DELIRIUM

TERAPIA

Dr.ssa Maia Nguyen

PERCHE' TRATTARE IL DELIRIUM

- Il delirium è un disturbo che , se gestito bene, va generalmente incontro a remissione
- Fondamentale conoscere il potenziale di morbilità e mortalità associato al delirium

OUTCOME DEL TRATTAMENTO

- Prevenzione nei soggetti a rischio
- Trattamento delle patologie concomitanti
- Controllo dell'agitazione e prevenzione dei danni
- Miglioramento delle funzioni cognitive
- Miglioramento dello stato funzionale
- Outcome a lungo termine (prevenzione del declino cognitivo e funzionale, riduzione della mortalità)

LA TERAPIA DEL DELIRIUM

Persegue 3 obbiettivi

A. Identificare e trattare cause e fattori di rischio
B. Controllare i sintomi
    1- terapia sintomatica generale
    2- psicofarmacoterapia
C. Migliorare le condizioni ambientali

A. CAUSE E FATTORI DI RISCHIO

Special Article

Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

Juliana Barr, MD, FCCM[1]; Gilles L. Fraser, PharmD, FCCM[2]; Kathleen Puntillo, RN, PhD, FAAN, FCCM[3]; E. Wesley Ely, MD, MPH, FACP, FCCM[4]; Céline Gélinas, RN, PhD[5]; Joseph F. Dasta, MSc, FCCM, FCCP[6]; Judy E. Davidson, DNP, RN[7]; John W. Devlin, PharmD, FCCM, FCCP[8]; John P. Kress, MD[9]; Aaron M. Joffe, DO[10]; Douglas B. Coursin, MD[11]; Daniel L. Herr, MD, MS, FCCM[12]; Avery Tung, MD[13]; Bryce R. H. Robinson, MD, FACS[14]; Dorrie K. Fontaine, PhD, RN, FAAN[15]; Michael A. Ramsay, MD[16]; Richard R. Riker, MD, FCCM[17]; Curtis N. Sessler, MD, FCCP, FCCM[18]; Brenda Pun, MSN, RN, ACNP[19]; Yoanna Skrobik, MD, FRCP[20]; Roman Jaeschke, MD[21]

Critical Care medicine 2013

DELIRIUM RISK FACTORS

a. *Question*: What baseline risk factor are associated with the development of delirium in the ICU?

Answer: Four baseline risk factors are positively and significantly associated with the development of delirium in the ICU: preexixting dementia; history of Hypertension and/or alcoholism; and a high severity of illness at admission (B)

DELIRIUM RISK FACTOR

b. *Question*: Is coma a risk factor for the development of delirium in ICU?

Answer: Coma is an independent risk factor for the development of delirium in ICU patients. Establishing a definitive relationship between various subtypes of coma (i.e. medication-related, structural, neurological, medical) and delirium in ICU patients will require further study (B)

DELIRIUM RISK FACTOR

c. *Question*: Which ICU treatment-related (acquired) risk factors (i.e. opioids, benzodiazepines, propofol and dexmedetomidine) are associated with the development of delirium in adult ICU patients?

Answer: Conflicting data surround the relationship between opioid use and the development of delirium in adult ICU patient(B). Benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients(B). There are insufficient data to determine the relationship between Propofol use and the development of delirium in adult ICU patients(C) . In mechanically ventilated adult patients at risk for developing delirium , dexmedetomidine infusions administered for sedation may be associated with a lower prevalence of delirium compared to benzodiazepine infusion administerd (B)

DELIRIUM RISK FACTOR

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CRITICAL CARE MEDICINE

Sedation and Delirium in the Intensive Care Unit

Michael C. Reade, M.B., B.S., D.Phil., and Simon Fir

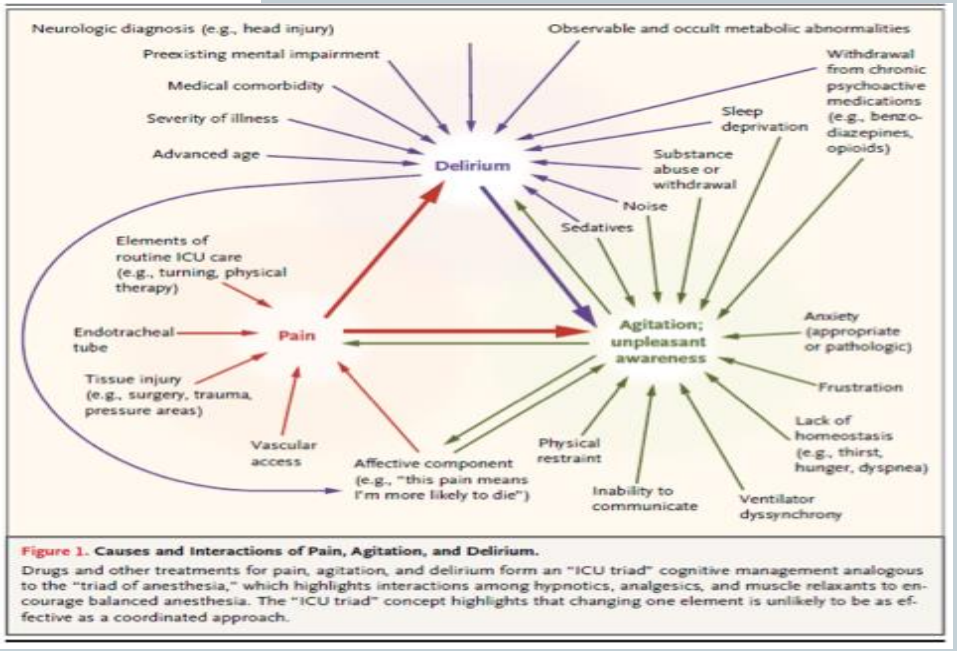


Figure 1. Causes and Interactions of Pain, Agitation, and Delirium.
Drugs and other treatments for pain, agitation, and delirium form an "ICU triad" cognitive management analogous to the "triad of anesthesia," which highlights interactions among hypnotics, analgesics, and muscle relaxants to encourage balanced anesthesia. The "ICU triad" concept highlights that changing one element is unlikely to be as effective as a coordinated approach.

New England 2014

DELIRIUM RISK FACTOR

BENZODIAZEPINES AND DELIRIUM RISK

CARING FOR THE
CRITICALLY ILL PATIENT

Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients

The MENDS Randomized Controlled Trial

JAMA 2007

Table 2. Outcomes in Mechanically Ventilated Patients Sedated With Dexmedetomidine vs Lorazepam[a]

Outcome Variable	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	*P* Value
Duration of brain organ dysfunction, d			
Delirium-free and coma-free[b]	7 (1-10)	3 (1-6)	.01
Delirium-free[b]	9 (5-11)	7 (5-10)	.09
Coma-free[b]	10 (9-12)	8 (5-10)	<.001
Delirium	2.5 (1-5)	4 (1-5)	.71
Coma	2 (0-3)	3 (2-5)	.003
Prevalence of brain organ dysfunction, No. (%)[c]			
Delirium or coma	45 (87)	50 (98)	.03
Delirium	41 (79)	42 (82)	.65
Coma	33 (63)	47 (92)	<.001
Other clinical outcomes			
Mechanical ventilator-free, d[d]	22 (0-24)	18 (0-23)	.22
Intensive care unit length of stay, d	7.5 (5-19)	9 (6-15)	.92
28-Day mortality, No. (%)	9 (17)	14 (27)	.18

[a] Median (interquartile range) unless otherwise noted.
[b] Indicates the number of days alive without stated dysfunction from study days 1 to 12.
[c] Prevalence is used to describe the rates of brain organ dysfunction instead of incidence because preintensive care unit delirium or coma status could not be determined. Prevalence represents the occurrence of brain organ dysfunction at any time during the 12-day assessment period.
[d] Indicates the number of days alive, breathing without mechanical ventilator assistance, from study day 1 to 28.

