63° CONGRESSO NAZIONALE SIGG

GLI ANZIANI: LE RADICI DA PRESERVARE

ROMA 28 novembre 01 dicembre 2018 Auditorium della Tecnica, Roma

IL MANAGEMENT DEL DELIRIUM NEI REPARTI OSPEDALIERI:
Perché usare i farmaci

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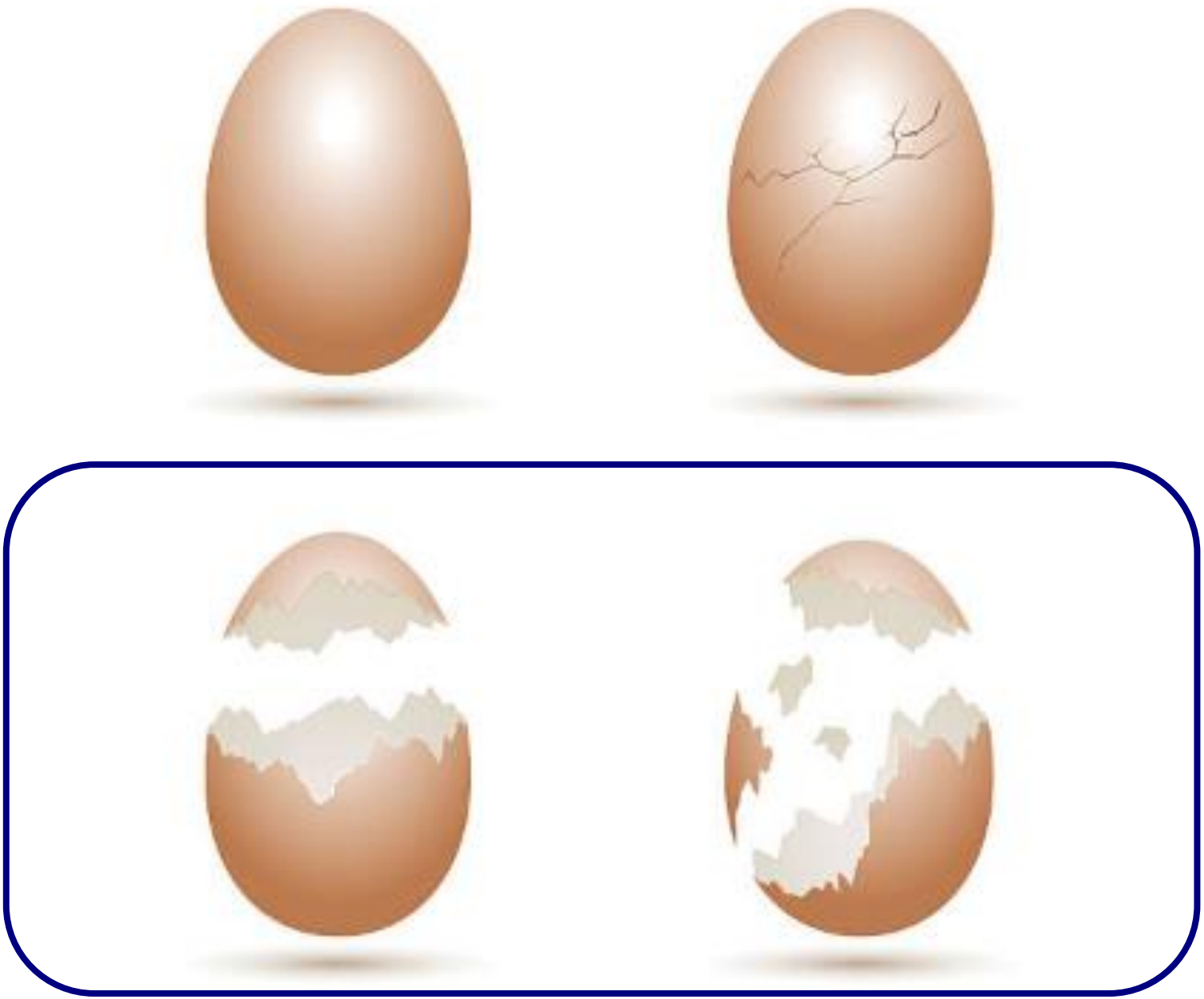

L’esperienza del delirium

http://www.nancyandrews.net

L'esperienza del delirium

• "There I was laying in my bed, speculating, dreaming and making thing worse. I felt so restless, slept badly" • "There was this red lamp in my room. This lamp was so irritating, made me so frustrated . . . don't know why, but this lamp created these horrifying feelings . . . " • "There was this pipe along the ceiling. It was fully packed with crawling animals . . . I think I panicked, screamed out in such a tone of voice . . . "	• Being anxious over the loss of control • Feeling restless about comprehensibility of the situation • The delirium generated horrifying feelings and panic	Existing in a twilight zone
• "I remember removing all sorts of medical equipment, had to get loose and to get off to this concert" • "I woke up during night tied into tubes, medical tubes. One in particular was spun around my feet and made me feel uncomfortable. I jerked it away . . . "	• Experiencing the medical equipment as an obstacle to getting away • Feeling the medical tubes as a reduction of movement	Trapped in medical tubes
• "I was among others in the USA twice. On the first trip I met this flight attendant whom I thought looked familiar. I met her again the next day . . . 'Don't you recognize me', she said. 'We did talk yesterday' . . . I remember it all very clearly"	• Experiencing being in surroundings other than the hospital room	Moving between different surroundings
• "Apparently I was lying in a coffin and I remember saying to myself; at least I could have been covered by a duvet. It is the strangest feelings" • "My daughter died some years before the heart surgery, and she, I get chills, she was present nearly every evening in my room. It was so real that I still carry it with me . . . "	• Experiencing the feeling of being close to death, like lying in a coffin • The presence of deceased relatives in the hospital room nearly every evening	Meeting with the dead and the deceased

Instenes I et al., Heart Lung Circ, 2018

The NEW ENGLAND JOURNAL of MEDICINE

2018

ORIGINAL ARTICLE

Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

T.D. Girard, M.C. Exline, S.S. Carson, C.L. Hough, P. Rock, M.N. Gong, I.S. Douglas, A. Malhotra, R.L. Owens, D.J. Feinstein, B. Khan, M.A. Pisani, R.C. Hyzy, G.A. Schmidt, W.D. Schweickert, R.D. Hite, D.L. Bowton, A.L. Masica, J.L. Thompson, R. Chandrasekhar, B.T. Pun, C. Strength, L.M. Boehm, J.C. Jackson, P.P. Pandharipande, N.E. Brummel, C.G. Hughes, M.B. Patel, J.L. Stollings, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the MIND-USA Investigators*

- **Outcome primario**: giorni vivi **senza delirium** o coma (CAM-ICU) durante l'intervento (14 giorni)
- N=566 pazienti con delirium in terapia intensiva (età media 60 anni), 89% delirium ipoattivo
- Non vengono riportati dati su agitazione (RASS) e gravità

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

T.D. Girard, M.C. Exline, S.S. Carson, C.L. Hough, P. Rock, M.N. Gong,

- Dose media di aloperidolo 11 mg die (max 20 mg die)

  Dose iniziale 2,5 mg x 2 (1,25 mg x 2 >70 anni)

  Dosi successive: doppio della precedente se il delirium non era scomparso, non era raggiunta la dose massima (10 mg), e il farmaco era tollerato; invariata se paziente in coma da sedativi (RASS -4/-5); sospeso se non tollerato (compreso eccesso di sedazione 12 ore dopo la sospensione dei sedativi, sovrapponibile tra i gruppi)

  + sedativi (propofol/Dexdor) + benzodiazepine (60%, media midazolam 5 mg die) + antipsicotici open-label (20%, media aloperidolo 5 mg cumulativo)

