Delirium

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Lipowski and the modern concept

- "Delirium is a transient organic mental syndrome of acute onset, characterized by global impairment of cognitive functions, a reduced level of consciousness, attentional abnormalities, increased or decreased psychomotor activity, and a disordered sleep-wake cycle"

Lipowski Z.J. Delirium: acute confusional states OUP 1990

Table 1. DSM V Diagnostic Criteria for Delirium

A. A disturbance in attention (i.e. a reduced ability to direct , focus and shift and sustain attention) and awareness (reduced orientation to environment)

B. The disturbance develops over a short period of time …. represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.

C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability or perception)

D. The disturbances in Criteria A and C are not better explained by another preexisting, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.

E. There is evidence ….. that the disturbance is a direct physiological consequence of a general medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies

see Meagher et al BMC Medicine 2014, EDA BMC Medicine 2014

Epidemiology of delirium comparing oncology with palliative care with elderly populations

Population	*Authors*	Prevalence	Incidence
≥ 70	*Francis (1990)*	16.0	06.0
≥ 65	*Levfkoff (1992)*	10.5	31.3
≥ 70	*Inouye (1993)*		25.0
≥ 70	*Inouye (1996)*		18.0
Oncology	*Ljubisavjevic (2003)*		18.0
Oncology	*Gaudreau (2005)*		16.5
Hospice	*Minagawa (1999)*	28.0	
PC Unit	*Lawlor (2000)*	42.0	45.0
Homecare	*Caraceni (2000)*	28.0	-
Dying patient	*Massie et al.(1983)*		85

From Caraceni & Simonetti The Lancet Oncology 2009

Assessment tools aims at operationalize

- **Cli**nical diagnosis domains
  - Attention
  - Consciousness level
  - Cognitive functions
  - Acute/fluctuating course
  - Psychotic symptoms
  - Psychomotor changes
  - Sleep/wakefulness cycle alterations

(Meagher et al Br J Psychiatry 2007)

Delirium screening instruments

- MMSE 4 item possono essere sufficienti

Fayers PM et al J Pain Sympt Manage 2005; 30: 41-50

- NUDESC

Gaudreau et al. The nursing delirium screening scale J Pain Sympt Manage 2005; 29: 368-375

