Approccio enterale per la sedazione cosciente del paziente critico: un ruolo per la melatonina?

Giovanni Mistraletti, MD
Dipartimento di Anestesiologia, Terapia Intensiva e Scienze Dermatologiche
Università degli Studi di Milano
AO San Paolo – Polo Universitario
Milano, Italy

XIX Meeting GiViTI
Pesaro, 28 ottobre 2010.

Sedazione “cosciente”

Approccio enterale

Un ruolo per la Melatonina ?

XIX Meeting GiViTI
Pesaro, 28 ottobre 2010.

Sedazione “cosciente”

Approccio enterale

Un ruolo per la Melatonina ?

XIX Meeting GiViTI
Pesaro, 28 ottobre 2010.

“Divinum est sedare dolorem”

Ippocrate, 400 a.C.

Why analgo-sedation in ICU? It's really necessary?

- Optimal patient comfort
- "Stress response" reduction
- Less cardiac and respiratory complications
- Aid in diagnostic and therapeutic procedures
- Agitation and delirium decreased

Which strategy in recent history?

- 1980: Patient have to suit machineries.
  - Hardly sedated, and paralysed!
- 1990: Machineries have to suit patients, but memories of ICU are terribles!
  - No muscle-relaxants, still hard sedation
- 2000: Goal-directed sedation…
  …daily interruption & protocols, but delirium.
- 2010: ?

Over-sedation: drawbacks

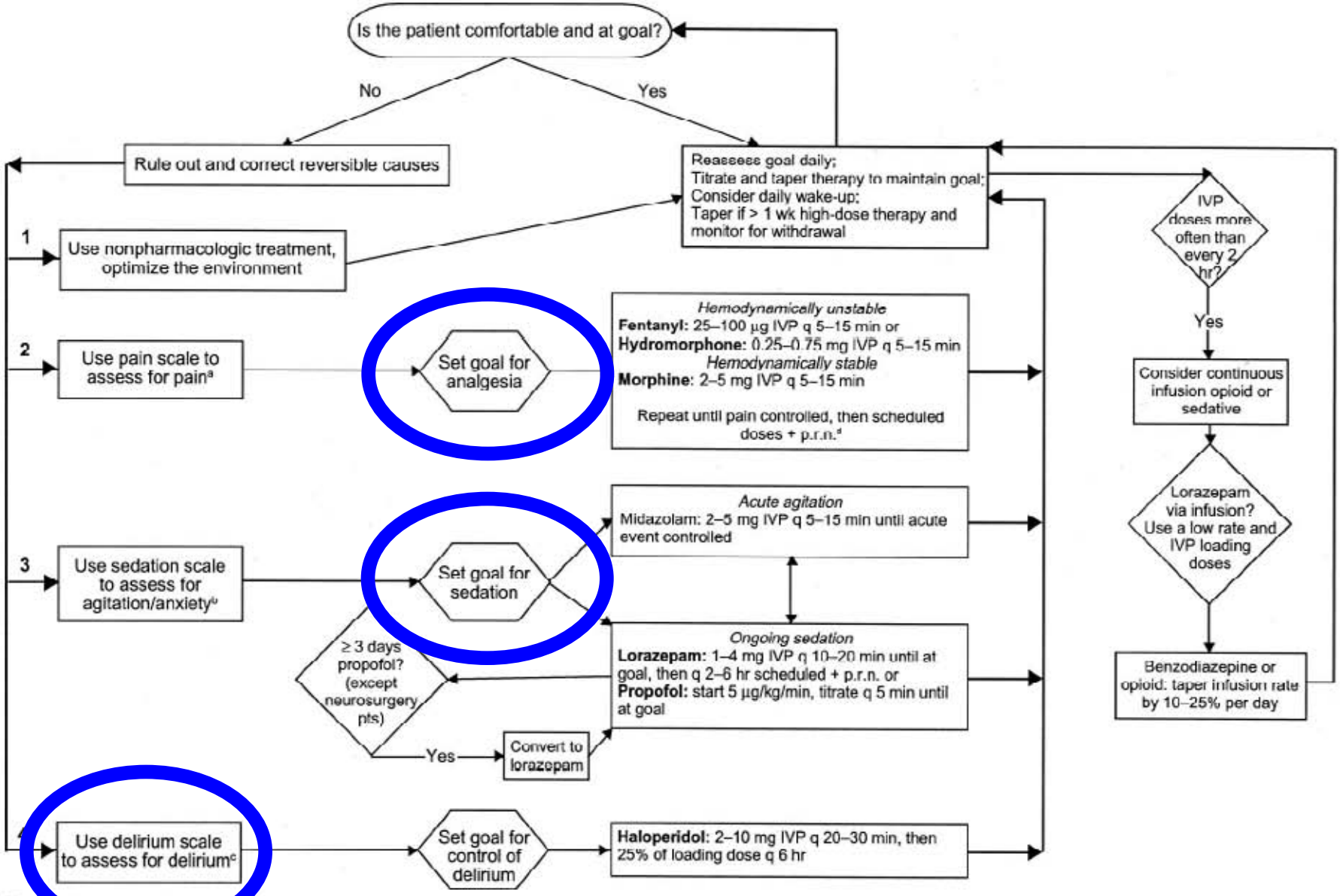
- Hypotension, bradycardia, cardiac impairment
- Respiratory depression
- Ileus
- Venous stasis, deep vein thrombosis
- Delayed weaning from mechanical ventilation
- Prolonged ICU stay
- Increased costs
- Failure to evaluate CNS alterations

Guidelines CCM 2002
Task-force for ICU analgesia & sedation

Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult

Judith Jacobi, PharmD, FCCM, BCPS; Gilles L. Fraser, PharmD, FCCM; Douglas B. Coursin, MD; Richard R. Riker, MD; Dorrie Fontaine, RN, DNSc, FAAN; Eric T. Wittbrodt, PharmD; Donald B. Chalfin, MD, MS, FCCM; Michael F. Masica, MD, MPH; H. Scott Bjerke, MD; William M. Coplin, MD; David W. Crippen, MD, FCCM; Barry D. Fuchs, MD; Ruth M. Kelleher, RN; Paul E. Marik, MDBCh, FCCM; Stanley A. Nasraway, Jr, MD, FCCM; Michael J. Murray, MD, PhD, FCCM; William T. Peruzzi, MD, FCCM; Philip D. Lumb, MB, BS, FCCM. Developed through the Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), in collaboration with the American Society of Health-System Pharmacists (ASHP), and in alliance with the American College of Chest Physicians; and approved by the Board of Regents of ACCM and the Council of SCCM and the ASHP Board of Directors

Jacobi J, *Crit Care Med,* 2002



Jacobi J, *Crit Care Med*, 2002

A new frontier in critical care: saving the injured brain.

E. Wesley Ely, 2010

Sedation and analgesia in German ICU: how is it done in reality?

Coma

St. Dolore

St. Verbale

Soporoso

Tranquillo

Agitato

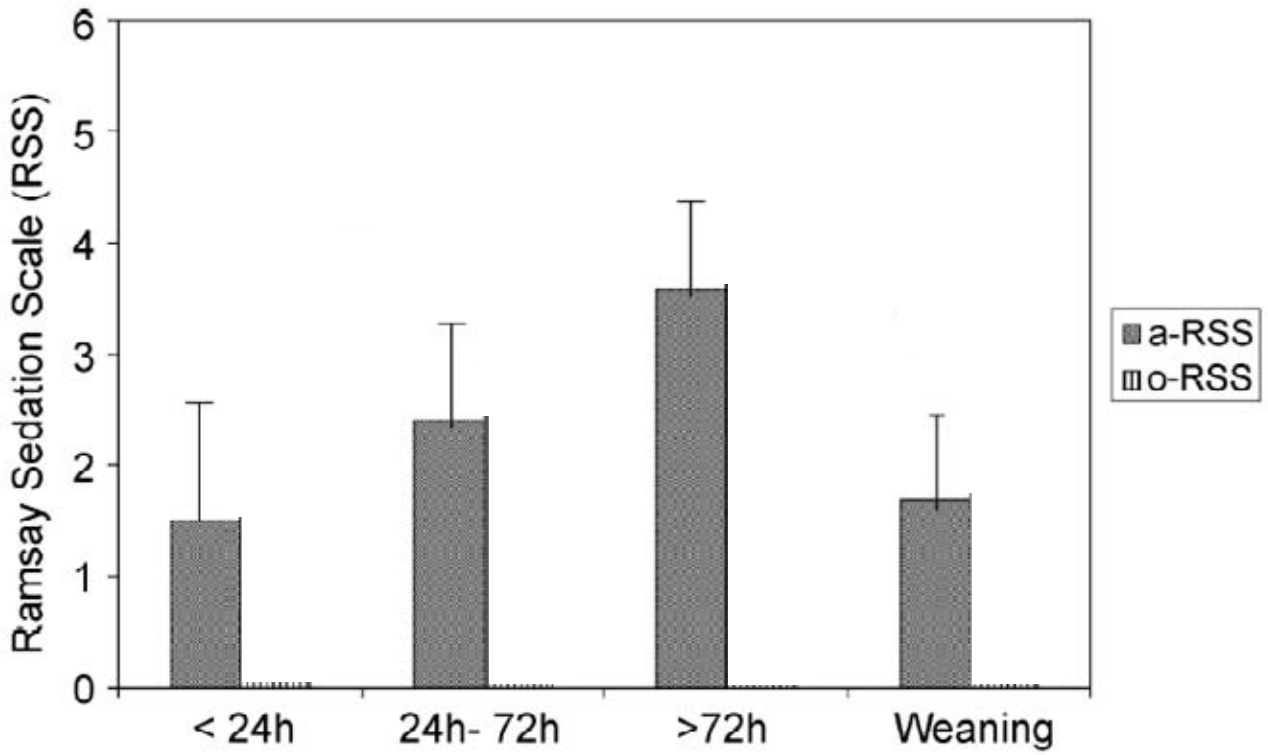


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a-RSS*) and that which was obtained (*o-RSS*). $^{*}p \leq 0.05$ (Mann-Whitney *U* test)

Martin J, *Intensive Care Med,* 2006

Sedation and analgesia in German ICU: how is it done in reality?

Coma

St. Dolore

St. Verbale

Soporoso

Tranquillo

Agitato

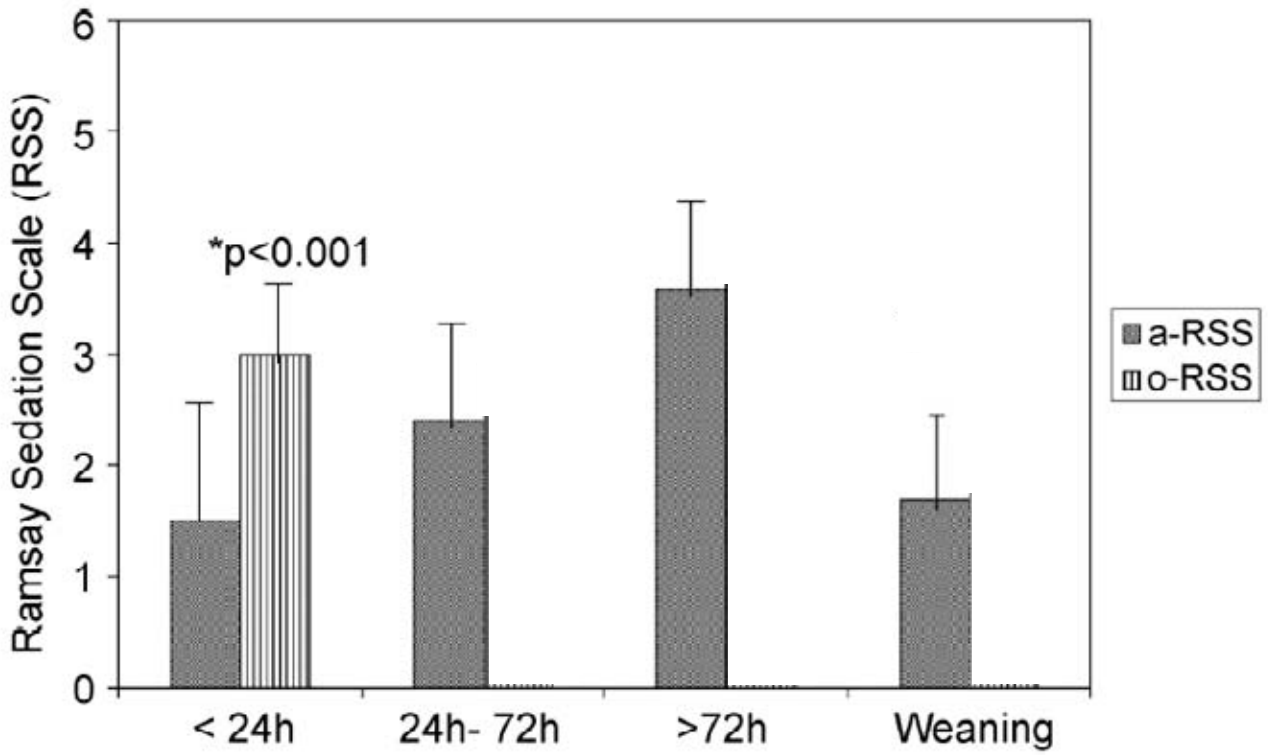


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a-RSS*) and that which was obtained (*o-RSS*). $^{*}p \leq 0.05$ (Mann-Whitney *U* test)

Martin J, *Intensive Care Med,* 2006

Sedation and analgesia in German ICU: how is it done in reality?

Coma

St. Dolore

St. Verbale

Soporoso

Tranquillo

Agitato

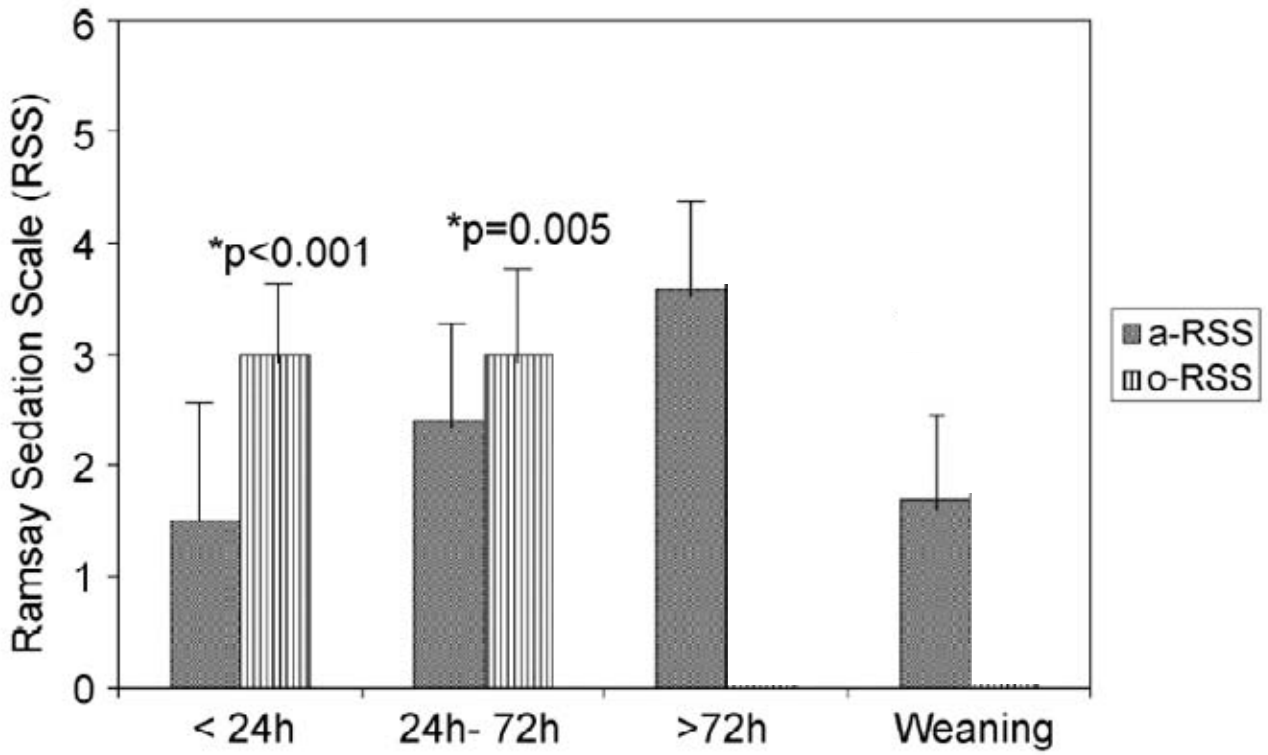


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a-RSS*) and that which was obtained (*o-RSS*). $^{*}p \leq 0.05$ (Mann-Whitney *U* test)

Martin J, *Intensive Care Med,* 2006

Sedation and analgesia in German ICU: how is it done in reality?

Coma

St. Dolore

St. Verbale

Soporoso

Tranquillo

Agitato

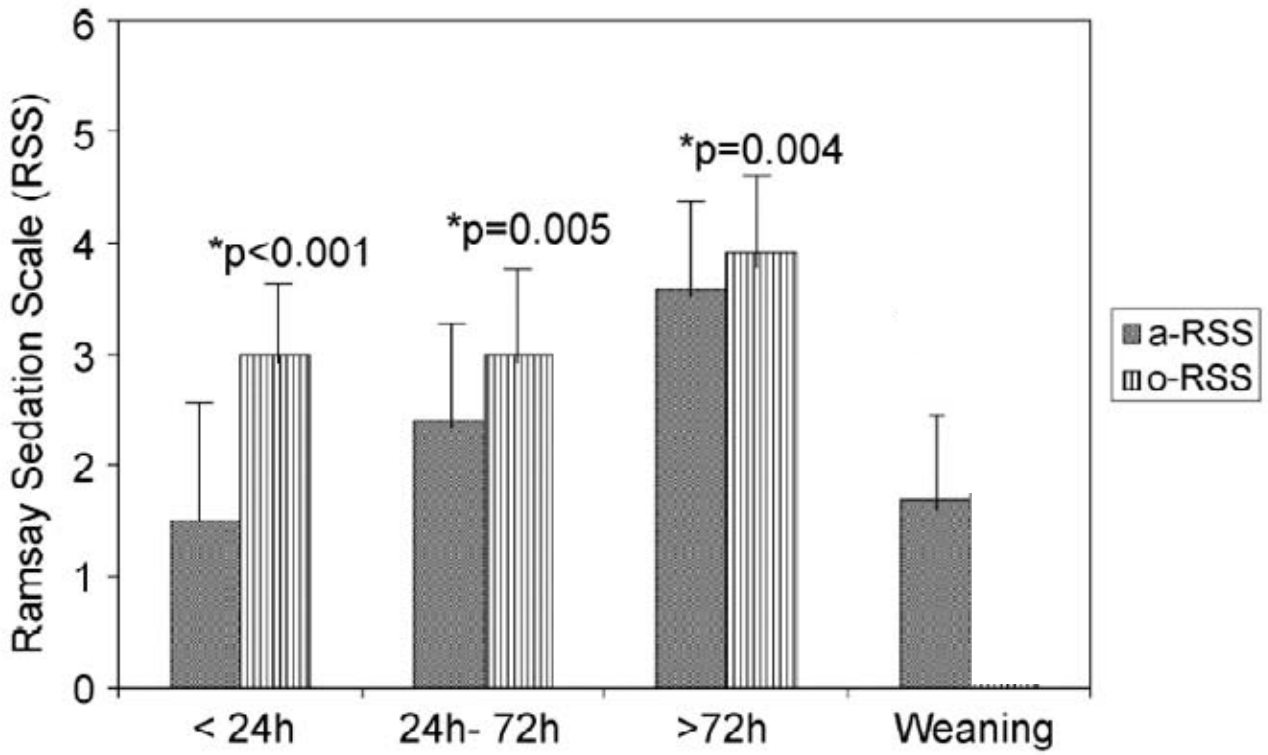


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a-RSS*) and that which was obtained (*o-RSS*). $^{*}p \leq 0.05$ (Mann-Whitney *U* test)

Martin J, *Intensive Care Med,* 2006

Sedation and analgesia in German ICU: how is it done in reality?

