Sleep meds and snags:

New avenues and safe use of hypnotics 2021

FIORE LALLA

Divulgation des conflits d'intérêts

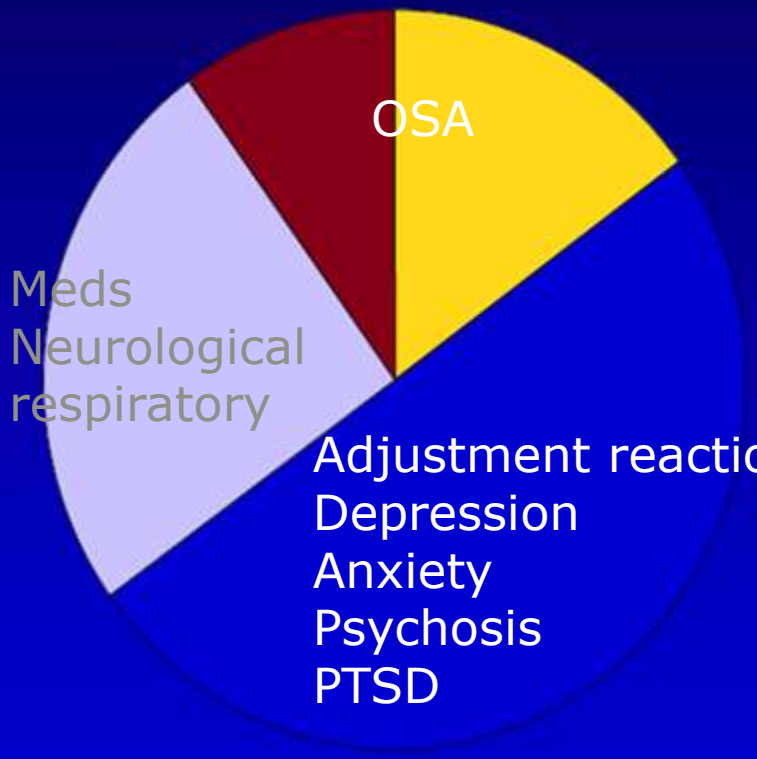
Conseil consultatif ou comité analogue	
Essais cliniques ou études	
Honoraires ou autres revenus	Valeant, BMS, Otsuka, Eli Lilly, Lundbeck, Janssen, Shire, Eisai, Sunovion
Subventions de recherche	

Despite any potential conflicts of interest, my presentation will be strictly scientific and will not be influenced by any commercial interests

Goals of presentation

- Give participants a working knowledge of sleep medicine as regards mental health
- To help clinicians prescribe treatments safely but with the knowledge that sleep disorders are chronic, and require ongoing therapy
- To present clinicians with safe modern hypnotic modalities

Frequency of Insomnia Causes



- Primary Insomnia (15%)
- Psychiatric Disorders (50%)
- Other Illnesses, Medications, etc (25%)
- Other Sleep Disorders (10%)

Ford and Kamerow, 1989.


SLEEP WAKE DISORDERS
Insomnia Disorder
Hyper - somnolence Disorder
Narcolepsy
Breathing-related sleep disorders
Circadian Rhythm sleep-wake disorders
Non-REM sleep arousal disorders
Nightmare disorder
REM sleep behavior disorder
Restless Leg Syndrome
Substance /Medication induced sleep disorder

A simple paradigm

- Medical illness & meds (psychiatric)
- Obstructive
- Psychiatric, especially acute stress
- Primary sleep problem
- Environmental
- "MOPPE"

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5548844/#

Effects of Antidepressants on Sleep
Adam Wichniak

Antidepressant Insomnia

- In the STAR*D study, 55% on chronic Celexa had frequent wakening and 70% sleep disruption independent of depression severity

- Luvox (high dose)
  - Over 30% mod-sev insom
- Effexor XR (Reg dose)
  - 24% each insom+somnol in GAD, half as much in depn
- Remeron
  - No insomnia, 54% somnol vs 18% placebo
- Trazodone
  - 46% somnolence vs 19% placebo (more unpredictable)
- Trintellix
  - Sleep wake problems disappear with dosings

La sérotonine n'est pas toujours bonne

L'ISRS active →

Récepteur $5HT_{1A}$ Régénération neurale
Anxiolytique
Dopamine
Élévation de l'humeur

$5HT_{2A}$/$5HT_{2C}$: moins de NA/D au CPF
Insomnie
Agitation
Dysfonction sexuelle
Apathie
Déficit cognitif
Apathie
Obésité (?)

→ Détérioration de l'humeur

Résistance intrinsèque

Résumé d'après Stahl's Essential Psychopharmacology.

CPF : cortex préfrontal; D : dopamine; ISRS : inhibiteur du recaptage de la sérotonine; NA : noradrénaline

SYNDROME 2:
DEPRESSION AND INSOMNIA

- Insomnia patients without depression have an odds ratio (OR) of 6.2 for developing depression
- Fava et al. ont démontré que les patients présentant une insomnie à composante dépressive répondent plus rapidement et plus efficacement aux antidépresseurs lorsqu'ils prennent aussi des somnifères
- 25% more clinical response , less suicidality in acute phase

SYNDROME 3: SLEEP APNEA

The Lalla Experience

- PSG results of 18 psychiatric patients complaining of months-long fatigue and/or insomnia not responsive to medication changes and sleep hygiene (9 lab tested, 9 HST):
  - 1 patient: no sleep apnea
  - 6:mild
  - 4:moderate
  - 7:severe

SYNDROME 4:
RESTLESS LEGS SYNDROME

Restless Legs

end-stage renal disease and hemodialysis

•iron deficiency

•certain medications that may aggravate RLS symptoms, such as antinausea drugs (e.g. prochlorperazine or metoclopramide), antipsychotic drugs (e.g., haloperidol or phenothiazine derivatives), antidepressants that increase serotonin (e.g., fluoxetine or sertraline), and some cold and allergy medications that contain older antihistamines (e.g., diphenhydramine)

•use of alcohol, nicotine, and caffeine

•pregnancy, especially in the last trimester; in most cases, symptoms usually disappear within 4 weeks after delivery

•neuropathy (nerve damage).

