Melatonin Trials

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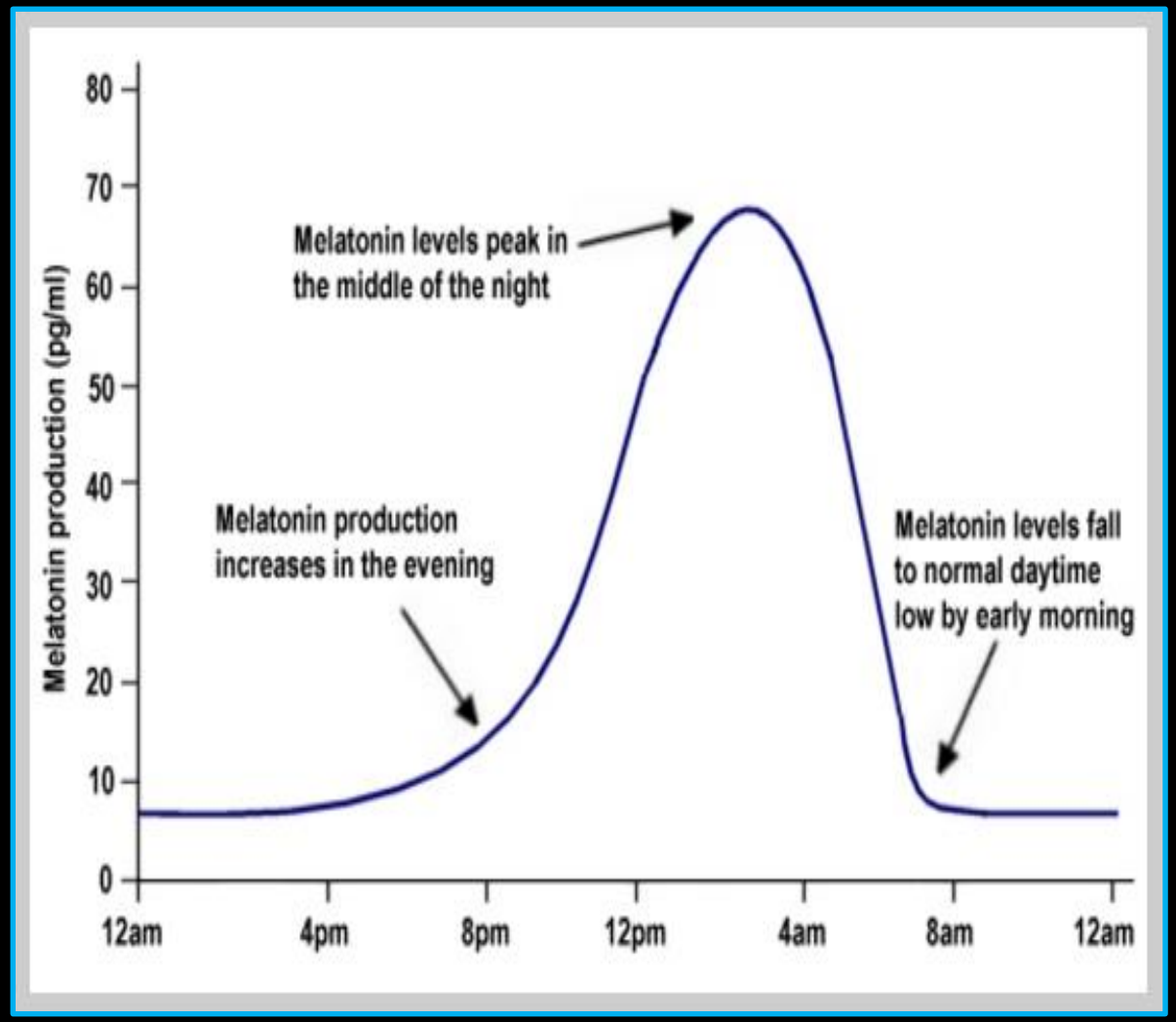
NO DISCLOSURES

What I would like to cover….