Coma

St. Dolore

St. Verbale

Soporoso

Tranquillo

Agitato

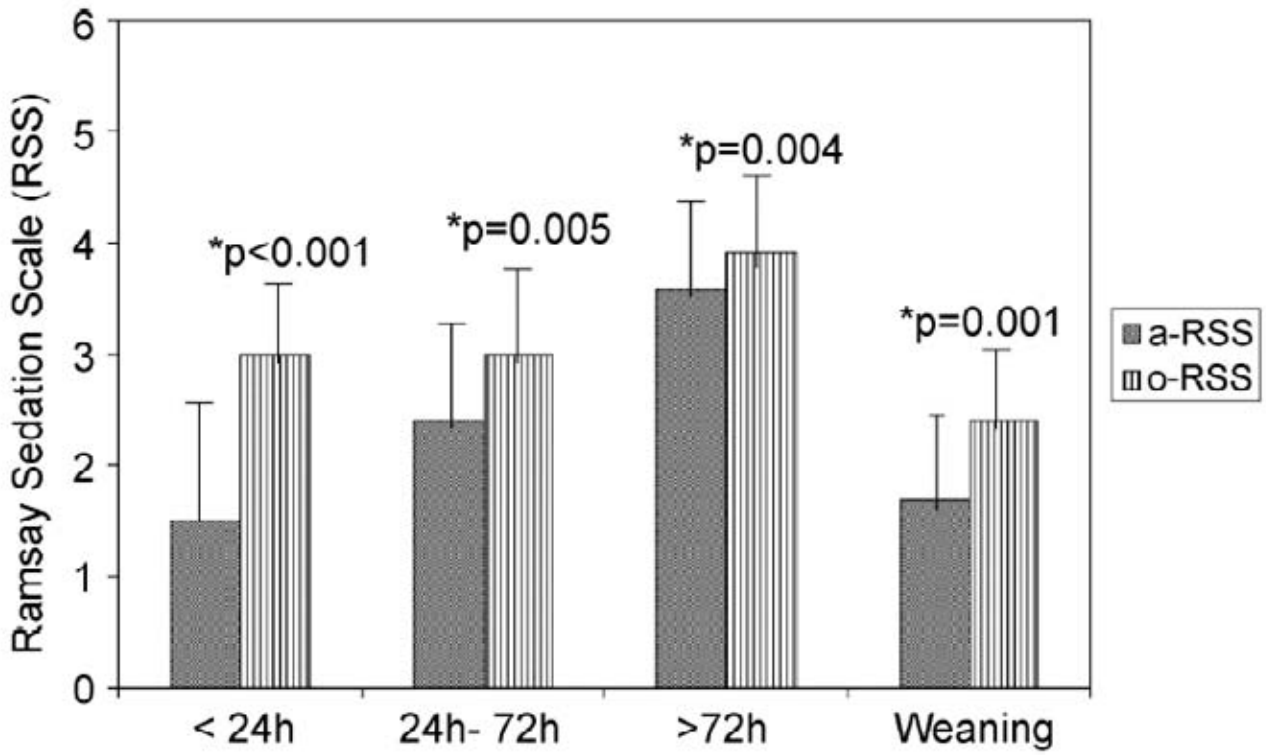


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a-RSS*) and that which was obtained (*o-RSS*). $^{*}p \leq 0.05$ (Mann-Whitney *U* test)

Martin J, *Intensive Care Med,* 2006

CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Patient-Focused Sedation and Analgesia in the ICU*

Curtis N. Sessler, MD, FCCP; and Kimberly Varney, PharmD

Patient-focused sedation and analgesia in the ICU encompasses a strategy of comprehensive structured management that matches initial evaluation, monitoring, medication selection, and the use of protocols with patient characteristics and needs. This is best accomplished through interdisciplinary management by physicians, nurses, and pharmacists. An early consideration is that of the potential predisposing and precipitating factors, as well as prior sedative or analgesic use, factors that may influence pharmacologic and supportive therapy. Frequent monitoring with validated tools improves communication among clinicians and plays an important role in detecting and treating pain and agitation while avoiding excessive or prolonged sedation. Patient-focused management encompasses selecting medications best suited to patient characteristics, including the presence of organ dysfunction that may influence drug metabolism or excessive risk for side effects. The use of protocols to optimize drug therapy has emerged as a key component of management, resulting in reductions in the duration of sedation, mechanical ventilation, and ICU length of stay demonstrated with strategies to titrate medications to specific targets, daily interruption of sedation, intermittent rather than continuous therapy, and analgesia-based therapy. While much attention is paid to the initiation and maintenance of therapy, greater emphasis must be placed on careful de-escalation of therapy in order to avoid analgesic or sedative withdrawal. Finally, more work is needed to explore the relationship of critical illness and sedation management with long-term psychological outcomes.

(CHEST 2008; 133:552–565)

Key words: analgesia; delirium; medications; protocols; sedation

OPEN ACCESS

This is the original (English) version.
The translated (German) version starts at p. 16.

Review Article

Evidence and consensus-based German guidelines for the management of analgesia, sedation and delirium in intensive care – short version

Jörg Martin[1]
Anja Heymann[2]
Katrin Bäsell[3]

Abstract

Targeted monitoring of analgesia, sedation and delirium, as well as their appropriate management in critically ill patients is a standard of care in intensive care medicine. With the undisputed advantages of goal-oriented therapy established, there was a need to develop our own

Martin J, *Ger Med Sci,* 2010

2. Overall-scheme for analgesia, sedation and delirium treatment in adults

Assessment of the patient and formulation of analgesia and sedation goals

Ventilation

- Formuliation of a ventilation goal
- Adjustment of the ventilator

Sedation

- Daily check: SAT+SBT
- No anxiety
- No stress

Goal: RASS 0/-1

< 7 days

- Propofol (> 16 y., max 4 mg/kgKG/h)
- Midazolam (bolus)

> 7 days

- Midazolam (cont.)
- Lorazepam (bolus)
- Propofol (bolus adjunktive)

RASS: Richmond Agitation Sedation Scale (-5 to +4)
VAS: Visual Analogue Scala, VRS: Verbale Rating Scala, NRS: Numeric Rating Scale (0-10)
BPS: Behavioral Pain Scale (3-12), PAINAD: Pain Assessment in Advanced Dementia (0-10)
CAM-ICU: Confusion Assessment Method for the ICU (positive/negative)
ICDSC: Intensive Care Delirium Screening Checklist (0-8)

Martin J, *Ger Med Sci,* 2010

Journal of Critical Care (2008) 23, 349–353

ELSEVIER

Journal of Critical Care

Clinical Care

Conscious sedation in the critically ill ventilated patient

Marco Cigada MD[a,*], Davide Corbella MD[a], Giovanni Mistraletti MD[a], Chiara Reali Forster MD[a], Concezione Tommasino MD[a], Alberto Morabito PhD[b], Gaetano Iapichino MD[a]

[a] *Istituto di Anestesiologia e Rianimazione, Università degli Studi di Milano, Azienda Ospedaliera San Paolo di Milano, 20142 Milano, Italy*
[b] *Cattedra di Statistica Medica, Università degli Studi di Milano, Azienda Ospedaliera San Paolo di Milano, 20142 Milano, Italy*

Keywords:
Sedation;
Conscious sedation;
Enteral sedation;
Critically ill;
Mechanical ventilation

Abstract

Purpose: The aim of sedation is to provide comfort and minimize anxiety. However, adverse effects are noteworthy, and the optimal end point of sedation in intensive care unit patients is still debated. We analyzed if a level 2 on the Ramsay Scale (ie, awake, cooperative, oriented, tranquil patient) is suitable for an invasive therapeutic approach.

Materials and Methods: Forty-two patients requiring respiratory support and sedation for at least 4 days were enrolled in a prospective interventional cohort study aiming at maintaining patients awake and collaborative. The Ramsay score was recorded 3 times a day. Once a day, the nurse in charge evaluated adequacy of sedation according to the compliance with nursing care and therapeutic maneuvers in the previous 24 hours. Data were collected until patients were ventilated.

Results: Overall, 264 of 582 days were classified as conscious. Sedation was adequate in 93.9% of them. In conscious days, a higher Simplified Acute Physiology Score II score and male sex significantly correlated with inadequate sedation.

Conclusions: In a population of severe intensive care unit patients, conscious sedation was achieved in almost half of the days spent on ventilation. The positive implications (eg, on length of weaning and cost of sedation) of a conservative sedation strategy may be highly relevant.

Cigada M, *J Crit Care*, 2008

Table 3 Univariate analysis for observing a day of conscious sedation and for being adequately sedated in overall days or only in conscious sedation days

	Conscious sedation	Adequacy (in overall days)	Adequacy (in conscious days)
SAPS II	−0.01 (−0.04 to 0.02)	**−0.05 (−0.08 to −0.01)**	**−0.08 (−0.14 to −0.03)**
Age	0.02 (−0.01 to 0.05)	−0.01 (−0.05 to 0.03)	−0.01 (−0.09 to 0.07)
Male sex	−0.65 (−1.42 to 0.11)	**−1.53 (−2.49 to −0.58)**	**−2.90 (−5.22 to −0.58)**
Medical admission	−0.32 (−1.15 to 0.52)	0.31 (−0.87 to 1.49)	0.14 (−1.58 to 1.87)
Infection at admission	0.41 (−0.44 to 1.25)	−0.07 (−0.96 to 0.83)	0.21 (−1.53 to 1.95)
Trauma at admission	[a]	−0.02 (−1.00 to 0.97)	−0.73 (−2.94 to 1.49)
Open abdominal treatment	**−1.63 (−2.09 to −1.17)**	0.16 (−0.71 to 1.03)	0.13 (−2.11 to 2.37)
>8 d since ICU admission	–	**−0.99 (0.39 to 1.58)**	**1.36 (0.15 to 2.57)**
>2 d since ICU admission	**2.37 (1.51 to 3.24)**	–	−0.98 (−1.00 to 2.96)
Daily lowest Spo_2 >94%	**1.15 (0.53 to 1.76)**	0.84 (0.21 to 1.47)	−0.19 (−1.51 to 1.13)
Presence of shock	**−1.00 (−1.59 to −0.42)**	−0.53 (−1.15 to 0.09)	−0.67 (−1.86 to 0.53)
Presence of a tracheostomy	**0.98 (0.29 to 1.67)**	0.70 (−0.03 to 1.42)	1.46 (−0.26 to 3.17)

Values are correlation coefficients (95% confidence interval). Variables included in the multilevel analysis are in bold.

[a] Two trauma patients were always awake during ICU stay.

Cigada M, *J Crit Care*, 2008

"Conscious sedation"

non è possibile:

- giorni con shock
- tratt. addominale aperto

è "augurabile":

- dopo il 2° giorno in ICU
- se SpO_2 è sempre > 94%
- con la tracheostomia

Table 4 Multilevel analysis for observing a day of conscious sedation and for being adequately sedated in overall days or only in conscious sedation days

	Conscious sedation	Adequacy (in overall days)	Adequacy (in conscious days)
SAPS II	–	**−0.05 (−0.09 to −0.01)**	−0.06 (−0.11 to −0.02)
Male sex		−0.98 (−2.03 to 0.07)	**−21.24 (−23.38 to −19.10)**
Open abdominal treatment	**−2.10 (−3.48 to −0.73)**	–	–
>8 d since ICU admission	–	**−0.73 (0.06 to 1.40)**	0.68 (−0.52 to 1.88)
>2 d since ICU admission	**2.21 (1.26 to 3.16)**	–	–
Lowest Spo_2 >94%	**1.14 (0.49 to 1.79)**	0.79 (0.08 to 1.50)	–
Presence of shock	**−0.76 (−1.37 to −0.14)**		
Presence of a tracheostomy	0.23 (−0.61 to 1.07)	–	–
Conscious sedation	–	**−0.87 (0.17 to 1.58)**	–
Constant	−2.05	[illegible]	25.36

Numbers are correlation coefficients (95% confidence interval). Significant values are in bold.

Cigada M, *J Crit Care,* 2008

“Conscious sedation” è correlata all’adeguatezza!

Intensive Care Med (2010) 36:1505–1513
DOI 10.1007/s00134-010-1874-9

ORIGINAL

Marek A. Mirski
John J. Lewin III
Shannon LeDroux
Carol Thompson
Peter Murakami
Elizabeth K. Zink
Michael Griswold

Cognitive improvement during continuous sedation in critically ill, awake and responsive patients: the Acute Neurological ICU Sedation Trial (ANIST)

2010: Continuous sedation in…

- critically ill
- awake
- responsive

} patients

Mirski MA, *Intensive Care Med,* 2010

A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial

Thomas Strøm, Torben Martinussen, Palle Toft

Summary

Background Standard treatment of critically ill patients undergoing mechanical ventilation is continuous sedation. Daily interruption of sedation has a beneficial effect, and in the general intesive care unit of Odense University Hospital, Denmark, standard practice is a protocol of no sedation. We aimed to establish whether duration of mechanical ventilation could be reduced with a protocol of no sedation versus daily interruption of sedation.

Methods Of 428 patients assessed for eligibility, we enrolled 140 critically ill adult patients who were undergoing mechanical ventilation and were expected to need ventilation for more than 24 h. Patients were randomly assigned in a 1:1 ratio (unblinded) to receive: no sedation (n=70 patients); or sedation (20 mg/mL propofol for 48 h, 1 mg/mL midazolam thereafter) with daily interruption until awake (n=70, control group). Both groups were treated with bolus doses of morphine (2·5 or 5 mg). The primary outcome was the number of days without mechanical ventilation in a 28-day period, and we also recorded the length of stay in the intensive care unit (from admission to 28 days) and in hospital (from admission to 90 days). Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00466492.

Lancet 2010; 375: 475–80

Published Online January 29, 2010 DOI:10.1016/S0140-6736(09)62072-9

See Comment page 436

Department of Anesthesia and Intensive Care Medicine, Odense University Hospital (T Strøm MD, Prof P Toft DMSc), and Department of Biostatistics, Faculty of Health Sciences (Prof T Martinussen PhD), University of Southern Denmark, Denmark

- 2010: No sedation strategy ?!?!?!?!?!?!?!

Strom T, *Lancet*, 2010

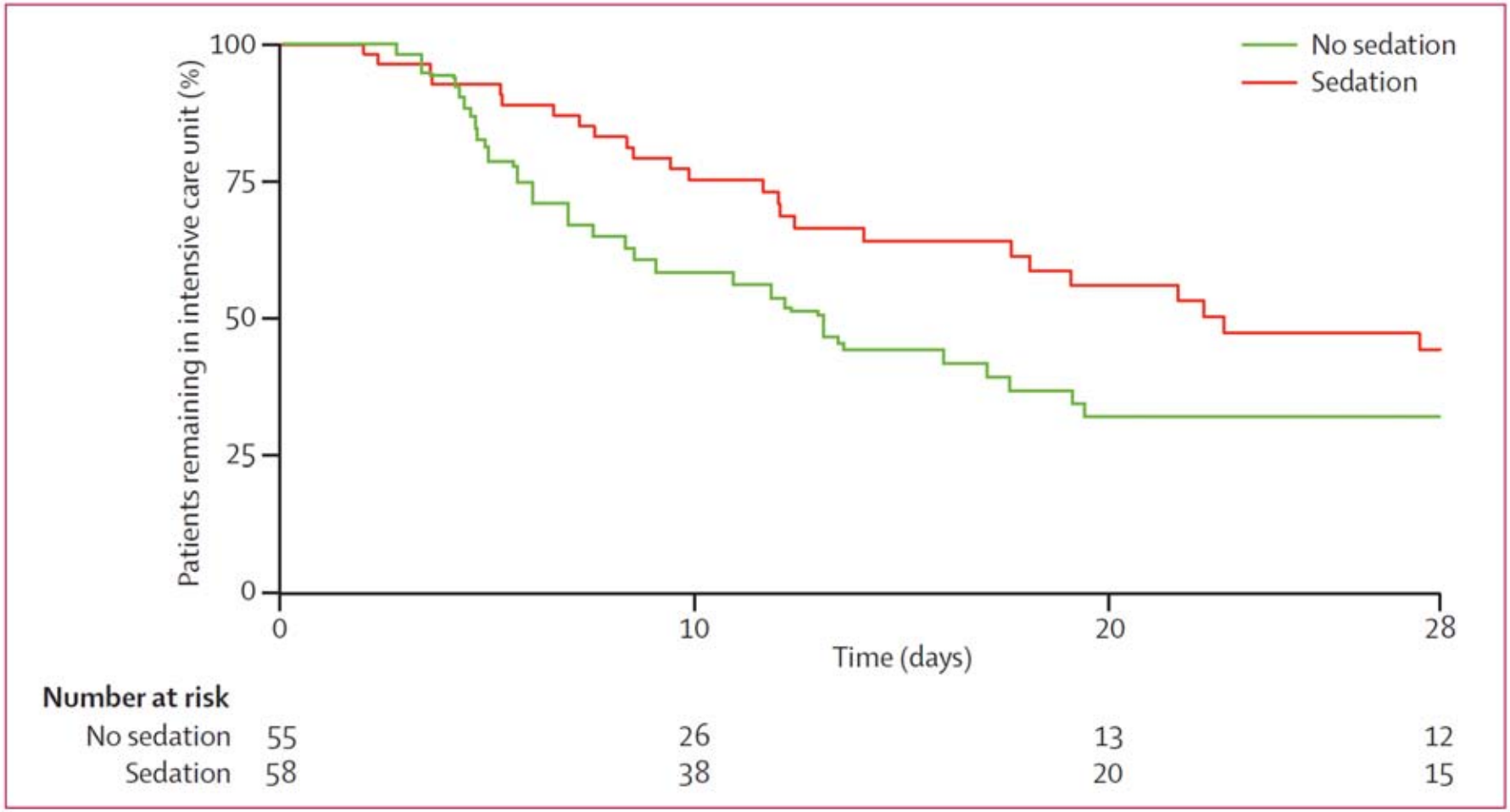


Figure 2: **Kaplan-Meier plot of length of stay in the intensive care unit and number at risk from admission to 28 days**

Strom T, *Lancet*, 2010

Il livello di sedazione ideale
varia per ogni paziente
e per ogni momento della storia clinica…

Ma siamo disposti a desiderare
che i nostri pazienti critici
siano “il più svegli possibile”… ? ! ? !

