Giuseppe Bellelli

# Sonno e delirium

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Roma, 30 novembre - 3 dicembre 2022
UNIVERSITÀ CATTOLICA DEL SACRO CUORE

# My talk today

Sonno

Delirium

Evidenze di una relazione tra alterazioni del sonno e delirium

Potenziali link fisiopatologici

Trattamento

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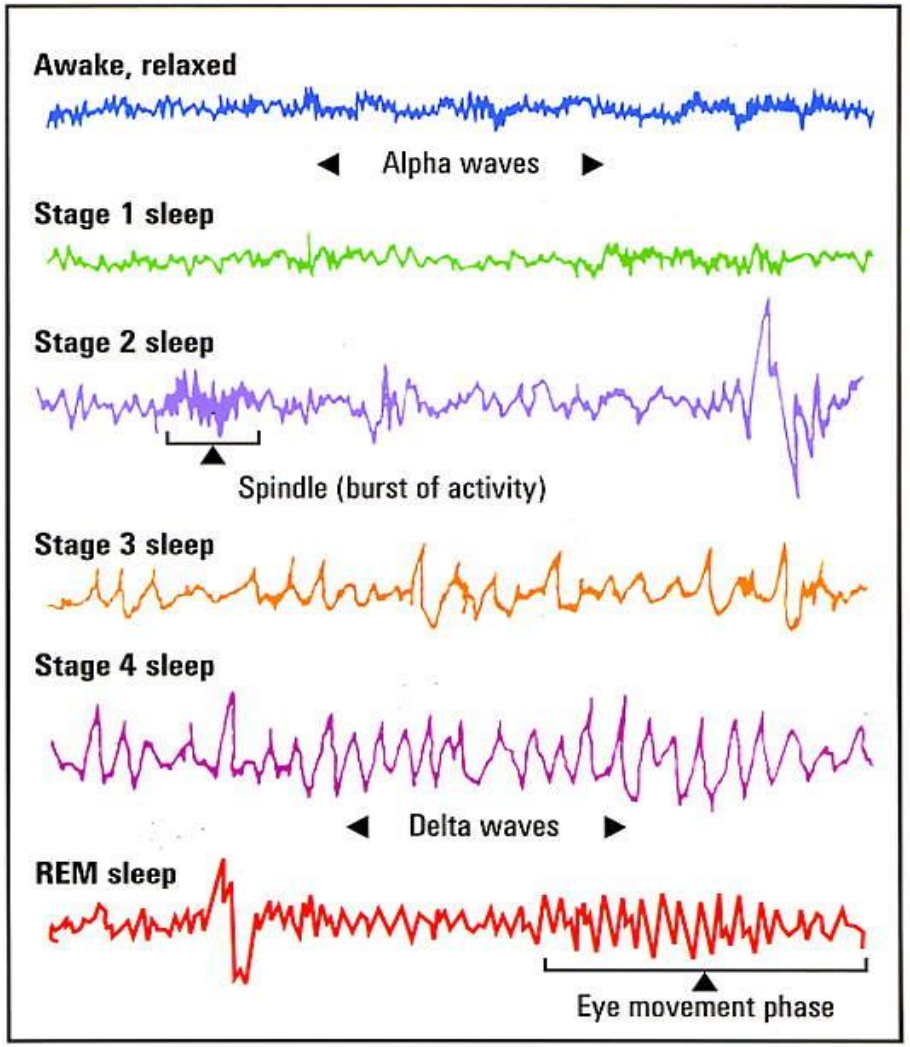
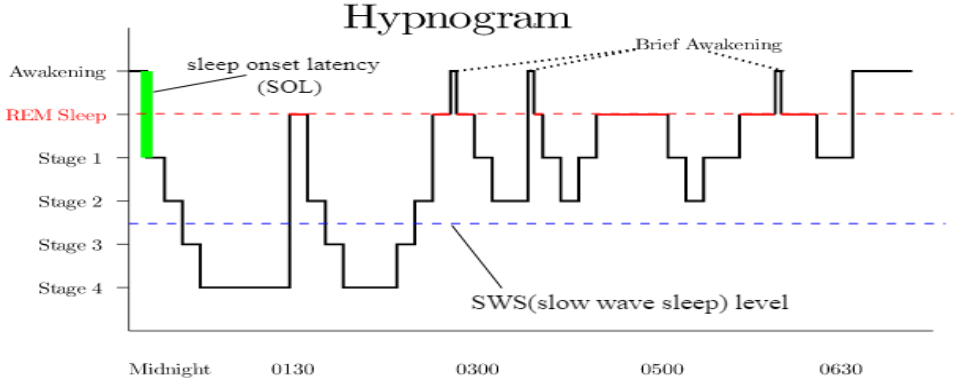
# Il sonno

- Stato biologico, comportamentale, comune a tutti gli animali, indispensabile per il cervello
- Non è soltanto uno stato di “non-veglia”, ma un vero e proprio stato comportamentale, con caratteristiche ben precise: - bassa reattività - postura stereotipata - occhi chiusi - reversibilità – periodicità
- Il sonno ha una funzione fondamentale per il funzionamento del cervello: permette la consolidazione delle memorie, permette di dimenticare, ristabilisce la possibilità di apprendere nuove informazioni il giorno seguente e permette di integrarle nel corpus di conoscenze che già possediamo

# Stages of sleep:




| Stage | | Definition |
|---|---|---|
| Stage 1: | NREM LIGHT | **Drowsiness**; small wave freq. (4-7hz), on EEG, NREM Sleep |
| Stage 2: | | **Asleep**; EEG dominated by **theta** waves but hz increases, high energy bursts on EEG (sleep spindles), NREM Sleep |
| Stage 3: | NREM DEEP | **Delta** waves, (1-4hz), less sleep spindles, NREM Sleep |
| Stage 4: | | Deepest stage of NREM, **delta** waves, hard to wake, growth **hormone** released here, SWS (slow wave sleep) |
| REM Sleep (paradoxical sleep) | | Fast desynchronised EEG, body effectively paralysed, dreaming more likely to occur |
| Move back to stage 2 (approx 20 mins): | | Move back into REM, repeat pattern, approx every 90 minutes, 4/5 a night |



*Review*

## Sleep Disturbance, Sleep Disorders and Co-Morbidities in the Care of the Older Person

Christine E. Mc Carthy [1,2]

*Med. Sci.* 2021, 9, 31. https://doi.org/10.3390/medsci9020031

CLINICAL REVIEW

## Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis

Le Shi [a, b], Si-Jing Chen [b], Meng-Ying Ma [c], Yan-Ping Bao [a], Ying Han [a], Yu-Mei Wang [d], Jie Shi [a], Michael V. Vitiello [e], Lin Lu [b, a, *]

Sleep Medicine Reviews 40 (2018) 4–16

## The effect and relative importance of sleep disorders for all-cause mortality in middle-aged and older asthmatics

Zhigang Hu[1,2,3*], Yufeng Tian[4], Xinyu Song[1,3], Fanjun Zeng[1,3], Ke Hu[5] and Ailan Yang[2]

*BMC Geriatrics* *(2022) 22:855*

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*«Acute confusion is a far more common herald of the onset of physical illness in an old person than are, for example, fever, pain or tachycardia»*

*Lipowski ZJ, 1983*

Il delirium è una **sindrome neuropsichiatrica acuta** caratterizzata in particolar modo da disturbi dell'**attenzione** e della **consapevolezza** di sé nell'ambiente.

È espressione di una **sofferenza metabolica cerebrale** conseguenza di **problemi clinici acuti** quali infezioni, squilibri elettrolitici, interventi chirurgici, intossicazione da farmaci o loro sospensione.