- Delirium Observation Screening Scale

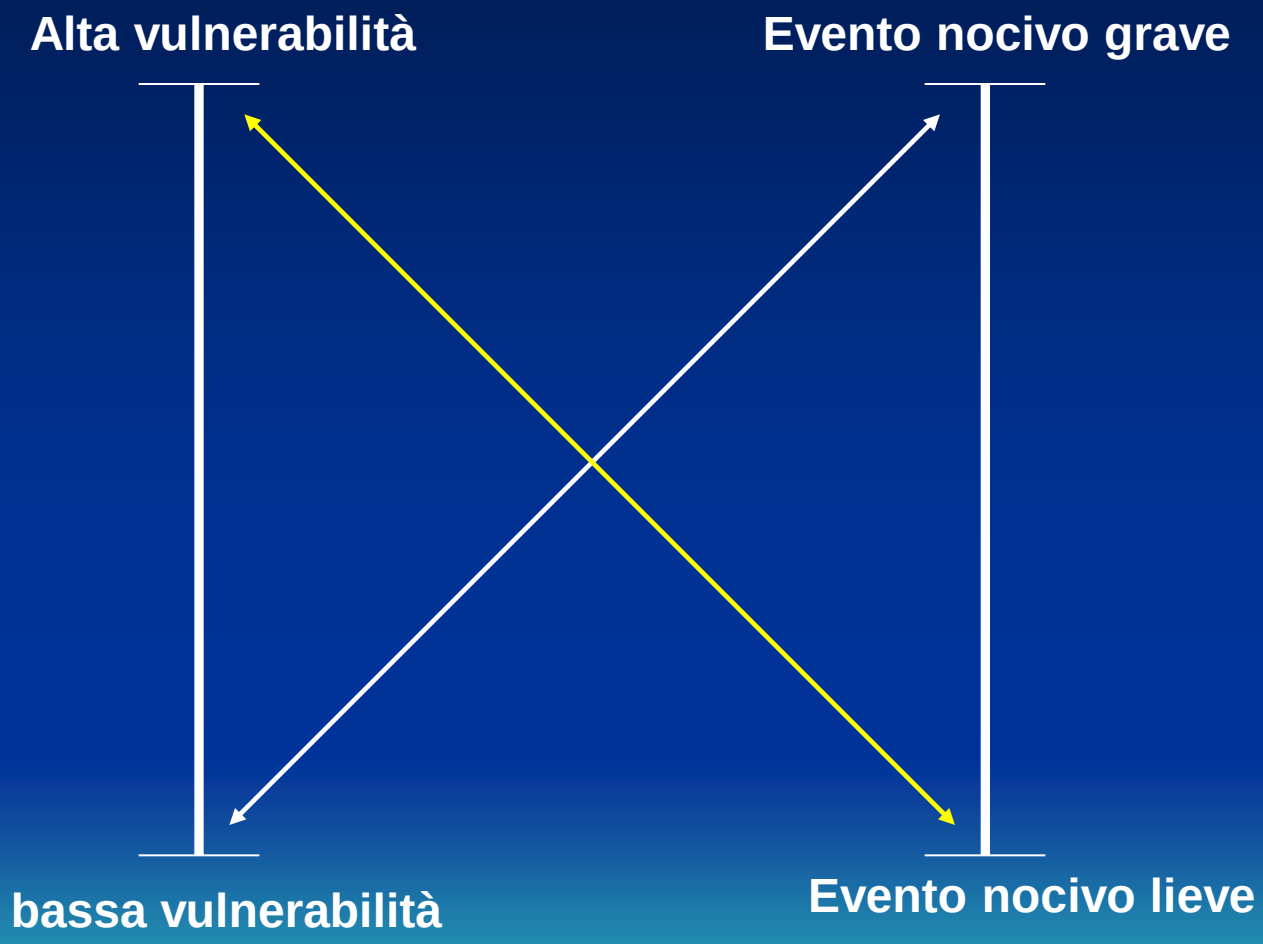
Detroyer E et al 2014 Pall Med

Risk factors, significant at multivariate analysis reflect the complex pathophysiology and potential multifactor etiology

- **Age**
- **Previous cognitive failure**
- **Severity of associated illness**
- **Functional impairment**
- **Renal function**
- **Metabolic abnormalities**
- **Low albumin**
- **Opiods**
- **Benzodiazepines**
- **Fever infection**
- **History of delirium**
- **Bone metastases**
- **Liver metastases**
- **Metastasis to CNS**

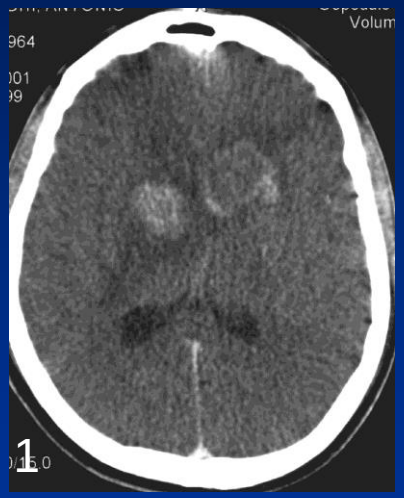
Caraceni & Simonetti Lancet Oncology 2009

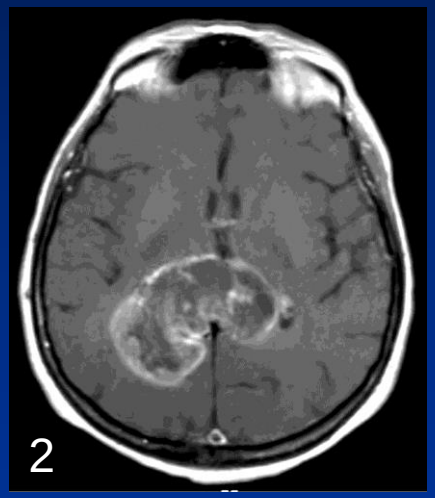
Multifactor model with baseline vulnerability and precipitating factors