Sedazione "cosciente"

Approccio enterale

Il ruolo della Melatonina

XIX Meeting GiViTI
Pesaro, 28 ottobre 2010.

Quali farmaci usiamo ?

Available drugs

Analgesics:

- Opioids (morphin, fentanyl, sufentanil, alfentanil, hydromorfone, remifentanil, tramadol)
- NSAIDs, acetaminophen

Sedatives:

- BZDP (Diazepam, Lorazepam, Midazolam)
- Propofol
- **A_2**-agonist (clonidine, dexmedetomidine)
- Atypical:
  - Butyrophenone (Haloperidol, Droperidol)
  - Etomidate
  - Ketamin
  - Barbiturates (Sodium thiopental, Phenobarbital)
  - Inhalational agents (Halogenated, Xenon)

Canadian survey of the use of sedatives, analgesics & NMBA in ICU…

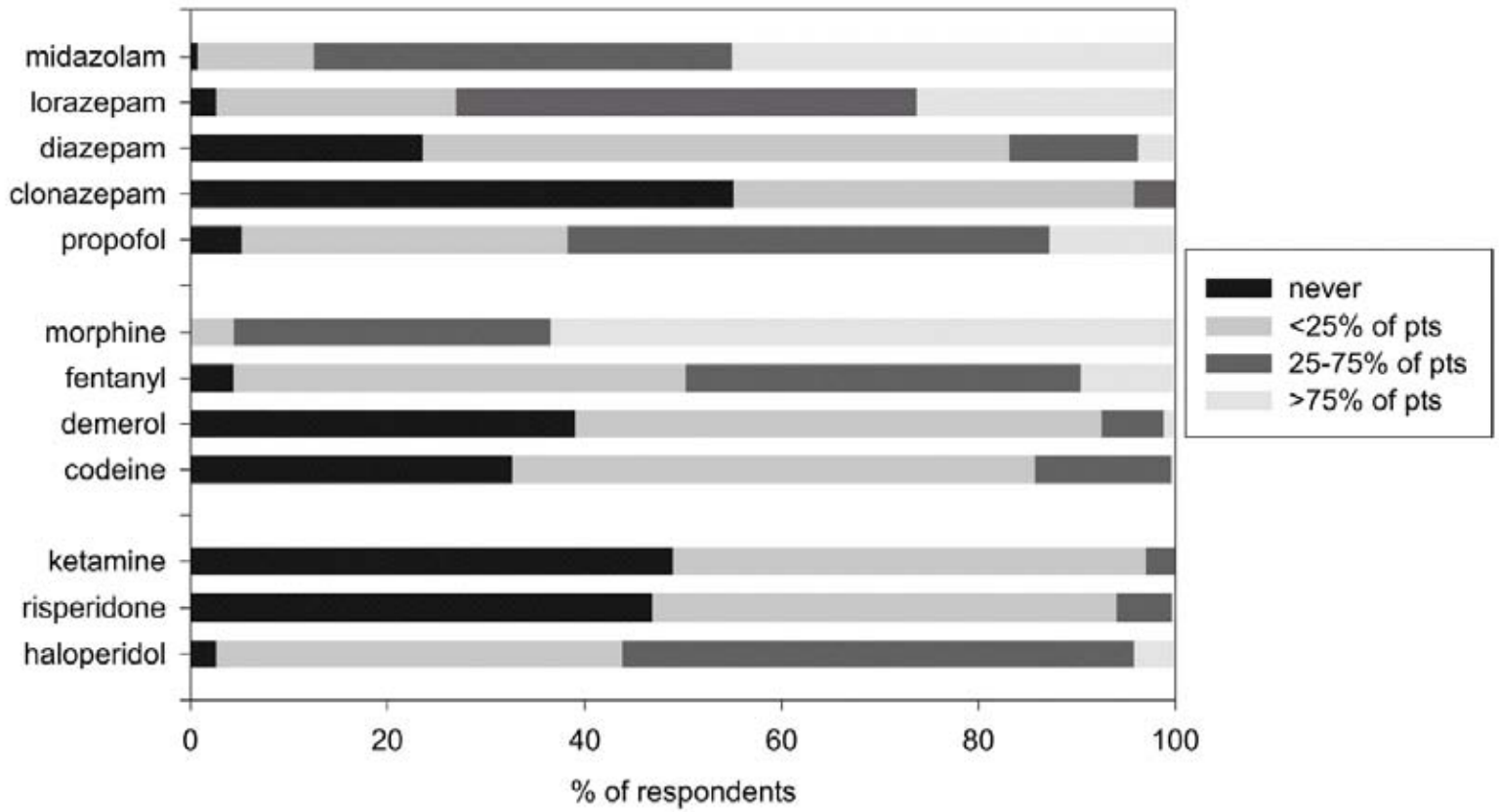


Figure 1. We asked respondents about the frequency of their use of each of these sedatives, analgesics, and antipsychotics.

Metha S, et al., *Crit Care Med*, 2006

Use of NMB in Canadian ICUs…

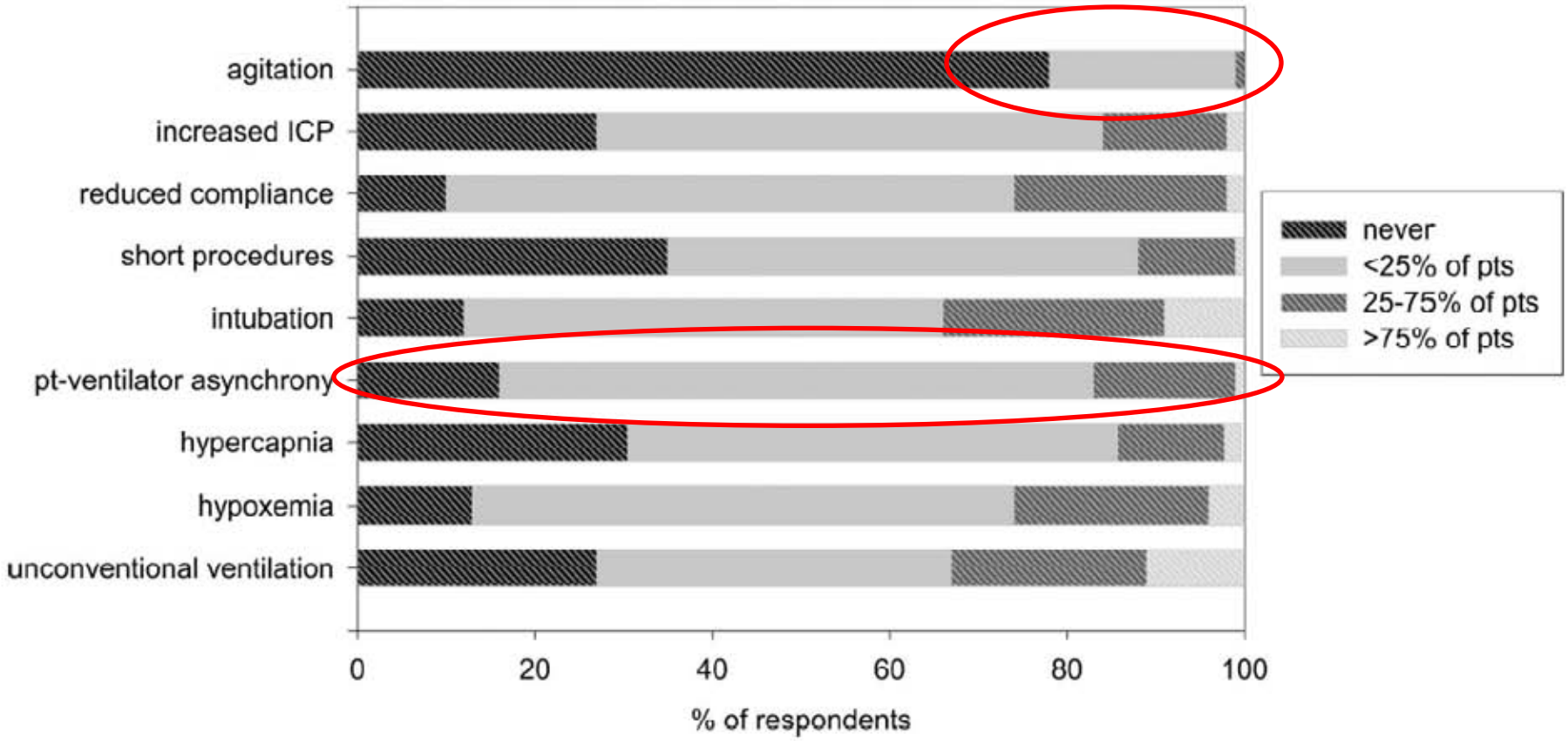
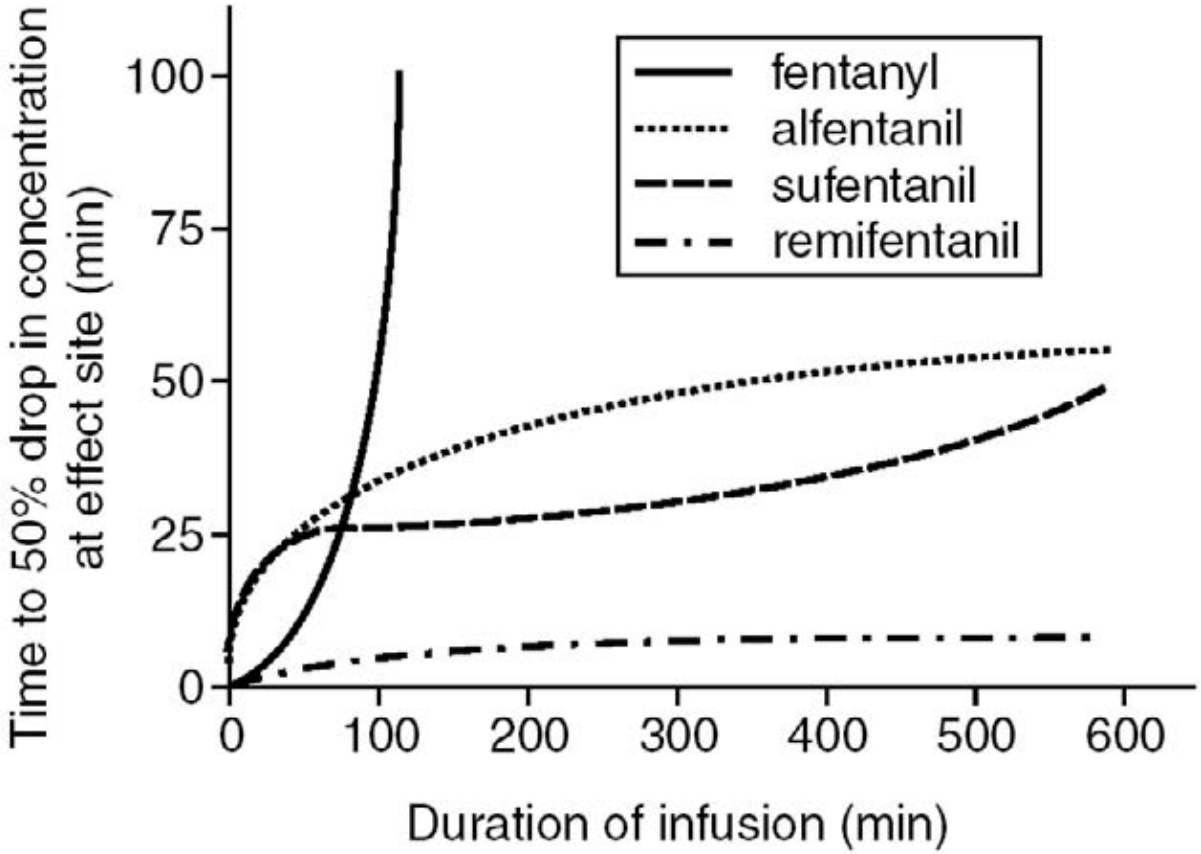


Figure 2. We asked respondents about the frequency of use of neuromuscular blockers for each of these indications. *ICP*, intracranial pressure; *pt*, patient.

…!!!

Metha S, *Crit Care Med*, 2006



Context-sensitive half-times of remifentanil and the other 4-anilido-piperidine opioids. Remifentanil has a context-sensitive half-time of 3 to 4 minutes, regardless of the duration of infusion, whereas continuous infusion of the other opioids results in accumulation and considerable prolongation of effect, making these opioids intermediate-acting or long-acting agents, depending on the duration of infusion.

Egan TD, *Anesthesiology*, 1993

Sedation and analgesia in German ICU: how is it done in reality?

Coma

St. Dolore

St. Verbale

Soporoso

Tranquillo

Agitato

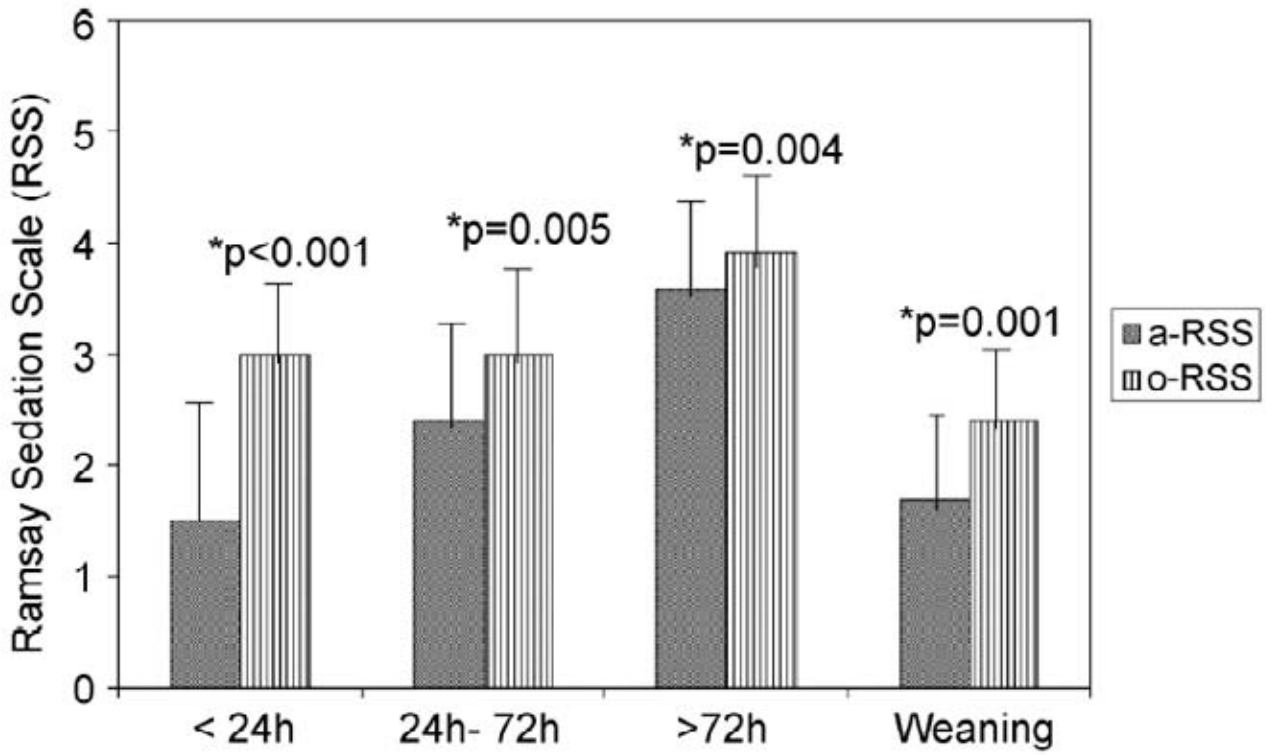


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a-RSS*) and that which was obtained (*o-RSS*). $^{*}p \leq 0.05$ (Mann-Whitney *U* test)

Martin J, *Intensive Care Med,* 2006

Goals of Analgo-Sedation

- Individualized approach to sedation
- Ability to tolerate physical enviroment
- Ability to tolerate ICU procedures
- Prevention/reduction of stress
- Patient safety

The ideal sedative…

Properties of the ideal sedative

Rapid onset and offset
Minimal respiratory depression
No effect on cardiovascular function
Inactive metabolites or lack of metabolites
Metabolism and elimination not dependent on hepatic function
Metabolism and elimination not dependent on renal function
No drug interactions
No pain on injection
No associated tolerance or withdrawal
Amnestic
Inexpensive

Angelini G, *Crit Care Clin,* 2001

- Realized in drug association ?

- Have the "enteral approach" some advantages ?

Già nel 1989…

Anest. Rianim., 30, 75-78, 1989

TRATTAMENTO SEDATIVO POLIFARMACOLOGICO PER VIA ENTERALE IN PAZIENTI CRITICI

G. Iapichino, M. Borelli, G. Breda, R. Ciceri, S. Ferraris, M. Passoni

Introduzione

La sedazione è un presidio terapeutico abitualmente utilizzato nei reparti di rianimazione per alleviare il disagio del paziente e per una migliore applicazione delle varie tecniche di assistenza utilizzate (respiratoria, monitoraggio emodinamico: Merriman, 1981; Farina et al., 1981; Bion et al., 1986)

macopea dispone di molti più preparati ma che è generalmente considerata via di scarso affidamento nei pazienti critici.

Scopo del lavoro è presentare la nostra esperienza clinica sull'argomento.

Metodi

Iapichino G, *Anest Rianim,* 1989

La sedazione enterale: perché ?

- Minori effetti collaterali
- Minori costi
- Garantire gli obiettivi di sedazione… cosciente!!!
- Diminuito periodo di weaning (?)
- "Cinetica" più lenta: peggio… o meglio?
  (delirium)
- **Pz più svegli: è possibile ? ! ?**

PRESUPPOSTI

L’intestino funziona precocemente !!

