63° CONGRESSO NAZIONALE SIGG

GLI ANZIANI: LE RADICI DA PRESERVARE

ROMA 28 novembre 01 dicembre 2018

Il management del delirium nei reparto ospedalieri
Perché non usare i farmaci nella prevenzione e terapia del delirium

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European Delirium Association

22 Novembre 2018

Fondazione Teresa Camplani
Casa di Cura ANCELLE

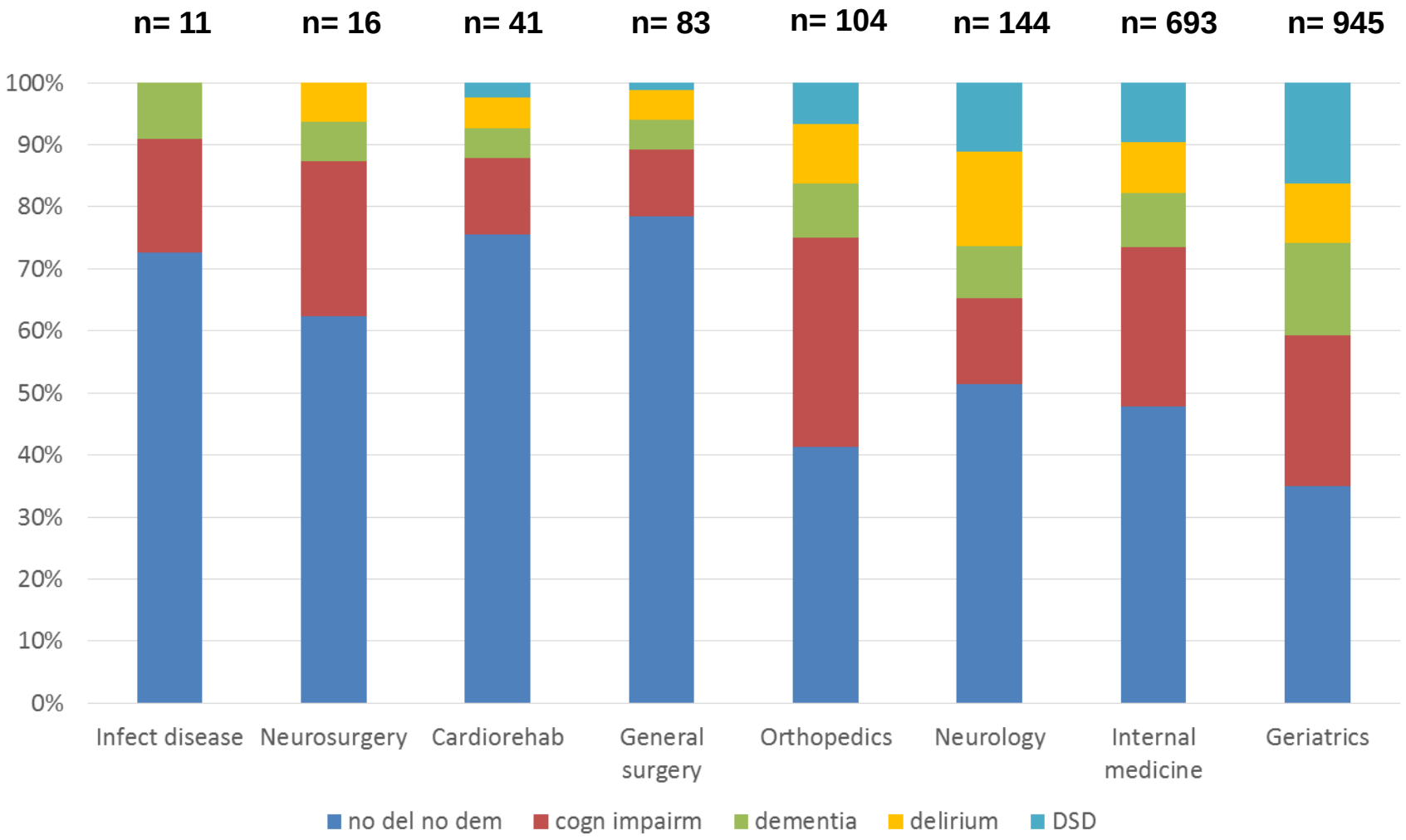
Outline

- Quali reparti ospedalieri?
- Quali basi fisiopatologiche?
- Che cosa trattiamo?
- Quali farmaci?
- E gli interventi non farmacologici?

Outline

- **Quali reparti ospedalieri?**
- **Quali basi fisiopatologiche?**
- **Che cosa trattiamo?**
- **Quali farmaci?**
- **E gli interventi non farmacologici?**

Prevalence (%) of delirium alone, DSD, cognitive impairment/dementia alone or neither in hospital wards (Delirium Day 2016)



Morandi A et al J Geront In Press 2018

Outline

- Quali reparti ospedalieri?
- **Quali basi fisiopatologiche?**
- Che cosa trattiamo?
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- E gli interventi non farmacologici?

“Un modello di base sulla fisiopatologia del delirium”