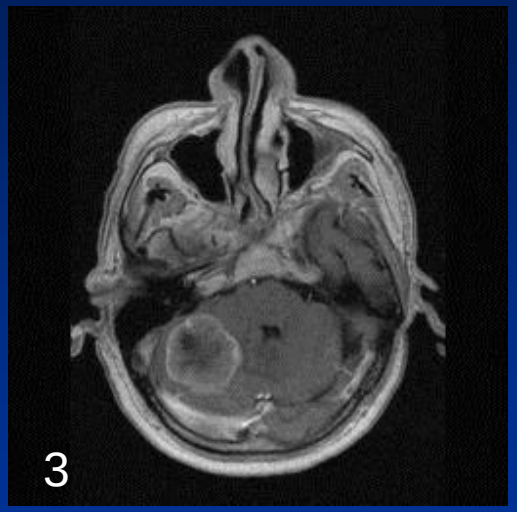


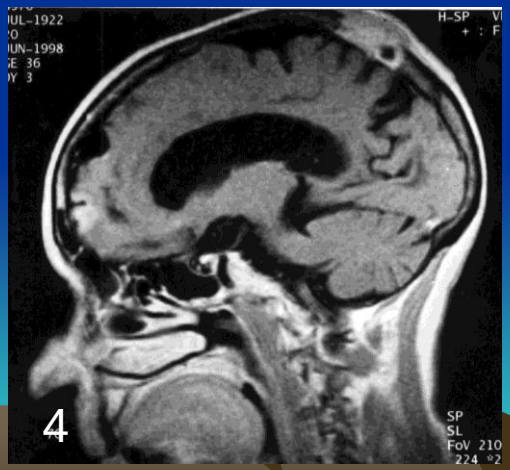
Inouye and Chapentier JAMA 1996

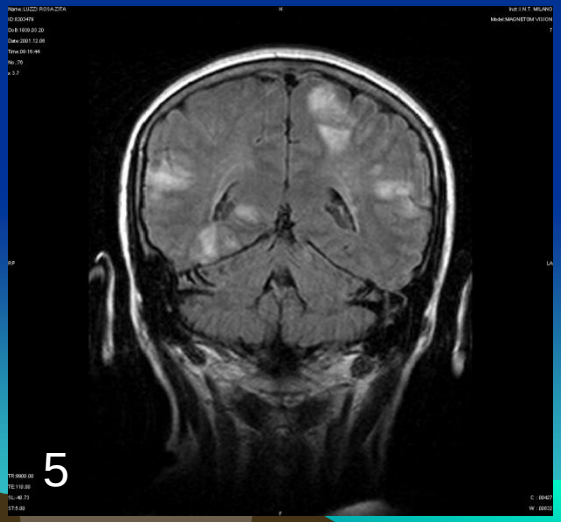
Cause strutturali di delirium nel paziente oncologico