E’ necessaria una sedazione profonda ?

IDROSSIZINA (Atarax)

Indicazioni:	antiistaminico, preanestesia
Effetti collaterali:	anticolinergici
Tossicità (> 45mg/kg):	depressione SNC convulsioni allucinazioni ipotensione
Dosi ridotte in:	insufficienza epatica/renale
Costo ospedaliero:	100 mg = 0.42 €
Dosi utilizzate:	6-12 mg/kg*die

Il protocollo attualmente in vigore nella Terapia Intensiva del San Paolo:

Prime 24-48 ore: endovena

Propofol (1-4 mg/kg*h) oppure **Midazolam** (0.02-0.3 mg/kg*h)

associare ad entrambi **Morfina** o **Fentanyl** ev

Da subito: embricare sedazione "per os" (via SNG)

Idrossizina (6-12 mg/kg*die) ed eventualmente (se necessario) **Lorazepam** (0.06-0.2 mg/kg*die)

associare ad entrambi **Morfina** o **Fentanyl** ev

In caso di Delirium: **Aloperidolo** "per os"

Oltre le 48 ore: stop sedazione endovena !

Nel 2005 …

Intensive Care Med (2005) 31:482–486
DOI 10.1007/s00134-005-2559-7

BRIEF REPORT

Marco Cigada
Angelo Pezzi
Piero Di Mauro
Silvia Marzorati
Andrea Noto
Federico Valdambrini
Matteo Zaniboni
Morena Astori
Gaetano Iapichino

Sedation in the critically ill ventilated patient: possible role of enteral drugs

Cigada M, *Intensive Care Med,* 2005

CHEST Postgraduate Education Corner
CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Patient-Focused Sedation and Analgesia in the ICU*

However, administration of transdermal or enteral medications may have a role in some patients, particularly those who require longer term sedation and analgesia management, resulting in elimination or reduction in IV dosages[82].

82 Cigada M, Pezzi A, Di Mauro P, et al. Sedation in the critically ill ventilated patient: possible role of enteral drugs. Intensive Care Med 2005; 31:482–486

Sessler CN, *Chest,* 2008

E in futuro ?

Enteral Conscious Sedation

vs

Standard Protocol Sedation

Idrossizina e Lorazepam SNG

Propofol o Midazolam ev

SCHEDA PROGETTO

Titolo	STRATEGIE INNOVATIVE PER LA SEDAZIONE DEI PAZIENTI AD ALTO RISCHIO IN TERAPIA INTENSIVA	
Area	AREA INTENSIVISTICA – TERAPIA INTENSIVA GENERALE	
Proponente	Soggetto	Prof. Gaetano Iapichino U.O. Anestesia e Rianimazione A.O. San Paolo – Polo Universitario
	Indirizzo	Via Di Rudinì, 8 – 20142 Milano

Sedazione “cosciente”

Approccio enterale

Un ruolo per la Melatonina ?

XIX Meeting GiViTI
Pesaro, 28 ottobre 2010.

Available online http://ccforum.com/content/12/3/146

Commentary

Good night, sleep tight: the time is ripe for critical care providers to wake up and focus on sleep

Randall S Friese

Department of Surgery, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd Room E5.508, Dallas, Texas 75390 USA

Corresponding author: Randall S Friese, randall.friese@utsouthwestern.edu

Published: 12 May 2008
This article is online at http://ccforum.com/content/12/3/146

Critical Care 2008, **12:**146 (doi:10.1186/cc6884)

See related research by Bourne *et al.*, http://ccforum.com/content/12/2/R52

Friese RS, *Crit Care*, 2008

Sleep is an essential biological function.

Sleep disturbances in ICU are still inadequately elucidated, but they determine:

- Alterate catecholamines and hormones secretion
- Worsen insulin resistance
- Determine immune dysfunction
- Alterate nitrogen balance, wound healing
- Induce psychopathology
- Worsen quality of life after ICU discharge

Necessità di sedazione…


… ma COME
dormono?

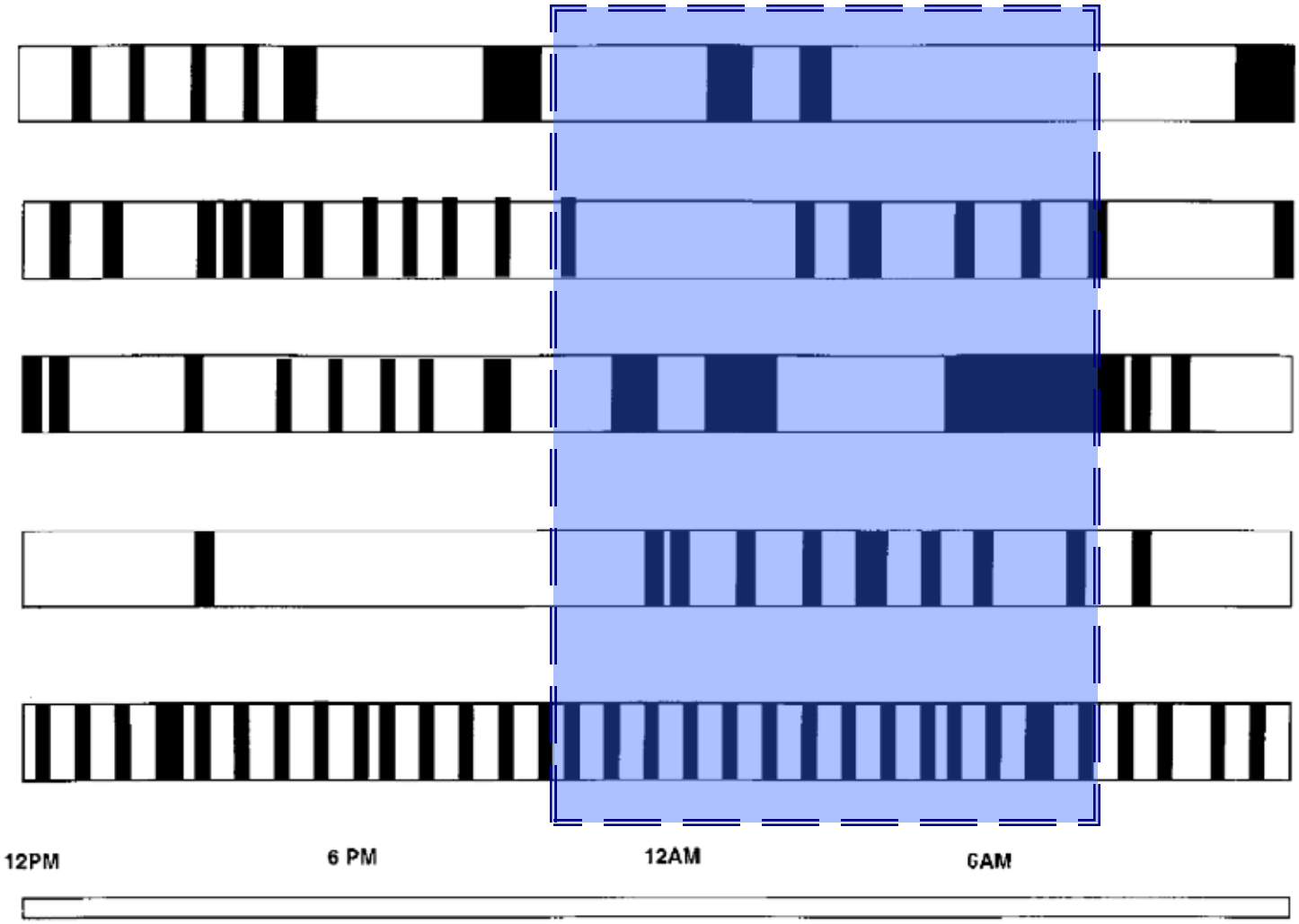
ICU patients almost uniformly have sleep alterations

- Long sleep onset
- Frequent arousals
- Sleep fragmentation

Quantity

- Poor sleep efficiency
- Predominance of stage 1 & 2 non-
- Decreased stage 3 nREM (the most
- Decreased or absent REM sleep

Quality



Time of Day

Freedman NS, *AJRCCM*, 2001

Stressors in ICU

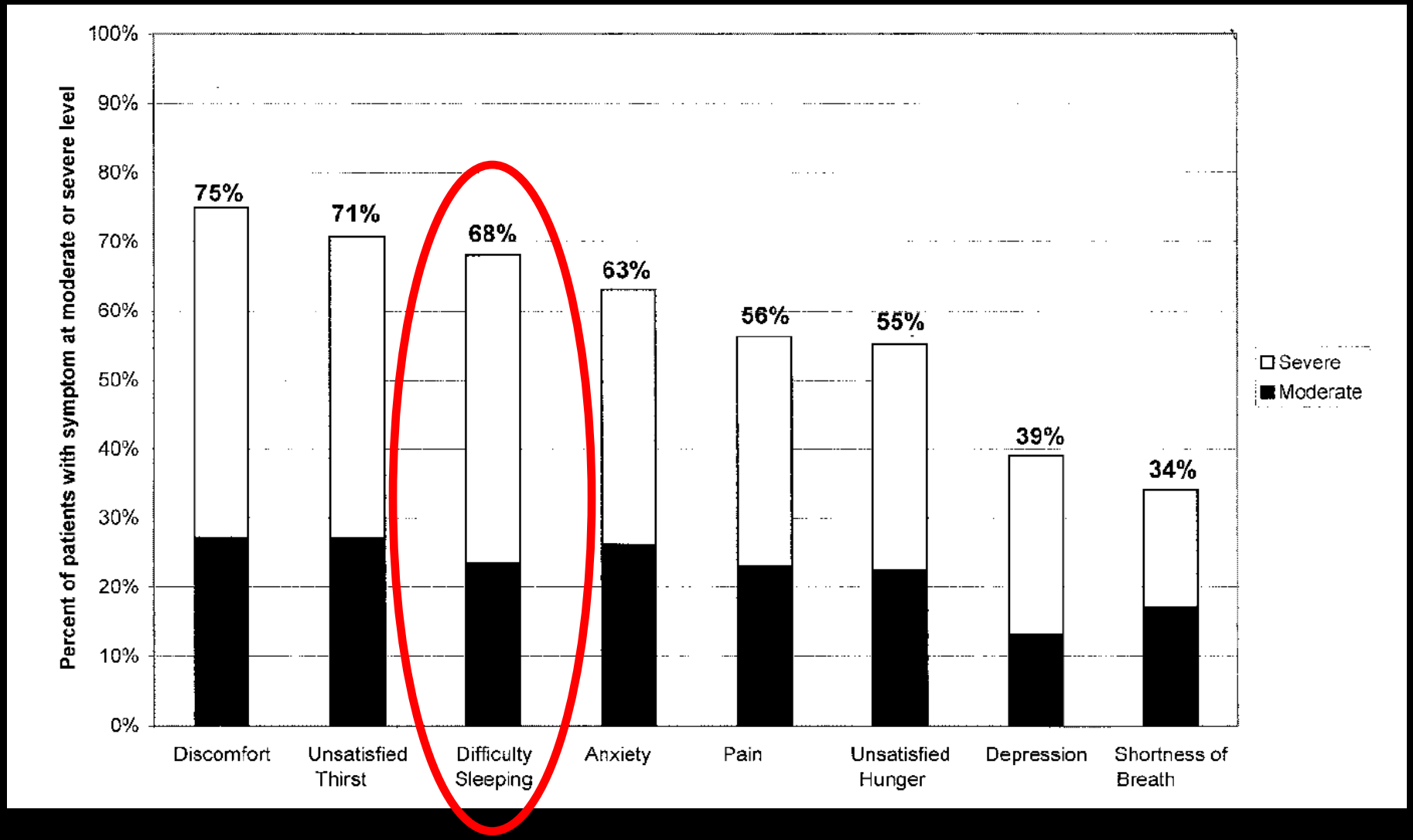
Novaes,

Intensive Carre Med, 1997

Table 1 Ranking of stressors

Ranking	Description	Mean	Standard deviation
01	Have pain	3.36	1.01
02	Not being able to sleep	3.34	0.98
03	Having tubes in your nose or mouth	3.26	1.01
04	Not being in control of yourself	3.10	1.11
05	Being tied down by tubes	3.02	1.12
06	Not having treatments explained to you	3.02	1.22
07	Not being able to move your hands because of i. v. line	2.90	1.15
08	Not knowing when to expect things will be done to you	2.84	1.06
09	Being stuck with needles	2.80	1.18
10	Being thirsty	2.76	1.22
11	Having lights on constantly	2.72	1.25
12	Seeing family and friends for only a few minutes each day	2.66	1.22
13	Uncomfortable bed and/or pillow	2.64	1.26
14	Having no privacy	2.64	1.24
15	Nurses and doctors talking too loudly	2.54	1.15
16	Being bothered	2.52	1.15
17	Having to wear oxygen	2.50	1.20
18	Hearing other patients cry out	2.46	1.23
19	Being in a room that is too hot or too cold	2.46	1.05
20	Not knowing where you are	2.46	1.33
21	Not knowing what time it is	2.44	1.18
22	Unfamiliar and unusual noises	2.40	1.11
23	Having nurses be in too much of a hurry	2.40	1.14
24	Missing your husband or wife	2.34	1.19
25	Hearing the heart monitor alarm go off	2.26	1.16
26	Not knowing what day it is	2.20	1.21
27	Having the team use words you cannot understand	2.20	1.20
28	Being awakened by nurses	2.14	1.13
29	Having to look at the pattern of holes in the ceiling	2.14	1.25
30	Feeling the nurses are watching the machines closer than they are watching you	2.08	1.08
31	Having nurses constantly doing things around your bed	2.06	1.08
32	Hearing buzzers and alarms from machinery	2.02	0.91
33	Being cared for by unfamiliar doctors	1.96	1.18
34	Constantly being examined by doctors and nurses	1.96	1.11
35	Hearing the telephone ring	1.92	1.12
36	Being aware of unusual smells around you	1.92	1.07
37	Having strange machines around you	1.90	1.16
38	Having your blood pressure taken often each day	1.74	0.90
39	Not having the nurses introduce themselves	1.64	0.88
40	Seeing i. v. bags hanging over your head	1.58	0.91

Symptoms experienced in ICU



Nelson JE, *CCM* 2001

Intensive Care Med (2010) 36:1751–1758
DOI 10.1007/s00134-010-1902-9

ORIGINAL

Pierre Kalfon
Olivier Mimoz
Pascal Auquier
Anderson Loundou
Rémy Gauzit
Alain Lepape
Jean Laurens
Bernard Garrigues
Thierry Pottecher
Yannick Mallédant

Development and validation of a questionnaire for quantitative assessment of perceived discomforts in critically ill patients

Table 2 Characteristics of dimension scales: discomfort scores, floor effect, ceiling effect, Cronbach's alpha, Rasch statistics (INFIT), and intraclass correlation coefficient of the 16 items of the IPREA questionnaire, for the 868 analyzed patients

Items	Score mean ± SD, median	Floor effect, %	Ceiling effect, %	Cronbach's alpha	INFIT	ICC
Noise	27 ± 27, 20	35.3	2.4	0.776	0.91	0.84
Excessive light	16 ± 22, 0	54.5	1.0	0.771	0.83	0.90
Bed-related discomfort	20 ± 27, 0	52.8	2.6	0.770	1.03	0.81
Sleep deprivation	35 ± 32, 30	33.1	5.8	0.770	0.94	0.89
Thirst	32 ± 34, 20	40.4	8.1	0.778	1.23	0.87
Hunger	13 ± 23, 0	68.0	2.2	0.778	1.25	0.82
Feeling of cold	15 ± 23, 0	60.0	1.4	0.779	1.10	0.91
Feeling of heat	14 ± 23, 0	65.0	1.7	0.775	1.08	0.84
Pain	32 ± 30, 30	29.0	4.3	0.776	0.95	0.70
Perfusion lines etc.	33 ± 29, 30	28.8	4.0	0.767	0.80	0.78
Lack of privacy	12 ± 21, 0	65.3	1.0	0.771	0.84	0.84
Anxiety	27 ± 31, 20	43.7	4.1	0.765	0.95	0.86
Isolation	15 ± 24, 0	62.7	1.6	0.764	0.94	0.76
Limited visiting hours	21 ± 29, 0	57.3	3.1	0.770	1.11	0.73
Absence of phone	21 ± 31, 0	59.0	4.7	0.776	1.31	0.92
Lack of information	19 ± 27, 0	58.5	2.6	0.766	1.02	0.91
Overall score of discomfort	22 ± 14	0.3	0.1	0.783	1.01	0.91

Fattori stressanti in Terapia Intensiva - A.O. San Paolo

		rank
Non poter assumere liberamente la posizione che si desidera	9 [4-12]	1
Avere tubi nel naso o nella bocca che limitano i movimenti	8.5 [6-12]	2
Non riuscire ad esprimere i propri disagi, non poter parlare	8 [4-12]	3
Avere sete	8 [4-12]	3
Non riuscire a dormire	6 [3-12]	5
Dover continuare a guardare il soffitto con luci sempre accese	6 [2.5-9]	6
Mancanza delle persone care (del proprio marito/moglie/figli)	6 [2-9]	7
Non sapere che giorno o che ore sono	5 [2-9]	8
Essere preoccupati / avere paura	5 [2.5-8]	9
Non avere intimità	5 [1-9]	10
Avere dolore	4 [2-8]	11
Avere strani macchinari intorno o flebo appese sopra la testa	3 [2-8.5]	12
Sentire che il bracciale della pressione si gonfia spesso	3 [1.5-9]	13
Materasso o cuscini scomodi	3 [1-9]	14
Orario di visita dei parenti ridotto	3 [1-6]	15
Non sapere dove si è e perchè	3 [1-6]	15
Non sapere quando si verrà sottoposti a qualcosa	3 [1-5]	17
Non avere il controllo su se stessi	2.5 [1-7]	18
Non ricevere spiegazioni sui trattamenti a cui si è sottoposti	2.5 [1-7]	18
Sentire suoni o rumori insoliti (allarmi dei macchinari, monitor,…)	2.5 [1-6]	20
Stare in una stanza che è troppo calda o troppo fredda	2.5 [1-5]	21
Vedere il personale sanitario troppo indaffarato, stressato, frettoloso	2.5 [1-4]	22
Essere punti con aghi	2 [1.5-5]	23
Personale sanitario che parla, scherza o discute a voce alta	2 [1-5]	24
Essere svegliati dal personale sanitario	2 [1-4]	25
Avere delle persone che lavorano continuamente attorno al suo letto	2 [1-3.5]	26
Sentire altri pazienti che soffrono, piangono o si lamentano	1.5 [1-5]	27
Personale sanitario che non si presenta	1.5 [1-4]	28
Avere la sensazione di non mangiare	1.5 [1-3.5]	29
Essere curato da medici che non conosce	1.5 [1-3]	30
Sentire lo squillo del telefono	1 [1-2.5]	31
Avere fame	1 [1-2]	32
Poca considerazione del proprio credo religioso	1 [1-1]	33

stato fisico
4 [2-8]

emozioni
4 [1-7]

ambiente
2.5 [1-5]

affetti
2 [1-4]

28 pz ICU
ventilazione > 4 gg

intervistati nel giorno
della dimissione
da Terapia Intensiva

rank	
1	Non poter assumere liberamente la posizione che si desidera
2	Avere tubi nel naso o nella bocca che limitano i movimenti
3	Non riuscire ad esprimere i propri disagi, non poter parlare
3	Avere sete
5	Non riuscire a dormire
6	Dover continuare a guardare il soffitto con luci sempre accese
7	Mancanza delle persone care (del proprio marito/moglie/figli)
8	Non sapere che giorno o che ore sono
9	Essere preoccupati / avere paura
10	Non avere intimità
11	Avere dolore

- Typ
- Pat
- Pai
- ICU
  - I
    l
- Me
  - I
    t
- Pha

Table 1 Drugs commonly used in ICU and their effects on sleep pattern.

