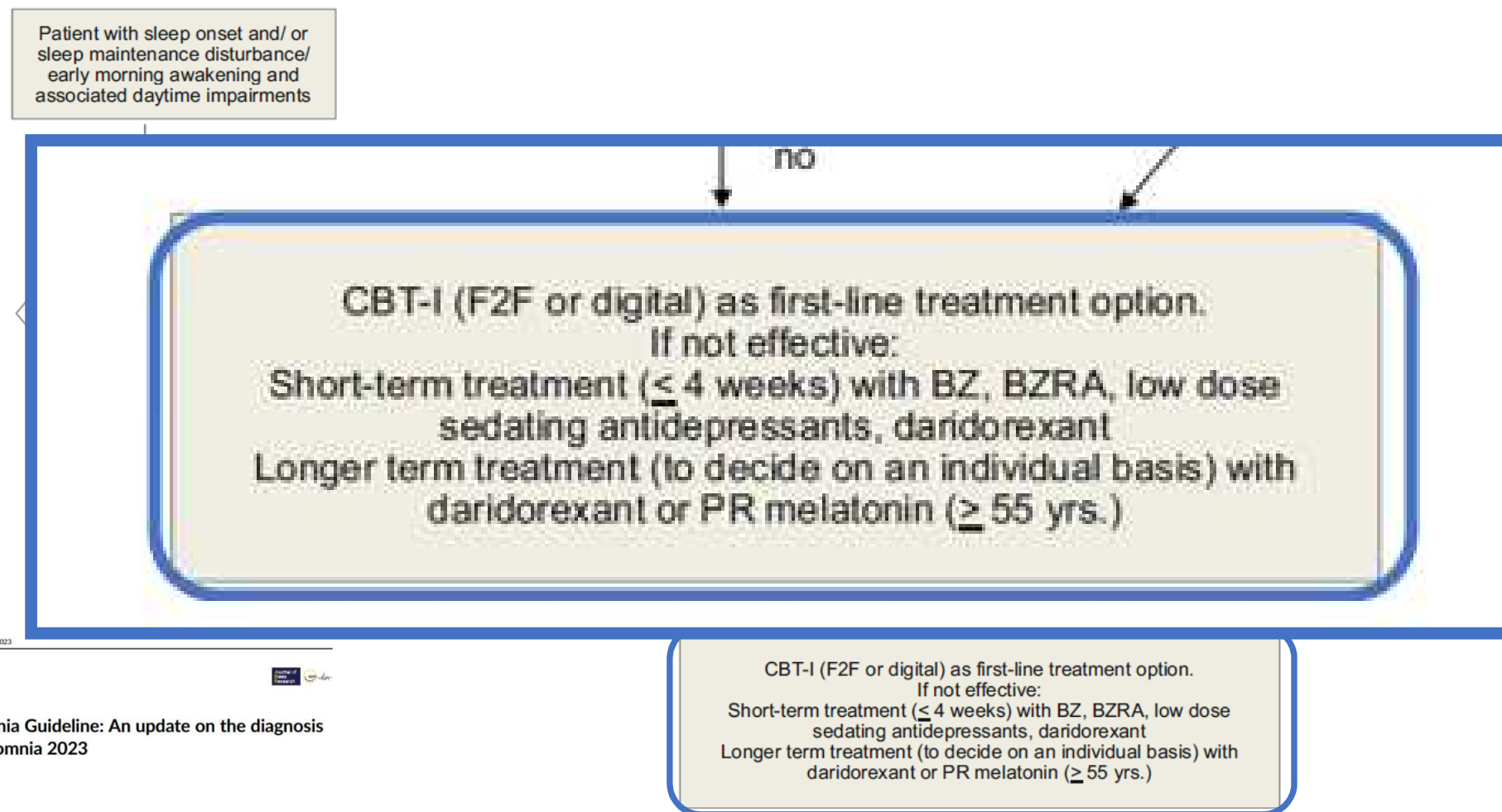
Received: 16 August 2023 | Accepted: 21 August 2023
DOI: 10.1111/jpr.14035

REVIEW ARTICLE

The European Insomnia Guideline: An update on the diagnosis and treatment of insomnia 2023

FIGURE 1 Clinical algorithm. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

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The European Insomnia Guideline: An update on the diagnosis and treatment of insomnia 2023

Cognitive-behavioural therapy for insomnia is recommended as **the first-line treatment for chronic insomnia in adults of any age** (including patients with comorbidities), either applied in-person or digitally (A).

The CBT-I is typically provided as a multicomponent treatment comprising psychoeducation (including sleep hygiene), relaxation therapy, sleep-restriction therapy (SRT), stimulus control therapy (SCT) and several cognitive therapeutic strategies. These are administered over four–eight therapy sessions in single or group format by certified health professionals (mainly clinical psychologists/psychological or medical psychotherapists)

Review

A Review of Digital Cognitive Behavioral Therapy for Insomnia (CBT-I Apps): Are They Designed for Engagement?

Begum Erten Uyumaz *, Loe Feijs and Jun Hu

Int. J. Environ. Res. Public Health **2021**, *18*, 2929.

Sleep Hygiene	Stimulus Control	Sleep Restriction	Relaxation	Cognitive	Wrap-Up
 appropriate bedroom environment	 using bedroom only to sleep	 restricting sleep times	 taking short and long relaxations during the day	 restructuring undesired thinking patterns	going over each component to prevent the relapse of insomnia
 avoiding screen-based devices before bedtime	 leaving bedroom when cannot fall asleep	 increasing in-bed sleep times			
 avoiding coffee or alcohol consumption					

The structure of CBT-I components in in-person treatment.



Efficacy of cognitive behavioral therapy for insomnia (CBT-I) in older adults with insomnia: A systematic review and meta-analysis

Kexin Huang¹, Su Li², Rendong He¹, Tangsheng Zhong¹, Haiqi Yang¹, Li Chen¹, Hui Gao³,
Yann Li¹

Abstract

Objectives: The aim is to evaluate the efficacy of cognitive behavioral therapy for insomnia (CBT-I) in older adults. We searched six databases to identify articles published in English or Chinese until January 30th, 2022. **Methods:** The two authors of the review independently selected the studies, assessed the risk of bias, and extracted the data. Fourteen studies were included. **Results:** Based on the results from sleep logs, a significant pooled effect size was observed for sleep efficiency (SE%) (MD = 8.36; 95% CI, 5.96-10.76; $I^2 = 77\%$; $p < .00001$), sleep onset latency (SOL) (MD = -9.29; 95% CI, -13.62 to -4.96; $I^2 = 64\%$; $p < 0.0001$), wake after sleep onset (WASO) (MD = -23.44; 95% CI, -32.41 to -14.47; $I^2 = 85\%$; $p < .00001$), and total sleep time (TST) (MD = -12.35; 95% CI, -21.27 to -3.42; $I^2 = 63\%$; $p = 0.007$). **Conclusions:** Our study suggests that CBT-I may be a safe and effective approach for improving insomnia in older adults.

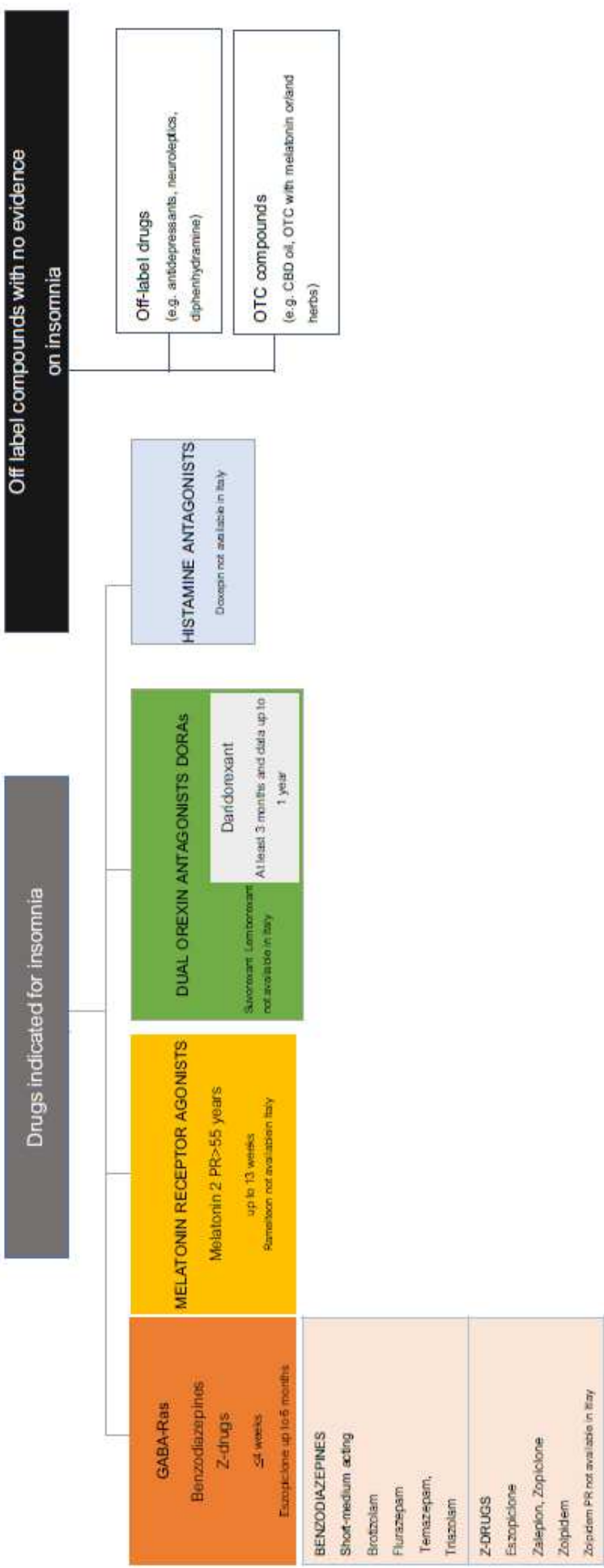
Supporting a good night's sleep

- **Treating underlying conditions** (id pain, constipation, urinary infections).
- **Establishing a routine**
- **Avoiding stimulants** (id alcohol, caffeine and nicotine; avoid TV during periods of wakefulness at night).
- **Encouraging physical activity**
- **Limit daytime sleep**
- **Set a peaceful mood in the evening** (reading out loud or playing soothing music... comfortable bedroom temperature).
- **Managing medications**
- **Providing regular daylight exposure**
- **Prescription of drugs**

