Nuove prospettive di gestione dell'insonnia cronica

ANDREA ROMIGI
Centro di Medicina del Sonno
IRCCS Neuromed Pozzilli (IS)

Outline

European and AASM guidelines

CBTi

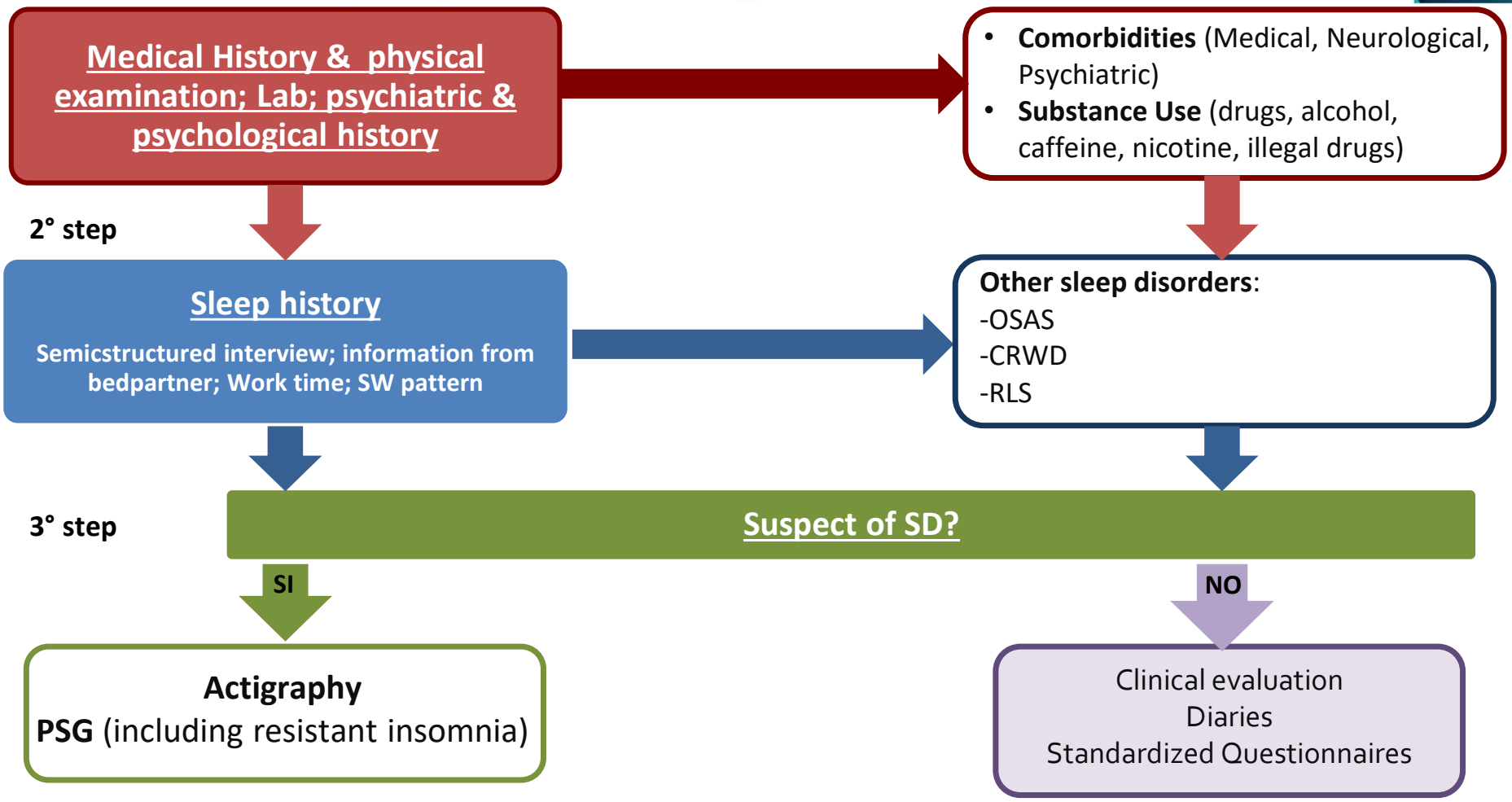
Acute treatment: BDZ, Z-drug

- Long term effects/risks

DORA

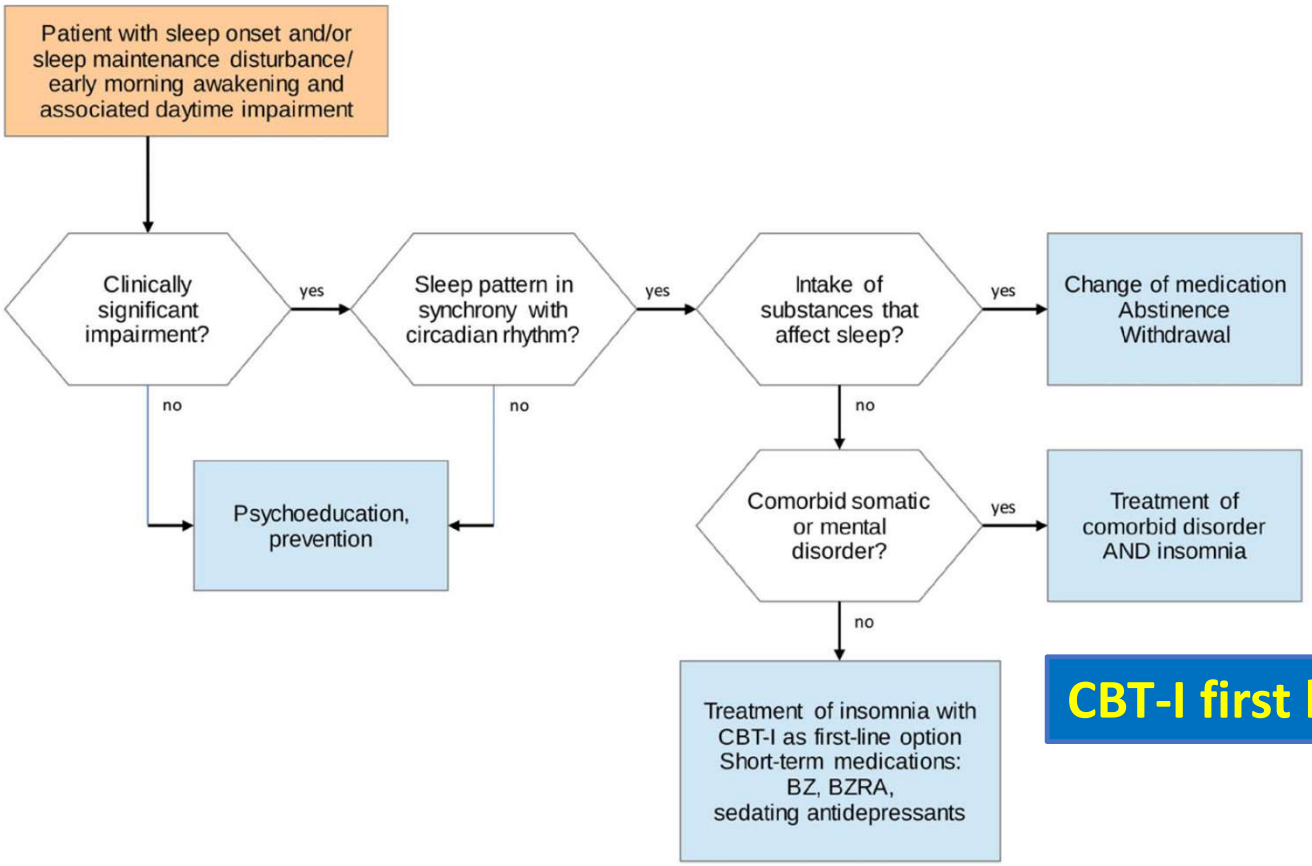
- Orexin receptors and pharmacodynamic
- Flip-flop model
- FDA/EMA Approved DORA
- Daridorexant:
  - phase 3 data
  - Special populations: long duration; elderly

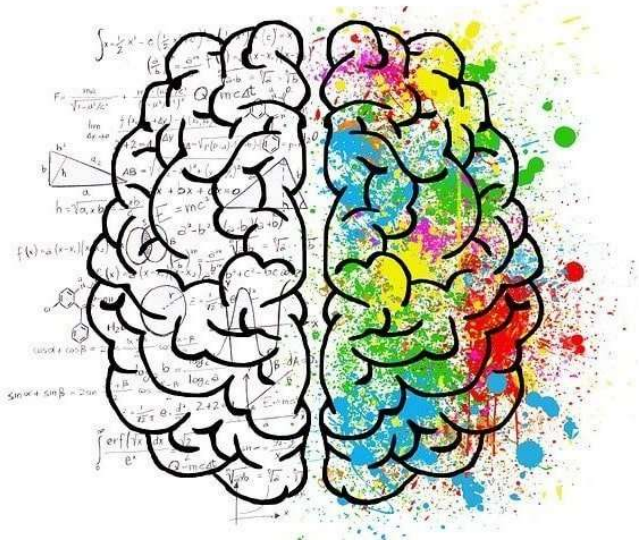
European guideline for the diagnosis and treatment of insomnia



European guideline for the diagnosis and treatment of insomnia

Clinical algorithm for the diagnosis and treatment of insomnia





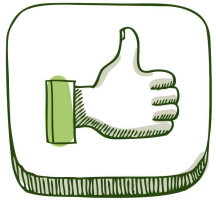
CBT-I first line treatment

Non Pharmacological Management of insomnia: CBT-I …

«an old-new strategy»

CBT-I

PRO



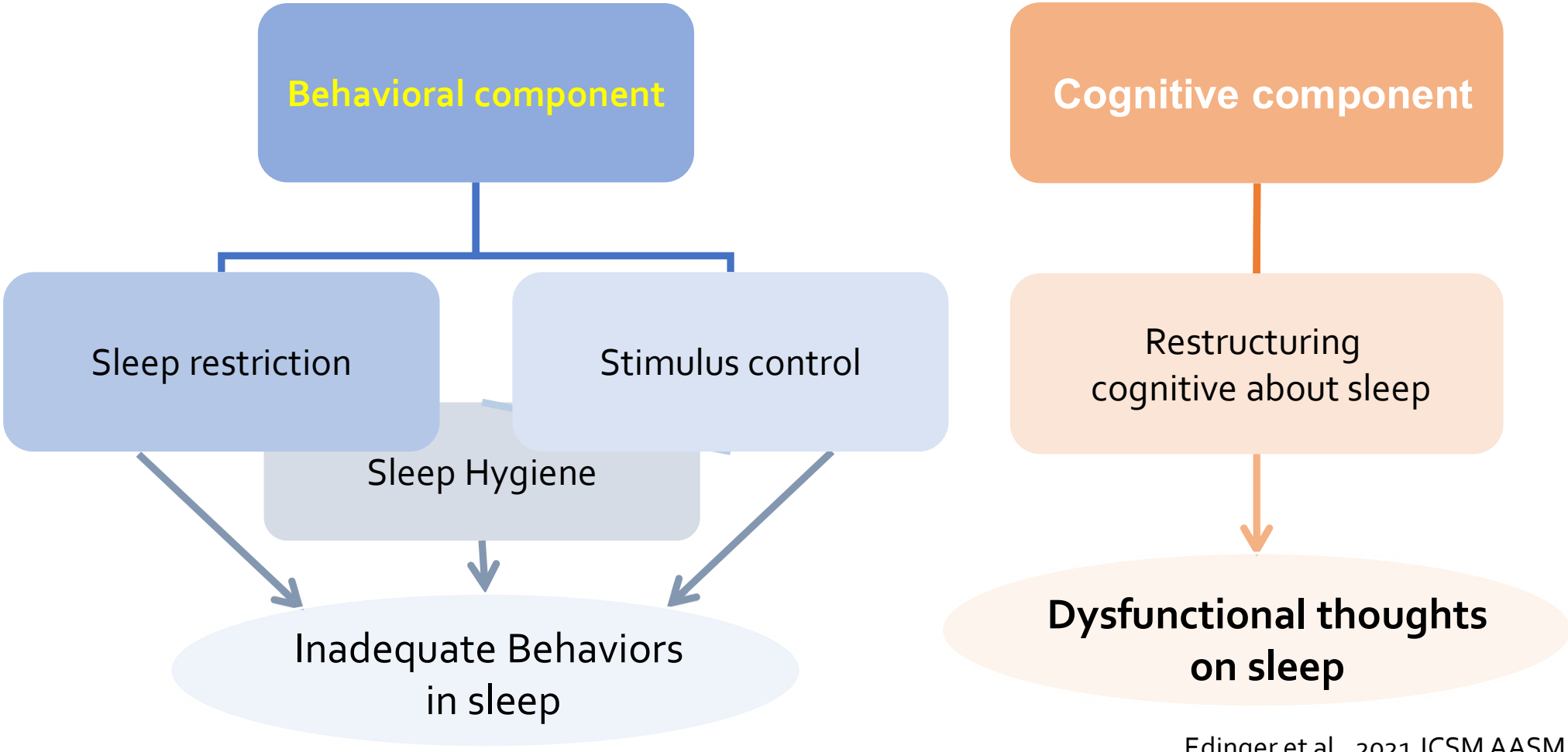
- efficacy
- Few contraindications and side effects
- Long term efficacy

CONS

- Scarce skilled & qualified professionals
- Accessibility
- not satisfactory results (19-26%)
- Sleep restriction & stimulus control transient discomfort

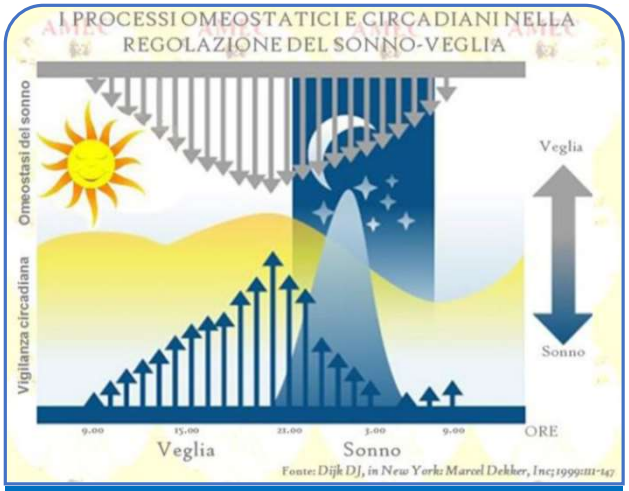
Edinger et al., 2021 JCSM AASM Guideline
Wu et al., 2015 JAMA
Baglioni et al., 2019 JSR Eur Guidelines CBTi

Cognitive Behavioral Treatment of Insomnia (CBT-I)



Edinger et al., 2021 JCSM AASM Guideline
Baglioni et al., 2019 JSR Eur Guidelines CBTi

CBT-I Behavioral Component



Sleep Restriction

shorten the amount of time spent in bed in order to **consolidate sleep**

Beware to
- high risk works
- Predisposed to hypomania or mania
- Refractory epilepsy

AASM 2021: **COND** USE a single-component

Stimulus control

to strengthen the bed as a cue for sleep and weaken it as a cue for wakefulness

Beware to
- high risk of falls
- Using sedative-hypnotics
- Refractory epilepsy

AASM 2021: **COND** USE a single-component

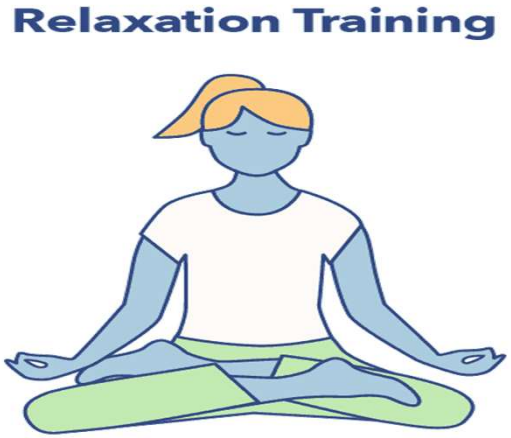
Sleep Hygiene

A set of general recommendations about lifestyle and environmental factors

No contraindications

AASM 2021: NOT USE a single-component

CBT-I Cognitive Component

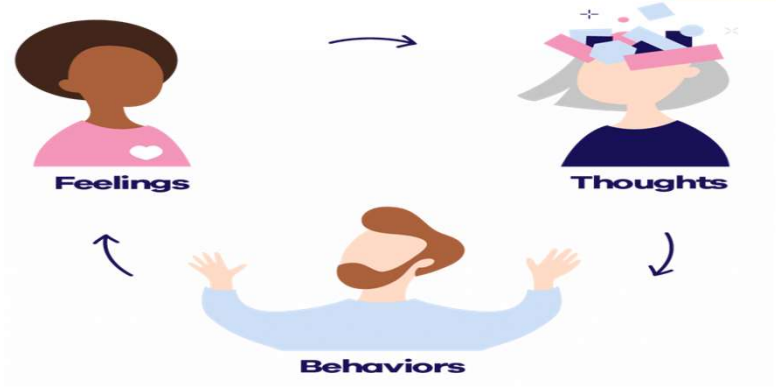


Relaxation (C&B)

A set of methods that aim to reduce somatic or cognitive hyperarousal

muscle relaxation,
autogenic training,
imagery training, meditation

AASM 2021: **COND** USE a single-component



Cognitive control

to reduce dysfunctional beliefs, attitudes, concerns, and false beliefs about the cause of insomnia and about the inability to sleep

