

Le nuove frontiere nella terapia dell'insonnia

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Insomnia is a disorder with nighttime and daytime symptoms

According to the DSM-5 diagnostic guidelines, insomnia is characterized by **both** sleep and daytime impairments



Sleep difficulties include:

- Difficulty initiating asleep
- Difficulty maintaining asleep
- Early-morning awakening despite adequate opportunity for sleep



Daytime impairments include clinically significant distress or impairment in:

- Social
- Occupational
- Educational
- Academic
- Behavioral
- Other important areas of functioning

Presence of **daytime impairments is necessary** for diagnosis of Insomnia Disorder, per the DSM-5¹



Nighttime Symptoms



Daytime Symptoms



Frequency and Duration



Differential Diagnosis^a

^aInsomnia is not better explained by another sleep-wake disorder, a coexisting mental disorders or medical conditions and is not attributable to the physiological effects of a substance.

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013; 2. Sateia MJ. *Chest* 2014;146:1387–94

Insomnia disorder: it is a mental disorder *per se*

Predispositions

- Polygenic risk
- Mutations in:
- Orexin 1 and 2
- Clock genes
- Gabaergic system

Precipitants

- Life events – stress
- Comorbid conditions

Perpetuating factors

- Maladaptive sleep habits and cognitions
- Neurobiological alterations

Hyperarousal

- Insomnia as a 24-hour disease
- Nighttime symptoms-subjective poor sleep
- Daytime symptoms

Physiology and neurobiology of hyperarousal



Brain

- Increased EEG fast frequencies during sleep
- Increased number of arousals during REM sleep
- Increased SOL and short sleep duration



Heart

- Increased heart rate
- Altered heart rate variability



Pituitary-adrenal axis

- Increased activity

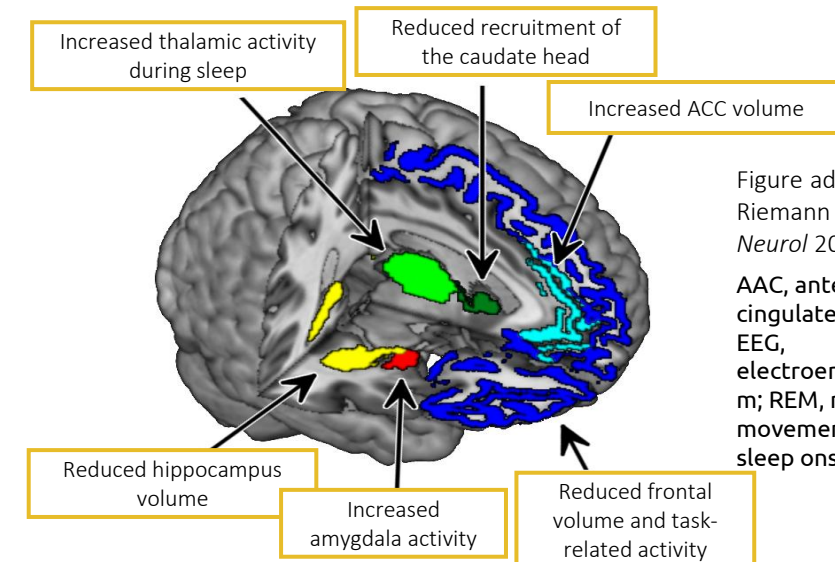
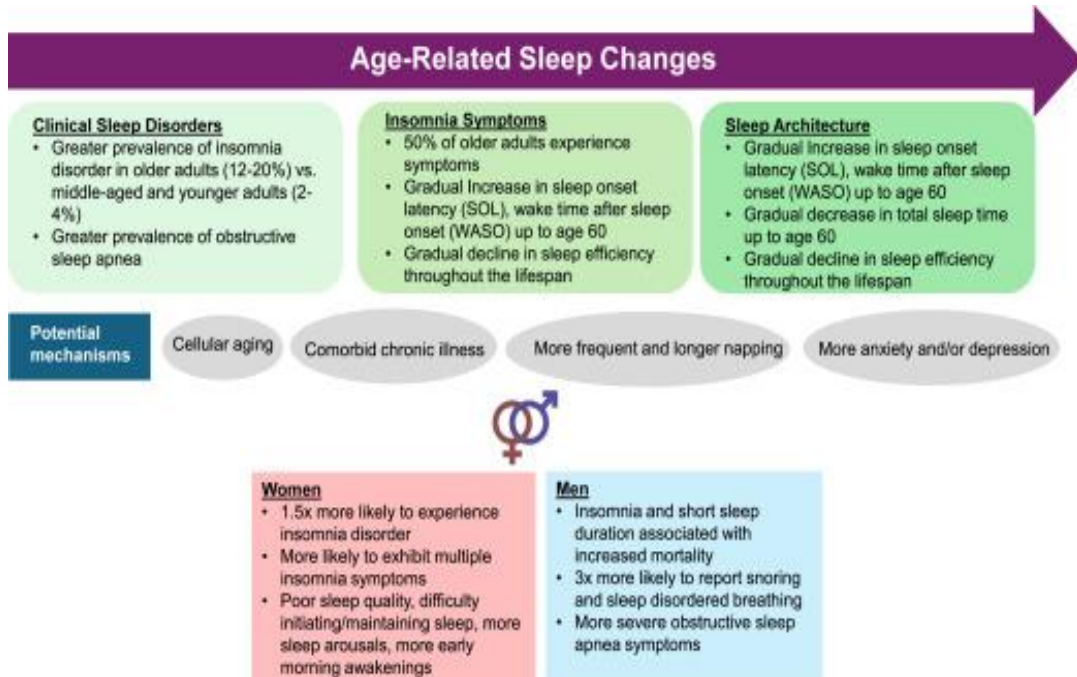


Figure adapted from Riemann D, et al. *Lancet Neurol* 2015

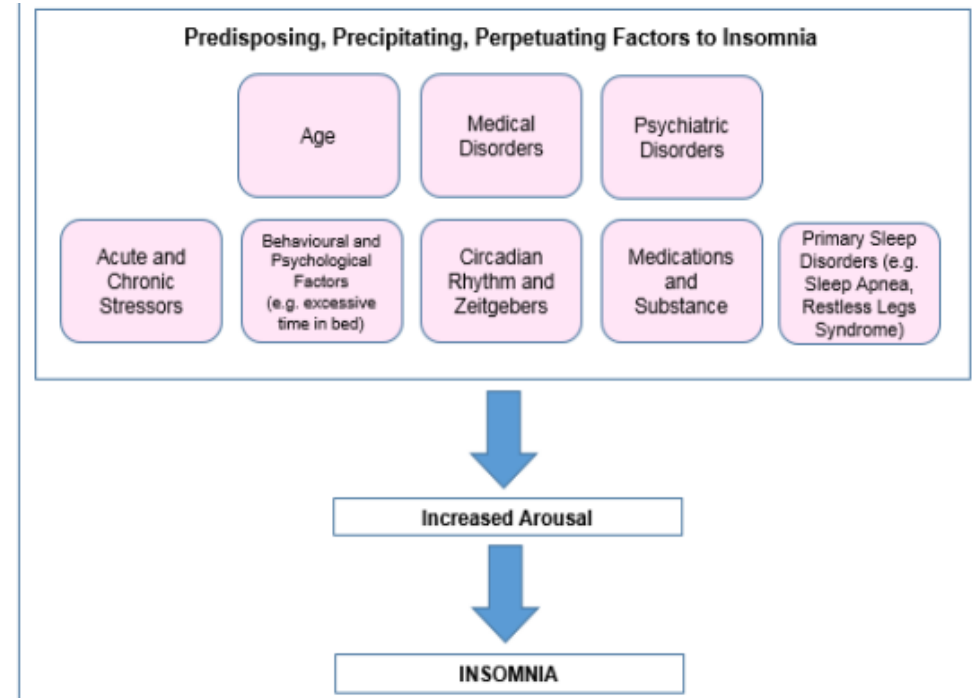
AAC, anterior cingulate cortex; EEG, electroencephalogram; REM, rapid eye movement; SOL, sleep onset latency.