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Table 1 Agents for insomnia treatment



PR prolonged release, GABA Gamma-aminobutyric acid, 5HT serotonin

*Not available in Italy

American Geriatrics Society 2023 updated AGS Beers Criteria[®] for potentially inappropriate medication use in older adults

By the 2023 American Geriatrics Society Beers Criteria[®] Update Expert Panel 

Benzodiazepines	The use of benzodiazepines exposes users to risks of abuse, misuse, and addiction. Concomitant use of opioids may result in profound sedation, respiratory depression, coma, and death.	Avoid
Alprazolam		
Chlordiazepoxide (alone or in combination with amitriptyline or clidinium)		
Clobazam		
Clonazepam		
Clorazepate		
Diazepam		
Estazolam		
Lorazepam		
Midazolam		
Oxazepam		
Temazepam		
Triazolam		
Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents; the continued use of benzodiazepines may lead to clinically significant physical dependence. In general, all benzodiazepines increase the risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults.		
May be appropriate for seizure disorders, rapid eye movement sleep behavior disorder, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, and procedural anesthesia.		
Nonbenzodiazepine benzodiazepine receptor agonist hypnotics (“Z-drugs”)		
Eszopiclone		
Zaleplon		
Zolpidem		
Nonbenzodiazepine benzodiazepine receptor agonist hypnotics (“Z-drugs”) have adverse events similar to those of benzodiazepines in older adults (e.g., delirium, falls, fractures, increased emergency room visits/hospitalizations, motor vehicle crashes); minimal improvement in sleep latency and duration.		Avoid

Special Patient Groups

1) Elderly Patients

Benzodiazepines are the most commonly used psychotropic drug in older people and can be very effective anti anxiety agents. However, adverse effects in this group include impaired cognition and gait and the development of tolerance dependence and withdrawal. Reduced drug clearance with consequent higher plasma levels may be responsible for increased adverse effects in older people. Benzodiazepines with a long duration of action are particularly likely to accumulate and therefore have an even greater potential for sedative effects and psychomotor impairment. Long acting benzodiazepines, therefore, with active metabolites should usually be avoided in the elderly e.g. diazepam, chlordiazepoxide, flurazepam, nitrazepam. When benzodiazepines are prescribed in older people, short acting benzodiazepines with few active metabolites are preferable e.g. lorazepam 0.5mg bd/tid, temazepam 10-20mg nocte, alprazolam 0.25mg bd/tid.

Older people should be checked regularly at the start of treatment in order to minimize the dosage and/or the frequency of administration to prevent undesirable effects due to accumulation.

Older people who are taking benzodiazepines with a long elimination half-life have been shown to have an increased risk of falls and involvement in road traffic accidents compared to users of short-acting benzodiazepines.

Late life depression can present with anxiety symptoms and should primarily be treated with antidepressant medication rather than benzodiazepines. Benzodiazepines may also be used on a time limited period for the short term treatment of severe insomnia.

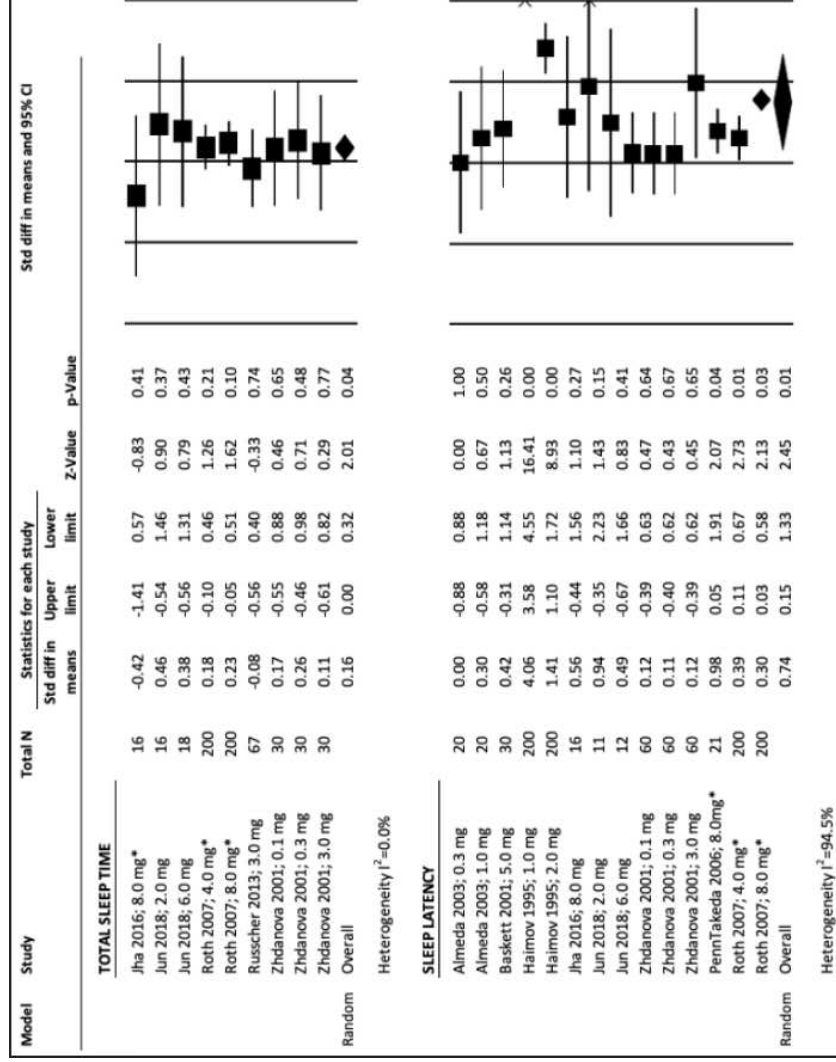
Many elderly patients have been taking benzodiazepines on a long term basis and are physiologically and psychologically dependent. It is appropriate to try and taper and discontinue benzodiazepines in these cases; however it may be very difficult to discontinue benzodiazepine use completely. Best practice would be to discuss the issue with the patient and see if the patient will agree to a slow taper and possible discontinuation.

Use of Melatonin and/or Ramelteon for the Treatment of Insomnia in Older Adults: A Systematic Review and Meta-Analysis

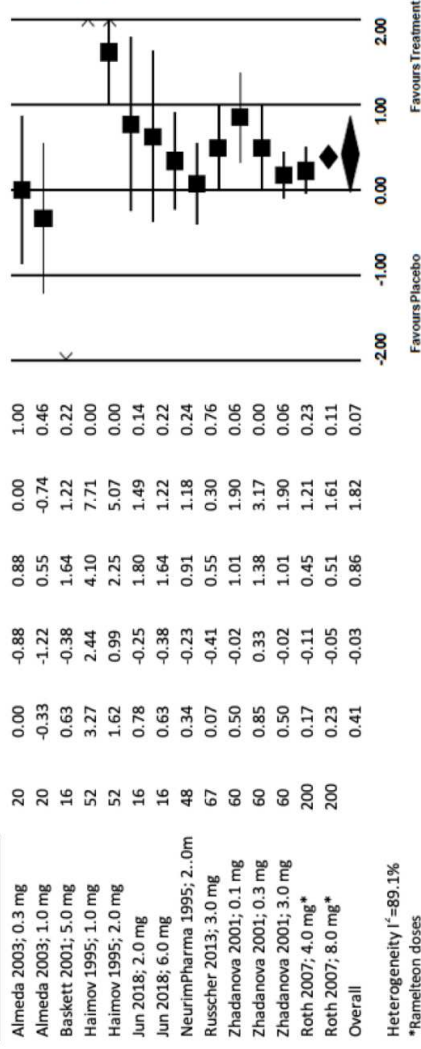
Snijitha Marupuru , Daniel Arku , Ashley M. Campbell , Marion K. Slack and Jeannie K. Lee 

Abstract: To investigate the efficacy of melatonin and/or ramelteon reporting sleep outcomes for older adults with chronic insomnia, a systematic review and a meta-analysis of PubMed, EMBASE, Cochrane library, International Pharmaceutical Abstracts, PsycINFO, science citation index, center for reviews and dissemination, CINAHL, grey literature and relevant sleep journal searches were conducted from 1 January 1990 to 20 June 2021. Randomized controlled trials and other comparative studies with melatonin and/or ramelteon use among older patients with chronic insomnia were included. Funnel plot and Egger's test was used to determine publication bias. A forest plot was constructed to obtain a pooled standardized mean difference using either a fixed or random effects model for each of the two broad categories of sleep outcomes: objective and subjective. Of 5247 studies identified, 17 studies met the inclusion criteria for MA. Study sample size ranged from 10 to 829

with the mean age ≥ 55 years. There were significant improvements in total sleep time (objective), sleep latency and sleep quality (objective and subjective) for melatonin and/or ramelteon users compared with placebo. Sleep efficiency was not significantly different. The effects of these agents are modest but with limited safe treatment options for insomnia in older adults, these could be the drugs of choice.



