Società Medico Chirurgica di Ferrara dal 1846

Deficit sensoriali e disturbi cognitivi

Delirium e disturbi cognitivi

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Università di Ferrara
- ex labore fructus -

Sommario: 6 domande

1. Che cosa è il delirium?
2. Chi è a rischio ?
3. Perché insorge?
4. Quali sono le conseguenze?
5. Se e come prevenirlo?
6. Quando insorto come trattarlo?

Delirium (Stato Confusionale acuto)

- E'una sindrome neuropsichiatrica, caratterizzata da disattenzione, alterazioni dello stato di coscienza e altri deficit cognitivi, ad insorgenza acuta ed andamento fluttuante
- E' un disturbo neurocognitivo complesso, conseguenza di un disturbo organico (a distanza) sottostante

- Si distinguono tre categorie di delirium:
  - Iperattiva (circa 25%)
  - Ipoattiva (circa 50%)
  - Mista (circa 25%)

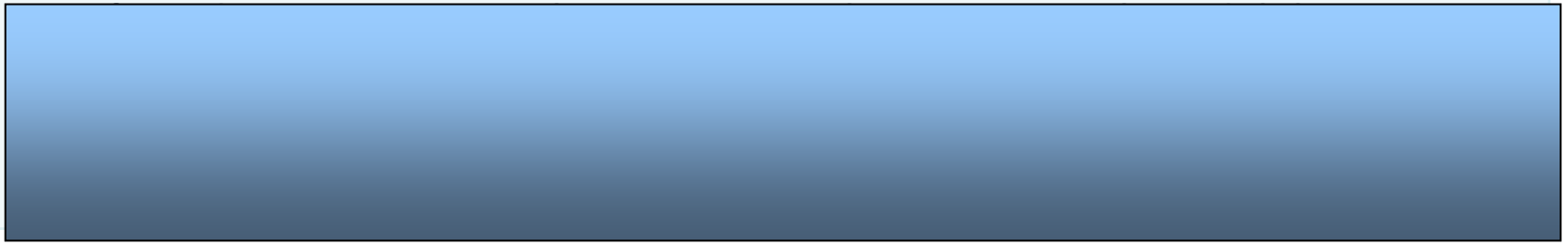
Delirium: criteri del DSM-5

A. Disturbo dell'attenzione (i.e., ridotta capacità a dirigere, focalizzare, sostenere e shiftare l'attenzione) e consapevolezza (ridotto orientamento del sé nell'ambiente).

B. Il deficit si sviluppa in un periodo di tempo relativamente breve (generalmente ore o pochi giorni), rappresenta un cambiamento dai livelli di attenzione e consapevolezza di base, e tende a fluttuare in gravità nel corso della giornata.

C. É presente un altro deficit cognitivo (es, memoria, disorientamento, linguaggio, abilità visuospaziali, o dispercezioni).

D. I deficit di cui ai criteri A e C non sono spiegabili sulla base di un preesistente (stazionario o in evoluzione) disturbo neurocognitivo e non si verificano in un contesto di grave riduzione dei livelli di arousal (es coma)



Il delirium è presente se tutti e 5 i criteri sono soddisfatti

Delirium sub-sindromico

Condizione clinica in cui i pazienti presentano uno o più sintomi del delirium ma non soddisfano tutti i criteri per la diagnosi di delirium.

Si verifica nel 21-76% dei pazienti anziani ospedalizzati

Tali sintomi possono precedere o seguire un episodio di delirium o possono non evolvere mai verso un quadro conclamato.

I pazienti con delirium subsindromico presentano:

- maggiore durata di ospedalizzazione,
- aumentata mortalità post-dimissione e
- peggiore performance cognitivo-funzionale al follow-up

Diagnosi: CAM
Confusion Assessment Method

1. Insorgenza acuta e andamento fluttuante
Dato acquisito di solito da un familiare: c'è stato un cambiamento acuto nello stato mentale del paziente rispetto alla sua situazione di base? Il comportamento anormale varia durante la giornata, per esempio va e viene o si modifica di intensità? *0= no* ***1=sì***

2. Perdita dell'attenzione
Il paziente presenta difficoltà nel concentrare la sua attenzione, per esempio è facilmente distraibile, non riesce a mantenere il filo del discorso ecc.? *0= no* ***1=sì***

3. Disorganizzazione del pensiero
Il pensiero del paziente è disorganizzato e incoerente, passa da un argomento all'altro senza filo logico, in modo imprevedibile?
0= no ***1=sì***

4. Alterato livello di coscienza
0= vigile
1= iperallerta, letargia, stupor, coma

La diagnosi di delirium richiede la presenza di 1, 2 ed alternativamente 3 o 4.

Sensibilità 94-100% e specificità 90-95% in setting medici e chirurgici

Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Inouye SK, et al. Ann Intern Med. 1990;113(12):941.

Epidemiologia

	Prevalence (%)*	Incidence (%)*	Outcomes (adjusted RR†)
Surgical			
Cardiac	..	11–46	Cognitive dysfunction 1·7; functional decline 1·9
Non-cardiac	..	13–50	Functional decline 2·1; cognitive dysfunction 1·6
Orthopaedic	17	12–51	Dementia or cognitive dysfunction 6·4–41·2; admission to institution 5·6
Medical			
General medical	18–35	11–14	Mortality 1·5–1·6; functional decline 1·5
Old age medicine	25	20–29	Falls 1·3; mortality 1·9; admission to institution 2·5
Intensive care	7–50	19–82	Mortality 1·4–13·0; longer length of stay 1·4–2·1; extended mechanical ventilation 8·6
Stroke	..	10–27	Mortality 2·0; any of increased length of stay, functional impairment, or death 2·1
Dementia	18	56	Cognitive decline 1·6–3·1; admission to an institution 9·3; mortality 5·4
Palliative care, cancer	..	47	..
Nursing home or postacute care	14	20–22	Mortality 4·9
Emergency department	8–17	..	Mortality 1·7

Inouye SK, Lancet 2014;383:911-22

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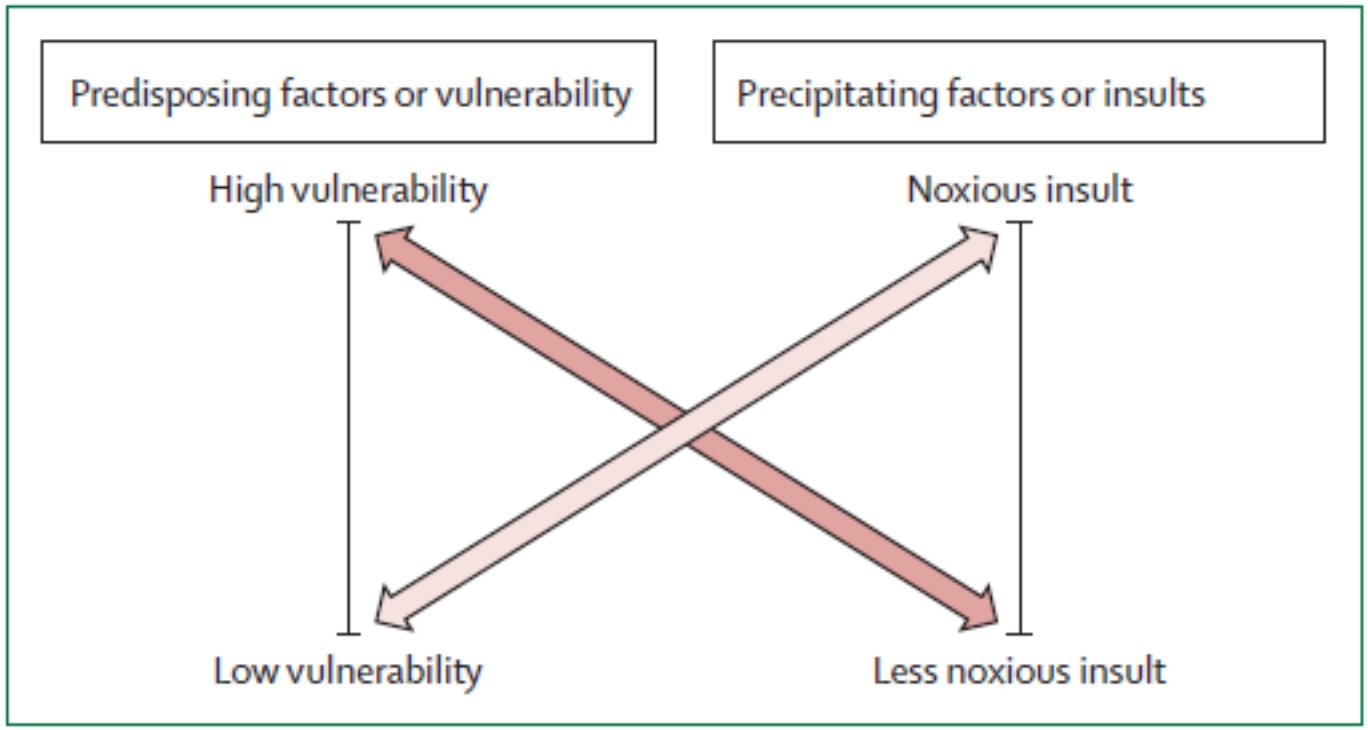
Patogenesi Multifattoriale