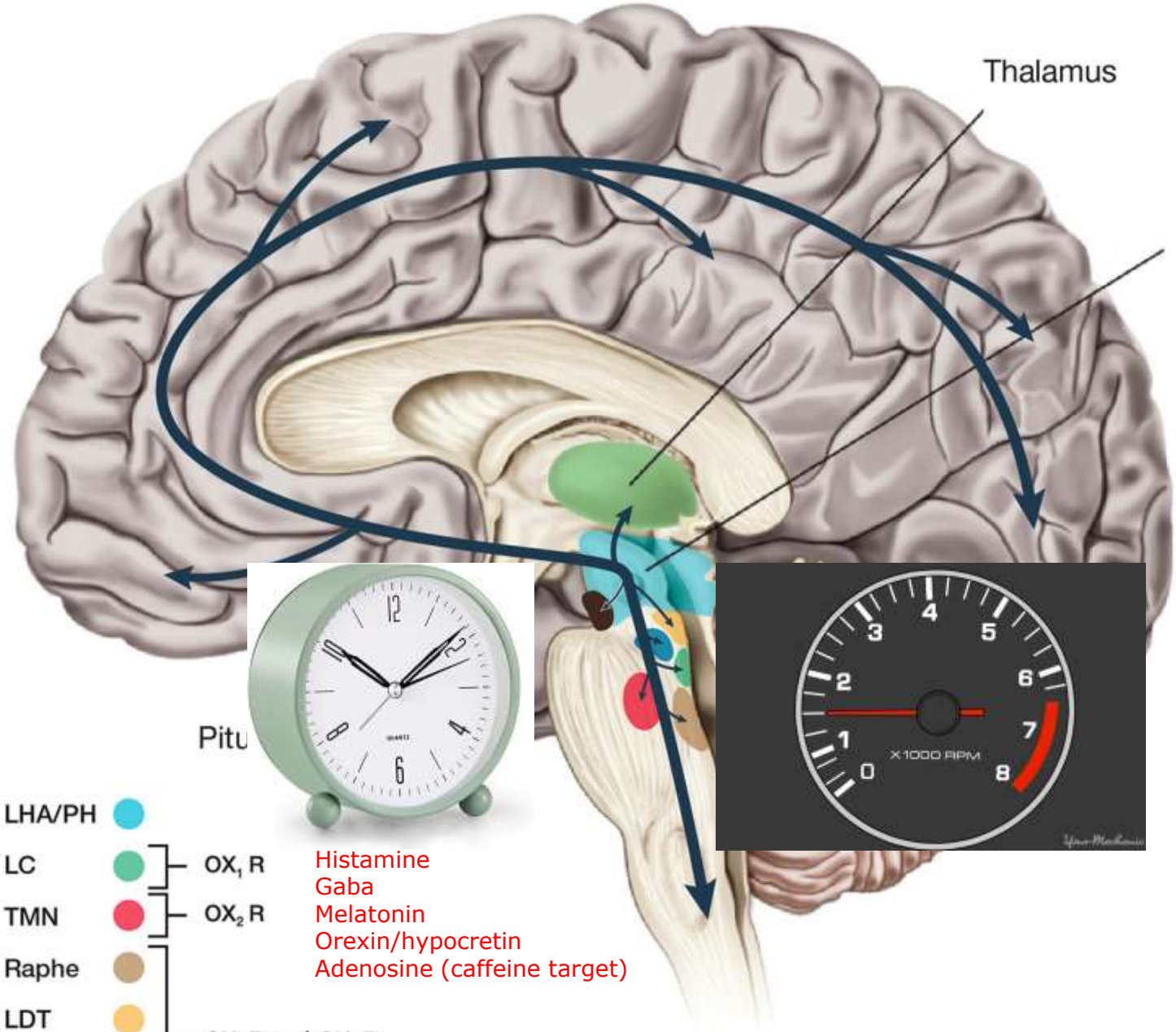
Sleep deprivation and other sleep conditions like sleep apnea

TABLE 2.

Antidepressant Effects on RLS

Antidepressants that Cause or Exacerbate RLS	Antidepressants with Neutral or Beneficial Effects
Venlafaxine	Amitriptyline
Fluoxetine	Nortriptyline
Sertraline	Doxepin
Paroxetine	Trazodone
Citalopram	Bupropion
Mianserin	

Abbreviation: RLS, restless legs syndrome.


Thalamus
Hypothalamus
Pitu
LHA/PH
LC
OX1 R
TMN
OX2 R
Raphe
LDT
VTA
PPT
OX1 R and OX2 R
Histamine
Gaba
Melatonin
Orexin/hypocretin
Adenosine (caffeine target)
Histamine
Dopamine
Norepinephrine
Serotonin
Acetylcholine