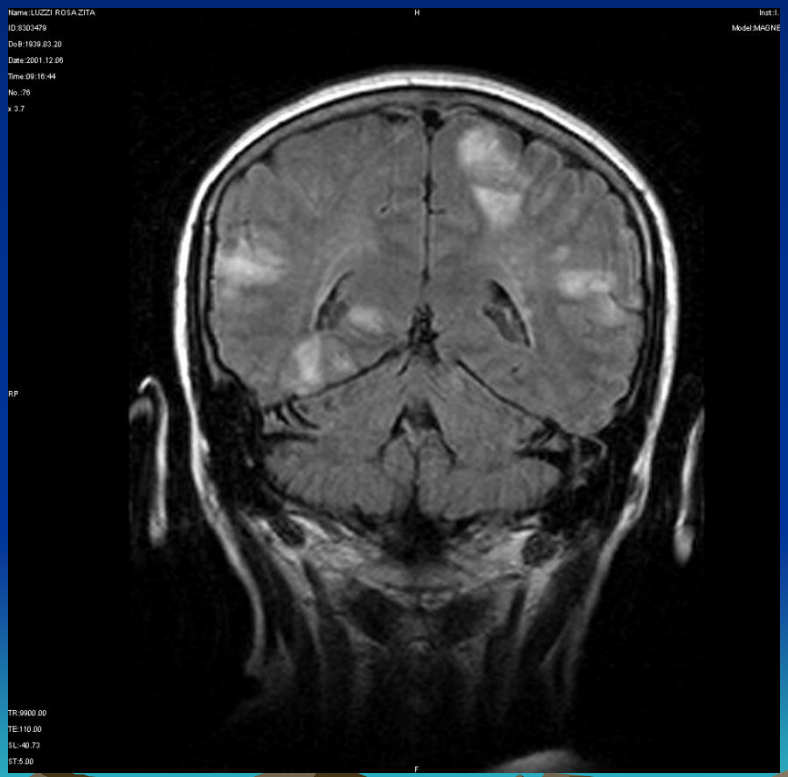




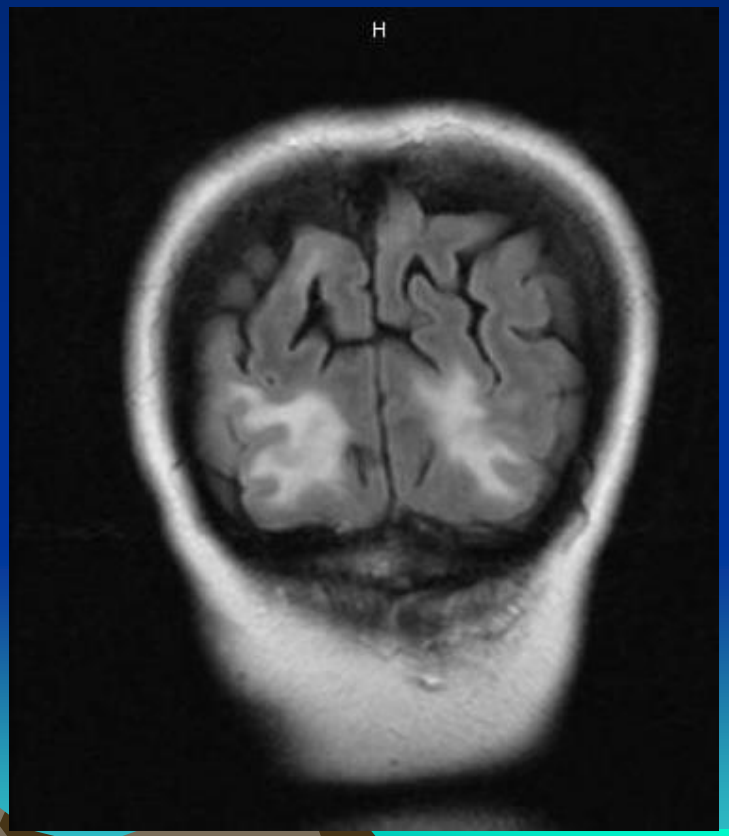


Structural causes of delirium in cancer patients not due to due to cancer

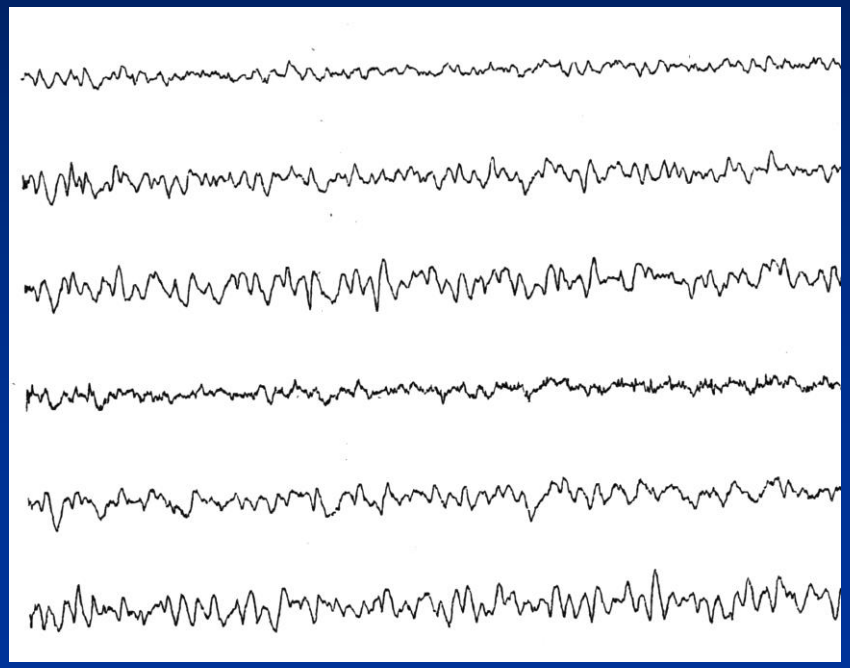
Multiple brain infarcts during 5-FU continuous infusion