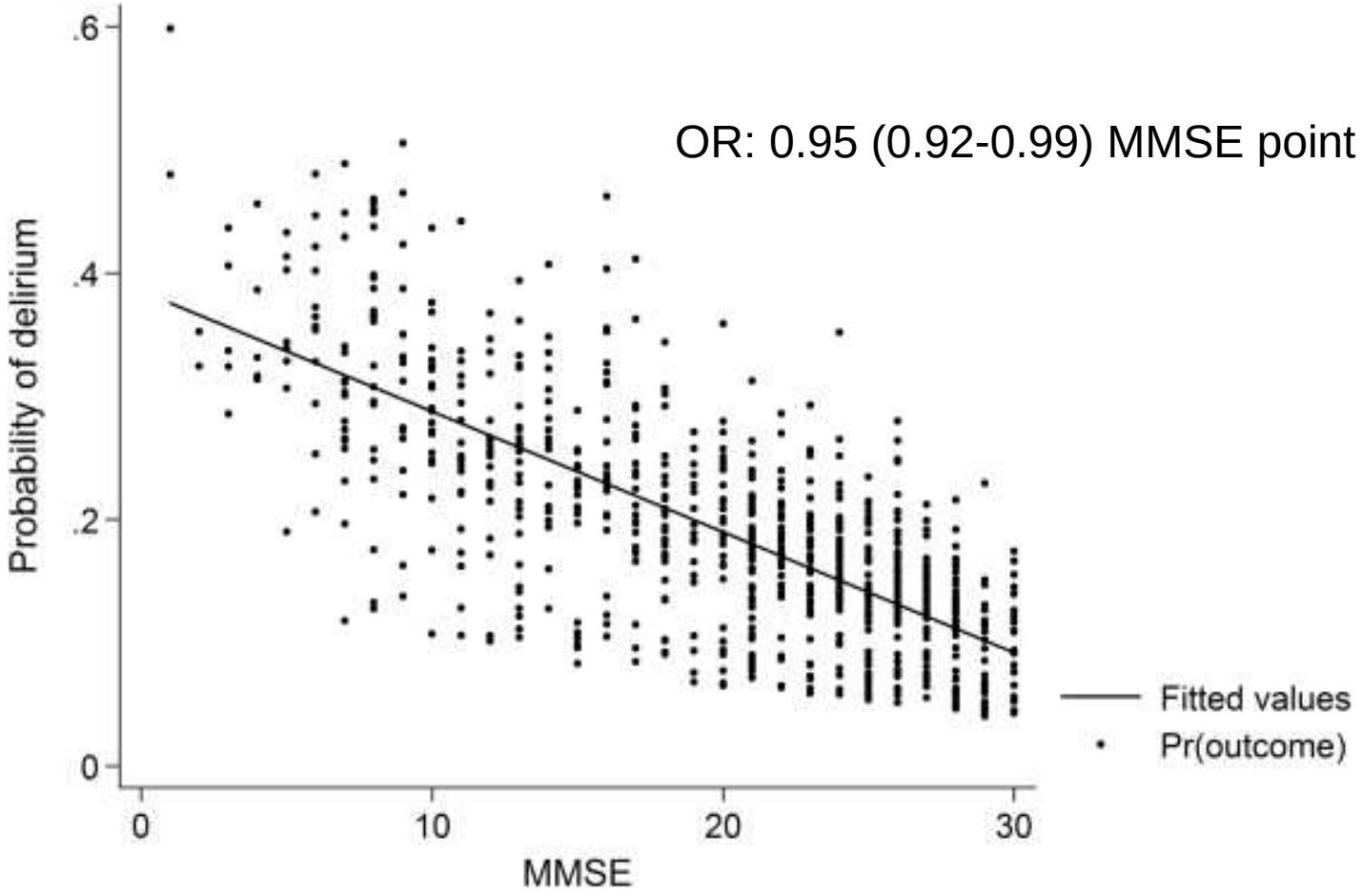


Fattori di rischio predisponenti

	General medicine	Surgery		Intensive-care unit
		Non-cardiac	Cardiac	
Predisposing factors	**Relative Risk**			
Dementia	2·3–4·7	2·8	..	..
Cognitive impairment	2·1–2·8	3·5–4·2	1·3	..
History of delirium	..	3·0	..	..
Functional impairment	4·0	2·5–3·5	..	..
Visual impairment	2·1–3·5	1·1–3·0	..	..
Hearing impairment	..	1·3	..	..
Comorbidity or severity of illness	1·3–5·6	4·3	..	1·1
Depression	3·2	..	1·2	..
History of transient ischaemia or stroke	..	..	1·6	..
Alcohol misuse	5·7	1·4–3·3	..	..
Older age (≥75 years)	4·0	3·3–6·6	..	1·1