Insomnia in the elderly

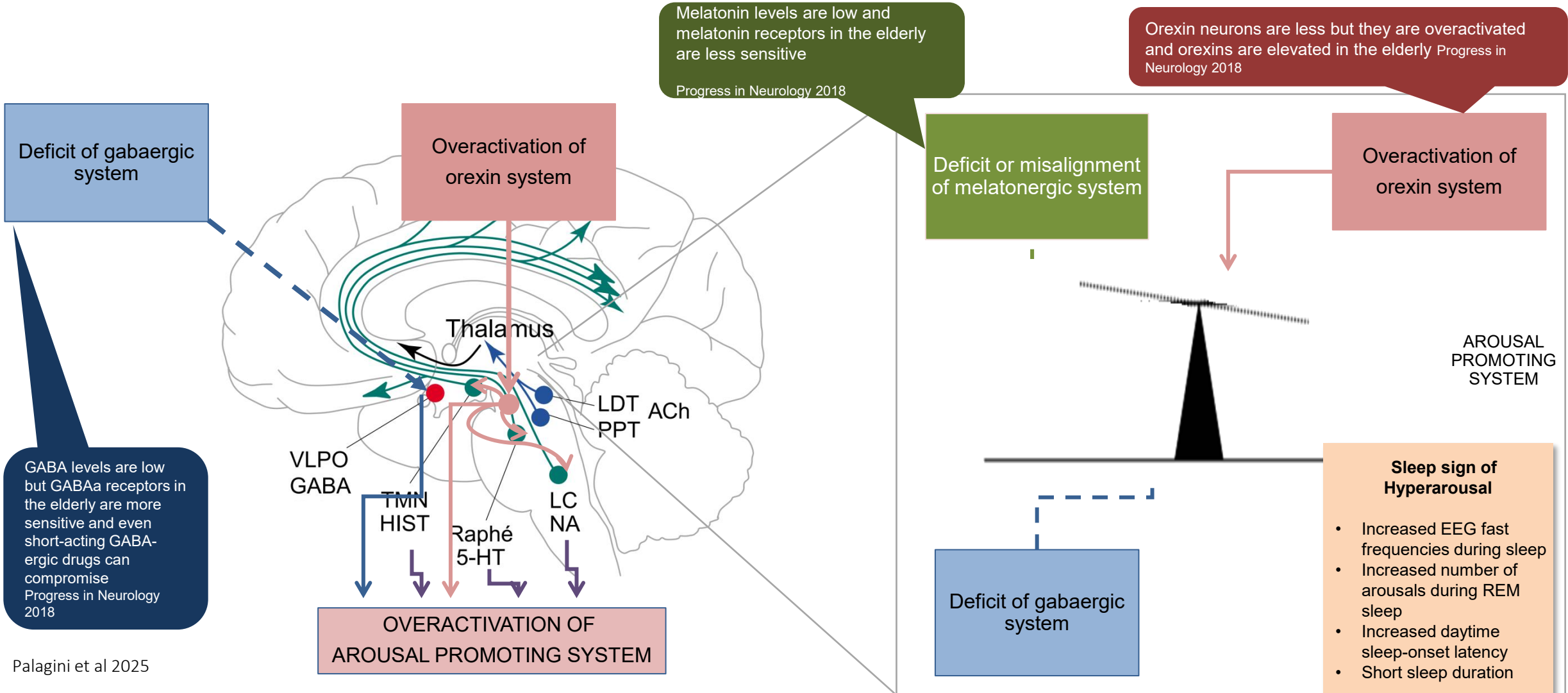
AGE-RELATED SLEEP CHANGES PREDISPOSE TO INSOMNIA



INSOMNIA IN THE ELDERLY: UPDATE ON ASSESSMENT AND MANAGEMENT

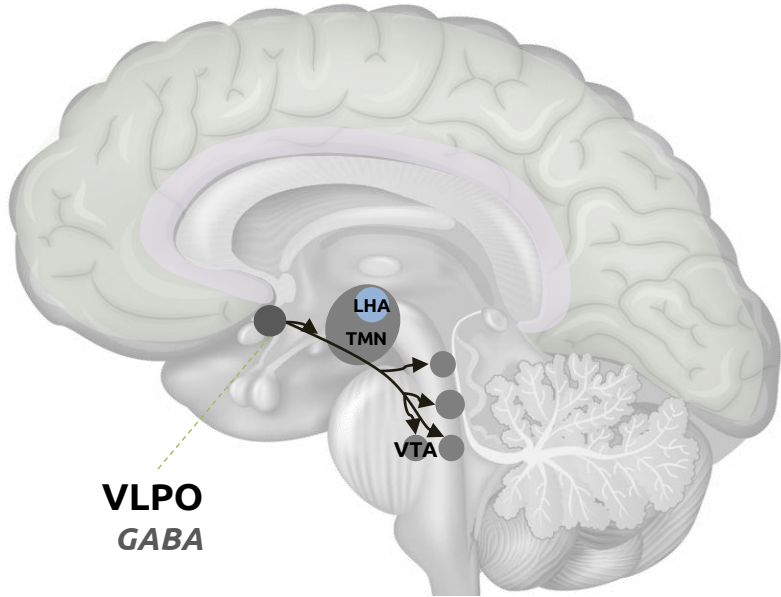


Abnormal neurotransmission in insomnia: imbalance in the flip-flop system with overactivation of arousal promoting systems, or loss of de-arousal system or deficit of sleep promoting system

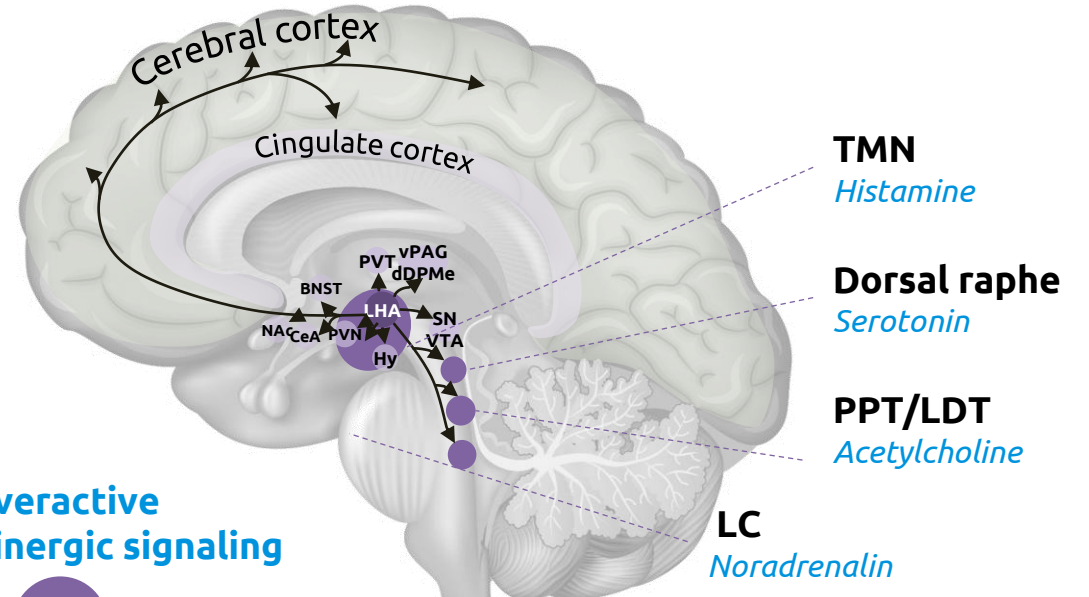


Pharmacological treatments for insomnia disorder differ in their mechanisms of actions: what's about elderly?

Increasing sleep signalling



Reducing wake signalling



ATTENTION! BDZ, Z-drugs
Melatonin receptor agonists

Deficit GABAergic signaling

Sleep

Overactive monoaminergic signaling

Orexin system regulation:
DORAs
Off-label anti-histamines, antidepressants, neuroleptics

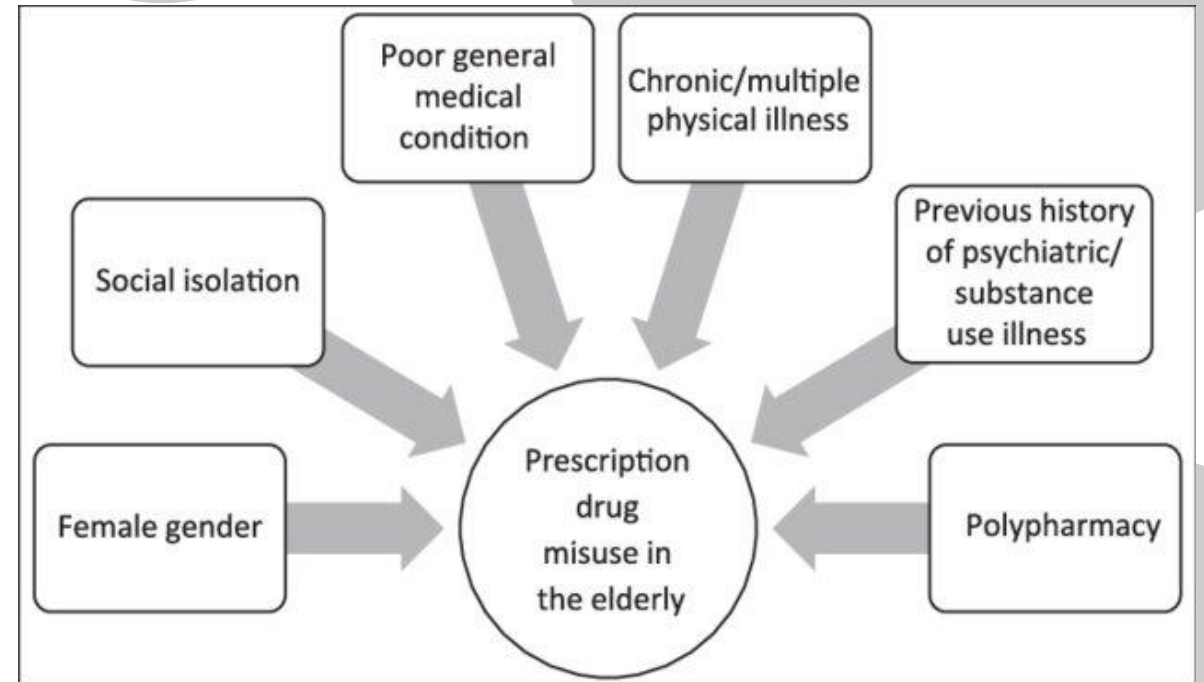
Wake

OFTEN USED OFF LABEL WITH IMPORTANT SEDATIVE EFFECTS

BNST, bed nucleus of the stria terminalis; CeA, central area of the amygdala; dDPMe, dorsal deep mesencephalic nucleus; DR, dorsal raphe; HPA, hypothalamic-pituitary axis; Hy, hypothalamus; ICV, intracerebroventricular; LC, locus coeruleus; LDT, laterodorsal tegmental nuclei; LHA, lateral hypothalamus; NAc, nucleus accumbens; OX1R, orexin receptor type 1; OX2R, orexin receptor type 2; PPT, pedunculopontine nuclei; PVN, paraventricular nucleus; PVT, paraventricular nucleus of the thalamus; SN, substantia nigra; vPAG, ventrolateral periaqueductal gray
Palagini L, and Fagiolini A, *Riv Psichiatr.* 2023;58:249-57.