L'esordio è improvviso e l'andamento tipicamente fluttuante

*DSM-5 Ed criteria*

## Hyperactive delirium

Predominantly restless and agitated

- Increased motor activity
- Loss of controll of activity
- Restlessness
- Wandering

## Mixed motor type

Evidence of both subtypes in the previous 24 hours

## Hypoactive delirium

Commonly mistaken for depression or dementia

Predominantly drowsy and inactive

- Decreased activity
- Decreased action speed
- Decreased speed of speech
- Decreased amount of speech
- Reduced awareness of surroundings
- Listlesness
- Withdrawal

## Adverse consequences

### All types of delirium

- Reduces functional ability
- Onset dementia
- Increased mortality
- Admission to long term care
- Distress
- Increased length of stay
- Hospital acquired complications
- Pressure sores
- Incontinence
- Falls

### Hypoactive delirium

- + Greater mortality
- Less reversibility
- + Greater length of stay
- Worse quality of life
- + Greater frequency of falls

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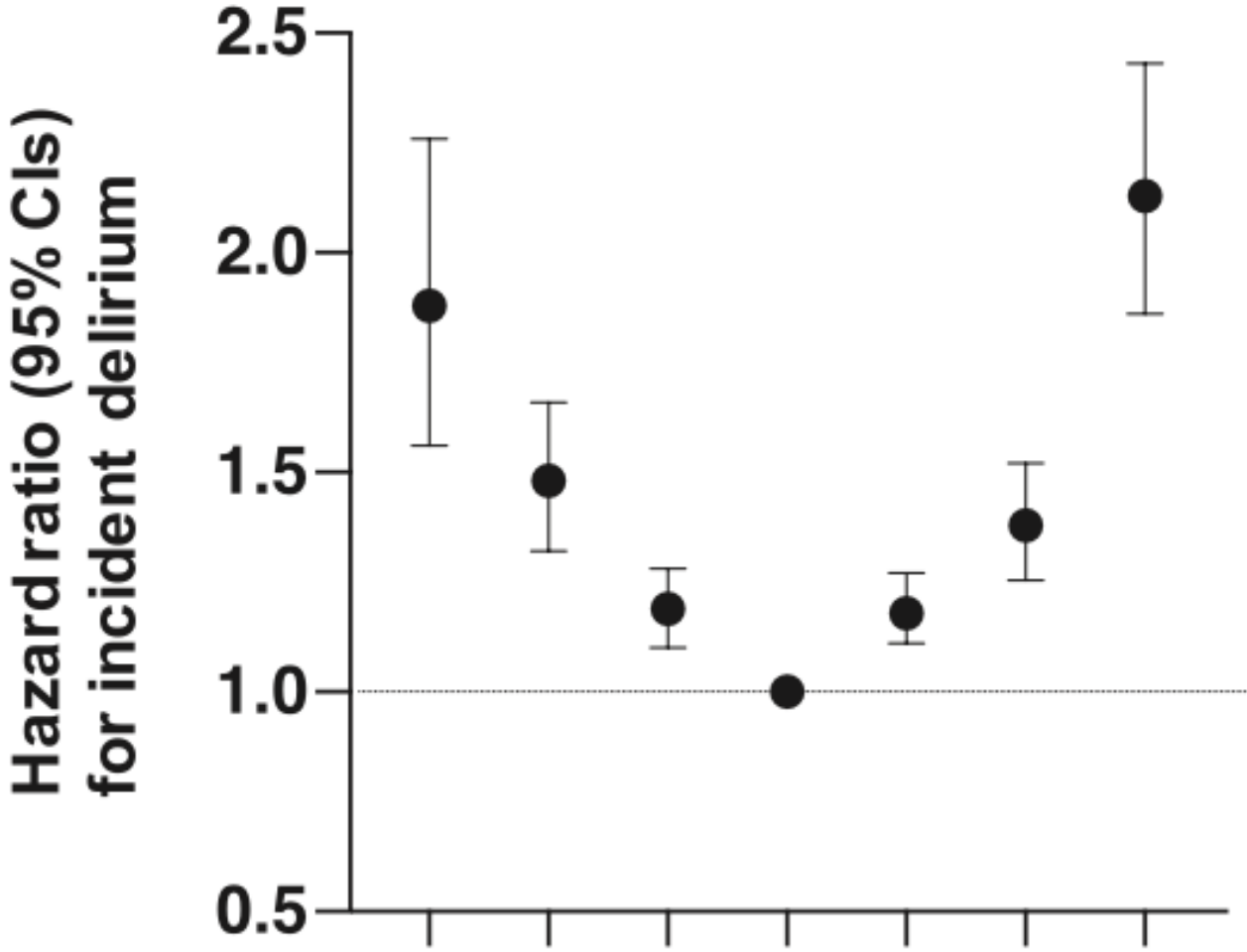
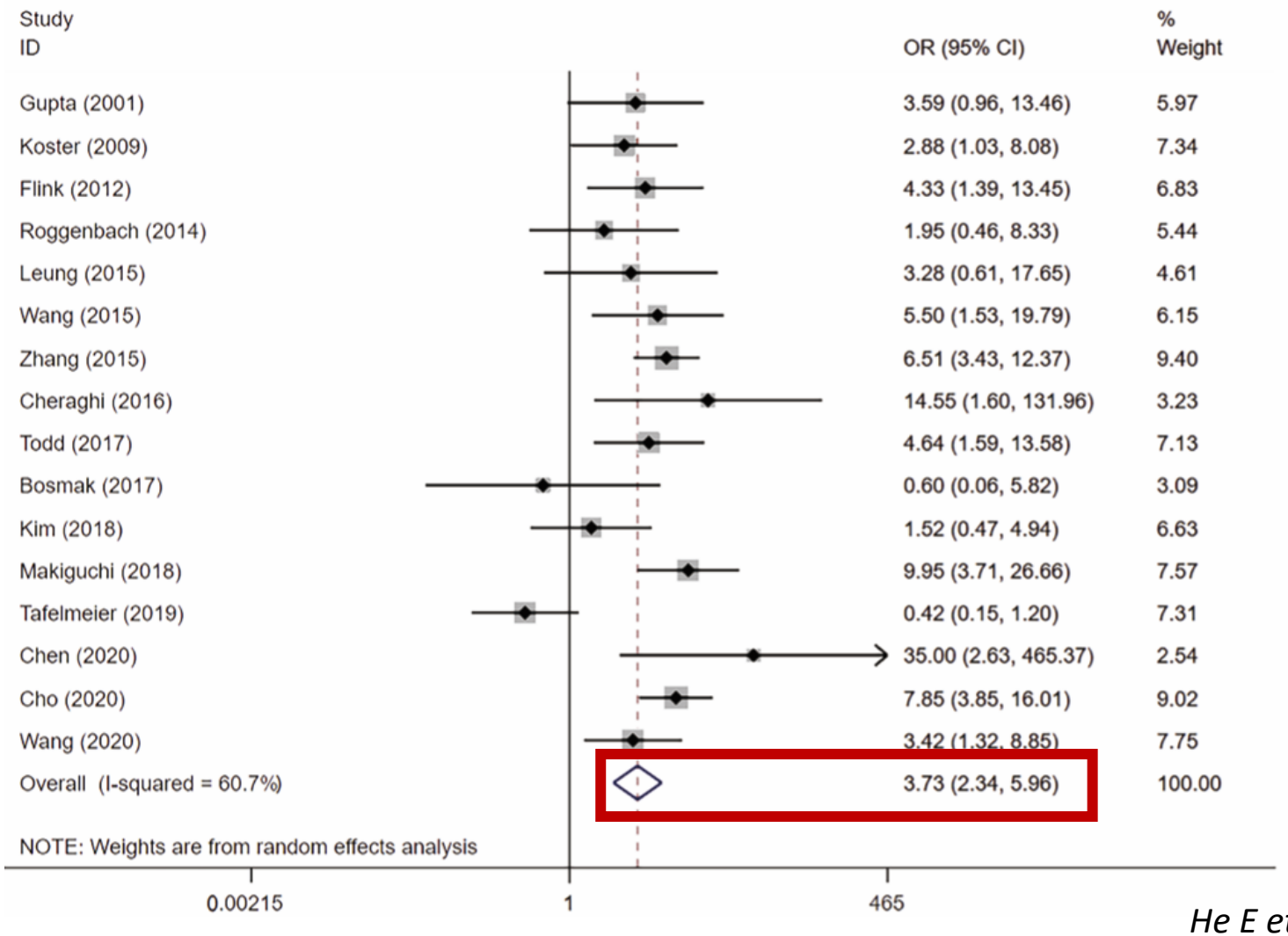
# Association of Poor Sleep Burden in Middle Age and Older Adults With Risk for Delirium During Hospitalization

321 818 participants from the UK Biobank (mean age 58±8 years; 2006–2010)




*Cherrysse Ulsa M et al, JGMS 2022*

# Relationship of sleep disturbance and postoperative delirium: a systematic review and meta-analysis




- PubMed, Embase, Cochrane Library, and Web of Science databases were searched for relevant studies from database inception to April 28, 2021
- 18 articles (2,714 patients), with most of the included literature being of moderate to high quality.