DELIRIUM PREVENTION STRATEGIES

a. *Question*: Should a non pharmacologic delirium protocol be used in the ICU to reduce the incidence or duration of delirium?

   Answer: We recommend performing early mobilization of adult ICU patients whenever feasible to reduce the incidence and duration of delirium (+1B)

DELIRIUM PREVENTION STRATEGIES

MOBILIZATION = LESS DELIRIUM

Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial

William D Schweickert, Mark C Pohlman, Anne S Pohlman, Celerina Nigos, Amy J Pawlik, Cheryl L Esbrook, Linda Spears, Megan Miller, Mietka Franczyk, Deanna Deprizio, Gregory A Schmidt, Amy Bowman, Rhonda Barr, Kathryn E McCallister, Jesse B Hall, John P Kress

	Intervention (n=49)	Control (n=55)	p value
Return to independent functional status at hospital discharge	29 (59%)	19 (35%)	0·02
ICU delirium (days)	2·0 (0·0–6·0)	4·0 (2·0–7·0)	0·03
Time in ICU with delirium (%)	33% (0–58)	57% (33–69)	0·02
Hospital delirium (days)	2·0 (0·0–6·0)	4·0 (2·0–8·0)	0·02
Hospital days with delirium (%)	28% (26)	41% (27)	0·01
Barthel Index score at hospital discharge	75 (7·5–95)	55 (0–85)	0·05
ICU-acquired paresis at hospital discharge	15 (31%)	27 (49%)	0·09
Ventilator-free days*	23·5 (7·4–25·6)	21·1 (0·0–23·8)	0·05
Duration of mechanical ventilation (days)	3·4 (2·3–7·3)	6·1 (4·0–9·6)	0·02
Duration of mechanical ventilation, survivors (days)	3·7 (2·3–7·7)	5·6 (3·4–8·4)	0·19
Duration of mechanical ventilation, non-survivors (days)	2·5 (2·4–5·5)	9·5 (5·9–14·1)	0·04
Length of stay in ICU (days)	5·9 (4·5–13·2)	7·9 (6·1–12·9)	0·08
Length of stay in hospital (days)	13·5 (8·0–23·1)	12·9 (8·9–19·8)	0·93
Hospital mortality	9 (18%)	14 (25%)	0·53

Data are n (%), median (IQR), or mean (SD). ICU=intensive care unit. *Ventilator-free days from study day 1 to day 28. Barthel Index scale 0–100, APACHE II scale 0–71.

Table 3: **Main outcomes according to study group**

Lancet 2009

DELIRIUM PREVENTION STRATEGIES

b. *Question*: Should a pharmacologic delirium prevention protocol be used in the ICU to reduce the incidence or duration of delirium?

Answer: We provide no recommandation for using a pharmacologic delirium prevention protocol in adult ICU patients, as no compelling data demostrate that this reduces the incidence or duration of delirium in these patient (c)

DELIRIUM PREVENTION STRATEGIES

c. *Question*: Should a combined nonpharmacologic and pharmacologic delirium prevention protocol be used in the ICU to reduce the incidence or duration of delirium?

Answer: We provide no raccomandation for the use of a combined non pharmacologic and pharmacologic delirium prevention protocol in adult ICU patient , as this has not been shown to reduce the incidence of delirium in these patient (c)

DELIRIUM PREVENTION STRATEGIES

d. *Question*: Should haloperidol or atypical antipsychotics be used prophylactically to prevent delirium in ICU patients?

Answer: We do not suggest that either haloperidol or atypical antipsychotics be administered to prevent delirium in adult ICU patients (C)

DELIRIUM PREVENTION STRATEGIES

Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial

Valerie J Page, E Wesley Ely, Simon Gates, Xiao Bei Zhao, Timothy Alce, Ayumi Shintani, Jim Jackson, Gavin D Perkins, Daniel F McAuley

Summary

Background Delirium is frequently diagnosed in critically ill patients and is associated with poor clinical outcomes. Haloperidol is the most commonly used drug for delirium despite little evidence of its effectiveness. The aim of this study was to establish whether early treatment with haloperidol would decrease the time that survivors of critical illness spent in delirium or coma.

Methods We did this double-blind, placebo-controlled randomised trial in a general adult intensive care unit (ICU). Critically ill patients (≥18 years) needing mechanical ventilation within 72 h of admission were enrolled. Patients were randomised (by an independent nurse, in 1:1 ratio, with permuted block size of four and six, using a centralised, secure web-based randomisation service) to receive haloperidol 2·5 mg or 0·9% saline placebo intravenously every 8 h, irrespective of coma or delirium status. Study drug was discontinued on ICU discharge, once delirium-free and coma-free for 2 consecutive days, or after a maximum of 14 days of treatment, whichever came first. Delirium was assessed using the confusion assessment method for the ICU (CAM-ICU). The primary outcome was delirium-free and coma-free days, defined as the number of days in the first 14 days after randomisation during which the patient was alive without delirium and not in coma from any cause. Patients who died within the 14 day study period were recorded as having 0 days free of delirium and coma. ICU clinical and research staff and patients were masked to treatment throughout the study. Analyses were by intention to treat. This trial is registered with the International Standard Randomised Controlled Trial Registry, number ISRCTN83567338.

Findings 142 patients were randomised, 141 were included in the final analysis (71 haloperidol, 70 placebo). Patients in the haloperidol group spent about the same number of days alive, without delirium, and without coma as did patients in the placebo group (median 5 days [IQR 0–10] *vs* 6 days [0–11] days; p=0·53). The most common adverse events were oversedation (11 patients in the haloperidol group *vs* six in the placebo group) and QTc prolongation (seven patients in the haloperidol group *vs* six in the placebo group). No patient had a serious adverse event related to the study drug.

Interpretation These results do not support the hypothesis that haloperidol modifies duration of delirium in critically ill patients. Although haloperidol can be used safely in this population of patients, pending the results of trials in progress, the use of intravenous haloperidol should be reserved for short-term management of acute agitation.