- Endogenous melatonin – why do we need it?
- Why do we think exogenous melatonin useful in the critically ill?
- Evidence for sleep
- Evidence for delirium prevention
- Evidence for delirium treatment
- Evidence for ventilation and sedation outcomes

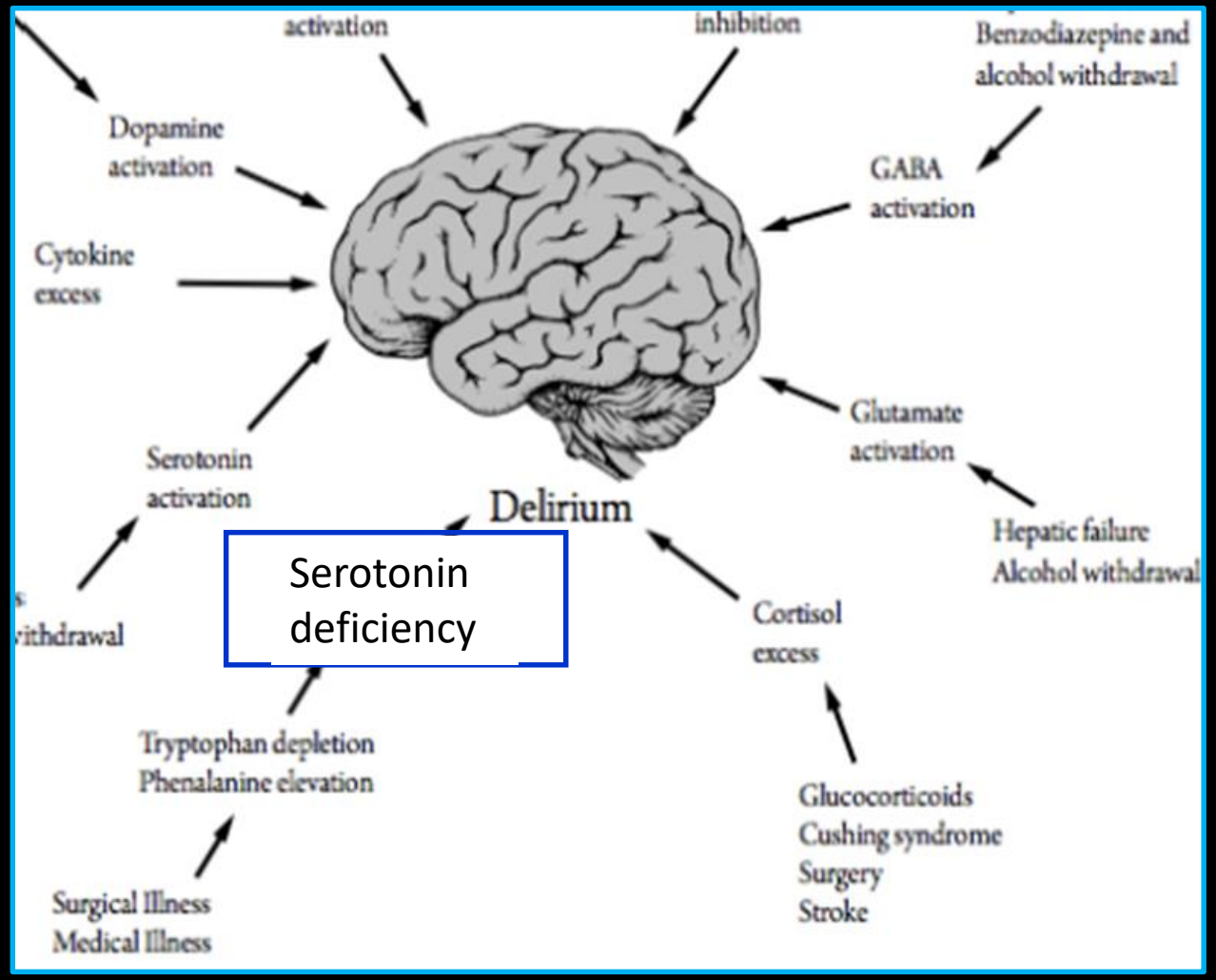
Endogenous melatonin- why we need it

- Hormone secreted by pineal gland
- Regulates & synchronizes circadian rhythm
- Secretion becomes entrained
  - anticipates onset of darkness/approach of day
- Accelerates sleep initiation
- Improves sleep maintenance & efficiency
- Anti-inflammatory, anti-oxidative analgesic properties



Why might exogenous melatonin be useful?