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

Lancet Respir Med 2013; 1: 515–23

- **Outcome primario**: giorni vivi **senza delirium** o coma (CAM-ICU) durante l'intervento (14 giorni)
- N=141 soggetti con delirium in terapia intensiva (età media 68 anni)
- Analisi secondaria su agitazione (RASS 2+), no outcome pre-specificato

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

Lancet Respir Med 2013; 1: 515–23

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

- Dose di aloperidolo 7,5 mg die (max 10 mg die)
- Dose 2,5 mg x 3 (aumentabile a 5 mg in presenza di agitazione)

  + sedativi (propofol/fentanyl) + benzodiazepine (20%, media midazolam 8 mg cumulativi, vs. 49 mg cumulativi nel gruppo placebo) + antipsicotici open-label (media aloperidolo 1,5 mg cumulativo)

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

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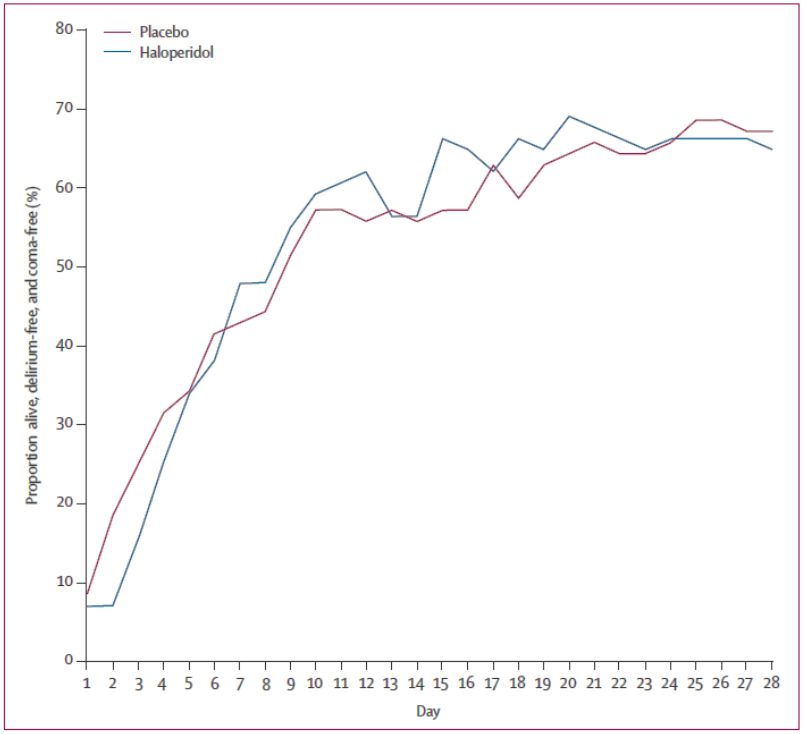
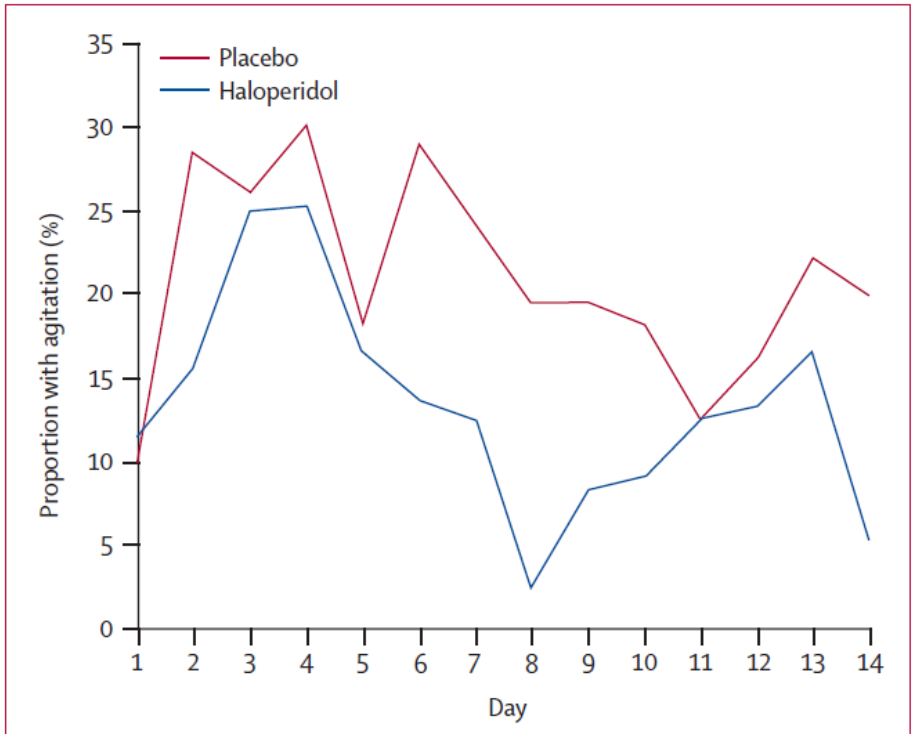


p=0.99



p=0.0075

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

Lancet Respir Med 2013; 1: 515–23

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

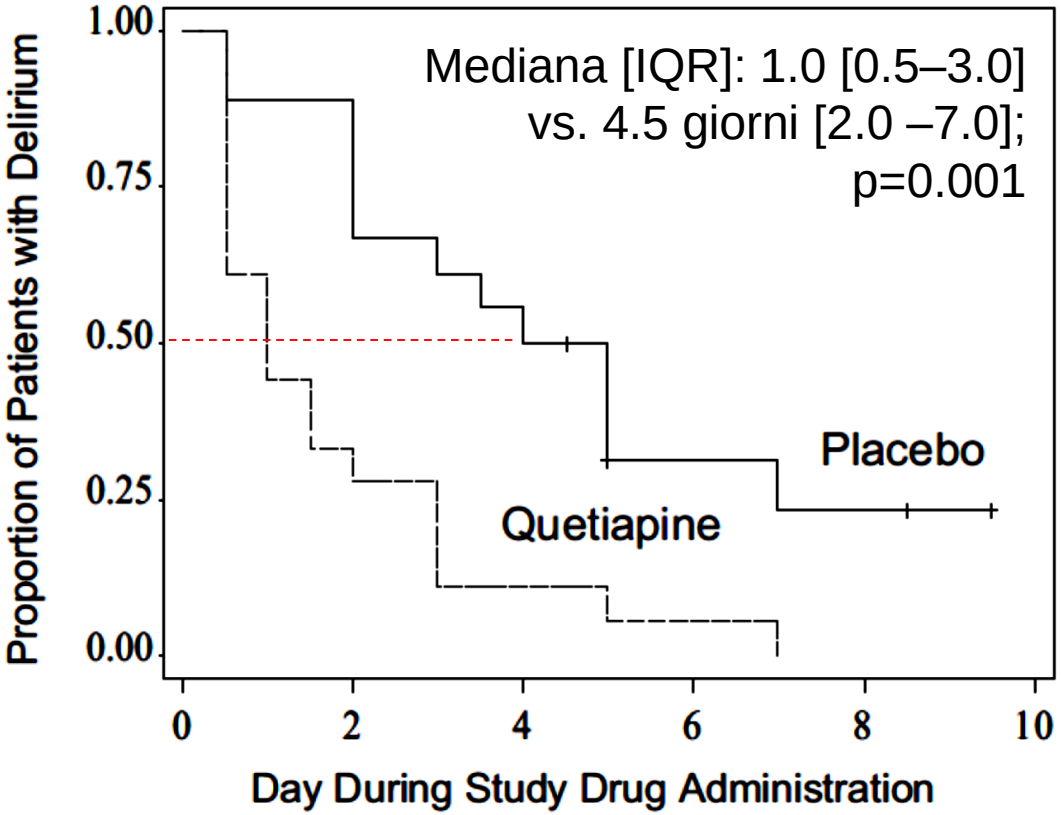
These results do not support the hypothesis that haloperidol modifies duration of delirium in critically ill patients. Although haloperidol can be used safely in this population of patients, pending the results of trials in progress, **the use of intravenous haloperidol should be reserved for short-term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

Terapia sintomatica vs. terapia patognetica

Qualcuno dei presenti smetterebbe di usare il paracetamolo in un paziente febbrile perché non riduce la durata dell’episodio infettivo?