L'anziano è a rischio di misuso di ipnotici sedativi

By the American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society*. 2015



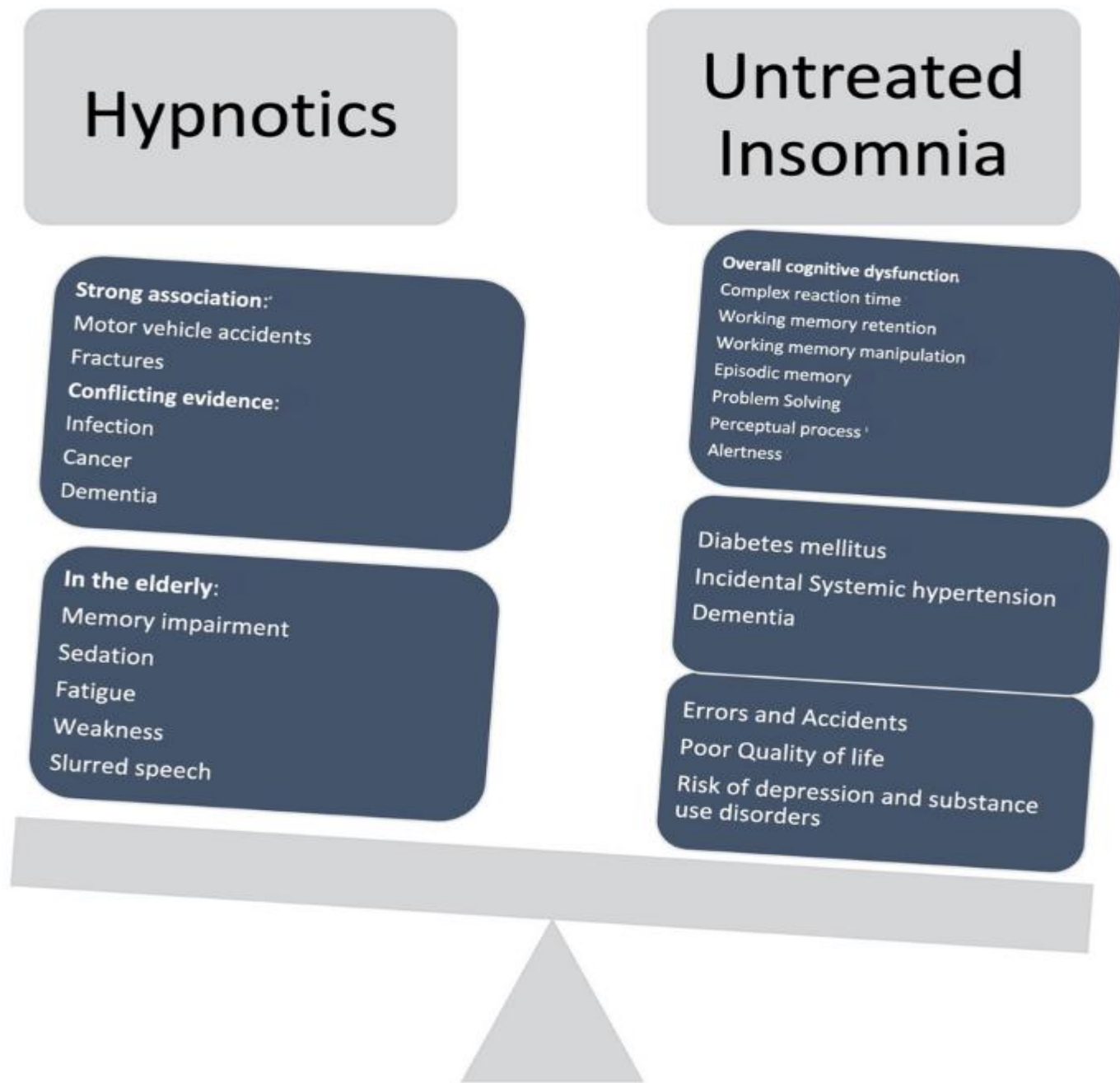
BEST PRACTICES IN SLEEP MEDICINE: RECOMMENDATIONS FROM THE CHOOSING WISELY CAMPAIGN

Recommendation	Sponsoring organization
Do not use benzodiazepines or other sedative-hypnotics in older adults as a first choice for insomnia, agitation, or delirium.	American Geriatrics Society
Avoid the use of hypnotics as primary therapy for chronic insomnia in adults; instead, offer cognitive behavior therapy and reserve medication for adjunctive treatment when necessary.	American Academy of Sleep Medicine
Do not routinely prescribe antipsychotic medications as a first-line intervention for insomnia in adults.	American Psychiatric Association

Source: For more information on the Choosing Wisely Campaign, see <http://www.choosingwisely.org>. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see <http://www.aafp.org/afp/recommendations/search.htm>.

Trattare o non trattare l'insonnia nell'anziano?

Meglio trattare ci sono nuove opzioni terapeutiche



Pharmacological treatment is recommended if CBTi is not effective

The European Insomnia Guidelines 2023



Recommendations for treatment

Dual orexin receptor antagonists

- Short term (≤ 4 weeks) (A)
- Up to 3 months (A)
- Longer term in certain cases (A)

Prolonged-release melatonin

- In patients > 55 years
- Longer term in some cases up to 3 months (B)

BZs and BZRAs

- Short term (≤ 4 weeks) (A)
- Longer term in certain cases (off-label use), either daily or preferably intermittently (B)

Sedative antidepressants

- Short term (≤ 4 weeks) at low doses (off-label use); Contraindications should be carefully considered (B)
- Longer term in certain cases, if without comorbidities: at low doses (off-label use) (B)