Beware to

- high risk of falls
- Using sedative-hypnotics
- Refractory epilepsy

AASM 2021: **COND** USE a single-component

Sleep Medicine Reviews 48 (2019) 101208

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

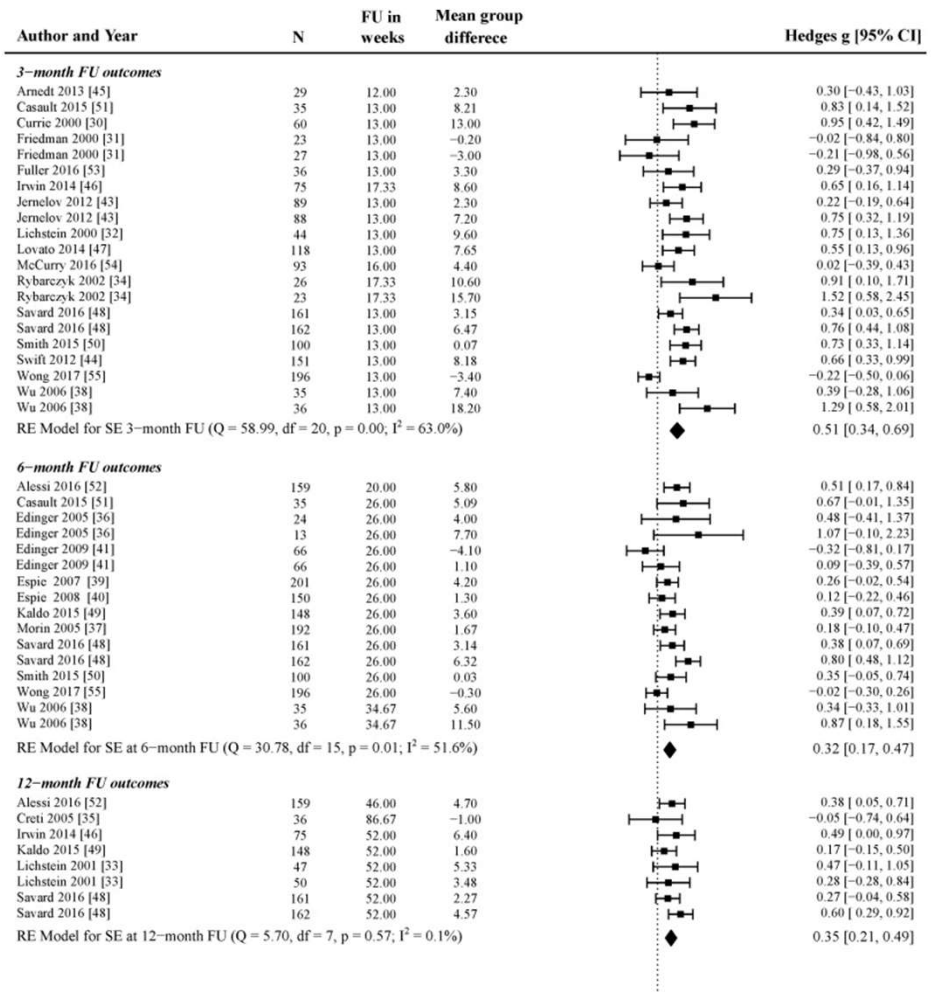
Cognitive behavioral therapy for insomnia: A meta-analysis of long-term effects in controlled studies

Tanja van der Zweerde [a, *], Lampros Bisdounis [b], Simon D. Kyle [c], Jaap Lancee [b, d], Annemieke van Straten [a]

Efficacy

- Lower **Insomnia Severity Index**
- Lower **Sleep Onset Latency** (SOL)
- Higher **Sleep efficiency** (SE)

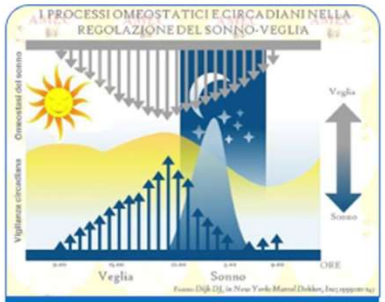
LONG TERM (3-6-12 months)



Author and Year	N	FU in weeks	Mean group differece	Hedges g [95% CI]
3−month FU outcomes				
Arnedt 2013 [45]	29	12.00	2.30	0.30 [−0.43, 1.03]
Casault 2015 [51]	35	13.00	8.21	0.83 [0.14, 1.52]
Currie 2000 [30]	60	13.00	13.00	0.95 [0.42, 1.49]
Friedman 2000 [31]	23	13.00	−0.20	−0.02 [−0.84, 0.80]
Friedman 2000 [31]	27	13.00	−3.00	−0.21 [−0.98, 0.56]
Fuller 2016 [53]	36	13.00	3.30	0.29 [−0.37, 0.94]
Irwin 2014 [46]	75	17.33	8.60	0.65 [0.16, 1.14]
Jernelov 2012 [43]	89	13.00	2.30	0.22 [−0.19, 0.64]
Jernelov 2012 [43]	88	13.00	7.20	0.75 [0.32, 1.19]
Lichstein 2000 [32]	44	13.00	9.60	0.75 [0.13, 1.36]
Lovato 2014 [47]	118	13.00	7.65	0.55 [0.13, 0.96]
McCurry 2016 [54]	93	16.00	4.40	0.02 [−0.39, 0.43]
Rybarczyk 2002 [34]	26	17.33	10.60	0.91 [0.10, 1.71]
Rybarczyk 2002 [34]	23	17.33	15.70	1.52 [0.58, 2.45]
Savard 2016 [48]	161	13.00	3.15	0.34 [0.03, 0.65]
Savard 2016 [48]	162	13.00	6.47	0.76 [0.44, 1.08]
Smith 2015 [50]	100	13.00	0.07	0.73 [0.33, 1.14]
Swift 2012 [44]	151	13.00	8.18	0.66 [0.33, 0.99]
Wong 2017 [55]	196	13.00	−3.40	−0.22 [−0.50, 0.06]
Wu 2006 [38]	35	13.00	7.40	0.39 [−0.28, 1.06]
Wu 2006 [38]	36	13.00	18.20	1.29 [0.58, 2.01]
RE Model for SE 3−month FU (Q = 58.99, df = 20, p = 0.00; I^2 = 63.0%)				0.51 [0.34, 0.69]
6−month FU outcomes				
Alessi 2016 [52]	159	20.00	5.80	0.51 [0.17, 0.84]
Casault 2015 [51]	35	26.00	5.09	0.67 [−0.01, 1.35]
Edinger 2005 [36]	24	26.00	4.00	0.48 [−0.41, 1.37]
Edinger 2005 [36]	13	26.00	7.70	1.07 [−0.10, 2.23]
Edinger 2009 [41]	66	26.00	−4.10	−0.32 [−0.81, 0.17]
Edinger 2009 [41]	66	26.00	1.10	0.09 [−0.39, 0.57]
Espie 2007 [39]	201	26.00	4.20	0.26 [−0.02, 0.54]
Espie 2008 [40]	150	26.00	1.30	0.12 [−0.22, 0.46]
Kaldo 2015 [49]	148	26.00	3.60	0.39 [0.07, 0.72]
Morin 2005 [37]	192	26.00	1.67	0.18 [−0.10, 0.47]
Savard 2016 [48]	161	26.00	3.14	0.38 [0.07, 0.69]
Savard 2016 [48]	162	26.00	6.32	0.80 [0.48, 1.12]
Smith 2015 [50]	100	26.00	0.03	0.35 [−0.05, 0.74]
Wong 2017 [55]	196	26.00	−0.30	−0.02 [−0.30, 0.26]
Wu 2006 [38]	35	34.67	5.60	0.34 [−0.33, 1.01]
Wu 2006 [38]	36	34.67	11.50	0.87 [0.18, 1.55]
RE Model for SE at 6−month FU (Q = 30.78, df = 15, p = 0.01; I^2 = 51.6%)				0.32 [0.17, 0.47]
12−month FU outcomes				
Alessi 2016 [52]	159	46.00	4.70	0.38 [0.05, 0.71]
Creti 2005 [35]	36	86.67	−1.00	−0.05 [−0.74, 0.64]
Irwin 2014 [46]	75	52.00	6.40	0.49 [0.00, 0.97]
Kaldo 2015 [49]	148	52.00	1.60	0.17 [−0.15, 0.50]
Lichstein 2001 [33]	47	52.00	5.33	0.47 [−0.11, 1.05]
Lichstein 2001 [33]	50	52.00	3.48	0.28 [−0.28, 0.84]
Savard 2016 [48]	161	52.00	2.27	0.27 [−0.04, 0.58]
Savard 2016 [48]	162	52.00	4.57	0.60 [0.29, 0.92]
RE Model for SE at 12−month FU (Q = 5.70, df = 7, p = 0.57; I^2 = 0.1%)				0.35 [0.21, 0.49]

"although effects decline over time, CBT-I produces clinically significant effects that last up to a year after therapy"

Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline



Sleep Restriction


Stimulus control

Sleep Hygiene

Relaxation (C&B)

Cognitive control

1. We recommend that clinicians use multicomponent cognitive behavioral therapy for insomnia for the treatment of chronic insomnia disorder in adults. (STRONG)
2. We suggest that clinicians use multicomponent brief therapies for insomnia for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)

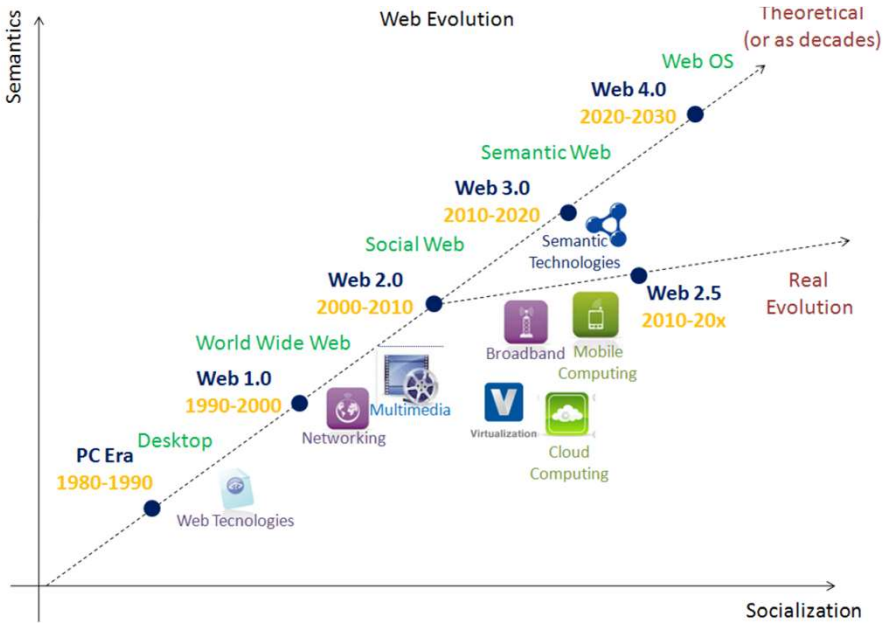
Patient Population*
Patients with insomnia and no comorbidities
Patients with insomnia and psychiatric comorbidities
Patients with insomnia and medical comorbidities

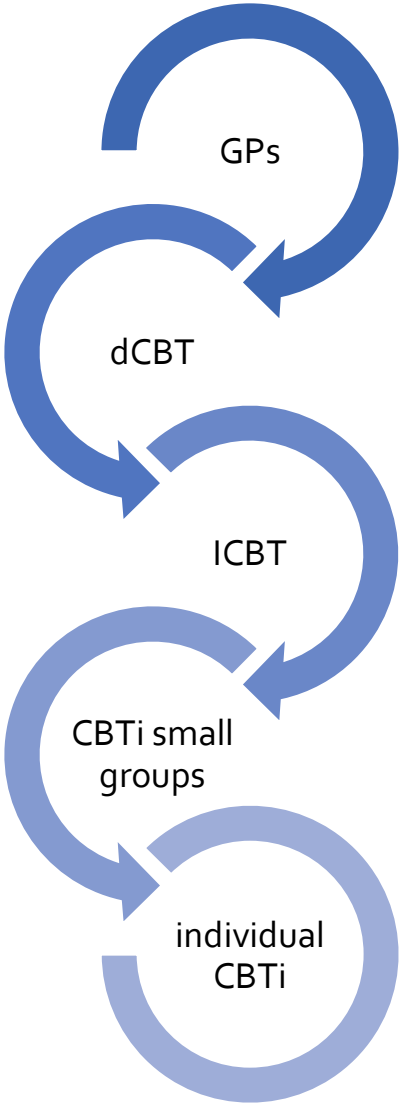
Brief therapies for insomnia (BTIs)	Multicomponent	BTIs include abbreviated versions of CBT-I (typically 1–4 sessions) emphasizing the behavioral components. BTIs typically consist of education about sleep regulation, factors that influence sleep, and behaviors that promote or interfere with sleep, along with a tailored behavioral prescription based on stimulus control and sleep restriction therapy and on information typically derived from a pretreatment sleep diary. Some therapies include brief relaxation or cognitive therapy elements.

Edinger et al., 2021 JCSM AASM Guideline

…BACK to the future…

…new perspective…





An evidence-based stepped-care model for CBT-I

Baglioni et al., 2019 JSR Eur Guidelines CBTi

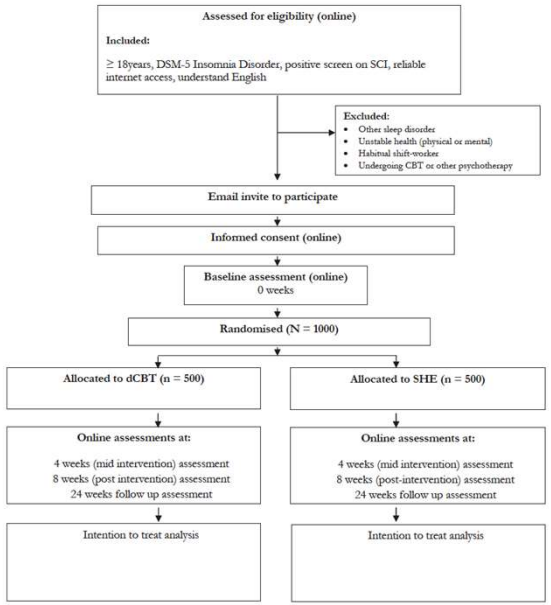
JAMA Psychiatry | Original Investigation

Effect of Digital Cognitive Behavioral Therapy for Insomnia on Health, Psychological Well-being, and Sleep-Related Quality of Life: A Randomized Clinical Trial

Colin A. Espie, PhD; Richard Emsley, PhD; Simon D. Kyle, PhD; Christopher Gordon, PhD; Christopher L. Drake, PhD; A. Niroshan Siriwardena, PhD; John Cape, PhD; Jason C. Ong, PhD; Bryony Sheaves, DClinPsy; Russell Foster, PhD; Daniel Freeman, PhD; Joan Costa-Font, PhD; Antonia Marsden, PhD; Annemarie I. Luik, PhD

Table 2. Effects of Digital Cognitive Behavioral Therapy vs Sleep Hygiene Education on Primary Outcomes: Physical Health, Psychological Well-being, Sleep-Related Quality of Life, and Insomnia

	Unadjusted, Mean (SD)				
Assessment[a]	SHE + TAU	dCBT + TAU	Adjusted Difference (95% CI)	Cohen *d*	*P* Value
PROMIS-10					
Week 4	32.52 (6.05)	33.84 (6.49)	0.90 (0.40 to 1.40)	0.16	<.001
Week 8	32.92 (6.18)	35.08 (6.65)	1.76 (1.24 to 2.28)	0.31	<.001
Week 24	33.10 (6.10)	35.24 (6.88)	1.76 (1.22 to 2.30)	0.31	<.001
WEMWBS					
Week 4	44.72 (8.21)	46.03 (8.55)	1.04 (0.28 to 1.80)	0.13	.007
Week 8	45.16 (8.77)	48.12 (8.82)	2.68 (1.89 to 3.47)	0.35	<.001
Week 24	45.31 (8.89)	48.62 (9.02)	2.95 (2.13 to 3.76)	0.38	<.001
GSII[b]					
Week 4	69.80 (23.64)	60.69 (26.20)	−8.76 (−11.83 to −5.69)	−0.69	<.001
Week 8	65.68 (25.86)	46.78 (29.90)	−17.60 (−20.81 to −14.39)	−1.38	<.001
Week 24	63.33 (27.26)	43.78 (31.25)	−18.72 (−22.04 to −15.41)	−1.46	<.001



6 sessions typically lasting 20 minutes each, and participants had access to the intervention for up to 12 weeks

*«dCBT is **effective** in improving **functional health**, **psychological well-being**, and **sleep-related QoL** in people reporting insomnia symptoms.*
A reduction in insomnia symptoms mediates these improvements»

Sleep Medicine Reviews 61 (2022) 101567

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Comparative efficacy of digital cognitive behavioral therapy for insomnia: A systematic review and network meta-analysis

Faizul Hasan [a], Yu-Kang Tu [b, c], Chien-Ming Yang [d, e], Christopher James Gordon [f, g], Dean Wu [h, i, j], Hsin-Chien Lee [j, k], Lia Taurussia Yuliana [a], Lucky Herawati [l], Ting-Jhen Chen [a], Hsiao-Yean Chiu [a, j, *]

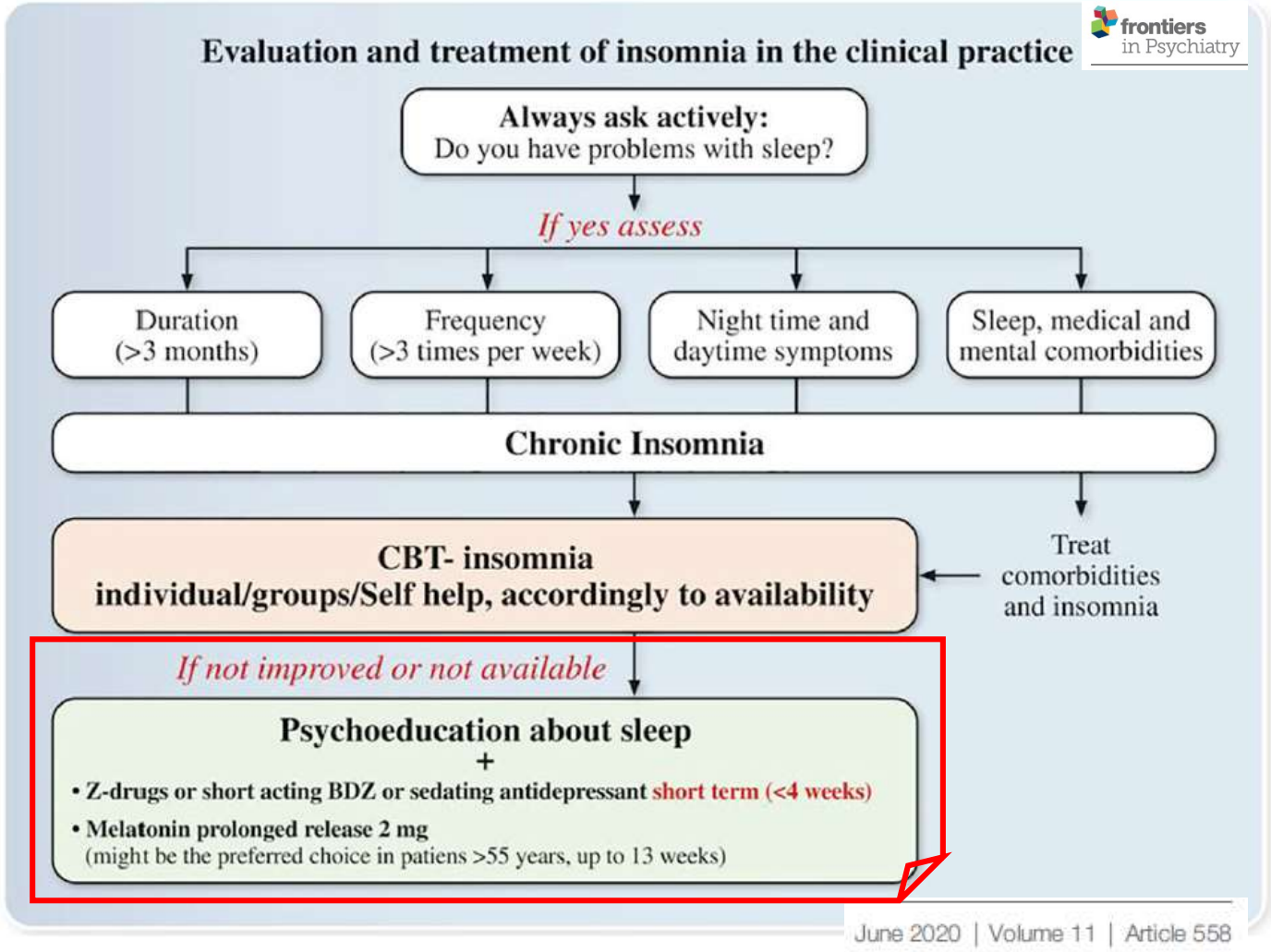
When face to face is unavailable, comparing with usual care (no active intervention)