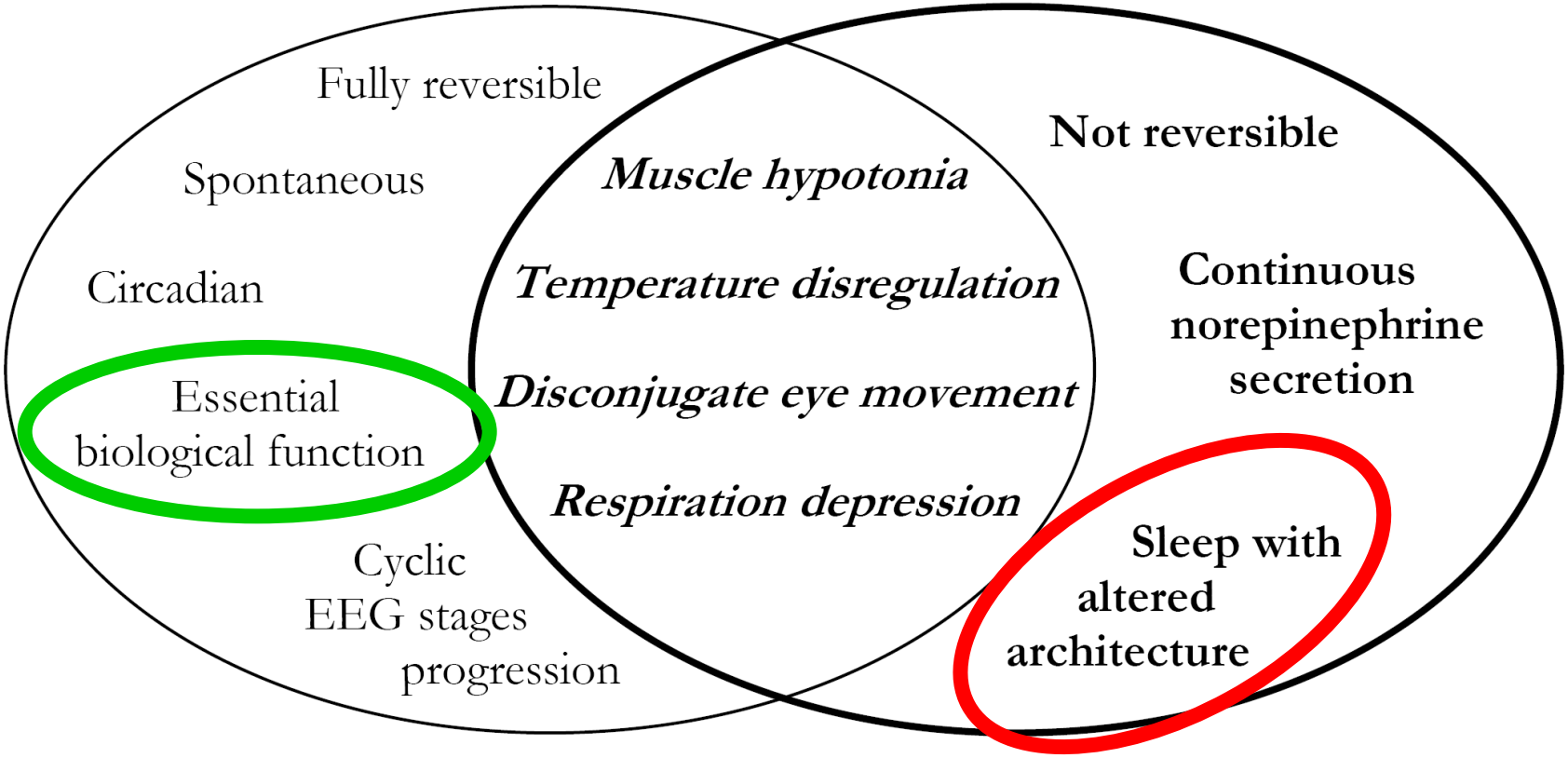
Drug Class or Individual Drug	Sleep Disorder Induced or Reported
Benzodiazepines	↓ REM, ↓ SWS
Opioids	↓ REM, ↓ SWS
Clonidine	↓ REM
Non steroidal anti-inflammatory drugs	↓ TST, ↓ SE
Norepinephrine/Epinephrine	Insomnia, ↓ REM, ↓ SWS
Dopamine	Insomnia, ↓ REM, ↓ SWS
β-Blockers	Insomnia, ↓ REM, Nightmares
Amiodarone	Nightmares
Corticosteroids	Insomnia, ↓ REM, ↓ SWS
Aminophylline	Insomnia,↓ REM, ↓ SWS, ↓ TST, ↓ SE
Quinolones	Insomnia
Tricyclic antidepressants	↓ REM
Selective serotonin reuptake inhibitors	↓ REM, ↓ TST, ↓ SE
Phenytoin	↑ Sleep Fragmentation
Phenobarbital	↓ REM
Carbamazepine	↓ REM

REM, rapid eye movement; SWS, slow wave sleep; TST, total sleep time; SE, sleep e

Bourne RS, *Anaesthesia* 2004

Sedation

plays a key role in ICU sleep disorders



Mistraletti G, *Minerva Anestesiol* 2008

Strategies to ameliorate sleep in ICU

- Adequate use of sedatives and analgesics
  - Measurement of neurological status and delirium
  - Treat pain, anxiety and delirium
  - Goal-directed sedation, for that patient in that time
- Ventilator setting (PAV > PSV > A/C V)
  - Avoid patient / ventilator asynchrony
- Reduce light, noise, nursing activities during night
- Earplugs, eye mask
- Actively prompt patient orientation (clock, calendars)
- Others (Music therapy - Relaxation tecniques - Massage - Hypnosys)
- Melatonin therapy ?

Mistraletti G, *Minerva Anestesiol* 2008

Metabolic and endocrine effects of sedative agents

Giovanni Mistraletti, Francesco Donatelli and Franco Carli

Purpose of review

To bring to the attention of the clinician the metabolic effects of most common sedatives and analgesics used in critically ill patients.

Recent findings

Most patients admitted to the intensive care unit require

Introduction

Injury initiates a series of physiologic responses, the magnitude of which depends on the intensity of the stressor. The defense mechanisms are also related to the nature of the injury and are activated during the initial period. If the noxious stimulus persists, exhausting mechanisms

Mistraletti G, *Curr Op Crit Care,* 2005

Le potenzialità terapeutiche della melatonina in pazienti critici non sono MAI state indagate…

21 luglio 2005

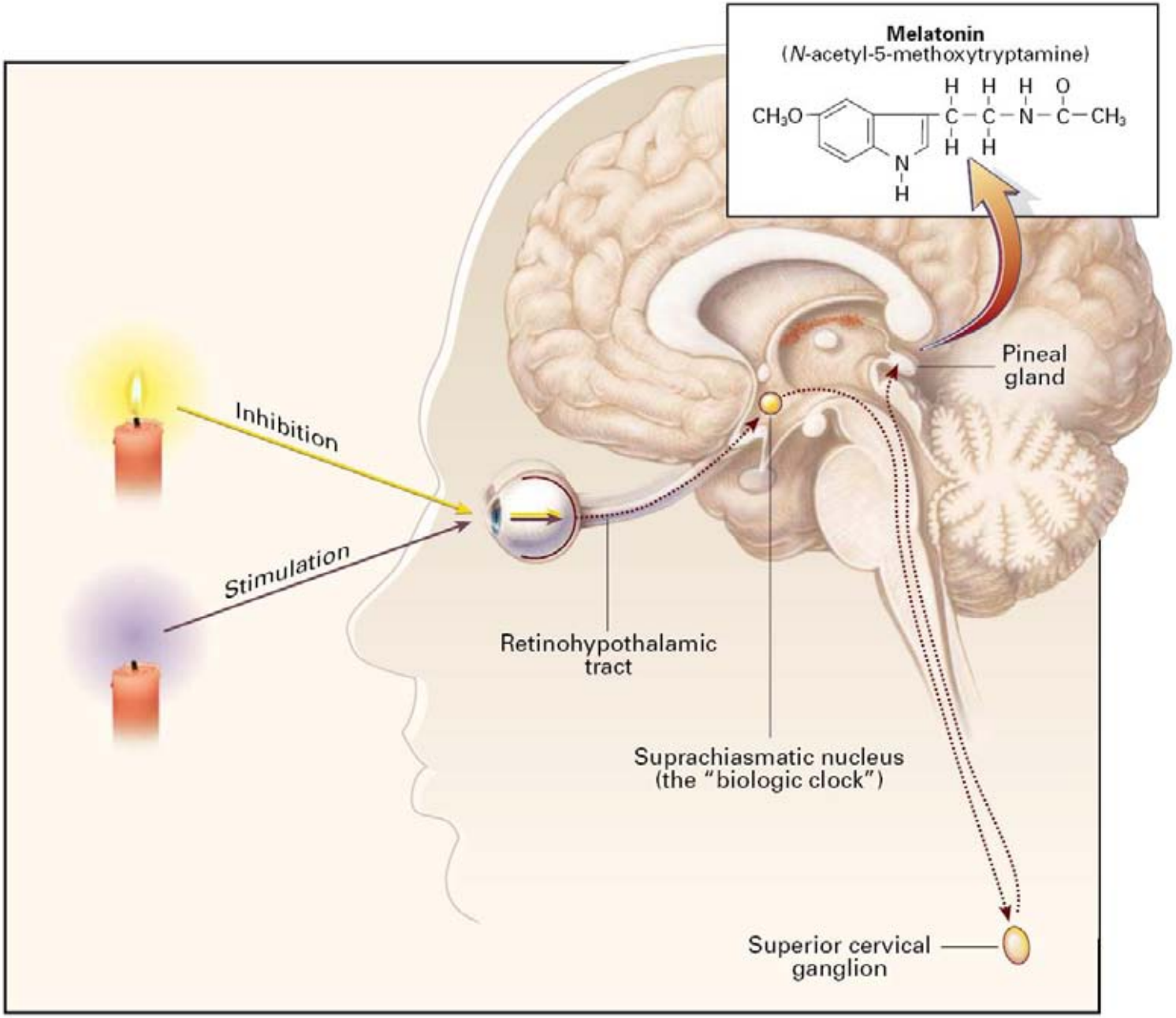
Medicus curat, natura sanat

MELA Study

Scopo: Testare l'utilizzo di **melatonina esogena** (somministrata per via orale) per migliorare la qualità del sonno dei pazienti critici, per diminuire la quantità di sedativi necessari, per migliorare la qualità di vita durante la degenza critica.

Background: Ventilazione meccanica determina sleep disruption e diminuzione dei livelli di melatonina endogena, con scomparsa dei picchi notturni di secrezione.
Somministrazione esogena di melatonina migliora la qualità del sonno nei pazienti con COPD.
Fra i ricordi della degenza in TI, la deprivazione di sonno è riferita come elemento di sconforto secondo solo al dolore…

Ipotesi: Il trattamento con melatonina esogena è relativamente sicuro e può ripristinare la naturale cronobiologia sonno-veglia anche in pazienti critici.
Somministrazione di melatonina diurna (15 µg/kg ore 8 e ore 16) e notturna (60 µg/kg ore 24) versus placebo.



Brzezinski A, *NEJM*, 1997

Melatonina

Buio

Recettori retinici

Recettori adrenergici pineali

Triptofano

Serotonina

(AA. essenziale, trasformazione complessa, compresenza della Vit. B6)

- **Eccezionale liposolubilità**
- **Minimo costo**
- **Non registrata come farmaco in nessuno stato UE …**

… è un alimento !!!

Effetti della melatonina

- Azioni principali:
  - Regola il ritmo sonno veglia (ipnoinduzione)
  - Termoregolazione
  - Azione antiossidante
- Secrezione circadiana
  - picco fra le 00:00 e le 02:00
  - nadir fra le 10:00 e le 16:00
- Azione specifica: recettori MT1 e MT2 (gabaergici, similBZDP)

- Recettori di membrana specifici:

MT-1 e MT-2, accoppiati a G-protein, presenti nel SNC ed in numerosi siti periferici.

Endocrine. 2005;27(2):101-10

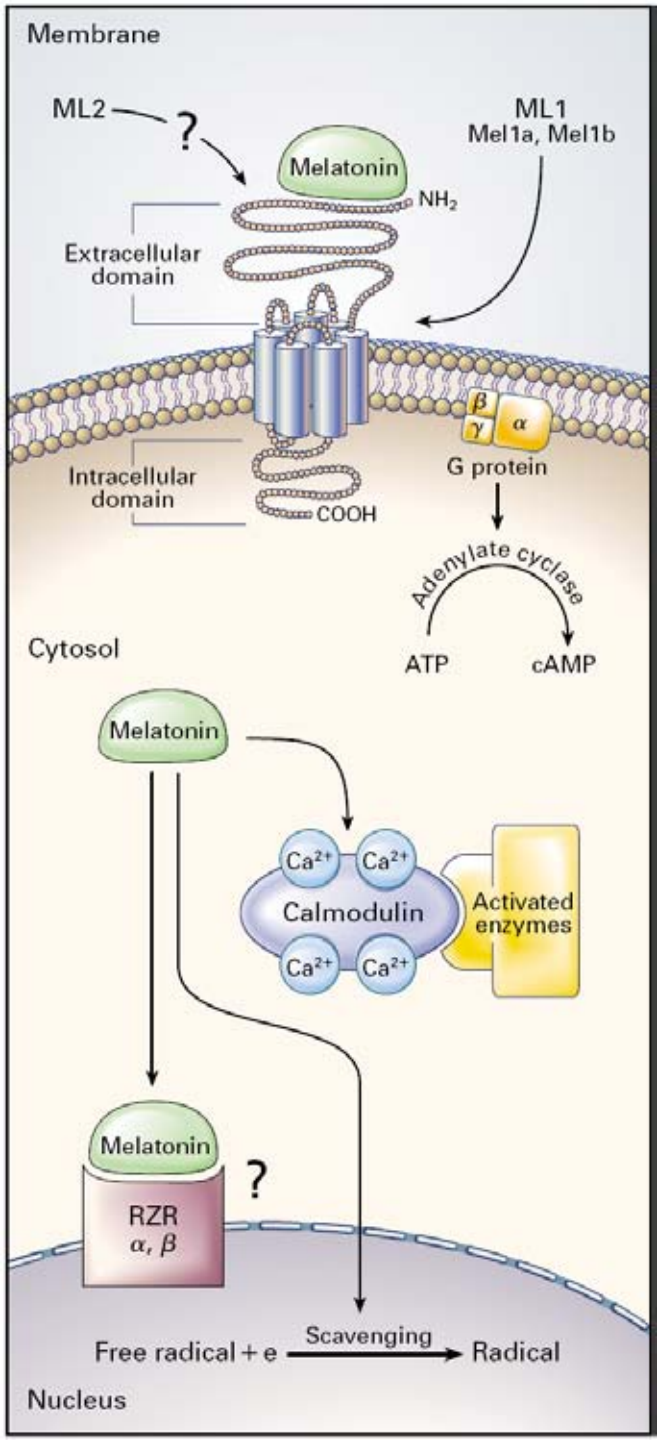
- Antiossidante:

possibilità di cessione (riduzione) verso specie reattive dell'ossigeno:

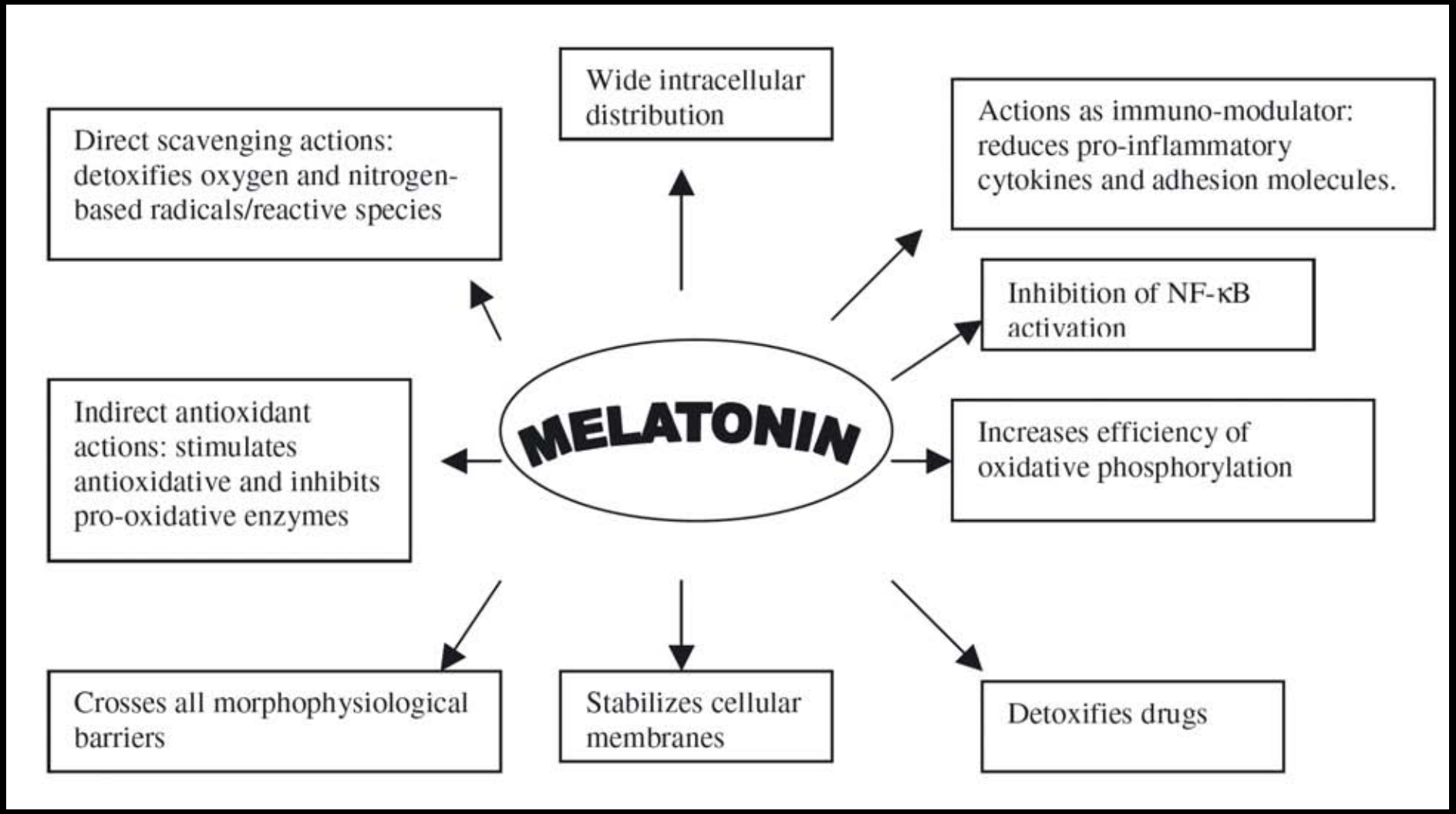
($OH^{\bullet}$ $O_2^{\bullet}$ H_2O_2 $NO^{\bullet}$)

+ protezione dal danno genotossico nella sepsi.