British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update

Psychopharm

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

DOI: 10.1177/0269881119855343
journals.sagepub.com/home/jop

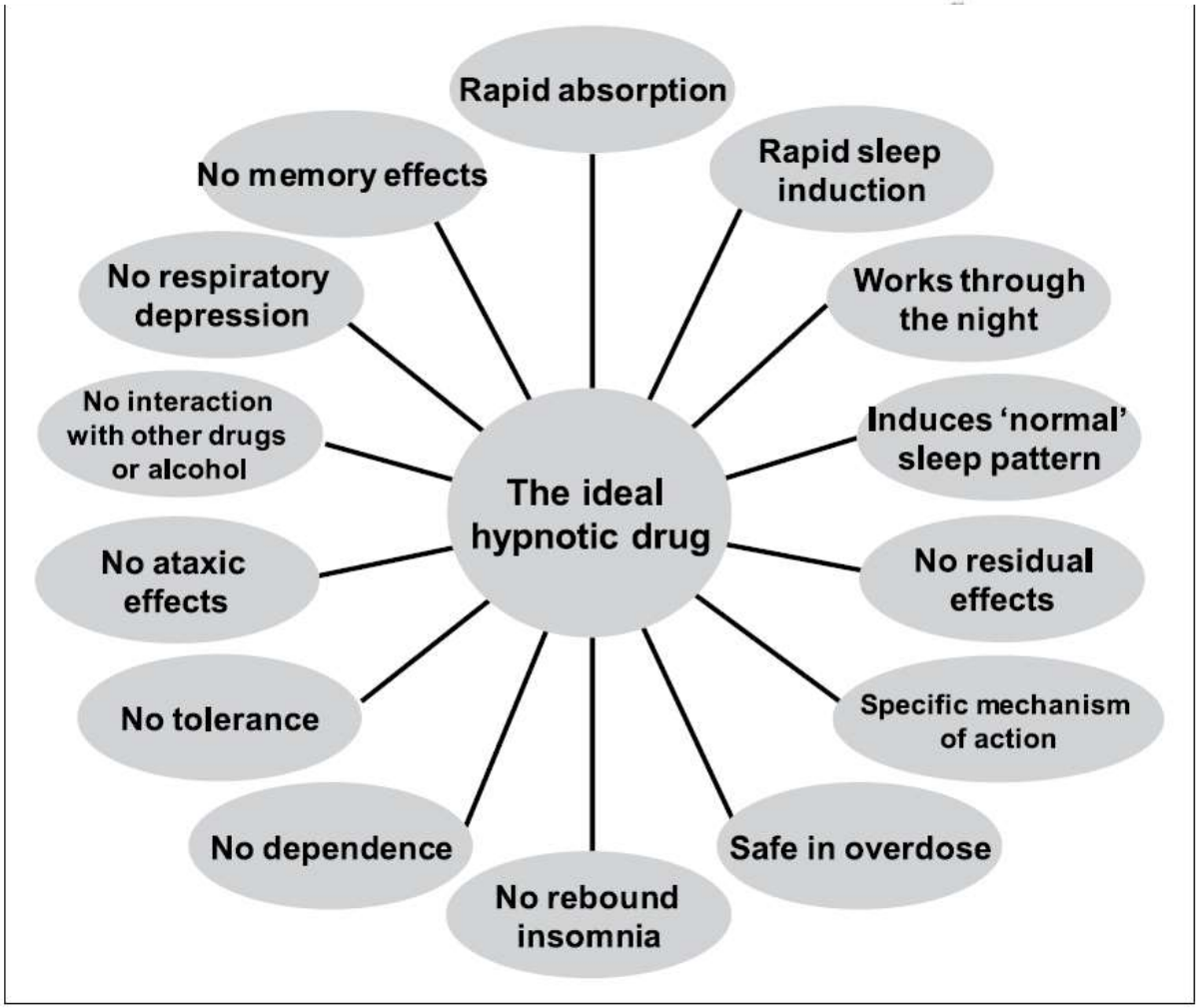


Figure 3. The ideal sleeping pill.

Modern sedatives: comparisons

2nd gen benzos & BZRAs (z drugs)

- Database: strong
- Effect size 0.7-0.9 on sleep variables
- Risks:
  - Dependence: varies widely amongst these
    - Psychomotor
    - Cognitive
  - Addiction or dependance 5 times or more with benzos vs. z drugs

Others: antipsychotics, antidepressants, histaminergics, antiepileptics

- Database:weak
- Usually work to help sleep on bkgrd of other illness
- Risks:
  - long half lives
  - Very inconsistent: melatonin only shown to work>55 and trazodone may worsen outcomes in drug abusers
  - Habituation: antihistamines
  - Medical and metabolics: frequent and severe: diabetes, lipids, urinary retention, severe constipation, cognitive impairment, hypotension, obesity
  - These appear surprise guests in a very unpredictable way

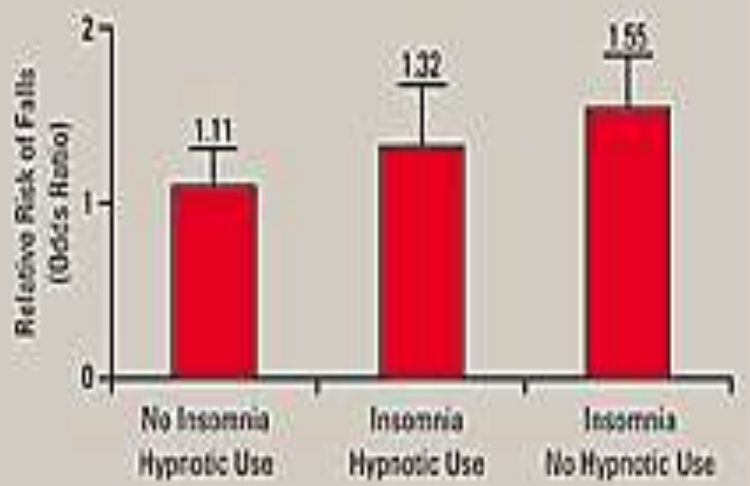
Rest Easy: Benzos, Z-Drugs, and Dementia

From The Carlat Psychiatry Report, January 2021, Mind-Gut Connection
Review of: Osler M and Jorgensen MB, Am J Psych 2020;177(6):497–505

- 235,000 subject cohort
- First mood disorder hospitalization followed for 3-11 years
- Dementia differences reviewed for patients started on z drugs or benzos and those not
- "there was a decreased risk of dementia in the first 2 years after study entry if a benzodiazepine or z-drug was prescribed (hazard ratio 0.7).
- For years 2 through 20 after study entry, there was no association between dementia and use of benzodiazepines or z-drugs, even when stratifying based on number of prescriptions, duration of use, combined use, and half-life."