TST, SOL, SE, WASO, insomnia symptoms

WebCBTi with therapist	• TST, SOL; WASO; SE • Insomnia Symptoms
WebCBTi	• TST, SOL; WASO; SE • Insomnia Symptoms
Telephone based	• SOL; WASO; SE • Insomnia Symptoms
Mobile app	• TST, WASO; SE
Group-delivered	• TST, SOL; WASO; SE • Insomnia Symptoms
Simplified CBT (1 component)	• NS vs usual care
Self-help book CBTi	• TST, SOL; WASO; SE • Insomnia Symptoms
Sleep Hygiene	• NS vs usual care

Expert Opinions and Consensus Recommendations for the Evaluation and Management of Insomnia in Clinical Practice: Joint Statements of Five Italian Scientific Societies

Laura Palagini[1*], Raffaele Manni[2], Eugenio Aguglia[3], Mario Amore[4,5], Roberto Brugnoli[6], Paolo Girardi[6], Luigi Grassi[7], Claudio Mencacci[8], Giuseppe Plazzi[9,10], Antonino Minervino[11], Lino Nobili[12,13] and Giovanni Biggio[14]



Sleep hygiene education as a treatment of insomnia: a systematic review and meta-analysis

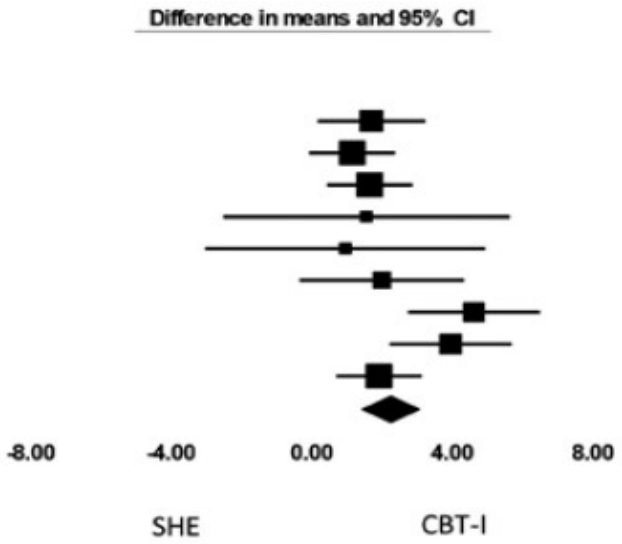
Family Practice, 2017, 1–11

Ka-Fai Chung[a,*], Chit-Tat Lee[b], Wing-Fai Yeung[c], Man-Sum Chan[d], Emily Wing-Yue Chung[e] and Wai-Ling Lin[f]

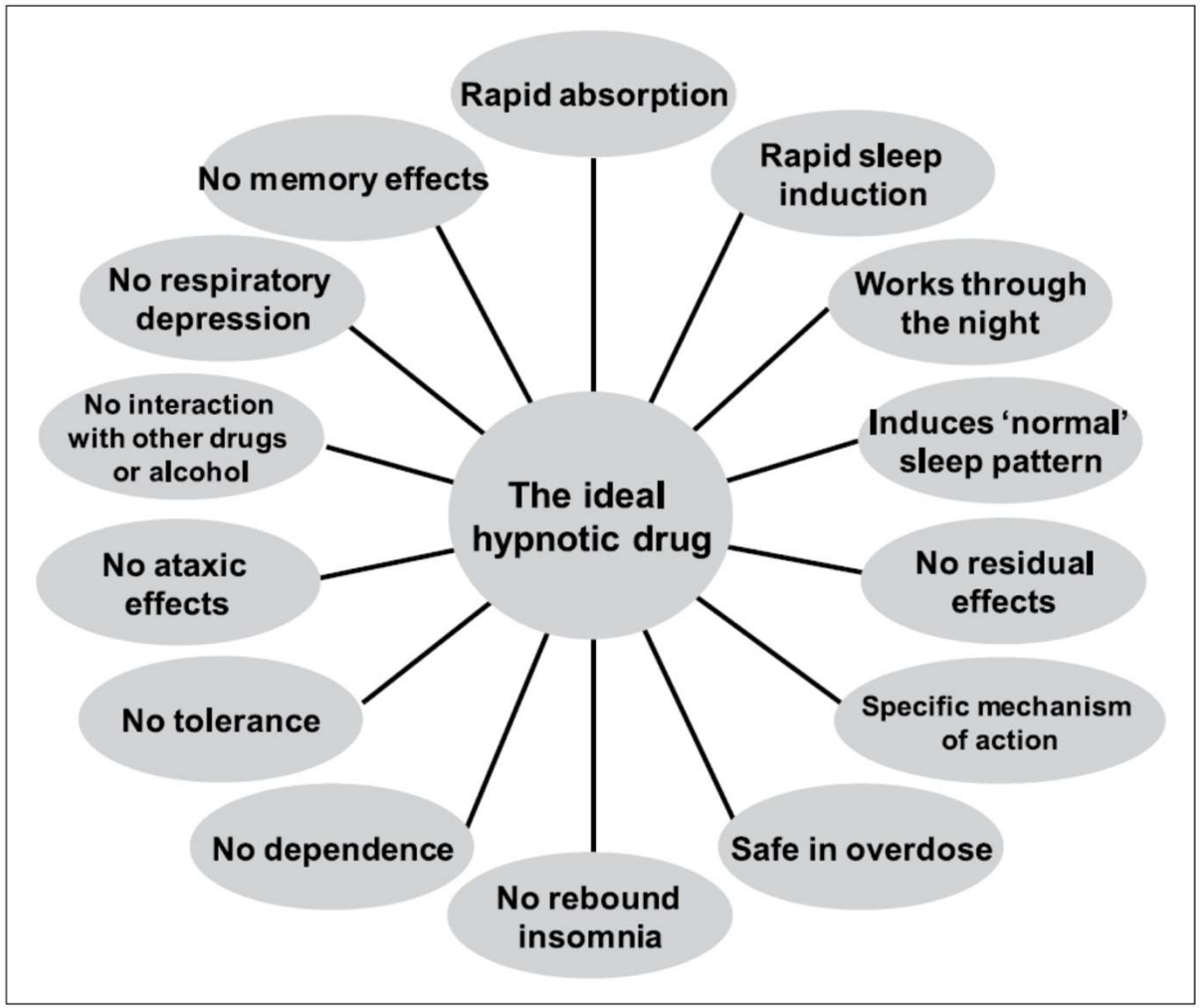
Sleep hygiene is effective in insomnia

Less effective than CBT-I

Study name	Outcome	Statistics for each study						
		Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Falloon (2015)	PSQI	1.750	0.792	0.627	0.198	3.302	2.210	0.027
Bjorvatn (2011)	PSQI	1.200	0.630	0.397	-0.035	2.435	1.904	0.057
Black (2015)	PSQI	1.700	0.628	0.394	0.469	2.931	2.708	0.007
Edinger (2009) PI	PSQI	1.600	2.087	4.356	-2.491	5.691	0.767	0.443
Edinger (2009) CMI	PSQI	1.000	2.038	4.154	-2.995	4.995	0.491	0.624
Martinez (2014)	PSQI	2.040	1.198	1.436	-0.308	4.388	1.703	0.089
Sun (2013)	PSQI	4.660	0.964	0.930	2.770	6.550	4.833	0.000
Alessi (2016)	PSQI	4.000	0.895	0.801	2.246	5.754	4.470	0.000
Wang (2016)	PSQI	1.960	0.628	0.394	0.729	3.191	3.122	0.002
		2.255	0.407	0.166	1.456	3.053	5.536	0.000



Pharmacological Management of insomnia: CBT-I …
«Pigliate 'na pastiglia siente a me»



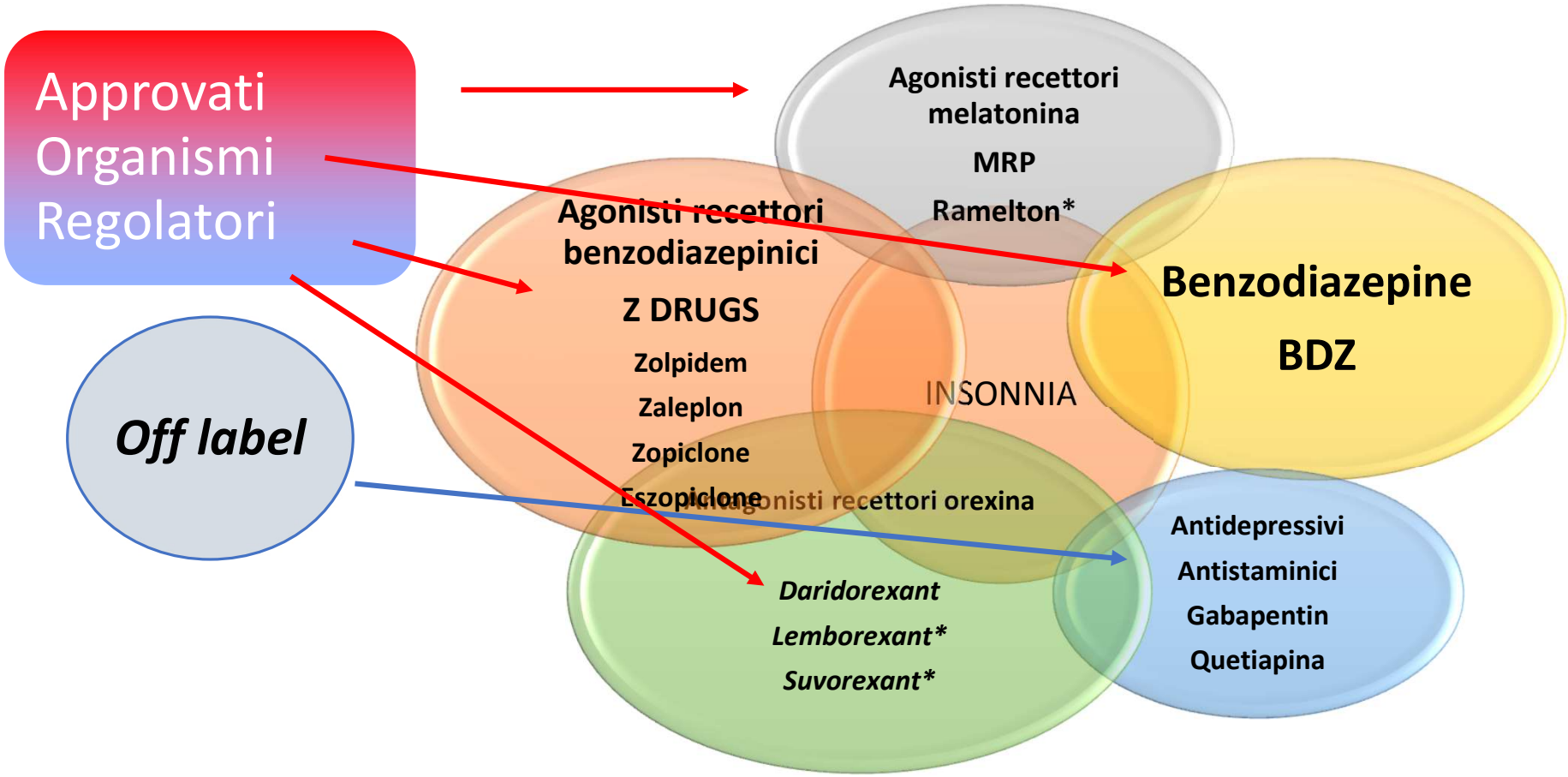
Journal of Psychopharmacology
2019, Vol. 33(8) 923–947

Most used drugs

- Trazodone
- Zolpidem
- Amitriptilina
- Mirtazapina
- Temazepam
- Quetiapine
- Zaleplon
- Clonazepam
- Triazolam
- Alprazolam
- Lorazepam
- Olanzapina
- Flurazepam
- Doxepin

Walsh et al, 2005

Farmaci per il trattamento dell'insonnia

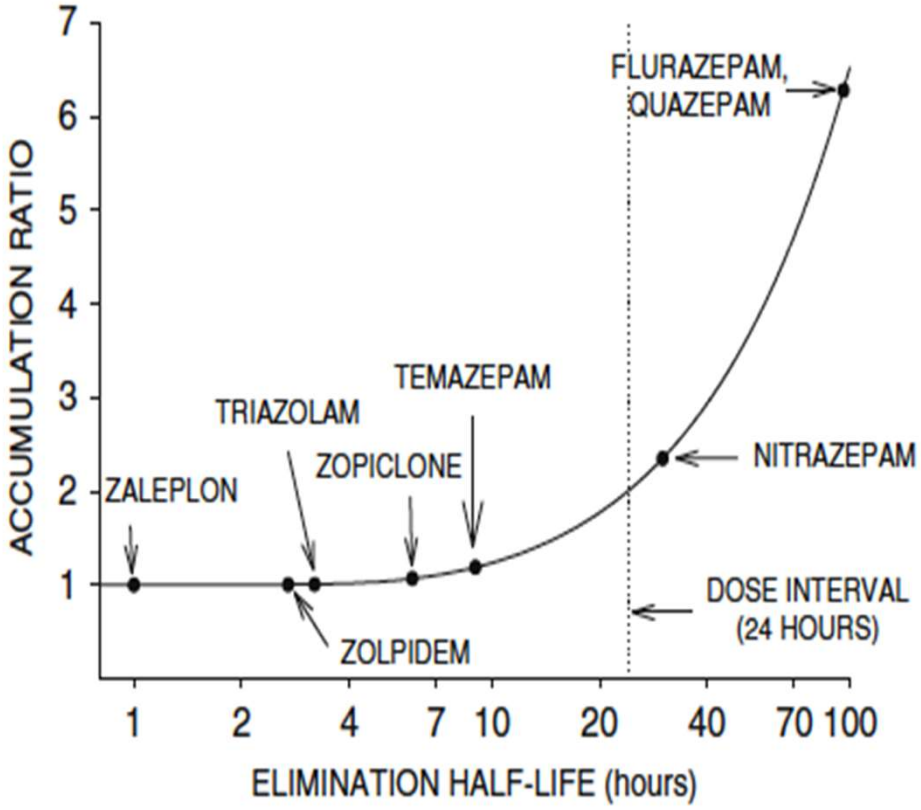


* Non disponibili in Italia

HYPNOTICS: BDZ

the duration of action of BDZ is correlated

- - $T_{1/2}$
- - to a lesser extent
  - to the permanence on the receptor
  - to the **distribution volume** (beware to Lipophilicity)



WHAT'S NEW ABOUT "OLD" HYPNOTICS?

Emivita breve/brevissima	Emivita breve/intermedia	Emivita lunga
Brotizolam	Alprazolam	Clonazepam
Etizolam	Bromazepam	Clordiazepossido
Midazolam	Flunitrazepam*	Diazepam
Triazolam	Lorazepam	Flurazepam
Oxazepam	Lormetazepam	Prazepam

Eszopiclone for insomnia (Review)

2018

Rösner S, Englbrecht C, Wehrle R, Hajak G, Soyka M

«Eszopiclone appears to be an efficient drug with moderate effects on sleep onset and maintenance. There was no or little evidence of harm if taken as recommended.»

Z DRUGS

Warning 2007 FDA

DoA

- Sleep walking
- Sleep-violence
- Sleep eating

Writing emails as part of sleepwalking after increase in Zolpidem

Fouzia Siddiqui [a,b,*], Edgar Osuna [a], Sudhansu Chokroverty [a]

Sleep Medicine 10 (2009) 262–264

A

Subj: !HELP ME P-LEEEEESE
Date: 12/7/2004 11:47:24 PM Eastern Standard Time
From: DUCKANDJOE
To: Docksea

i don't get it. please esplain LUCY!!

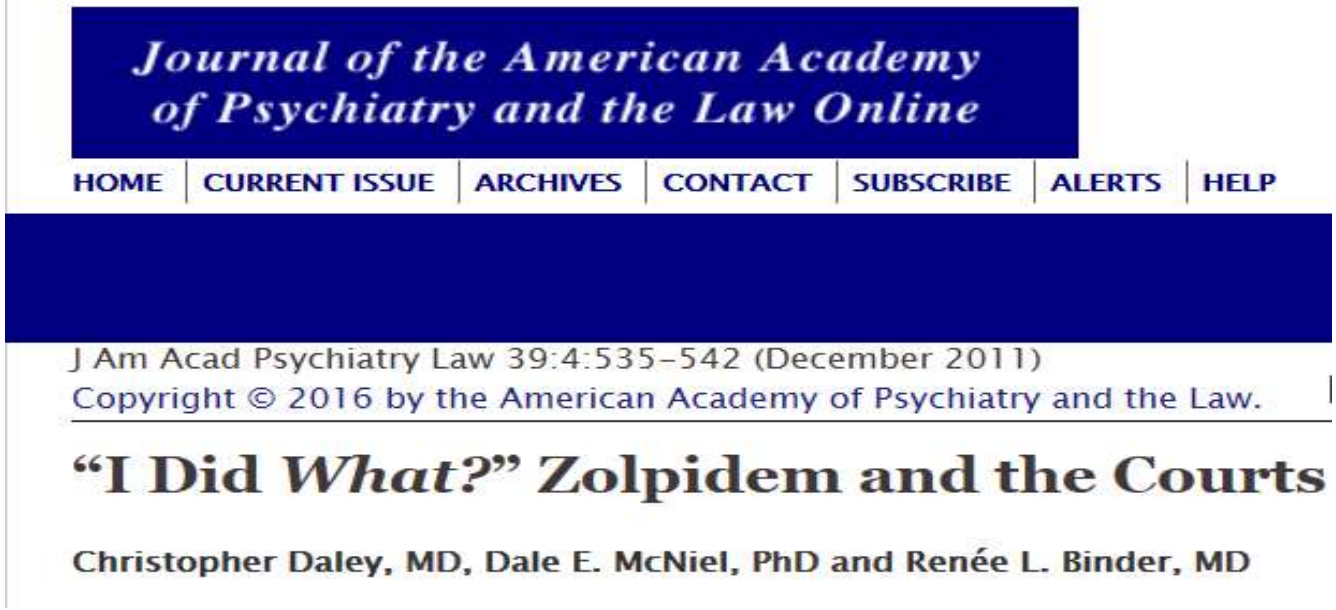
cOME TOMORROW AND SORT THIS HELL HOLE Out!!!!!

dinner & drinks, 4;00 pm shars house. Wine and caviar to bring only. everything else, a guess? MANANA XXOO D

B

Subj: I DON'T GETIT
Date: 12/7/2004 11:50:07 PM Eastern Standard Time
From: DUCKANDJOE
To: Suetheshoe13

WHAT THE?