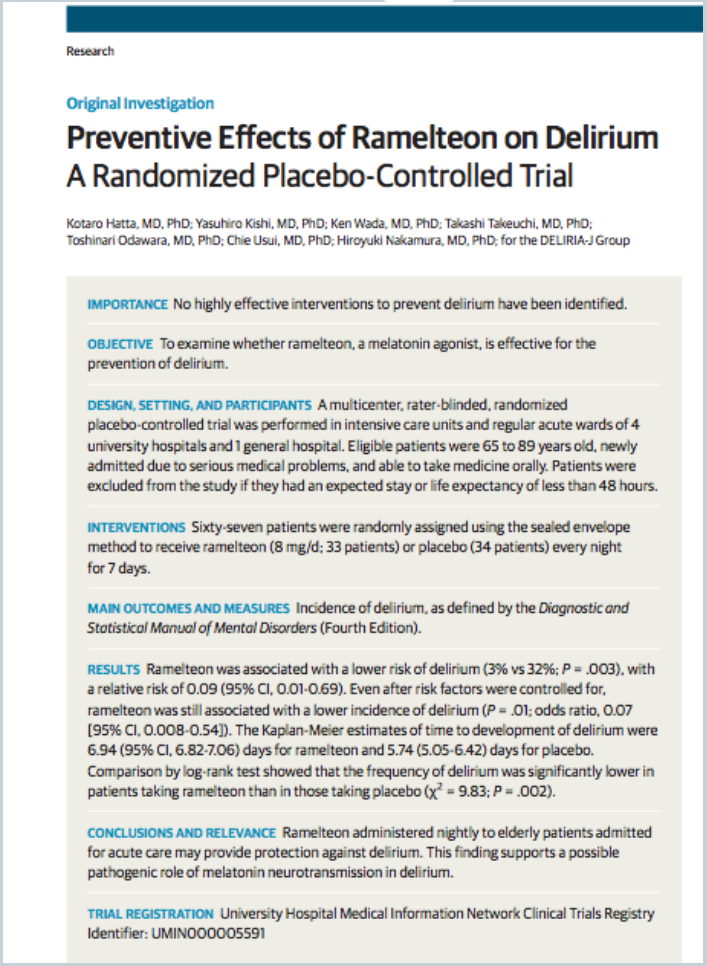
Lancet Resp Med 2013

DELIRIUM PREVENTION STRATEGIES

e. *Question*: Should dexmedetomidine be used prophylactically to prevent delirium in ICU patients?

Answer: We provide no recommendation for the use of dexmedetomidine to prevent delirium in adult ICU patients , as there is no evidence regarding its effectiveness in these patients

DELIRIUM PREVENTION STRATEGIES



Research

Original Investigation

Preventive Effects of Ramelteon on Delirium
A Randomized Placebo-Controlled Trial

Kotaro Hatta, MD, PhD; Yasuhiro Kishi, MD, PhD; Ken Wada, MD, PhD; Takashi Takeuchi, MD, PhD; Toshinari Odawara, MD, PhD; Chie Usui, MD, PhD; Hiroyuki Nakamura, MD, PhD; for the DELIRIA-J Group

IMPORTANCE No highly effective interventions to prevent delirium have been identified.

OBJECTIVE To examine whether ramelteon, a melatonin agonist, is effective for the prevention of delirium.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, rater-blinded, randomized placebo-controlled trial was performed in intensive care units and regular acute wards of 4 university hospitals and 1 general hospital. Eligible patients were 65 to 89 years old, newly admitted due to serious medical problems, and able to take medicine orally. Patients were excluded from the study if they had an expected stay or life expectancy of less than 48 hours.

INTERVENTIONS Sixty-seven patients were randomly assigned using the sealed envelope method to receive ramelteon (8 mg/d; 33 patients) or placebo (34 patients) every night for 7 days.

MAIN OUTCOMES AND MEASURES Incidence of delirium, as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).

RESULTS Ramelteon was associated with a lower risk of delirium (3% vs 32%; $P = .003$), with a relative risk of 0.09 (95% CI, 0.01-0.69). Even after risk factors were controlled for, ramelteon was still associated with a lower incidence of delirium ($P = .01$; odds ratio, 0.07 [95% CI, 0.008-0.54]). The Kaplan-Meier estimates of time to development of delirium were 6.94 (95% CI, 6.82-7.06) days for ramelteon and 5.74 (5.05-6.42) days for placebo. Comparison by log-rank test showed that the frequency of delirium was significantly lower in patients taking ramelteon than in those taking placebo ($\chi^2 = 9.83$; $P = .002$).

CONCLUSIONS AND RELEVANCE Ramelteon administered nightly to elderly patients admitted for acute care may provide protection against delirium. This finding supports a possible pathogenic role of melatonin neurotransmission in delirium.

TRIAL REGISTRATION University Hospital Medical Information Network Clinical Trials Registry Identifier: UMIN000005591

JAMA Psychiatry
February 2014

RAMELTEON

- Agonista selettivo dei recettori MT1 e MT2 della melatonina
- Studi in vitro mostrano una affinità di Ramelteon per i recettori MT1-MT2 da 3 a 6 volte superiore rispetto alla melatonina
- Azione più specifica sul processo di addormentamento rispetto alla melatonina.
- Il ramelteon riduce significativamente la latenza del sonno ed aumenta il tempo totale di sonno senza alcun effetto residuo il giorno dopo. A seguito dell'interruzione dell'assunzione non si rilevano insonnia di rimbalzo o effetti da astinenza
- A seguito di somministrazione orale, il ramelteon viene assorbito rapidamente

  Passa attraverso un esteso metabolismo di primo passaggio che produce quattro metaboliti principali, ciascuno dei quali risulta essere più attivo rispetto al composto precursore. Nei pazienti anziani, la clearance renale del ramelteon è ridotta; tuttavia, non è richiesta una regolazione del dosaggio nei pazienti con insufficienza renale.
- Dosaggio raccomandato 8 mg per os /die
- Inizio d'azione 30 minuti
- Emivita di eliminazione 2-5 ore

PREVENTIVE EFFECT OF RAMELTEON ON DELIRIUM

Table 2. Clinical Outcomes During Study Drug Administration

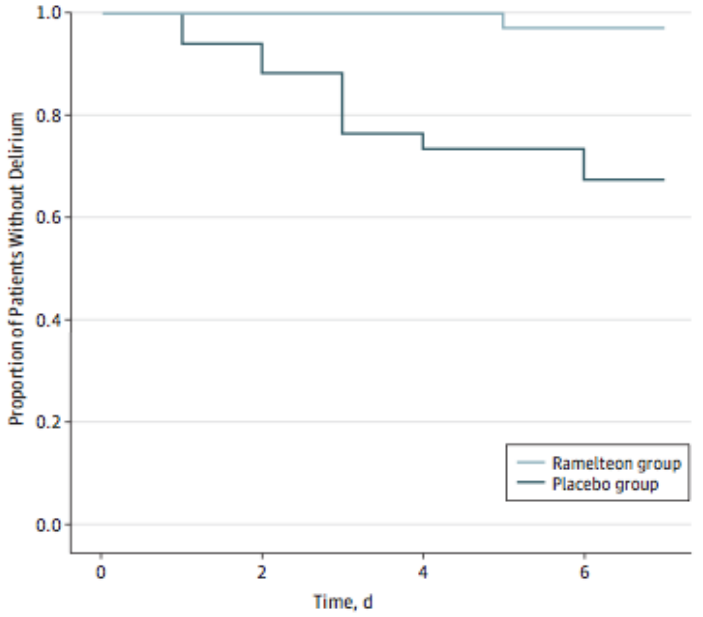
Outcome	Placebo Group (34 Patients)	Ramelteon (33 Patients)	*P* Value
Delirium, No. (%)	11 (32)	1 (3)	.003
Worst DRS-R98 score, mean (SD)			
Without delirium	5.0 (4.9)	4.9 (2.8)	.94
With delirium	24.6 (5.0)	33	
Discontinuation of study drug without delirium before 7 d, No. (%)	6 (18)	8 (24)	.56
Due to discharge	5 (15)	8 (24)	.37
Due to worsening of medical disease	1 (3)	0	>.99
Worst APACHE II score, mean (SD)	15.0 (2.8)	14.3 (2.7)	.36
Worst performance status score, mean (SD)	3.4 (0.8)	3.2 (0.8)	.35
Use of as-needed hydroxyzine for insomnia, No. (%)[a]	3 (9)	6 (18)	.30
Adverse event potentially attributable to study drug	0	0	...
Sleep parameters, No. (%)[b]			
Difficulty falling asleep	14 (41)	10 (30)	.45
Difficulty staying asleep	14 (41)	14 (42)	>.99
Waking too early	5 (15)	7 (21)	.54
Poor sleep quality	19 (56)	21 (64)	.62
Disturbance of natural sleep-wake rhythm	3 (9)	7 (21)	.19
Awakenings per night, mean (SD)	1.6 (1.2)	1.3 (1.6)	.28
Sleep duration, mean (SD), h	6.3 (1.6)	6.3 (1.6)	.67

Abbreviations: See Table 1.