Recommendations

(A) Very Strong

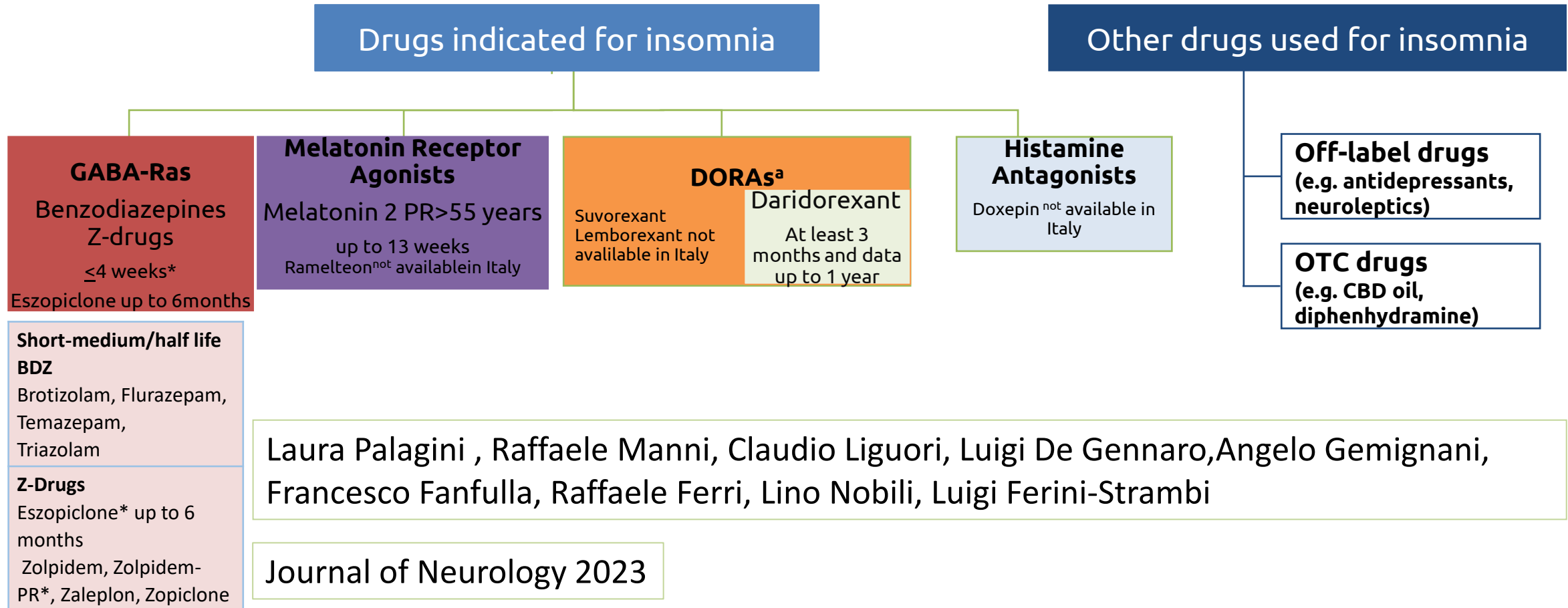
(B) Strong

Not to be used

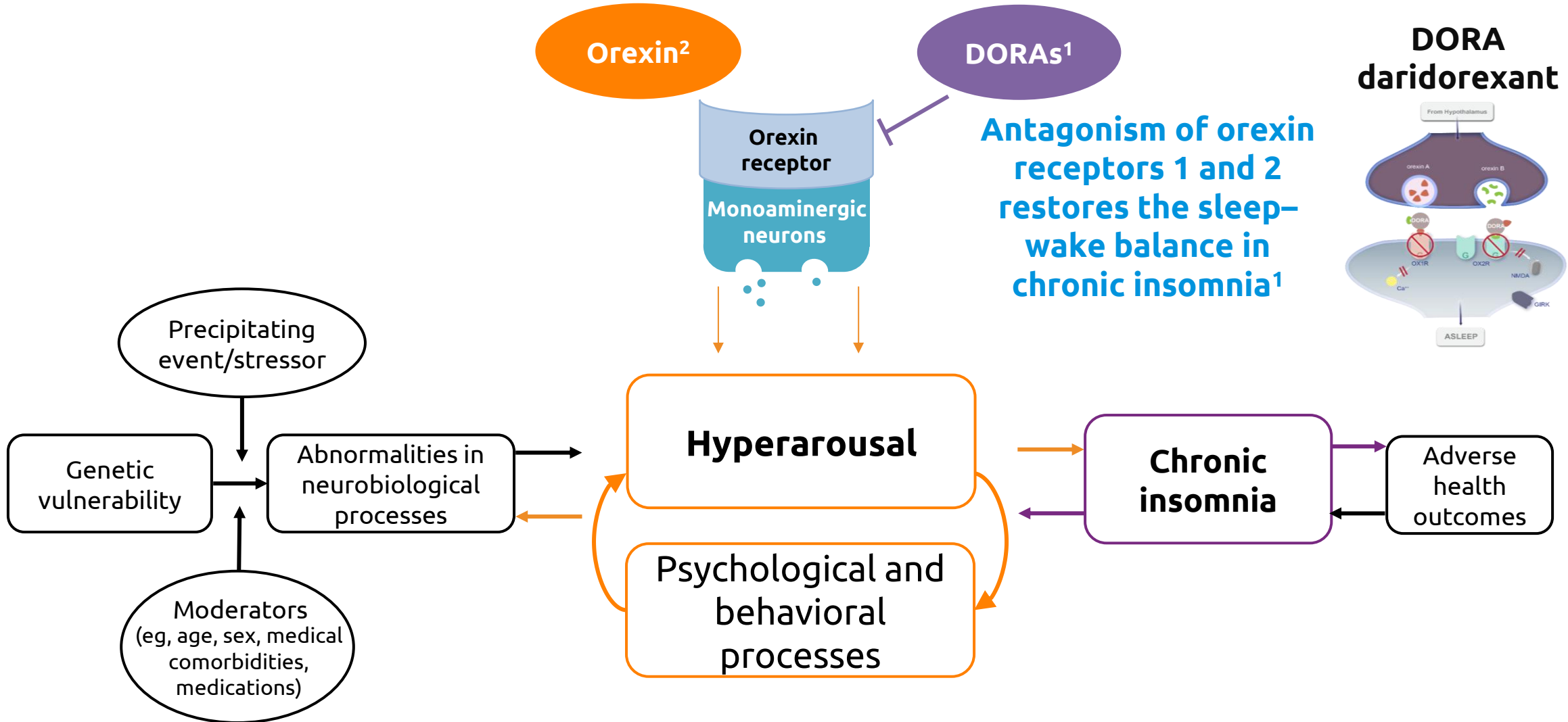
Antihistamines
Antipsychotics
FR Melatonin
Phytotherapeutics
Herbal remedies

Evaluation and Management of Insomnia in the Clinical Practice in Italy: A 2023 Update from the Insomnia Expert Consensus Group

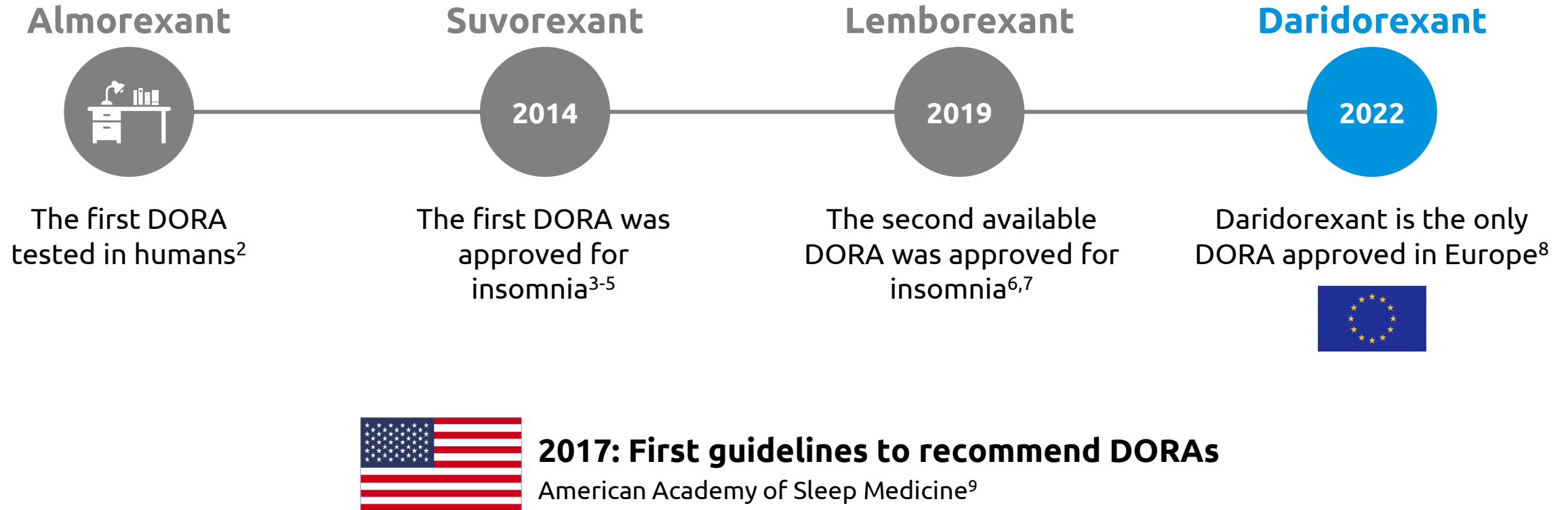
Pharmacotherapy is recommended in patients who still have symptoms despite undergoing CBT-I, or in patients unable to complete CBT-I



Chronic insomnia is characterized by a perpetuating cycle of hyperarousal favoring mental disorders¹⁻³



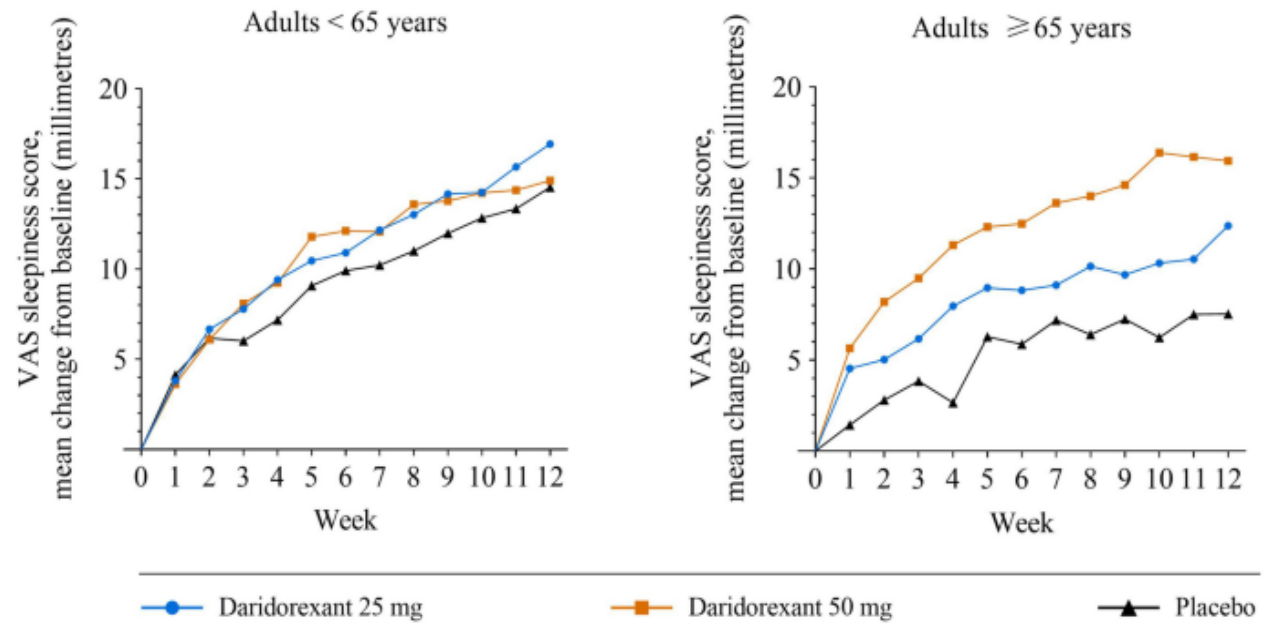
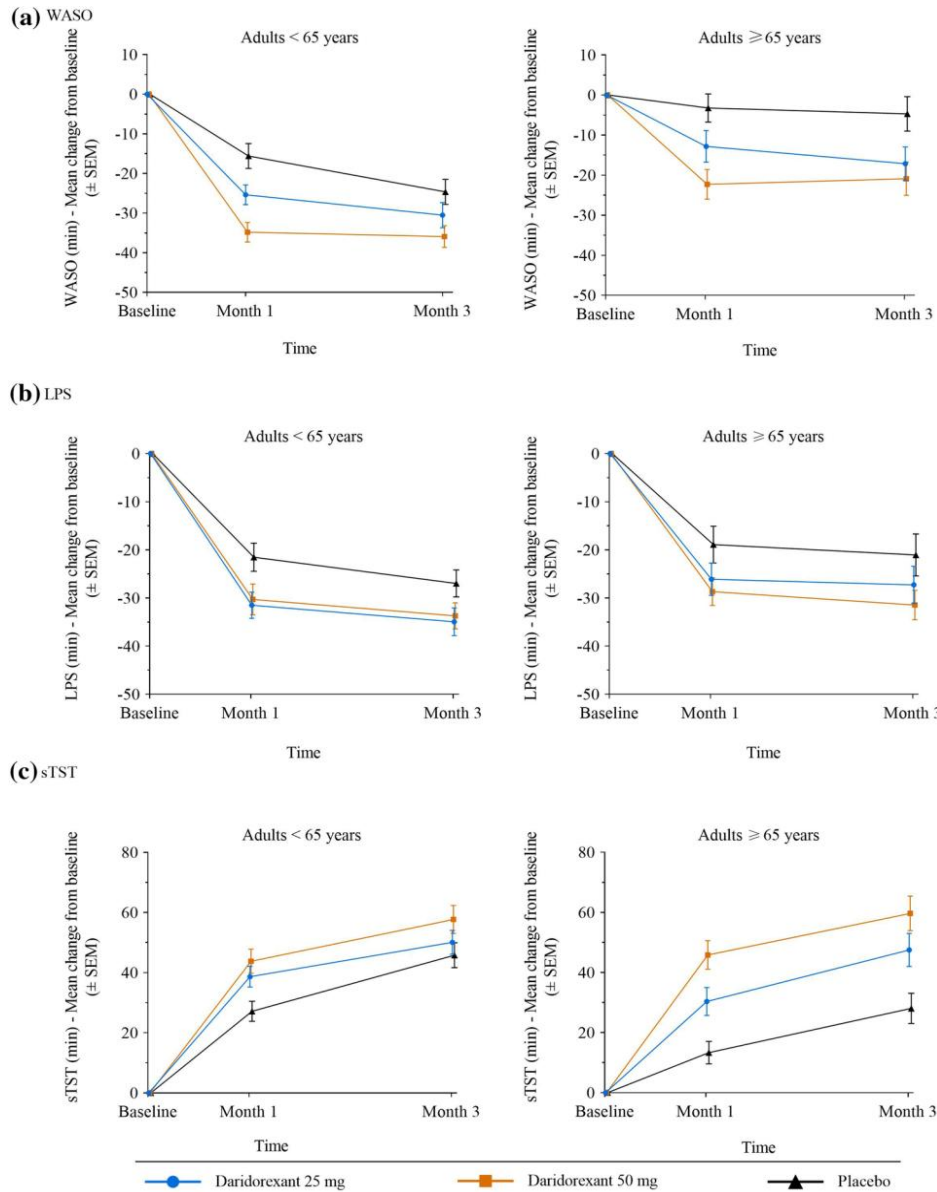
Over 10 years of global experience with DORAs¹