SLEEP EFFICIENCY



Heterogeneity $I^2=89.1\%$

*Ramelteon doses

Review

Use of Melatonin and/on Ramelteon for the Treatment of Insomnia in Older Adults: A Systematic Review and Meta-Analysis

Srujittha Marupurt , Daniel Arku , Ashley M. Campbell , Marion K. Slack and Jeannie K. Lee 

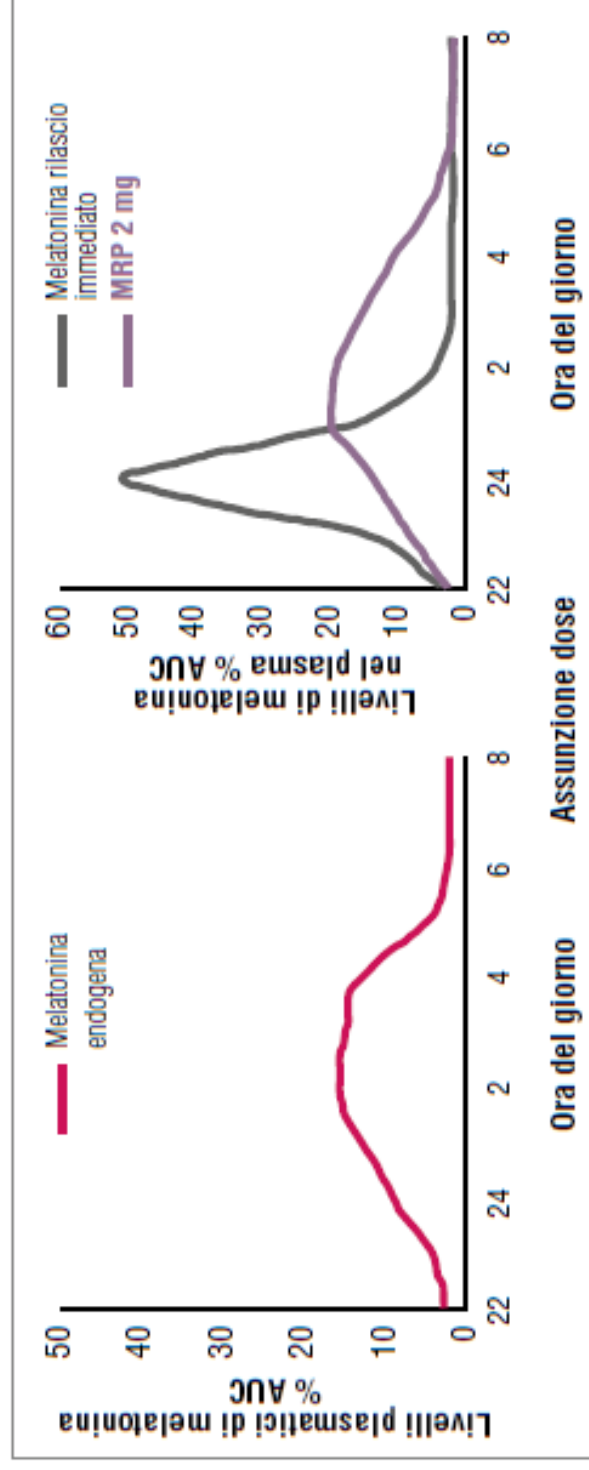


Figura 3. Profilo della melatonina a rilascio immediato e prolungato. Confronto con l'andamento circadiano fisiologico (da Zisapel, 2010, mod.)¹⁷.

Trazodone for Insomnia: A Systematic Review

by KARIM YAHIA JAFFER; TIFFANY CHANG; BRIGITTE VANLE, PhD;
JONATHAN DANG, MD; ALEXANDER J. STEINER, PsyD; NATALIE
LOERA, BA; MARINA ABDELMESEH, MD; ITAI DANOVITCH, MD;
and WAGUIH WILLIAM ISHAK, MD, FAPA

OBJECTIVE: While trazodone is approved for the treatment of depression, the off-label use of this medication for insomnia has surpassed its usage as an antidepressant. In this systematic review, we examined the evidence for the efficacy and safety of trazodone for insomnia. **METHODS:** A literature search was conducted using MEDLINE/PubMed databases from the past 33 years (1983–2016) and the keywords insomnia, trazodone, sedative, treatment, and hypnotics. The results were restricted to English language and human subjects. All randomized clinical trials, meta-analyses, observational studies, and placebo-controlled trials regarding trazodone for the treatment of primary or secondary insomnia were reported, per PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study selection process yielded a total of 45 studies.

RESULTS: Evidence for the efficacy of trazodone has been repeatedly demonstrated for primary insomnia, as well as secondary insomnia, including for symptoms that are a result of depression, dementia, and being a healthy man. Earlier studies (1980–2000) focused on utilizing trazodone at high doses ($\geq 100\text{mg/d}$) for the treatment of insomnia among the depressed population; however, since the 2000s, the utility of trazodone has been expanded to treat secondary insomnia among the non-depressed population as well. The side effects are dose-dependent, and the most common is drowsiness. **CONCLUSION:** A review of the literature suggests that there are adequate data supporting the efficacy and general safety of the low-dose use of trazodone for the treatment of insomnia.

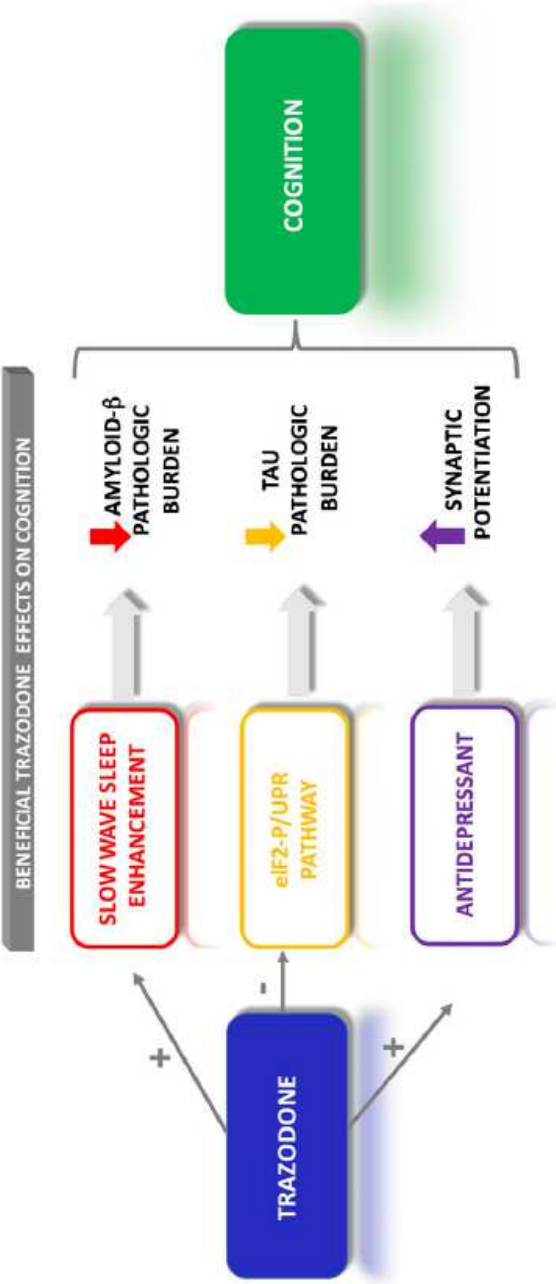


Fig. 1 . Association between long-term use of trazodone and cognition. Schematic representation of the main mechanisms underlying the beneficial effects of long-term use of trazodone on cognition.



Safety of Low Doses of Quetiapine When Used for Insomnia

Holly V Coe and Irene S Hong

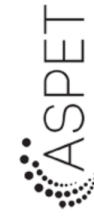
OBJECTIVE: To evaluate the safety of low doses of quetiapine when used for insomnia.

DATA SOURCES: A literature search was performed using PubMed and EMBASE (January 1990–November 2011) using the terms quetiapine, insomnia, sleep, low-dose, subtherapeutic, safety, and weight gain.

STUDY SELECTION AND DATA EXTRACTION: Two prospective trials were identified that evaluated the effect of quetiapine in primary insomnia. In addition, 2 retrospective cohort studies were identified that evaluated the safety of low doses of quetiapine when used for insomnia. Several case reports on adverse effects with low doses of the drug were also included.

DATA SYNTHESIS: Quetiapine is commonly used off-label for treatment of insomnia. When used for sleep, doses typically seen are less than the Food and Drug Administration–recommended dosage of 150–800 mg/day; those evaluated in the studies reviewed here were 25–200 mg/day). At recommended doses, atypical antipsychotics such as quetiapine are associated with metabolic adverse events (diabetes, obesity, hyperlipidemia). Adverse effects in the prospective trials were patient-reported and were minor, including drowsiness and dry mouth; however, the trials were limited by their small sample size and short duration. The retrospective cohort studies found that quetiapine was associated with significant increases in weight compared to baseline. Serious adverse events identified from case reports included fatal hepatotoxicity, restless legs syndrome, akathisia, and weight gain.