J. Pineal Res. 2003; 34:1–10



Brzezinski A, *NEJM*, 1997



Maldonado MD, *J Pineal Res,* 2007

Table 1. Biologic Functions and Processes That May Be Affected by Melatonin and Suggested Mechanisms of Action in Humans.

Function or Process	Effect	Suggested Mechanism	Type of Evidence
Sleep	Hypnotic effect and increased propensity for sleep	Hypothermic effect (at pharmacologic doses) Receptor-mediated action on limbic system	Placebo-controlled clinical trials
Circadian rhythm	Control of circadian rhythms and entrainment of light–dark cycle	Secretion of melatonin in response to retinal input from the eyes and suprachiasmatic nucleus Receptor-mediated effects on neural and peripheral tissues Thermoregulation	Studies in animals and in humans on the effects of light and the light–dark cycle on the pattern of melatonin secretion
Mood	Possible role in cyclic mood disorders (seasonal affective disorder, depression)	Unknown	Comparative clinical studies of the pattern of melatonin secretion and studies of phototherapy for mood disorders
Sexual maturation and reproduction	Inhibition of reproductive process	Inhibition of hypothalamic–pituitary–gonadal axis Effect on ovarian steroidogenesis	Studies in animals and comparative clinical studies of the pattern of melatonin secretion (during puberty and in women with ovarian cancer)
Cancer	Antiproliferative effects	Direct antiproliferative effect Enhanced immune response Scavenging of free radicals	In vivo and in vivo studies in animals, in vitro studies of human neoplastic cells and cell lines, and a few small clinical studies
Immune response	Enhanced immune response	Increased interleukin production by T-helper lymphocytes	Studies in animals and a few uncontrolled studies in humans
Aging	Possible protective effect and decreased cell damage	Scavenging of free radicals	In vitro and in vivo studies in animals

Riduce fase addormentam.

Aumenta il sonno REM

Migliora risp. immunitaria

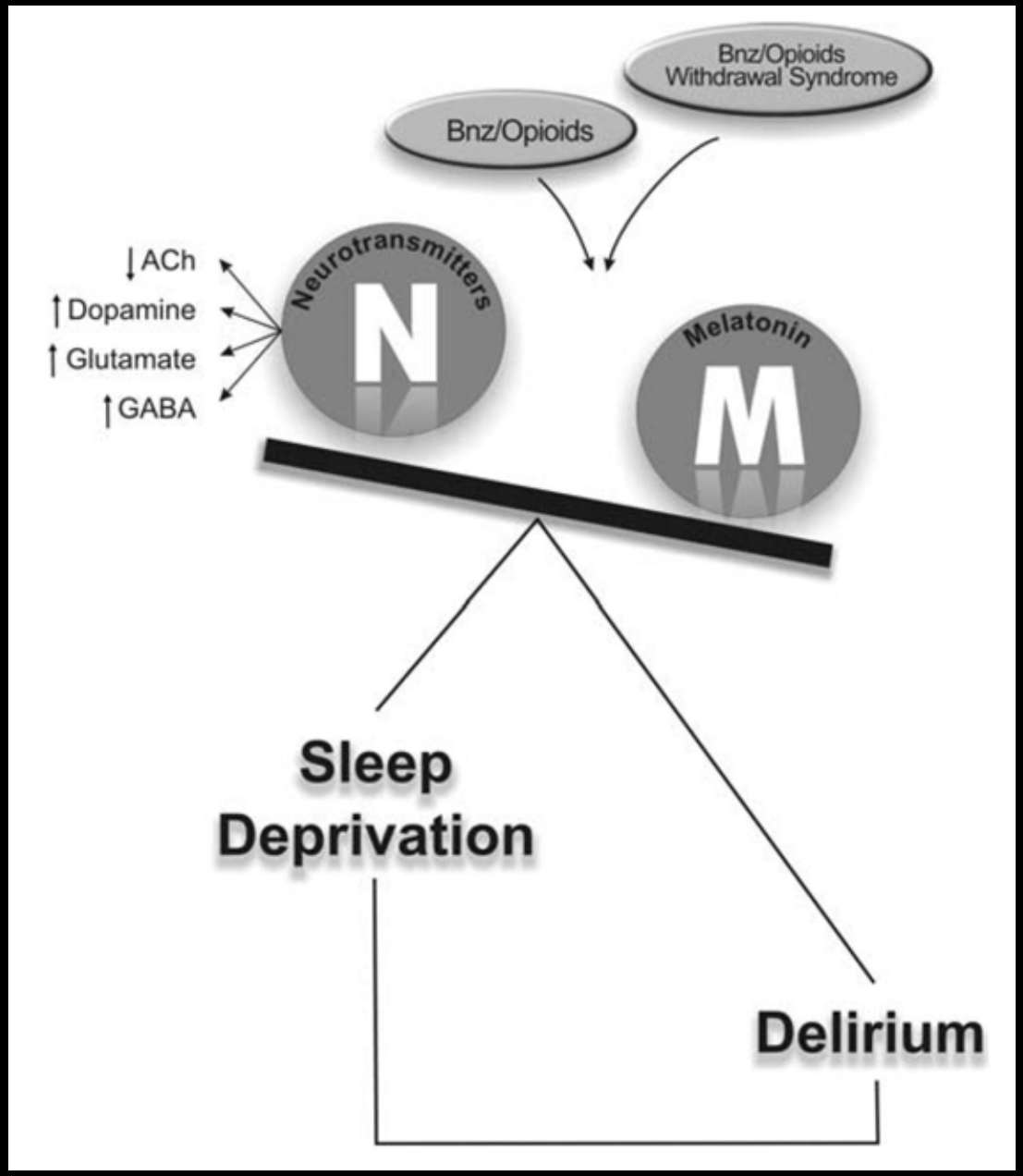
(è immunomodulante…)

Brzezinski A, *NEJM*, 1997

Nei pazienti critici
la melatonina plasmatica
è drasticamente diminuita

Ridotta produzione?

Aumentato consumo?



Figueroa-Ramos MI, *Intensive Care Med,* 2009

What impair sleep…

- Type and seve
- Pathophysiolo
- Pain, expecial
- ICU environn
  - Light, noise
    lab draws, vi
- Mechanical ve
  - Dysynchron
    tube, difficul
- Pharmacologi

Table 1 Drugs commonly used in ICU and their effects on sleep pattern.

Drug Class or Individual Drug	Sleep Disorder Induced or Reported
Benzodiazepines	↓ REM, ↓ SWS
Opioids	↓ REM, ↓ SWS
Clonidine	↓ REM
Non steroidal anti-inflammatory drugs	↓ TST, ↓ SE
Norepinephrine/Epinephrine	Insomnia, ↓ REM, ↓ SWS
Dopamine	Insomnia, ↓ REM, ↓ SWS
β-Blockers	Insomnia, ↓ REM, Nightmares
Amiodarone	Nightmares
Corticosteroids	Insomnia, ↓ REM, ↓ SWS
Aminophylline	Insomnia,↓ REM, ↓ SWS, ↓ TST, ↓ SE
Quinolones	Insomnia
Tricyclic antidepressants	↓ REM
Selective serotonin reuptake inhibitors	↓ REM, ↓ TST, ↓ SE
Phenytoin	↑ Sleep Fragmentation
Phenobarbital	↓ REM
Carbamazepine	↓ REM

REM, rapid eye movement; SWS, slow wave sleep; TST, total sleep time; SE, sleep

Bourne RS, *Anaesthesia* 2004

What impair melatonin serum concentration?

- Mechanical ve
  - Dysynchron
    tube, difficul
- Pharmacologi

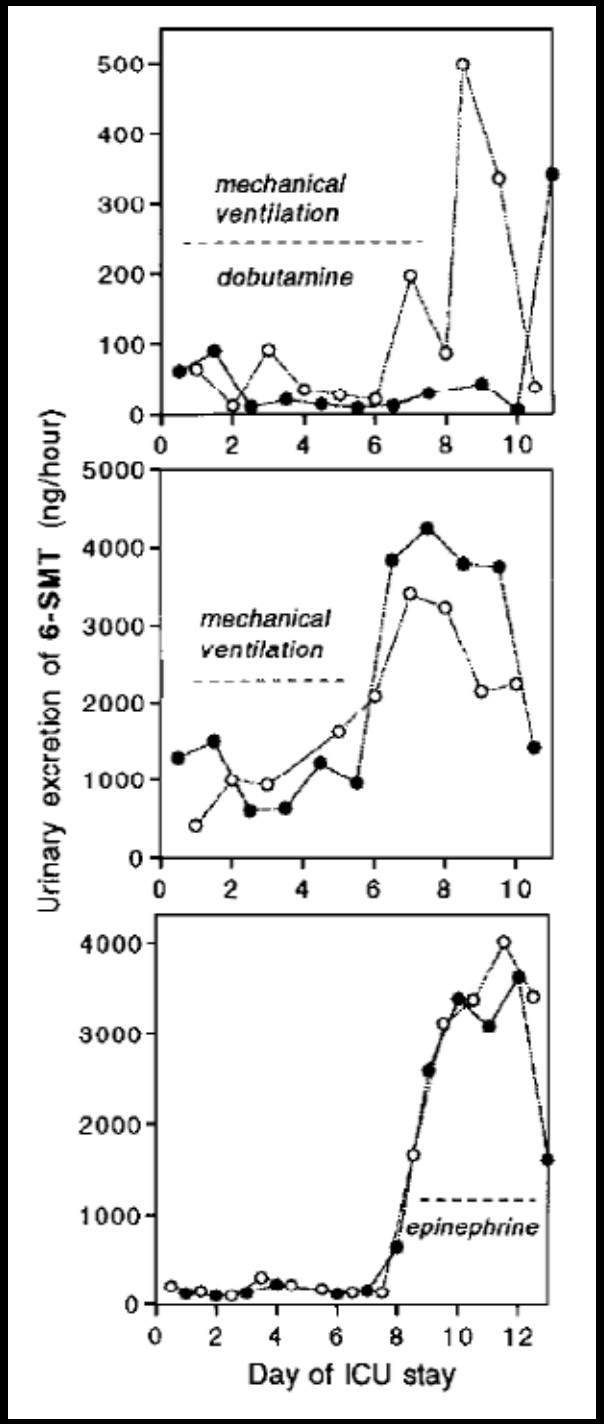
Table 1 Drugs commonly used in ICU and their effects on sleep pattern.

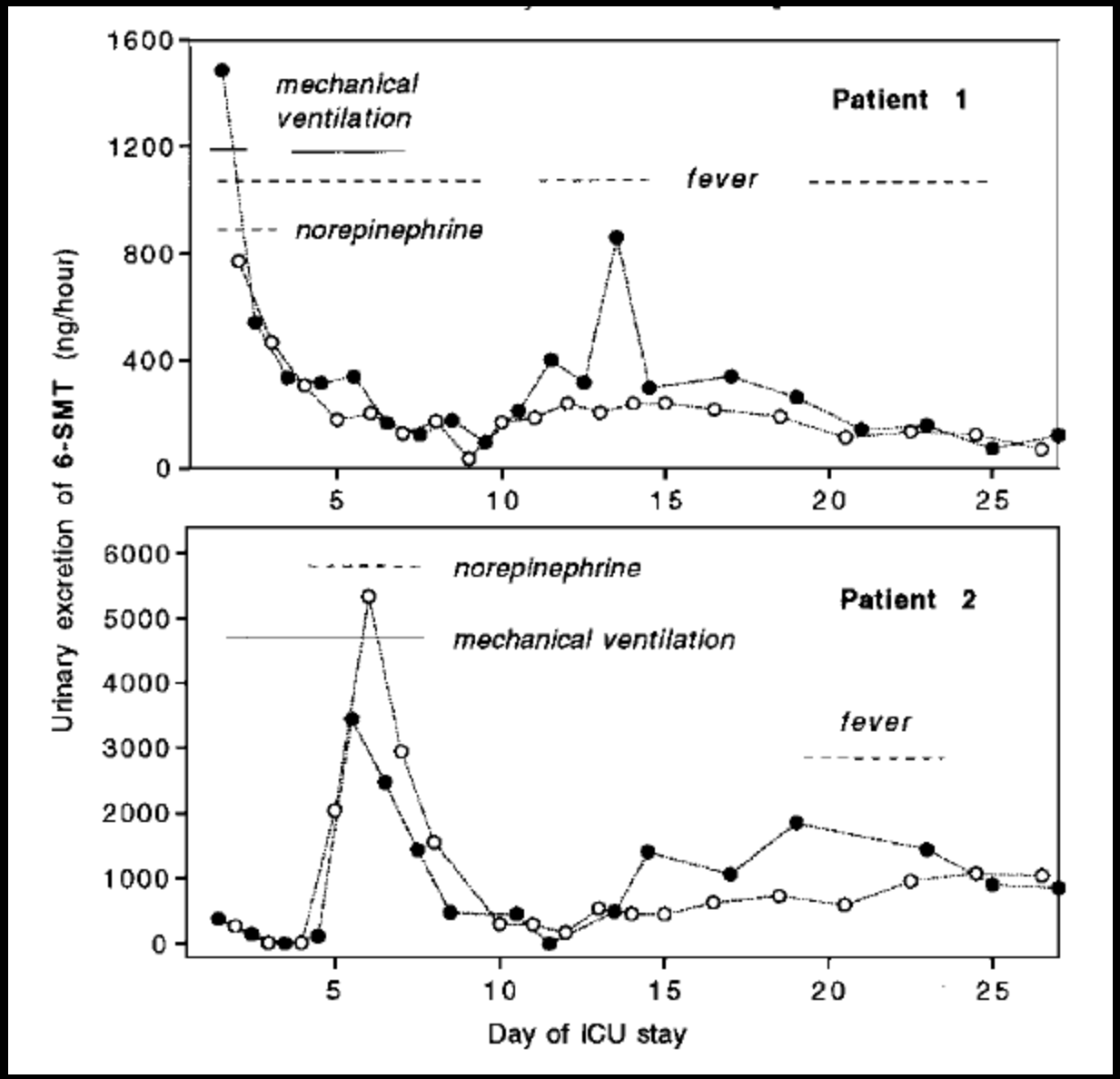
Drug group/drug	Proposed mechanism	Effect on melatonin serum concentration
Local anaesthetics	Inhibition of protein kinase C	–
Opioids	Opioid-mediated increase in NAT	+
Beta-blockers	CNS β_1-receptor blockade	–
Benzodiazepines	GABA receptor agonism	–
Corticosteroids	Decreased NAT activity	–
Calcium channel blockers (dihydropyridine)	Decreased NAT activity	–
Nonsteroidal anti-inflammatory drugs	Inhibition of prostaglandin synthesis	–
Clonidine	α_2 receptor agonism	–
Sodium valproate	Increased GABA levels	–
Tricyclic antidepressants	↓ REM, ↓ TST, ↓ SE	
Selective serotonin reuptake inhibitors	↓ REM, ↓ TST, ↓ SE	
Phenytoin	↑ Sleep Fragmentation	
Phenobarbital	↓ REM	
Carbamazepine	↓ REM	