Quetiapina vs. placebo: RCT in UCI

36 pazienti (età media 63, 80%) con delirium (ICDSC≥4) in UCI e **prescrizione di aloperiodolo al bisogno**, randomizzati a quetiapina (dose iniziale 50 mg x 2 per SNG, dose media 110 mg) vs. placebo



Outcome primario: rapidità di risoluzione del delirium

Devlin JW et al., Crit Care Med, 2010

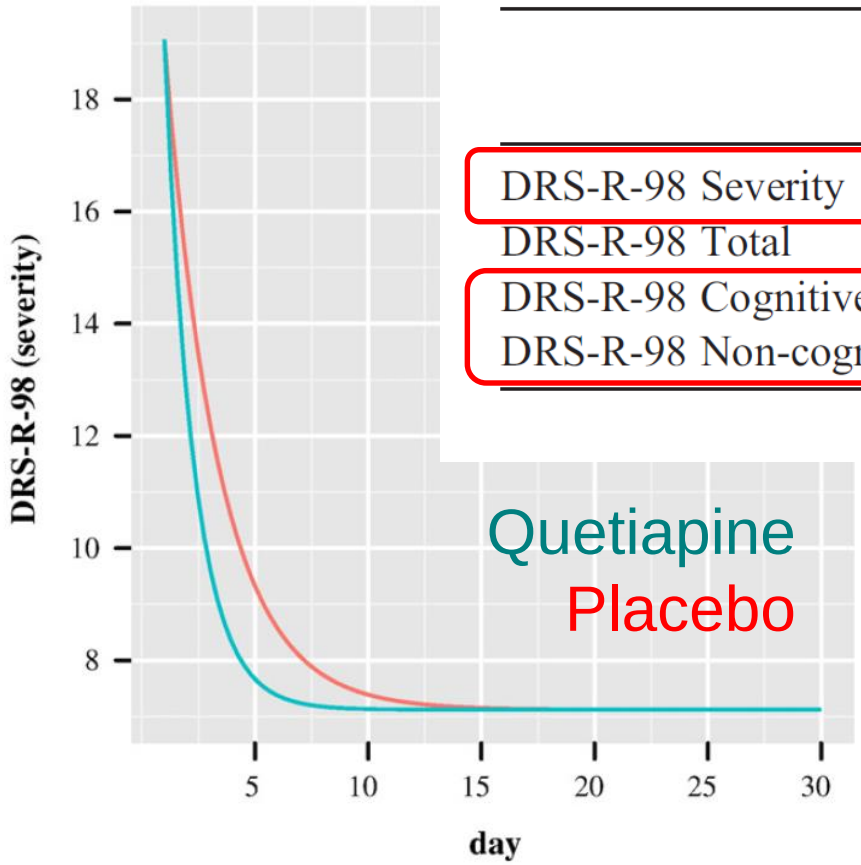
Quetiapina vs. placebo: RCT UCI

	Quetiapine (n = 18)	Placebo (n = 18)	p
Time of study drug administration, hrs	102 (84–168)	186 (108–228)	.04
Time in delirium			
Hours	36 (12–87)	120 (60–195)	.006
Percent[c]	53 (16–67)	69 (58–100)	.02
Number of subjects experiencing delirium recurrence after initial delirium resolution, %	22	44	.29
Time spent agitated, Sedation-Agitation Scale ≥5			
Hours	6 (0–38)	36 (11–66)	.02
Percent[c]	3 (0–22)	21 (8–41)	.03
Time spent deeply sedated, Sedation-Agitation Scale ≤2			
Hours	0 (0–8)	0 (1–2)	.54
Percent[c]	0 (0–8)	0 (0–0)	.39
Haloperidol			
Amount per day, mg	1.9 (0.8–3.8)	4.3 (1.2–6.1)	.26
Doses administered per day	0.9 (0.4–1.8)	1.6 (0.5–2.2)	.36
Days when ≥1 dose administered			
Total	3 (2–4)	4 (3–8)	.05
Percent[c]	44 (40–100)	60 (33–80)	.7
Sedative[d,e]			
Amount of midazolam equivalents per day, mg	5.3 (0–42)	26.5 (0.3–74)	.32
Days when ≥1 dose administered			
Total	1 (0–4)	4 (1–9)	.09
Percent[c]	27.7 (0–87.5)	41.7 (10–90)	.74

Devlin JW et al., Crit Care Med, 2010

Quetiapina vs. placebo: RCT in reparto acuti

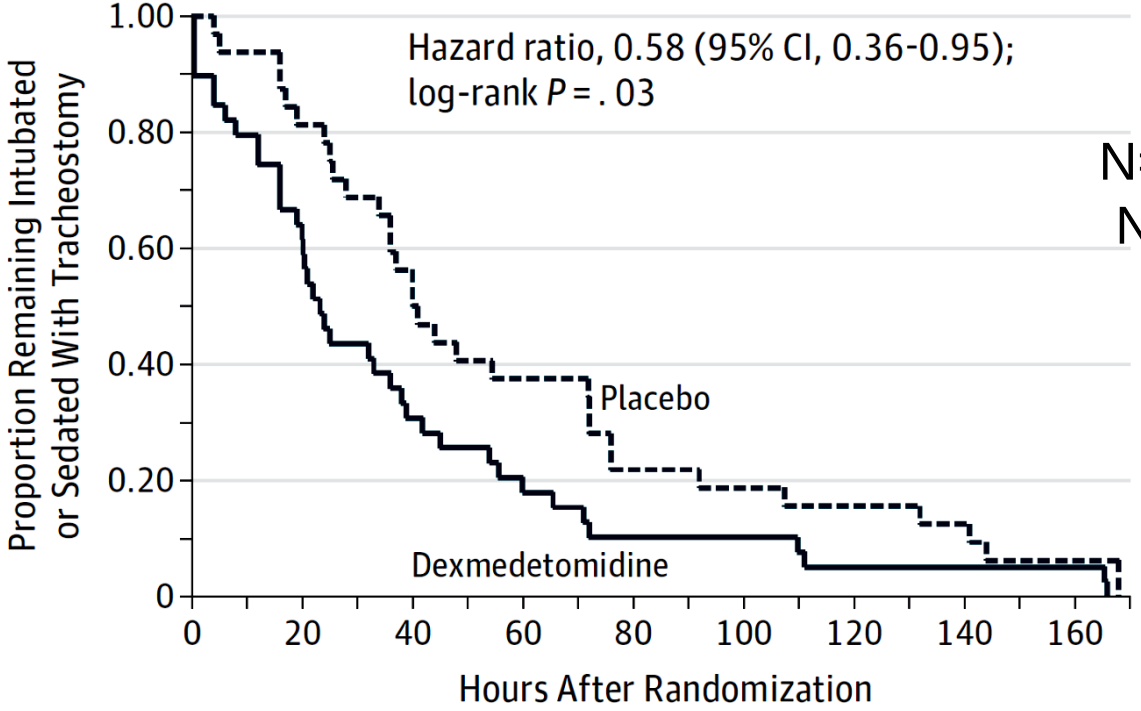
42 pazienti (età media 84) con delirium in ospedale per acuti, randomizzati a quetiapina (dose media 40 mg – start 25 mg, max 175 mg). Outcome: velocità di riduzione di DRS-R-98.