DORA: dual orexin receptor antagonist.

1. Muehlan C, et al. *J Sleep Res.* 2023;32:e13902; 2. Brisbare-Roch C, et al. *Nat Med.* 2007;13:150-5; 3. Suvorexant. Prescribing Information. FDA. 2014; 4. Asai Y, et al. *Drugs R D.* 2019;19:27-46; 5. Suvorexant. Regulatory decision summary. Health Canada. 2018; 6. Scott LJ. *Drugs.* 2020;80:425-32; 7. Lemborexant. Regulatory decision summary. Health Canada. 2019; 8. Riemann D, et al. *J Sleep Res.* 2023;32:e14035; 9. Sateia MJ, et al. *J Clin Sleep Med.* 2017;13:07-349.

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



Daridorexant has a favourable safety and tolerability profile



No evidence of rebound insomnia compared with placebo based on WASO, LPS, and sTST measures during the placebo run-out period*

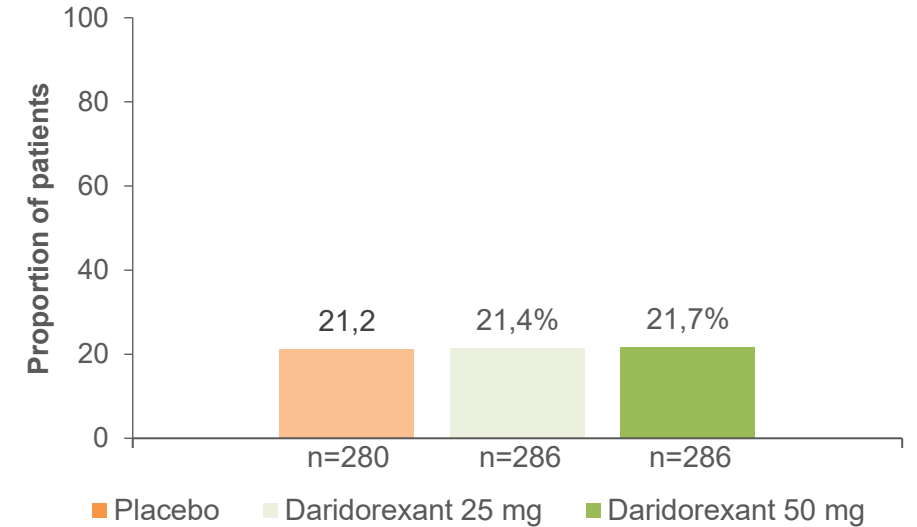


No withdrawal symptoms during the placebo run-out period in Benzodiazepine Withdrawal Symptom Questionnaire



No evidence of TEAEs suggestive of drug abuse potential

sTST negative change from baseline during placebo run-out period



*Comparison between first night of run-out and baseline for WASO and LPS; comparison between the mean value of the 7-day run-out and baseline for sTST. LPS, latency to persistent sleep; sTST, subjective total sleep time; TEAE, treatment-emergent adverse event; WASO, wake after sleep onset. Mignot E, et al. *Lancet Neurol* 2022;21:125–39; Data on file.

Daridorexant demonstrated a favorable safety profile

Severe OSA¹



50 mg administered to patients with severe OSA without insomnia

N = 16

No clinically meaningful difference in

- AHI: -3.74 events/hour
- SpO₂: -0.12 %

- sTST also improved: +32.5 min

No substantial difference observed between OSA severity

Daridorexant does not impair sleep-disorder breathing

Middle of the night²



Patients woken 4 hours after 25 or 50 mg dose

N = 36
5 nights

No difference vs placebo

- Auditory awakening threshold

Minimal difference vs placebo

- Body sway
- Timed up and go test
- Visual verbal learning test

Daridorexant does not reduce ability to operate safely during the night

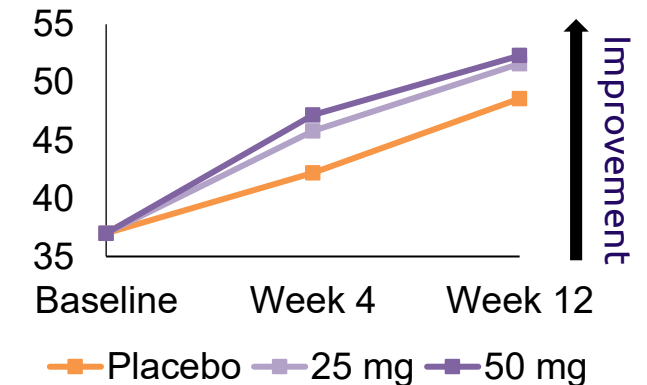
Next morning sleepiness³



Phase 3 *post hoc* analysis

N = 930

Visual analogue scale (VAS)*



Daridorexant improves next morning sleepiness

*Visual analogue scale: scale from 0 (more sleepy) to 100 (less sleepy).

AHI: Apnea/hypopnea index; OSA: obstructive sleep apnea; sTST, self-reported total sleep time.

1. Boof ML, et al. *Sleep Medicine*. 2024;115(Supp1):S380-1; 2. Magliocca M, et al. *J Psychopharmacol*. 2024; 6:2698811241293997; 3. Mignot E, et al. *Lancet Neurol*. 2022;21:125-39.

NUOVI DATI

Daridorexant 50 mg si è dimostrato efficace e sicuro anche nei pazienti con insonnia cronica e nicturia

Figure 2. Mean change from baseline in sTST

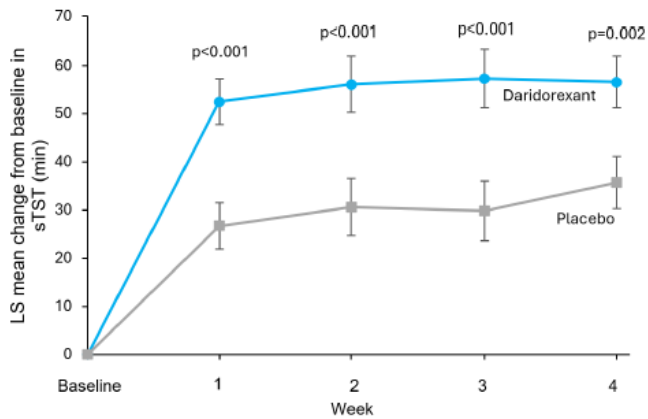


Figure 4. Mean change in the number of voids per night

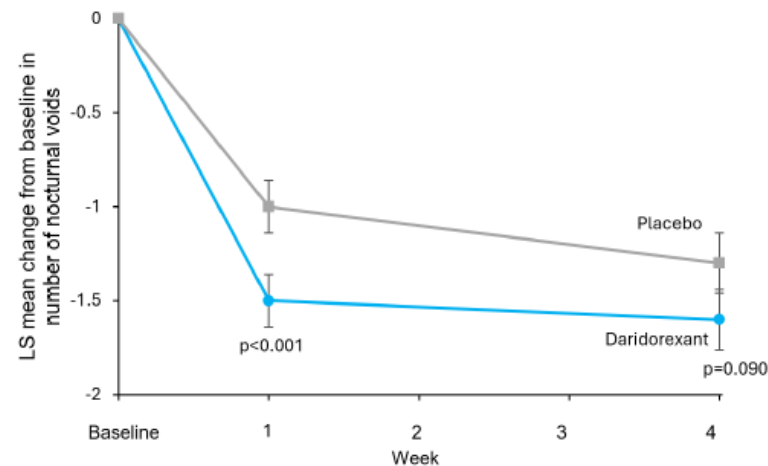


Table 2. Summary of adverse events

	Daridorexant N=60	Placebo N=60	Total N=60
Patients with ≥ 1 AE, n (%)	15 (25%)	10 (17%)	22 (37%)
AEs in ≥ 1 patient, n (%)			
Dry mouth	3 (5%)	2 (3.4)	4 (7%)
Nausea	2 (3%)	0	2 (3%)
Fatigue	3 (5%)	0	3 (5%)
Hangover	2 (3%)	0	2 (3%)
AEs of special interest, n (%)			
Fall	0	1 (2%)	1 (2%)
Incontinence	0	1 (2%)	1 (2%)