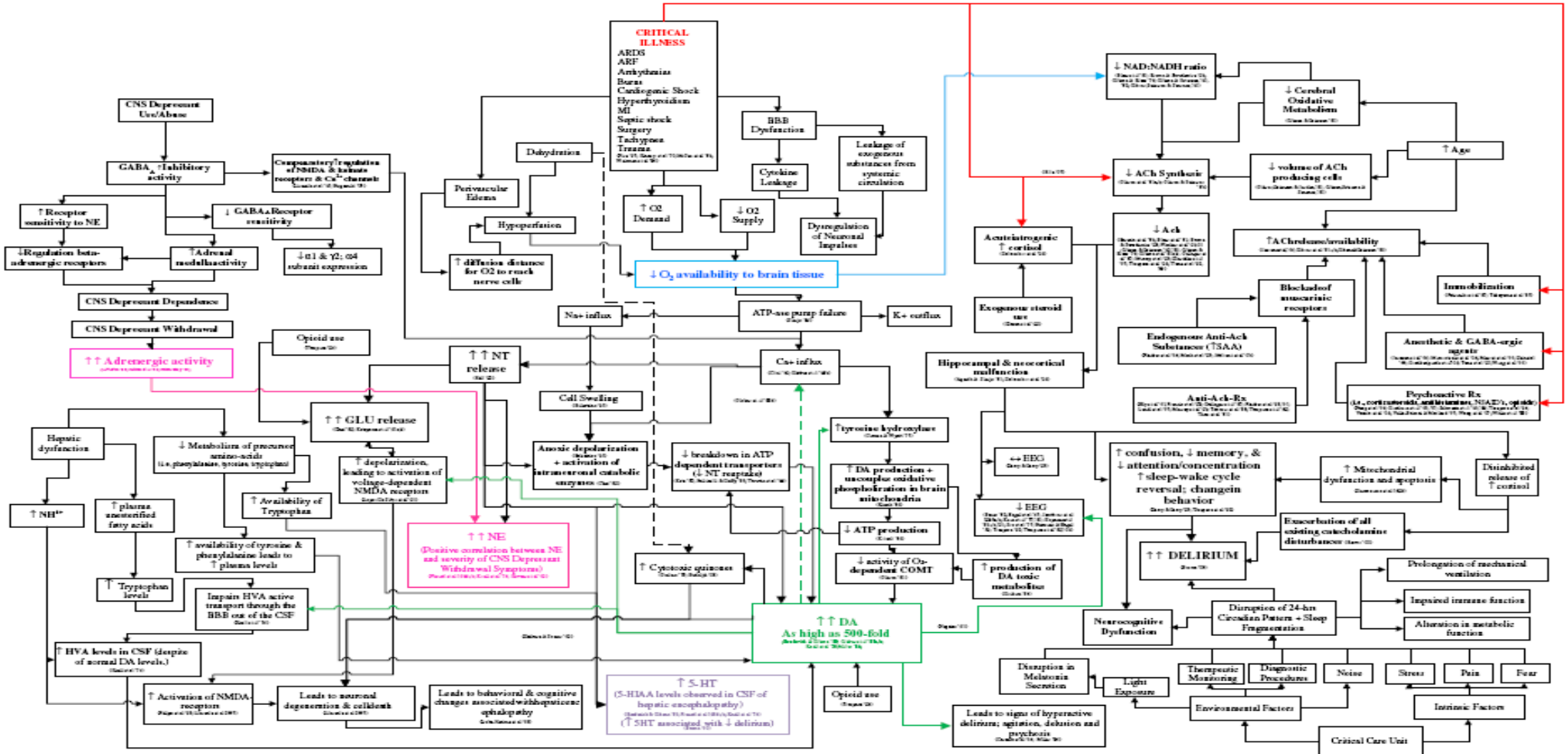

Fig. 1. A basic pathoetiological model of delirium.

NEUROBIOLOGY MODEL OF DELIRIUM

793

Maldonado J. Crit Care Clin 2008

La fisiopatologia del delirium: le sette ipotesi

Maldonado J. Am J Geriatr Psych 2013

“The neurotransmitter hypothesis”

Delirium Source	ACH	DA	GLU	GABA	5HT	NE	Trp	Mel	Phe	His	Cytok	HPA axis	Cort	NMDA activity	RBF Δ	Inflam	EEG
Anoxia/hypoxia	↓	↑	↑	↑	↓	↓	⇔	↓	↑	↑,↓	⇶↑	⇶	↑	↑	⇶	↑	↓
Aging	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	⇶↑	⇶	↑	↓	⇶	↑	↓
TBI	↑																↓
CVA	↓																↓
Hepatic Encephalopathy	⇔																↓
Sleep deprivation	↓																↓
Trauma, Sx, & Post-op	↓																↓
ETOH & CNS-Dep Withdrawal	↑																↑
Infection/Sepsis	↓																↓
Dehydration & Electrolyte Imbalance	⇔																⇶
Medical Illness	↓																⇶

The most commonly described neurotransmitter changes associated with delirium are:

- **Reduced availability of Ach (Ach);**
- **Excess release of DA (DA), NE (NE), and/or GLU (GLU);**
- **Alterations (e.g., both a decreased and increased activity depending on circumstances and etiological factors) in 5HT (5HT), histamine (H1 and H2), and/or GABA (GABA)**

Maldonado J. Crit Care Clin 2008

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osa trattiamo?

Table 3 DRS-R98 item severities (mean scores ± SD) for the four groups; significance is for comparisons using Mann—Whitney U test

DRS-R98 item	Controls (n = 40)	Delirium (n = 40)	Comorbid delirium-dementia (n = 40)	Dementia (n = 20)
1. Sleep-wake cycle disturbance	0.7 ± 0.7	1.6 ± 0.8†	1.5 ± 0.7†	1.0 ± 0.6¶
2. Perceptual disturbances and hallucinations	[illegible]	[illegible]1.2*	0.7 ± 1.0*	0.1 ± 0.3¶
3. Delusions	[illegible]0	0.2 ± 0.7	0.6 ± 1.0*	0.1 ± 0.5¶
4. Lability of affect	[illegible]	0.9 ± 0.8‡	0.7 ± 0.7†	0.2 ± 0.4¶
5. Language	0.3 ± 0.5	1.3 ± 0.7	1.0 ± 0.8	0.9 ± 0.6
6. Thought process abnormalities	0.4 ± 0.5	1.9 ± 1.0‡ §	1.1 ± 0.8*	0.6 ± 0.9¶
7. Motor agitation	0.1 ± 0.4	1.6 ± 3.4‡	0.9 ± 0.8‡	0.2 ± 0.4¶
8. Motor retardation	[illegible]	1.3 ± 0.8‡	0.9 ± 1.0*	0.4 ± 0.5¶
9. Orientation	0.1 ± 0.2	1.4 ± 0.7*	1.4 ± 0.7*	0.9 ± 0.7
10. Attention	0.2 ± 0.4	2.2 ± 0.9*	2.1 ± 0.9*	1.6 ± 1.1
11. Short-term memory	0.2 ± 0.5	1.9 ± 1.0	2.0 ± 1.0	1.5 ± 1.2
12. Long-term memory	0.3 ± 0.5	1.3 ± 0.9	1.7 ± 1.0	1.1 ± 1.1
13. Visuospatial ability	0.3 ± 0.6	1.9 ± 1.0	2.3 ± 1.9	1.8 ± 1.0
14. Temporal onset of symptoms	0	1.5 ± 0.6‡	1.6 ± 0.7‡	0.1 ± 0.2¶
15. Fluctuation in symptom severity	[illegible]	1.1 ± 0.5‡	1.0 ± 0.6‡	0.0 ± 0.0¶
16. Physical disorder	1.0 ± 0.2	1.5 ± 0.5‡	1.7 ± 0.5‡	1.0 ± 0.1¶

Meagher D J Neurol Neurosurg Psychiatry 2009

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Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis

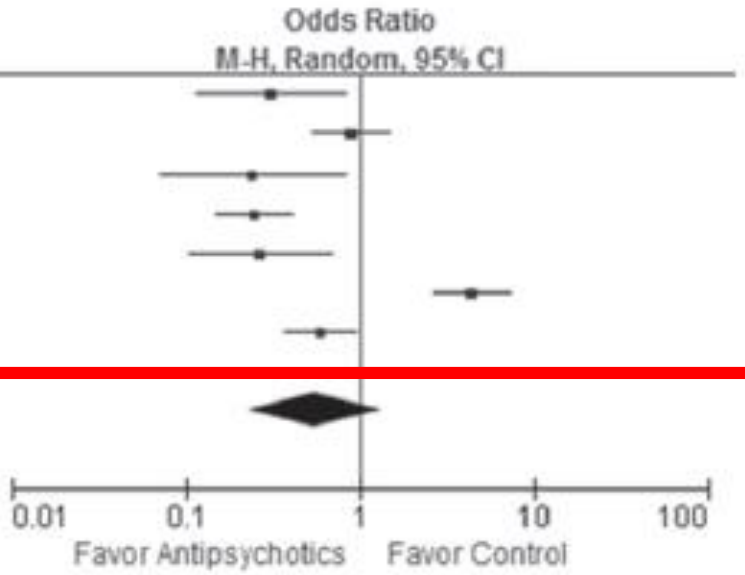
Karin J. Neufeld, MD, MPH,[*a] *Jirong Yue, MD,*[§a] *Thomas N. Robinson, MD, MPH,*[‖] *Sharon K. Inouye, MD, MPH,*[**††b] *and Dale M. Needham, MD, PhD*[††b]

A **Delirium Prevention in Postoperative Patients**

Study or Subgroup	Antipsychotics Events	Antipsychotics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Hakim 2012	7	51	17	50	13.3%	0.31 [0.11, 0.83]
Kalisvaart 2005	32	212	36	218	15.2%	0.90 [0.53, 1.51]
Kaneko 1999	4	38	13	40	12.2%	0.24 [0.07, 0.84]
Larsen 2010	28	196	82	204	15.3%	0.25 [0.15, 0.40]
Prakanrattana 2007	7	63	20	63	13.5%	0.27 [0.10, 0.69]
Vochteloo 2011	73	173	29	205	15.2%	4.43 [2.70, 7.27]
Wang 2012	35	229	53	228	15.3%	0.60 [0.37, 0.96]
Total (95% CI)		**962**		**1008**	**100.0%**	**0.56 [0.23, 1.34]**
Total events	186		250			