REM, rapid eye movement; SWS, slow wave sleep; TST, total sleep time; SE, sleep

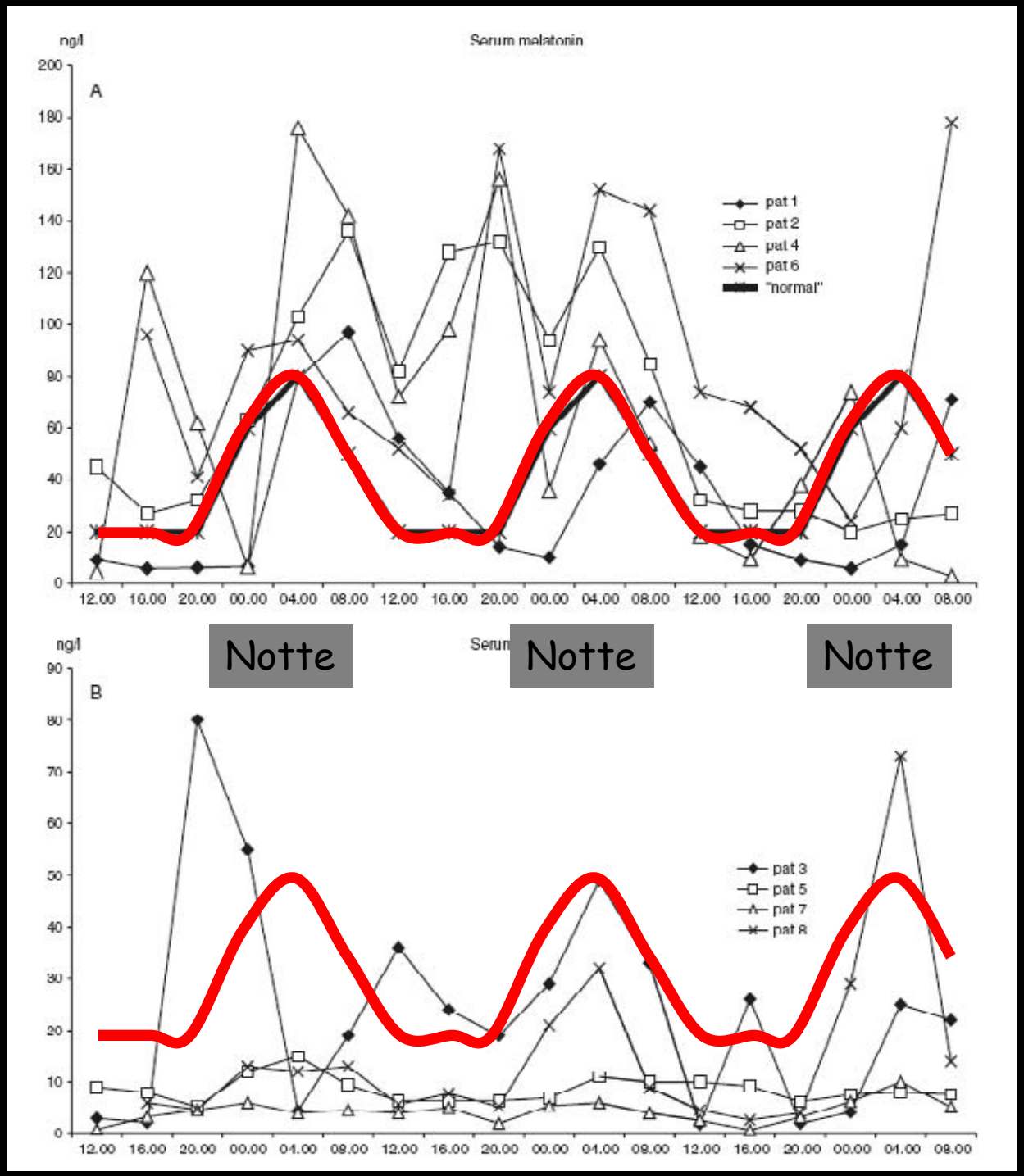
Bourne RS, *Intensive Care Med*, 2006

Bourne RS, *Anaesthesia* 2004





Frisk, *Clin Science*, 2004



Melatoninemia

in 8 pazienti critici, prelievi urinari raccolti ogni 4 h

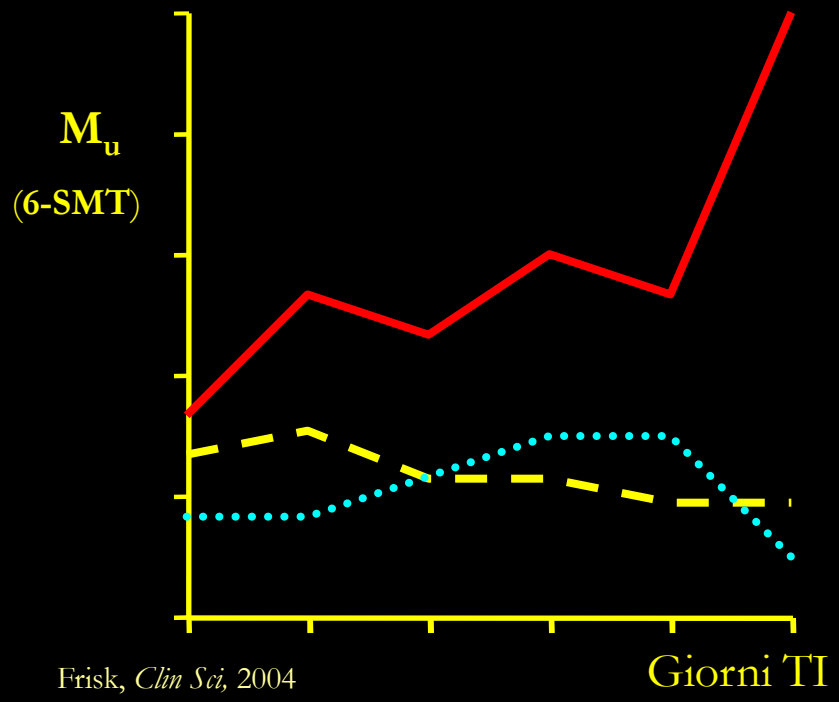
Nessuna correlazione con dosaggio sedativi

Olofsson, *Acta Anesth Scan*, 2004

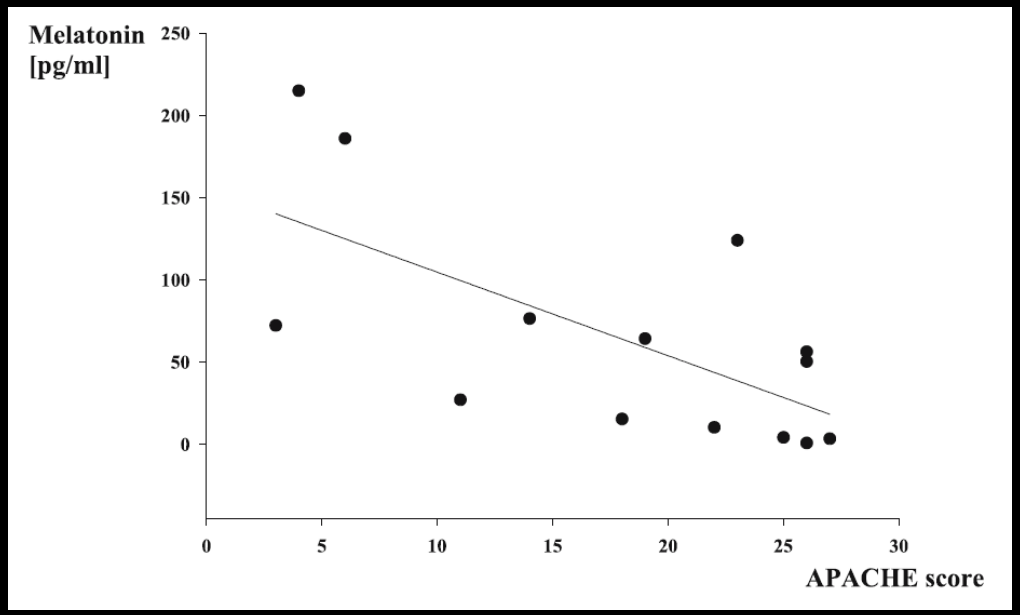
Nei pazienti critici la melatoninemia endogena è un marker di severità e di complessità del trattamento

Melatonina endogena nei pz critici

- Complessivamente diminuita:
  - Ventilazione meccanica
  - Correlata alla gravità nella sepsi



Frisk, *Clin Sci*, 2004



Perras, *Intensive Care Med*, 2006

Melatonina (endogena) e PTSD

- 41 pz esofagectomizzati
- 11 pz (27%) sviluppano PTSD
- Nessuna variabile chirurgica correlata
- Pz con PTSD:
  - **Più anziani**
  - **Ritmo circadiano melatonina irregolare**
  - **Melatoninemia complessivamente ridotta**

Miyazaki, *Surgery,* 2003

E la melatonina “esogena” ?

Quale effetto sul sonno in TI ?

Available online http://ccforum.com/content/12/2/R52

Research

Melatonin therapy to improve nocturnal sleep in critically ill patients: encouraging results from a small randomised controlled trial

Richard S Bourne[1], Gary H Mills[2] and Cosetta Minelli[3]

[1]Sheffield Teaching Hospitals, Critical Care Department, Northern General Hospital, Herries Road, Sheffield, UK, S5 7AU
[2]Sheffield Teaching Hospitals, Critical Care Directorate, Royal Hallamshire Hospital, Glossop Road, Sheffield, UK, S10 2JF
[3]Respiratory Epidemiology and Public Health Group, National Heart and Lung Institute, Imperial College London, Emmanuel Kaye Building, Manresa Road, London, UK, SW3 6LR

Corresponding author: Richard S Bourne, richard.bourne@sth.nhs.uk

Received: 8 Feb 2008 Revisions requested: 13 Mar 2008 Revisions received: 11 Apr 2008 Accepted: 18 Apr 2008 Published: 18 Apr 2008

Critical Care 2008, **12**:R52 (doi:10.1186/cc6871)
This article is online at: http://ccforum.com/content/12/2/R52

Bourne RS, *Crit Care,* 2008

Cosa succede nei COPD?

- 8 pazienti COPD in una terapia subintensiva
- Siccome si lamentano perché dormono male… somministrano melatonina e misurano il sonno tramite actigrafia del polso

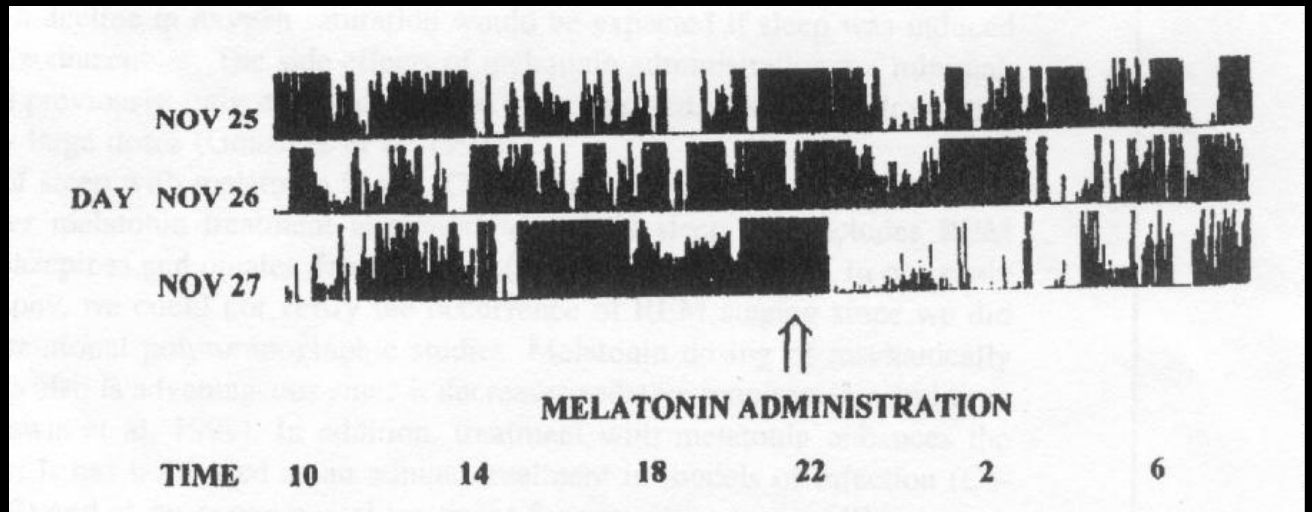


FIGURE 1. Effect of melatonin administration on sleep in the ICU.

E la melatonina “esogena” ?

Quale effetto sul sonno in TI ?

Quale effetto sulla sepsi ?

Melatonina esogena nello shock (da 10 a 100 volte le concentrazioni normali)

- In topini neonati con shock settico aumenta significativamente la sopravvivenza!!!

Ozdemir D, *Intensive Care Med,* 2007

- In topini adulti con shock emorragico:
  - **Migliora funzione e perfusione epatica**
  - **Diminuisce iNOS**
  - **Riduce la deplezione di antiossidanti**

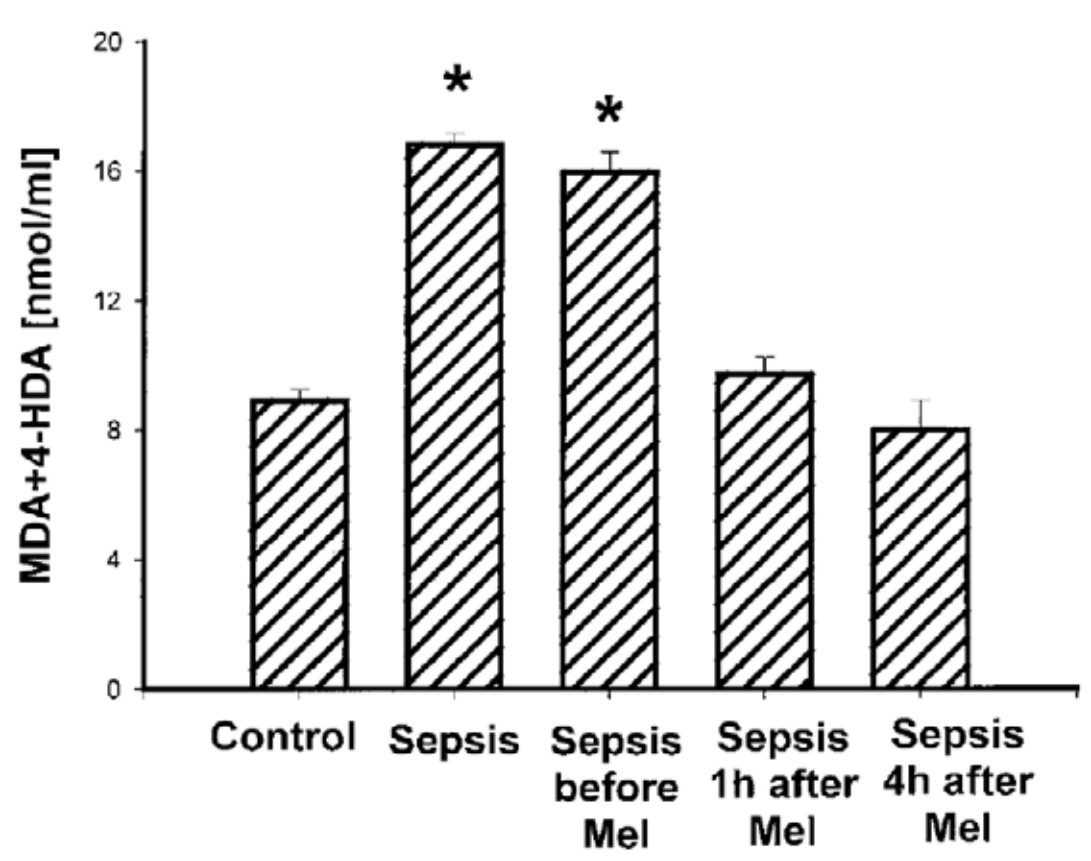
Mathes AM, *Crit Care Med,* 2007

0031-3998/01/5006-0756
PEDIATRIC RESEARCH
Vol. 50, No. 6, 2001

Printed in U.S.A.

Effects of Melatonin Treatment in Septic Newborns

ELOISA GITTO, MALGORZATA KARBOWNIK, RUSSEL J. REITER, DUN XIAN TAN, SALVATORE CUZZOCREA, PIETRO CHIURAZZI, SANTA CORDARO, GIUSEPPINA CORONA, GIUSEPPE TRIMARCHI, AND IGNAZIO BARBERI



Quindi potrebbe essere utile nei pazienti critici …

- Azioni principali:
  - Regola il ritmo sonno veglia (ipnoinduzione)
  - Termoregolazione
  - Azione antiossidante
  - Immunostimolante
  - Trombocitogenico
  - Antiaggregante “fisiologico”

Intensive Care Med (2006) 32:371–379
DOI 10.1007/s00134-005-0061-x

REVIEW

Richard S. Bourne
Gary H. Mills

Melatonin: possible implications for the postoperative and critically ill patient

Received: 26 December 2005
Accepted: 26 December 2005
Published online: 14 February 2006

R. S. Bourne (✉) · G. H. Mills
Royal Hallamshire Hospital,
[illegible] Care Unit, R Floor,
Glossop Road, S10 2JF Sheffield, UK
e-mail: ric[illegible]rd.[illegible]nhs[illegible]
Tel: +44-1[illegible]4-2[illegible]60[illegible]
Fax: +44-1[illegible]4-2[illegible]20[illegible]

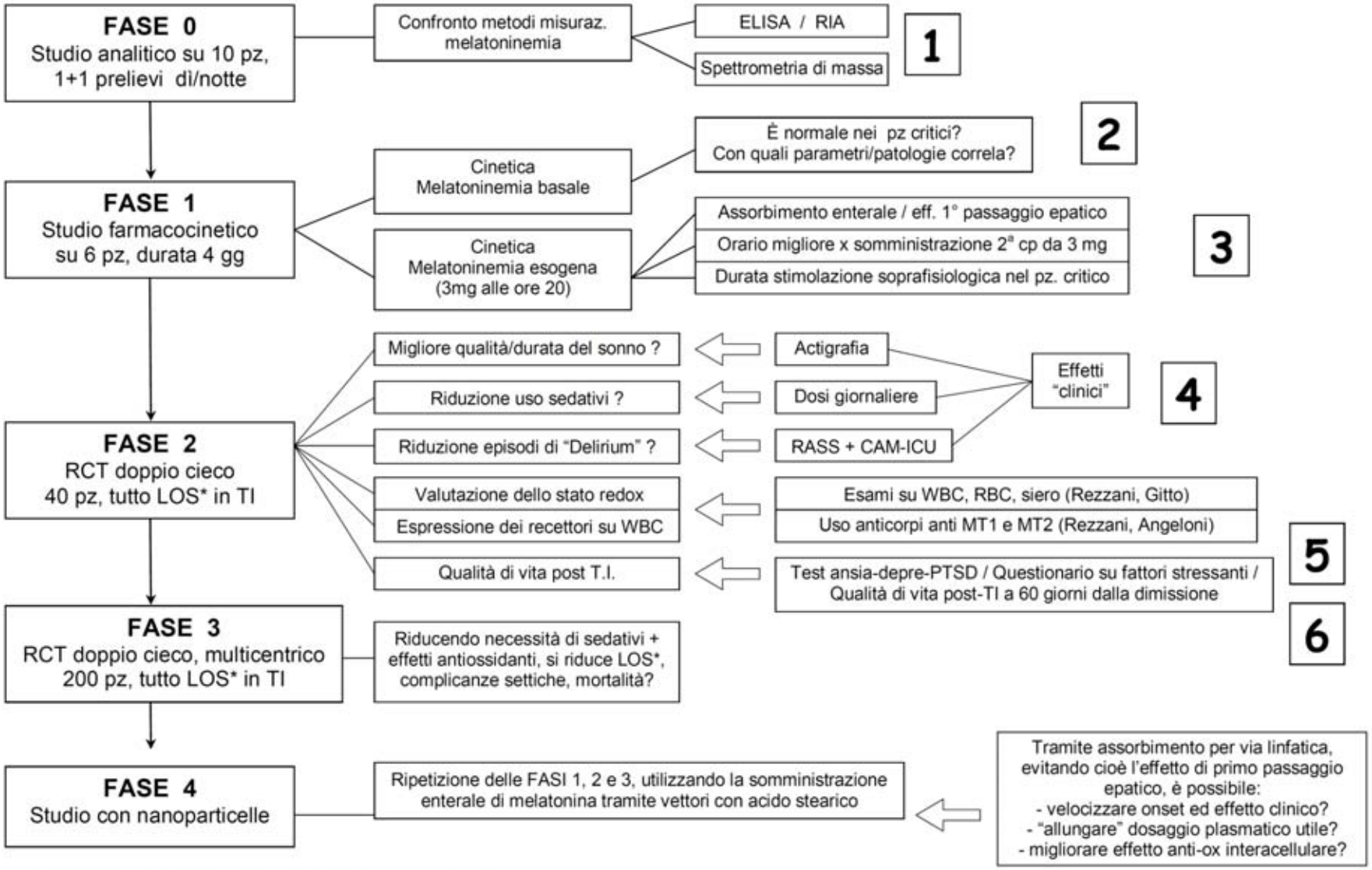
G. H. Mills
Royal Hallamshire Hospital,
Medical Economics and Research Centre,
Sheffield (MERCS), R Floor,
Glossop Road, S10 2JF Sheffield, UK

Abstract There is increasing interest in the hormone melatonin in postoperative and critically ill patients. The roles of melatonin in the regulation of the sleep-wake cycle, resetting of circadian rhythm disturbances and its extensive antioxidant activity have potential applications in these patient groups. The interaction between melatonin and the stresses of surgery and critical illness are explored in the [illegible] circadian rh[illegible] sleep disorders and delirium. The antioxidant activity is discussed in terms of the reduction of ischaemic reperfusion injury, prevention of multi-organ failure and treatment of sepsis. Unfortunately, there is currently insufficient evidence that exogenous melatonin is effective in preventing or treating postoperative delirium. Similarly, in the critically ill patient, sleep disorders are associated with disrupted melatonin circadian secretion, but there is a paucity of data to support routine exogenous melatonin supplementation. More clinical evidence to confirm the potential benefits of melatonin therapy is required before it [illegible] be [illegible] postoperative [illegible] critically ill [illegible]

Keywords [illegible]ircadian rhythm · Critic[illegible]ess · Delirium · Melatonin · Sepsis · Sleep disorders

Time to begin !