	Rate difference between quetiapine and placebo (S.E., *P* value)
DRS-R-98 Severity	0.827 (0.371, *P*=.026)
DRS-R-98 Total	0.55 (0.285, *P*=.054)
DRS-R-98 Cognitive	0.572 (0.443, *P*=.197)
DRS-R-98 Non-cognitive	0.577 (0.292, *P*=.048)

Tahir TA er al., J Psychosom Res, 2010

Dexmedetomidina vs. placebo nel paziente intubato con delirium ipercinetico



N=71 (Australia e Nuova Zelanda)

No. at risk				
Dexmedetomidine	39	10	4	2
Placebo	32	13	6	2

Reade MC et al., JAMA, 2016

Dolore, oppioidi e delirium (1)

Il trattamento inadeguato è un fattore di rischio

N=541 anziani con frattura di femore (55% con deficit cognitivo, 21% con dolore grave)→ incidenza di delirium 16%.

Predittori di delirium:

Risk Factor	Adjusted RR (95% CI)	*p* Value
Age (y)	1.0 (0.97–1.0)	.8
Women	0.6 (0.3–1.1)	.08
Residence in a nursing home	1.3 (0.6–2.8)	.5
Cognitive impairment	3.6 (1.8–7.2)	<.001
FIM score 68–88*	1.0 (0.5–1.9)	.98
FIM score 89–91	.7 (0.3–1.5)	.4
RAND score 2–3†	1.2 (0.6–2.3)‡	.5
RAND score 4–15†	1.1 (0.6–2.4)‡	.7
Abnormal BP on admission	2.3 (1.2–4.7)	.01
Abnormal heart rhythm on admission	1.7 (0.6–4.9)	.3
Chest pain on admission	1.9 (0.5–8.2)	.4
Heart failure on admission	2.9 (1.6–5.3)	.001
Medical complication	0.6 (0.2–1.4)	.2
Parenteral morphine sulfate equivalents/d‡		
10–30 mg	1.4 (0.6–3.3)	.4
<10 mg	5.4 (2.4–12.3)	<.001
Received meperidine	2.4 (1.3–4.5)	.004

Notes: RR = relative risk (for postadmission delirium); CI = confidence interval; FIM = Functional Independence Measure; BP = blood pressure.

Fattori di rischio di delirium:

- Dosaggio inadeguato di morfina
- Uso di meperidina
- Dolore grave (nei pazienti cognitivamente integri)

Morrison RS et al., J Gerontol A Med Sci, 2003

Dolore, oppioidi e delirium (2)

Il trattamento adeguato è sicuro ed efficace

- N=236 anziani con frattura di femore (28% con demenza, 12% con dolore grave) → incidenza di delirium 25%.
- Analgesia adeguata (target pain score <3/10, pain score medio 2.4): l'incidenza di delirium NON si associa a uso/dose di oppioidi né al dolore
- I pazienti con demenza hanno più delirium, riferiscono meno dolore e sono trattati con un dosaggio inferiore di oppioidi

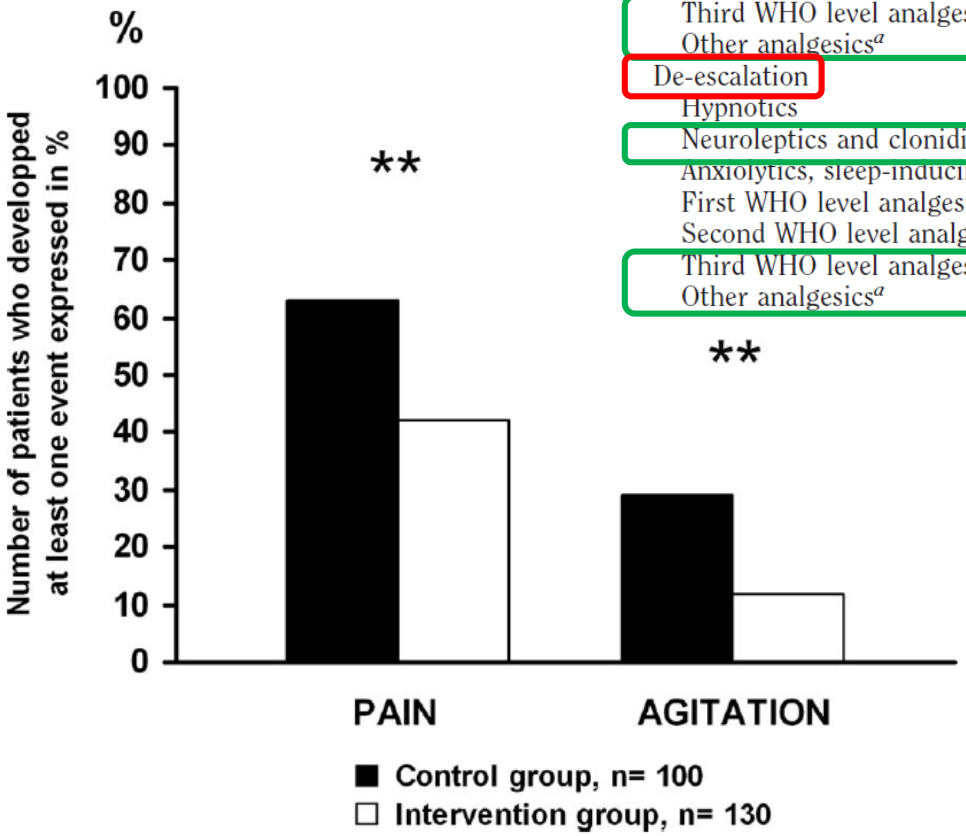
Il timore del delirium post-operatorio non deve impedire l'utilizzo di una dose di oppiodi sufficiente a conseguire un controllo adeguato del dolore.

Sieber FE et al., J Am Geriatr Soc, 2011

Effetti di valutazione sistematica di dolore e agitazione in Terapia Intensiva

Studio prima-dopo (N=230)

No. of Therapeutic Changes per Day of Stay in ICU for Ten Treated Patients	Control Group	Intervention Group	*p* Value
Escalation			
Hypnotics	5.0 (3.3–8.3)	5.0 (2.5–7.6)	.54
Neuroleptics and clonidine	1.1 (0.5–2.0)	1.7 (1.1–4.3)	.02
Anxiolytics, sleep-inducing drugs, and hydroxyzine	2.2 (1.3–4.4)	2.3 (1.4–4.0)	.76
First WHO level analgesics	3.3 (2.1–5.0)	3.7 (2.0–6.1)	.45
Second WHO level analgesics	1.6 (0.9–3.0)	2.2 (1.2–3.6)	.18
Third WHO level analgesics	1.2 (0.5–2.5)	2.2 (1.1–5.9)	.02
Other analgesics[a]	1.0 (0.6–1.8)	2.0 (1.2–3.8)	.002
De-escalation			
Hypnotics	2.0 (1.3–3.3)	2.5 (1.4–5.0)	.12
Neuroleptics and clonidine	0.8 (0.3–1.6)	1.6 (0.8–3.0)	.04
Anxiolytics, sleep-inducing drugs, and hydroxizine	1.0 (0.6–2.0)	1.2 (0.7–2.0)	.54
First WHO level analgesics	1.2 (0.8–2.3)	2.0 (1.1–2.8)	.11
Second WHO level analgesics	1.5 (0.7–2.0)	1.4 (0.9–2.0)	.87
Third WHO level analgesics	0.5 (0.2–0.9)	1.1 (0.9–1.9)	.06
Other analgesics[a]	0.3 (0.2–1.0)	1.7 (1.0–2.5)	<.0001