Heterogeneity: Tau² = 1.26; Chi² = 81.27, df = 6 (P < 0.00001); I² = 93%

Test for overall effect: Z = 1.31 (P = 0.19)



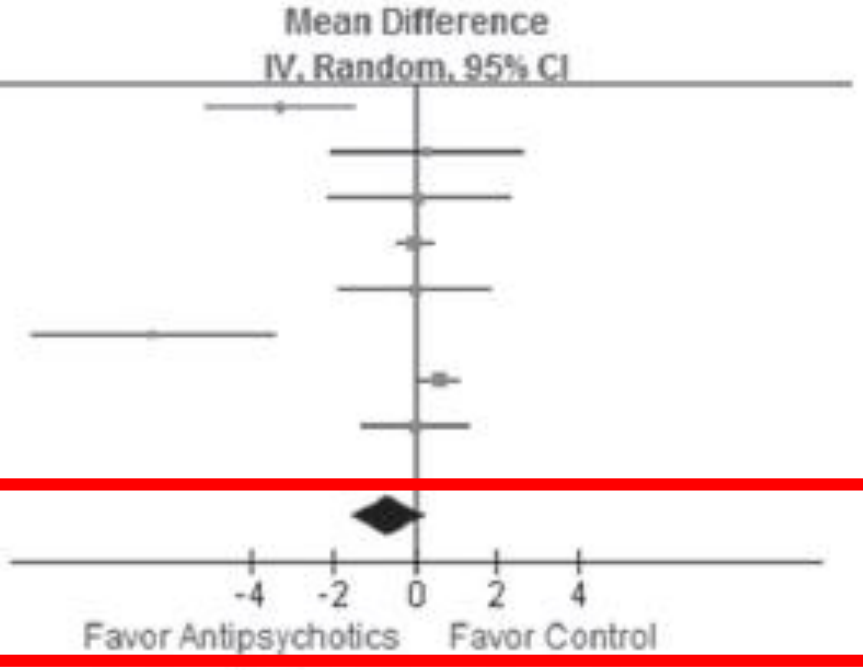
Neufeld K.J, JAGS 2016

B Delirium Duration in Hospitalized Patients

Study or Subgroup	Antipsychotics Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Devlin 2010	1.8	1.8	18	5.1	3.5	18	11.4%	-3.30 [-5.12, -1.48]
Girard 2010	5.1	4	30	4.8	4	18	8.9%	0.30 [-2.04, 2.64]
Girard 2010	4.9	3.7	35	4.8	4	18	9.4%	0.10 [-2.12, 2.32]
Hakim 2012	3	1.5	51	3	0.8	50	19.1%	0.00 [-0.47, 0.47]
Han 2004	4.2	2.5	12	4.2	2.1	12	11.3%	0.00 [-1.85, 1.85]
Kalisvaart 2005	5.4	4.9	32	11.8	7.5	36	6.6%	-6.40 [-9.38, -3.42]
Larsen 2010	2.2	1.3	28	1.6	0.7	82	18.9%	0.60 [0.10, 1.10]
Page 2013	5.3	3.8	71	5.3	4.1	70	14.4%	0.00 [-1.31, 1.31]
Total (95% CI)			277			304	100.0%	-0.65 [-1.59, 0.29]

Heterogeneity: Tau² = 1.14; Chi² = 35.67, df = 7 (P < 0.00001); I² = 80%

Test for overall effect: Z = 1.36 (P = 0.17)

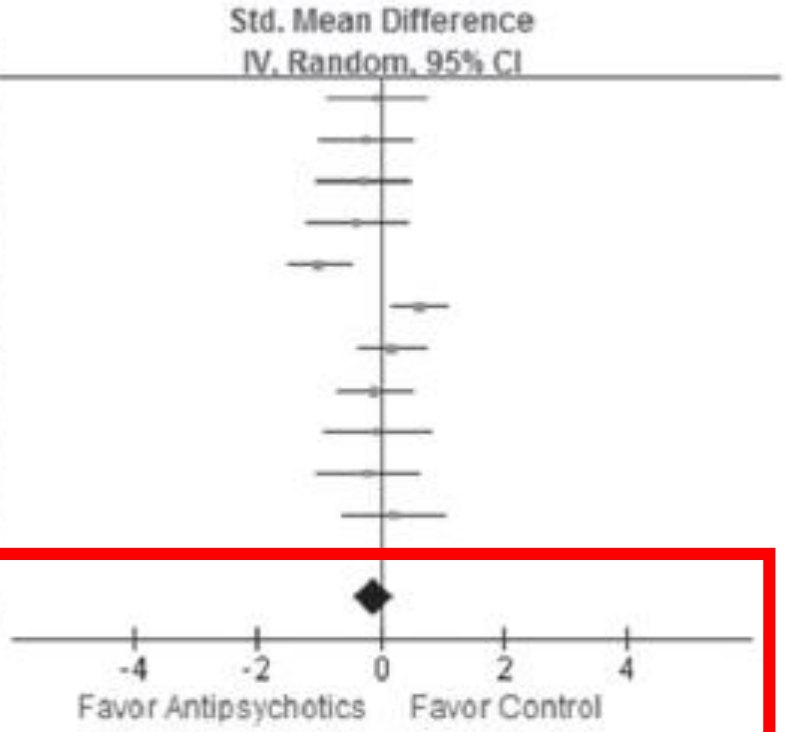


Neufeld K.J, JAGS 2016

C Delirium Severity in Hospitalized Patiens

Study or Subgroup	Antipsychotics Mean	Antipsychotics SD	Antipsychotics Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Breitbart 1996	11.6	6.1	11	11.9	6.7	13	8.0%	-0.05 [-0.85, 0.76]
Grover 2011	10.1	6.4	10	11.7	7.2	21	8.4%	-0.22 [-0.98, 0.53]
Grover 2011	10.1	6.4	10	12	6.8	23	8.5%	-0.28 [-1.02, 0.47]
Han 2004	21.8	4.4	12	23.5	4.2	12	7.9%	-0.38 [-1.19, 0.43]
Kalisvaart 2005	14.4	3.4	32	18.4	4.3	36	11.3%	-1.01 [-1.52, -0.51]
Larsen 2010	16.4	3.7	28	14.5	2.7	82	12.1%	0.63 [0.20, 1.07]
Maneeton 2013	-21.7	6.7	28	-22.9	6.9	24	10.8%	0.17 [-0.37, 0.72]
Tahir 2010	7.1	3.3	21	7.4	3.3	21	10.1%	-0.09 [-0.69, 0.52]
Yoon 2013	8.5	4.6	7	8.8	6	18	7.3%	-0.05 [-0.92, 0.82]
Yoon 2013	8.5	4.6	8	9.8	6.7	21	7.8%	-0.20 [-1.02, 0.61]
Yoon 2013	8.5	4.6	8	7.6	3.7	18	7.7%	0.22 [-0.62, 1.05]
Total (95% CI)			**175**			**289**	**100.0%**	**-0.11 [-0.43, 0.22]**

Heterogeneity: Tau² = 0.18; Chi² = 25.55, df = 10 (P = 0.004); I² = 61%
Test for overall effect: Z = 0.65 (P = 0.52)



Neufeld K.J, JAGS 2016

Haloperidol Prophylaxis for Elderly Hip-Surgery Patients at Risk for Delirium: A Randomized Placebo-Controlled Study