CONCLUSIONS: There are potential safety concerns when using low-dose quetiapine for treatment of insomnia. These concerns should be evaluated in further prospective studies. Based on limited data and potential safety concerns, use of low-dose quetiapine for insomnia is not recommended.



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Drugs for Insomnia beyond Benzodiazepines: Pharmacology, Clinical Applications, and Discovery

Tobias Atkin, Stefano Comai, and Gabriella Gobbi

4. Results in *Insomnia Disorder*

One RCT was identified in patients diagnosed with primary insomnia ([Tassniyom et al., 2010](#)).

Surprisingly, although observational evidence suggests that atypical antipsychotics like quetiapine are increasingly prescribed for insomnia, the 2010 study was the only RCT that was found in the literature of an atypical antipsychotic in primary insomnia, and it had a small sample size of only 13 patients who completed the study ([Tassniyom et al., 2010](#)). In the RCT, quetiapine 25 mg/day treatment was not significantly superior to placebo at increasing sleep time and reducing latency to sleep, although there was a trend toward the superiority of quetiapine ([Tassniyom et al., 2010](#)).

In contrast, an open-label trial of quetiapine 25–75 mg/day found that the drug was effective at reducing symptoms of insomnia, increasing total sleep time and reducing PSQI ([Wiegand et al., 2008](#)).

FDA Approves Daridorexant for Treatment of Insomnia

January 10, 2022

Ashley Gallagher, Assistant Editor

▪ Daridorexant è un DORA ovvero un antagonista selettivo e ad alta affinità di entrambi i recettori dell'orexina (OX1R e OX2R)

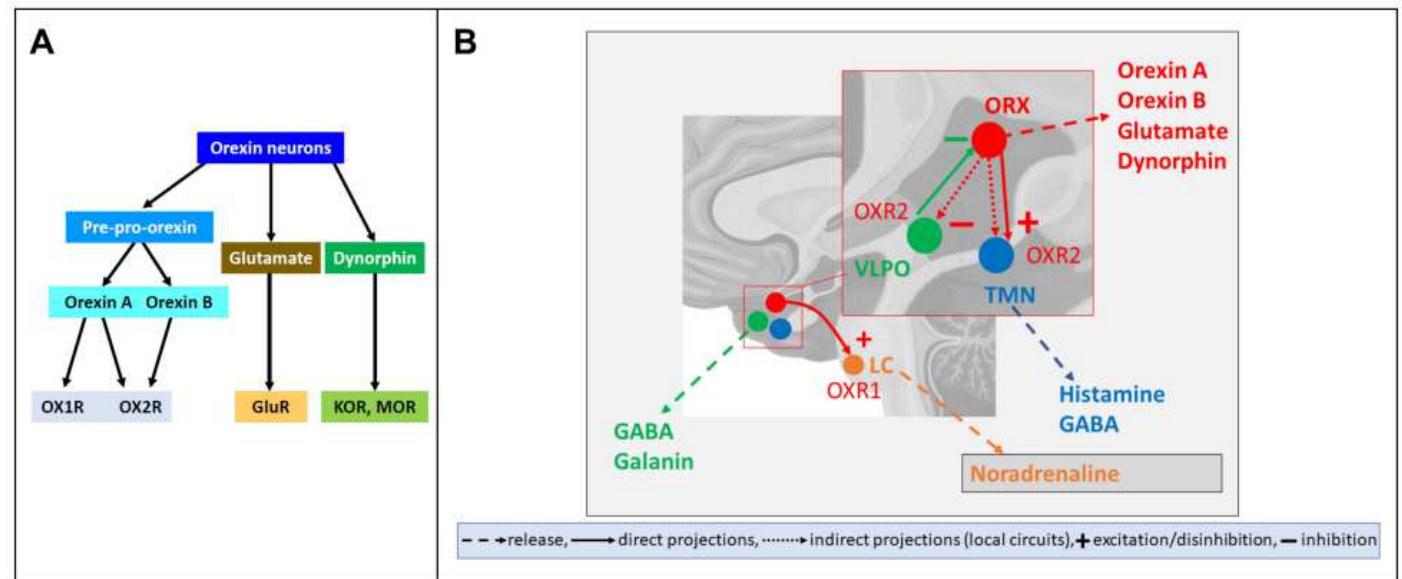


Figure 1 Neurochemistry and neuroanatomy of orexin neuron signaling. **(A)** summarizes the neurochemistry of orexin neuron signaling. Orexin neurons synthesize pre-pro-orexin, which is cleaved into the orexin (**A** and **B**) peptides (OXA and OXB, respectively). Orexin A acts by binding both orexin receptor 1 and (OXR1 and OXR2, respectively), whereas orexin B binds with high potency only OXR2. Orexin neurons may co-release glutamate, which binds its receptors (GluR), and dynorphin, which binds kappa opioid receptors (KOR) and mu opioid receptors (MOR). **(B)** illustrates three of the main projections of orexin neurons that are of particular relevance to wake-sleep control. Orexin (ORX) neurons indirectly inhibit neurons of the ventrolateral preoptic nucleus (VLPO) of the hypothalamus, which promote sleep, express gamma-aminobutyric acid (GABA) and galanin, and inhibit ORX neurons. In addition, ORX neurons directly excite and indirectly disinhibit neurons of the hypothalamic tuberomammillary nucleus (TMN), which co-release histamine and GABA to promote wakefulness. Finally, ORX neurons excite neurons of the locus coeruleus in the pons, which release noradrenaline and promote wakefulness. The effects of ORX neurons on the VLPO and TMN are mainly mediated by OX2R, whereas those on the LC are mainly mediated by OX1R. Other projections of ORX neurons as well as of VLPO, TMN, and LC neurons were omitted for clarity.

Table 1 Brief Profiles of the Main Orexin Receptor Antagonists Reported Above

Drug	Type	Half-Life, Hours	Side Effects*	Approved	WASO	TST	Sleep Latency
Suvorexant	DORA	12	Somnolence, headache	USA, Japan	↓	↑	↓
Lemborexant	DORA	17–19	Somnolence, fatigue, headache, abnormal dreams	USA, Canada, Australia, Japan	↓	↑	↓
Daridorexant	DORA	8	Headache, somnolence, fatigue	USA, EU	↓	↑	↓
Vornorexant (TS-142)	DORA	1.3–3.3		Under development/evaluation	↓	↑	↓
JNJ-48816274	OX2R SORA	1	Somnolence, abnormal dreams	Under development/evaluation	↓	↑	↓
Seltorexant (JNJ-42847922)	OX2R SORA	2–3	Somnolence, fatigue, dizziness, headache, abdominal discomfort, and nightmares	Under development/evaluation	↓	↑	↓

Note: *Possible narcoleptic-like symptoms, potentially for all agents, at high doses.

Abbreviations: SORA, selective orexin receptor antagonist; DORA, dual orexin receptor antagonist; WASO, wakefulness after sleep onset; TST, total sleep time; OX2R, orexin receptor 2; ↓, decreased; ↑, increased.

Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials

Emmanuel Mignot, David Mayleben, Ingo Fietze, Damien Leger, Gary Zammit, Claudio L A Bassetti, Scott Pain, Dalma Seboek Kinter, Thomas Roth, on behalf of the investigators*



Summary

Background Daytime functioning is impaired in people with insomnia disorder. Currently available dual orexin receptor antagonists have shown efficacy in insomnia disorder, but do not address all aspects of this disease. We aimed to assess safety and efficacy of daridorexant, a novel orexin receptor antagonist, on night-time and daytime symptoms of insomnia.

Methods We did two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials at 156 sites in 17 countries. Adults (aged ≥ 18 years) with insomnia disorder were randomly assigned using interactive response technology (1:1:1) to receive daridorexant 50 mg, 25 mg, or placebo (study 1) or daridorexant 25 mg, 10 mg, or placebo (study 2) every evening for 3 months. Participants, investigators, and site personnel were masked to treatment allocation. The primary endpoints were change from baseline in wake time after sleep onset (WASO) and latency to persistent sleep (LPS), measured by

Lancet Neurol 2022; 21: 125–39

See [Comment](#) page 104

*Investigators are listed in the appendix (p 3)

Stanford Center for Sleep Research and Medicine, Palo Alto, CA, USA (Prof E Mignot MD); CTI Clinical Research Center, Cincinnati, OH, USA (D Mayleben PhD); Center for Sleep Medicine,