FIGURE 12

Predicting Falls in the Elderly[1]



Insomnia, but not hypnotic use, is associated with greater risk of subsequent falls in 34,163 nursing home residents, mean age 84±8 years, 76% female.

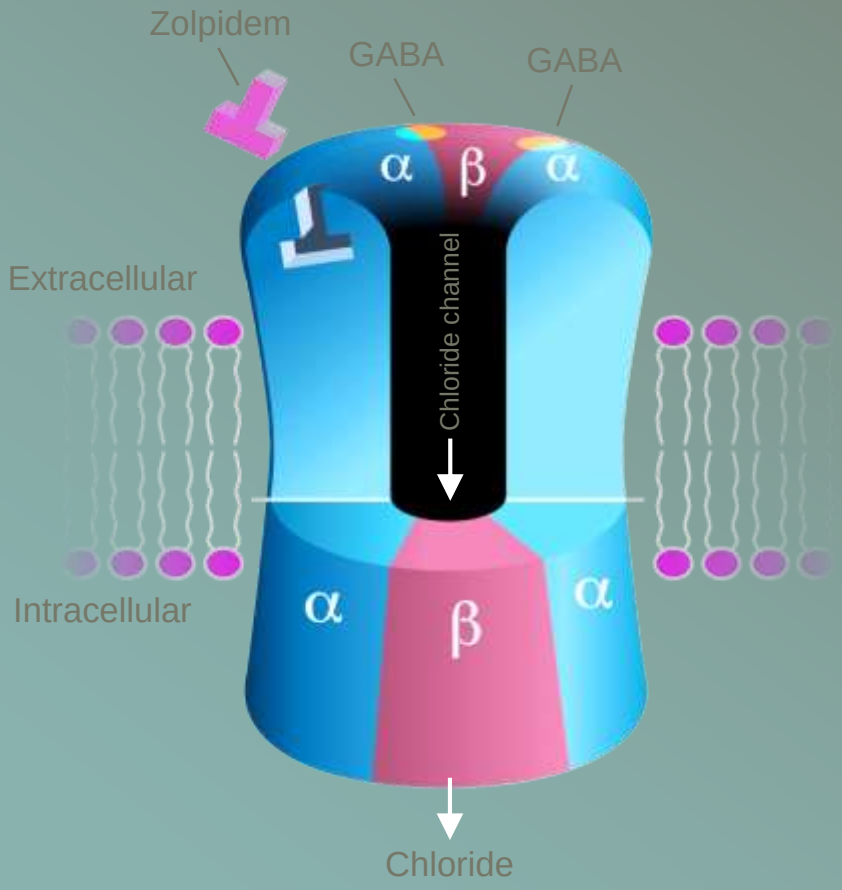
Note: These models were controlled for age, gender, functional status, cognitive status, intensity of resource utilization, burden of illness, number of medications taken, emergency department visits, and new admissions.

Practical perfection for hypnotics, especially in medical populations

- Keep half life and Tmax modest
  - Sublinox too short: then "abused"
  - Rivotril and even Ativan too long
  - Older BZDs and antideps: yikes!
- Avoid anticholinergic compounds
  - Doxepin is a strong one at all doses
  - Nozinan micro dosing a late option
- Avoid nonselective Gaba agonists
  - Benzos disinhibit elderly, axis 2, MH
  - Xanax can have a 15% dependency rate
  - Often needed for panic/GAD/depn comorbidity
- Avoid hypotensives
  - Seroquel, trazodone, not benign: LOW AND SLOW
  - Esp in elderly or antihypos already on board
- Avoid Prn dosings for sleep
  - 2/3 of benzos taken in overdose are prns
- Keep modern
  - Z drugs and DORAs: they were made for sleep (multiple sets of guidelines)

Z drugs Mechanism of Action

GABA A Receptors Mediate Effects



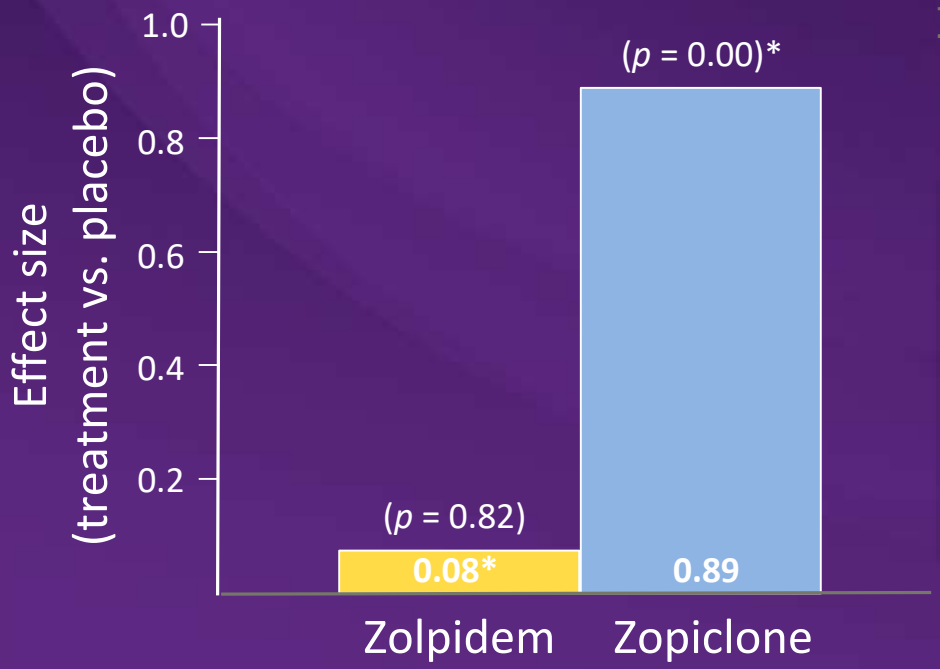
Distribution and Functional Effect of GABA-A Receptor Alpha Subunits		
Subunit	**Regional Distribution**	**Putative Role**
Alpha 1	All brain regions	Hypnotic, anticonvulsant, memory
Alpha 2	Cerebral cortex, hippocampus, amygdala, basal ganglia, hypothalamus, septal, and basal forebrain	EEG activity, anxiolytic
Alpha 3	Cerebral cortex, reticular thalmic nucleus	Sleep, anxiolytic, antidepressant
Alpha 5	Cerebral cortex, hippocampus	Learning and memory