Kees J. Kalisvaart, MD, Jos F. M. de Jonghe, PhD,* Marja J. Bogaards, PharmD,† Ralph Vreeswijk, RN, MSc,* Toine C. G. Egberts, PhD,‡ Bart J. Burger, MD, PhD,* Piet Eikelenboom, MD, PhD,§¶ and Willem A. van Gool, MD, PhD‖*

Table 3. Results of Patients Who Developed Delirium, According to Study Group: Intention-to-Treat Group

Delirium Characteristic	Haloperidol (n = 32)	Placebo (n = 36)	Mean Difference (95% Confidence Interval)	*P*-value
	Mean ± Standard Deviation			
Highest Delirium Rating Scale score	14.4 ± 3.4	18.4 ± 4.3	4.0 (2.0–5.8)	<.001
Delirium duration, days	5.4 ± 4.9	11.8 ± 7.5	6.4 (4.0–8.0)	<.001
Hospital days	17.1 ± 11.1	22.6 ± 16.7	5.5 (1.4–2.3)	<.001

JAGS 53:1658–1666, 2005

Administration of Olanzapine to Prevent Postoperative Delirium in Elderly Joint-Replacement Patients: A Randomized, Controlled Trial

Randomized, double-blind, placebo-controlled, prophylaxis trial at an orthopedic teaching hospital, enrolling 495 elderly patients age 65 years, who were undergoing elective knee- or hip-replacement surgery; 400 patients received either 5 mg of orally-disintegrating olanzapine or placebo just before and after surgery

KENNETH A. LARSEN, I Psychosomatics 51:5, September-October 2010

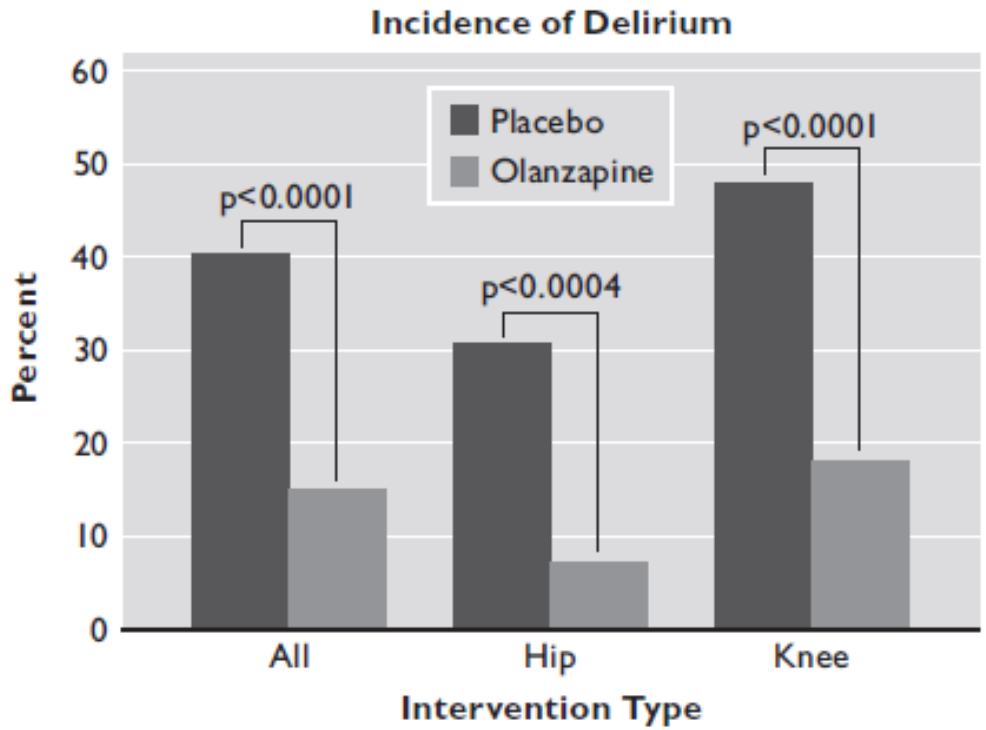
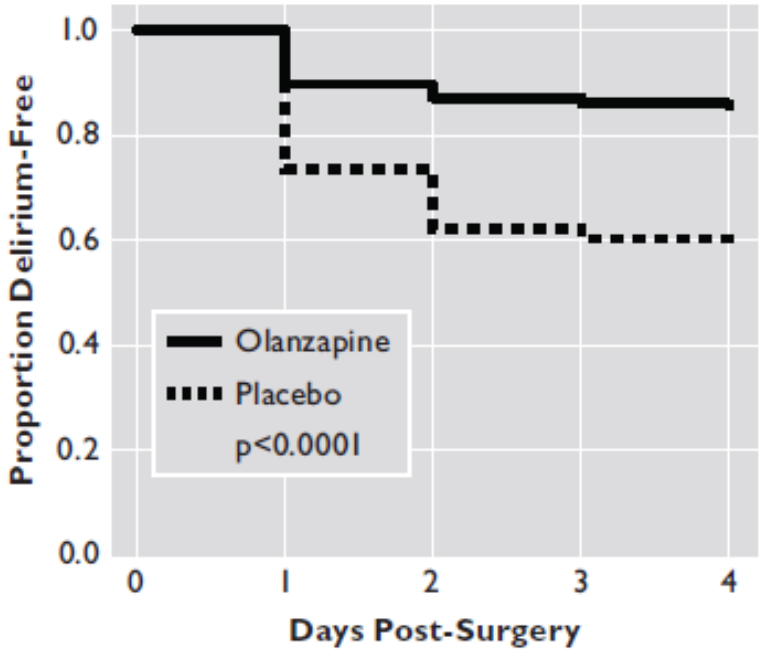


FIGURE 3. Time-to-First Day of Delirium, by Study Group



Delirium in the elderly

A systematic review of pharmacological and non-pharmacological treatments

Cecília Carboni Tardelli Cerveira[1], Cláudia Cristina Pupo[2], Sigrid De Sousa dos Santos[3], José Eduardo Mourão Santos[3]

Dement Neuropsychol 2017 September;11(3):270-275

Intervento farmacologico

- **Rivastigmina riduce la durata del delirium, migliora le funzioni c s del caregiver (4 studi);**
- **Olanzapin o la gravità del delirium;**
- **Droperido degenza e migliora la risoluzion**

Small studies
No placebo

Cholinesterase inhibitors for the treatment of delirium in non-ICU settings (Review)

Yu A, Wu S, Zhang Z, Dening T, Zhao S, Pinner G, Xia J, Yang D

We found one trial from the UK, which included 15 participants with delirium. Seven participants also had a history of dementia.
This trial compared rivastigmine with an inactive treatment (placebo).