Journal of the American Academy of Psychiatry and the Law Online

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J Am Acad Psychiatry Law 39:4:535–542 (December 2011)

"I Did *What?*" Zolpidem and the Courts

Christopher Daley, MD, Dale E. McNiel, PhD and Renée L. Binder, MD

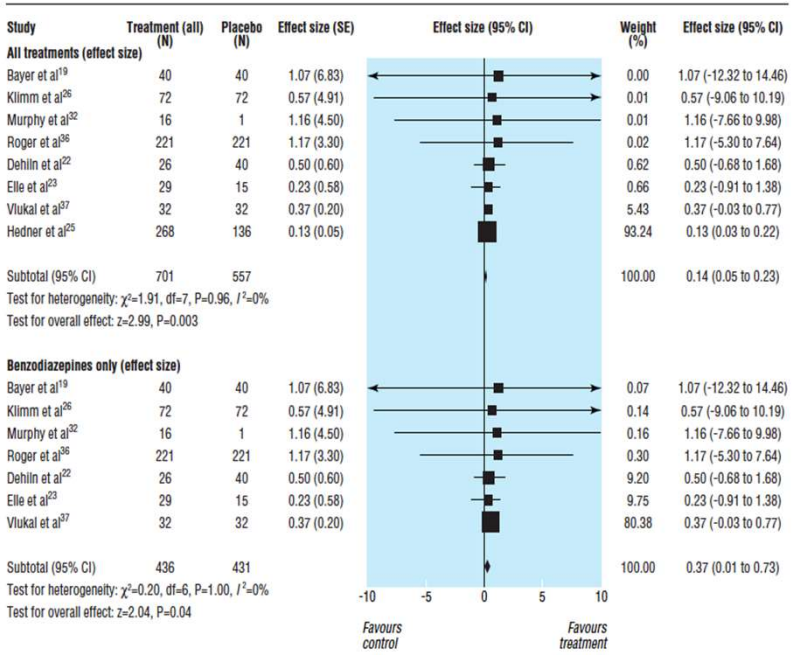
"…A young adult with ***no prior history of psychiatric*** illness used zolpidem once a week to fall asleep. One night, she took ***a shower after her dose of zolpidem*** and went to sleep later than her usual time. She woke up ***with a garden axe*** on her nightstand with no memory of how it got there. Later she scrolled through her text messages from the night before and ***discovered a conversation that she had had with her partner after her shower. She had no memory of writing the text messages***. In them, she described to her partner ***hearing voices from her kitchen and seeing moving images out of the corner of her eye***. Concerned for her safety, she ***had gotten the axe*** from the tool shed and placed it on her nightstand…"

Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits

Jennifer Glass, Krista L Lanctôt, Nathan Herrmann, Beth A Sproule, Usoa E Busto

BMJ 2005

Efficacy



Study	Treatment (all) (N)	Placebo (N)	Effect size (SE)	Weight (%)	Effect size (95% CI)
All treatments (effect size)					
Bayer et al[19]	40	40	1.07 (6.83)	0.00	1.07 (-12.32 to 14.46)
Klimm et al[26]	72	72	0.57 (4.91)	0.01	0.57 (-9.06 to 10.19)
Murphy et al[32]	16	1	1.16 (4.50)	0.01	1.16 (-7.66 to 9.98)
Roger et al[36]	221	221	1.17 (3.30)	0.02	1.17 (-5.30 to 7.64)
Dehiln et al[22]	26	40	0.50 (0.60)	0.62	0.50 (-0.68 to 1.68)
Elle et al[23]	29	15	0.23 (0.58)	0.66	0.23 (-0.91 to 1.38)
Vlukal et al[37]	32	32	0.37 (0.20)	5.43	0.37 (-0.03 to 0.77)
Hedner et al[25]	268	136	0.13 (0.05)	93.24	0.13 (0.03 to 0.22)
Subtotal (95% CI)	701	557		100.00	0.14 (0.05 to 0.23)
Test for heterogeneity: χ^2=1.91, df=7, P=0.96, I^2=0%					
Test for overall effect: z=2.99, P=0.003					
Benzodiazepines only (effect size)					
Bayer et al[19]	40	40	1.07 (6.83)	0.07	1.07 (-12.32 to 14.46)
Klimm et al[26]	72	72	0.57 (4.91)	0.14	0.57 (-9.06 to 10.19)
Murphy et al[32]	16	1	1.16 (4.50)	0.16	1.16 (-7.66 to 9.98)
Roger et al[36]	221	221	1.17 (3.30)	0.30	1.17 (-5.30 to 7.64)
Dehiln et al[22]	26	40	0.50 (0.60)	9.20	0.50 (-0.68 to 1.68)
Elle et al[23]	29	15	0.23 (0.58)	9.75	0.23 (-0.91 to 1.38)
Vlukal et al[37]	32	32	0.37 (0.20)	80.38	0.37 (-0.03 to 0.77)
Subtotal (95% CI)	436	431		100.00	0.37 (0.01 to 0.73)
Test for heterogeneity: χ^2=0.20, df=6, P=1.00, I^2=0%					
Test for overall effect: z=2.04, P=0.04					

Fig 2 Mean effect size (95% confidence intervals) for subjective improvements in sleep quality with any sedative treatment and benzodiazepines only compared with placebo for at least five nights in people aged 60 or older with insomnia

Safety

What is already known on this topic

Benzodiazepines and newer benzodiazepine receptor agonists are thought to be efficacious for sleep disturbances in elderly people

They are associated with risks that are particularly detrimental in elderly people, such as ataxia, cognitive effects, and falls

Little is known about how the risks and benefits compare for non-prescription sedative hypnotics

What this study adds

In people over 60, the benefits associated with sedative use are marginal and are outweighed by the risks, particularly if patients are at high risk for falls or cognitive impairment

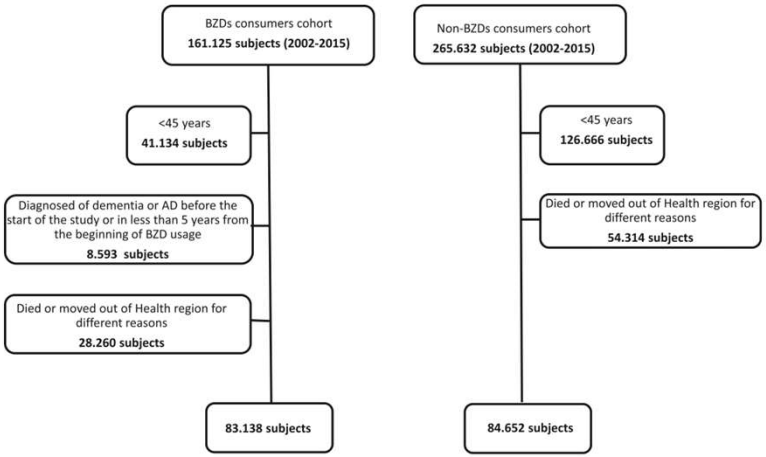
International Journal of Neuropsychopharmacology (2022) 25(4): 261–268

REGULAR RESEARCH ARTICLE

Benzodiazepine and Z-Drug Use and the Risk of Developing Dementia

Francisco Torres-Bondia, Farida Dakterzada, Leonardo Galván, Miquel Buti, Gaston Besanson, Eric Grill, Roman Buil, Jordi de Batlle, Gerard Piñol-Ripoll

Flowchart



BDZ users

- Unadjusted HR 1.22 (95% CI = 1.15 to 1.31)
- Adjusted for confounding factors HR = 1.01 (95% CI = 0.94 to 1.08) NOT SIGNIFICANT

SHORT-TO-INTERMEDIATE HALF LIFE

- BZD (HR = 1.11; 95% CI = 1.04 to 1.20) vs intermediate-to-long half-life BZDs (HR = 1.01; 95% CI = 0.94 to 1.08).
- Z-drugs (HR = 1.20; 95% CI = 1.07 to 1.33)

Higher doses

- HR = 1.38; (95% CI = 1.27 to 1.50) vs (HR = 1.23; 95% CI = 1.07 to 1.41

WOMEN

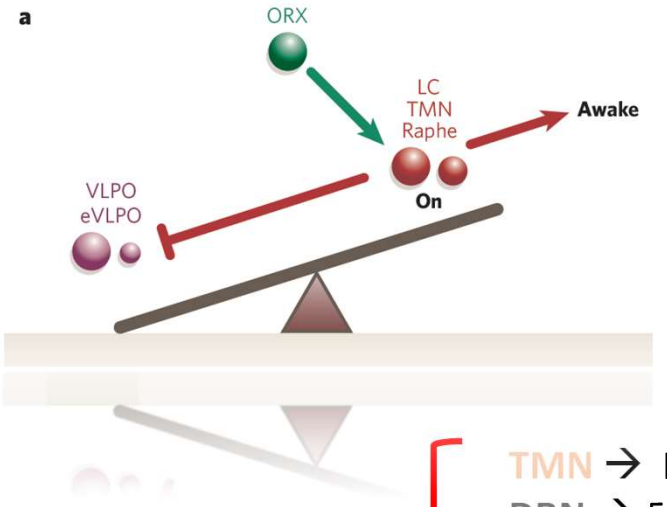
- (HR = 1.28; 95% CI = 1.14 to 1.44) than in men (HR = 1.09; 95% CI = 1.08 to 1.10) ALSO ADJUSTED FOR doses and treatment -→ surviuval bias?

«We observed that BZDs users did not present an increased risk of dementia as a whole group. However, we observed an increased risk of dementia related with ***short-to-intermediate half-life BZD*** *and* ***BZDRs****. This risk was* ***higher in women*** *and it increased with* ***higher doses*** *of BZD.* ***These results address the importance of avoiding long-term use of these medications****»*

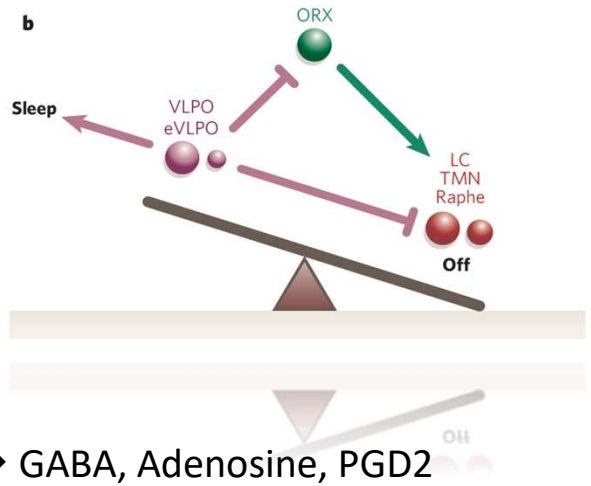
…BACK to the future…

Flip-flop switch model

Veglia



Sonno



LAT HYP → ORX

- TMN → HIS
- DRN → 5HT
- VTA → DA
- LC → NA

VLPO → GABA, Adenosine, PGD2

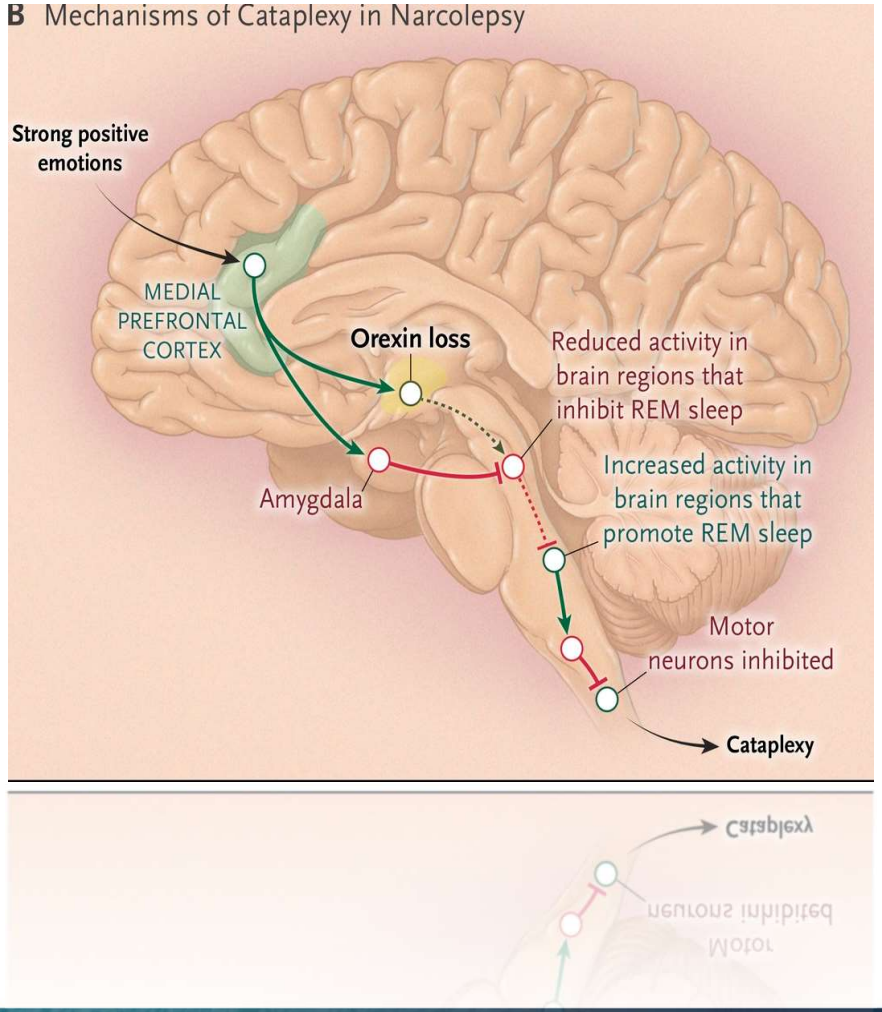
Saper, 2005

Sistema orexinergico

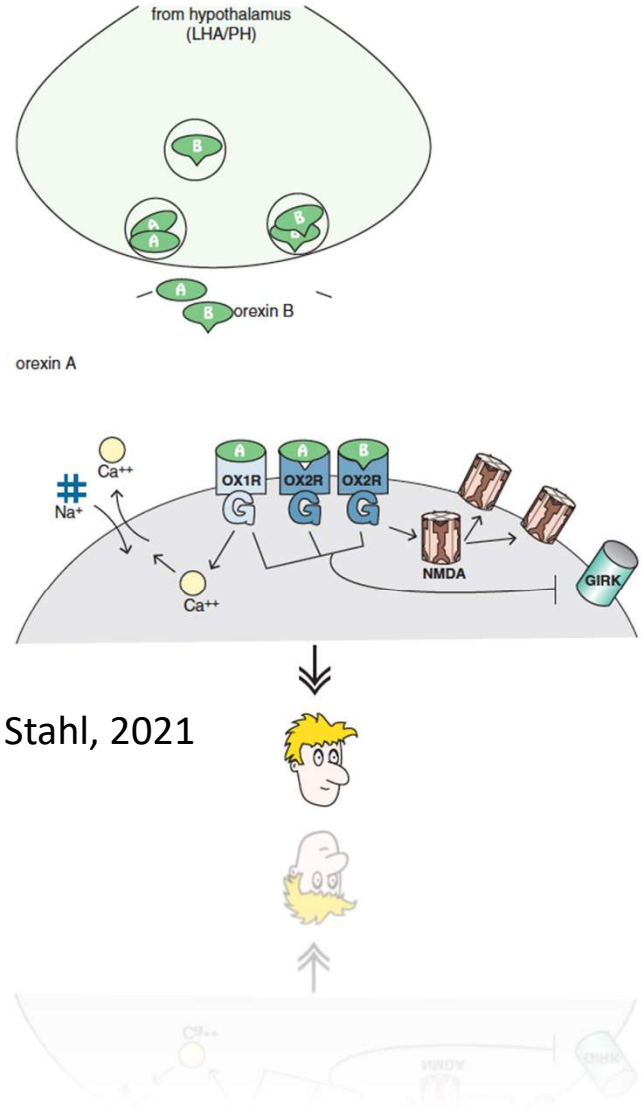
~ solo 70.000 neuroni situati nell'ipotalamo laterale

I neuroni che producono orexina stimolano neuroni della «veglia» (corteccia, tronco encefalo, proencefalo basale)

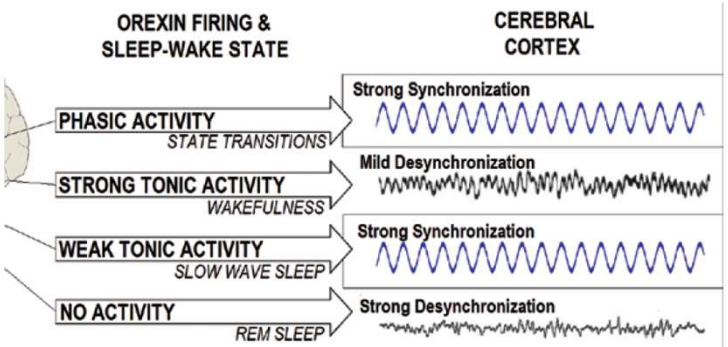
Hanno un ruolo importante nell'eccitare regioni del tronco encefalo che sopprimono il sonnoREM



Ruolo dell'orexina



Stahl, 2021



Fame	Aumento assunzione cibo
Sospensione sostanze abuso	Ricerca sostanze
Freddo	Termogenesi periferica
Ipercapnia	Tachipnea
Stress	attivazione asse ipot-ipofisario
stimoli emotivi	aumento processi cognitivi attenzione e apprendimento

INSIGHTS

PERSPECTIVES

NEUROSCIENCE

Losing sleep with age

Hypocretin neuron hyperexcitability underlies disrupted sleep quality associated with age

By Laura H. Jacobson[1,2,3] and Daniel Hoyer[1,2,4]

Sleep quality declines with aging. In mice, wake-promoting hypocretin neurons, normally silent during sleep, become hyperexcitable with age, resulting in intrusions of wakefulness into sleep. This discovery may lead to new therapies to improve sleep in aging and related disorders.