Zolpidem is a hypnotic agent which binds to the GABA A alpha 1 subunit

Adapted from Nutt DJ. *J Clin Sleep Med* 2006; 2(2):S7-11.
Adapted from: van Zyl LT, et al. *C J Diagnosis* 2013; 30(11):37-47.

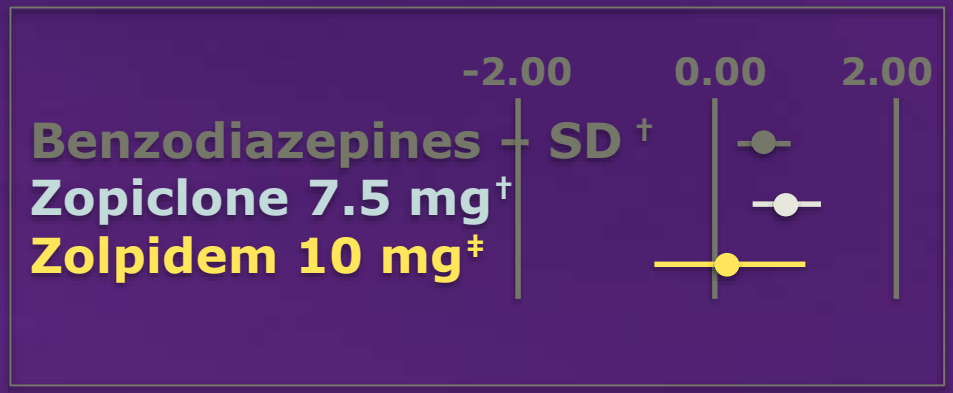
Hypnotics and Driving Safety Meta-Analysis

Zolpidem, in comparison to zopiclone, was associated with a lower risk of driving impairment** in the morning (10-11 hrs after bedtime administration)



*Significant driving impairment was found if $p < 0.05$

10-11 hours after bedtime administratio
Effect Sizes



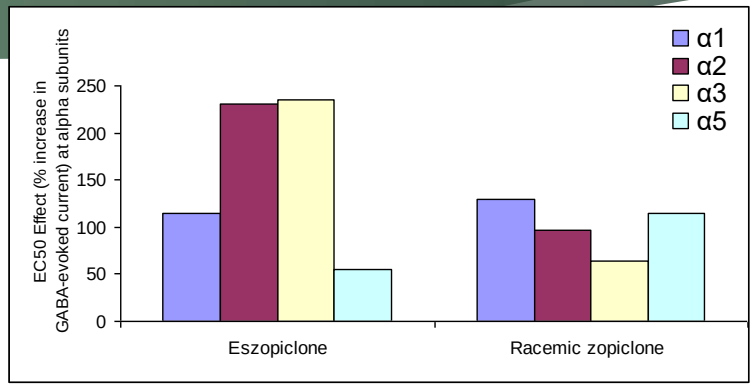
†$p = 0.00$, ‡$p = 0.82$

*Impairment was evaluated by comparing the treatment differences for each drug (effect size) versus placebo

Verster JC, et al. *Curr Drug Saf* 2006; 1(1):63-71.

Le retrait des isomères R crée un changement de pharmacocinétique

- **Zopiclone racémique :** les effets principalement médiés par **α1, α5**
- **Eszopiclone :** des effets provenant principalement de **α2, α3**



	α1	α2	α3	α5
Implications cliniques proposées de la modulation	Effet Sédatif Amnésique Anticonvulsivant	Effet Hypnotique, Anxiolytique et Myorelaxant Module l'EEG	Effet Anxiolytique Myorelaxant Douleur	Altère la cognition Effet amnésique
	zopiclone	eszopiclone		zopiclone

Nutt and Stahl J Psychopharmacol. 2010 Nov;24(11):1601-12

CLINICS

CLINICAL SCIENCE

Eszopiclone *versus* zopiclone in the treatment of insomnia

Luciano Ribeiro Pinto Jr*, Lia Rita Azeredo Bittencourt, Erika Cristine Treptow, Luciano Rotella Braga, Sergio Tufik

Universidade Federal de São Paulo (UNIFESP), Departamento de Psicobiologia, São Paulo/SP, Brazil.

Eszopiclone is effective in the treatment of insomnia, improving the severity of insomnia and demonstrating a favorable safety profile. Treatment with eszopiclone also resulted in longer total sleep time and greater sleep efficiency by polysomnography than zopiclone. However, further studies may be required to validate the polysomnographic results.