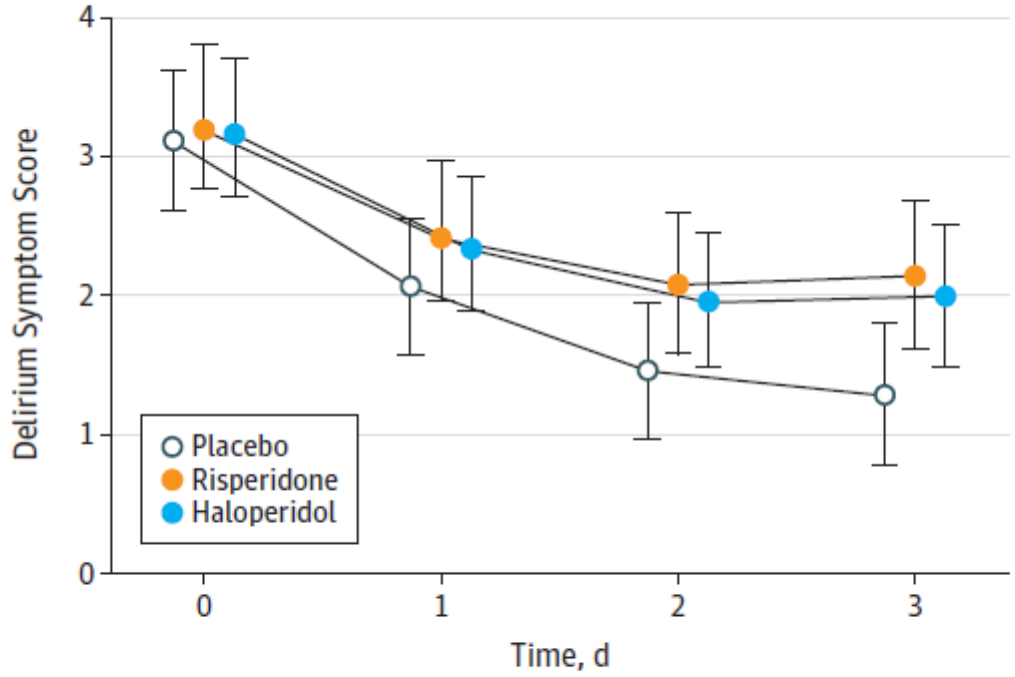
The trial did not show any difference in effect between those participants given rivastigmine and those given placebo

Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD012494.

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

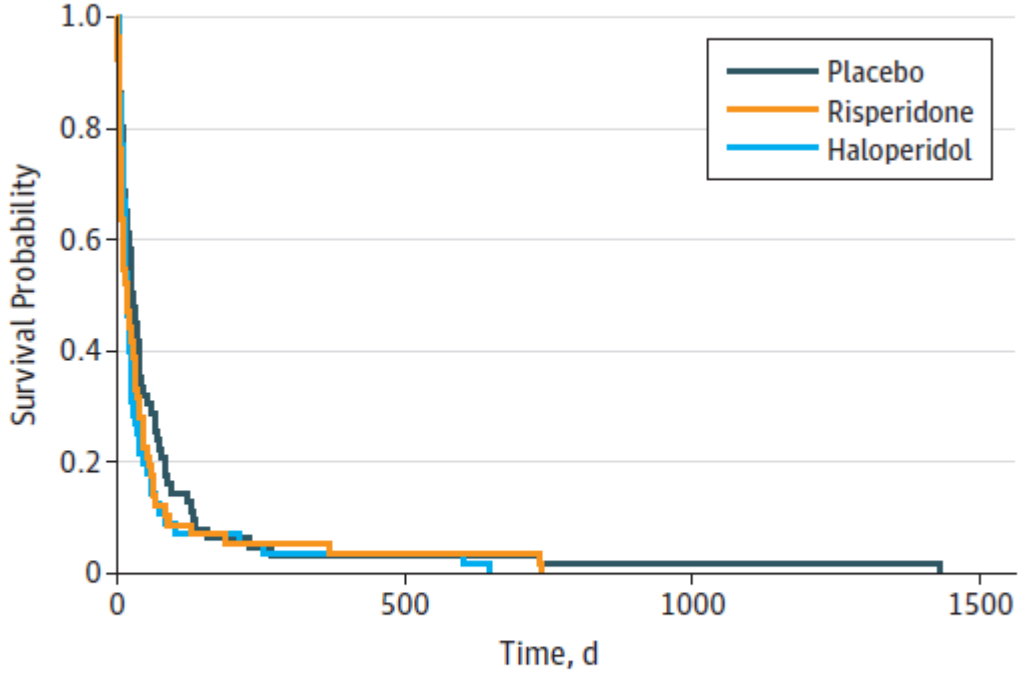
A Randomized Clinical Trial

Figure 2. Secondary Multivariable Mixed-Model Analysis of Delirium



No. at risk				
Placebo	84	63	59	55
Risperidone	82	58	49	39
Haloperidol	81	64	55	51