*He E et al, Gland Surg 2022;11(7):1192-1203*

# Sleep deprivation and delirium common neurocognitive traits

Inattention

Fluctuating mental status

Altered level of consciousness

Cognitive slowing

Incoordination

Irritability

Psychoses

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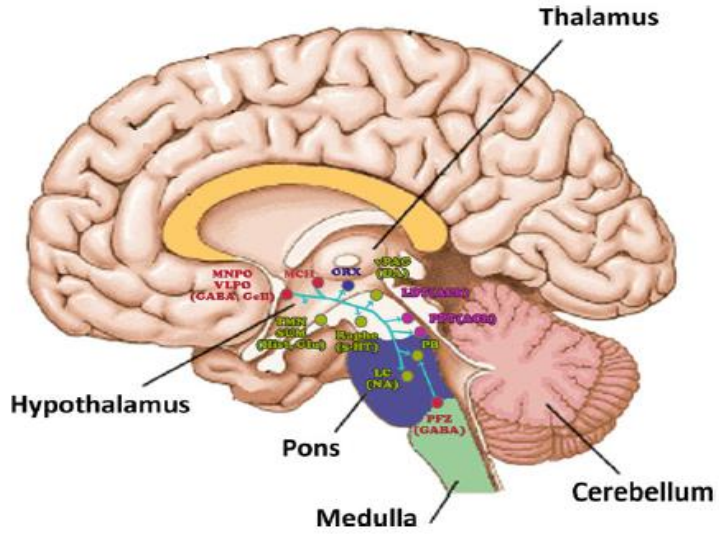
SLEEP




WAKE

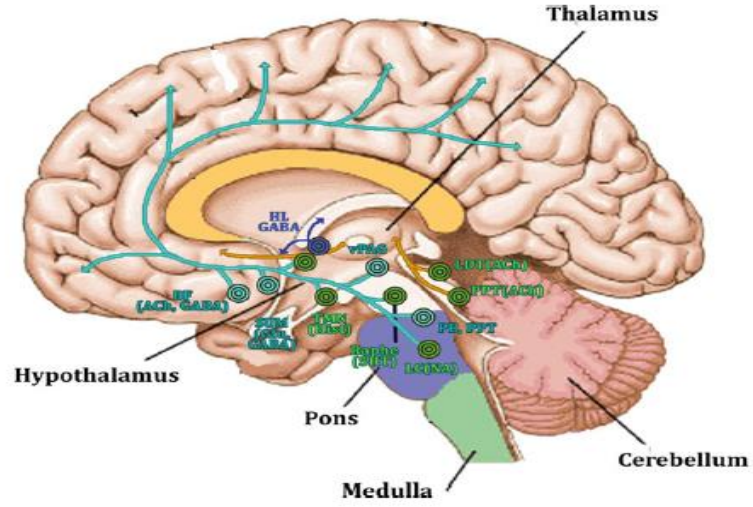



**Fig. 1.2** Wakefulness tract

**Table 2** Components of the wake–sleep-regulatory system

| Components | Projection | Substance | Effect |
|---|---|---|---|
| ARAS 1st pathway | | | |
| PPT | Thalamus | Acetylcholine | Wakefulness, REM sleep |
| LDT | Thalamus | Acetylcholine | Wakefulness, REM sleep |
| ARAS 2nd pathway | | | |
| TM | Forebrain | Histamine | Wakefulness, suppress NREM |
| LC | Forebrain | Noradrenaline | Wakefulness, suppress REM |
| Raphe[a] | Forebrain | Serotonin (5-HT) | NREM sleep, wakefulness, suppress REM |
| vPAG | Forebrain | Dopamine | Wakefulness, REM sleep |
| Other components | | | |
| LH area | Forebrain | Melatonin | REM sleep |
| | ARAS | Orexin | Wakefulness |
| | | Glutamate | Wakefulness |
| BF area | Forebrain | Acetylcholine | Wakefulness, REM sleep |
| | | GABA | Sleep |
| | | Glutamate | Wakefulness |
| VLPO | | | |
| VLPO cluster and VLPO extended | ARAS | GABA and galanin | Sleep |

*ARAS* ascending reticular activating pathway, *PPT* pedunculopontine nucleus, *LDT* laterodorsal tegmental nucleus, *TM* tuberomammillary nucleus, *LC* locus coeruleus nucleus, *vPAG* ventral periacueductal grey matter, *LH* lateral hypothalamic, *BF* basal forebrain, *GABA* gamma-amino-butiric-acid, *VLPO* ventrolateral preoptic

[a] Raphe, dorsal, and median raphe nuclei

Sleep Science 9 (2016) 285–288

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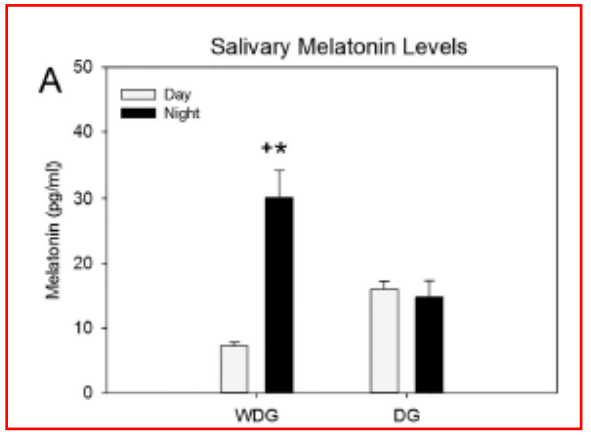
journal homepage: www.elsevier.com/locate/ssci

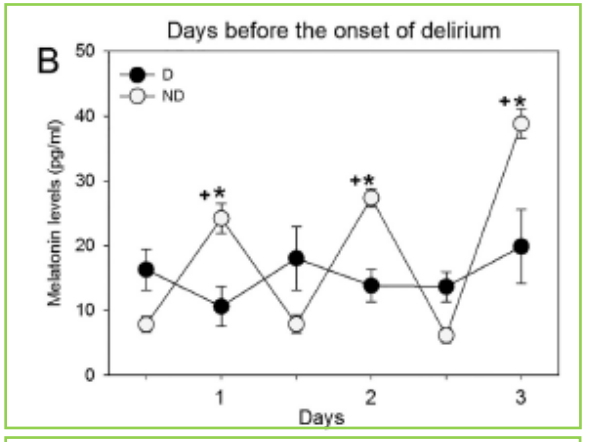
Short communication

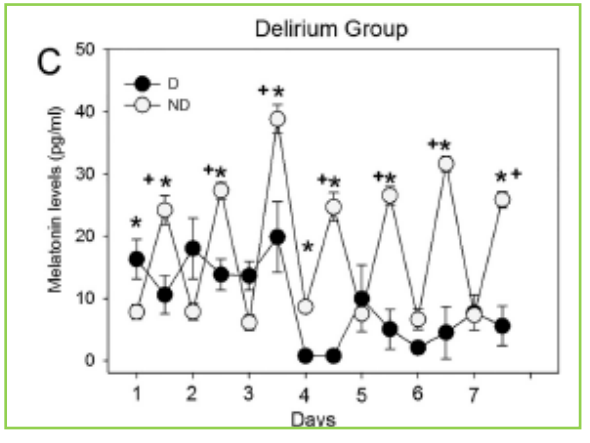
# Loss of melatonin daily rhythmicity is asociated with delirium development in hospitalized older adults

Manuel Ángeles-Castellanos [a,*], Fátima Ramírez-Gonzalez [b], Laura Ubaldo-Reyes [a], Oscar Rodriguez-Mayoral [c], Carolina Escobar [a]

[a] Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico
[b] Hospital "Manuel Gea González", S.S. México, Mexico
[c] Instituno Nacional de Cancerología, S.S. México, Mexico