Inouye SK, Lancet 2014;383:911-22

Worsening cognitive impairment progressively increase risk for incident delirium



Random effects logistic regression,
adjusting for age, sex, and co-morbidity

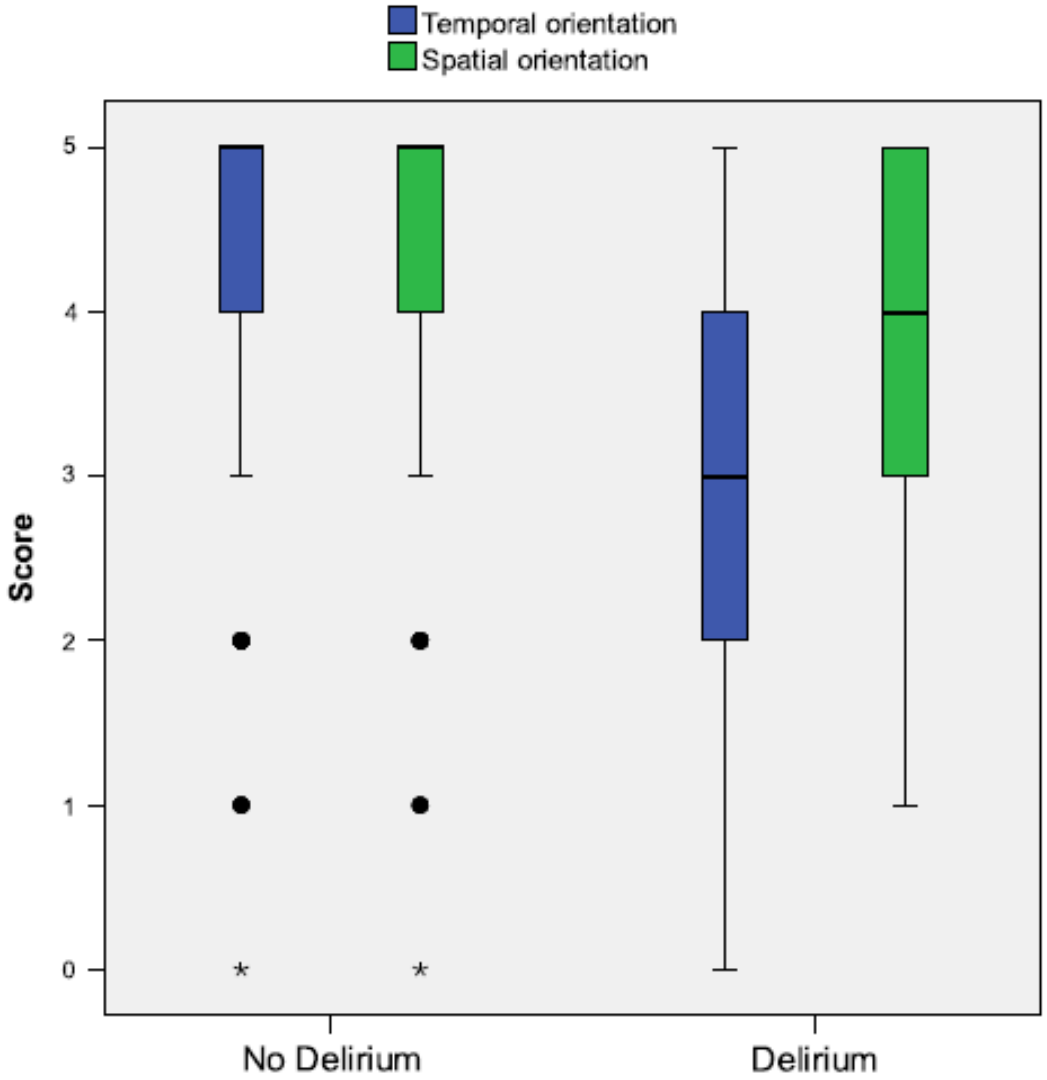
Davis DH et al, Am J Ger Psych 2014

MMSE items predicting incident delirium in older medical inpatients

MMSE cognitive function	Cutoff (Score range)	Sensitivity %	Specificity %	LR+	LR−
Temporal orientation	**< 5 (0–5)**	**82.3 (64.8–92.6)**	**55.2 (48.9–61.4)**	**1.8 (1.5–2.3)**	**0.3 (0.1–0.67**
Spatial orientation	**< 5 (0–5)**	**64.7 (46.5–79.7)**	**73.1 (67.2–78.4)**	**2.4 (1.7–3.3)**	**0.5 (0.3–0.8)**
Immediate recall	< 3 (0–3)	2.9 (0.1–17.0)	98.4 (95.8–99.5)	1.9 (0.2–16.4)	1 (0.9–1.1)
Attention/calculation	< 2 (0–5)	73.5 (55.3–86.5)	39.7 (33.7–46.0)	1.2 (1.0–1.5)	0.7 (0.4–1.2)
Delayed recall	< 2 (0–3)	47.1 (30.2–64.6)	66.9 (60.8–72.6)	1.4 (0.9–2.1)	0.8 (0.6–1.1)
Naming	< 2 (0–2)	2.9 (0.1–17)	97.7 (94.7–99.0)	1.3 (0.2–10.1)	1 (0.9–1.1)
Phrase repetition	< 1 (0–1)	11.8 (3.8–28.4)	89.9 (85.4–93.2)	1.2 (0.4–3.1)	1 (0.9–1–1)
Comprehension	< 3 (0–3)	44.1 (27.6–62.0)	75.1 (69.3–80.2)	**1.8 (1.1–2.7)**	0.7 (0.5–1.0)
Reading	< 1 (0–1)	29.4 (15.7–47.7)	82.4 (77.1–86.8)	1.7 (0.9–3.0)	0.9 (0.7–1.1)
Writing	< 1 (0–1)	64.7 (46.5–79.7)	57.0 (50.7–63.1)	**1.5 (1.1–2.0)**	0.6 (0.4–1)
Visuoconstructional ability	< 1 (0–1)	76.5 (58.4–88.6)	54.3 (48.0–60.5)	**1.7 (1.3–2.1)**	**0.4 (0.2–0.8)**
Cognitive impairment overall		55.9 (38.1–72.4)	75.5 (69.7–80.5)	**2.3 (1.6–3.3)**	**0.6 (0.4–0.9)**

Franco JG. Psychiatr. Research. 2014;220:975-981

MMSE items predicting incident delirium and hypoactive subtype in older medical inpatients



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Fattori di rischio precipitanti

	General medicine	Surgery		Intensive-care unit
		Non-cardiac	Cardiac	
Precipitating factors	**Relative Risk**			
Drugs				
Several drugs used	2·9	..	..	..
Psychoactive drugs	4·5	..	..	..
Sedatives or hypnotics	..	..	..	4·5
Use of physical restraints	3·2–4·4	..	..	..
Use of bladder catheter	2·4	..	..	..
Physiological				
Increased serum urea	5·1	..	..	1·1
Increased BUN:creatinine ratio	2·0	2·9	..	..
Abnormal serum albumin	..	..	1·4	..
Abnormal sodium, glucose, or potassium	..	3·4	..	..
Metabolic acidosis	..	..	..	1·4
Infection	..	..	..	3·1
Any iatrogenic event	1·9	..	..	..
Surgery				
Aortic aneurysm	..	8·3	..	..
Non-cardiac thoracic	..	3·5	..	..
Neurosurgery	..	..	..	4·5
Trauma admission	..	..	..	3·4
Urgent admission	..	..	..	1·5
Coma	..	..	..	1·8–21·3

Inouye SK, Lancet 2014;383:911-22

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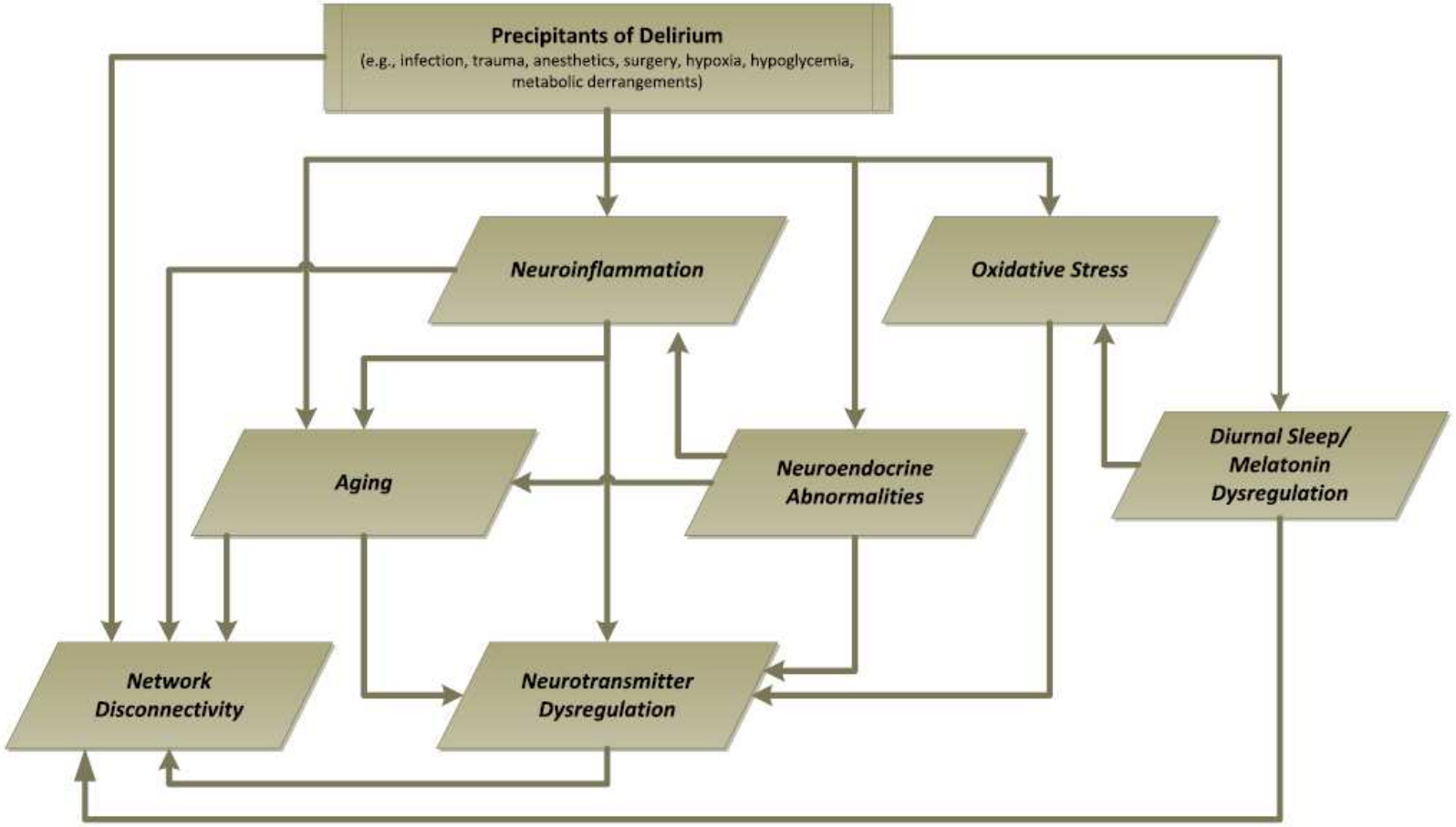
Fisiopatologia: sette ipotesi