Monitoraggio e aggiustamento dei farmaci come intervento terapeutico

Chanques G et al., Crit Care Med, 2006

Rischio di delirium: oppioidi a confronto

References	Agent	Control group	Administration	Dose	Timing and duration	Type of analysis	Result OR/HR/RR (95% CI)
Adunsky [23]	Meperidine	Morphine	Intramuscular	Single 62.4 ± 13.2 mg	Perioperative	Multivariate	OR 2.5 (1.15–4.17)[a]
Adunsky [23]	Morphine	Meperidine	Intramuscular. Sublingual	Single 4.4 ± 1.8 mg morphine sulfate. Single 15 mg morphine immediate release	Perioperative	Multivariate	OR 1.3 (0.82–5.81)[a]
Brouquet [20]	Tramadol	No tramadol	Intravenous	Daily dose of 300 mg	First 3 days postoperative	Multivariate	HR 7.1 (2.2–22.5)[b]
Marcantonio [7]	Meperidine	No opioid	Epidural or PCA	Unclear	24 h before delirium developed	Univariate	OR 2.7 (1.3–5.5)
Marcantonio [7]	Morphine	No opioid	Epidural or PCA	Unclear	24 h before delirium developed	Univariate	OR 1.2 (0.6–2.4)
Marcantonio [7]	Fentanyl	No opioid	Epidural or PCA	Unclear	24 h before delirium developed	Univariate	OR 1.5 (0.6–4.2)
Marcantonio [7]	Oxycodone	No opioid	Epidural or PCA	Unclear	24 h before delirium developed	Univariate	OR 0.7 (0.3–1.6)
Marcantonio [7]	Codeine	No opioid	Epidural or PCA	Unclear	24 h before delirium developed	Univariate	OR 1.1 (0.4–3.6)
Morrison [9]	Meperidine	No meperidine	Unknown	Unclear	Postoperative days 1–3/ within 24 h of a delirious episode	Multivariate	RR 2.4 (1.3–4.5). Cognitively intact patients: RR 2.6 (0.4–15.8)
Nandi [21]	Hydromorphone	Other opioid	Unknown	Unclear	Intra- and postoperative	Multivariate	OR 0.30 (0.14–0.65)[d]
Nandi [21]	Oxycodone	Other opioid	Unknown	Unclear. Controlled release	Intra- and postoperative	Multivariate	OR 0.13 (0.01–1.41)[d]
Nandi [21]	Morphine	Other opioid	Unknown	Unclear. Sustained release	Intra- and postoperative	Multivariate	OR 2.32 (0.03–1.97)[d]
Nandi [21]	Hydrocodone-APAP	Other opioid	Unknown	Unclear	Intra- and postoperative	Multivariate	OR 1.94 (0.61–6.22)[d]
Nandi [21]	Tramadol	Other opioid	Unknown	Unclear	Intra- and postoperative	Multivariate	OR 0.34 (0.04–2.68)[d]
Shiiba [22]	Fentanyl	Morphine	PCA	Unclear	Postoperative	Multivariate	OR 0.22 (0.07–0.69)[e]

Meperidina >morfina

Tramadolo >no oppioidi

Meperidina >no oppioidi

Meperidina >no oppioidi

Swart L; et al., Drugs Aging, 2017

Table 4. High-Risk Drugs in Delirium and Potential Substitutes.*

Drug	Mechanism of Adverse Effect	Substitutes or Alternative Strategies	Comments
Benzodiazepines	CNS sedation and withdrawal	Nonpharmacologic sleep protocol[36]	Associated with delirium in hospitalized patients; if patient is already taking, maintain or lower dose, but do not discontinue abruptly
Opioid analgesics (especially meperidine)	Anticholinergic toxicity, CNS sedation, and fecal impaction	Local and regional analgesic measures; nonpsychoactive pain medications (e.g., acetaminophen and NSAIDs) around the clock; reserve opioids for breakthrough and severe pain	Consider risks versus benefits, since uncontrolled pain can also cause delirium; patients with renal insufficiency are at elevated risk for adverse effects; naloxone can be used for severe overdoses
Nonbenzodiazepine sedative hypnotics (e.g., zolpidem)	CNS sedation and withdrawal	Nonpharmacologic sleep protocol[36]	Like other sedatives, these agents can cause delirium
Antihistamines, especially first-generation sedating agents (e.g., doxylamine and diphenhydramine)	Anticholinergic toxicity	Nonpharmacologic sleep protocol,[36] pseudoephedrine for upper respiratory congestion, and nonsedating antihistamines for allergies	Patients should be asked about the use of over-the-counter medications; many patients do not realize that drugs with names ending in "PM" contain diphenhydramine or other sedating antihistamines
Alcohol	CNS sedation and withdrawal	If patient has a history of heavy intake, monitor closely and use benzodiazepines for withdrawal symptoms	The history taking must include questions about alcohol intake
Anticholinergics (e.g., oxybutynin and benztropine)	Anticholinergic toxicity	Lower the dose or use behavioral approaches for urinary incontinence (e.g., scheduled toileting)	Delirium is unusual at low doses
Anticonvulsants (e.g., primidone, phenobarbital, and phenytoin)	CNS sedation	Use an alternative agent or consider stopping if patient is at low risk for seizures and has no recent history of them	Delirium can occur despite therapeutic drug concentrations
Tricyclic antidepressants, especially tertiary amines (e.g., amitriptyline, imipramine, and doxepin)	Anticholinergic toxicity	Serotonin-reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and secondary amine tricyclics (e.g., nortriptyline and desipramine)	Newer agents (e.g., duloxetine) are as effective as tertiary amines for adjuvant treatment of chronic pain
Histamine H_2–receptor blockers	Anticholinergic toxicity	Lower the dose or substitute antacids or proton-pump inhibitors	Anticholinergic toxic effects occur primarily with high-dose intravenous infusions
Antiparkinsonian agents (e.g., levodopa and amantadine)	Dopaminergic toxicity	Lower the dose or adjust dosing schedule	Dopaminergic toxic effects occur primarily in advanced disease and at high doses
Antipsychotics, especially low-potency typical antipsychotics (e.g., chlorpromazine and thioridazine)	Anticholinergic toxicity as well as CNS sedation	Discontinue entirely or, if necessary, use low doses of high-potency agents	Carefully consider risks vs. benefits of use in delirium
Barbiturates	CNS sedation and severe withdrawal syndrome	Gradual discontinuation or benzodiazepine substitution	In most cases, barbiturates should not be prescribed; avoid inadvertent or abrupt discontinuation

* In older adults, the risks and benefits of all medications should be considered carefully. Adverse effects should be monitored whenever any medication is started or the dose is adjusted. CNS denotes central nervous system, and NSAIDs nonsteroidal antiinflammatory drugs.

Marcantonio ER, N Engl J Med, 2017

JAMA Internal Medicine | Original Investigation

Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care
A Randomized Clinical Trial

Meera R. Agar, PhD; Peter G. Lawlor, MB; Stephen Quinn, PhD; Brian Draper, MD; Gideon A. Caplan, MBBS; Debra Rowett, BPharm; Christine Sanderson, MPH; Janet Hardy, MD; Brian Le, MBBS; Simon Eckermann, PhD; Nicola McCaffrey, PhD; Linda Devilee, MBus; Belinda Fazekas, BN; Mark Hill, PhD; David C Currow, PhD

2017

- **Outcome primario**: gravità dei **sintomi di delirium fonte di sofferenza nell'arco di 72 ore** (comportamenti inappropriati, comunicazione inappropriata, allucinazioni)
- N=249 pazienti con delirium in cure palliative (cancro 90%, età media 75)
- Non viene valutata la remissione delirium
- Dose raggiunta: 1,75 mg die <65 anni, 0,75 mg die 65+ anni. Utilizzo di midazolam in aperto più frequente con gli antipsicotici che con placebo (34% vs. 17%)!