# FLIP-FLOP switch mechanism of sleep-wake cycle

**Fig. 1** Representation of the "flip-flop" switch mechanism that regulates sleep–wake-cycle. Ascending reticular activating system (ARAS) is "On" during wakefulness by active firing from wakefulness-promoting neurons (pedunculopontine *PPT*; laterodorsal tegmental *LDT*, locus coeruleus *LC*, tuberomammillary *TM*, dorsal and median raphe nuclei, and ventral periaqueductal grey *vPAG*). Neurotransmitters (noradrenaline *NA*, histamine, and serotonin 5-*HT*) are released from the ARAS neurons to inhibit ventrolateral preoptic (*VLPO*) neurons which provoke VLPO to turn "off". Orexin peptide strengthens the ARAS by direct excitation of the monoaminergic neurons, while monoaminergic neurons simultaneously send an inhibitory influence to orexin neurons. *Solid arrow* represents excitatory input, *dashed arrow* represents inhibitory input

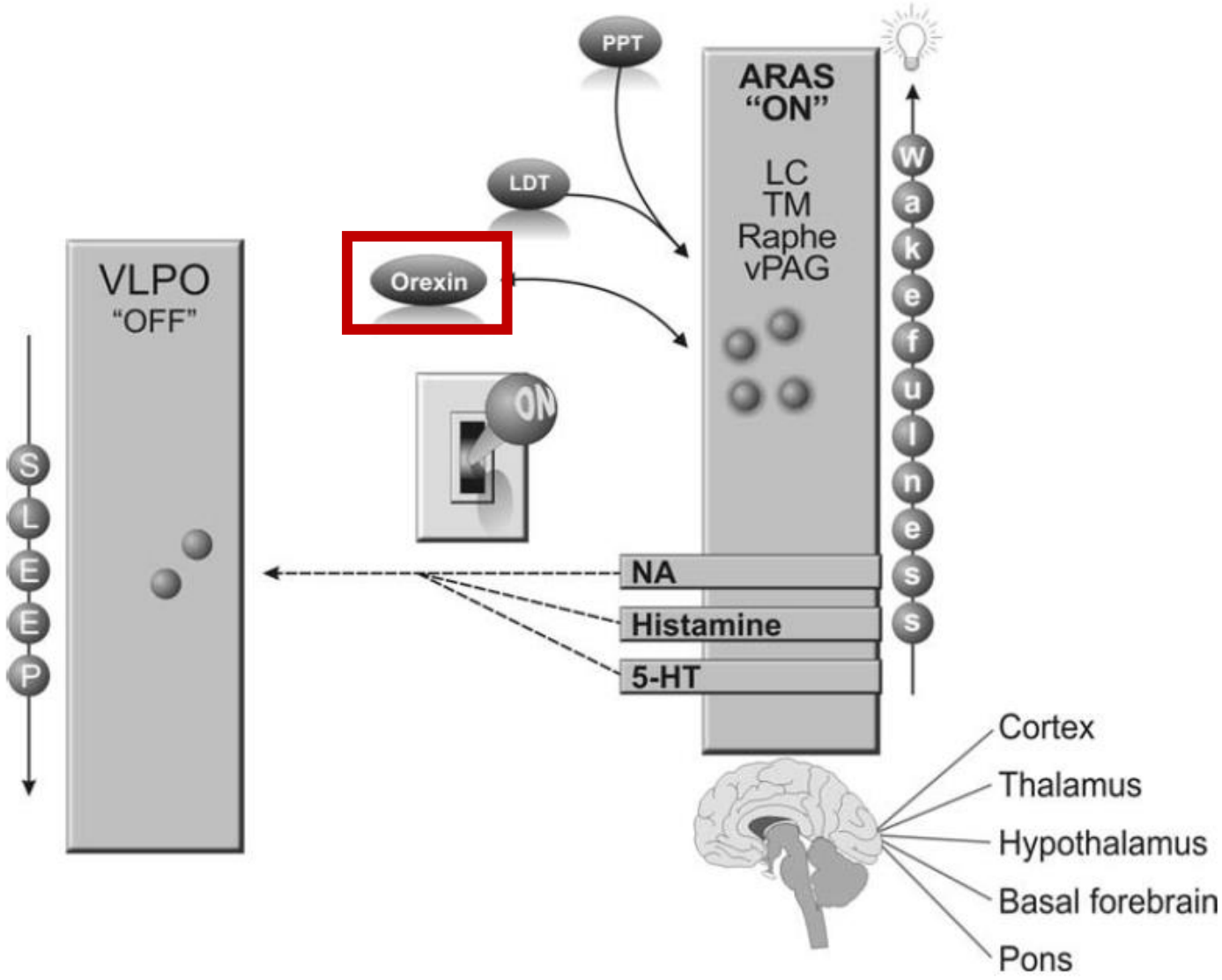
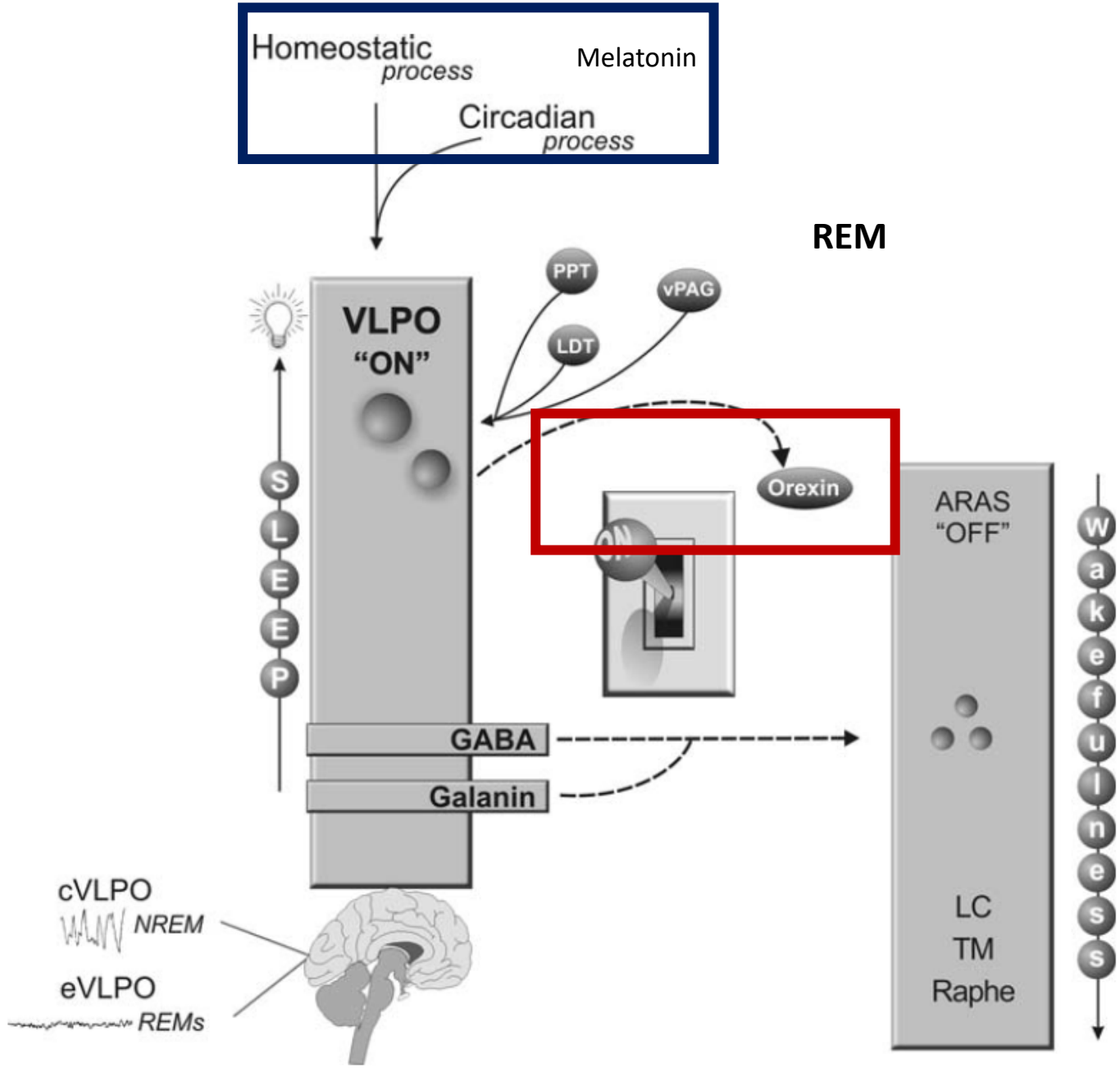
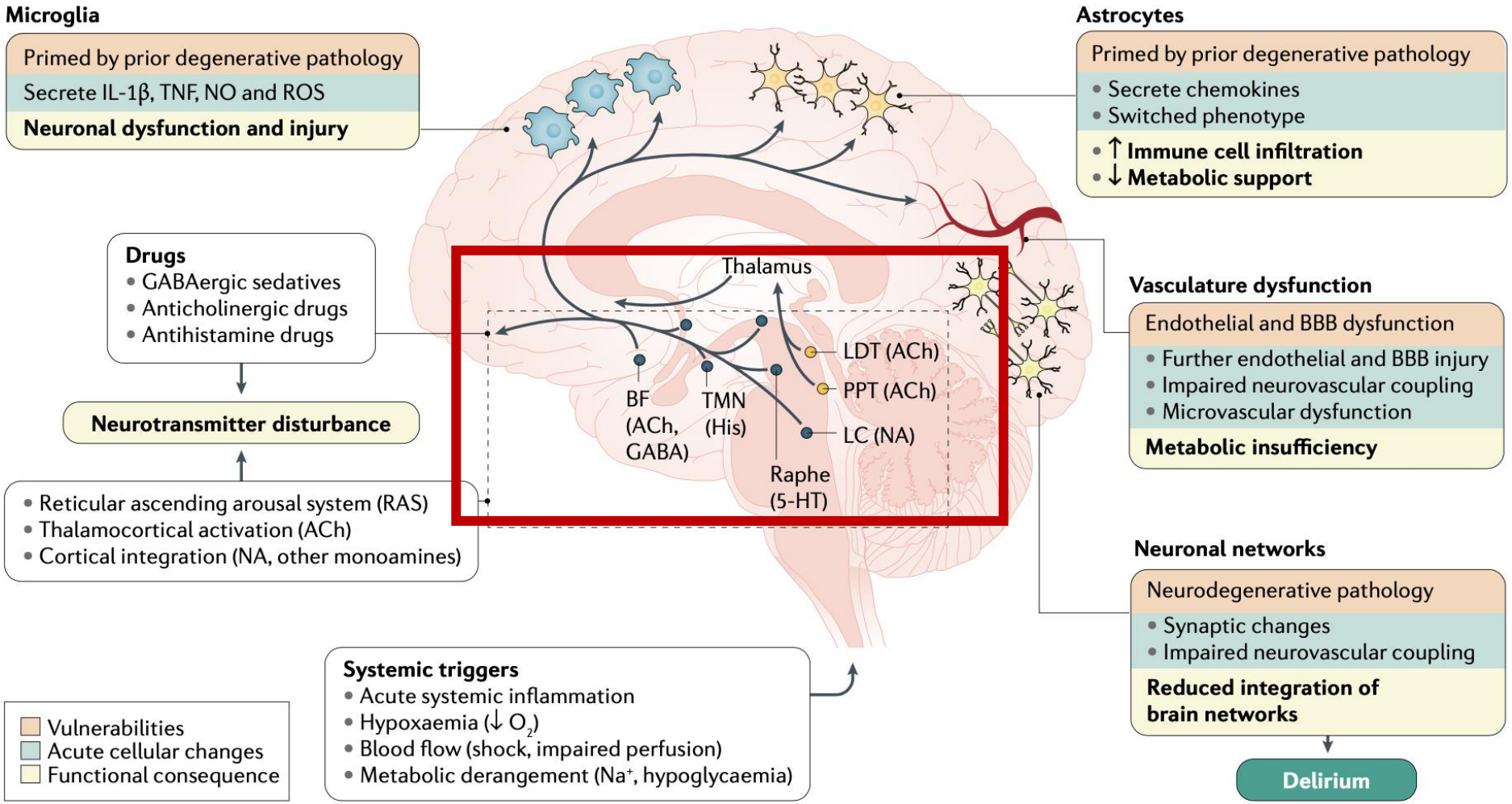