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY
2020, VOL. 16, NO. 11, 1063–1078
https://doi.org/10.1080/17425255.2020.1817380

Introducing DORA

Taylor & Francis
Taylor & Francis Group

REVIEW

Clinical pharmacology, efficacy, and safety of orexin receptor antagonists for the treatment of insomnia disorders

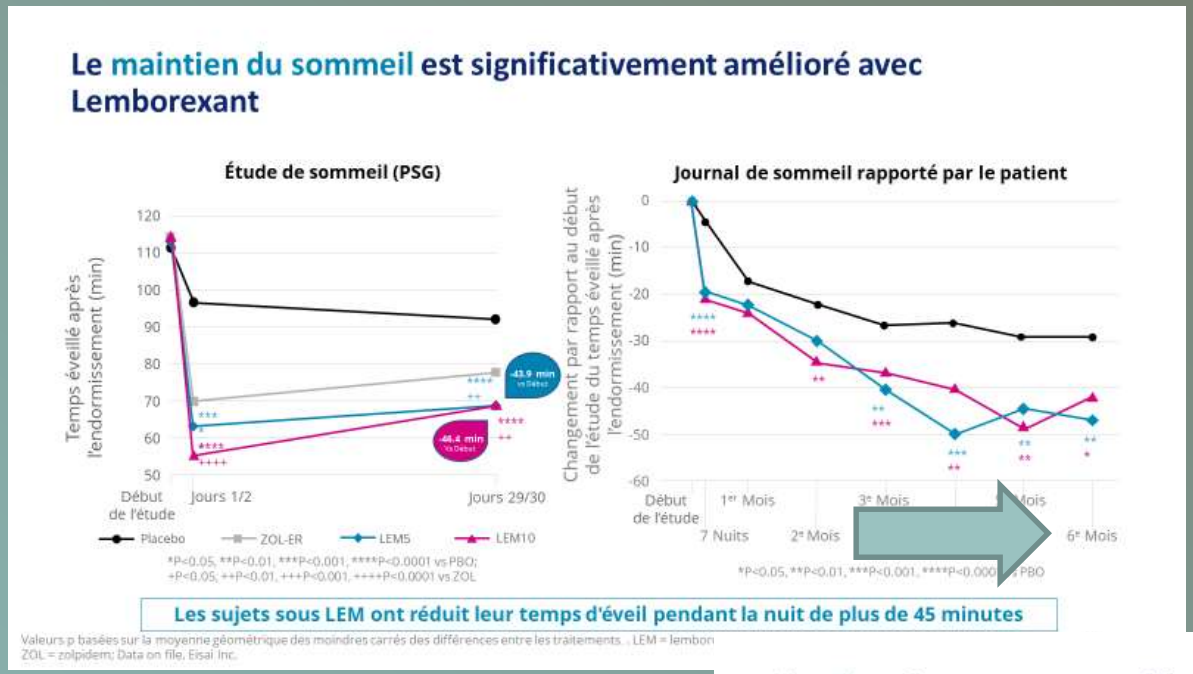
The safety and tolerability profile of ORAs clearly differ from those of more traditional sleep-promoting drugs. Further research is needed to demonstrate benefits to patients suffering from insomnia disorder, e.g., with respect to improving not only sleep but also daytime functioning. In addition, ongoing and future research will show whether ORAs may have beneficial effects in patients with various psychiatric and neurodegenerative disorders, including Alzheimer's disease.

Lemborexant (DAYVIGO):
Nouveau régulateur veille-sommeil

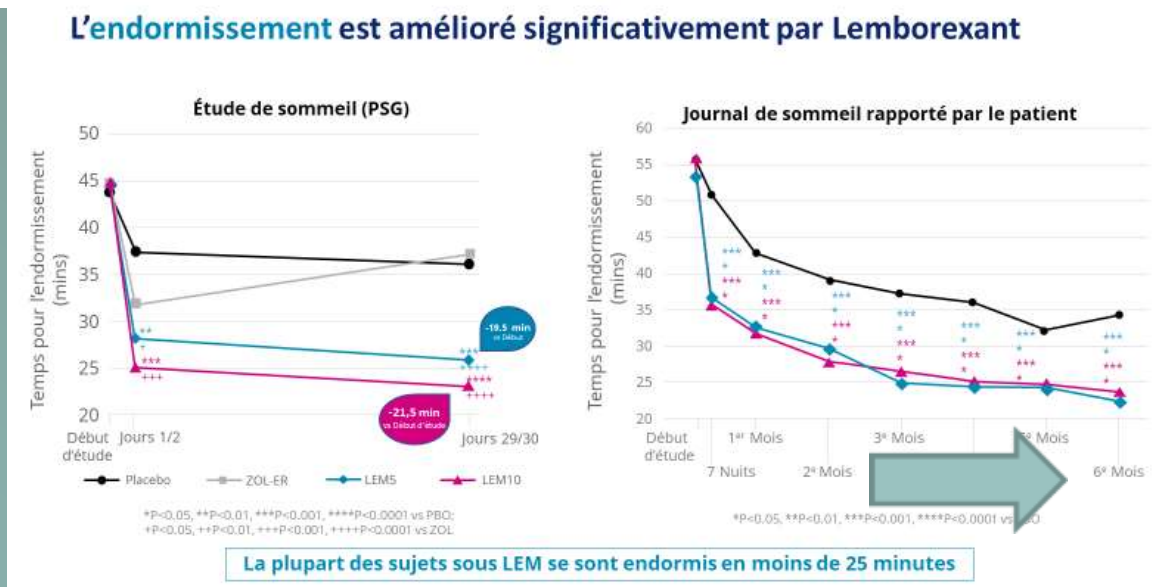
- **Mécanisme d'action:**
  - Antagoniste double des récepteurs de l'orexine (DORA):
    - Bloque les deux types de récepteurs de l'orexine pour atténuer l'éveil excessif la nuit
- **Indication:**
  - Le traitement de l'insomnie caractérisée par des difficultés d'endormissement et/ou de maintien du sommeil
- **Dosage:**
  - 5-10 mg au coucher (HS) avec au moins 7 heures avant le réveil prévu
    - Aucun ajustement nécessaire pour l'âge, le sexe ou l'IMC
    - « agit rapidement, arrête rapidement »