«sleep complaints in older people are associated with **increased risks of impaired physical and mental health** and with **mortality**»

Jacobson & Hoyer, 2022 (27/2/22)

Table 2. Unadjusted and adjusted survival ratio

		Unadjusted hazard ratio (95% CI)	p	Adjusted hazard ratio (95% CI)	p
ADL	A	1.0			
	B	3.25 (1.49–7.13)	0.003		
	C	7.48 (3.39–17.00)	<0.0001		
Sleep disturbance	*Nighttime insomnia*				
	Absent	1.0			
	Present	1.84 (1.23–2.75)	0.003	1.59 (1.05–2.40)	0.028
	Daytime sleepiness				
	Absent	1.0			
	Present	1.69 (1.13–2.52)	0.011	1.48 (0.98–2.23)	0.057
	Early awakening				
	Absent	1.0			
	Present	0.84 (0.53–1.35)	0.476	0.91 (0.57–1.45)	0.689
	Sleep-onset delay				
	Absent	1.0			
	Present	2.22 (1.49–3.32)	<0.0001	1.83 (1.22–2.75)	0.004

Manabe, 2000 Gerontology

RESEARCH ARTICLE

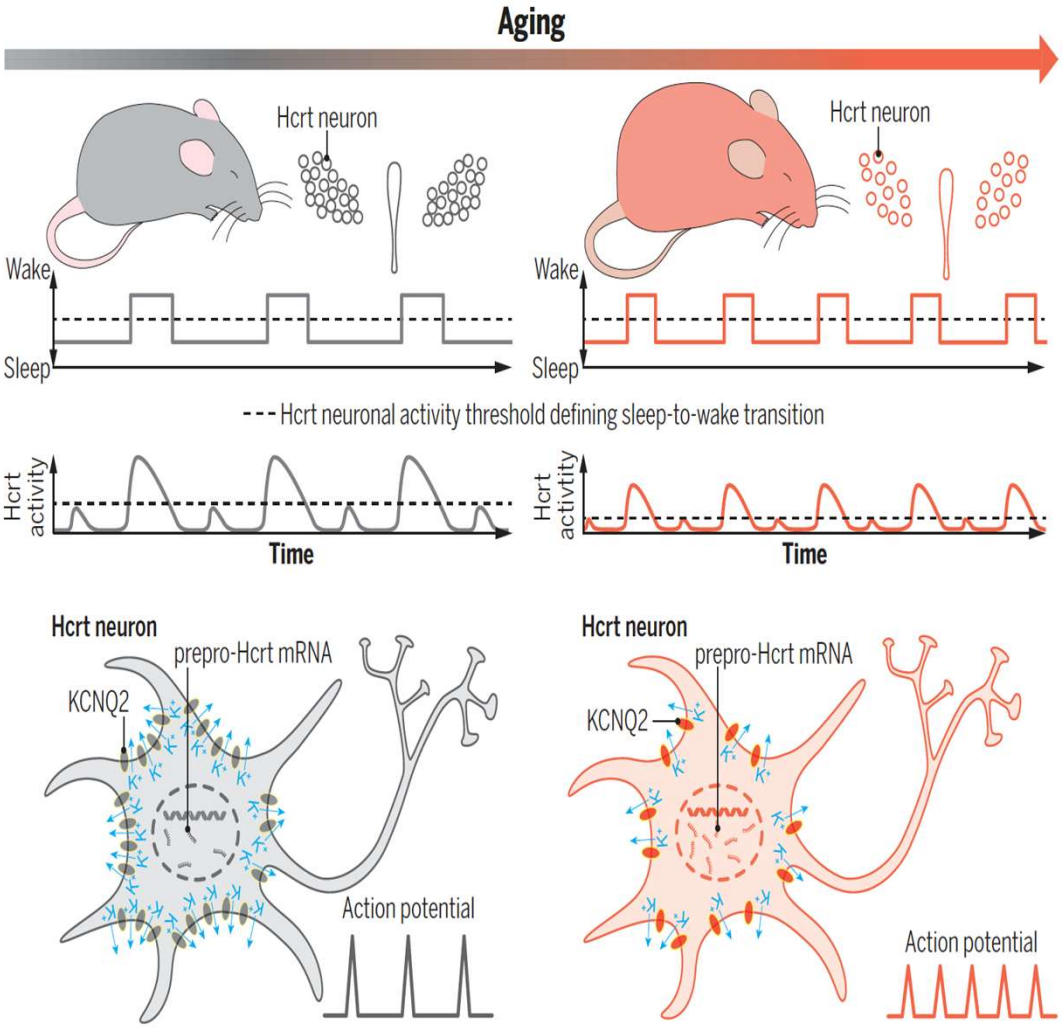
NEUROSCIENCE

Hyperexcitable arousal circuits drive sleep instability during aging

25/02/2022

Shi-Bin Li[1,2]†, Valentina Martinez Damonte[1,2]†, Chong Chen[3,4], Gordon X. Wang[1], Justus M. Kebschull[5]‡, Hiroshi Yamaguchi[1,2]§, Wen-Jie Bian[1,2], Carolin Purmann[1,6], Reenal Pattni[1,6], Alexander Eckehart Urban[1,6], Philippe Mourrain[1,7], Julie A. Kauer[1,2], Grégory Scherrer[3,4], Luis de Lecea[1,2]*

- age-dependent decreased hypocretin neuron density
- calcium peaks in hypocretin neurons associated with wakefulness
- During the inactive phase («*sleep*»), calcium transients were **more frequent and lower in amplitude in old** versus young associated with increased wakefulness

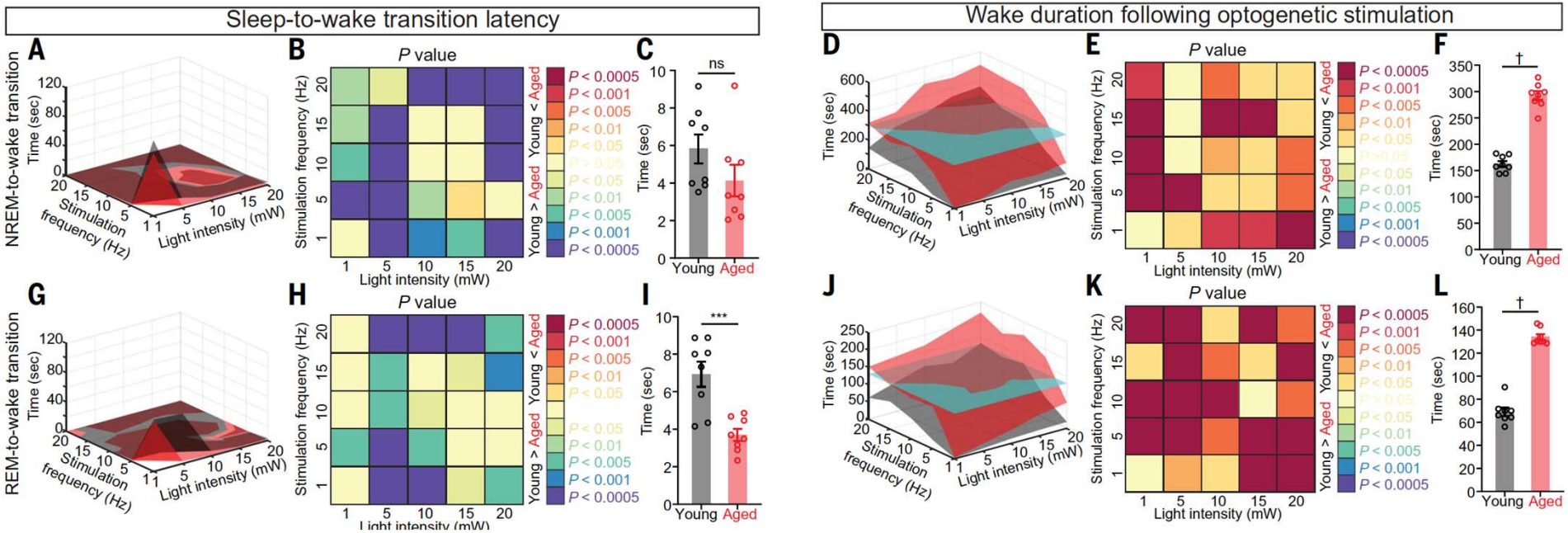


RESEARCH ARTICLE SUMMARY

NEUROSCIENCE

Hyperexcitable arousal circuits drive sleep instability during aging

Shi-Bin Li†, Valentina Martinez Damonte†, Chong Chen, Gordon X. Wang, Justus M. Kebschull, Hiroshi Yamaguchi, Wen-Jie Bian, Carolin Purmann, Reenal Pattni, Alexander Eckehart Urban, Philippe Mourrain, Julie A. Kauer, Grégory Scherrer, Luis de Lecea*



lower threshold to arousal in aged hypocretin neurons

Increased wakefulness by optogenetic stimulation of orx neurons

RESEARCH ARTICLE SUMMARY

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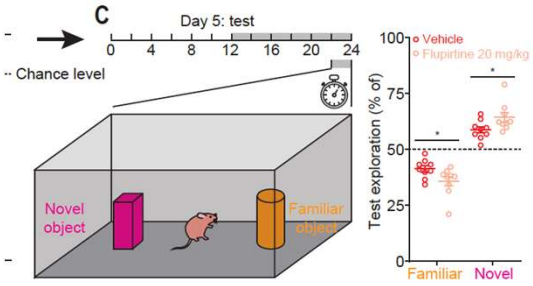
reduced expression KCNQ2 → hyperexcitability ORX → Sleep instability → decrease NREM

Aging

KCNQ2 «opener» flupirtine → reduce excitability ORX → Sleep stability → increase NREM

DORA / SORA



Cognitive improvement

RESEARCH ARTICLE SUMMARY

NEUROSCIENCE

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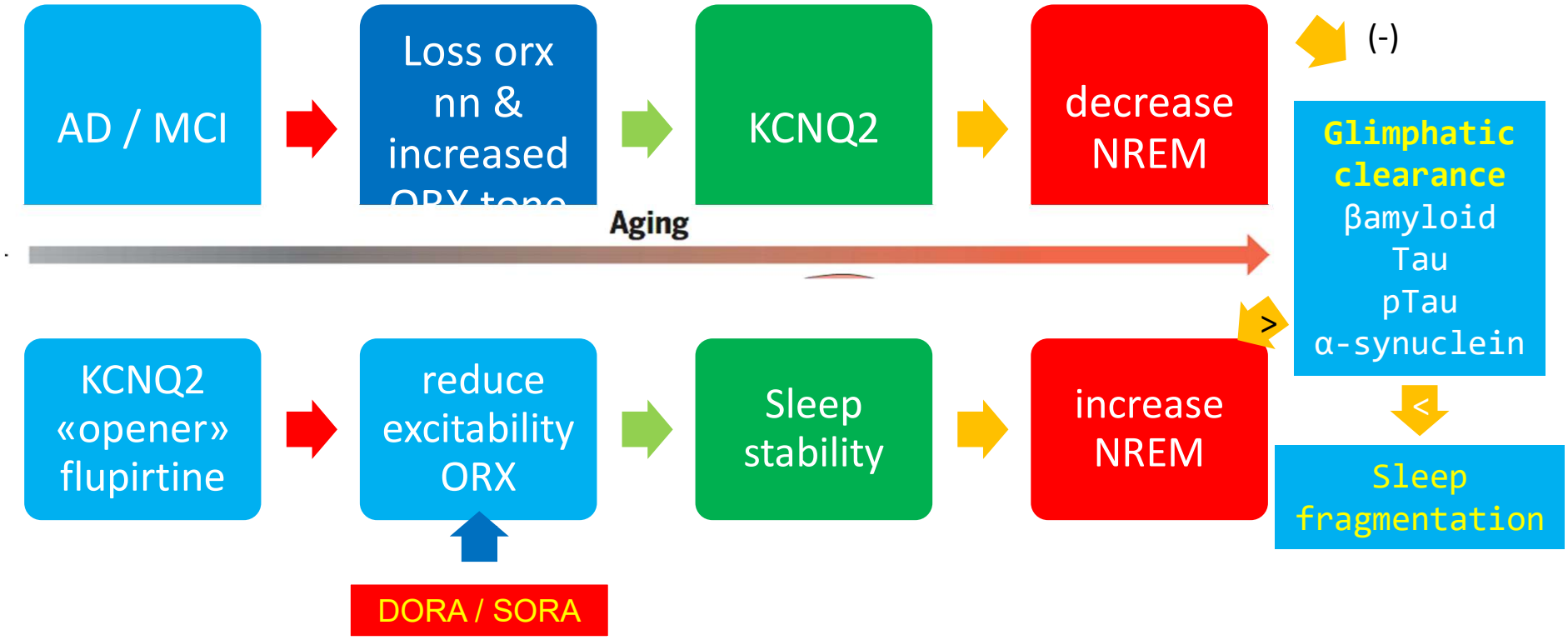
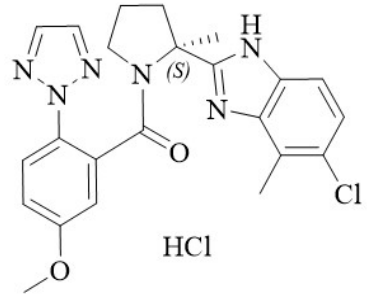
Shi-Bin Li†, Valentina Martinez Damonte†, Chong Chen, Gordon X. Wang, Justus M. Kebschull, Hiroshi Yamaguchi, Wen-Jie Bian, Carolin Purmann, Reenal Pattni, Alexander Eckehart Urban, Philippe Mourrain, Julie A. Kauer, Grégory Scherrer, Luis de Lecea*



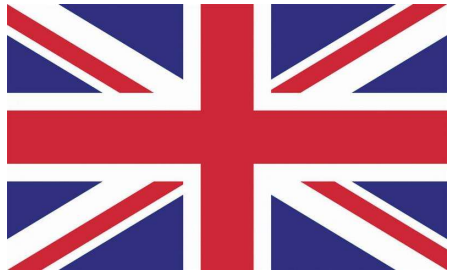
Daridorexant is approved for the treatment of insomnia in the USA, EU and the UK

Approved by the US FDA in January 2022:
Indicated for the treatment of adult patients with insomnia characterized by ***difficulties with sleep onset and/or sleep maintenance***[1]

Daridorexant[4,5]



Approved by the EMA in April 2022 and UK MHRA in September 2022:
Indicated for the treatment of adult patients with insomnia characterised by ***symptoms present for at least 3 months and considerable impact on daytime functioning***[2,3]



EMA, European Medicines Agency; FDA, Food and Drug Administration; MHRA, Medicines and Healthcare products Regulatory Agency.

1. Idorsia. Highlights of prescribing information. Daridorexant. US FDA, 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214985s000lbl.pdf (accessed September 2022); 2. Idorsia. Summary of product characteristics, Daridorexant. EMA, 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/quviviq-epar-product-information_en.pdf (accessed September 2022); 3. Idorsia. Summary of product characteristics. Daridorexant. UK MHRA, 2022. Available from: https://mhraproducts4853.blob.core.windows.net/docs/m1000021 (accessed September 2022); 4. Lebold TP, et al. *Bioorg Med Chem Lett* 2013;23:4761–9;
5. Coleman PJ, et al. *ChemMedChem* 2012;7:415–24.

Daridorexant's PK profile is adapted to the patient's needs

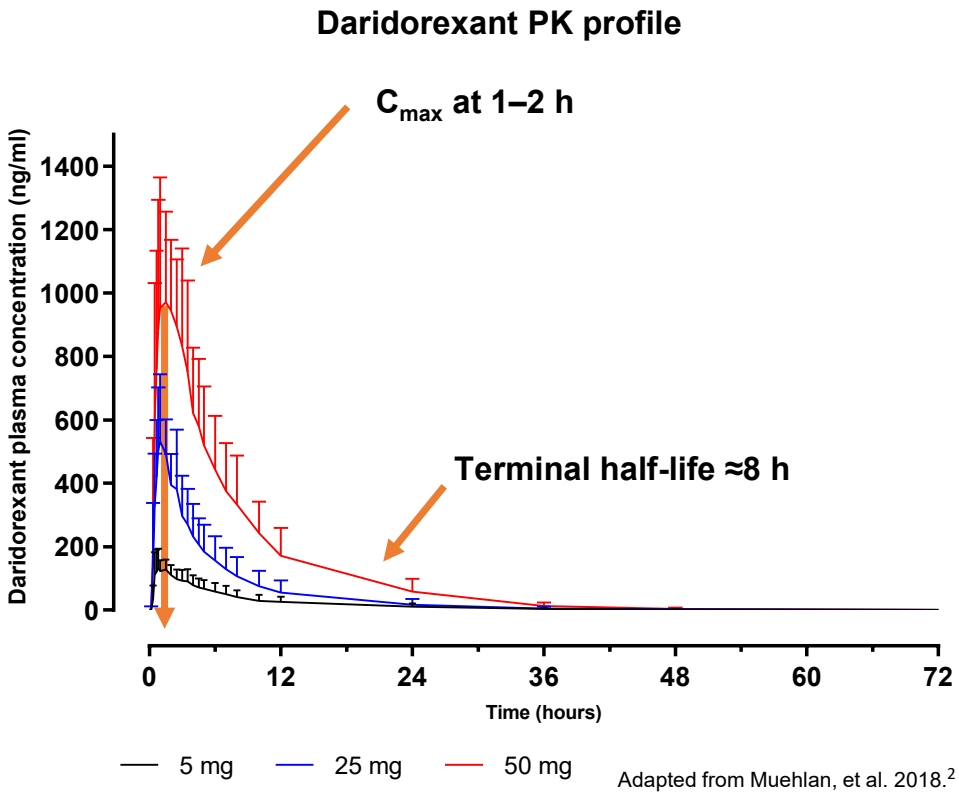
Rapid absorption for fast sleep onset[1]

- C_{max} reached 1–2 h after administration

Rapid decline in plasma concentrations[2] enabling sleep maintenance without next-morning residual effects

Terminal half-life ≈8 h[2–4] **explaining absence of accumulation after repeated daily dosing**

- Measured during final elimination of the drug when concentrations have already markedly decreased
- Time to eliminate half the *remaining concentration*



Adapted from Muehlan, et al. 2018.[2]

C_{max}, maximum serum concentration; PK, pharmacokinetic.