**Fig. 2** Representation of the "flip-flop" switch mechanism that regulates sleep–wake-cycle. Ventrolateral preoptic (*VLPO*) nucleus is "On" during sleep by activation of both VLPO cluster (*cVLPO*) and VLPO extended (*eVLPO*) neurons. These neurons release gamma-amino-butiric-acid (*GABA*) and galanin and inhibit both ascending reticular activating (*ARAS*) neurons (locus coeruleus *LC*, tuberomammillary *TM*, and dorsal and median raphe nuclei) and orexin peptide. These provoke ARAS to turn "off". Cholinergic neurons (pedunculopontine *PPT* and laterodorsal tegmental *LDT*) and ventral periaqueductal grey *vPAG* promotes REM sleep. Homeostatic and circadian processes influence VLPO. *Solid arrow* represents excitatory input, *dashed arrow* represents inhibitory input

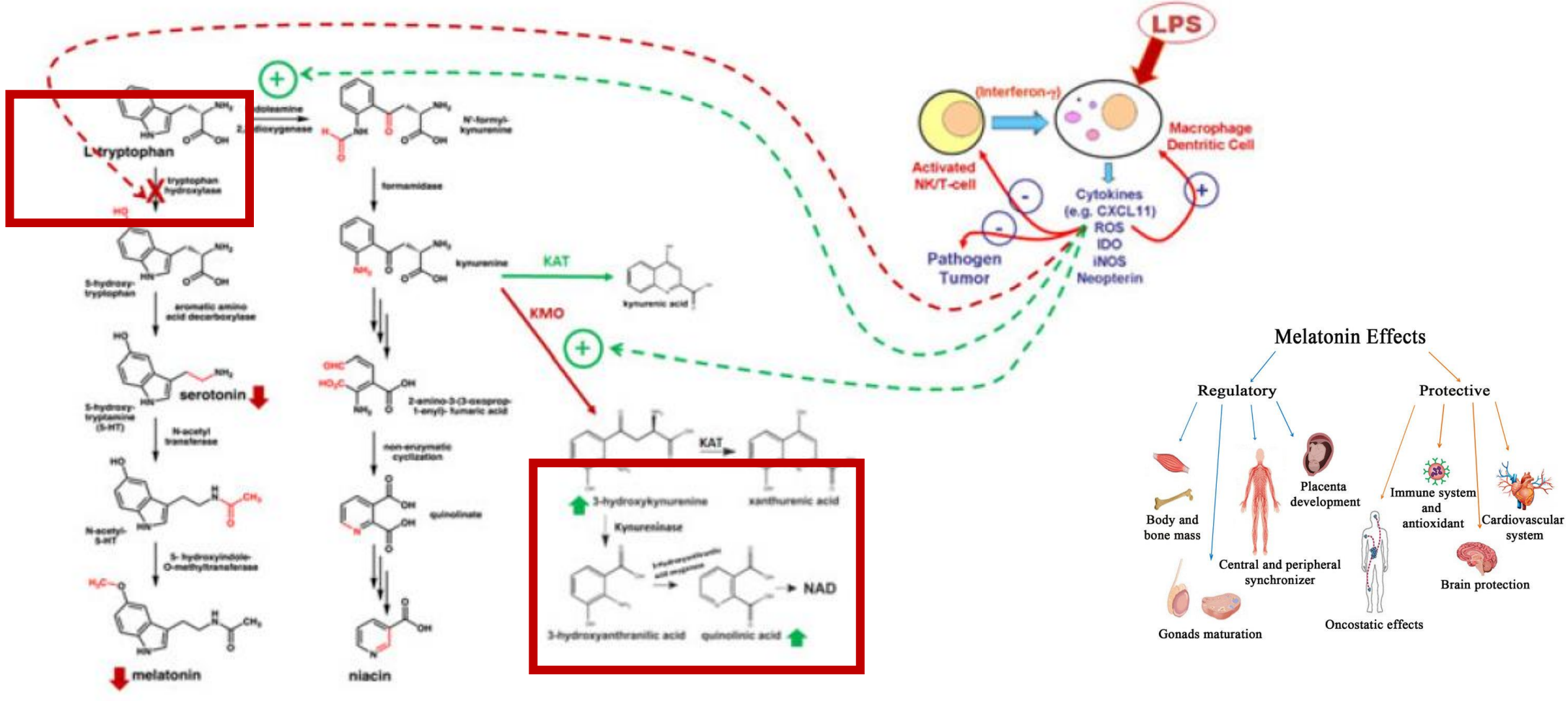


# Major mechanisms in delirium pathophysiology

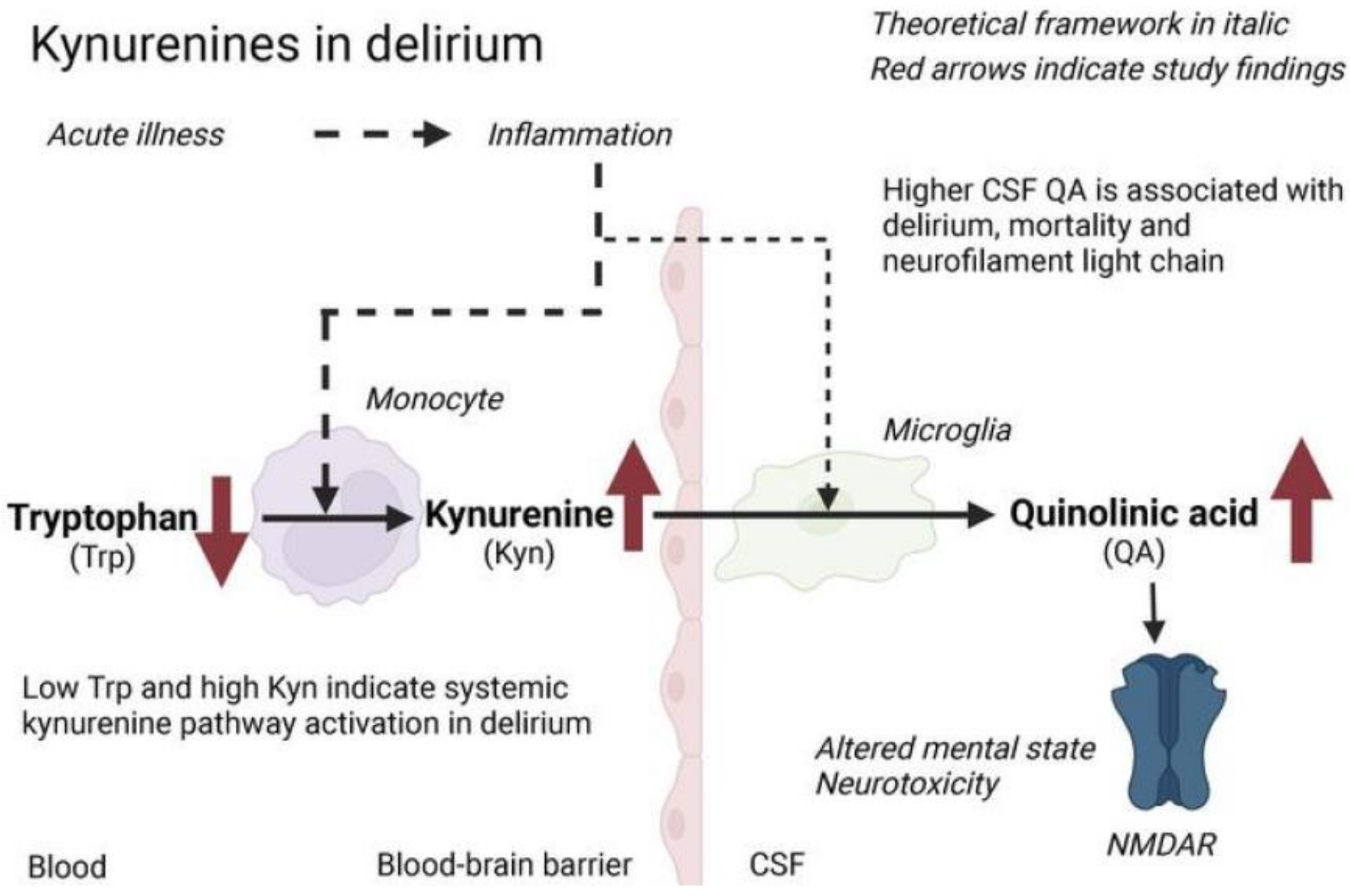



*Wilson JE, Nature Review 2020*

# Metabolic pattern of tryptophan, 5-hydroxytryptamine, melatonin, and kynurenic and quinolinic acid




*mod from Stone TW et al, 2012*




*Watne LO et al, accepted J Clin Invest 2023*

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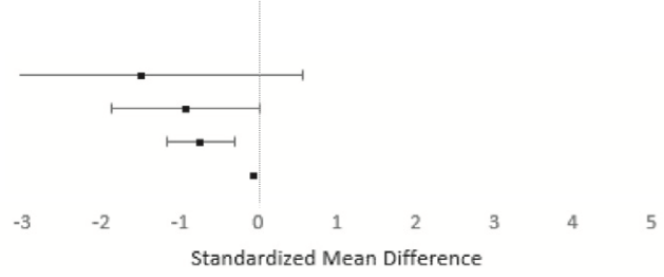
Potenziali link fisiopatologici

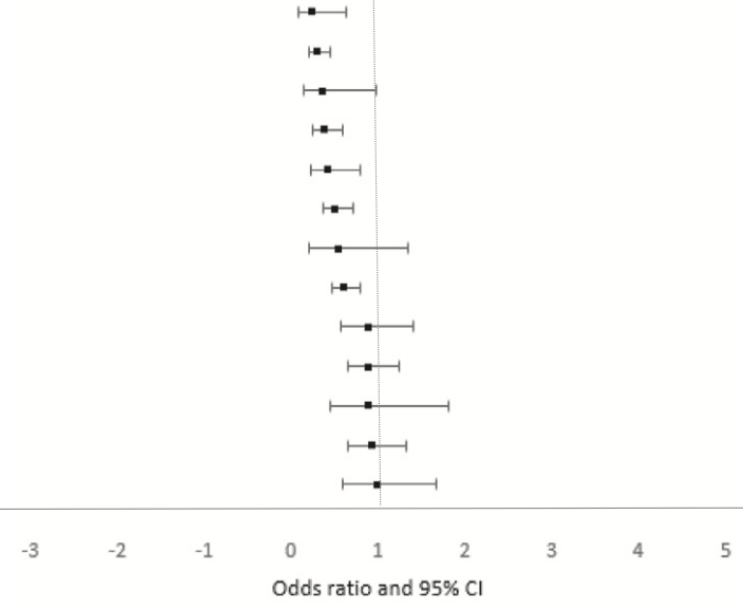
Trattamento

# Effects of nonpharmacological interventions on sleep improvement and delirium prevention in critically ill patients: A systematic review and meta-analysis