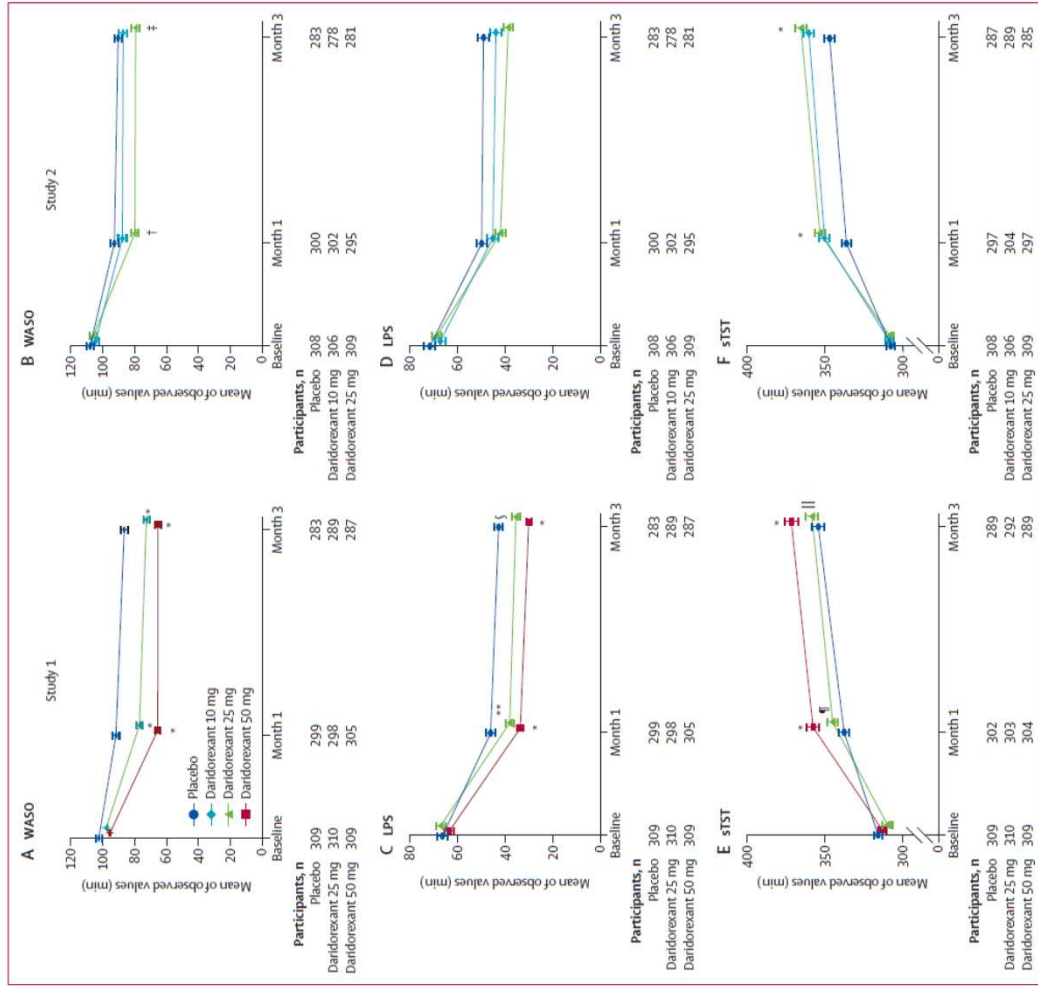


Figure 2: Night-time efficacy endpoints
Mean of observed WASO values at study timepoints in study 1 (A) and study 2 (B). Mean of observed LPS values at study timepoints in study 1 (C) and study 2 (D). Mean of observed sTST values at study timepoints in study 1 (E) and study 2 (F). WASO and LPS values are the mean of polysomnography recordings obtained over two consecutive nights during the 3-month double-blind treatment period. Data for sTST are based on the mean of daily entries in the 7 days before polysomnography nights. Error bars show SEM. Two-sided p values shown are versus placebo, calculated using the linear mixed effects model for repeated measures. LPS=latency to persistent sleep. sTST=total sleep time. WASO=wake time after sleep onset. *p<0.0001. †p=0.0018. ‡p=0.0015. ¶p=0.0013. ||p=0.003. **p=0.0005.

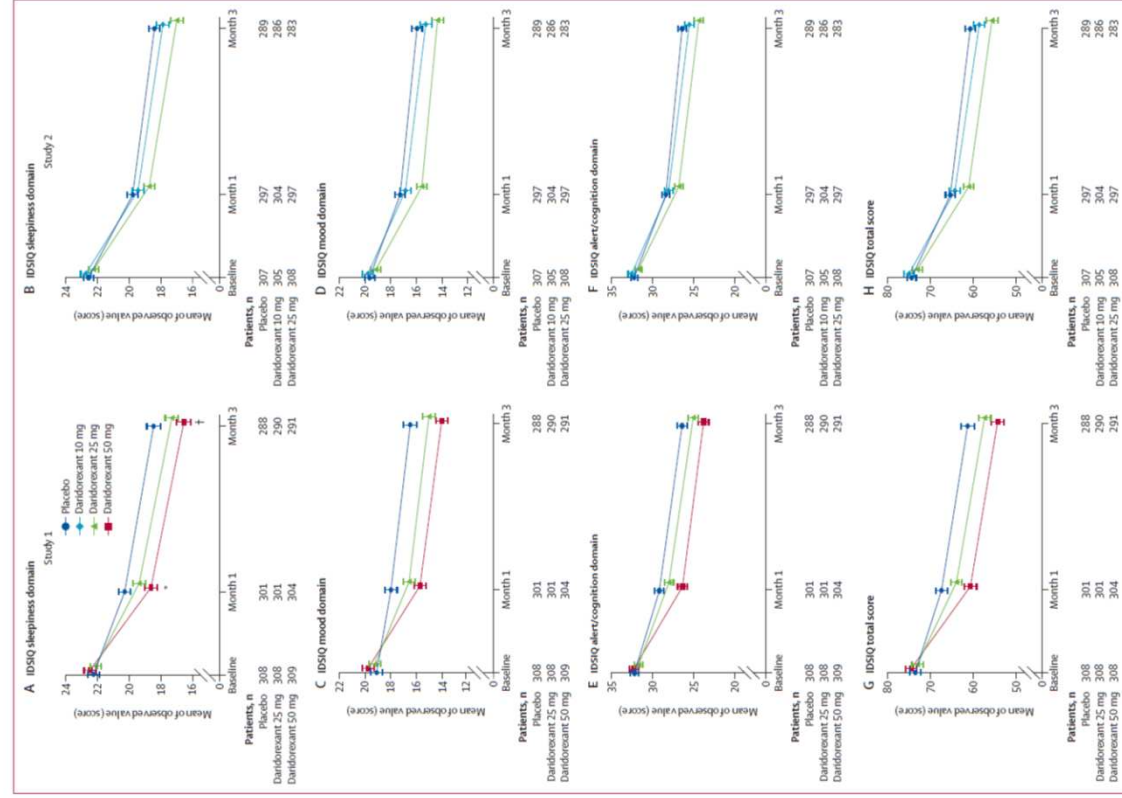


Figure 3: IDSQ endpoints
Mean of observed IDSQ sleepiness domain scores at study timepoints in study 1 (A) and study 2 (B). Mean of observed IDSQ mood domain scores at study timepoints in study 1 (C) and study 2 (D). Mean of observed IDSQ alert/cognition domain scores at study timepoints in study 1 (E) and study 2 (F). Mean of observed IDSQ total scores at study timepoints in study 1 (G) and study 2 (H). IDSQ scores are based on the mean of daily entries in the 7 days before polysomnography nights. Error bars show SEM. Two-sided p values shown are versus placebo, calculated using the linear mixed effects model for repeated measures. p values for the mood domain, alert/cognition domain, and total score comparisons versus placebo (not adjusted for multiplicity) are reported in the appendix (p 37). IDSQ=Insomnia Daytime Symptoms and Impacts Questionnaire. *p<0.0001. †p=0.0002.



Efficacy and Safety of Daridorexant in Older and Younger Adults with Insomnia Disorder: A Secondary Analysis of a Randomised Placebo-Controlled Trial

Ingo Fietze^{1,2} · Claudio L. A. Bassetti³ · David W. Mayleben⁴ · Scott Pain⁵ · Dalma Seboek Kinter⁵ · William V. McCall⁶ 

Conclusions In older patients with insomnia, as in younger patients, the efficacy of daridorexant is maximal on night-time and daytime variables at the higher dose of 50 mg. Older patients particularly require this dose to improve daytime functioning. Older patients are not at an increased risk of adverse events or residual effects the next morning after night-time administration of daridorexant, even at 50 mg. The dose of daridorexant does not need to be decreased for older patients. **Clinical Trial Registration** ClinicalTrials.gov (NCT03545191) [first posted: 4 June, 4 2018], <https://clinicaltrials.gov/ct2/show/NCT03545191>.



The European Insomnia Guideline: An update on the diagnosis and treatment of insomnia 2023

These interesting data remain to be validated through practical experience in everyday practice. In general, orexin receptor antagonists can be used for periods of up to 3 months. In individual cases, treatment can be extended for longer-term periods (up to 1 year) following discussion with the patient regarding the advantages and disadvantages reported in the 1-year study

Outline

- I disturbi del sonno nell'anziano: elementi caratteristici
- L'approccio al trattamento dei disturbi del sonno
- I trattamenti non farmacologici
- I trattamenti farmacologici: approccio tradizionale e elementi innovativi
- I disturbi del sonno nella demenza

Sleep Disorders in Dementia

- **Insomnia** **49%**
- **Excessive Daytime Sleepiness** **50%**
- **Obstructed sleep apnea (OSA)** **50% (70% in VD)**
- **REM behavior disorder (RBD)** **20% (75% in DLB)**
- **Sleep Time alteration**
 - **Short sleep (less than 7 hours)**
 - **Long sleep (more than 8 hours)**