[a] Only 25 mg hydroxyzine per night was allowed, as needed. In the placebo group, 1 patient received hydroxyzine for 3 nights in 6 days, and 2 for 1 night in 7 days. In the ramelteon group, 1 patient received hydroxyzine for 3 nights in 7 days and 1 for 2 nights in 7 days; the remaining 4 patients received hydroxyzine for 1 night in 7 days.

[b] For sleep parameters, the presence or absence of symptoms in each patient was determined according to the dominant category during study drug administration. The frequency and duration for each patient were determined by using mean values during study drug administration. Data were excluded for the night on which delirium occurred.

Figure 3. Time to Development of Delirium



The Kaplan-Meier estimates of the interval to the development of delirium were 6.94 (95% CI, 6.82-7.06) days for patients receiving ramelteon and 5.74 (5.05-6.42) days for those receiving placebo. Comparison by log-rank test showed that delirium developed significantly less frequently in the ramelteon group ($\chi^2 = 9.83$; $P = .002$).

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A. Identificare e trattare cause e fattori di rischio
B. Controllare i sintomi
    1- terapia sintomatica generale
    2- psicofarmacoterapia
C. Migliorare le condizioni ambientali

B1. TERAPIA SINTOMATICA GENERALE

- Idratazione/ equilibrio idro elettrolitico
- Nutrizione /glicemia
- Stato infettivo
- Alvo e minzione
- Ossigenazione
- Temperatura corporea e altri parametri neuro-vegetativi
- Sonno
- Mobilizzazione
- Stimolazione cognitiva

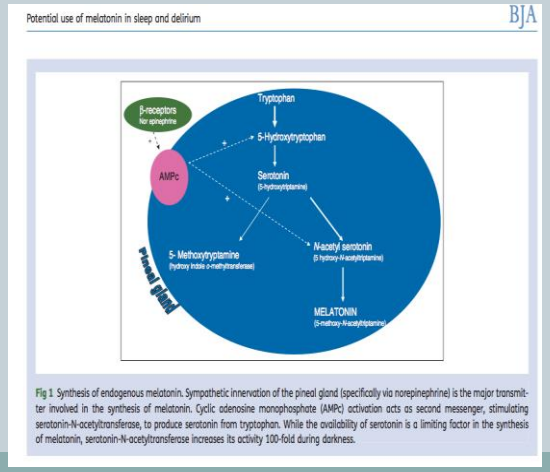
A MODEL FOR MANAGING DELIRANT PATIENTS

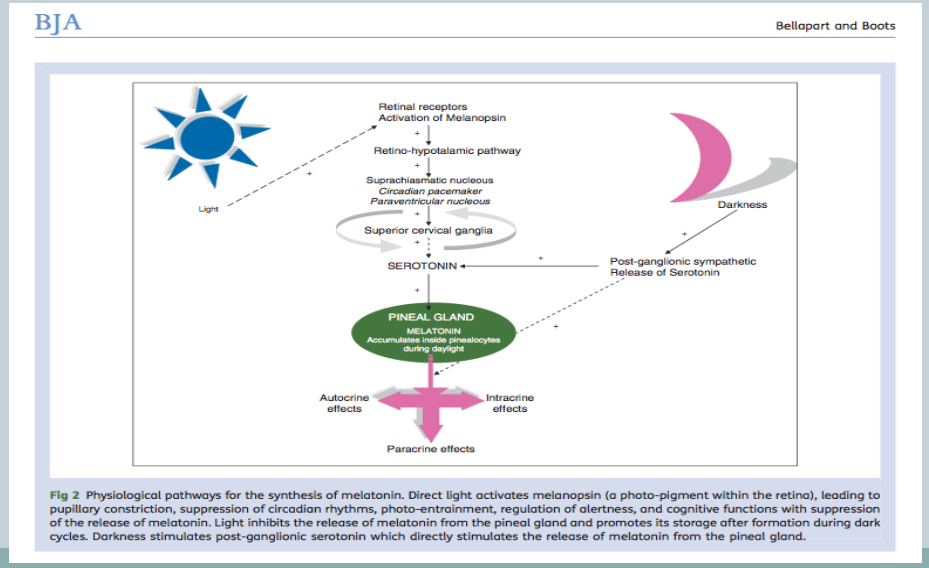
• ***D*rugs**	***Farmaci***
• ***E*ye, ears**	***Deficit sensoriali***
• ***L*ow oxygen**	***Ipossia***
• ***I*schemia**	***IMA, ictus, etc***
• ***R*etention**	***Stipsi, ritenzione urinaria***
• ***I*nfections**	***Infezioni***
• ***U*nderhydration**	***Disidratazione***
• ***M*etabolic**	***Disordini metabolici***
• ***S*ubdural**	***Ematoma subdurale***

Flaherty, JAGS 2003

PERCHE' LA MELATONINA

- Ormone endogeno responsabile della regolazione del ritmo circadiano, viene rilasciata in circolo dalla ghiandola pineale in risposta ai segnali ambientale luce/buio regolando il ciclo sonno veglia .
- Agisce sui recettori MT1 MT2 e MT3 a livello del nucleo sovrachiasmatico





SONNO E DELIRIUM

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Melatonin decreases delirium in elderly patients: A randomized, placebo-controlled trial†

Tareef Al-Aama[1,2], Christopher Brymer[1], Iris Gutmanis[3,4,5], Sarah M. Woolmore-Goodwin[4], Jacquelin Esbaugh[4] and Monidipa Dasgupta[1,5]

Table 2 Primary and secondary outcomes and adverse outcomes by treatment group

Outcome	Placebo ($n=61$)	Melatonin ($n=61$)	p-value
Delirium (assessed with CAM[a])	19 (31%)	7 (12%)	0.01
Incident delirium (excluding prevalent delirium[b])	10/52 (19.2%)	2/56 (3.6%)	0.01
Initial MDAS[c] score[d] (SD)[e] (all participants)	4.4 (4.6)	5.2 (4.3)	0.31
Initial MDAS[cd] score (SD)[e] (if developed delirium)	11.4 (3.0)	10.5 (5.3)	0.77
Use of paid patient attendant services	3/60 (1 missing) (5.0%)	2/57 (4 missing) (3.5%)	0.52
Restraints	6 (10%)	4 (7%)	0.74
Use of PRN[f] sedatives	38 (62%)	33(54%)	0.46
Mean LOS[gh] (SD)[e]	14.5 (21.6)	18.5 (26.4)	0.36
Sleep disturbance[i]			
None	37 (60.7%)	39 (63.9%)	0.81
Mild	21 (34.4%)	18 (29.5%)	
Moderate/severe	3 (4.9%)	4 (6.6%)	
Deceased	8 (13%)	6 (10%)	0.78

2011

SONNO E DELIRIUM

British Journal of Anaesthesia **108** (4): 572–80 (2012)
doi:10.1093/bja/aes035

BJA

Potential use of melatonin in sleep and delirium in the critically ill

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Editor's key points

- Sleep deprivation may be a causal factor in intensive care delirium in critically ill patients.
- Melatonin is involved in control of circadian rhythms and sleep regulation.
- Melatonin may have a potential therapeutic role in intensive care unit patients.
- Further studies are required before this can be established.