Figure 3. Kaplan-Meier Curves for Overall Survival

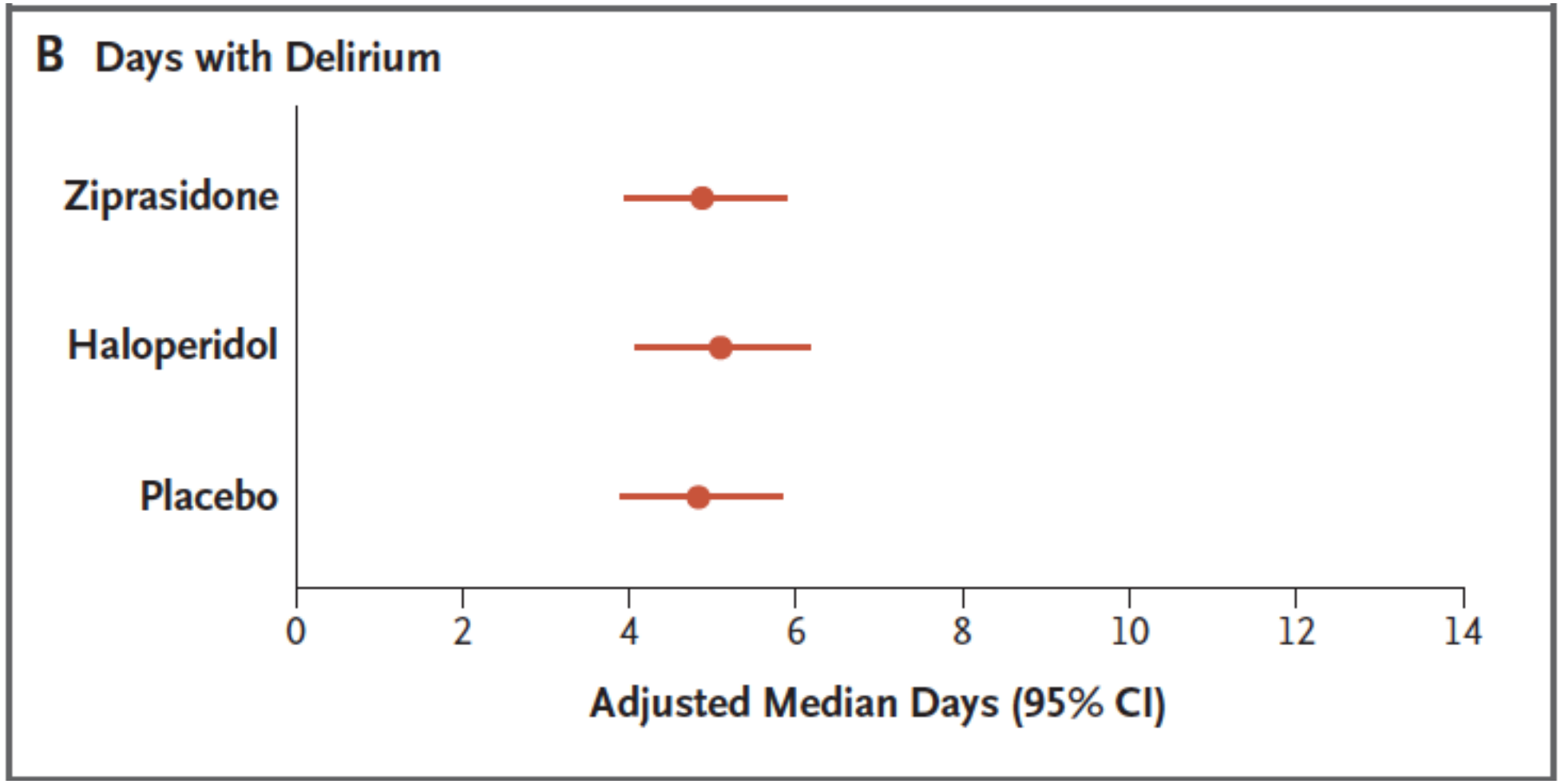


No. at risk				
Placebo	81	2	1	0
Risperidone	80	2	0	0
Haloperidol	79	2	0	0

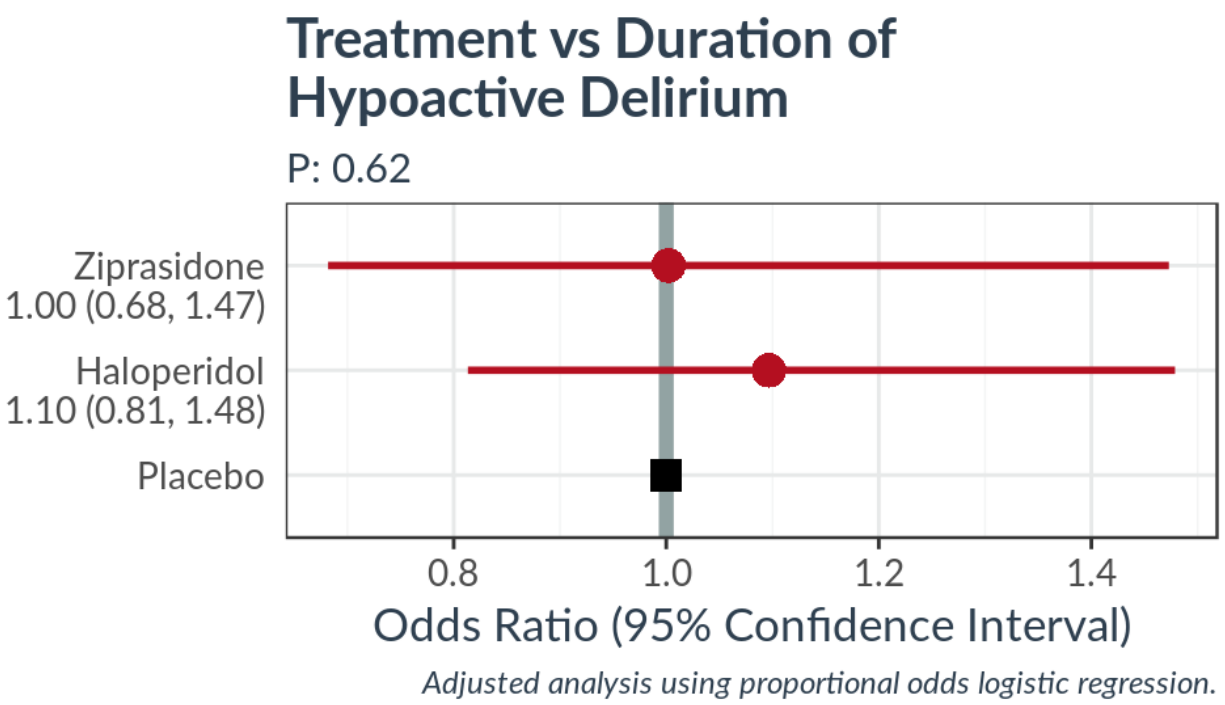
JAMA Intern Med. 2017;177(1):34-42. doi:10.1001/jamainternmed.2016.7491

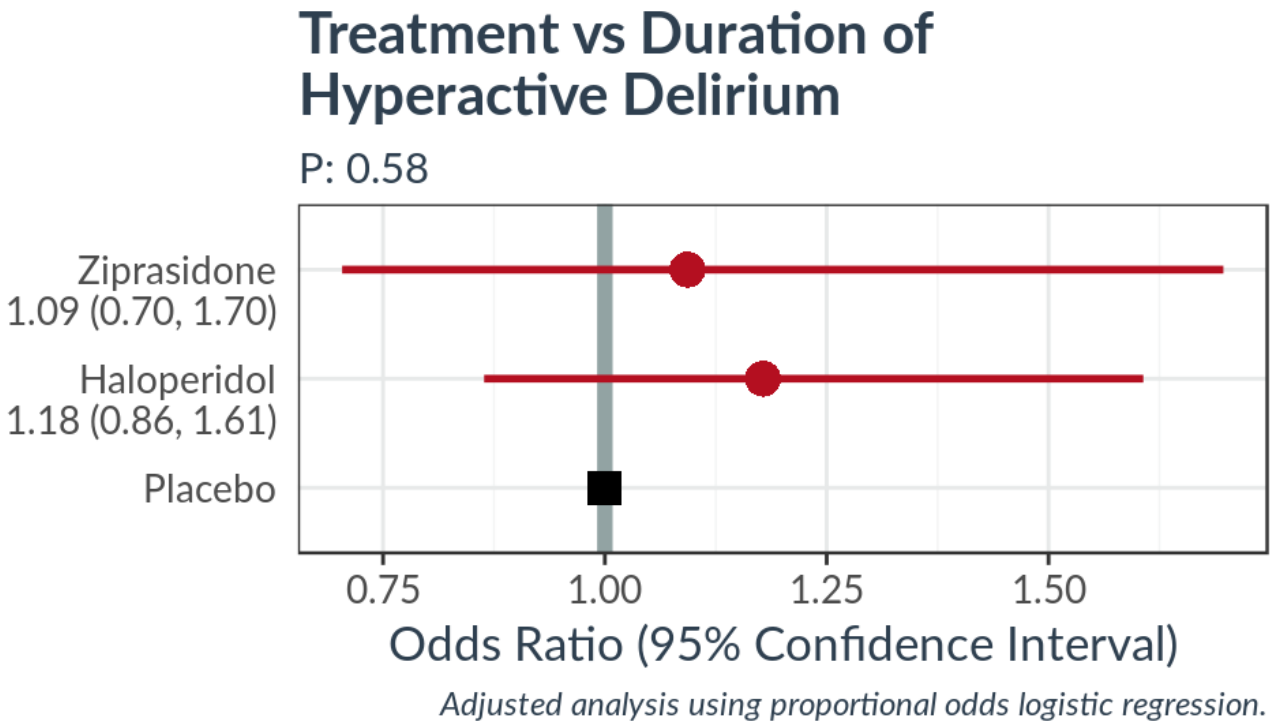
Table 1. Baseline Characteristics of the Trial Population.*

Characteristic	Placebo (N=184)	Haloperidol (N=192)	Ziprasidone (N=190)
Median age (IQR) — yr	59 (52–67)	61 (51–69)	61 (50–69)
Female sex — no. (%)	77 (42)	84 (44)	82 (43)
Race — no. (%)†			
White	153 (83)	163 (85)	151 (79)
Black	26 (14)	23 (12)	27 (14)
Multiple races or other race	5 (3)	6 (3)	12 (6)
Median short-form IQCODE score (IQR)‡	3.1 (3.0–3.3)	3.0 (3.0–3.2)	3.1 (3.0–3.3)
Median Charlson Comorbidity Index score (IQR)§	2 (1–4)	2 (1–3)	2 (1–4)
Received antipsychotic treatment — no. (%)			
Before admission	6 (3)	8 (4)	11 (6)
Between admission and randomization	18 (10)	20 (10)	22 (12)
Hyperactive delirium at randomization — no. (%)	22 (12)	19 (10)	16 (8)
Hypoactive delirium at randomization — no. (%)	161 (88)	172 (90)	172 (91)



N Engl J Med. 2018





N Engl J Med. 2018

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- **E gli interventi non farmacologici?**