Maldonado J. Am J Geriatr Psych 2013

Fisiopatologia

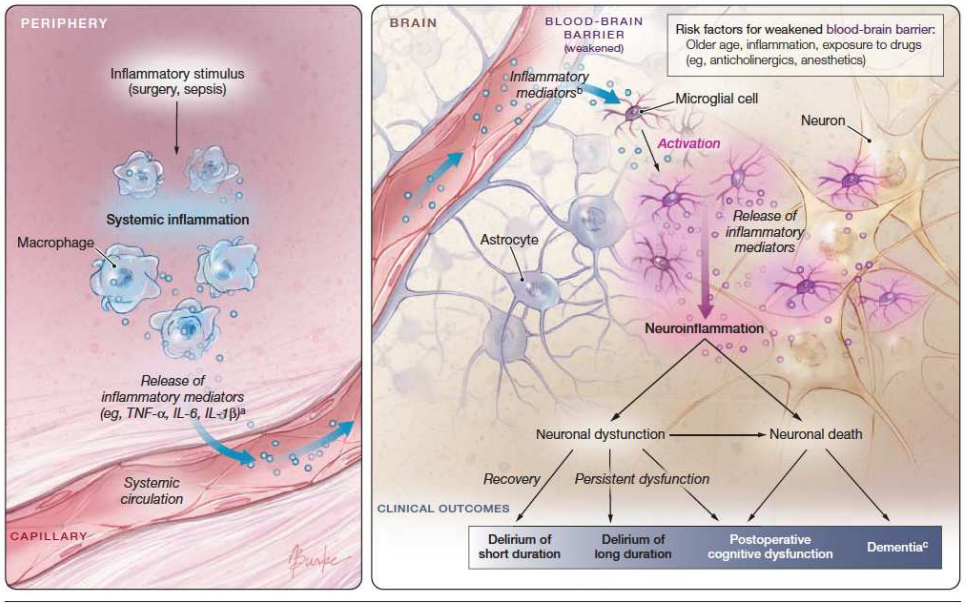
- Alterazione neurotrasmettitoriali
  - Acetilcolina (Ach): ↓ Ach, ↑ SAA (Serum Anticholinergic Activity), ↑ farmaci ad attività anticolinergica
  - Dopamina: ↑ dopa, squilibrio fra Ach e dopa (soprattutto nelle forme iperattive)
  - Serotonina: ↑ o ↓ causano deficit colinergico, ↑ stimola attività dopaminergica
  - Norepinefrina: ↑ causa soprattutto delirium iperattivo
  - Acido gamma-amino-butirrico (GABA) e glutammato: ↓ GABA (neurotrasmettitore inibitorio) e glutammato (suo precursore)

Tammy T, et al. J Gerontol A Biol Sci Med Sci. 2008; 63(7): 764–772
Gunther ML, et al. Crit Care Clin. 2008;24(1):45-65.

Fisiopatologia

- Processi infiammatori
  - Marker infiammatori: ↑ PCR incrementa rischio di delirium[1]
  - Citochine pro-infiammatorie (IL-1B, TNF-α, IL-6): stimolazione della microglia → risposta neurotossica → delirium[2]

Figure. Inflammatory Model of the Pathophysiology of Postoperative Delirium



[1]Macdonald A, et al. Age Aging. 2007;36:222-225.
[2]Cerejeira J, et al. Acta Neuropathol. 2010;119:737–754.

Fisiopatologia

- Altre cause
  - Cortisolo: iperattività dell'asse ipotalamo-ipofisi-surrene → cortisolo si lega a R per glucocorticoidi (presenti in alte concentrazioni nell'ippocampo) → morte cellulare → riduzione delle funzioni dell'ippocampo → delirium[1]
  - Ipossia cerebrale: ridotta ossigenazione cerebrale (patologie cardiache o polmonari, ipotensione, anemia…) → disfunzione cerebrale → maggiore suscettibilità allo sviluppo di delirium[2]
  - Farmaci (con attività anticolinergica, sedativi, analgesici…): ↓ Ach, ↑ dopamina e glutammato

[1]MacLullich AM, et al.Journal of Psychosomatic Research. 2008;65:229–238
[2]Croughwell ND, et al. Ann Thorac Surg. 1994;58:1702-8

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Conseguenze

REVIEW

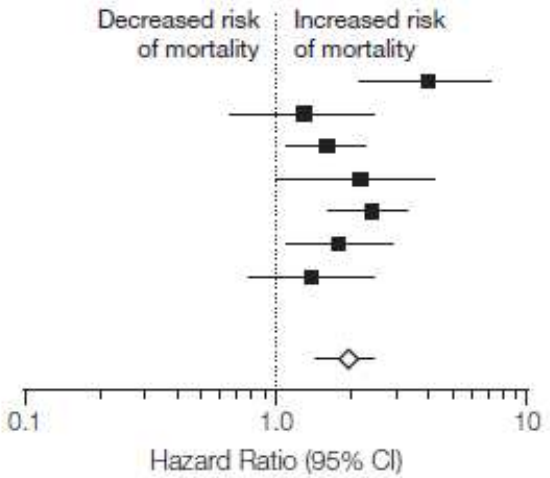
Delirium in Elderly Patients and the Risk of Postdischarge Mortality, Institutionalization, and Dementia

A Meta-analysis

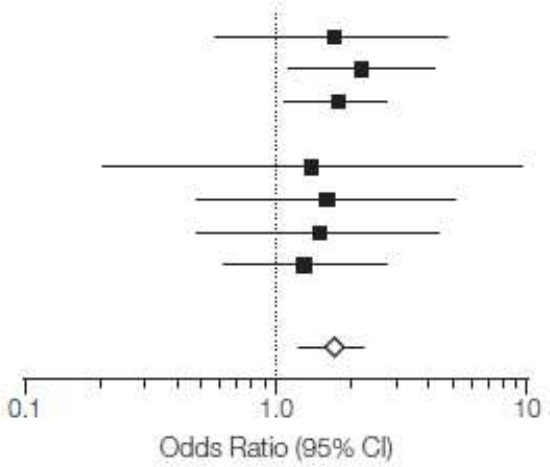
JAMA. 2010;304(4):443-451

Mortality

Mortality	Hazard Ratio (95% CI)	Weight, %
González et al,[45] 2009	4.04 (2.19-7.46)	11.63
Furlaneto and Garcez-Leme,[41] 2007	1.28 (0.66-2.48)	10.53
Leslie et al,[52] 2005	1.62 (1.13-2.33)	20.29
McCusker et al,[6] 2002	2.16 (1.06-4.41)	9.42
Nightingale et al,[60] 2001	2.40 (1.66-3.48)	19.93
Rockwood et al,[55] 1999	1.80 (1.11-2.92)	15.45
Francis and Kapoor,[40] 1992	1.40 (0.79-2.48)	12.76
Heterogeneity: $I^2 = 44.0\%$; $P = .10$		
Random-effects model: $P < .001$	1.95 (1.51-2.52)	100