Pao W; Prat Neur, 2019; Leng Y et al, Lancet Neur, 2019

Prevalenza dei disturbi del sonno nei vari tipi di demenza

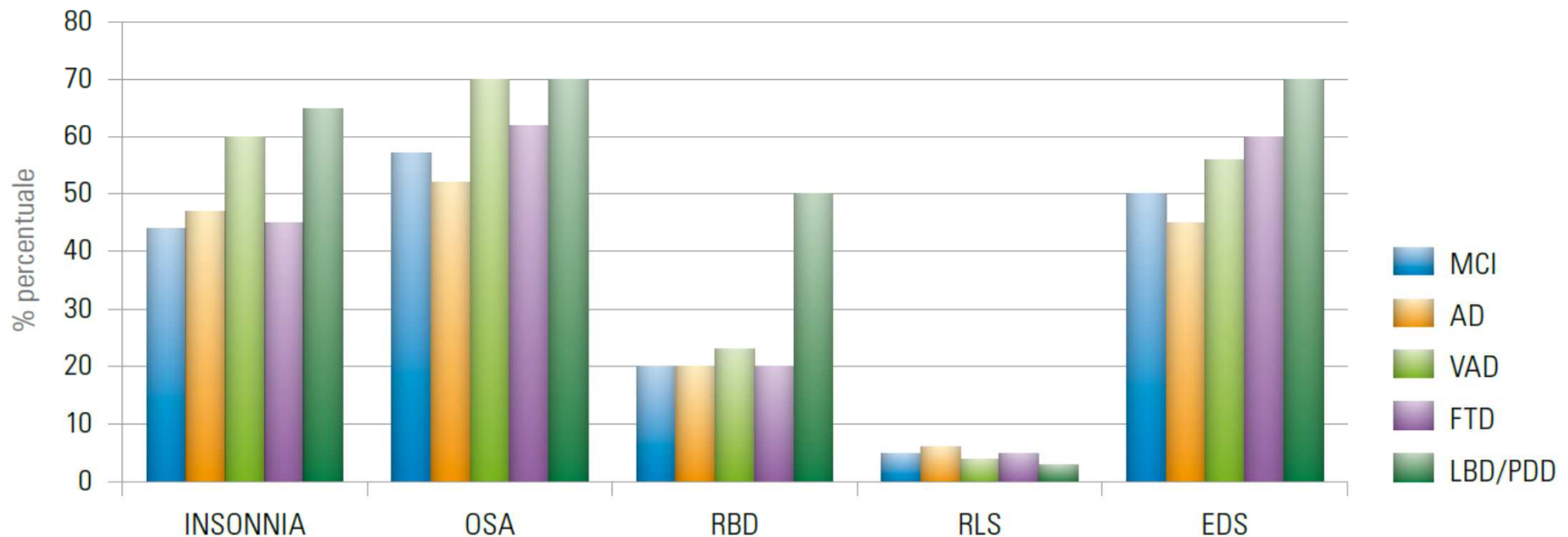


Figura 1: Prevalenza di Insonnia e altri disturbi del sonno per tipo di demenza. MCI = decadimento cognitivo lieve; AD = malattia di Alzheimer; VaD = demenza vascolare; FTD = demenza frontotemporale; LBD = demenza con Corpi di Lewy; PDD = demenza Parkinsoniana; OSA = apnea ostruttiva nel sonno; RBD = disturbo comportamentale del sonno REM; RLS = sindrome delle gambe senza riposo; EDS = sonnolenza diurna eccessiva (modificato da Guarnieri B, et al. *Dement Geriatr Cogn Disord.* 2012).

Alessandro Padovani^{1,2}, Andrea Scalvini¹, Andrea Pilotto^{1,3}

1. Clinica Neurologica, Università degli Studi di Brescia | 2. Centro per i Disturbi del Comportamento e per le Malattie Neurodegenerative, Università degli Studi di Brescia | 3. FERB, Trescore Balneario

- Sleep disorders in patients with AD tend to vary with disease severity and institutional placement.
- In those who have these disorders, rates of aggression (65% vs 40%), global behavioral problems (80% vs 58%), and anxiety (67% vs 50%) are higher than in patients with AD who do not have sleep problems.
- For caregivers, AD patients with comorbid sleep and behavioral issues are particularly problematic. Nocturnal agitation may be the single most common reason that a patient with dementia enters a nursing home

Moran M, Lynch CA, Walsh C, et al. Sleep disturbance in mild to moderate Alzheimer's disease. *Sleep Med.* 2005;6:347-352.



Association of a History of Sleep Disorder With Risk of Mild Cognitive Impairment and Alzheimer's Disease Dementia

Young Min Choe^{1,2}, Guk-Hee Suh^{1,2}, and Jee Wook Kim^{1,2}

¹Department of Neuropsychiatry, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Republic of Korea

²Department of Psychiatry, Hallym University College of Medicine, Chuncheon, Republic of Korea

Objective We explored whether a history of sleep disorder affected a current diagnosis of cognitive impairment and clinical conversion in a non-demented elderly population.

Methods Comprehensive clinical data collected as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI) was analyzed. A history of sleep disorder was recorded in the recent ADNI medical database. Standard clinical and neuropsychological tests were performed both at baseline and follow-up visit. Multiple logistic regression analysis was performed after adjusting for age, sex, education, apolipoprotein E ε4 status, vascular risk score, body mass index, Geriatric Depression Scale score, and use of sleeping pills.

Results A total of 391 cognitively normal individuals, 303 with early mild cognitive impairment (MCI) and 364 with late MCI were included. Sleep disorder history was significantly associated with an increased risk of MCI but not with clinical conversion. A history of insomnia or obstructive sleep apnea (OSA) significantly increased the risk of MCI, but only an OSA history predicted progression to Alzheimer's disease (AD) dementia.

Conclusion Our findings suggest that a sleep disorder history usefully aids early detection of cognitive impairment and emphasize that such sleep disorder, particularly OSA, is important as potential target for AD prevention. **Psychiatry Investig** 2022;19(10):840-846

Keywords Sleep disorder; Insomnia; Obstructive sleep apnea; Restless legs syndrome; Mild cognitive impairment; Alzheimer's disease.

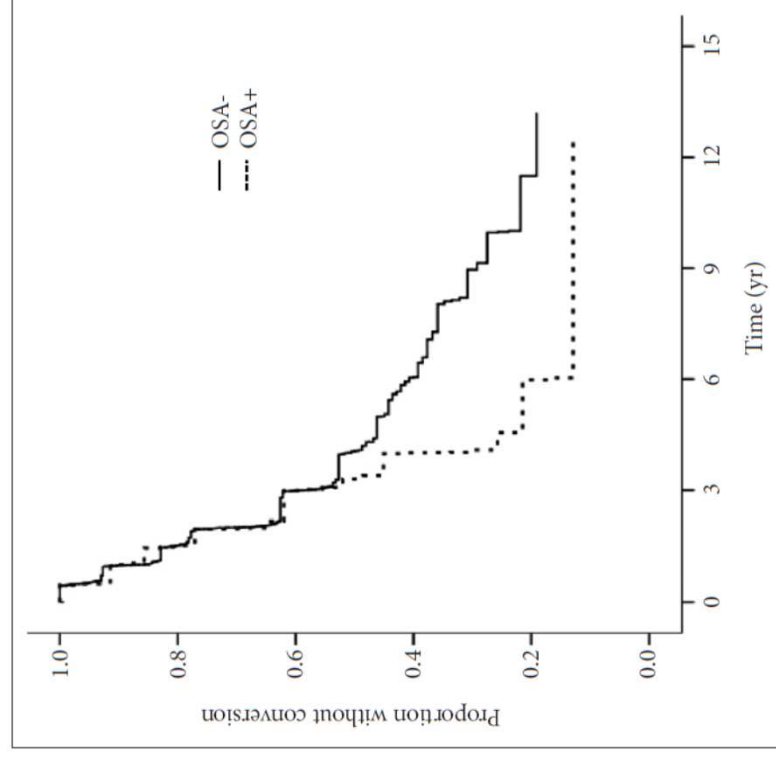


Figure 1. Kaplan-Meier survival curves showing the relationship between a history of OSA and clinical conversion in late mild cognitive impairment. OSA, obstructive sleep apnea.

Association of Short and Long Sleep Duration With Amyloid-β Burden and Cognition in Aging

Joseph R. Winer, PhD; Kacie D. Deters, PhD; Gabriel Kennedy, BSc; Meghan Jin; Andrea Goldstein-Plekanski, PhD; Kathleen L. Poston, MD, MS; Elizabeth C. Mormino, PhD

IMPORTANCE Disrupted sleep is common in aging and is associated with cognition. Age-related changes to sleep are associated with multiple causes, including early Alzheimer disease pathology (amyloid β [Aβ]), depression, and cardiovascular disease.

OBJECTIVE To investigate the associations between self-reported sleep duration and brain Aβ burden as well as the demographic, cognitive, and lifestyle variables in adults with normal cognition.

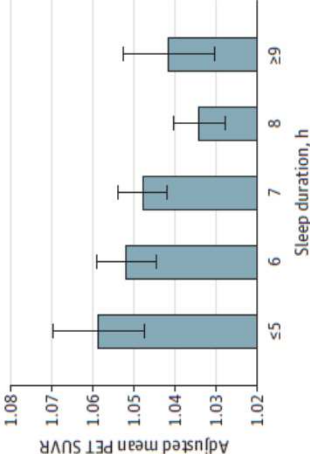
DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study obtained data from participants in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study, which is being conducted in 67 sites in the United States, Canada, Australia, and Japan. The sample for this analysis consisted of individuals aged 65 to 85 years who underwent an Aβ positron emission tomography (PET) scan, had complete apolipoprotein E (APOE) genotype data, and were identified as clinically normal (per a Clinical Dementia Rating score of 0) and cognitively unimpaired (per a Mini-Mental State Examination score of 25 to 30 and Logical Memory Delayed Recall test score of 6 to 18). Data were analyzed from April 3, 2020, to June 20, 2021.