THINK DELIRIUM

NHS Education for Scotland

SCOTTISH DELIRIUM ASSOCIATION

Etiologic Mnemonic

- **I**nfectious
- **W**ithdrawal
- **A**cute metabolic
- **T**rauma
- **C**entral nervous system pathology
- **H**ypoxia
- **D**eficiencies (nutritional)
- **E**ndocrinopathies
- **A**cute vascular
- **T**oxins/drugs
- **H**eavy metals

CCSMH Delirium Guidelines

- **D**rugs
- **E**ye, ears
- **L**ow oxygen
- **I**schemia
- **R**etention
- **I**nfections
- **U**nderhydration
- **M**etabolic
- **S**ubdural

Flaherty, JAGS 2003

The New England
Journal of Medicine

VOLUME 340 MARCH 4, 1999 NUMBER 9

A MULTICOMPONENT INTERVENTION TO PREVENT DELIRIUM IN HOSPITALIZED OLDER PATIENTS

SHARON K. INOUYE, M.D., M.P.H., SIDNEY T. BOGARDUS, JR., M.D., PETER A. CHARPENTIER, M.P.H., LINDA LEO-SUMMERS, M.P.H., DENISE ACAMPORA, M.P.H., THEODORE R. HOLFORD, PH.D., AND LEO M. COONEY, JR., M.D.

Table 1. Risk Factors for Delirium and Intervention Protocols.

Targeted Risk Factor and Eligible Patients		Targeted Outcome
Cognitive impairment*		
All patients, protocol once daily; patients with base-line MMSE score of < 20 or orientation score of < 8, protocol three times daily		
Sleep deprivation		
All patients; need for protocol assessed once daily		
Immobility		
All patients; ambulation whenever possible, and range-of-motion exercises when patients chronically non-ambulatory, bed or wheel-chair bound, immobilized (e.g., because of an extremity fracture or deep venous thrombosis), or when prescribed bed rest		
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 key-pads, 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.

1- Deficit cognitivo
2- Alterazione ritmo sonno-veglia
3- Ipomobilità
4- Deficit visivi
5- Deficiti uditivi
6- Disidratazione

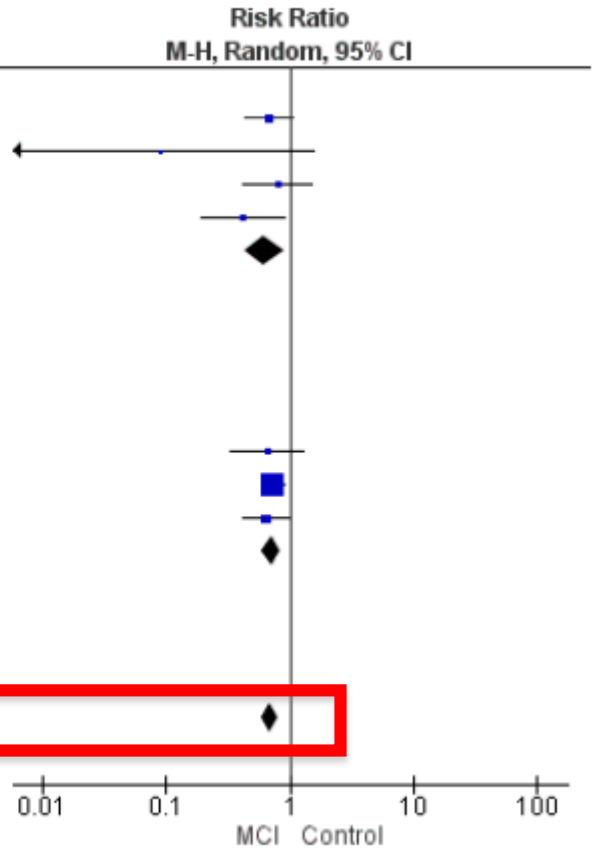
Interventions for preventing delirium in hospitalised non-ICU patients (Review)

2016

Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, Simpkins SA

Figure 3. Forest plot of comparison: 1 Multi-component delirium prevention intervention (MCI) versus usual care, outcome: 1.1 Incident delirium.

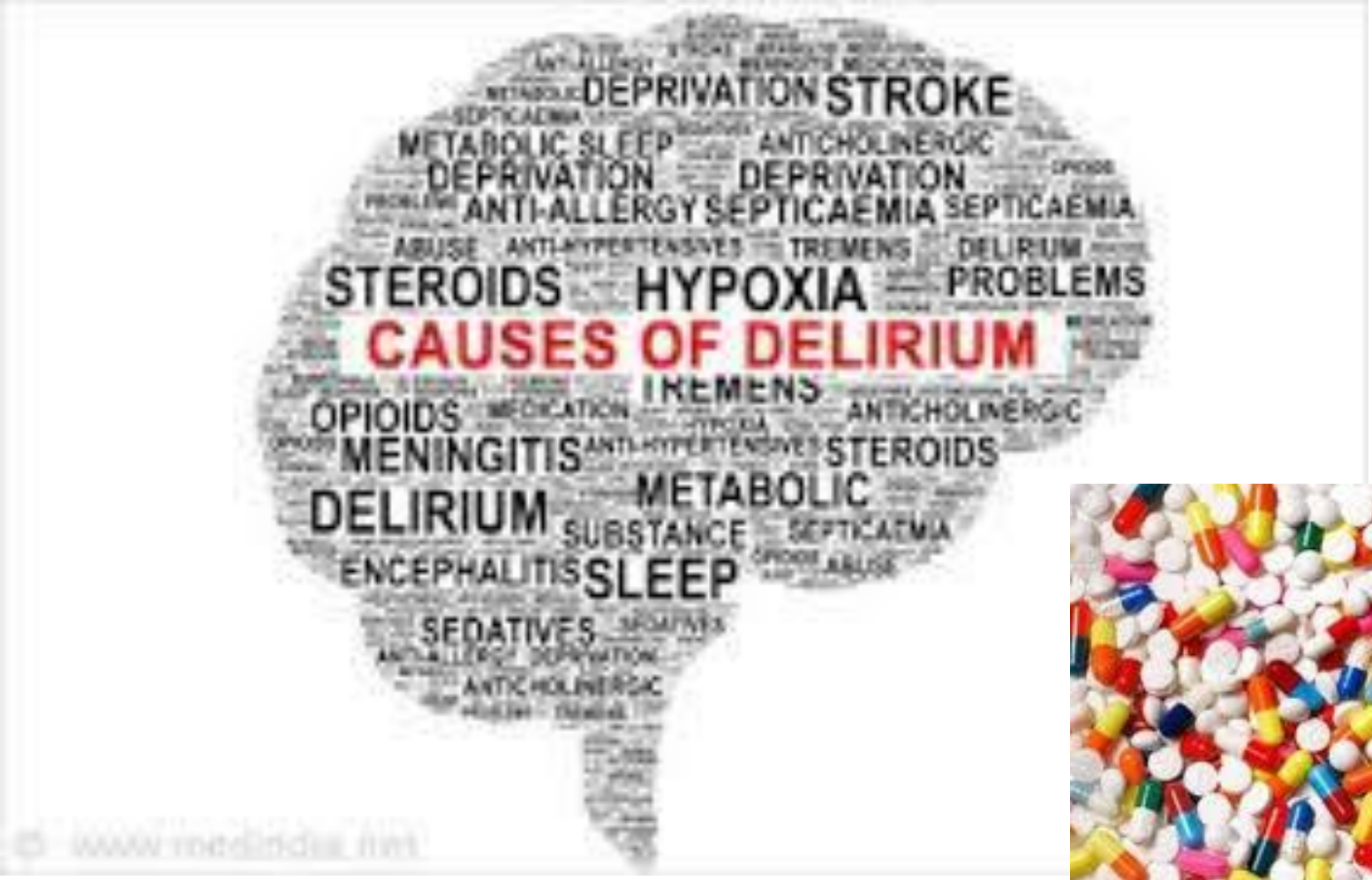
Study or Subgroup	MCI Events	MCI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Medical patients						
Abizanda 2011	27	186	39	184	12.8%	0.68 [0.44, 1.07]
Bonaventura 2007	0	30	5	30	0.3%	0.09 [0.01, 1.57]
Jeffs 2013	15	305	21	343	6.1%	0.80 [0.42, 1.53]
Martinez 2012	8	144	19	143	4.0%	0.42 [0.19, 0.92]
Subtotal (95% CI)		**665**		**700**	**23.3%**	**0.63 [0.43, 0.92]**
Total events	50		84			
Heterogeneity: Tau² = 0.03; Chi² = 3.53, df = 3 (P = 0.32); I² = 15%						
Test for overall effect: Z = 2.40 (P = 0.02)						
1.1.2 Surgical patients						
Hempenius 2013	12	127	19	133	5.5%	0.66 [0.33, 1.31]
Lundstrom 2007	56	102	73	97	57.9%	0.73 [0.59, 0.90]
Marcantonio 2001	20	62	32	64	13.4%	0.65 [0.42, 1.00]
Subtotal (95% CI)		**291**		**294**	**76.7%**	**0.71 [0.59, 0.85]**
Total events	88		124			
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 3.70 (P = 0.0002)						
Total (95% CI)		**956**		**994**	**100.0%**	**0.69 [0.59, 0.81]**
Total events	138		208			
Heterogeneity: Tau² = 0.00; Chi² = 4.32, df = 6 (P = 0.63); I² = 0%						
Test for overall effect: Z = 4.53 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.56), I² = 0%						