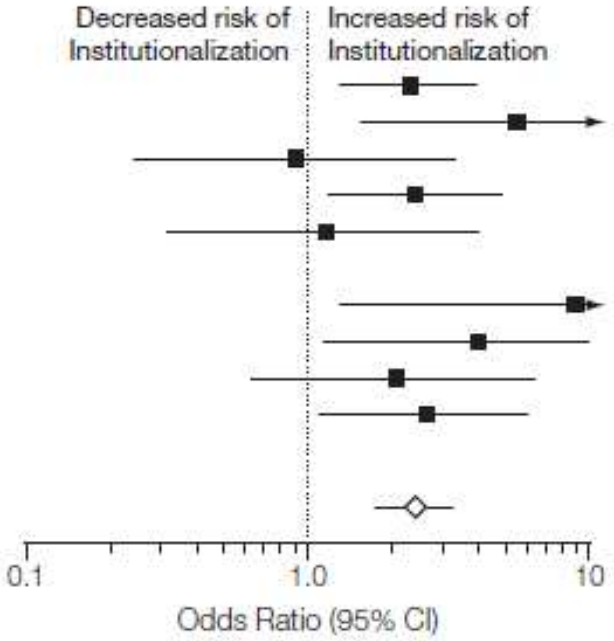
	Odds Ratio (95% CI)	
Bickel et al,[32] 2008	1.70 (0.59-4.91)	7.89
de Rooij et al,[35] 2007	2.20 (1.12-4.32)	19.52
Pitkala et al,[63] 2005	1.76 (1.10-2.81)	40.61
Inouye et al,[7] 1998		
Chicago	1.40 (0.20-9.60)	2.39
Cleveland	1.60 (0.50-5.16)	6.46
Yale	1.50 (0.50-4.55)	7.20
Levkoff et al,[51] 1992	1.30 (0.62-2.74)	15.93
Heterogeneity: $I^2 = 0\%$; $P = .98$		
Random-effects model: $P < .001$	1.71 (1.27-2.23)	100



Witlox J et al, JAMA 2010; 304: 443-451

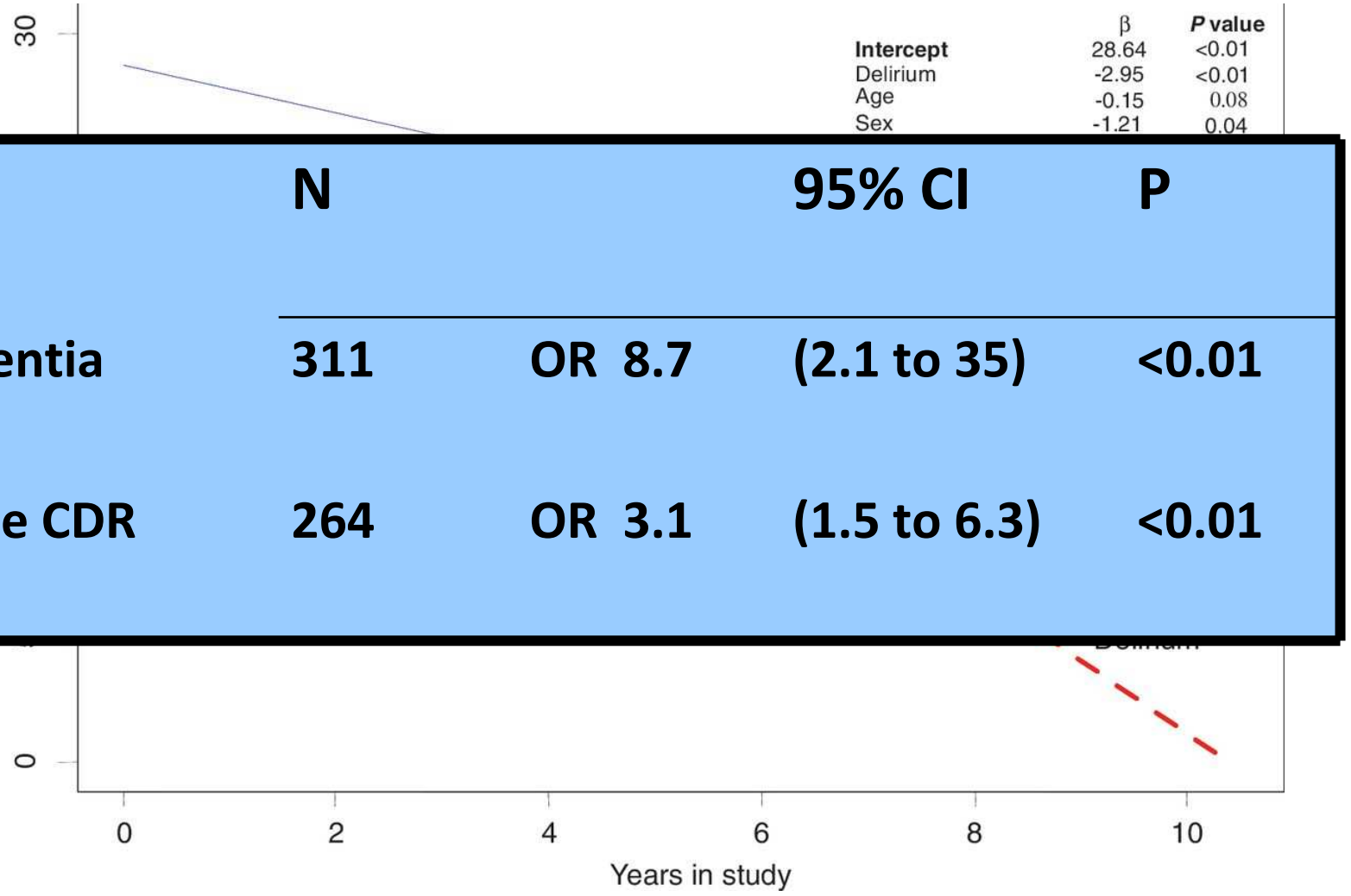
Dimissione difficile e Istitutionalizzazio

Institutionalization		
Bellelli et al,[30] 2008	2.30 (1.33-3.98)	32.35
Bickel et al,[32] 2008	5.60 (1.60-19.65)	6.17
Giusti et al,[43] 2006	0.93 (0.25-3.47)	5.61
Pitkala et al,[63] 2005	2.45 (1.21-4.95)	19.66
McCusker et al,[6] 2002	1.15 (0.33-4.05)	6.19
Inouye et al,[7] 1998		
Chicago	8.60 (1.31-56.45)	2.74
Cleveland	3.90 (1.12-13.56)	6.26
Yale	2.00 (0.63-6.33)	7.34
Francis and Kapoor,[40] 1992	2.56 (1.10-5.93)	13.77
Heterogeneity: $I^2 = 0\%$; $P = .48$		
Random-effects model: $P < .001$	2.41 (1.77-3.29)	100



Witlox J et al, JAMA 2010; 304: 443-451

Cognitive decline/Dementia

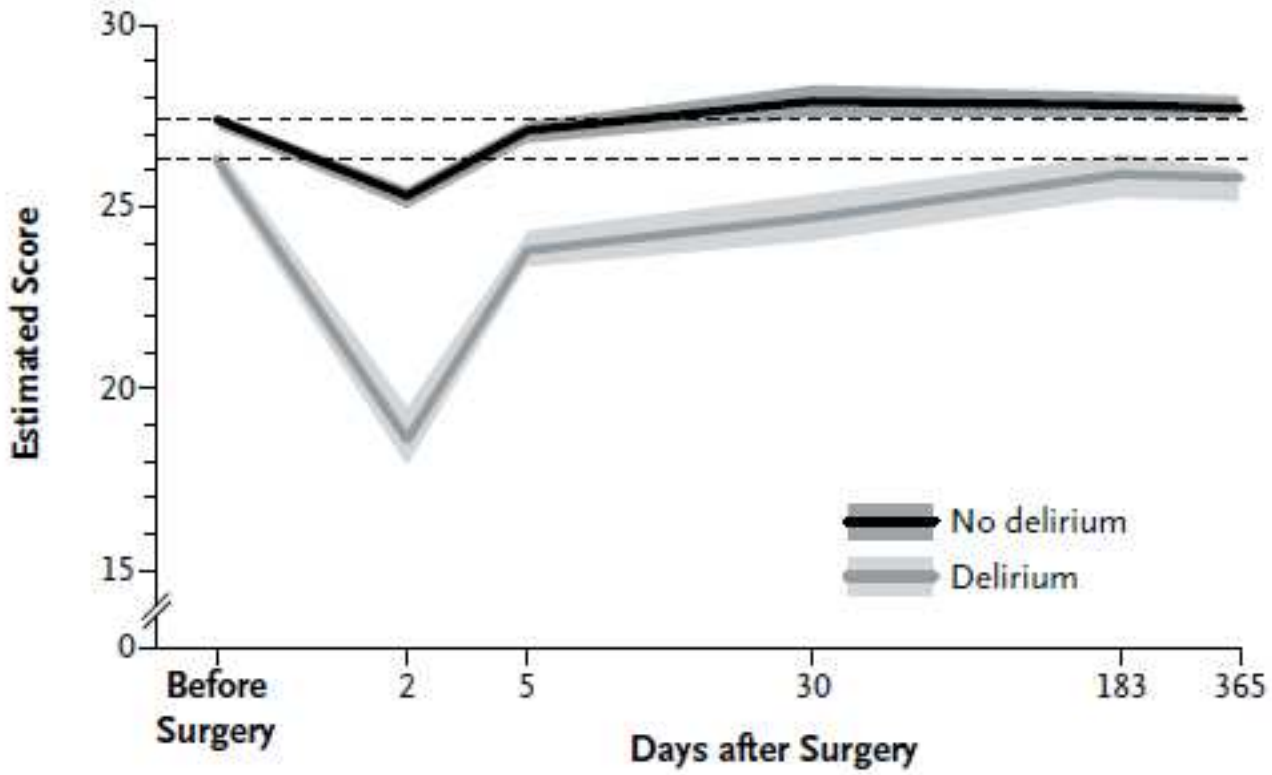


	N		95% CI	P
Dementia	311	OR 8.7	(2.1 to 35)	<0.01
Worse CDR	264	OR 3.1	(1.5 to 6.3)	<0.01