Systematic review included 118 studies and the meta-analysis 100 studies

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Delirium duration | | | | | | | | |
| Delirium prevention protocol (A) | 2 | 98.4 | <.001 | R | -1.52 | -3.49 | 0.45 | 0.130 |
| Exercise intervention (C) | 5 | 96.2 | <.001 | R | -0.98 | -1.88 | -0.09 | 0.031 |
| ABCDEF multi-intervention approach (A) | 5 | 93.7 | <.001 | R | -0.80 | -1.22 | -0.38 | <.001 |
| Family participation (C) | 4 | 0.0 | 0.537 | F | -0.15 | -0.59 | 0.29 | 0.508 |
| Delirium incidence | | | | | | | | |
| Exercise intervention (C) | 7 | 78.1 | <.001 | R | 0.23 | 0.09 | 0.64 | 0.004 |
| Family participation (C) | 6 | 51.9 | 0.070 | F | 0.31 | 0.21 | 0.46 | <.001 |
| Combined (C) | 3 | 47.4 | 0.150 | F | 0.37 | 0.14 | 0.98 | 0.045 |
| Information giving (C) | 4 | 0.0 | 0.525 | F | 0.38 | 0.25 | 0.59 | <.001 |
| Light/noise blocking (B) | 3 | 0.0 | 0.496 | F | 0.42 | 0.22 | 0.80 | 0.008 |
| Delirium prevention protocol (A) | 23 | 84.3 | <.001 | R | 0.51 | 0.37 | 0.72 | <.001 |
| Quiet time protocol (A) | 2 | 85.7 | <.001 | R | 0.54 | 0.21 | 1.35 | 0.188 |
| Delirium early detection protocol (A) | 21 | 65.8 | <.001 | R | 0.61 | 0.47 | 0.80 | <.001 |
| Bright light therapy (C) | 4 | 64.7 | 0.037 | R | 0.89 | 0.57 | 1.40 | 0.620 |
| Architectural intervention (A) | 7 | 67.1 | 0.006 | R | 0.90 | 0.65 | 1.24 | 0.515 |
| Massage (C) | 4 | 0.0 | 0.750 | F | 0.90 | 0.45 | 1.81 | 0.770 |
| ABCDEF multi-intervention approach (A) | 7 | 78 | <.001 | R | 0.93 | 0.65 | 1.33 | 0.675 |
| Cognitive stimulation (C) | 2 | 0.0 | 0.600 | F | 0.99 | 0.59 | 1.67 | 0.980 |



# *Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients*

*Pratik Pandharipande, M.D., M.S.C.I.,* Ayumi Shintani, Ph.D., M.P.H.,† Josh Peterson, M.D., M.P.H.,‡ Brenda Truman Pun, R.N., M.S.N., A.C.N.P.,§ Grant R. Wilkinson, Ph.D., D.Sc.,‖ Robert S. Dittus, M.D., M.P.H.,# Gordon R. Bernard, M.D.,** E. Wesley Ely, M.D., M.P.H.††*

Anesthesiology 2006, Vol. 104, 21–26.

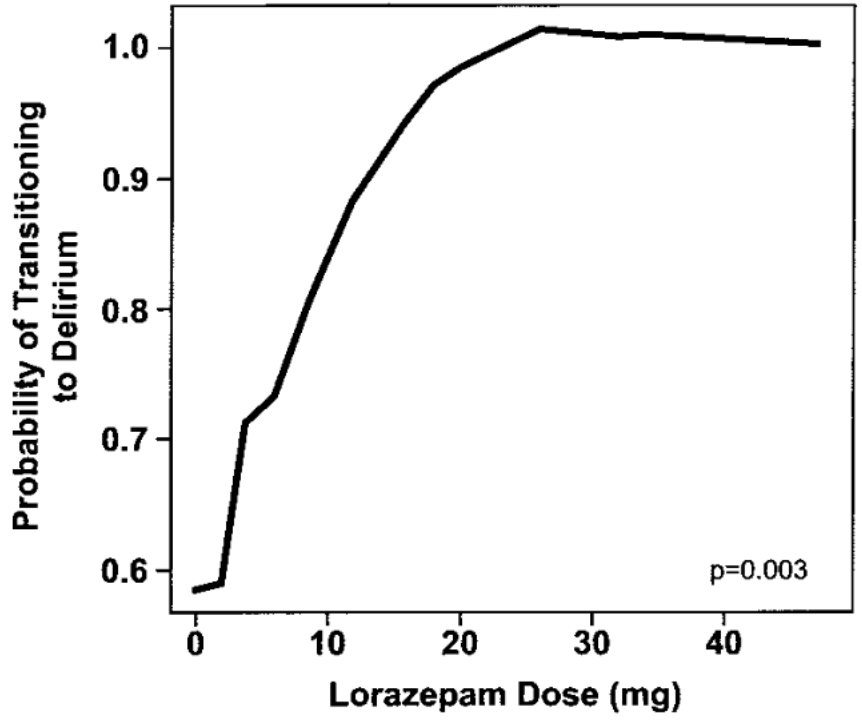



**Fig. 1. Lorazepam and the probability of transitioning to delirium. The probability of transitioning to delirium increased with the dose of lorazepam administered in the previous 24 h. This incremental risk was large at low doses and plateaued at around 20 mg/day.**

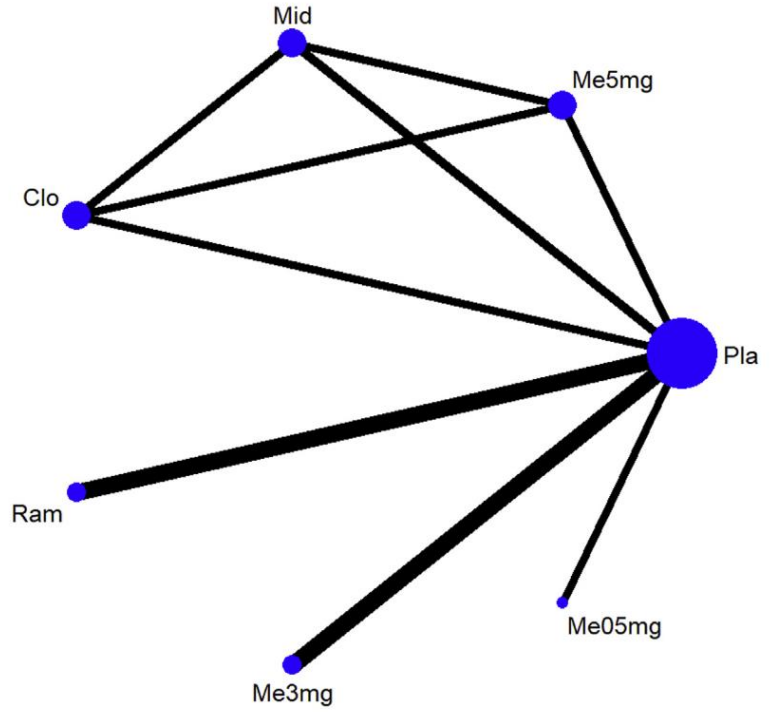
# Melatonergic agents in the prevention of delirium: A network meta-analysis of randomized controlled trials

Sleep Medicine Reviews 50 (2020) 101235

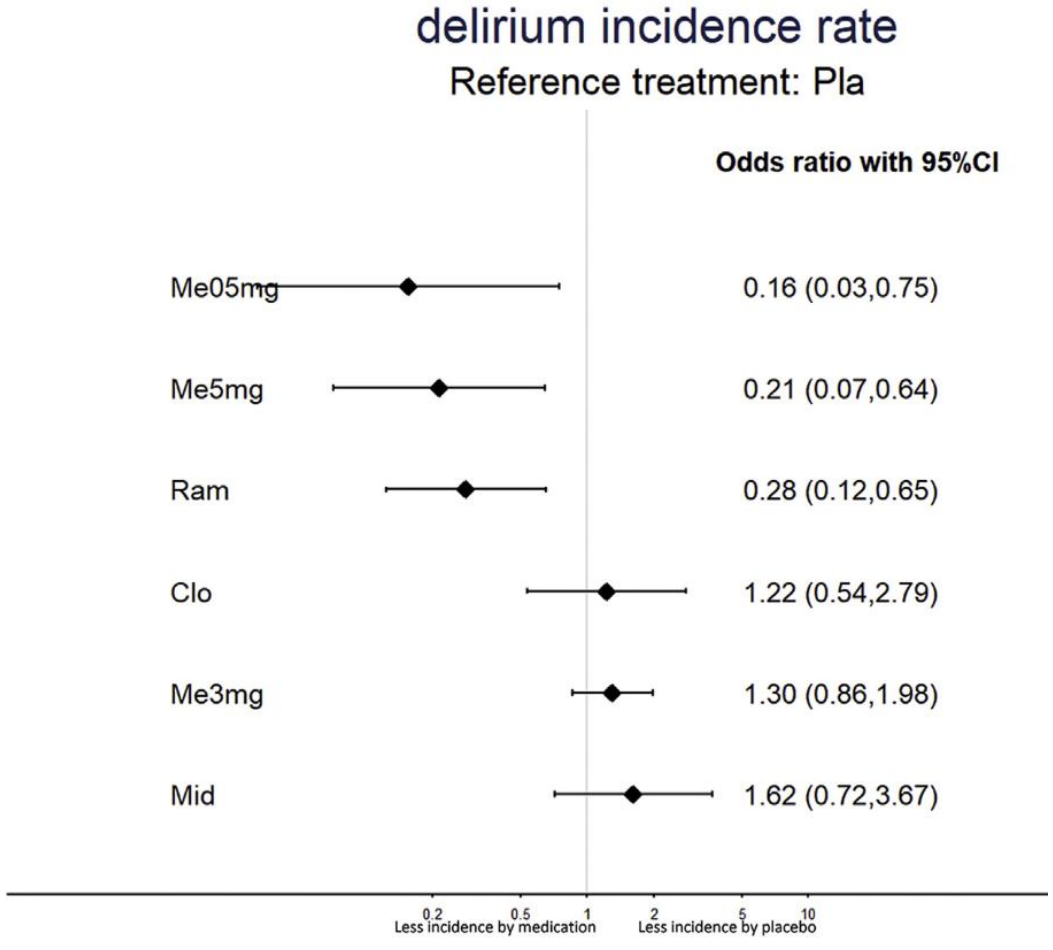
Chun-Pai Yang [a, b, 1], Ping-Tao Tseng [c, d, e, 1], Jane Pei-Chen Chang [f, g], Huanxing Su [h], Senthil Kumaran Satyanarayanan [g, h], Kuan-Pin Su [g, i, *]