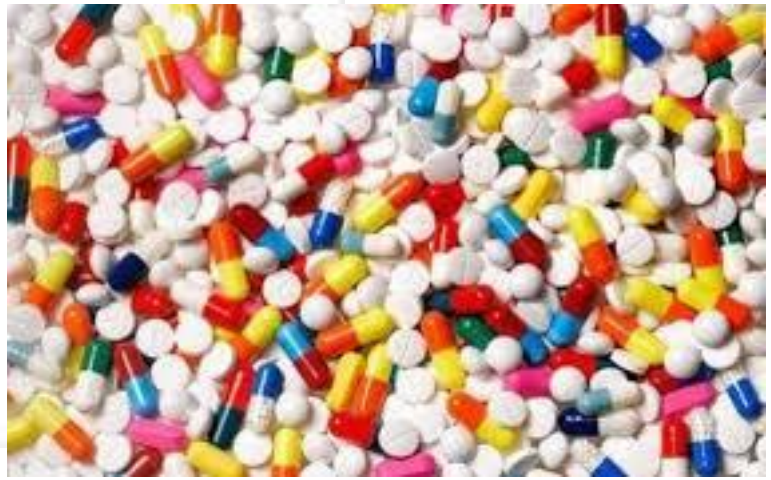


Conclusioni: non-pharmacological first

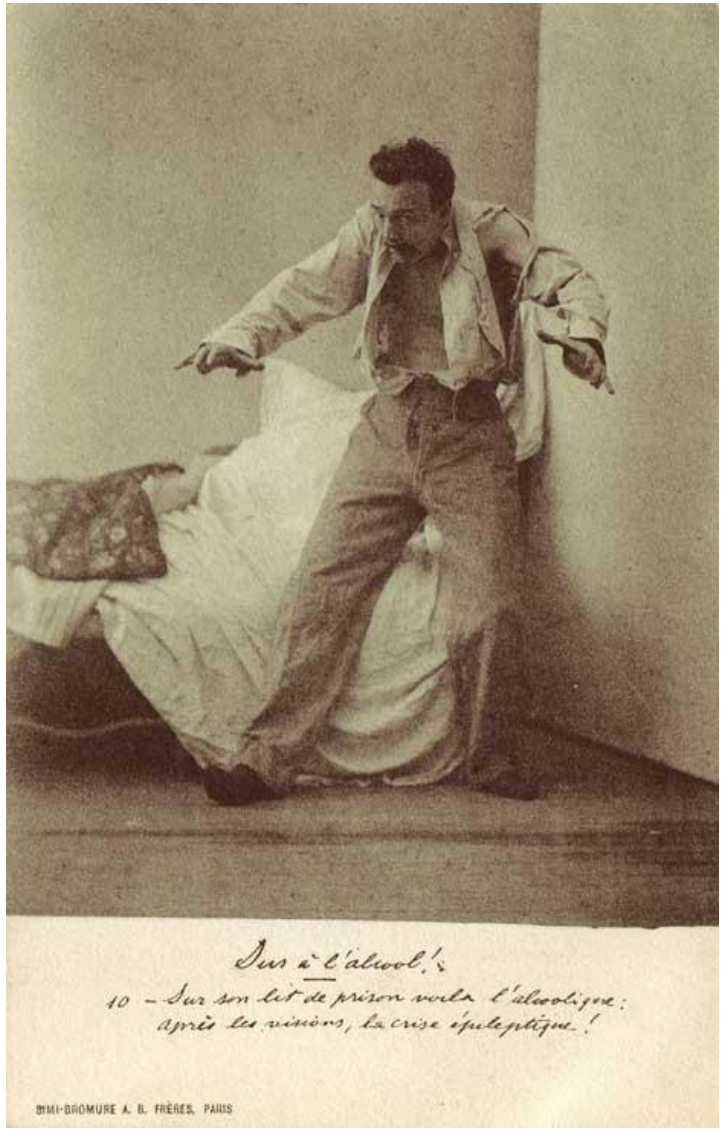
5	3			7				
6			1	9	5			
	9	8					6	
8				6				3
4			8		3			1
7				2				6
	6					2	8	
			4	1	9			5
				8			7	9

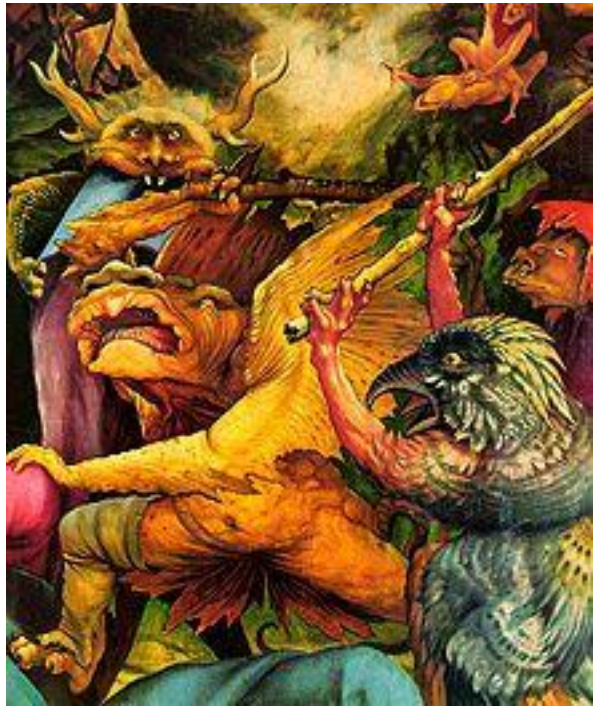
Conclusioni: trattare le cause sottostanti





Conclusioni: neurolettici come ultimo step?





Grazie per l’attenzione

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