Daridorexant significantly improved insomnia symptoms, mood anxiety and executive functions in patients with insomnia disorder

+++

Patients attending the Insomnia Clinic, Psychiatric Clinic, University Hospital Pisa in Italy, treated December 2023 to December 2024 (N = 90)

90 patients

Gender: Female: 48%; Male: 52%

Age: Mean 53 ± 13.6 years

Comorbidities, n (%)

Unipolar/bipolar depression: 41 (46%)

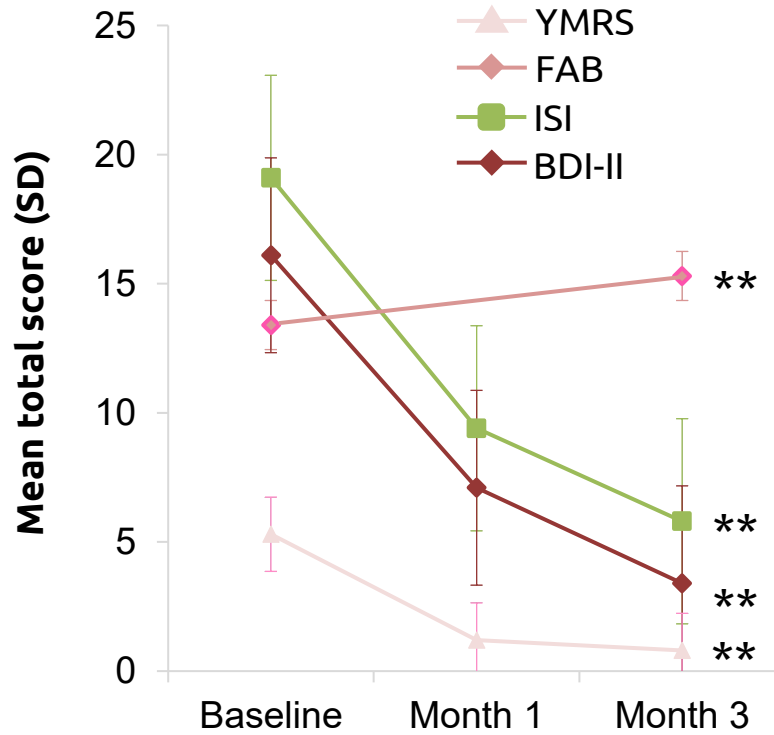
Sedative hypnotic use or misuse: 46 (51%)

Best prediction of improvements in:

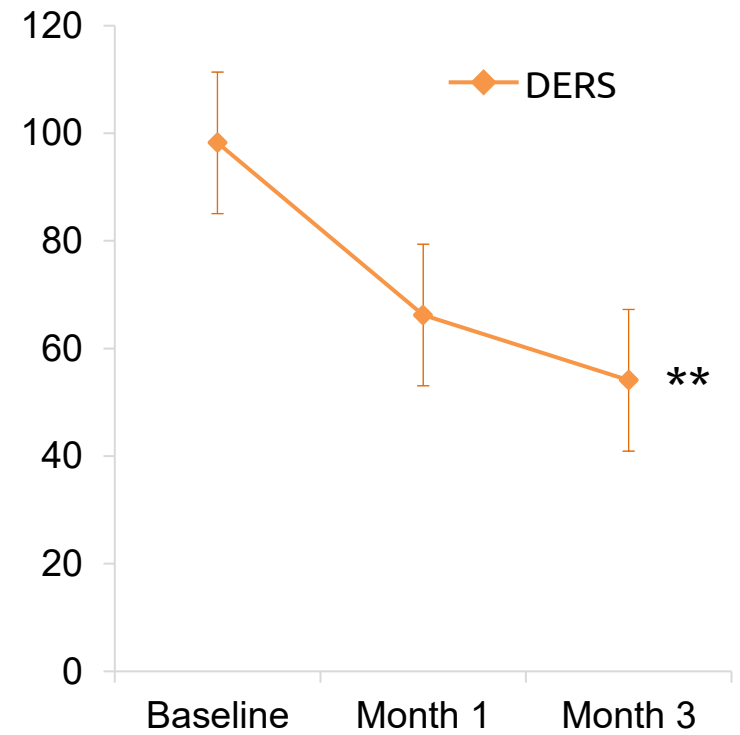
Depressive symptoms by **DERS** and **ISI** improvement

Mixed symptoms by **ISI** and **FAB** improvements

Insomnia severity and mood & anxiety measures



Emotional regulation measure



Analysis of variance; ** $p < 0.001$.

BDI, Beck Depression Inventory; DERS, Difficulties in Emotional Regulation Scale; FAB, Frontal Assessment Battery; ISI, Insomnia Severity Index; SD, standard deviation; YMRS, Young Mania Rating Scale.

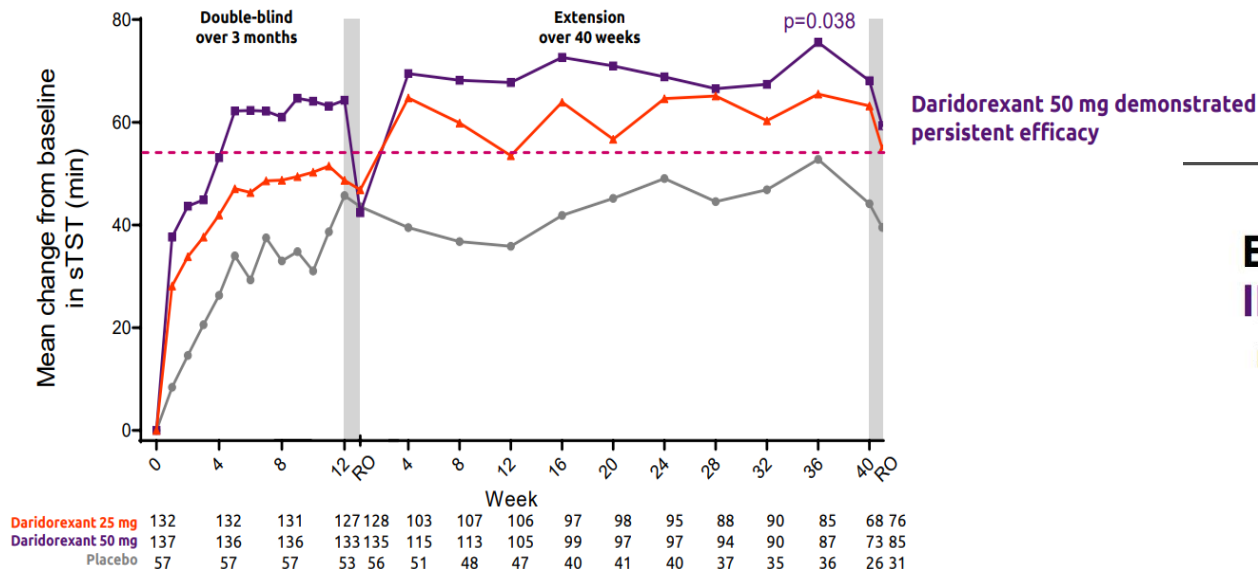
Palagini L, et al. *J Sleep Res*. 2025; doi: 10.1111/jsr.70158. Online ahead of print.



Daridorexant significantly improved sleep and daytime outcomes in patients with chronic insomnia disorder in the long term

Extension study: Effect on sleep (sTST)

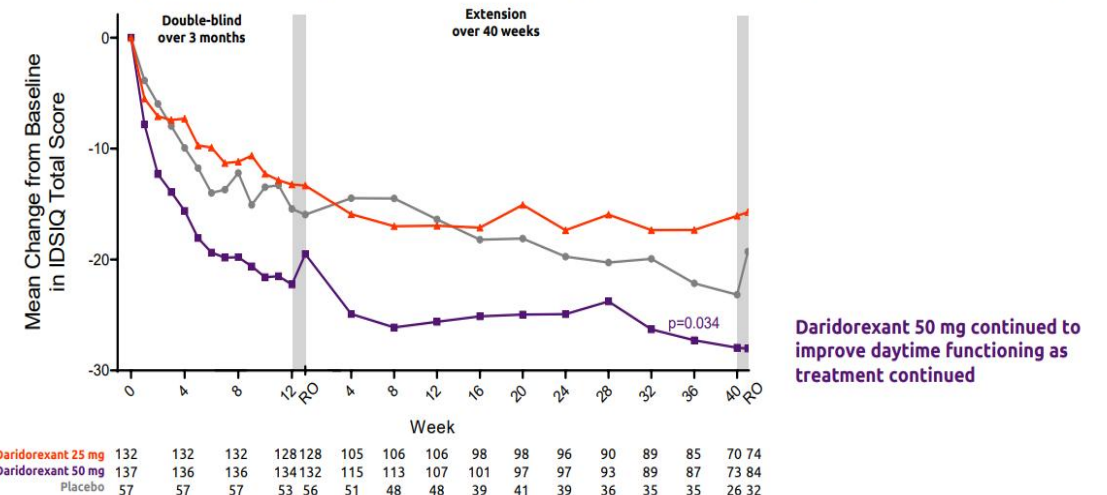
Post hoc analysis: Mean change from baseline in sTST in Study 1 and extension study



*P-value versus placebo, Daridorexant 50 mg; n=137, Placebo; n=57. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; min, minute; RO, run-out; sTST, self-reported total sleep time.

Extension study: Daytime functioning – IDSIQ total score

Post hoc analysis: Mean change from baseline in IDSIQ total score in Study 1 and extension study



Baseline refers to the baseline of the confirmatory study 1. RO, runout; sTST, subjective total sleep time. Kunz D, et al. CNS Drugs. 2023;37:93-106.