1. U.S. FDA Approves Eisai's DAYVIGO™ (Lemborexant) for Treatment of Insomnia in Adult Patients. URL https://www.eisai.com/news/2019/news201993.html
2. DAYVIGO™ (lemborexant) Approved for Treatment of Insomnia in Japan. URL https://www.eisai.com/news/2020/news202005.html

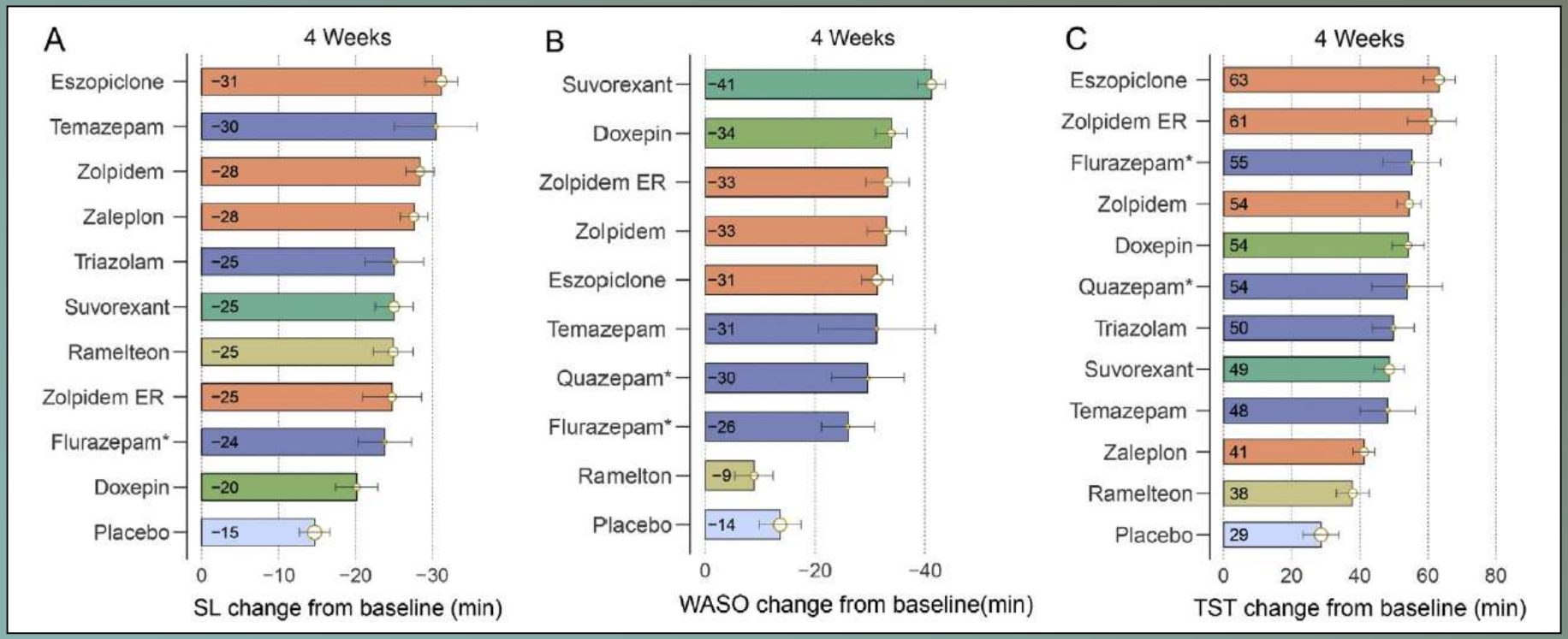
Long term efficacy



Improvement in latency, wakenings, total sleep time persist unchanged in 12 month studies



Comparaison de l'efficacité de diverses pharmacothérapies utilisées dans le traitement de l'insomnie (modélisation)



Model-estimated drug and placebo effect on sleep latency; SL (A), wake after sleep Onset; WASO (B), and total sleep time; TST (C) at 4 weeks. The baseline of SL, WASO and TST were limited to 60 min, 80 min and 330 min in model-estimation, respectively. Each point and bar represent the typical value and standard error from model simulations. Each color represents a group of treatments that belong
to the same cluster. The point size is proportional to the sample size

Zheng, Sleep Medicine 72 (2020) 41-49

Neuropsychiatric Disease and Treatment

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

A comparison of complex sleep behaviors with two short-acting Z-hypnosedative drugs in nonpsychotic patients

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
8 August 2013
Number of times this article has been viewed

Among 1,220 zolpidem or zopiclone users, 40 (3.28%) patients reported incidents of somnambulism or amnesic sleep-related behavior problems.
There was no significant association with older age, sex, side effects.

Since Ambien was approved in 1992, the FDA has identified 66 serious cases of complex sleep behaviors after a Z-drug, 20 of which resulted in death.

Comparative efficacy of lemborexant and other insomnia treatments: a network meta-analysis

Heather McElroy, MMedStat; Beth O'Leary, MPH, MSc; Michael Adena, PhD; Renee Campbell, MD, MBA, MPH; Amir Abbas Tahami Monfared, MD, PhD; and Genevieve Meier, PhD

September 2021

- 16 drugs compared including benzos,from randomized studies
- Of the objective efficacy outcomes, lemborexant was the only treatment superior to placebo on TST prolonging sleep by an average of 32 minutes.
- Lemborexant was superior to placebo, zolpidem, and ramelteon for WASO (average reduction of 20-25 minutes), and to placebo, zolpidem, zaleplon, and triazolam for latency (13-23 minutes).