1. Muehlan C, et al. *J Clin Psychopharmacol* 2020;40:157–66; 2. Muehlan C, et al. *Clin Pharmacol Ther* 2018;104:1022–9;
3. Muehlan C, et al. *Eur Neuropsychopharmacol* 2019;29:847–57; 4. Muehlan C, et al. *J Psychopharmacol* 2020;34:326–35

Daridorexant has been investigated in two multicentre, randomised, double-blind phase 3 trials

Mignot E, Mayleben D, Fietze I, Leger D, Zammit G, Bassetti CLA, Pain S, Kinter DS, Roth T; investigators. Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials. Lancet Neurology 2022;21(2):125–139

- **Two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials**
- 156 sites
- 17 countries
- Interactive response technology (1:1:1)
- Daridorexant 50 mg, 25 mg, or placebo (study 1)
- Daridorexant 25 mg, 10 mg, or placebo (study 2)
- Medication intake every evening for 3 months
- Extension study[2]

1,854 patients
with insomnia disorder
for ~11 years
~5.5 hours sleep/night
aged ≥18 years

Placebo, n=618
Daridorexant 10 mg, n=307
Daridorexant 25 mg, n=619
Daridorexant 50 mg, n=310

IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; LPS, latency to persistent sleep; PBO, placebo; PSG, polysomnography; sTST, subjective total sleep time; WASO, wake after sleep onset.
1. Mignot E, et al. *Lancet Neurol* 2022;21:125–39; 2. Kunz D, et al. *Sleep Med* 2022;100(Suppl 1):S130.

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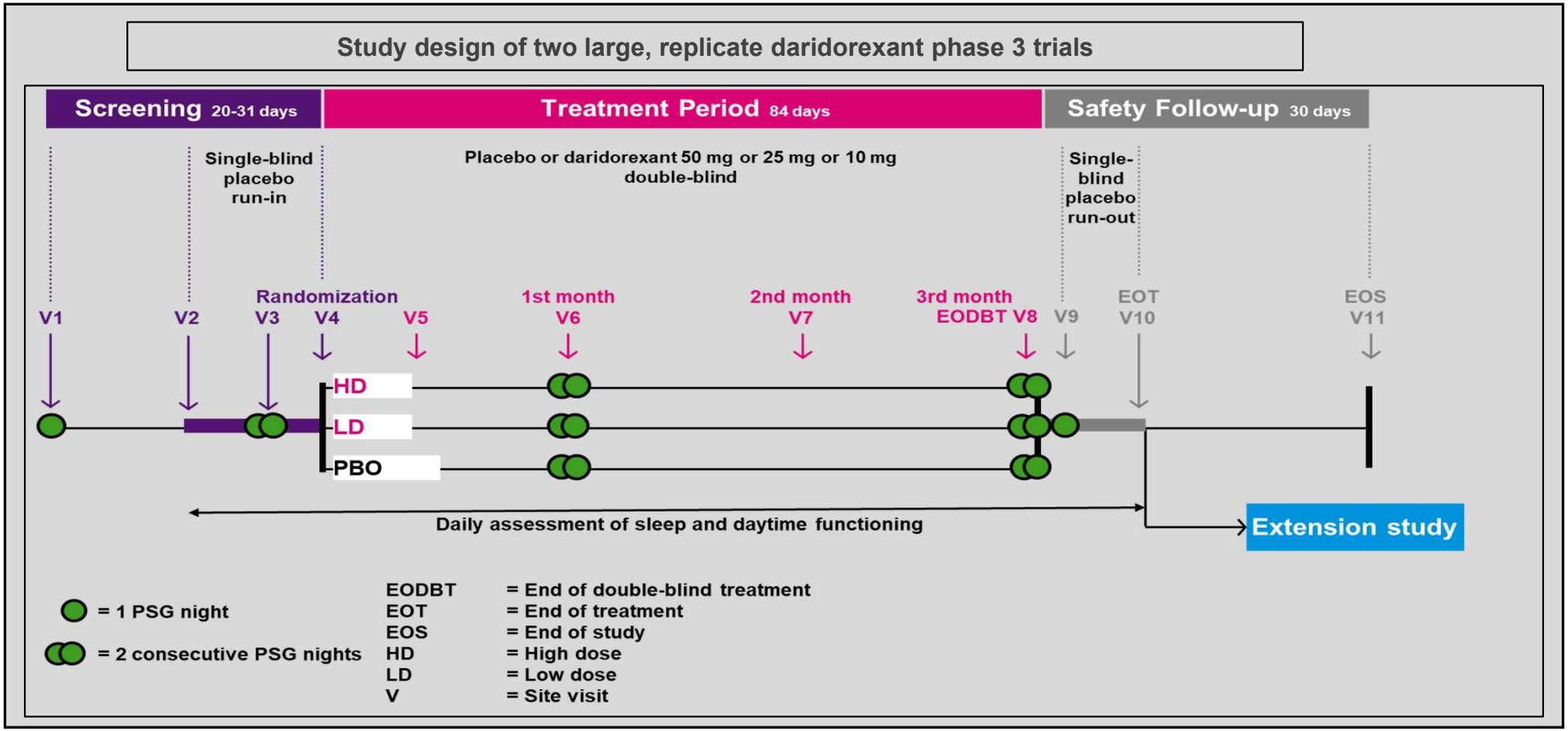

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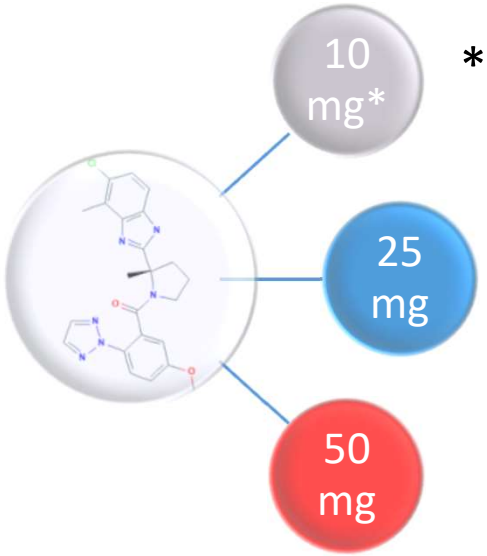


*NS

Objective sleep parameters

- Sleep Onset
- WASO

Subjective Sleep paramters

- sTST (TIB-WASO/SO)

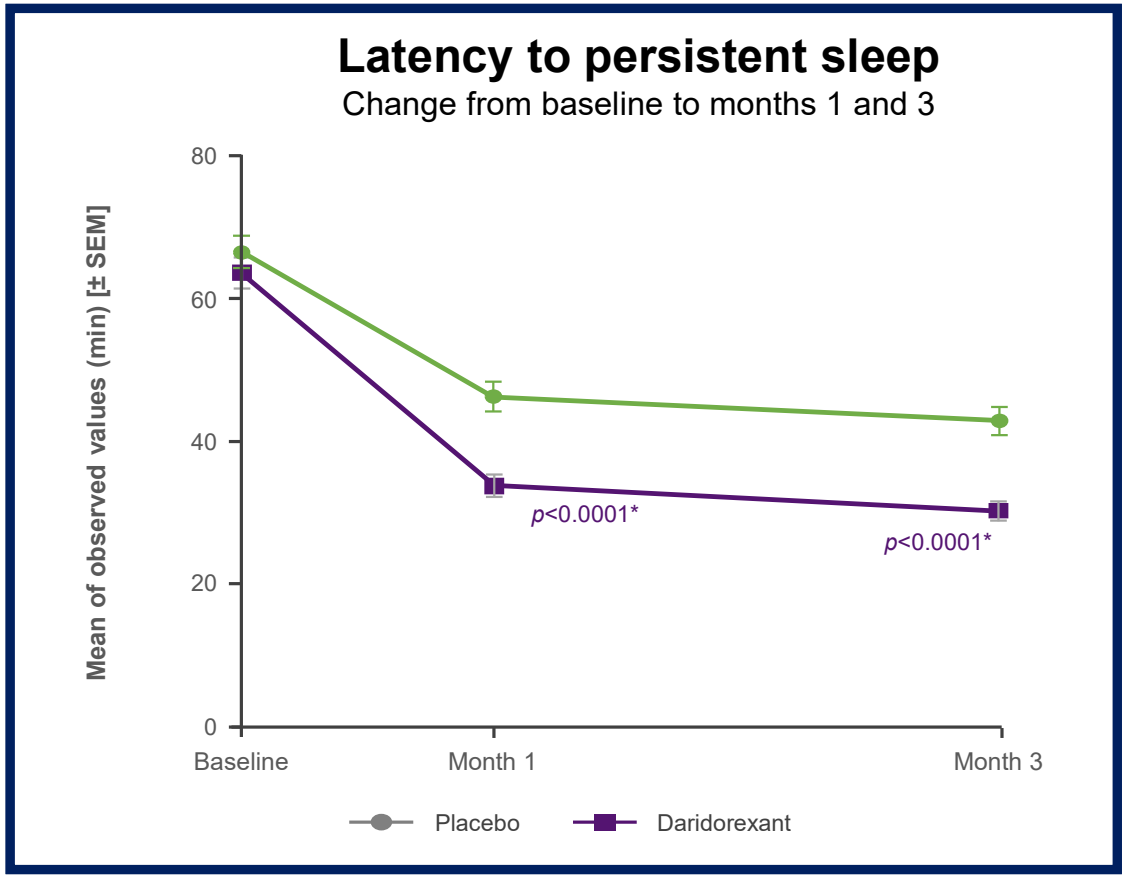
Subjective Daytime Parameter

- IDSIQ Sleepiness Domain

IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; LPS, latency to persistent sleep; PBO, placebo; PSG, polysomnography; sTST, subjective total sleep time; WASO, wake after sleep onset.

1. Mignot E, et al. *Lancet Neurol* 2022;21:125–39; 2. Kunz D, et al. *Sleep Med* 2022;100(Suppl 1):S130.

Daridorexant effects on sleep in insomniacs



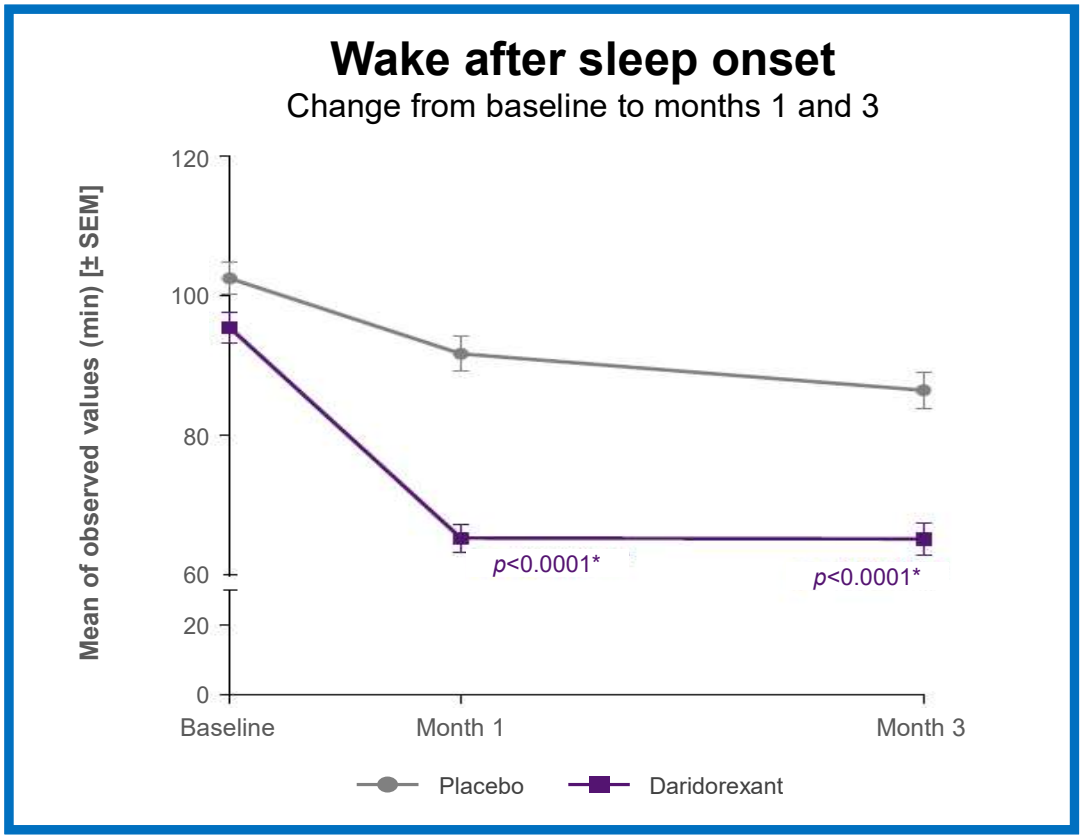
Month 3
Reduction in minutes

−23.1 (−26.5 to −19.8)

−34.8 (−38.1 to −31.5)

*Statistically significant vs placebo after multiplicity adjustment. Numbers in brackets indicate 95% confidence interval.
CBT-I, cognitive behavioural therapy for insomnia; DORA, dual orexin receptor antagonist; SEM, standard error of the mean; sTST, subjective total sleep time.
Mignot E, et al. *Lancet Neurol* 2022;21:125–39.

Daridorexant effects on sleep in insomniacs



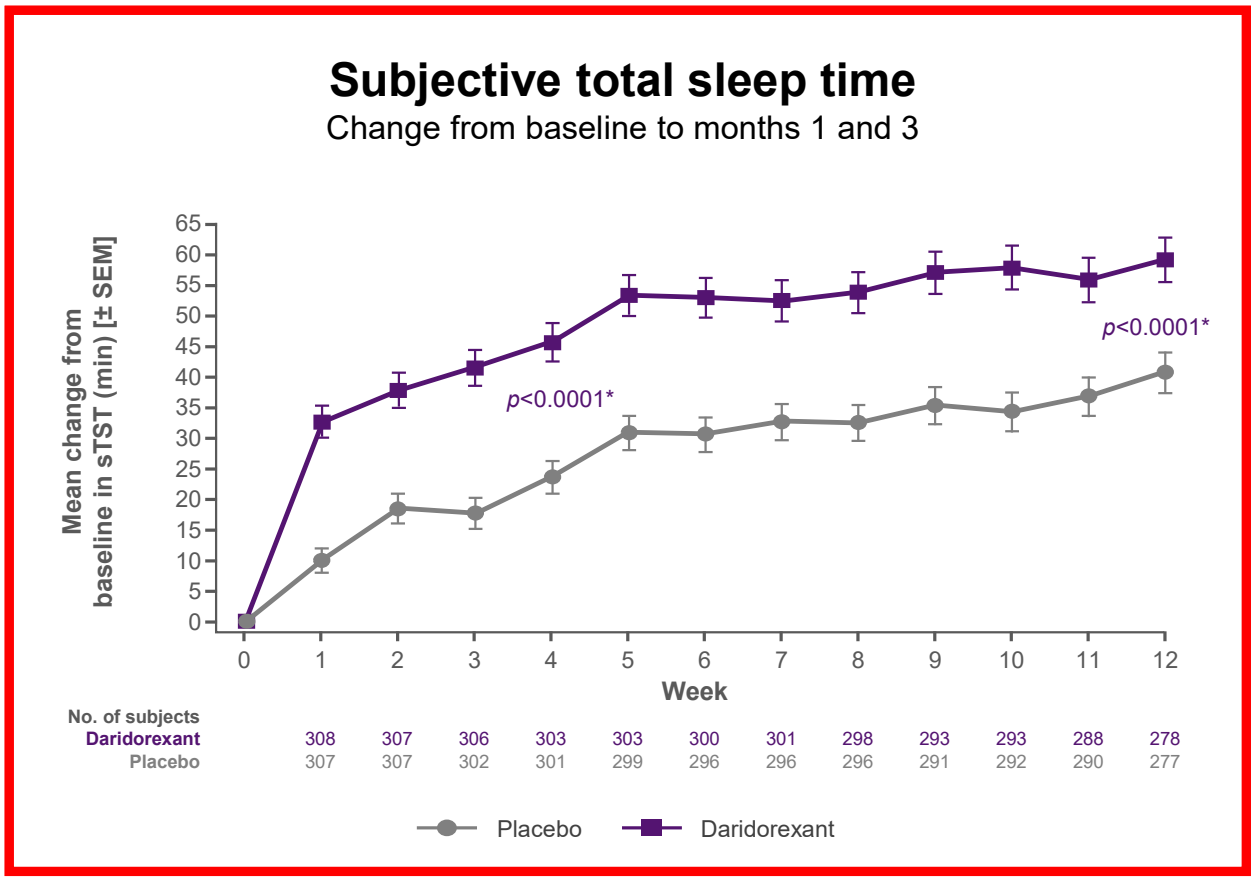
Month 3
Reduction in minutes

−11.1 (−15.1 to −7.1)

−29.4 (−33.4 to −25.4)

*Statistically significant vs placebo after multiplicity adjustment. Numbers in brackets indicate 95% confidence interval.
CBT-I, cognitive behavioural therapy for insomnia; DORA, dual orexin receptor antagonist; SEM, standard error of the mean; sTST, subjective total sleep time.
Mignot E, et al. *Lancet Neurol* 2022;21:125–39.