- Critically ill exhibit abnormalities in melatonin metabolism
- Bright light (blue wavelengths) suppress secretion
- ICU environment disturbs sleep
  - light, noise, patient care & invasive monitoring
- Disturbed circadian sleep-wake cycle
  - >75% of delirious patients



EVIDENCE FOR SLEEP

Why might exogenous melatonin be useful?

Pharmacological interventions for sleepiness and sleep disturbances caused by shift work (Review)

Cochrane Database of Systematic Reviews 2014, Issue 8. Art. No.: CD009776.

9 melatonin trials –
low quality evidence of ↑ day (md 24 mins)
& night (md 17 mins) sleep duration

Melatonin for the prevention and treatment of jet lag (Review)

Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD001520.

8/10 melatonin trials –
↓jetlag when flying over 5 time-zones

Melatonin for the promotion of sleep in adults in the intensive care unit (Review)

Lewis SR, Pritchard MW, Schofield-Robinson OJ, Alderson P, Smith AF

Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD012455.

Outcomes	No of participants (studies)	Quality of the evidence (GRADE)
Quantity and quality of sleep as measured through reports of participants or of family members or by personnel assessments Data collected at end of follow-up	139 (3 studies)	⊕◯◯◯ very low [a]
Quantity and quality of sleep as measured by PSG, actigraphy, BIS, or EEG Data collected at end of follow-up	37 (2 studies)	⊕◯◯◯ very low[b]

No difference

Non-pharmacological interventions for sleep promotion in the intensive care unit (Review)

Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD008808.

30 trials, 1569 participants

Authors' conclusions

Studying sleep in the critically ill is challenging

The quality of existing evidence relating to the use of non-pharmacological interventions for promoting sleep in adults in the ICU was low or very low. We found some evidence that the use of earplugs or eye masks or both may have beneficial effects on sleep and the incidence of delirium in this population, although the quality of the evidence was low. Further high-quality research is needed to strengthen the evidence base.

EVIDENCE FOR DELIRIUM PREVENTION

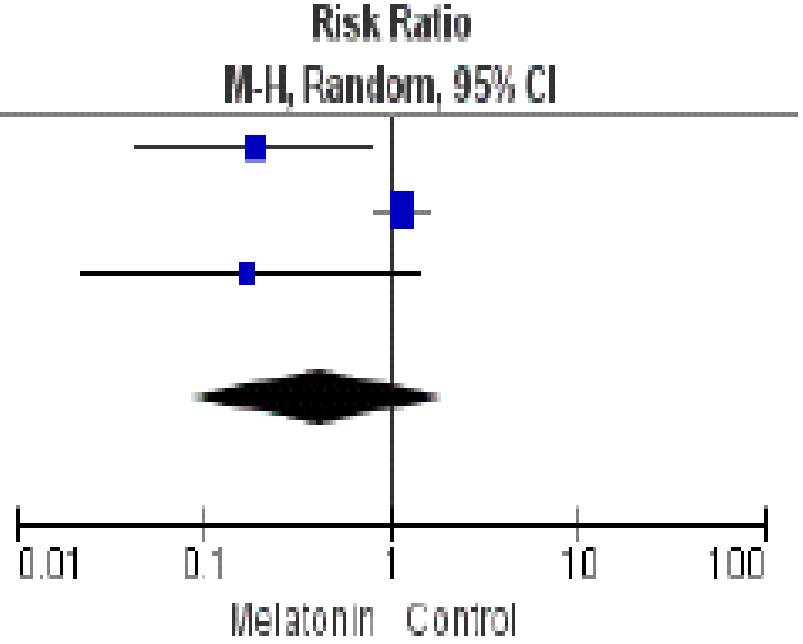
Interventions for preventing delirium in hospitalised non-ICU patients (Review)

Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD005563.

Study or Subgroup	Melatonin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Al-Aama 2011	2	56	10	52	31.6%	0.19 [0.04, 0.81]
de Jonghe 2014	55	186	49	192	43.7%	1.16 [0.83, 1.61]
Hatta 2014	1	23	5	20	24.7%	0.17 [0.02, 1.37]
Total (95% CI)		**265**		**264**	**100.0%**	**0.41 [0.09, 1.89]**
Total events	58		64			

Heterogeneity: Tau² = 1.37; Chi² = 8.97, df = 2 (P = 0.01); I² = 78%

Test for overall effect: Z = 1.15 (P = 0.25)



There is no clear evidence that melatonin or melatonin agonists reduce delirium incidence compared to placebo (RR 0.41, 95% CI 0.09 to 1.89; three studies, 529 participants; low-quality evidence).