Daniel H. J. Davis et al. Brain 2012;135:2809-2816

Cognitive Trajectories after Postoperative Delirium

225 patients (≥ 60 yrs) undergoing coronary-artery bypass grafting or valve replacement



Saczynsky JS. NEJM 2012: 367:30-9

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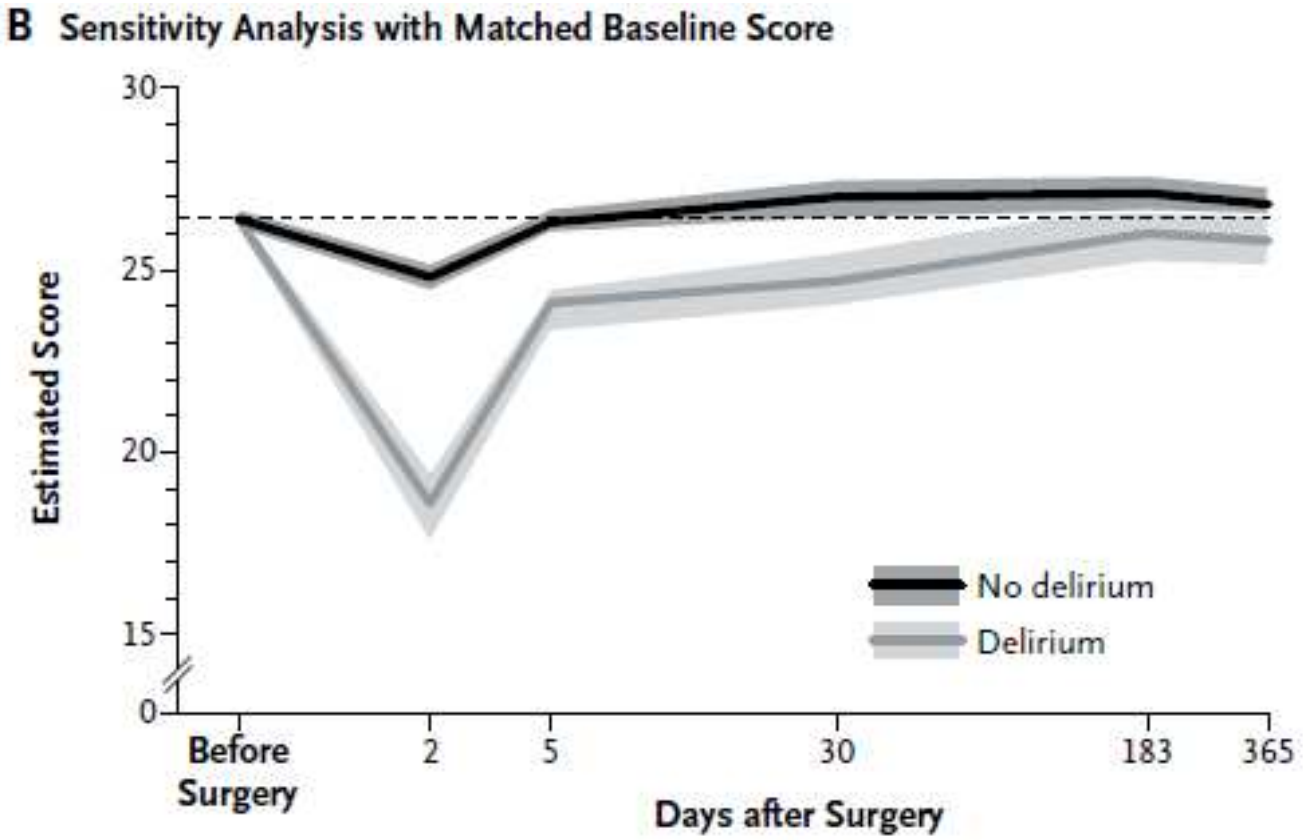

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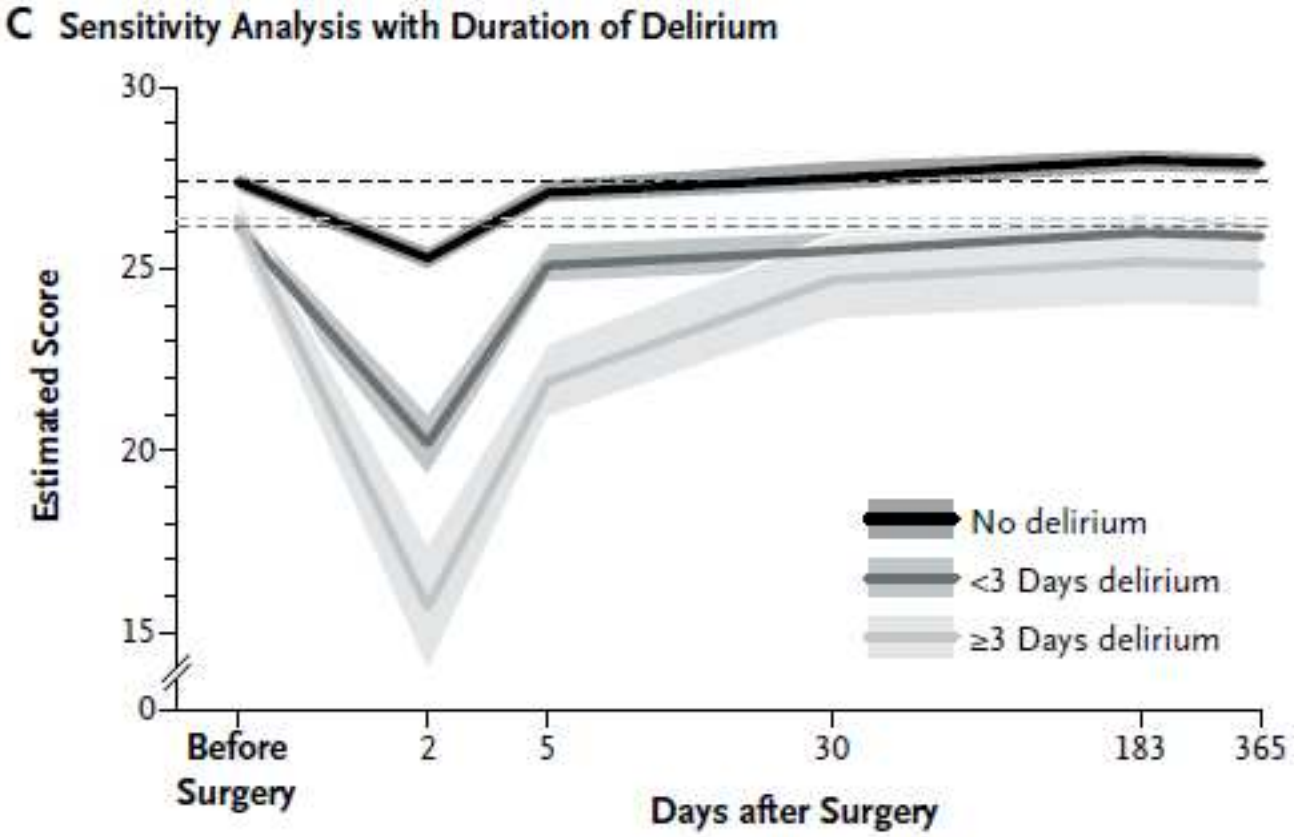

Saczynsky JS. NEJM 2012: 367:30-9

Altre Conseguenze

Il delirium è indipendentemente associato a:

- Costi sanitari elevati
- Incremento della durata di degenza
- Declino funzionale
- Disagio per il caregiver e il personale sanitario

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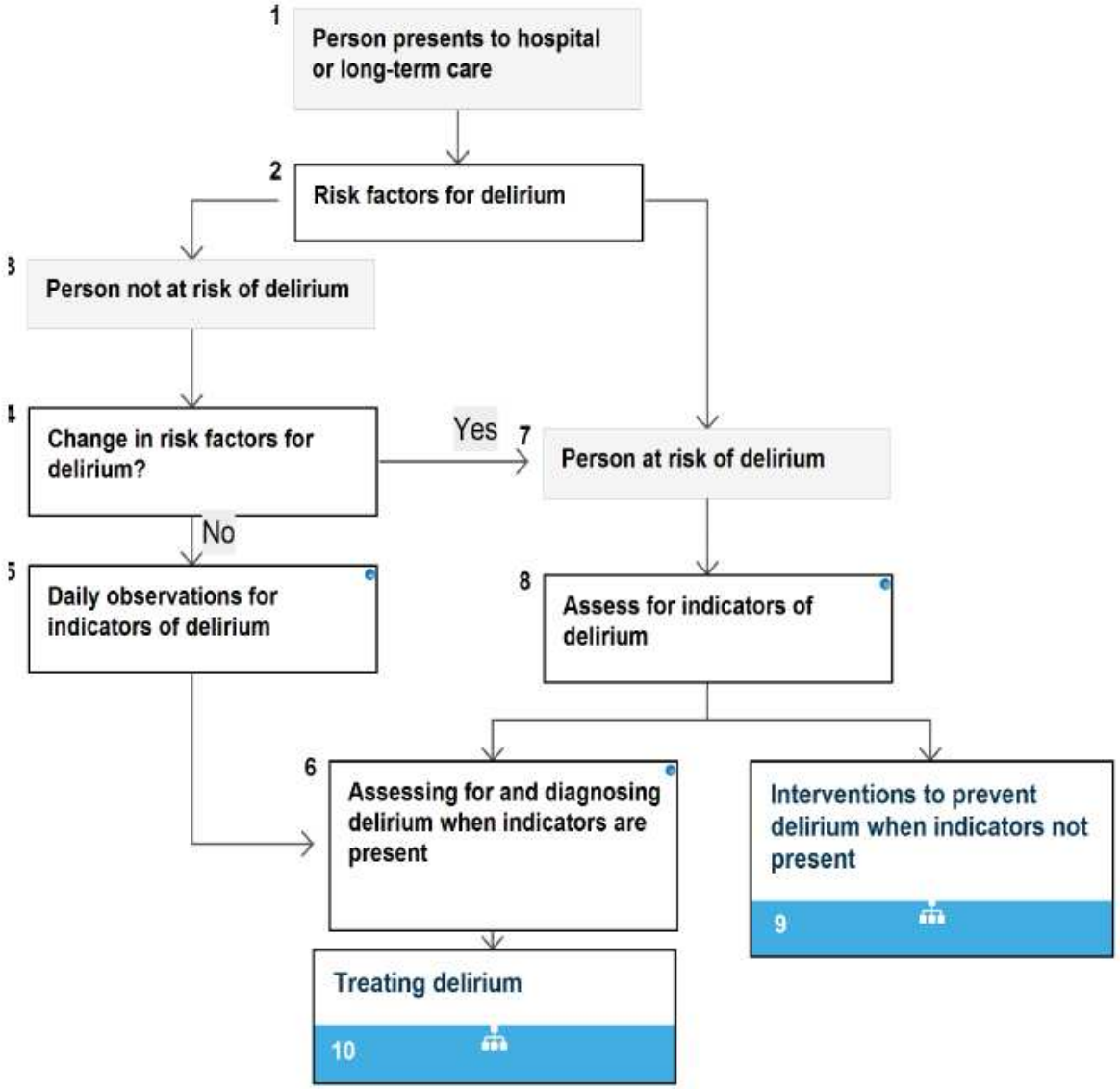
NICE National Institute for Health and Care Excellence



NICE National Institute for Health and Care Excellence

5 Daily observations for indicators of delirium

Has the person any indicators of delirium? These are **recent** (within hours or days) changes in:

- Cognitive function: for example, **worsened concentration**, **slow responses**, confusion.
- Perception: for example, visual or auditory hallucinations.
- Physical function: for example, **reduced mobility**, **reduced movement**, restlessness, agitation, **changes in appetite**, sleep disturbance.
- Social behaviour: for example, lack of cooperation with reasonable requests, **withdrawal**, or alterations in communication, mood and/or attitude.

These may be reported by the person at risk, or a carer or relative.

Be particularly vigilant for signs of hypoactive delirium (marked in **bold**).

Interventions to prevent delirium

- **Cognitive impairment or disorientation**
- **Dehydration or constipation**
- **Hypoxia**
- **Immobility or limited mobility**
- **Infection**
- **Multiple medications**
- **Pain**
- **Poor nutrition**
- **Sensory impairment**
- **Sleep disturbance**

NICE Pathways

A multicomponent intervention to prevent delirium in hospitalized older patients

TARGETED RISK FACTOR AND ELIGIBLE PATIENTS	STANDARDIZED INTERVENTION PROTOCOLS	TARGETED OUTCOME FOR REASSESSMENT
Cognitive impairment* All patients, protocol once daily; patients with base-line MMSE score of <20 or orientation score of <8, protocol three times daily	Orientation protocol: board with names of care-team members and day's schedule; communication to reorient to surroundings Therapeutic-activities protocol: cognitively stimulating activities three times daily (e.g., discussion of current events, structured reminiscence, or word games)	Change in orientation score
Sleep deprivation All patients; need for protocol assessed once daily	Nonpharmacologic sleep protocol: at bedtime, warm drink (milk or herbal tea), relaxation tapes or music, and back massage Sleep-enhancement protocol: unit-wide noise-reduction strategies (e.g., silent pill crushers, vibrating beepers, and quiet hallways) and schedule adjustments to allow sleep (e.g., rescheduling of medications and procedures)	Change in rate of use of sedative drug for sleep†
Immobility All patients; ambulation whenever possible, and range-of-motion exercises when patients chronically non-ambulatory, bed or wheelchair bound, immobilized (e.g., because of an extremity fracture or deep venous thrombosis), or when prescribed bed rest	Early-mobilization protocol: ambulation or active range-of-motion exercises three times daily; minimal use of immobilizing equipment (e.g., bladder catheters or physical restraints)	Change in Activities of Daily Living score
Visual impairment Patients with <20/70 visual acuity on binocular near-vision testing	Vision protocol: visual aids (e.g., glasses or magnifying lenses) and adaptive equipment (e.g., large illuminated telephone keypads, large-print books, and fluorescent tape on call bell), with daily reinforcement of their use	Early correction of vision, ≤48 hr after admission
Hearing impairment Patients hearing ≤6 of 12 whispers on Whisper Test	Hearing protocol: portable amplifying devices, earwax disimpaction, and special communication techniques, with daily reinforcement of these adaptations	Change in Whisper Test score
Dehydration Patients with ratio of blood urea nitrogen to creatinine≥18, screened for protocol by geriatric nurse-specialist	Dehydration protocol: early recognition of dehydration and volume repletion (i.e., encouragement of oral intake of fluids)	Change in ratio of blood urea nitrogen to creatinine

*The orientation score consisted of results on the first 10 items on the Mini–Mental State Examination (MMSE).

†Sedative drugs included standard hypnotic agents, benzodiazepines, and antihistamines, used as needed for sleep.

Inouye SK, et al. N Engl J Med. 1999;340:669-76.