Daridorexant effects on sleep in insomniacs



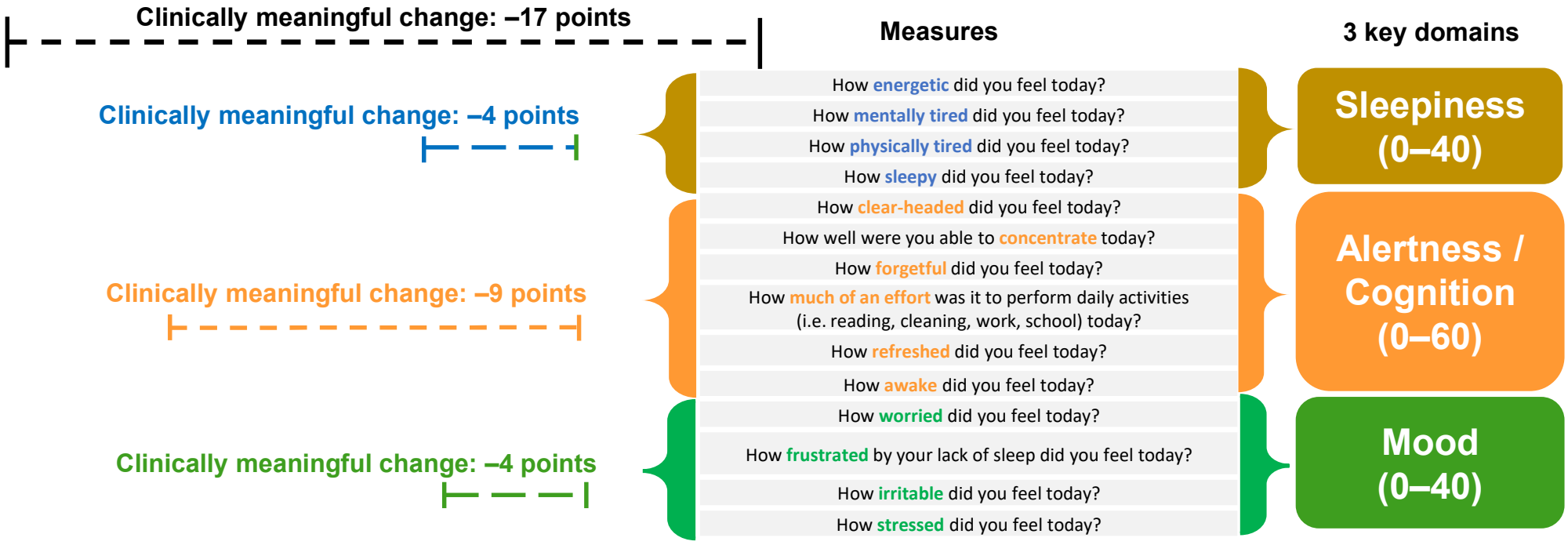
Month 3
Increase in minutes

37.9 (31.4 to 44.4)

57.7 (51.2 to 64.2)

*Statistically significant vs placebo after multiplicity adjustment. Numbers in brackets indicate 95% confidence interval.
CBT-I, cognitive behavioural therapy for insomnia; DORA, dual orexin receptor antagonist; SEM, standard error of the mean; sTST, subjective total sleep time.
Mignot E, et al. *Lancet Neurol* 2022;21:125–39.

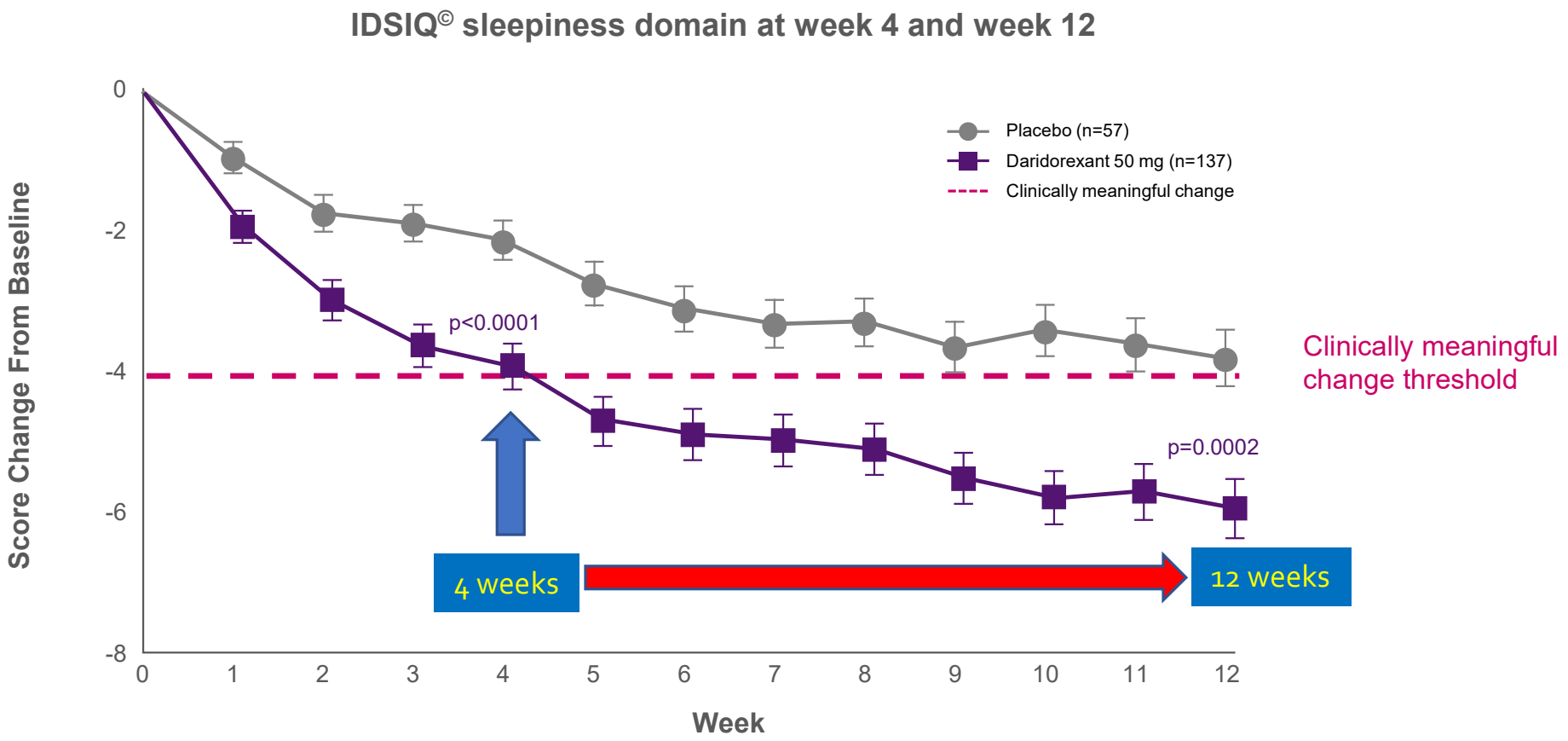
Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ©*†) is used to assess multiple facets of daytime functioning in insomnia according to FDA guidelines



 †Developed by Buysse DJ, Thompson W, Scott J, Franzen PI, Germain A, Hall M, Moul DE, Nofzinger EA and Kuper DJ of the University of Pittsburgh and as amended by Idorsia Pharmaceuticals Ltd. FDA, US Food and Drug Administration; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire.

Hudgens S, et al. *Patient* 2021;14:249–68; Phillips-Beyer A, et al. *Sleep* 2022;45(Suppl 1):A201–2 [Abstract 0455].

Daridorexant improves IDSIQ©*† scores over time



*© 2020, University of Pittsburgh. All rights reserved. IDSIQ-14 derivative created 2020 by Idorsia Pharmaceuticals Ltd under license and distributed by Idorsia Pharmaceuticals Ltd under license. †Developed by Buysse DJ, Thompson W, Scott J, Franzen PI, Germain A, Hall M, Moul DE, Nofzinger EA and Kuper DJ of the University of Pittsburgh and as amended by Idorsia Pharmaceuticals Ltd. P-value vs placebo. Error bars represent standard error of the mean. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire.

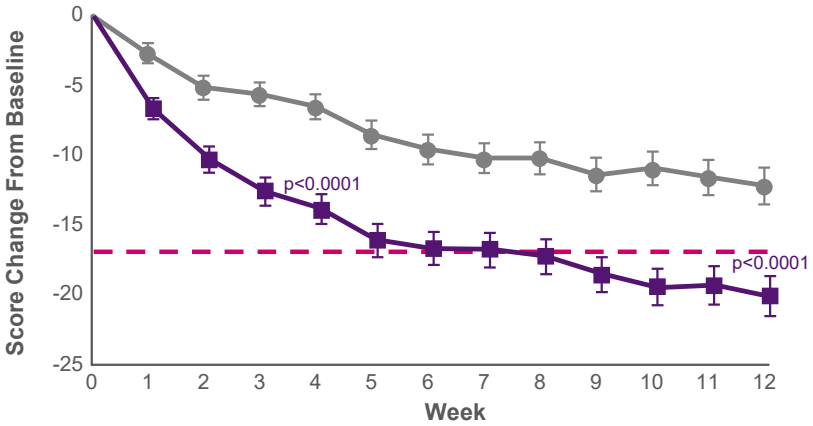
Mignot E, et al. *Lancet Neurol* 2022;21:125–39; Data on File.

Daridorexant improves IDSIQ©*† scores over time

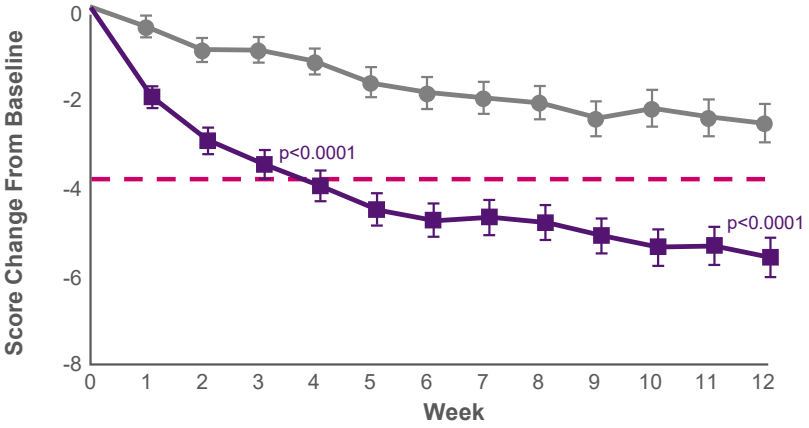
Exploratory endpoints at week 4 (month 1) and week 12 (month 3):

- IDSIQ total score
- IDSIQ mood domain score
- IDSIQ alert/cognition domain score

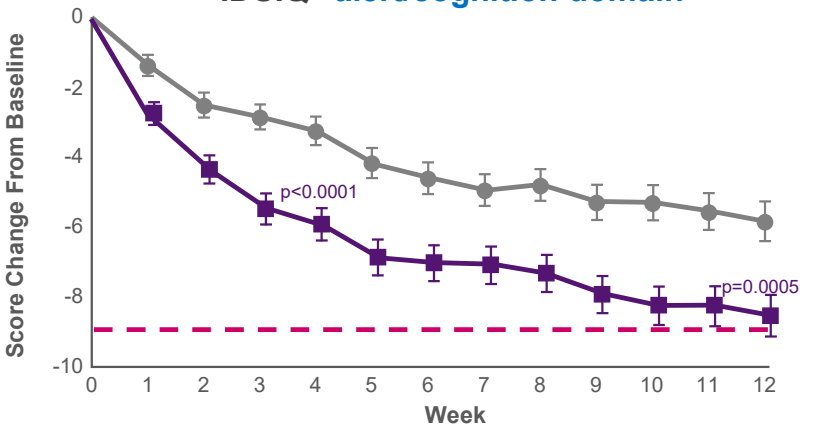
IDSIQ© total score

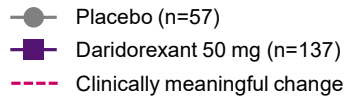


IDSIQ© mood domain



IDSIQ© alert/cognition domain



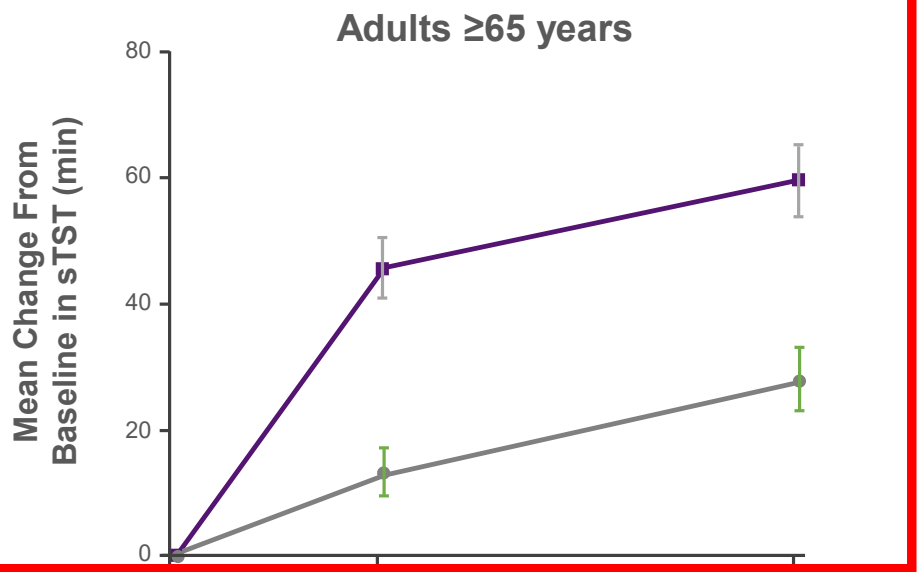


Clinically meaningful improvements with daridorexant can be achieved over time

Sleep outcomes with daridorexant are also significant in elderly patients with insomnia disorder

Subjective total sleep time

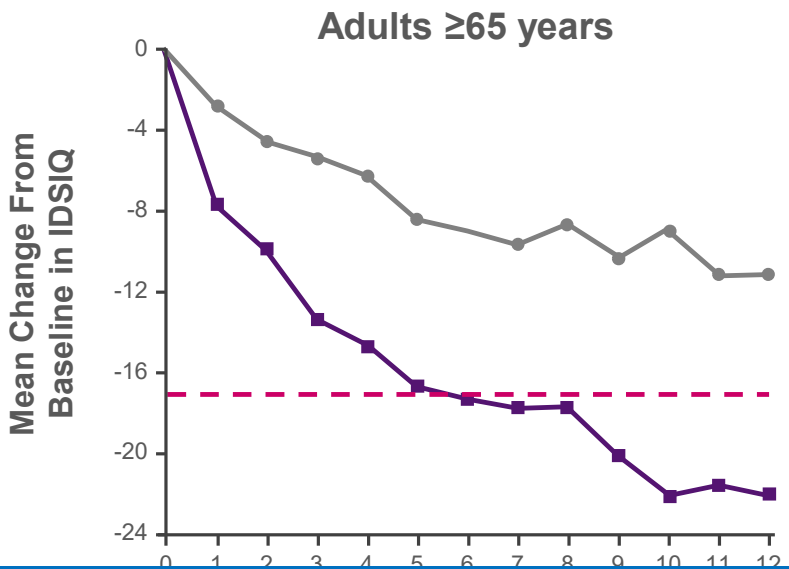
Change from baseline to months 1 and 3



Increased **sTST** by 59.9 minutes (95% CI: 49.6 minutes, 70.3 minutes)

IDSIQ*† total score

Change from baseline to months 1 and 3



Decreased **IDSIQ total scores** by −21.0 (95% CI: −24.7, −17.3)

 †Developed by Buysse DJ, Thompson W, Scott J, Franzen PI, Germain A, Hall M, Moul DE, Nofzinger EA and Kuper DJ of the University of Pittsburgh and as amended by Idorsia Pharmaceuticals Ltd. P-value vs placebo, IDSIQ total score, not adjusted for multiplicity. Error bars represent standard error of the mean. CI, confidence interval; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; sTST, subjective total sleep time. Fietze I, et al. *Drugs Aging* 2022; doi: 10.1007/s40266-022-00977-4.

Tolerability

Summary of adverse events	Full population[1] Daridorexant 50 mg (n=308)	Full population[1] Placebo (n=309)	Adults ≥65 years[2] Daridorexant 50 mg (n=119)	Adults ≥65 years[2] Placebo (n=122)
Participants with ≥1 adverse event, n (%)	**116 (38)**	**105 (34)**	42 (35)	38 (31)
Adverse event leading to treatment discontinuation, n (%)	3 (1)	10 (3)	1 (1)	6 (5)
Participants with ≥1 serious adverse event, n (%)	3 (1)	7 (2)	0	3 (3)
Participants with a given adverse event (≥2% in any group), n (%)				
Nasopharyngitis	20 (6)	20 (6)	7 (5.9)	4 (3.3)
Headache	19 (6)	12 (4)	6 (5.0)	5 (4.1)
Accidental overdose	8 (3)	5 (2)	3 (2.5)	0
Fatigue	7 (2)	2 (1)	3 (2.5)	1 (0.8)
Dizziness	7 (2)	2 (1)	1 (0.8)	1 (0.8)
Nausea	7 (2)	3 (1)	4 (3.4)	1 (0.8)
Somnolence	5 (2)	6 (2)	1 (0.8)	1 (0.8)
Fall	1 (<1)	8 (3)	1 (0.8)	4 (3.3)
Upper respiratory tract infection	1 (<1)	3 (1)	0	0
Adverse events of special interest, n (%)				
Excessive daytime sleepiness	1 (<1)	1 (<1)	0	0
Sleep paralysis	1 (<1)	0	1 (1)	0
Hallucinations	0	0	0	0
Suicidal ideation/self-injury	0	0	0	0

AE rate for daridorexant 50 mg **was low and comparable to placebo**

No <u>adverse events</u> of <u>narcolepsy or cataplexy</u> were observed

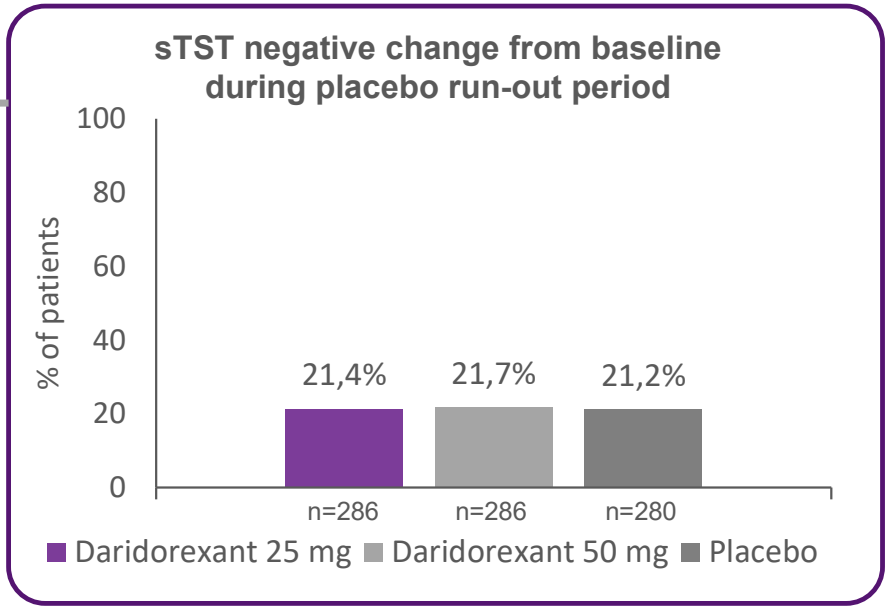
NR, not reported. 1. Mignot E, et al. *Lancet Neurol* 2022;21:125–39; 2. Fietze I, et al. *Drugs Aging* 2022; doi: 10.1007/s40266-022-00977-4.