Intensive care delirium is a well-recognized complication in critically ill patients. Delirium is an independent risk factor for death in the intensive care unit (ICU), leading to oversedation, increased duration of mechanical ventilation, and increased length of stay. Although there has not been a direct causal relationship shown between sleep deprivation and delirium, many studies have demonstrated that critically ill patients have an altered sleep pattern, abnormal levels of melatonin, and loss of circadian rhythms. Melatonin has a major role in control of circadian rhythm and sleep regulation and other effects on the immune system, neuroprotection, and oxidant/anti-oxidant activity. There has been interest in the use of exogenous melatonin as a measure to improve sleep. However, there are only a few studies of melatonin in ICU patients and these use heterogeneous methodologies. Therefore, it is not possible at this stage to make any clear recommendations regarding the clinical use of melatonin in this setting. There is a need for well-designed randomized controlled trials examining the role of melatonin in ICU.

Keywords: critical illness delirium; melatonin; polysomnography; sleep deprivation

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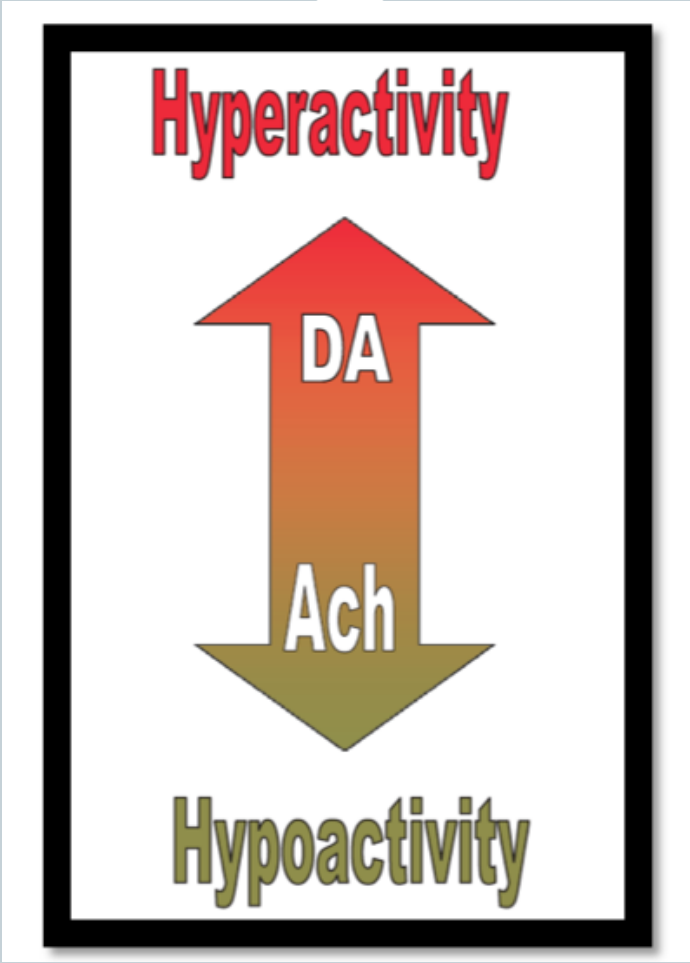
RAZIONALE



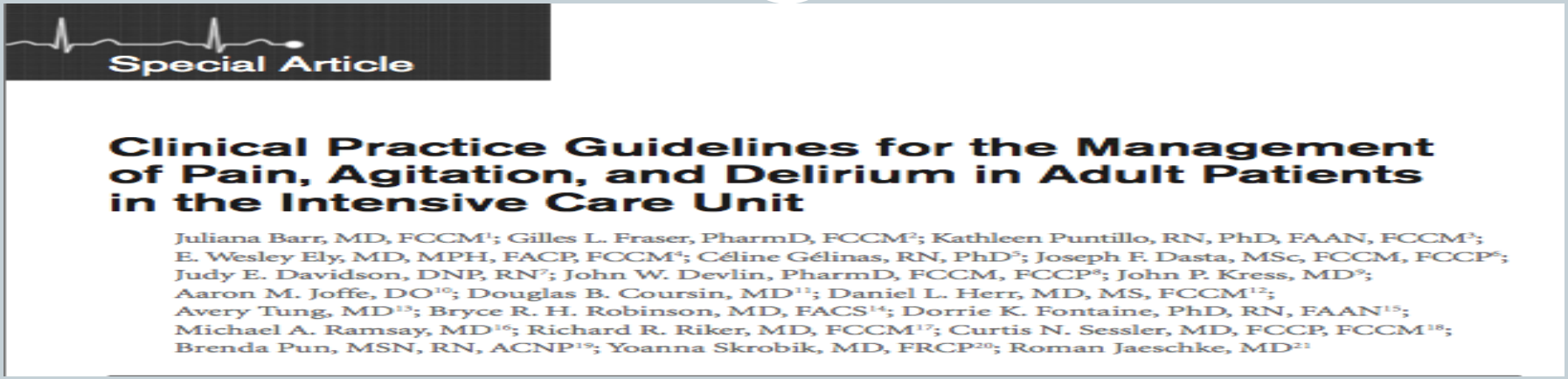
B2. TERAPIA PSICOFARMACOLOGICA

- I farmaci non vanno usati come alternativa al riconoscimento, trattamento o eliminazione delle cause scatenanti
- Non esistono farmaci approvati per il trattamento del delirium
- Scopo della terapia farmacologica è la sedazione e il trattamento di stati di agitazione
- Di conseguenza , il trattamento di elezione è costituito dagli antipsicotici ad alta potenza

FARMACI ANTIPSICOTICI

ANTIPSICOTICI TIPICI	ANTIPSICOTICI ATIPICI
1. DERIVATI DELLE FENOTIAZINE Promazina (Talofen) Clorpromazina (Largactil) Levopromazina (Nozinan) Prometazina (Fargan) Tioridazina (Melleril) Flufenazina (Anatensol, Modinet) 2. BUTIRROFENONI Aloperidolo (Serenase, Haldol) 3. DIBENZODIAZEPINE Clotiapina (Entumin) 4. BENZAMIDI Sulpiride (Dobren)	Amisulpiride (Solian) Aripiprazolo (Abilify) Clozapina (Leponex) Olanzapina (Zyprexa) Quetiapina (Seroquel) Risperidone (Risperdal

TREATMENT OF DELIRIUM


Special Article

Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

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a. *Question*: Does treatment with haloperidol reduce the duration of delirium in adult ICU patient?