Original Investigation | HEALTH CARE REFORM

Effectiveness of Multicomponent Nonpharmacological Delirium Interventions

A Meta-analysis

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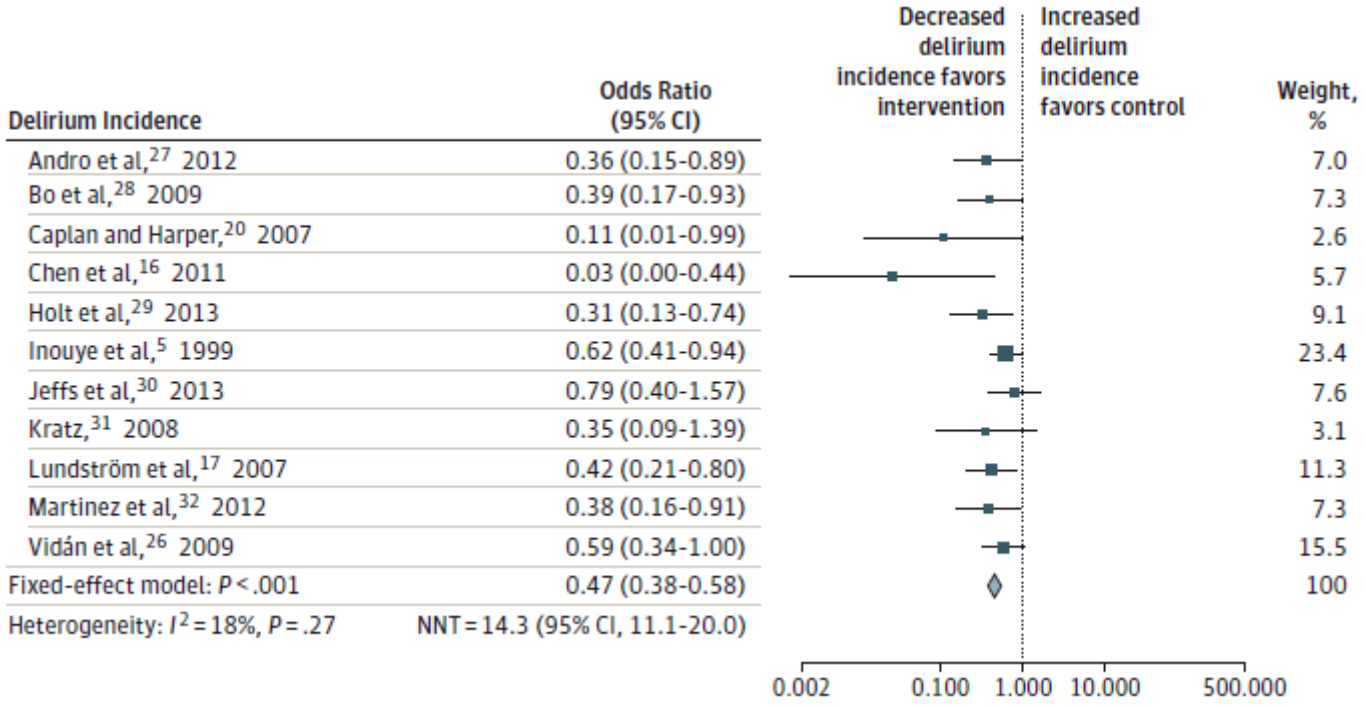


Sommario: 6 domande

1. Che cosa è il delirium?
2. Perché insorge?
3. Chi è a rischio ?
4. Quali sono le conseguenze?
5. E’ possibile prevenirlo?
    1. Se si come?
6. **Quando insorto come trattarlo?**

2 Initial management

Identify and manage the underlying cause or combination of causes.

Ensure effective communication and reorientation (for example, explaining where the person is, who they are, and what your role is) and provide reassurance.

Consider involving family, friends and carers to help with this.

Ensure that people are cared for by a team of healthcare professionals familiar to them.

Avoid moving people within and between wards or rooms unless necessary.

Diagnosi eziologica: cause trattabili

• **D**rugs	Farmaci
• **E**motional	Alterata emotività
• **L**ow oxygen	Ipossia
• **I**nfection	Infezioni
• **R**etention	Stipsi, ritenzione urinaria
• **I**ctal states	Ictus
• **U**nderhydration	Disidratazione
• **M**etabolic	Disordini metabolici
• **S**ubdural	Ematoma subdurale

Flaherty JH, et al. J Gerontol A Biol Sci Med Sci. 2004;59:341-3.

Terapia non farmacologica

Drug adjustments	Reduce or remove psychoactive drugs (eg, anticholinergics, sedatives or hypnotics, opioids); lower dosages; avoid as required dosing Substitute less toxic alternatives Use non-pharmacological approaches for sleep and anxiety, including music, massage, relaxation techniques
Address acute medical issues	Treat problems identified in work-up (eg, infection, metabolic disorders) Maintain hydration and nutrition Treat hypoxia
Reorientation strategies	Encourage family involvement; use companions as needed Address sensory impairment; provide eyeglasses, hearing aids, interpreters
Maintain safe mobility	Avoid use of physical restraints, tethers, and bed alarms Ambulate patient at least three times per day; active range-of-motion Encourage self-care and regular communication
Normalise sleep–wake cycle	Discourage napping and encourage exposure to bright light during the day Try to provide uninterrupted period for sleep at night Provide non-pharmacological sleep protocol and quiet room at night with low level lighting

Delirium in elderly people. Inouye SK, et al. Lancet 2014; 383: 911–22

NICE National Institute for Health and Care Excellence

3 Delirium symptoms not resolved and person is distressed or considered a risk to themselves or others

Using verbal and non-verbal de-escalation techniques

Use verbal and non-verbal techniques to de-escalate the situation. For more information on de-escalation techniques, see NICE's pathway on violence and aggression.

If verbal and non-verbal de-escalation techniques are not appropriate, or do not resolve symptoms

Consider short-term (usually for 1 week or less) haloperidol[1] or olanzapine. Start at the lowest clinically appropriate dose and titrate cautiously according to symptoms.

In people with conditions such as Parkinson's disease or dementia with Lewy bodies use antipsychotics with caution or not at all. (For more information on the use of antipsychotics for
Re-evaluate for underlying causes.

Follow up and assess for possible dementia (for more information see the NICE pathway on dementia).

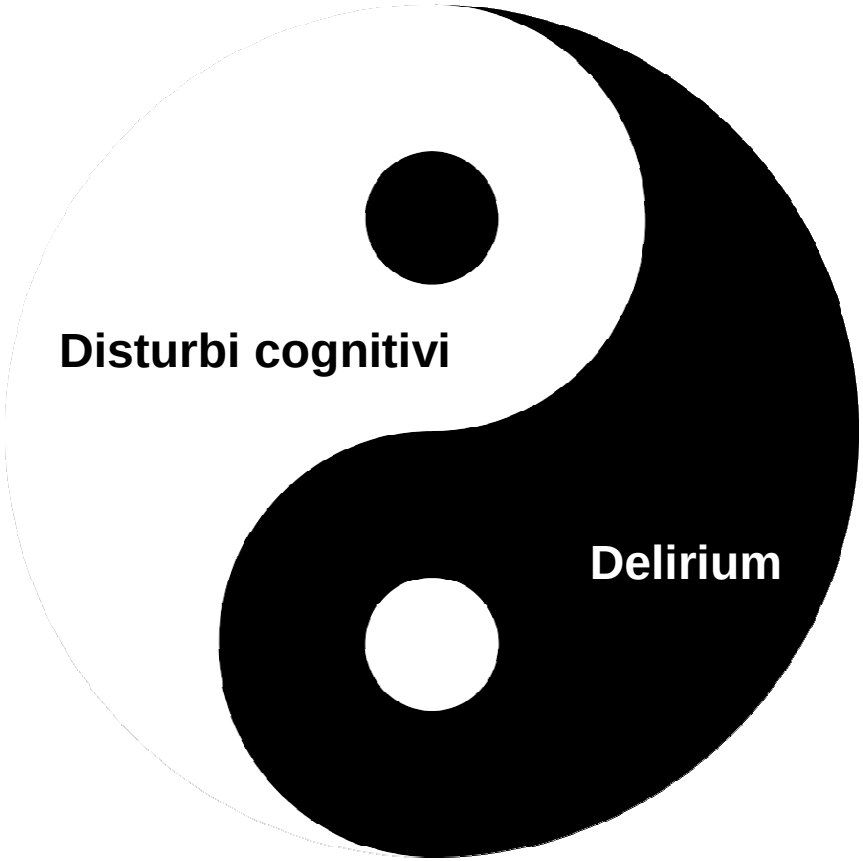
Terapia farmacologica

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	25 mg twice 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.

Delirium in Older Persons. Inouye S. N Engl J Med 2006;354:1157-65.

Delirium e disturbi cognitivi



«Lo yin e lo yang hanno radice uno nell'altro: sono interdipendenti, hanno origine reciproca, l'uno non può esistere senza l'altro»