Daridorexant significantly improved insomnia and mood symptoms for up to 24 months

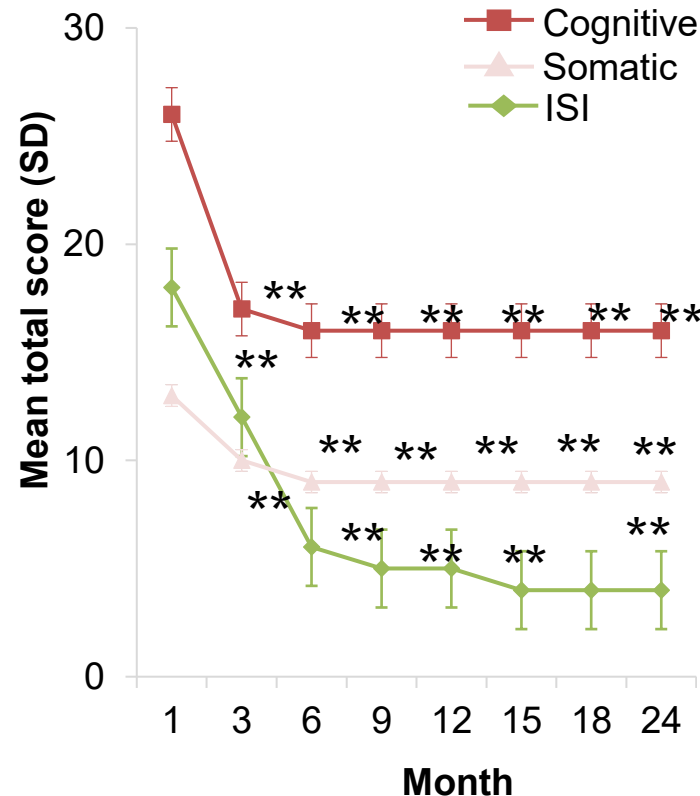
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Patients attending the Insomnia Clinic, Psychiatric Clinic, University Hospital Pisa in Italy, treated February 2022 to February 2025 (N = 60)

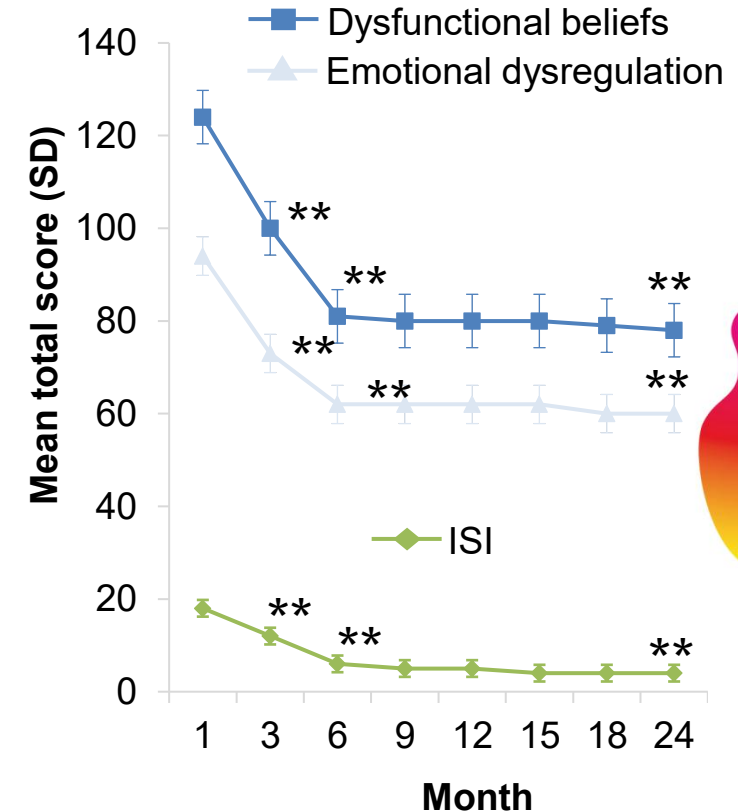
Study characteristics

Study design	Naturalistic observational, uncontrolled
Female (%)	60 %
Mean age (years ± SD)	53 ± 12.6
Observation period	From 6 months to 24 months
Patients	N = 60
Daridorexant dose	50 mg
Discontinued after 12 months*	N = 10
Psychiatric comorbidity	N = 23

Arousal measures



Emotional regulation

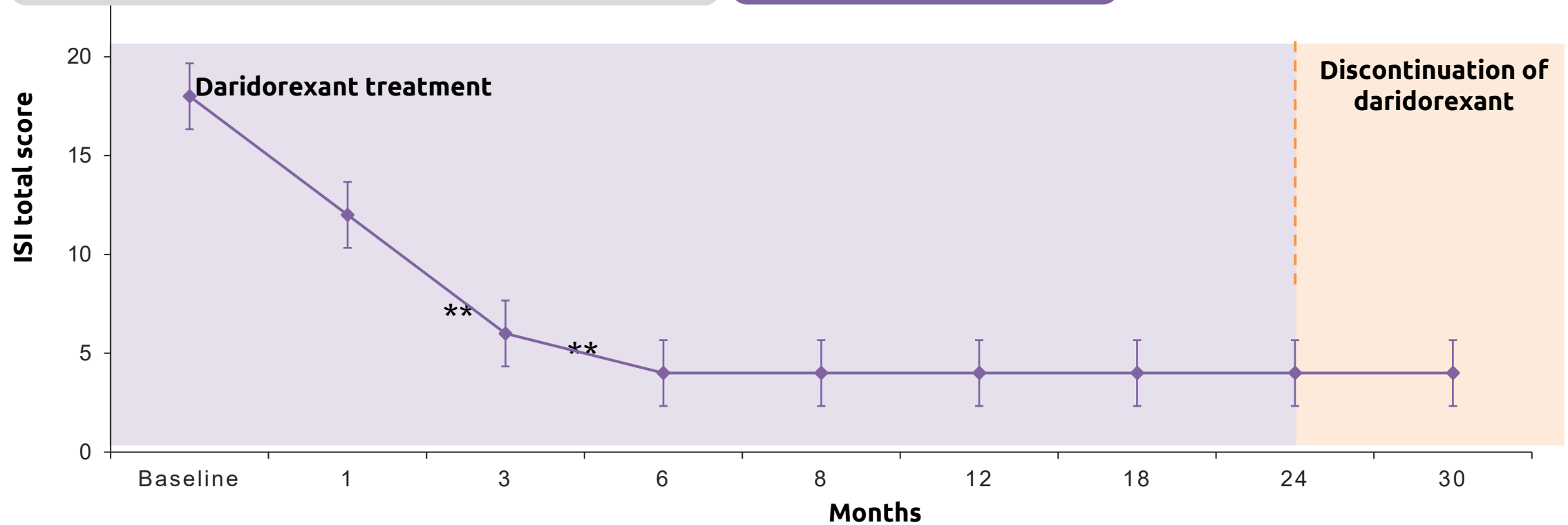


No relapse after discontinuation: preliminary data

N = 20

Gender: Female: 70%; Male: 30%
Age: Mean 55.2 ± 12.2 years

60% with psychiatric comorbidity



*Pseudonym of real case. ** $p < 0.001$.

ISI, insomnia severity index.

Slide courtesy of Laura Palagini.