   Answer: There is no published evidence that treatment with haloperidol reduces the durationof delirium in adult ICU patient

ALOPERIDOLO

- Farmaco antipsicotico capostipite della famiglia dei butirrofenoni
- Neurolettico dotato di effetto antipsicotico, sedativo e antiemetico
- Scarso effetto anticolinergico e breve emivita
- Azione anti-psicotica **veloce ed efficace**
- Antidopaminergico selettivo dei recettori della dopamina D2; antagonista alfa-adrenergico

ANTIPSICOTICI TIPICI: EPS

- ***Acatisia***
  Dondolamento, incapacità a stare fermo.
  Ansia irritabilità
  Di norma compare dopo una dose iniziale alta e che può somigliare all'esacerbazione della malattia che si sta trattando;

- ***Distonia***
  Contrazioni toniche involontarie del volto e del corpo
  Puo' comparire già dopo poche dosi

- ***Parkinsonismo***
  Tremore, rigidità, bradicinesia, amimia, ecc.
  Puo' insorgere gradualmente

- ***Discinesia tardiva***
  Movimenti involontari ipercinetici(movimenti ritmici involontari della lingua, della faccia e della mandibola) . Di solito si sviluppa con terapie a lungo termine o con alte dosi, ma può comparire con dosi basse a breve termine - una discinesia tardiva di breve durata può comparire dopo la sospensione del trattamento.

ANTIPSICOTICI TIPICI: ALTRI E.C.

- Sindrome Maligna da Neurolettici
- Disturbi SNA
- Soglia convulsivante piu' bassa
- Disturbi cardiaci

La somministrazione parenterale è a maggior rischio di **tossicita` cardiaca** (allungamento del QTc) ma a minor rischio di EPS

TREATMENT OF DELIRIUM

b. *Question*: Does treatment with atypical antipsychotics reduce he duration of delirium in adult ICU patients?

Answer: Atypical antipsychotics may reduce the duration of delirium in adult ICU patients (C)

QUETIAPINA

- Antipsicotico atipico appartenente alla classe delle benzodiazepine

- Antagonista multirecettoriale
  Antagonista del recettore della serotonina 5-HT2A
  Agonista parziale del recettore serotoninergico 5-HT1A
  Antagonista del recettore della dopamina D2
  Bloccante del recettore della noradrenalina alfa1
  Bloccante del recettore per l'istamina H1
  Debole azione anticolinergica sui recettori muscarinici

- La modalità con cui la quetiapina si lega al recettore dopaminergico D2 spiega la bassa incidenza di sintomi extrapiramidali. Il legame fra quetiapina e recettore dopaminergico è infatti un legame di breve durata (elevata cinetica di dissociazione), ma di sufficiente stabilità per indurre gli effetti antipsicotic

TREATMENT OF DELIRIUM

Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study*

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Objective: To compare the efficacy and safety of scheduled quetiapine to placebo for the treatment of delirium in critically ill patients requiring as-needed haloperidol.

Design: Prospective, randomized, double-blind, placebo-controlled study.

Setting: Three academic medical centers.

Patients: Thirty-six adult intensive care unit patients with delirium (Intensive Care Delirium Screening Checklist score ≥4), tolerating enteral nutrition, and without a complicating neurologic condition.

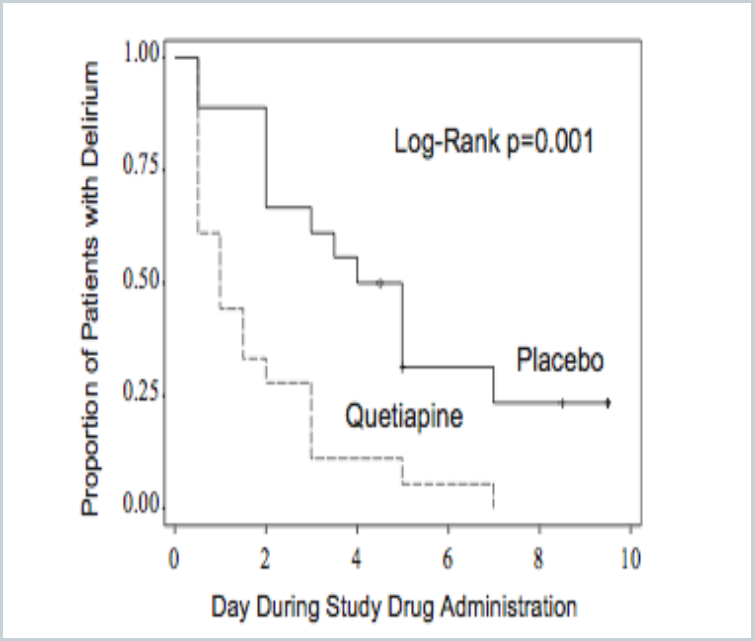
Interventions: Patients were randomized to receive quetiapine 50 mg every 12 hrs or placebo. Quetiapine was increased every 24 hrs (50 to 100 to 150 to 200 mg every 12 hrs) if more than one dose of haloperidol was given in the previous 24 hrs. Study drug was continued until the intensive care unit team discontinued it because of delirium resolution, therapy ≥10 days, or intensive care unit discharge.

Measurements and Main Results: Baseline characteristics were similar between the quetiapine (n = 18) and placebo (n = 18) groups. Quetiapine was associated with a shorter time to first resolution of delirium [1.0 (interquartile range [IQR], 0.5–3.0) vs. 4.5 days (IQR, 2.0–7.0; $p = .001$)], a reduced duration of delirium [36 (IQR, 12–87) vs. 120 hrs (IQR, 60–195; $p = .006$)], and less agitation (Sedation-Agitation Scale score ≥5) [6 (IQR, 0–38) vs. 36 hrs (IQR, 11–66; $p = .02$)]. Whereas mortality (11% quetiapine vs. 17%) and intensive care unit length of stay (16 quetiapine vs. 16 days) were similar, subjects treated with quetiapine were more likely to be discharged home or to rehabilitation (89% quetiapine vs. 56%; $p = .06$). Subjects treated with quetiapine required fewer days of as-needed haloperidol [3 [(IQR, 2–4)] vs. 4 days (IQR, 3–8; $p = .05$)]. Whereas the incidence of QTc prolongation and extrapyramidal symptoms was similar between groups, more somnolence was observed with quetiapine (22% vs. 11%; $p = .66$).

Conclusions: Quetiapine added to as-needed haloperidol results in faster delirium resolution, less agitation, and a greater rate of transfer to home or rehabilitation. Future studies should evaluate the effect of quetiapine on mortality, resource utilization, post-intensive care unit cognition, and dependency after discharge in a broader group of patients. (Crit Care Med 2010; 38: 419–427)

KEY WORDS: delirium; quetiapine; haloperidol; antipsychotic; drug therapy; treatment; critical care; intensive care unit; randomized controlled trial; outcomes

Crit Care Med 2010 Vol 38 No2



TREATMENT OF DELIRIUM

ORIGINAL RESEARCH

Quetiapine versus haloperidol in the treatment of delirium: a double-blind, randomized, controlled trial

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Background: Atypical antipsychotic drugs may have low propensity to induce extrapyramidal side effects in delirious patients. This study aimed to compare the efficacy and tolerability between quetiapine and haloperidol in controlling delirious behavior.

Methods: A 7-day prospective, double-blind, randomized controlled trial was conducted from June 2009 to April 2011 in medically ill patients with delirium. Measures used for daily assessment included the Delirium Rating Scale-revised-98 (DRS-R-98) and total sleep time. The Clinical Global Impression, Improvement (CGI–I) and the Modified (nine-item) Simpson–Angus Scale were applied daily. The primary outcome was the DRS-R-98 severity scores. The data were analyzed on an intention-to-treat basis.