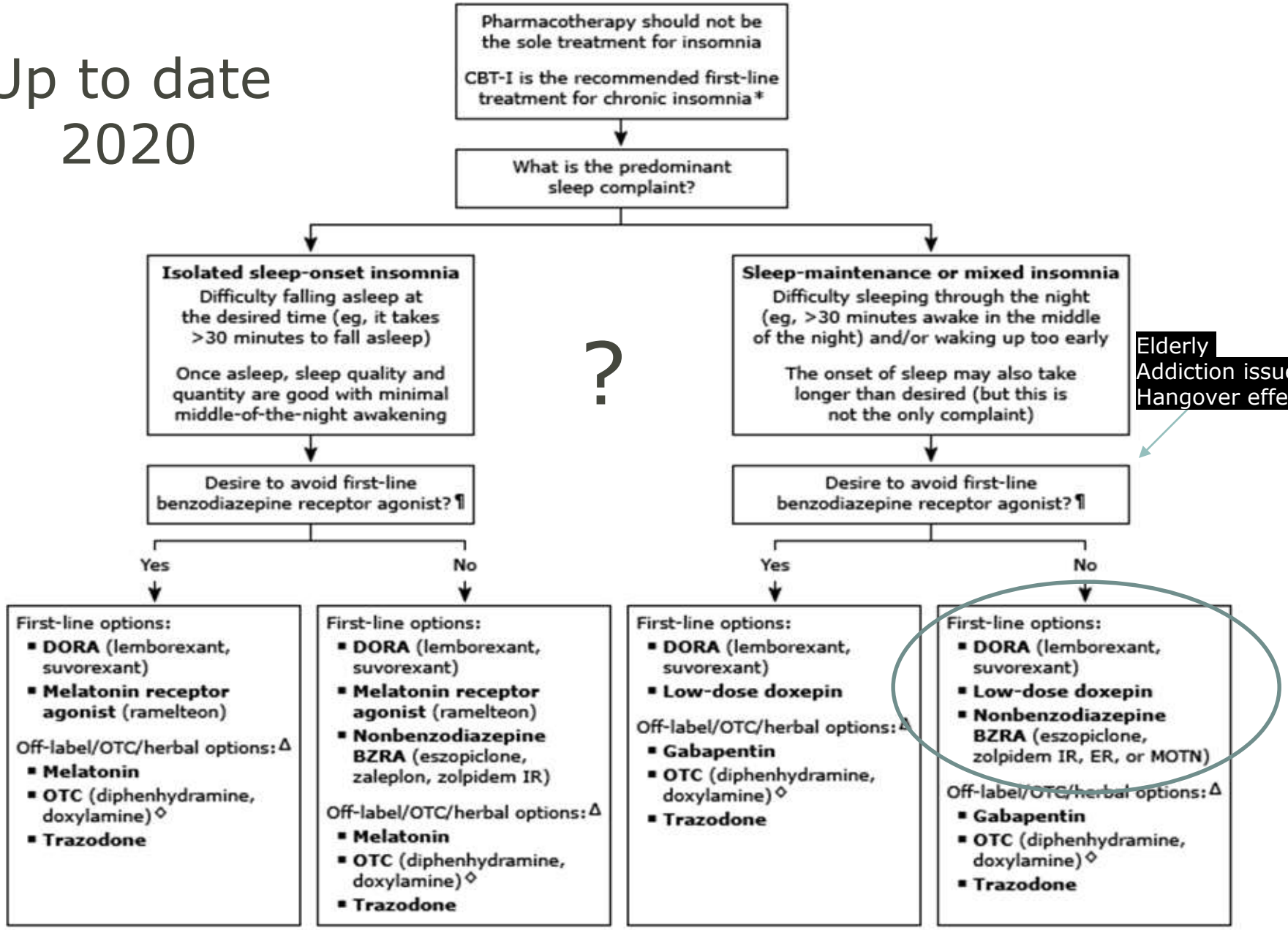
Adverse effects of lemborexant include:

(from pubmed NCBI statpearls online November 9,2021)
As with all hypnotics:

- Somnolence
- Drowsiness
- daytime impairment
- Sleep paralysis (less than 1.6% transient)
- Hypnagogic/hypnopompic hallucinations (0.1-0.7%)
- Complex sleep behaviors (2 cases in monograph)

Overview of pharmacotherapy for insomnia in adults

Up to date 2020



A final word…

- No guidelines recommend the use of sedating antidepressants or antipsychotics if avoidable
- Medication combinations have not been studied nor recommended.
- Combinations **should not**:
  - Come from same med class
  - Have similar long half lives
  - Have similar cognitive, anticholinergic, metabolic, or cardiovascular sfx

Insomnia choices

Condn comorbid w Insomnia	Preferable choices (best to least)
Depression, GAD, Panic	eszopiclone, dayvigo, zolpidem, trazodone, Seroquel, doxepin
Dementia (low doses!, DORAs in future?)	Dayvigo, Trazodone, seroquel, lyrica, doxepin, BDZ –avoid. Last choices: olanzapine, elavil, Benadryl
PTSD	(Clonidine, prazosin) +the choices above, careful with BDZ. Atypicals almost always neededDayvigo needed in mix.
Cardiorespiratory	Avoid BDZ or use low dose shorter acting ones. See dementia Rx.
Drug or alcohol dependency	See dementia Rx
Palliative care	Dayvigo, eszopiclone, trazodone, lyrica, doxepin, trazodone, avoid anticholinergics or BDZ
Personality disorders	As in dementia, avoid prns and benzos
Chronic primary insomnia	As in depression, with a preference for Z drugs and dayvigo
Sleep apnea	Z drugs with Cpap; avoid benzos