Tolerability

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

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

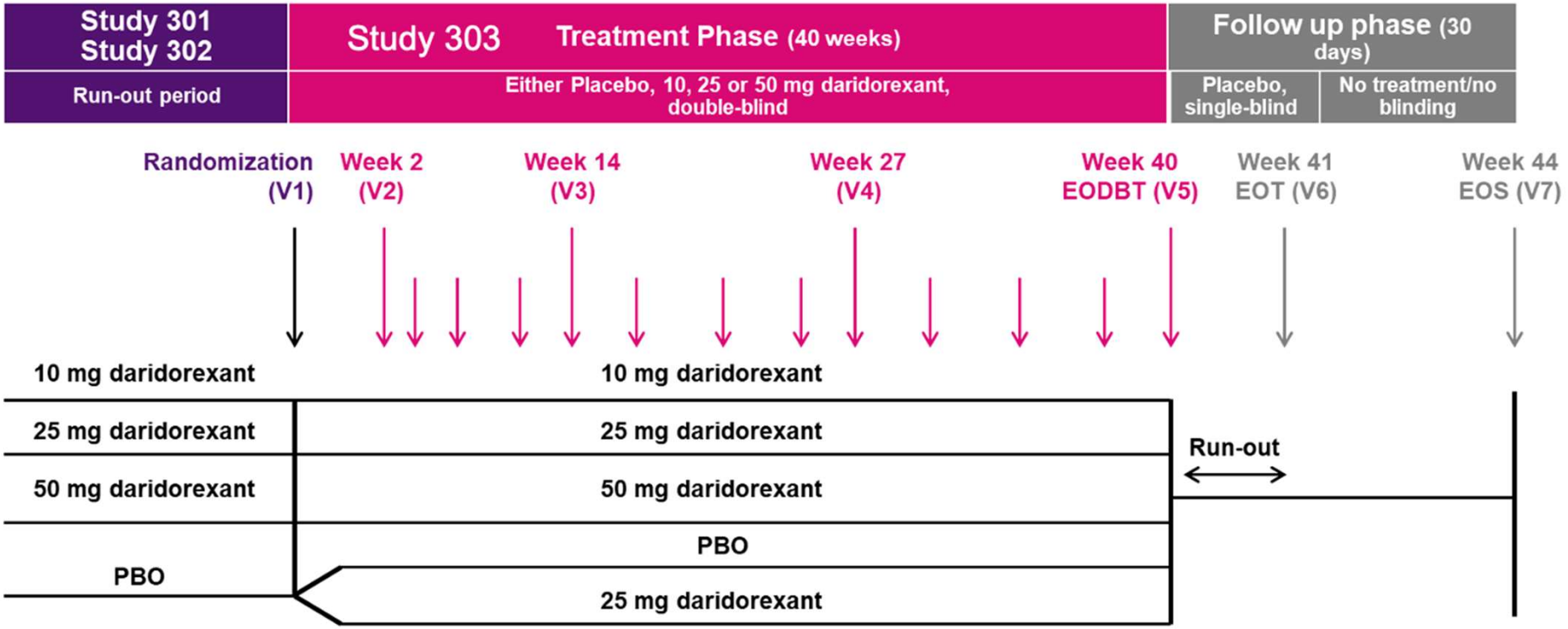
No evidence of TEAEs suggestive of **drug abuse potential**



Well tolerated and safe in patients with insomnia disorder

[a]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.

Long term safety extension study (40 weeks)

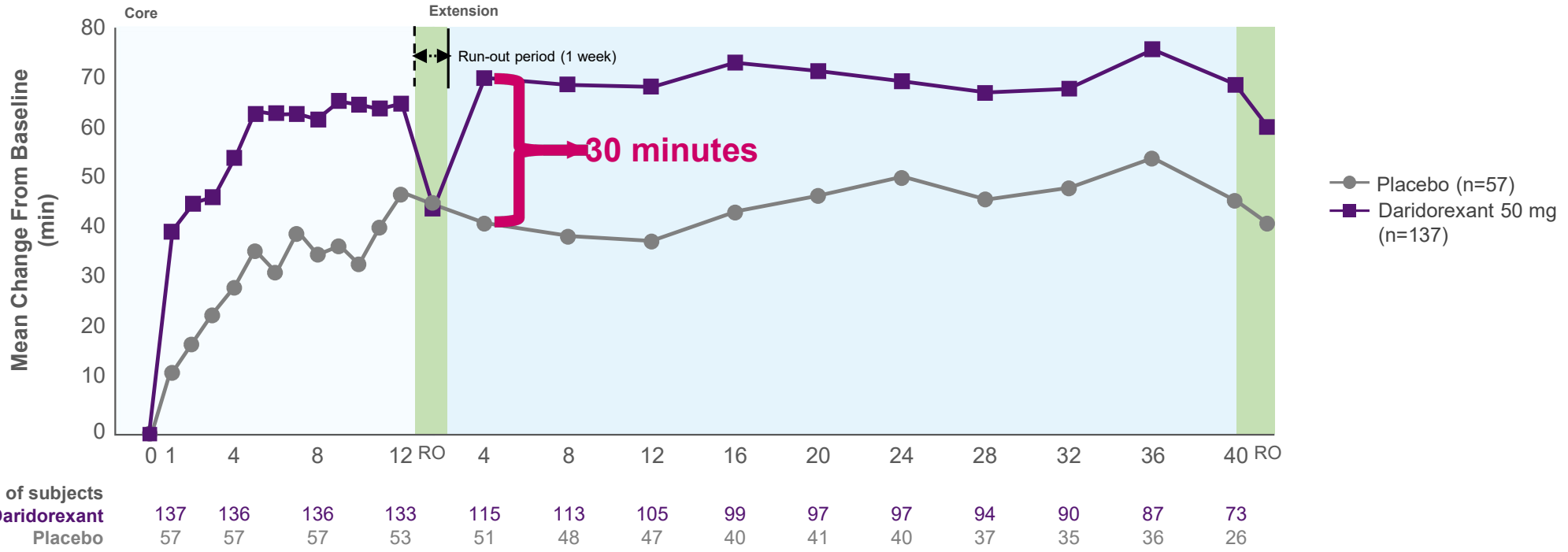


No new safety signals observed in the extension study

EODBT, end of double-blind treatment; EOS, end of study; EOT, end of treatment; PBO, placebo; V, site visit.
Kunz D, et al. *Sleep Med* 2022;100(Suppl 1):S130.

Daridorexant treatment improvements were maintained over 1 year

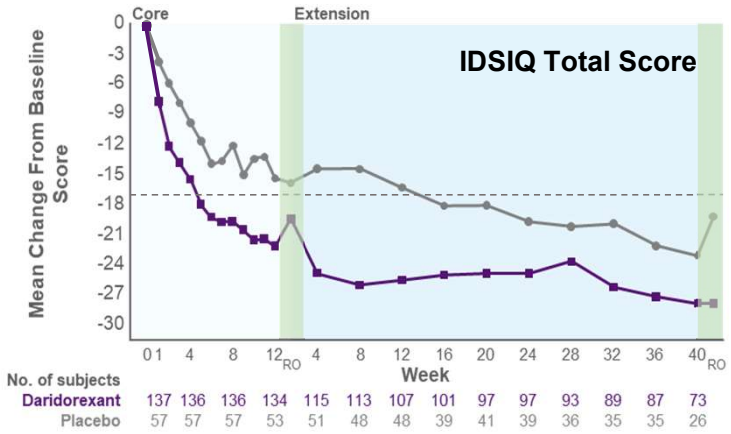
Subjective Total Sleep Time exploratory endpoint at weeks 12, 24 and 36: 12-week core and 40-week extension study

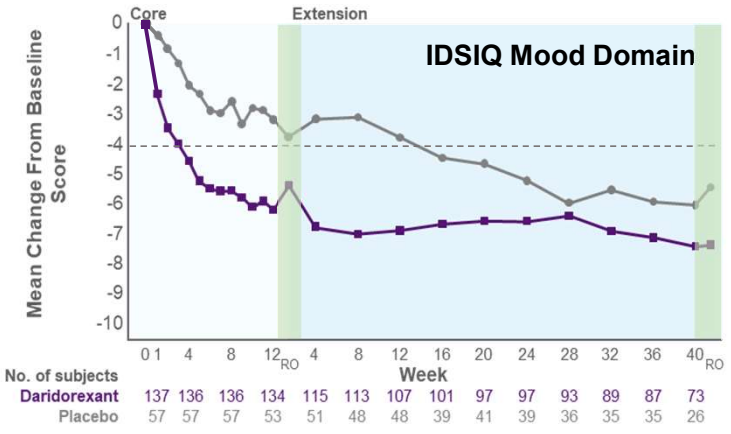


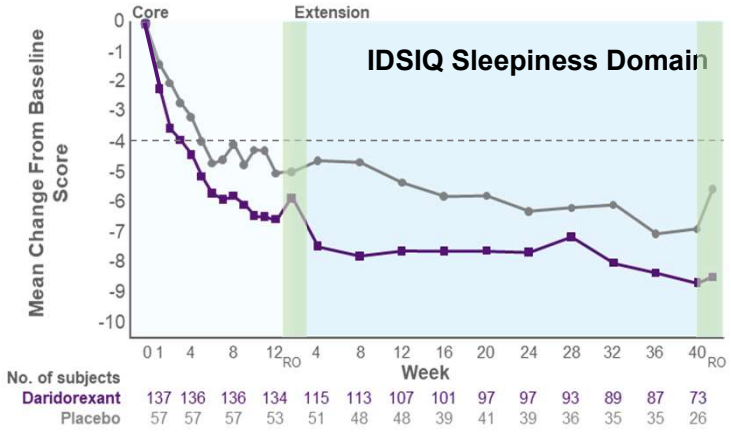
No. of subjects														
Daridorexant	137	136	136	133	115	113	105	99	97	97	94	90	87	73
Placebo	57	57	57	53	51	48	47	40	41	40	37	35	36	26

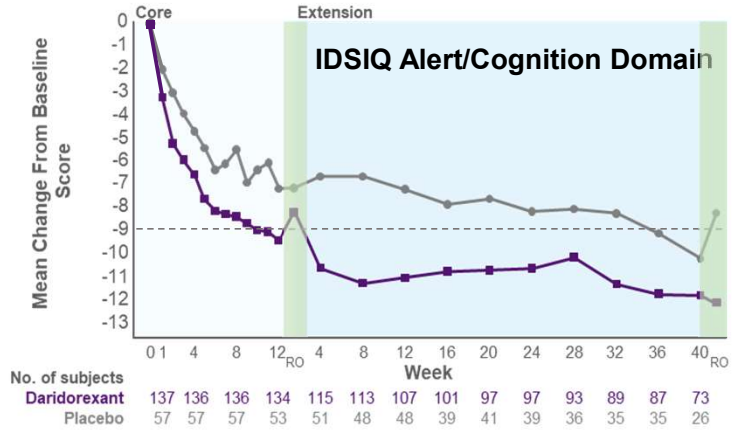
Grey shading indicates run-out period with both arms receiving placebo only.
NS, not significant; RO, run-out.
Mignot E, et al. *Lancet Neurol* 2022;21:125–39; Kunz D, et al. *Sleep Med* 2022;100(Suppl 1):S130.

Improvement in IDSIQ©[a]† continued up to 1 year







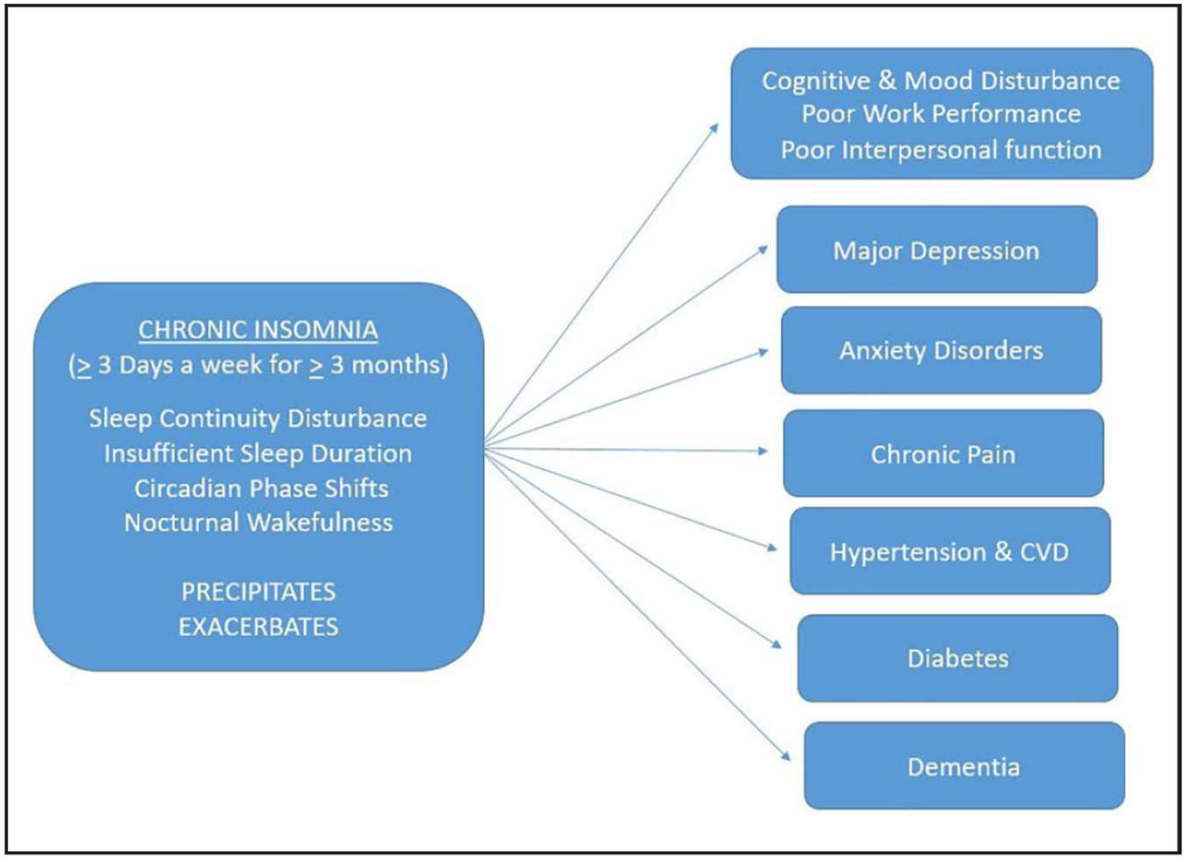


Exploratory endpoints at weeks 12, 24 and 36

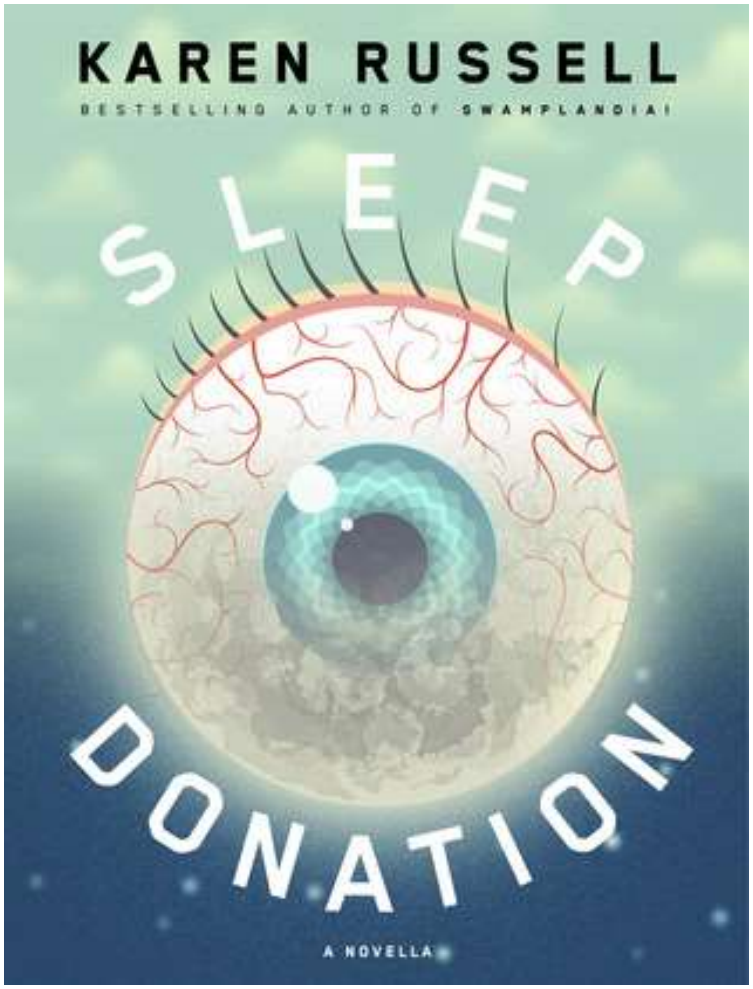
Placebo (n=57)
Daridorexant 50 mg (n=137)
Clinically meaningful change

[a]© 2020, University of Pittsburgh. All rights reserved. IDSIQ-14 derivative created 2020 by Idorsia Pharmaceuticals Ltd under license and distributed by Idorsia Pharmaceuticals Ltd under license. †Developed by Buysse DJ, Thompson W, Scott J, Franzen PI, Germain A, Hall M, Moul DE, Nofzinger EA and Kuper DJ of the University of Pittsburgh and as amended by Idorsia Pharmaceuticals Ltd. Grey shading indicates run-out period with both arms receiving placebo only. FDA, US Food and Drug Administration; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; RO, run-out. Mignot E, et al. *Lancet Neurol* 2022;21:125–39; Kunz D, et al. *Sleep Med* 2022;100(Suppl 1):S130.

Why treat insomnia…or simply how to treat?



Perlis et al., 2021 Journal of Primary Care & Community Health



America has been suffering from an insomnia crisis where hundreds of thousands of cases are terminal…

What if sleep were a commodity?

And what if sleep may be bought or sold?

Patiens are called «***orexins***»

an infant donor — a miracle child really — who possesses the soundest sleep in the country


Giuseppe Vitrani


Simone Cappellano


Marco Caccamo


Federica Testa


Andrea Romigi

Sleep Medicine Center

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Grazie!