Results: Fifty-two subjects (35 males and 17 females) were randomized to receive 25–100 mg/day of quetiapine (n = 24) or 0.5–2.0 mg/day of haloperidol (n = 28). Mean (standard deviation) doses of quetiapine and haloperidol were 67.6 (9.7) and 0.8 (0.3) mg/day, respectively. Over the trial period, means (standard deviation) of the DRS-R-98 severity scores were not significantly different between the quetiapine and haloperidol groups (–22.9 [6.9] versus –21.7 [6.7]; $P = 0.59$). The DRS-R-98 noncognitive and cognitive subscale scores were not significantly different. At end point, the response and remission rates, the total sleep time, and the Modified (nine-item) Simpson–Angus scores were also not significantly different between groups. Hypersomnia was common in the quetiapine-treated patients (33.3%), but not significantly higher than that in the haloperidol-treated group (21.4%).

Limitations: Patients were excluded if they were not able to take oral medications, and the sample size was small.

Conclusion: Low-dose quetiapine and haloperidol may be equally effective and safe for controlling delirium symptoms.

TREATMENT OF DELIRIUM

Psychiatry

RESEARCH ARTICLE Open Access

Efficacy and safety of haloperidol versus atypical antipsychotic medications in the treatment of delirium

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Abstract

Background: Most previous studies on the efficacy of antipsychotic medication for the treatment of delirium have reported that there is no significant difference between typical and atypical antipsychotic medications. It is known, however, that older age might be a predictor of poor response to antipsychotics in the treatment of delirium. The objective of this study was to compare the efficacy and safety of haloperidol versus three atypical antipsychotic medications (risperidone, olanzapine, and quetiapine) for the treatment of delirium with consideration of patient age.

Methods: This study was a 6-day, prospective, comparative clinical observational study of haloperidol versus atypical antipsychotic medications (risperidone, olanzapine, and quetiapine) in patients with delirium at a tertiary level hospital. The subjects were referred to the consultation-liaison psychiatric service for management of delirium and were screened before enrollment in this study. A total of 80 subjects were assigned to receive either haloperidol (N = 23), risperidone (N = 21), olanzapine (N = 18), or quetiapine (N = 18). The efficacy was evaluated using the Korean version of the Delirium Rating Scale-Revised-98 (DRS-K) and the Korean version of the Mini Mental Status Examination (K-MMSE). The safety was evaluated by the Udvalg Kliniske Undersogelser side effect rating scale.

Results: There were no significant differences in mean DRS-K severity or K-MMSE scores among the four groups at baseline. In all groups, the DRS-K severity score decreased and the K-MMSE score increased significantly over the study period. However, there were no significant differences in the improvement of DRS-K or K-MMSE scores among the four groups. Similarly, cognitive and non-cognitive subscale DRS-K scores decreased regardless of the treatment group. The treatment response rate was lower in patients over 75 years old than in patients under 75 years old. Particularly, the response rate to olanzapine was poorer in the older age group. Fifteen subjects experienced a few adverse events, but there were no significant differences in adverse event profiles among the four groups.

Conclusions: Haloperidol, risperidone, olanzapine, and quetiapine were equally efficacious and safe in the treatment of delirium. However, age is a factor that needs to be considered when making a choice of antipsychotic medication for the treatment of delirium.

Trial registration: Clinical Research Information Service, Republic of Korea, (http://cris.nih.go.kr/cris/en/search/basic_search.jsp, Registered Trial No. KCT0000632).

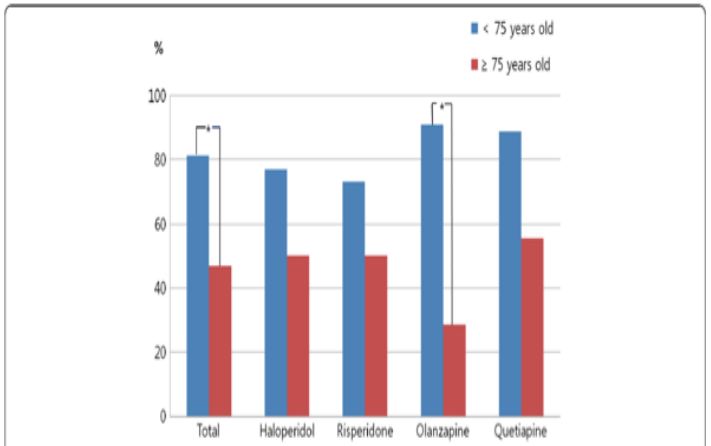

Figure 3 Treatment response rate between young-old and old-old groups in the four antipsychotic groups. * $p < 0.05$ by Chi-square test or Fisher's exact test. Treatment response was defined as a ≥50% reduction from the baseline DRS-K score.

TREATMENT OF DELIRIUM

c. *Question*: Should treatment with cholinesterase inhibitors (rivastigmine), be used to reduce the duration of delirium in ICU patients?

Answer: We do not recommend administering rivastigmine to reduce the duration of delirium in ICU patient (1B)

TREATMENT OF DELIRIUM

Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial

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Summary

Background Delirium is frequently diagnosed in critically ill patients and is associated with adverse outcome. Impaired cholinergic neurotransmission seems to have an important role in the development of delirium. We aimed to establish the effect of the cholinesterase inhibitor rivastigmine on the duration of delirium in critically ill patients.

Methods Patients (aged ≥18 years) who were diagnosed with delirium were enrolled from six intensive care units in the Netherlands, and treated between November, 2008, and January, 2010. Patients were randomised (1:1 ratio) to receive an increasing dose of rivastigmine or placebo, starting at 0·75 mL (1·5 mg rivastigmine) twice daily and increasing in increments to 3 mL (6 mg rivastigmine) twice daily from day 10 onwards, as an adjunct to usual care based on haloperidol. The trial pharmacist generated the randomisation sequence by computer, and consecutively numbered bottles of the study drug according to this sequence to conceal allocation. The primary outcome was the duration of delirium during hospital admission. Analysis was by intention to treat. Duration of delirium was censored for patients who died or were discharged from hospital while delirious. Patients, medical staff, and investigators were masked to treatment allocation. Members of the data safety and monitoring board (DSMB) were unmasked and did interim analyses every 3 months. This trial is registered with ClinicalTrials.gov, number NCT00704301.

Findings Although a sample size of 440 patients was planned, after inclusion of 104 patients with delirium who were eligible for the intention-to-treat analysis (n=54 on rivastigmine, n=50 on placebo), the DSMB recommended that the trial be halted because mortality in the rivastigmine group (n=12, 22%) was higher than in the placebo group (n=4, 8%; p=0·07). Median duration of delirium was longer in the rivastigmine group (5·0 days, IQR 2·7–14·2) than in the placebo group (3·0 days, IQR 1·0–9·3; p=0·06).

Interpretation Rivastigmine did not decrease duration of delirium and might have increased mortality so we do not recommend use of rivastigmine to treat delirium in critically ill patients.

Lancet 2010

TREATMENT OF DELIRIUM

d. *Question*: Should haloperidol and atypical antipsychotics be witheld in patients at high risk for torsades de pointes?

Answer: We do not suggest using antipsychotics in patients at significant risk for torsades de pointes (i.e. patients with baseline prolongation of QT interval, patients receiving concomitant medications known to prolong the QT interval, or patients with a history of this arrhytmia) (2C)

TREATMENT OF DELIRIUM

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Articles

QTc Prolongation with Antipsychotics: Is Routine ECG Monitoring Recommended?