MAIN RESULTS AND MEASURES The outcome was self-reported nightly sleep duration (grouped by short sleep duration: ≤6 hours, normal sleep duration: 7–8 hours, and long sleep duration: ≥9 hours) compared with demographic characteristics, Aβ burden (as measured with a fluorine 18-labeled-florbetapir PET scan), objective and subjective cognitive function measures, and lifestyle variables.

RESULTS The 4417 participants in the study included 2618 women (59%) and had a mean (SD) age of 71.3 (4.7) years. Self-reported shorter sleep duration was linearly associated with higher Aβ burden (β [SE] = −0.01 [0.00]; *P* = .005), and short sleep duration was associated with reduced cognition that was mostly in memory domains. No difference in Aβ was found between long and normal sleep duration groups (β [SE] = 0.00 [0.01]; *P* = .99). However, compared with normal sleep duration, both short and long sleep durations were associated with higher body mass index (short vs normal sleep duration: β [SE] = 0.48 [0.17]; *P* = .01; long vs normal sleep duration: β [SE] = 0.97 [0.31]; *P* = .002), depressive symptoms (short vs normal sleep duration: β [SE] = 0.31 [0.05]; *P* < .001; long vs normal sleep duration: β [SE] = 0.39 [0.09]; *P* < .001), and daytime napping (short vs normal sleep duration: β [SE] = 2.66 [0.77]; *P* = .001; long vs normal sleep duration: β [SE] = 3.62 [1.38]; *P* = .01). Long sleep duration was associated with worse performance across multiple cognitive domains.

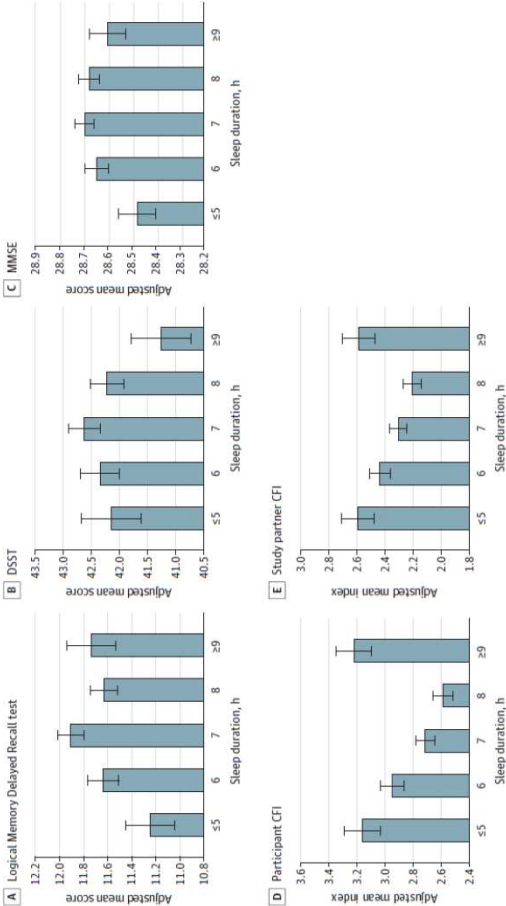
CONCLUSIONS AND RELEVANCE In this cross-sectional study, both short and long sleep durations were associated with worse outcomes for older adults, such as greater Aβ burden, greater depressive symptoms, higher body mass index, and cognitive decline, emphasizing the importance of maintaining adequate sleep.

Figure 1. Association of Sleep Duration With Amyloid-β Positron Emission Tomography (PET) Standardized Uptake Value Ratio (SUVR)



Adjusted mean (SE) within each sleep duration group (≤5, 6, 7, 8, and ≥9 hours) was calculated for a mean age (71.3 [4.7] years), mean years of education (16.6 [2.8] years), and non-Hispanic White male participants with an APOE ε33 allele genotype.

Figure 2. Association of Sleep Duration With Cognitive Function



Adjusted mean (SE) within each sleep duration group (≤5, 6, 7, 8, and ≥9 hours) was calculated for a mean age (71.3 [4.7] years), mean years of education (16.6 [2.8] years), and non-Hispanic White male participants with an APOE ε33 allele genotype. CFI indicates Cognitive Function Index (score range: 0–15, with higher scores indicating better cognitive performance).

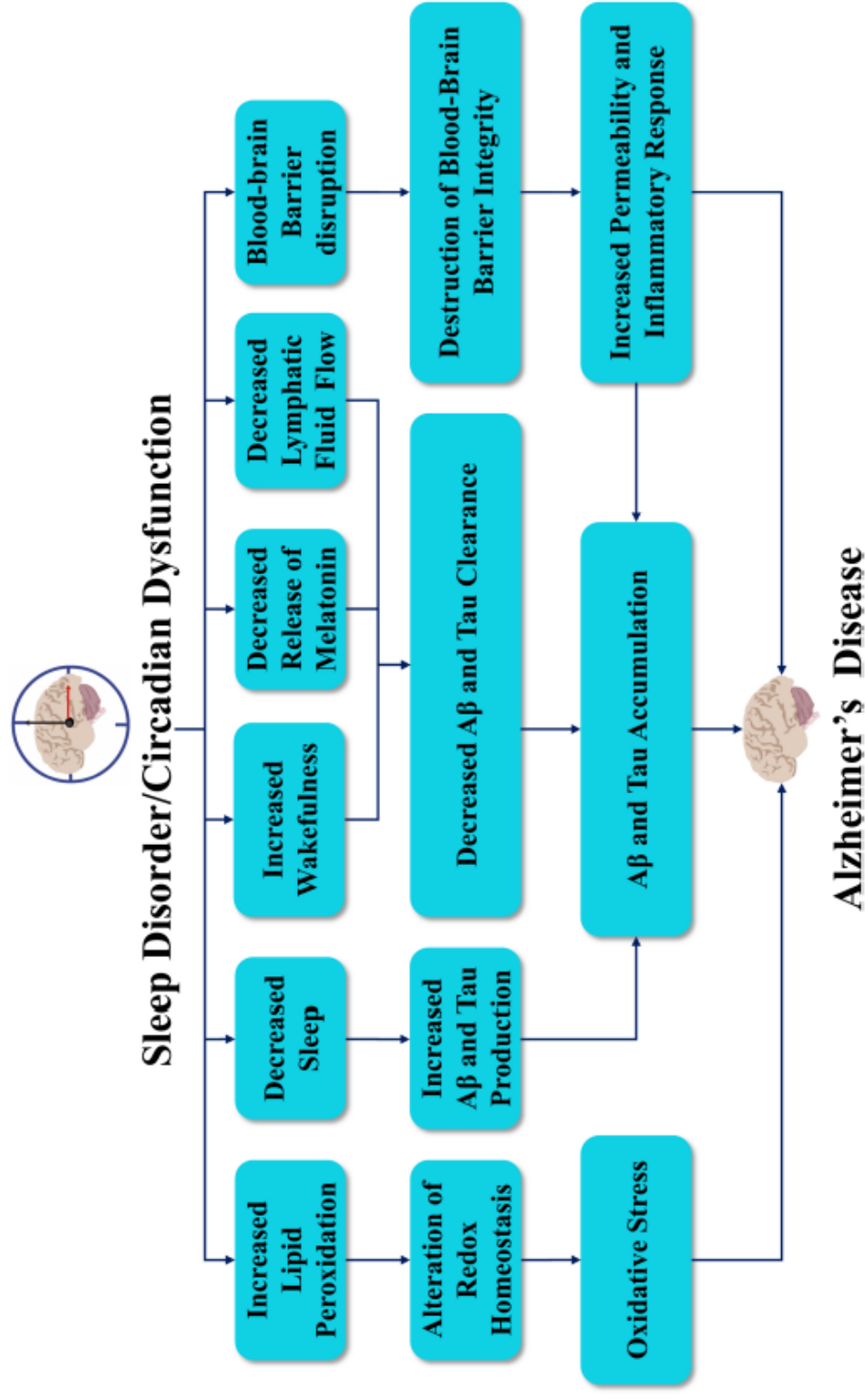


FIGURE 2

The link between sleep deprivation and circadian dysfunction in the pathogenesis of Alzheimer's disease. Sleep and circadian rhythm disorders may lead to oxidative stress, accumulation of A β and tau proteins, decreased release of melatonin, reduced lymphatic flow, and damage to the blood-brain barrier, which may lead to the development of AD.