Insomnia in older adults: A review of treatment options 2023

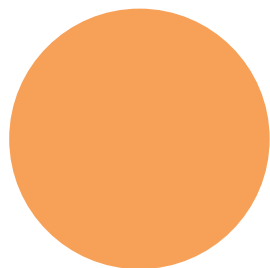
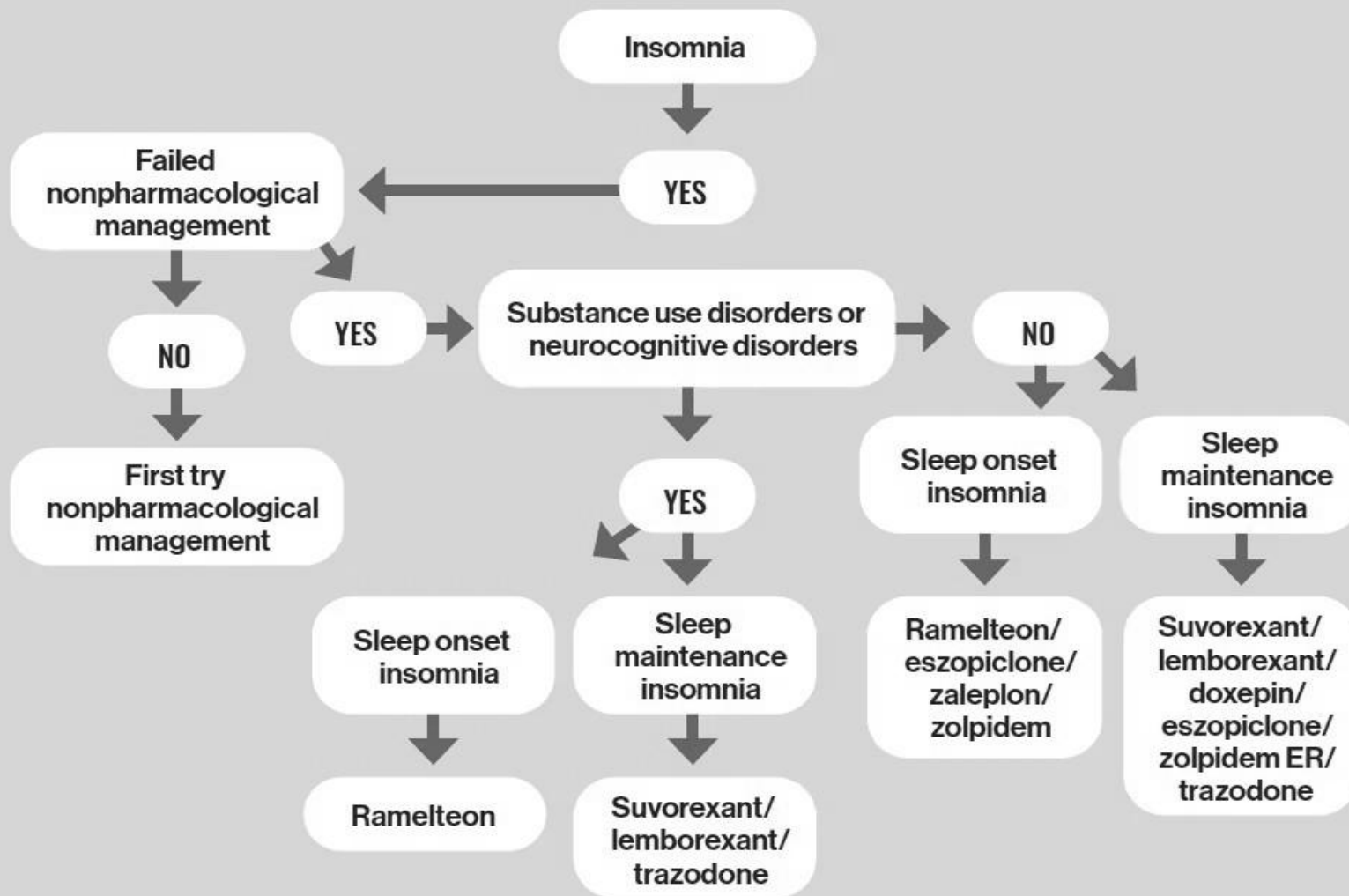
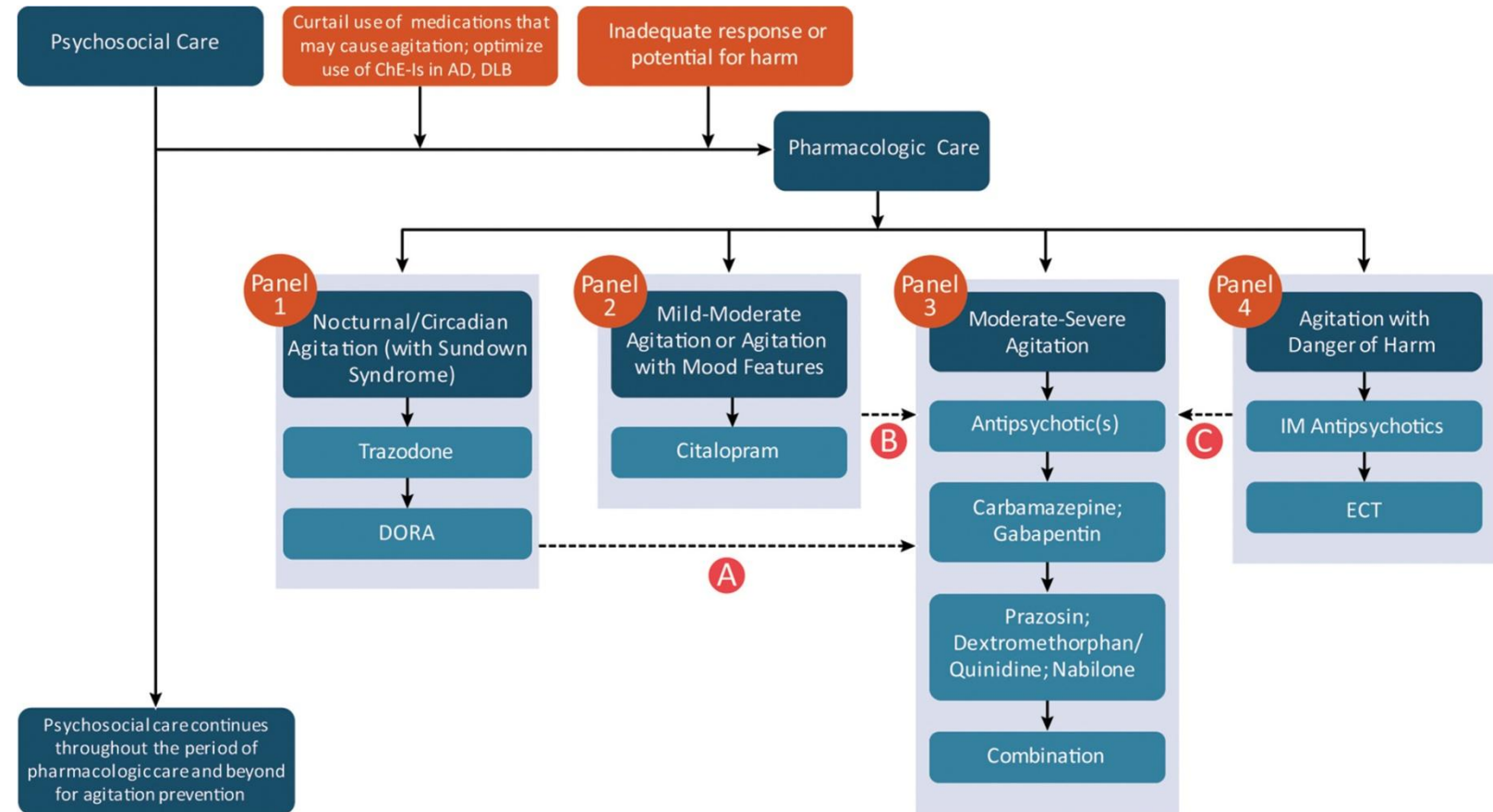


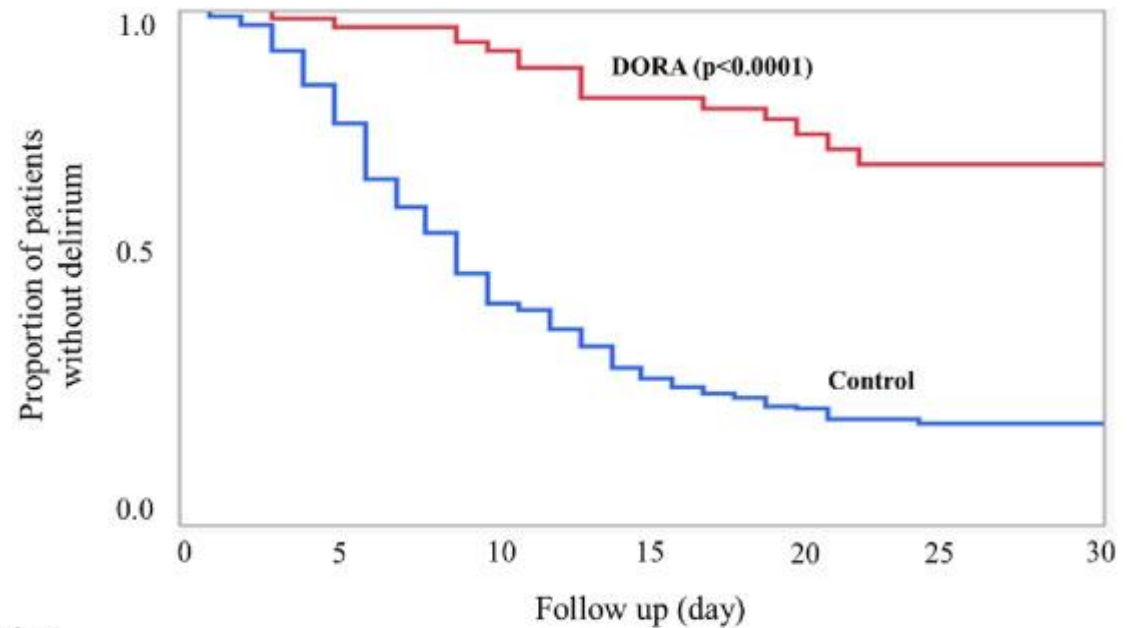
FIGURE 3. Pathways for Choosing Treatment for Insomnia in Older Adults^{21,34,39-41}



Reduction and prevention of agitation in persons with neurocognitive disorders: an international psychogeriatric association consensus algorithm 2024



Evaluation of the delirium preventive effect of dual orexin receptor antagonist (DORA) in critically ill adult patients requiring ventilation with tracheal intubation at an advanced emergency center: A single-center, retrospective, observational study



Patients at risk, n

DORA	67	65	57	43	27	25	19
Control	230	191	96	54	30	23	18

DARIDOREXANT



ETÀ
ANZIANO



POLYPHARMACY
SI COMBINA CON ALTRI FARMACI



ALMENO 3 MESI E
FINO AD 1 E 2 ANNI

Daridorexant and insomnia in the clinical practice. A Nominal Group Technique consensus study among Italian sleep and insomnia experts.

Luigi Ferini Strambi, Dario Arnaldi, Enrica Bonanni, Alessandro Cicolin, Gian Luigi Gigli, Claudio Liguori, Carolina Lombardi, Liborio Parrino, Federica Provini, Monica Puligheddu, Andrea Romigi, Rosalia Silvestri, Laura Palagini.

- Daridorexant, via its dual orexin receptor antagonism, may address insomnia without increasing sedation, making **it suitable for a broad patient profile**, including complex patients, such as the elderly and those with comorbid conditions.
- While it avoids common GABAergic-related side effects like tolerance and dependence, daridorexant was recognized as **particularly effective in long-term use**, showing benefits for sleep and daytime functioning.
- The consensus underscores **the importance of a multidisciplinary approach**, combining pharmacological and psychosocial interventions to optimize outcomes.

Proposta ufficiale di collaborazione per l'adattamento delle linee guida italiane del trattamento dell'insonnia nel paziente anziano

Evaluation and Management of Insomnia in the Clinical Practice in the elderly: A 2025 Update from the Insomnia Expert Consensus Group



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