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Abstract

Whether or not QTc interval should be routinely monitored in patients receiving antipsychotics is a controversial issue, given logistic and fiscal dilemmas. There is a link between antipsychotic medications and prolongation of QTc interval, which is associated with an increased risk of torsade de pointes (TdP). Our goal is to provide clinically practical guidelines for monitoring QTc intervals in patients being treated with antipsychotics. We provide an overview of the pathophysiology of the QT interval, its relationship to TdP, and a discussion of the QT prolonging effects of antipsychotics. A literature search for articles relevant to the QTc prolonging effects of antipsychotics and TdP was conducted utilizing the databases PubMed and Embase with various combinations of search words. The overall risk of TdP and sudden death associated with antipsychotics has been observed to be low. Medications, genetics, gender, cardiovascular status, pathological conditions, and electrolyte disturbances have been found to be related to prolongation of the QTc interval. We conclude that, while electrocardiogram (ECG) monitoring is useful when administering antipsychotic medications in the presence of co-existing risk factors, it is not mandatory to perform ECG monitoring as a prerequisite in the absence of cardiac risk factors. An ECG should be performed if the initial evaluation suggests increased cardiac risk or if the antipsychotic to be prescribed has been established to have an increased risk of TdP and sudden death. (*Journal of Psychiatric Practice* 2014;20:196–206)

REVIEW ARTICLE

QTc Prolongation by Psychotropic Drugs and the Risk of Torsade de Pointes

Katharina Wenzel-Seifert, Mark

SUMMARY

Introduction: Many psychotropic drugs can delay cardiac repolarization and thereby prolong the rate-corrected QT interval (QTc). A prolonged QTc often arouses concern in clinical practice, as it can be followed, in rare cases, by the life-threatening polymorphic ventricular tachyarrhythmia called torsade de pointes (TdP).

Method: We searched PubMed for pertinent literature on the risk of QTc prolongation and/or TdP associated with commonly used psychotropic drugs.

Results: Thioridazine and ziprasidone confer the highest risk of QTc prolongation and/or TdP. There is also a clinically significant risk associated with haloperidol given intravenously in high doses. TdP has been reported in a few cases in association with the use of newer antipsychotic drugs (mainly quetiapine and amisulpride), most of the tri- and tetracyclic antidepressants, and the selective monoamine reuptake inhibitors citalopram, fluoxetine, paroxetine, and venlafaxine. As a rule, however, QTc prolongation and/or TdP occur only in the presence of multiple additional risk factors, such as age over 65 years, pre-existing cardiovascular disease, bradycardia, female sex, hypokalemia, hypomagnesemia, a supratherapeutic or toxic serum concentration, or the simultaneous administration of other drugs that delay repolarization or interfere with drug metabolism.

Conclusion: Before prescribing a psychotropic drug, the physician should carefully assess its risks and benefits to avoid this type of adverse reaction, particularly when additional risk factors are present. The ECG and electrolytes should be regularly monitored in patients taking psychotropic drugs.

TREATMENT OF DELIRIUM

e. *Question* : For mechanically ventilated, adult ICU patients with delirium who require continuous IV infusion of sedative medications, is dexmedetomidine preferred over benzodiazepines to reduce the duration of delirium?

Answer: We suggwst that in adult ICU patient with delirium unrelated to alcohol or benzodiazepine withdrawal, continuous IV infusions of dexmedetomidine rather than benzodiazepine infusions be administered for sedation in order to reduce the duration of delirium in these patiens (2B)

DOSAGGI DEGLI ANTIPSICOTICI

Table 4. Pharmacologic Treatment of Delirium.

Class and Drug	Dose	Adverse Effects	Comments
Antipsychotic			
Haloperidol	0.5–1.0 mg twice daily orally, with additional doses every 4 hr as needed (peak effect, 4–6 hr) 0.5–1.0 mg intramuscularly; observe after 30–60 min and repeat if needed (peak effect, 20–40 min)	Extrapyramidal symptoms, especially if dose is >3 mg per day Prolonged corrected QT interval on electrocardiogram Avoid in patients with withdrawal syndrome, hepatic insufficiency, neuroleptic malignant syndrome	Usually agent of choice Effectiveness demonstrated in randomized, controlled trials[20,37] Avoid intravenous use because of short duration of action
Atypical antipsychotic			
Risperidone	0.5 mg twice daily	Extrapyramidal effects equivalent to or slightly less than those with haloperidol Prolonged corrected QT interval on electrocardiogram	Tested only in small uncontrolled studies Associated with increased mortality rate among older patients with dementia
Olanzapine	2.5–5.0 mg once daily		
Quetiapine	2.5–5.0 mg once daily		
Benzodiazepine			
Lorazepam	0.5–1.0 mg orally, with additional doses every 4 hr as needed*	Paradoxical excitation, respiratory depression, oversedation	Second-line agent Associated with prolongation and worsening of delirium symptoms demonstrated in clinical trial[37] Reserve for use in patients undergoing sedative and alcohol withdrawal, those with Parkinson's disease, and those with neuroleptic malignant syndrome
Antidepressant			
Trazodone	25–150 mg orally at bedtime	Oversedation	Tested only in uncontrolled studies

* Intravenous use of lorazepam should be reserved for emergencies.

COME USARE I FARMACI

- Utilizzare i farmaci al dosaggio piu' basso possibile, in relazione alla gravità della sintomatologia
- Valutare la risposta a breve termine, monitorizzando la risposta e gli eventi avversi
- Ripetere la prescrizione giornalmente e valutare risposta/tollerabilità
- Riportare la dose totale somministrata
- Alla risoluzione dei sintomi proseguire la terapia per 48 ore, poi ridurre fino alla sospensione in 1-5 gg(in relazione alla severità e durata dei sintomi

LA TERAPIA DEL DELIRIUM

Persegue 3 obbiettivi

A. Identificare e trattare cause e fattori di rischio
B. Controllare i sintomi
    1- terapia sintomatica generale
    2- psicofarmacoterapia
C. Migliorare le condizioni ambientali

PROVVEDIMENTI NON FARMACOLOGICI ED AMBIENTALI

- Evitare sia l'eccessiva **esposizione a stimoli sensoriali** (luci, rumori, voci), che l'isolamento completo della stanza del paziente
- Consentire un'illuminazione naturale durante il giorno e una luce artificiale attenuata durante la notte
- Collocare **punti di riferimento temporali** (orologio, calendario) a vista del paziente
- Se il paziente di solito indossa occhiali o una protesi per l'udito, farglieli indossare per **ripristinare il normale input sensoriale**
- Il personale di reparto ed i familiari vanno istruiti perche´ diano **frequenti stimoli di ri-orientamento** al paziente
- Ruolo **chiave dell'assistenza infermieristica**

DELIRIUM MANAGEMENT

LA PREVENZIONE DEL DELIRIUM è L'UNICO TRATTAMENTO SICURAMENTE EFFICACE

- Identificare i pz a rischio
- Intervenire sui fattori di rischio modificabili
- Interventi ambientali
- Interventi farmacologici

CONCLUSIONI

- Il delirium è una condizione clinica che puo' essere prevenuta con un intervento multifattoriale
- Un singolo intervento (farmacologico/ non farmacologico) non è sufficiente per prevenire/trattare il delirium
- La cura del delirium rappresenta un luogo di collaborazione tra medico e infermiere
- Importanza della creazione di protocolli gestionali