JAMA Internal Medicine | Original Investigation

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2017

Antipsychotic drugs **should not be added** to manage specific symptoms of delirium that are known to be associated with distress in patients receiving palliative care who have mild to moderately severe delirium. Rather, management relies on ensuring systematic screening reversing the precipitants of delirium, and providing supportive interventions.

Dose troppo bassa?? O realmente inefficaci (effetto di classe!) nel paziente con neoplasia avanzata?

JAMA | Preliminary Communication

Effect of Lorazepam With Haloperidol vs Haloperidol Alone on Agitated Delirium in Patients With Advanced Cancer Receiving Palliative Care

A Randomized Clinical Trial

2017

David Hui, MD, MSc; Susan Frisbee-Hume, MS; Annie Wilson, MSN; Seyedeh S. Dibaj, PhD; Thuc Nguyen, RN; Maxine De La Cruz, MD; Paul Walker, MD; Donna S. Zhukovsky, MD; Marvin Delgado-Guay, MD; Marieberta Vidal, MD; Daniel Epner, MD; Akhila Reddy, MD; Kimerson Tanco, MD; Janet Williams, MPH; Stacy Hall, MSN; Diane Liu, MSc; Kenneth Hess, PhD; Sapna Amin, PharmD; William Breitbart, MD; Eduardo Bruera, MD

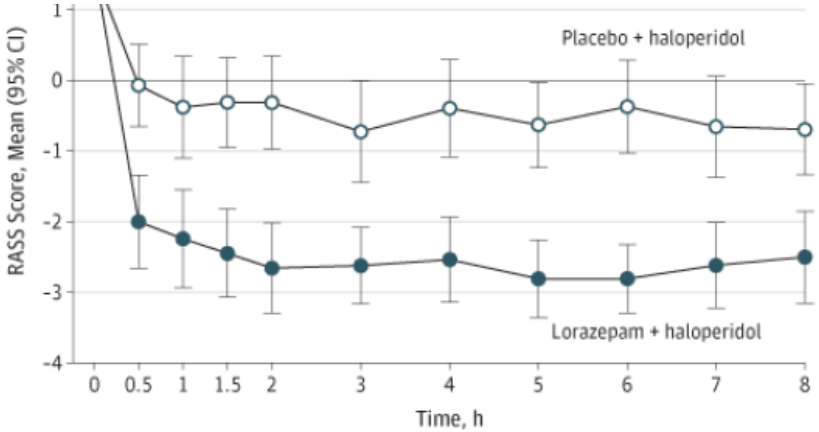
- **Outcome primario**: agitazione (punteggio RASS) dopo 8 ore
- N=93 (età media 65), 100% pazienti con cancro e delirium iperattivo (RASS 2+)
- Dose: aloperidolo 2 mg vs. aloperidolo 2 mg + lorazepam 3 mg
- No differenza significativa nella gravità del delirium

JAMA | Preliminary Communication

Effect of Lorazepam With Haloperidol vs Haloperidol Alone on Agitated Delirium in Patients With Advanced Cancer Receiving Palliative Care

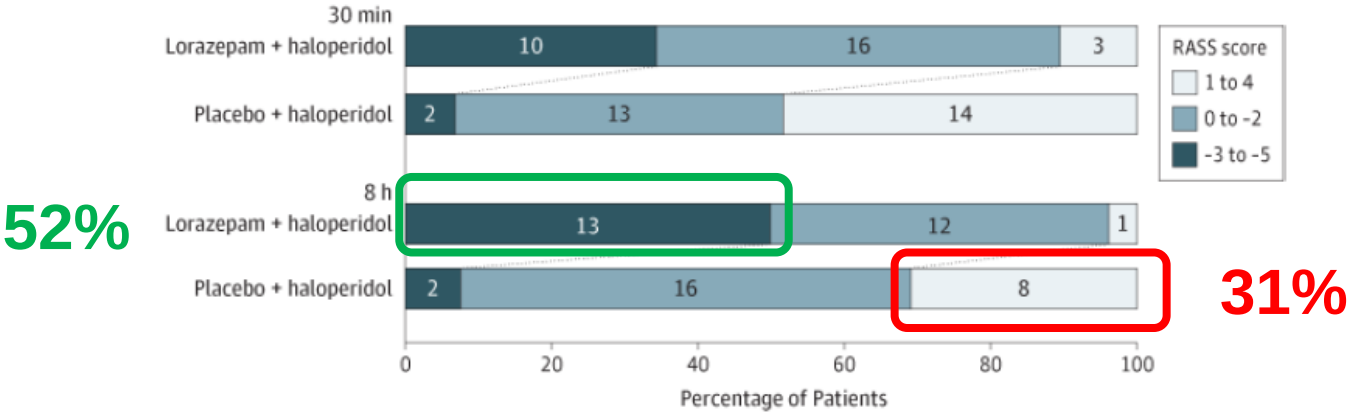
A Randomized Clinical Trial

2017



No. of patients											
Lorazepam + haloperidol	29	29	29	29	29	29	28	26	26	26	26
Placebo + haloperidol	29	29	29	29	29	29	28	27	27	26	26

B Distribution of RASS scores at 30 min and 8 h



PLOS | ONE

RESEARCH ARTICLE

Efficacy of Non-Pharmacological Interventions to Prevent and Treat Delirium in Older Patients: A Systematic Overview. The SENATOR project ONTOP Series

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I (pochi) trial di intervento disponibili (1)

Study	Type of study	Population	Intervention	Outcome	Study period	Setting	Funding
Cole 1994 [79]	Randomized trial	88 pts with delirium; mean age 85, male 58%	Consultation by geriatrician or psychiatrist and follow up by a liaison nurse.	Cognitive function (SPMSQ), behavior, mortality rate, length of stay, discharge	8 weeks	Medical ward	Not reported
Cole 2002 [78]	Randomized trial	227 older patients with delirium admitted to a general medical service; mean age: 82; male 54%.	Consultation by a geriatric internist or psychiatrist and follow up by a liaison nurse. Nursing intervention protocol, Environment, Orientation, Familiarity, Communication, counteraction of immobilization	Primary outcomes: improvement of cognitive status. Secondary outcomes: severity of delirium; length of stay; functional status; death.	8 weeks	Medical ward	Not reported
Pitkala 2006 [80]	Randomized trial	174 pts with delirium, age 83, male 25%	Comprehensive geriatric assessment and treatments, Avoiding conventional neuroleptics, Orientation, Physiotherapy, Geriatric interventions (nutrition, hip protection), Comprehensive discharge planning	Primary: mortality or permanent institution, secondary: length of stay, cognitive function, delirium intensity	From September 2001 to November 2002	Medical ward	Not reported
Lundstrom 2005[81]	Randomized trial	125 pts with delirium, mean age 81, male 44%.	Multifactorial intervention program (Course in Geriatric Medicine Focusing on Delirium Training Concerning Caregiver-Patient Interaction, Reorganization of Nursing Care, Guidance for Nursing Staff)	Duration of delirium (diagnosis with DSM-IV), mortality, length of stay	8 months	Medical ward	Not reported