Melatonina Esogena in Pazienti Critici



*LOS = Lenght of Stay (durata della degenza critica)

Flow Chart – 23 febbraio 2007

Ipotesi di studio

La somministrazione orale di melatonina esogena :

- riduce il dosaggio di sedativi somministrati ?

- diminuisce gli episodi di agitazione / delirium ?

- migliora gli outcome clinici (sepsi) ?

… soministrazione per os!!!

Il percorso del progetto

FASE 1

FARMACO CINETICA

12 pz

FASE 2

STUDIO PILOTA

RCT monocentrico

Doppio cieco

40 + 40 pz

FASE 3

STUDIO CLINICO

RCT multicentrico

Doppio cieco

400 + 400 pz

… in base ai risultati delle prime due fasi…

Il percorso del progetto

FASE 1

FARMACO CINETICA

12 pz

FASE 2

STUDIO PILOTA

RCT monocentrico

Doppio cieco

40 + 40 pz

FASE 3

STUDIO CLINICO

RCT multicentrico

Doppio cieco

400 + 400 pz

… in base ai risultati delle prime due fasi…

Clinical Aspects of Melatonin

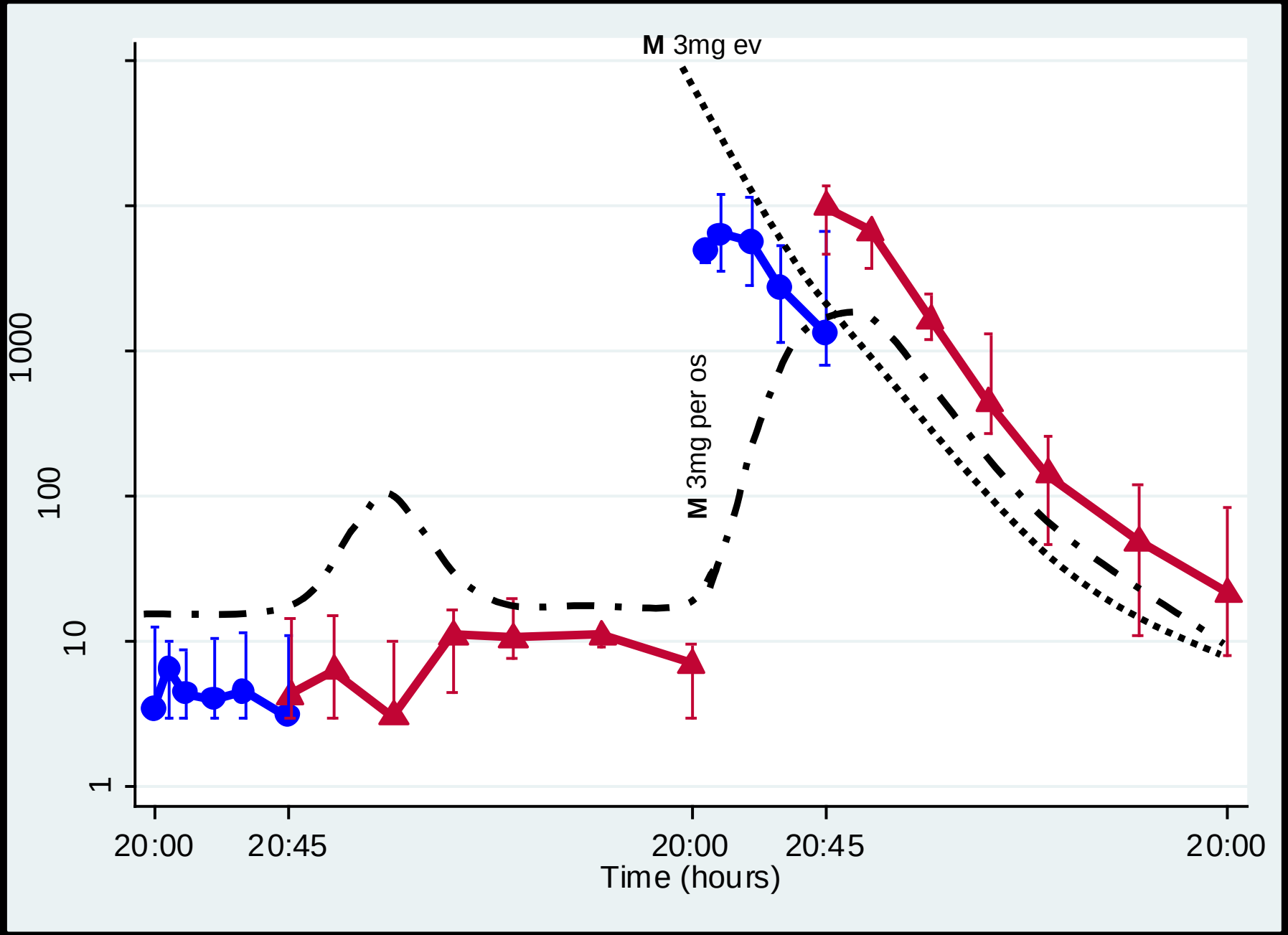
J. Pineal Res. 2010; 48:142–147
Doi:10.1111/j.1600-079X.2009.00737.x

Journal of Pineal Research

Pharmacokinetics of orally administered melatonin in critically ill patients

Abstract: Critically ill patients exhibit reduced melatonin secretion, both in nocturnal peaks and basal daytime levels. Oral melatonin supplementation may be useful for known sedative and antioxidant properties. Its early enteral absorption and daily pharmacokinetics were determined in two cohorts of six high-risk patients in this prospective trial. During their third and fourth Intensive Care Unit (ICU) day, they underwent two different sets of repeated blood samples to detect serum melatonin levels through radio-immuno-assay. Cohort 1: samples taken at 20:00, 20:45, 21:30, 24:00, 03:00, 06:00, 14:00, 20:00 to describe the daily pharmacokinetics. Cohort 2: 20:00

Giovanni Mistraletti[1], Giovanni Sabbatini[1], Martina Taverna[1], Maria Adele Figini[1], Michele Umbrello[1], Paolo Magni[2], Massimiliano Ruscica[2], Elena Dozio[3], Roberto Esposti[4], Germana DeMartini[5], Franco Fraschini[5], Rita Rezzani[6], Russel J. Reiter[7] and Gaetano Iapichino[1]



Mistraletti G, *J Pineal Res*, 2010

Il percorso del progetto

FASE 1

FARMACO CINETICA

12 pz

FASE 2

STUDIO PILOTA

RCT monocentrico

Doppio cieco

40 + 40 pz

FASE 3

STUDIO CLINICO

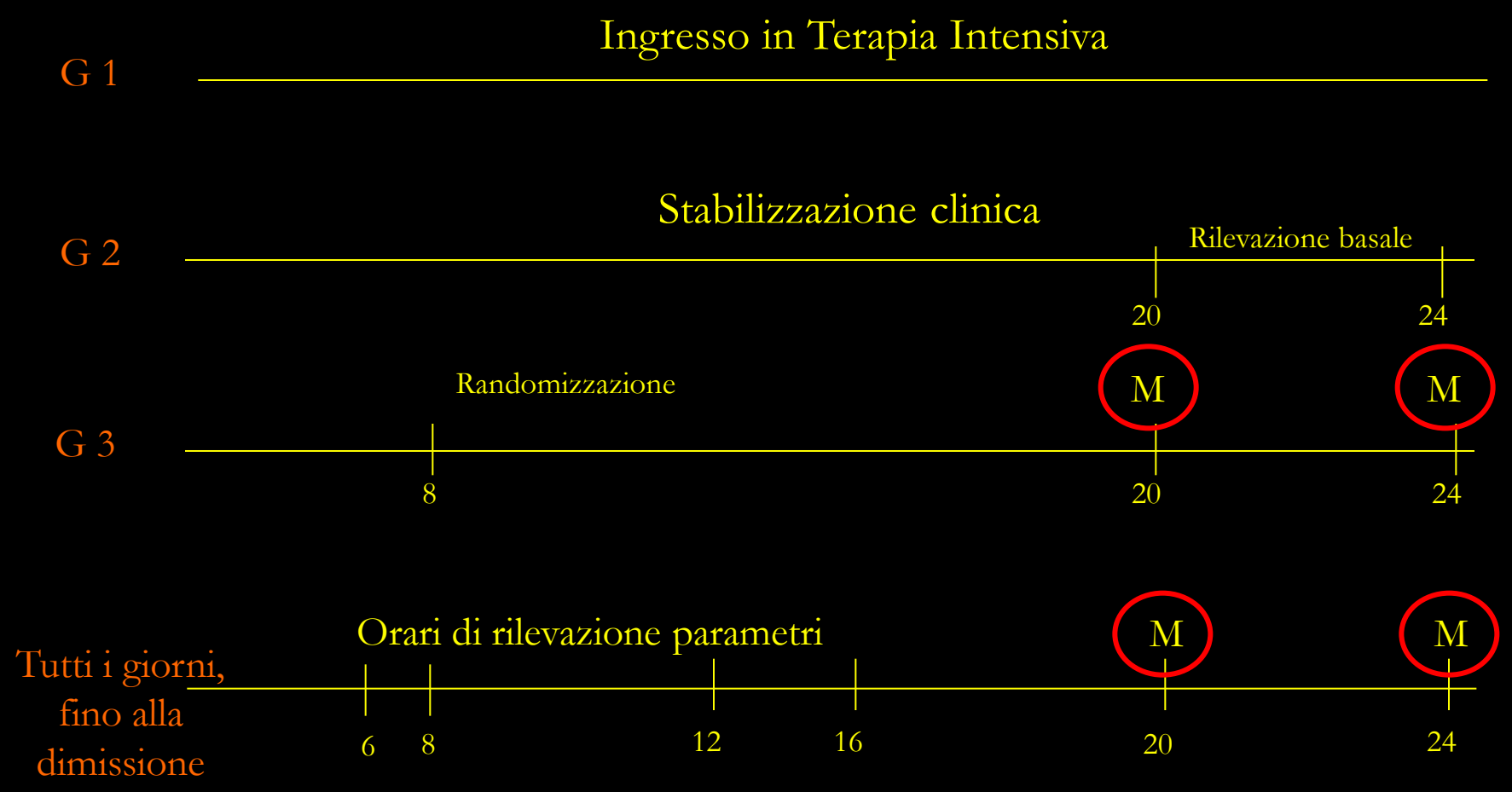
RCT multicentrico

Doppio cieco

400 + 400 pz

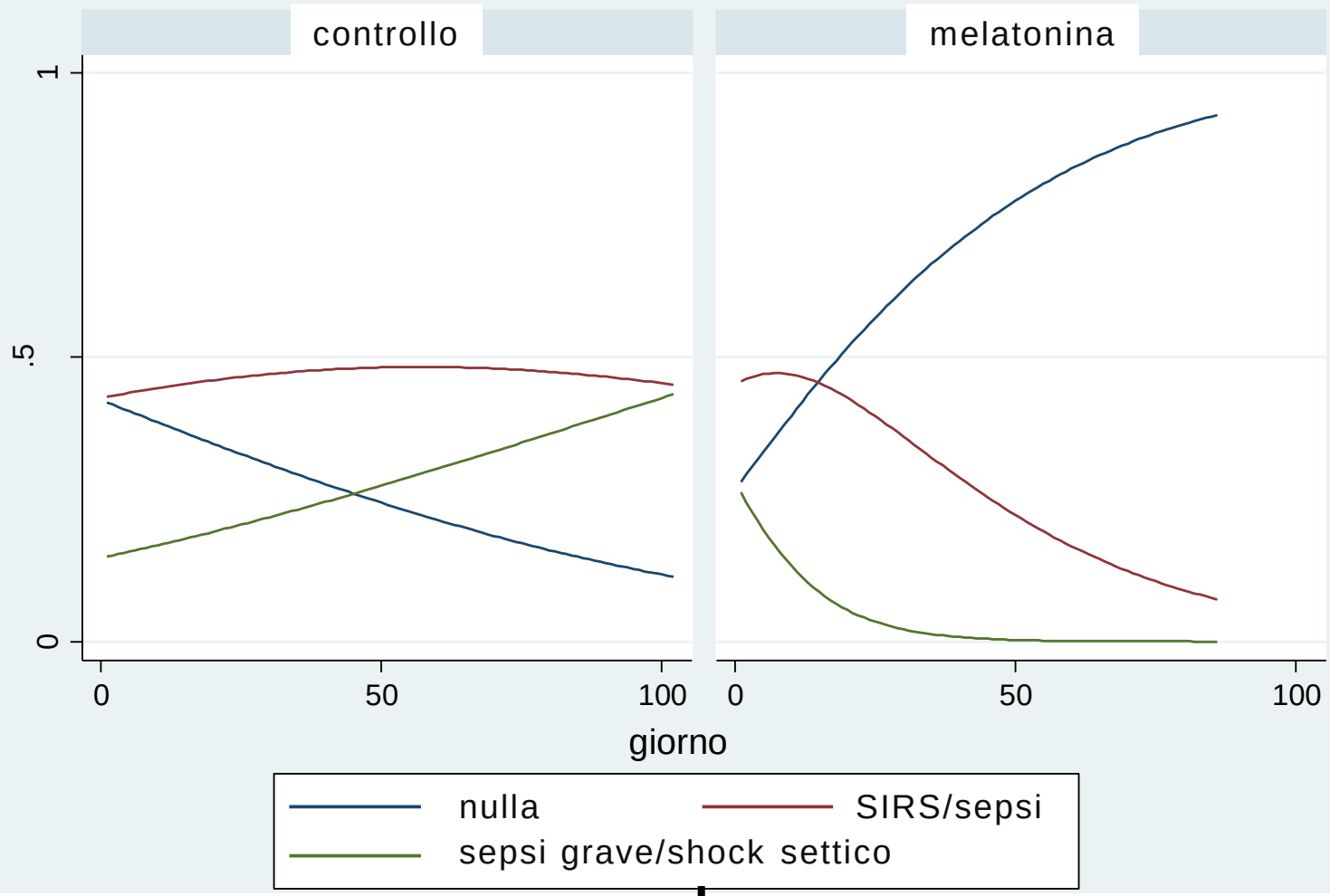
… in base ai risultati delle prime due fasi…

clinicaltrial.gov # NCT00470821



I risultati sono promettenti…
…ma non sono ancora definitivi
su tutti i 96 pazienti arruolati!

Stato settico durante degenza in T. I.



Day	1	10	20	30	40	50	1	10	20	30	40	50
N	46	26	15	9	6	5	44	25	9	4	3	3

$p < 0.001$

Il percorso del progetto

FASE 1

FARMACO CINETICA

12 pz

FASE 2

STUDIO PILOTA

RCT monocentrico

Doppio cieco

40 + 40 pz

FASE 3

STUDIO CLINICO

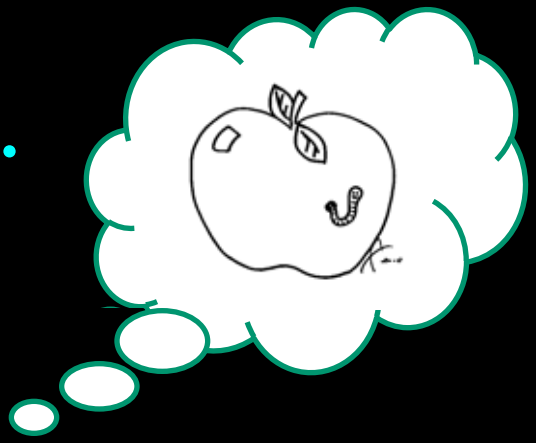
RCT multicentrico

Doppio cieco

400 + 400 pz

… in base ai risultati delle prime due fasi…

E se il GiViTI…



"Petalo" Mela ?

RCT doppio cieco multicentrico

- 3 mg x 2 alle ore 20 e 24
- tutto il resto della terapia: così com'è !

Obiettivi "Petalo" Mela

- Durata ventilazione
- Durata degenza in TI
- Mortalità
- Sepsi (gravità max, infez. dopo 8° giorno in TI)

  - 3 mg x 2 alle ore 20 e 24
  - tutta la terapia così com'è…

Perché il GiViTI ?

- Utilizzo dati Margherita
- Semplicità obiettivi
- Costi ridottissimi…
- Variabilità fra i protocolli di sedazione

- 3 mg x 2 alle ore 20 e 24
- tutta la terapia così com'è…

e nel 2012…

The New England
Journal of Medicine

VOLUME 345 OCTOBER 8, 2012 NUMBER 19

MELATONIN TREATMENT IN CRITICALLY ILL PATIENTS

THE GIVITI GROUP
ITALIAN GROUP FOR THE EVALUATION OF INTERVENTIONS IN INTENSIVE CARE MEDICINE

- 3 mg x 2 alle ore 20 e 24
- tutta la terapia così com'è…

A new frontier in critical care: saving the injured brain.

E. Wesley Ely, 2010

giovanni.mistraletti@unimi.it