Prophylactic Melatonin for Delirium in Intensive Care (Pro-MEDIC): study protocol for a randomised controlled trial

Martinez et al. Trials (2017) 18:4

850 pts with ICU LOS > 72 hrs
4mg melatonin vs placebo
within 1st 48 hours to ICU dx
or 14 days

The Healthy Heart-Mind trial: melatonin for prevention of delirium following cardiac surgery: study protocol for a randomized controlled trial

Ford et al. Trials (2016) 17:55

210 CV pts over 50
3mg melatonin vs placebo
7 days post op

Feasibility of melatonin for prevention of delirium in critically ill patients: a protocol for a multicentre, randomised, placebo-controlled study

Burry L, et al. BMJ Open 2017;7:e015420.

69 pts with ICU LOS >48 hrs
Confirmed delirium negative
2mg vs 0.5mg melatonin
vs placebo
ICU dx or 14 days

EVIDENCE FOR DELIRIUM TREATMENT

No RCTs in the critically ill

EVIDENCE FOR OTHER OUTCOMES in the CRITICALLY ILL

Melatonin reduces the need for sedation in ICU patients: a randomized controlled trial

(Minerva Anestesiol 2015;81:1298-310)

	Placebo (N.=41)	Melatonin (N.=41)	P value
Primary outcome			
Enteral hydroxyzine (mg/ventday)	240.0 [19.4-304.1]	35.1 [0-167.1]	<0.01
Enteral hydroxyzine (mg/kg/ventday)	3.0 [0.2-3.8]	0.6 [0-2.4]	0.01
Secondary outcomes			
Total administered enteral sedatives			
Lorazepam (mg/ventday)	0.16 [0-2.35]	0 [0-0.71]	0.11
Lorazepam (mcg/kg/ventday)	1.8 [0-27.1]	0 [0-9.7]	0.10
Total administered intravenous sedatives			
Propofol (mg/ventday)	3.2 [0-53.7]	0 [0-1.5]	<0.01
Propofol (mg/kg/ventday)	0.07 [0-0.61]	0 [0-0.03]	<0.01
Midazolam (mg/ventday)	0 [0-1.57]	0 [0-0]	0.33
Midazolam (mcg/kg/ventday)	0 [0-27]	0 [0-0]	0.33
Total administered analgesics			
Morphine equivalents (mg/ventday)	0.23 [0-6.72]	0.03 [0-2.56]	0.20
Morphine equivalents (mcg/kg/ventday)	15 [0-82]	2 [0-13]	0.23
Total administered antipsychotics			
Haloperidol (mg/ventday)	0 [0-1.5]	0 [0-0.4]	0.33
Haloperidol (mcg/kg/ventday)	0 [0-17]	0 [0-7]	0.34

Melatonin Supplementation May Improve the Outcome of Patients with Hemorrhagic Stroke in the Intensive Care Unit

J Res Pharm Pract. 2017 Jul-Sep; 6(3): 173–177.

40 pts: 30 mg melatonin vs placebo; protocolized sedation

Variables	Groups		*P*
	Melatonin	Control	
Duration of mechanical ventilation (days)	4 (2-16)	12 (4-20)	0.065
Length of ICU stay (days)	8 (6-21)	12 (8-25)	0.041
In ICU mortality	3 (15.0)	6 (30.0)	0.451

Numerical values are reported as median (IQR), and nominal factors as *n* (%). Mann-Whitney U-test and Chi-square test were used to compare these values, respectively. IQR=Interquartile range, ICU=Intensive Care Unit

Conclusion

- Melatonin has good biologic plausibility
  - improving sleep quantity/quality
  - preventing/treating delirium
- Current evidence is low quality
  - Small volume of studies
  - Mostly underpowered
  - Inconsistent selection of outcomes and measures
- No consensus on best dose
- More evidence in terms of delirium prevention soon!

THANK YOU FOR YOUR ATTENTION

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Big thanks to my research buddy
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