Benefici modesti o assenti

Possibile beneficio sulla durata dei sintomi

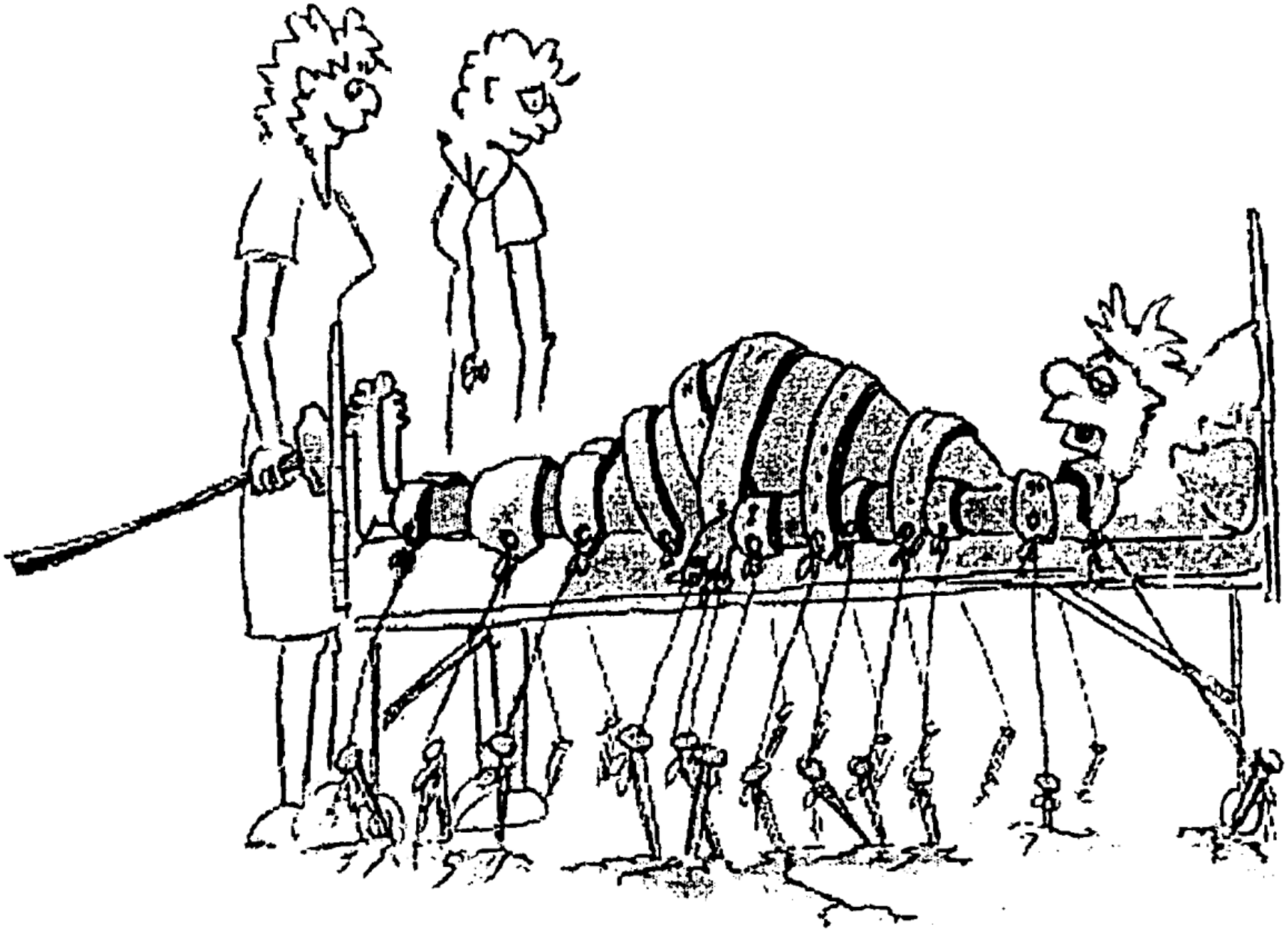
DSI, Delirium Symptom Interview; CAM, Confusion Assessment Method; MDAS, the Memorial Delirium Assessment Scale; MMS, Mini-Mental State Examination; SPMSQ, Short Portable Mental Status Questionnaire

Abraha I et l., Plos One, 2015

I (pochi) trial di intervento disponibili (2)

- Notevoli limiti metodologici (scarsa numerosità; outcome disomogenei – no metaanalisi; randomizzazione non chiara in Lundstrom)
- Forse si riduce la durata del delirium (Lundstrom, 2005; Pitkala, 2006), dati opposti sulla durata della degenza (gruppo intervento: Lundstrom 9 giorni, Pitkala 52!)
- Notevole diversità dei campioni: buon livello cognitivo-funzionale basale in Lundstrom (demenza 5%, MMSE 25), basso in Pitkala (demenza 30%, MMSE 14) → prognosi complessivamente buona in Lundstrom, bassa in Pitkala
- Nessuna evidenza solida su outcome «forti»

Abraha I et l., Plos One, 2015



Ehi! Credo si sia mosso! Aggiungine un altro!

Delirium e utilizzo di contenzioni

In Ospedale per acuti (Delirium Day 2015)

	Delirium (*N* = 429, 22.9 %)	No delirium (*N* = 1438, 77.1 %)	*p* value
Feeding tubes (NT or PEG), *n* (%)	20 (4.7)	20 (1.4)	< .001
Venous catheter, *n* (%)	244 (56.9)	694 (42.0)	< .001
Urinary catheter, *n* (%)	199 (46.4)	340 (23.6)	< .001
Physical restraints, *n* (%)	268 (62.5)	427 (29.7)	< .001

Bellelli G et al., BMC Medicine, 2016

In Terapia Intensiva

Variable	CAM-ICU+ (n = 44)		CAM-ICU− (n = 22)		Comatose (n = 27)		*p* Value
Patients requiring physical restraints, no. (%)	34	(77.3)	11	(50.0)	12	(44.4)	.010[a,c]
Duration of physical restraints, days	3	(2–4.75)	1	(1–3)	2	(1–4.25)	.037[a]

Micek ST et al., Crit Care Med, 2005

In RSA (Delirium Day 2015)

Patient characteristics	Delirium (*n* = 535, 36.8%)	No delirium (*n* = 919, 63.2%)	*p* value
Tracheotomy	0 (0)	2 (0.2)	0.280
Nasogastric tubes or PEG	7 (1.3)	4 (0.4)	0.064
Urinary catheter	35 (6.5)	28 (3.0)	0.002
Physical restraints	134 (25.0)	62 (6.7)	<0.001

Morichi V et al., Dementia Geriatr Cogn Disord, 2018

Mediatori di mortalità in corso di delirium incidente in ospedale: il ruolo delle contenzioni

N=469 soggetti (età media 80) in reparto medico per acuti

Risk Factor	HR for Delirium (95% CI)	HR for Adverse Hospital Exposure (95% CI)	Percent Change in Parameter Estimate of Delirium
Delirium only	4.2 (2.8–6.3)		
Restraining devices			
Physical restraints	4.0 (2.6–6.1)	1.2 (0.8–1.8)	3.6%
Urinary catheter use	4.2 (2.8–6.3)	1.5 (1.0–2.2)	0.3%
Any restraining device	3.9 (2.5–5.9)	1.4 (1.0–2.0)	5.6%
Hospital-acquired conditions (HACs)			
Fall	3.7 (2.5–5.7)	2.6 (1.7–3.9)	8.0%
Pressure ulcer	3.7 (2.4–5.7)	1.6 (1.1–2.3)	8.9%
Any HAC	3.9 (2.5–5.9)	1.3 (0.9–1.9)	5.6%
Other noxious insults			
Sleep deprivation	4.2 (2.8–6.3)	2.5 (1.8–3.5)	0.3%
Acute malnutrition	3.3 (2.1–5.0)	2.8 (2.0–3.9)	17.5%
Dehydration	4.2 (2.8–6.4)	0.3 (0.1–1.1)	−0.7%
Aspiration pneumonia	3.6 (2.4–5.5)	6.4 (4.2–9.7)	9.9%
Any noxious insult	3.9 (2.6–5.9)	2.3 (1.6–3.3)	4.9%

Dharmarajan K et al., J Am Geriatr Soc, 2017

Early Pharmacological Treatment of Delirium May Reduce Physical Restraint Use: A Retrospective Study

Annals of Pharmacotherapy
2014, Vol. 48(3) 328–334
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DOI: 10.1177/1060028013513559
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Christopher J. Michaud, PharmD[1], Wendy L. Thomas, PharmD[1], and Karen J. McAllen, PharmD, FCCM[1]