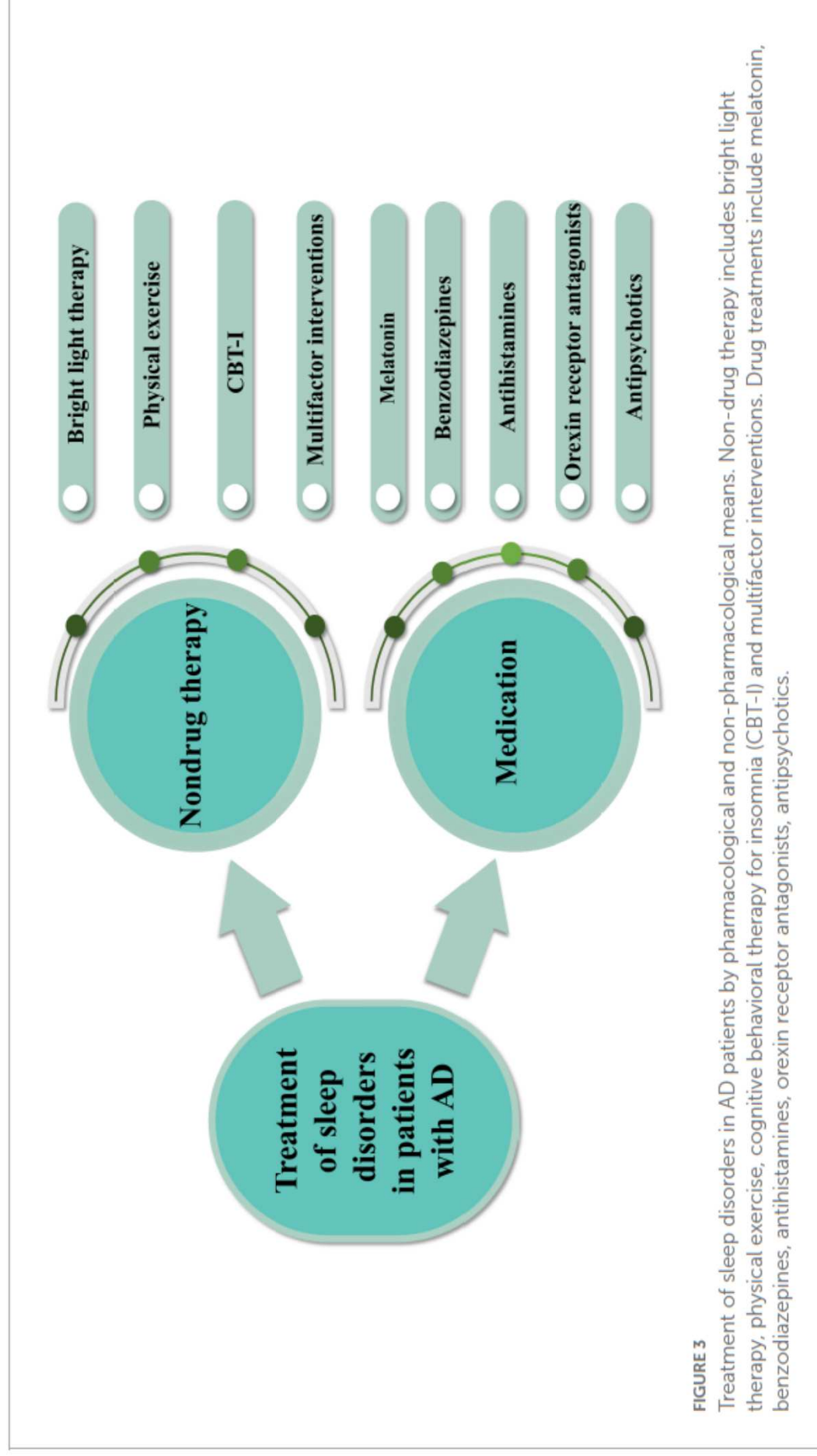


FIGURE 3

Treatment of sleep disorders in AD patients by pharmacological and non-pharmacological means. Non-drug therapy includes bright light therapy, physical exercise, cognitive behavioral therapy for insomnia (CBT-I) and multifactor interventions. Drug treatments include melatonin, benzodiazepines, antihistamines, orexin receptor antagonists, antipsychotics.

Pharmacotherapies for sleep disturbances in dementia (Review)

McCleery J, Sharpley AL

We discovered a distinct lack of evidence to guide decisions about drug treatment of sleep problems in dementia. In particular, we found no RCTs of many widely prescribed drugs, including the benzodiazepine and non-benzodiazepine hypnotics, although there is considerable uncertainty about the balance of benefits and risks for these common treatments. We found no evidence for beneficial effects of melatonin (up to 10 mg) or a melatonin receptor agonist. There was evidence of some beneficial effects on sleep outcomes from trazodone and orexin antagonists and no evidence of harmful effects in these small trials, although larger trials in a broader range of participants are needed to allow more definitive conclusions to be reached. Systematic assessment of adverse effects in future trials is essential.

TABLE 2

Pharmacological interventions for the management of sleep issues in dementia

Disorder	Intervention
REM behavioral disorder	Clonazepam; consider melatonin ^a ; atypical antipsychotics may be needed
Circadian rhythm disorders	Melatonin; hypnotics (eg, zolpidem); consider atypical antipsychotics

^a Judicious use is recommended in patients with possible cardiac or cerebrovascular disease.

RESEARCH ARTICLE

Open Access

Adverse effects of Z-drugs for sleep disturbance in people living with dementia: a population-based cohort study

Kathryn Richardson^{1*}, Yoon K. Loke¹, Chris Fox¹, Ian Maidment², Robert Howard³, Nicholas Steel¹, Antony Arthur⁴, Penelope J. Boyd¹, Clare Aldus⁴, Clive Ballard⁵ and George M. Savva^{4,6}



Abstract

Background: Sleep disturbance is common in dementia and often treated with Z-drugs (zopiclone, zaleplon, and zolpidem). While some observational studies suggest that Z-drugs are associated with adverse events such as falls and fracture risks in older people, this has not been studied in dementia.

Methods: We used data from 27,090 patients diagnosed with dementia between January 2000 and March 2016 from the Clinical Practice Research Datalink linked to Hospital Episodes Statistics data in England. We compared adverse events for 3532 patients newly prescribed Z-drugs by time-varying dosage to (1) 1833 non-sedative-users with sleep disturbance; (2) 10,214 non-sedative-users with proximal GP consultation matched on age, sex, and antipsychotic use; and (3) 5172 patients newly prescribed benzodiazepines. We defined higher dose Z-drugs and benzodiazepines as prescriptions equivalent to ≥ 7.5 mg zopiclone or > 5 mg diazepam daily. Cox regression was used to estimate hazard ratios (HRs) for incident fracture, hip fracture, fall, mortality, acute bacterial infection, ischaemic stroke/transient ischaemic attack, and venous thromboembolism over a 2-year follow-up, adjusted for demographic- and health-related covariates.

Results: The mean (SD) age of patients was 83 (7.7) years, and 16,802 (62%) were women. Of 3532 patients prescribed Z-drugs, 584 (17%) were initiated at higher doses. For patients prescribed higher dose Z-drugs relative to non-users with sleep disturbance, the HRs (95% confidence interval) for fractures, hip fractures, falls, and ischaemic stroke were 1.67 (1.13–2.46), 1.96 (1.16–3.31), 1.33 (1.06–1.66), and 1.88 (1.14–3.10), respectively. We observed similar associations when compared to non-sedative-users with proximal GP consultation. Minimal or inconsistent excess risks were observed at ≤ 3.75 mg zopiclone or equivalent daily, and for mortality, infection, and venous thromboembolism. We observed no differences in adverse events for Z-drugs compared to benzodiazepines, except lower mortality rates with Z-drugs (HR [95% confidence interval] of 0.73 [0.64–0.83]).

Conclusions: Higher dose Z-drug use in dementia is associated with increased fracture and stroke risks, similar or greater to that for higher dose benzodiazepines. Higher dose Z-drugs should be avoided, if possible, in people living with dementia, and non-pharmacological alternatives preferentially considered. Prescriptions for higher dose Z-drugs in dementia should be regularly reviewed.

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 DOI: 10.1002/hrc2.12309

RESEARCH ARTICLE

Benzodiazepine use and the risk of dementia

Geoffrey Joyce^{1,2} | Patricia Ferido¹ | Johanna Thunell¹ | Bryan Tysinger^{1,3} | Julie Zissimopoulos^{1,3}

Abstract

Introduction: Benzodiazepines (BZDs) are commonly prescribed for anxiety and agitations, which are early symptoms of Alzheimer's disease and related dementias (ADRD). It is unclear whether BZDs causally affect ADRD risk or are prescribed in response to early symptoms of dementia.

Methods: We replicate prior case-control studies using longitudinal Medicare claims. To mitigate bias from prodromal use, we compare rates of ADRD diagnosis for beneficiaries exposed and unexposed to BZDs for cervical/lumbar pain, stenosis, and sciatica, none of which are associated with dementia.

Results: Approximately 8% of Medicare beneficiaries used a BZD in 2007, increasing to nearly 13% by 2013. Estimates from case-control designs are sensitive to duration of look-back period, health histories, medication use, and exclusion of decedents. Incident BZD use is not associated with an increased risk of dementia in an "uncontaminated" sample of beneficiaries prescribed a BZD for pain (odds ratios (ORs) of 1.007 [95% confidence interval (CI) = 0.885, 1.146] and 0.986 [95% CI = 0.877, 1.108], respectively, in the 2013 and 2013 to 2015 pooled samples). Higher levels of BZD exposure (> 365 days over a 2-year period) are associated with increased odds of a dementia diagnosis, but the results are not statistically significant at the 5% or 10% levels (1.190 [95% CI = 0.925, 1.531] and 1.167 [95% CI = 0.919, 1.483]).

Discussion: We find little evidence of a causal relation between BZD use and dementia risk. Nonetheless, providers should limit the extended use in elderly populations.

Conclusioni

- I disturbi del sonno sono frequenti nei soggetti anziani, spesso in comorbidità con patologie somatiche e neurologiche
- Alla base dei disturbi del sonno nell'anziano vi sono spesso problemi psichici, ansia, depressione, cambiamenti nelle condizioni di vita
- L'approccio non farmacologico è fondamentale ed efficace anche nell'anziano
- L'uso di farmaci tradizionalmente utilizzati quali le benzodiazepine dovrebbe essere limitato nel tempo e nelle dosi
- L'uso di melatonina e trazodone è efficace e ben tollerato
- I nuovi farmaci DORA aprono una prospettiva di nuovo trattamento dell'insonnia anche nella persona anziana



El sueño de la razón produce monstruos
Francisco Goya



La meridienne, Vincent Van Gogh