6 RCTs, 913 adult participants (mean age = 78.8, mean female =59.4%)

A




B



# Suvorexant for the prevention of delirium

## A meta-analysis

Shu Xu, BS[a], Yuanyuan Cui, BS[b], Jinhua Shen, BS[c,*], Peili Wang, BS[b,*]

**Abstract**

**Background:** Delirium is a frequently encountered complication, which is associated with increased mortality. Suvorexant, an approved agent for the treatment of insomnia, is recently suggested to be also effective for prevention of delirium by some authors. However, a consensus has yet to be reached. The goal of this study was to perform a meta-analysis to overall estimate the effectiveness of suvorexant in preventing delirium and its related consequences.

**Methods:** Eligible studies were identified by searching online databases of PubMed, EMBASE, and Cochrane Library. The pooled OR was calculated for binary outcomes (e.g., the incidence of delirium, mortality, or adverse events), while standardized mean difference (SMD) were expressed for continuous outcomes (e.g., time to delirium onset, length of stay in hospital and ICU, time on ventilation).

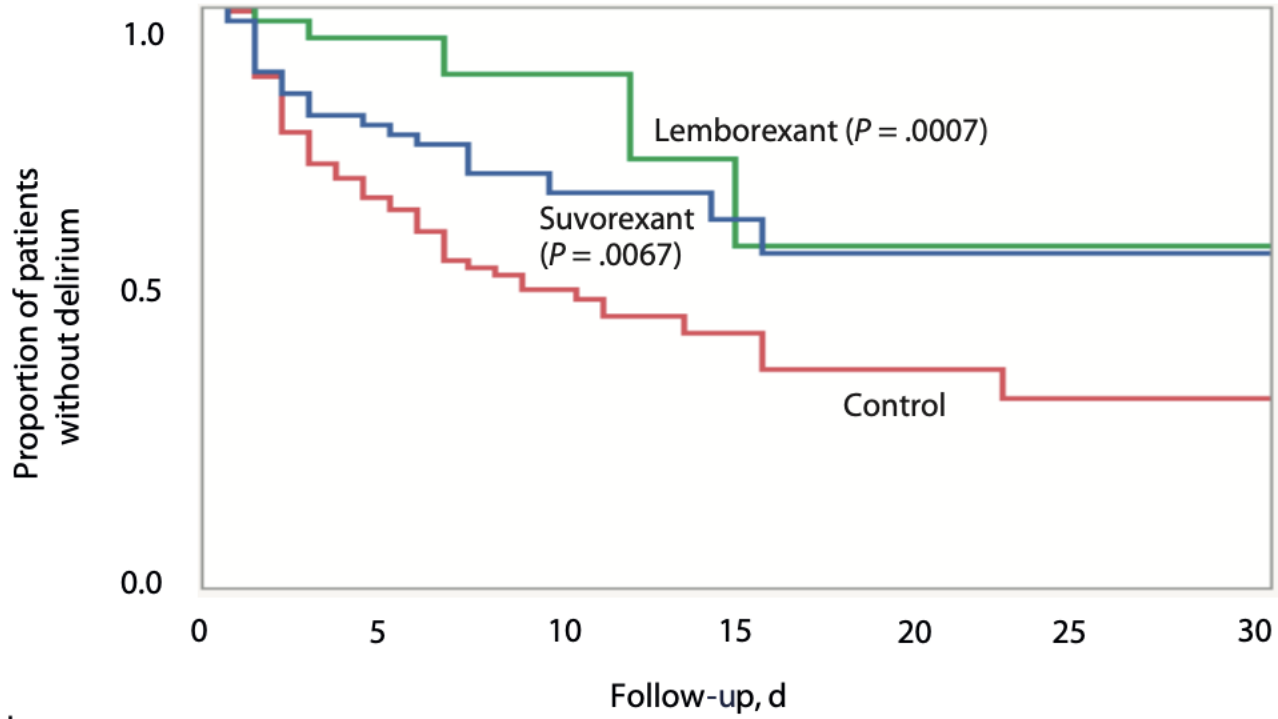
**Results:** Seven studies which comprised 402 suvorexant treatment patients and 487 patients with control treatment were included in this meta-analysis. Overall, pooled analysis indicated the incidence of delirium could be significantly reduced (OR, 0.30; $P < .001$) and time to delirium onset was significantly lengthened (SMD, 0.44; $P = .006$) in patients undergoing suvorexant treatment compared with controls. Suvorexant had no beneficial effects on the secondary outcomes [length of stay in hospital (SMD, −0.65; $P = .161$) and ICU (SMD, 0.34; $P = .297$), time on ventilation (SMD, 1.09; $P = .318$), drug-related adverse events (OR, drug-related adverse events (OR, 1.66; $P = .319$) and mortality (OR, 2.21; $P = .261$)]. Subgroup analysis also confirmed the benefit of suvorexant on the development of delirium, which was significant in any subgroup.

**Conclusion:** Suvorexant should be recommended for the prevention of delirium in clinic.

**Abbreviations:** CAM-ICU = Confusion Assessment Method for Intensive Care Unit, CI = confidence interval, DSM-5 = the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, ICDSC = Intensive Care Delirium Screening Checklist, ICU = intensive care unit, IL = interleukin, NOS = Newcastle–Ottawa Scale, OR = odd ratio, RCTs = randomized controlled trials, SMD = standardized mean difference.

**Keywords:** delirium, orexin receptor antagonist, suvorexant

Medicine 2020




Patients at risk, n

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Suvorexant | 82 | 56 | 30 | 17 | 11 | 10 | 8 |
| Lemborexant | 41 | 28 | 12 | 8 | 5 | 2 | 2 |
| Control | 510 | 338 | 108 | 51 | 23 | 11 | 8 |

[a]Log rank test showed significantly lower numbers of delirium events in the suvorexant and lemborexant groups than that in the control group (control vs suvorexant group, $P = .0067$; control vs lemborexant group, $P = .0007$).

Retrospective observational study including 82 treated with suvorexant and 41 with lemborexant

After adjustment for delirium risk factors, the HR were 0.34 (0.20-0.58) for suvorexant and 0.21 (0.08-0.52) for lemborexant

*Matsuoka A et al., J Clin Psych 84:1; 2023*

# Conclusioni

- I disturbi del sonno e il delirium sono due condizioni strettamente collegate dal punto di vista temporale e clinico
- Vi sono numerosi punti di convergenza fisiopatogenetici che potrebbero spiegare le aree di overlap
- Ad oggi non vi è alcun trattamento farmacologico attivo sui disturbi del sonno che sia raccomandato per la prevenzione del delirium (solo interventi non farmacologici)
- Gli inibitori delle orexine sono una promettente strategia di intervento farmacologico, ma sono necessari ulteriori studi