Antipsychotics for treatment of delirium in hospitalised non-ICU patients (Review)

2018

Burry L, Mehta S, Perreault MM, Luxenberg JS, Siddiqi N, Hutton B, Fergusson DA, Bell C, Rose L

No trial reported on hospital length of stay, hospital discharge disposition, health-related quality of life, or physical restraint use,

Come usare i farmaci (se dobbiamo usarli)

- Nel trattamento di pazienti con agitazione grave:
  - se il delirium rischia di interrompere un trattamento essenziale (es. intubazione orotracheale)
  - se mette a rischio se stesso o gli altri
  - se è fonte di sofferenza
- Iniziare con un solo farmaco (minori potenzialità di eventi avversi) e con bassa dose
- Scelta di un farmaco a bassa attività anticolinergica
- Titolare rapidamente la dose fino al raggiungimento di quella efficace
- Proseguire il trattamento 2-3 giorni alla dose efficace
- Continuare gli interventi non farmacologici

Modificato da Inouye, N Engl J Med, 2006

Terapia farmacologica (1)

1. **Aloperidolo:** farmaco di riferimento (ma no studi vs pbo)
   - dosaggio iniziale: **0,5-1 mg da ripetere al bisogno dopo 30 minuti**
   - mantenimento: **0,5-1 mg 1-3 volte al dì**

- ✓ Elevato rischio di parkinsonismo (dipendente da dose, particolarmente se durata della terapia > 7 giorni)
- ✓ Rara ma grave sindrome maligna da neurolettici
- ✓ Controindicato nel cardiopatico instabile, somministrazione e.v. *off-label* per maggior rischio di tossicità cardiaca (allungamento del tratto QTc → lieve ma significativo aumento del rischio di torsioni di punta ed arresto cardiaco)

Terapia farmacologica (2)

2. **Antipsicotici atipici** – efficacia paragonabile ad aloperidolo con < effetti collaterali extrapiramidali; maggior costo
   - **Quetiapina: 12,5-50 mg due volte al dì**
     [l'unico consentito se c'è parkinsonismo]
   - **Risperidone: 0,5-1 mg due volte al dì**
   - **Olanzapina: 2,5-10 mg die**
     (anche s.l. e i.m.)

Oh ES et al., JAMA, 2017

Trazodone: 10-50 mg? *(anche e.v.)*
No evidence! (Ma ben tollerato…)

Terapia farmacologica (3)

3. **Benzodiazepine a breve-media emivita (lorazepam, midazolam)**

   Utilizzabili come seconda scelta quando gli antipsicotici non funzionano o quando prevale la componente ansiosa

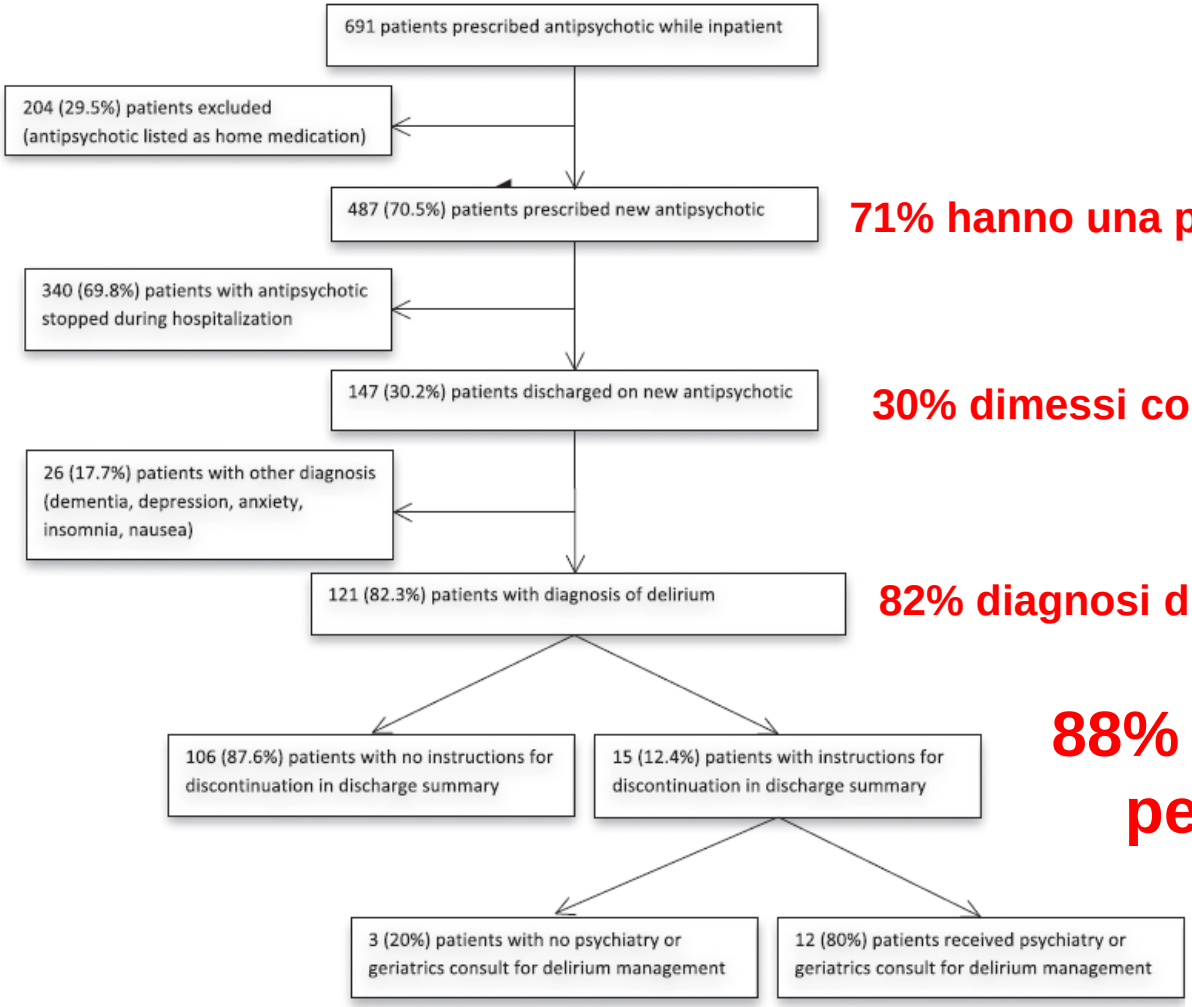
   Lorazepam 0,5-1 mg i.m. o p.o.

   Midazolam 1-2 mg i.m. o e.v. (sedazione rapida, brevissima emivita): necessità di monitorizzare il paziente (rischio di depressione respiratoria).

   Caratteristiche:

   – rapida insorgenza d'azione
   – rischio di effetto paradosso nell'anziano
   – Indicata per Delirium secondario ad astinenza da alcool o benzodiazepine o barbiturici
   – Sconsigliate le BDZ a lunga emivita (no diazepam!)

Ma sospendere alla dimissione (o pochi giorni dopo)!



71% hanno una prima prescrizione in ospedale

30% dimessi con un nuovo antipsicotico

82% diagnosi di delirium

88% nessuna istruzione per la sospensione

Lo faremmo per un antibiotico?....

Johnson KG et al., J Am Geriatr Soc, 2017

Perché usare i farmaci?

- ✖ Non per guarire il delirium, ma per ridurre l'agitazione fonte di sofferenza e pericolo
- ✓ Perché talora c'è bisogno di un «provare» un sintomatico, malgrado l'incertezza delle evidenze
- ✓ Perché, nel bene e nel male, i farmaci influenzano (molto) lo stato mentale degli anziani
- ✓ Perché l'efficacia delle terapie di supporto non farmacologico è limitata dopo che il delirium si è manifestato
- ✓ Perché le contenzioni sono peggio!