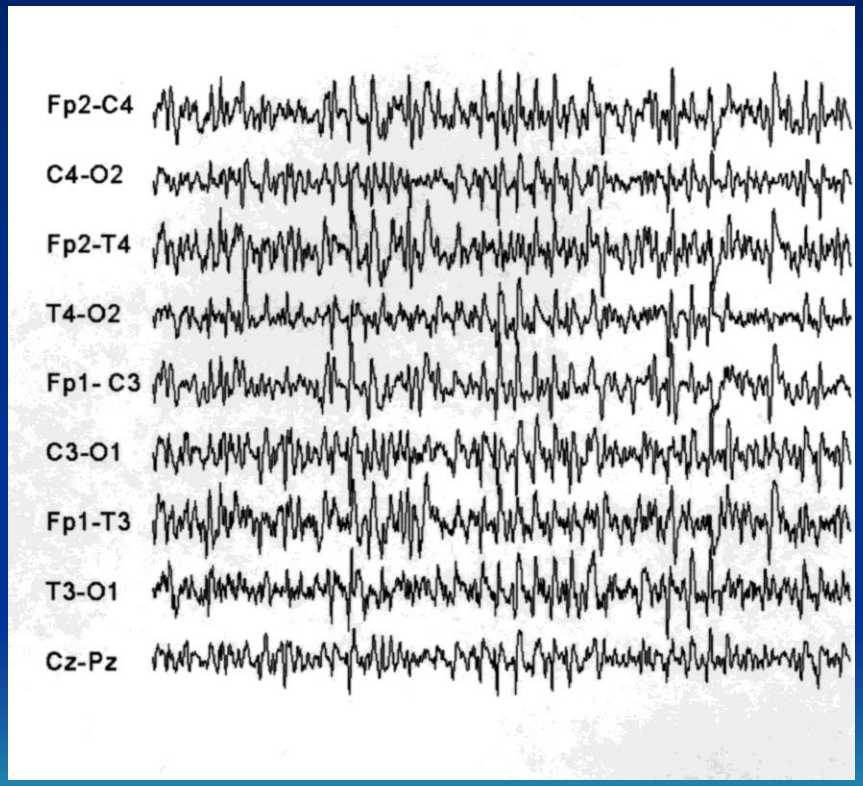
RPLE cytarabine and oxaliplating regimen



Delirium aspecific EEG slowing



Non convulsive status epilepticus due to ifosfamide infusion



DIAGNOSTIC PROCESS RATIONALE
Identify potentially toxic metabolic conditions (drugs , drug interactions)
Check metabolic factors and vitamin deficiency
Rule out acute psychotic reactions
Rule out structural brain lesions Consider Posterior reversible encephalopathy (MRI required)
Rule out seizures non convulsive status epilepticus
Think of more rare conditions (e.g. paraneoplastic syndromes)

Potentially specific predisposing factors
Advaced age
Previously impaired cognition
History of delirium
Metastatic CNS lesion

Unspecific Factors associated with disease progression/ or deterioration
Functional impairment
Severity of illness
Low albumin
Bone metastases
Liver metastases
Hematological malignancies

Potentially specific incident factors
Metabolic abnormalities
Metastases to brain or meninges
Opiods (dose related)
Benzodiazepines
Corticosteroids(dose related)

Precipitating factors in 40 reversible delirium episodes in a palliative care unit

Factor	Prob.	Poss.	Total
• Opioids	35	3	38
• Psy. Drugs	8	5	13
• Dehydration	18	8	26
• Nonresp. Infection	10	2	12
• Alcohol withdrawal	2	2	4
• Intracranial cause	3	0	3
• Hypoxia	12	1	13
• Metabolic	5	6	11
• Hematologic	4	1	5
Totals	98	28	126

Lawlor et al Arch Int Med 2000

Precipitating factors and reversibility in PC

Type of factor	Reversed	Non rev.	Hazard r. (95 C.I.)
Psychoactive d.	38 (95%)	15 (48%)	6.65 (1.5-29)
Dehydration	26 (65%)	8 (26%)	1.5 (.7-3.2)
Hypoxia	11 (28%)	22 (71%)	0.32 (.15-.7)
Miscellaneous	7 (18%)	7 (23%)	
Nonresp. Infection	10 (25%)	8 (26%)	
Metabolic	10 (25%)	18 (58%)	
Hematologic	5 (13%)	7 (23%)	

Lawlor P. et al 2000 Arch Int Med

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Lawlor et al Arch Int Med 2000

Delirium reversibility in hospice

Total 121 Cases

	reversible	irreversible
	33 (27%)	88 (73%)
survival	39+/- 69	16 +/- 10
organ failure	++	+
attention	++	+
vigilance	++	+

Leonard et al Pall Med 2008; 22 : 848-854

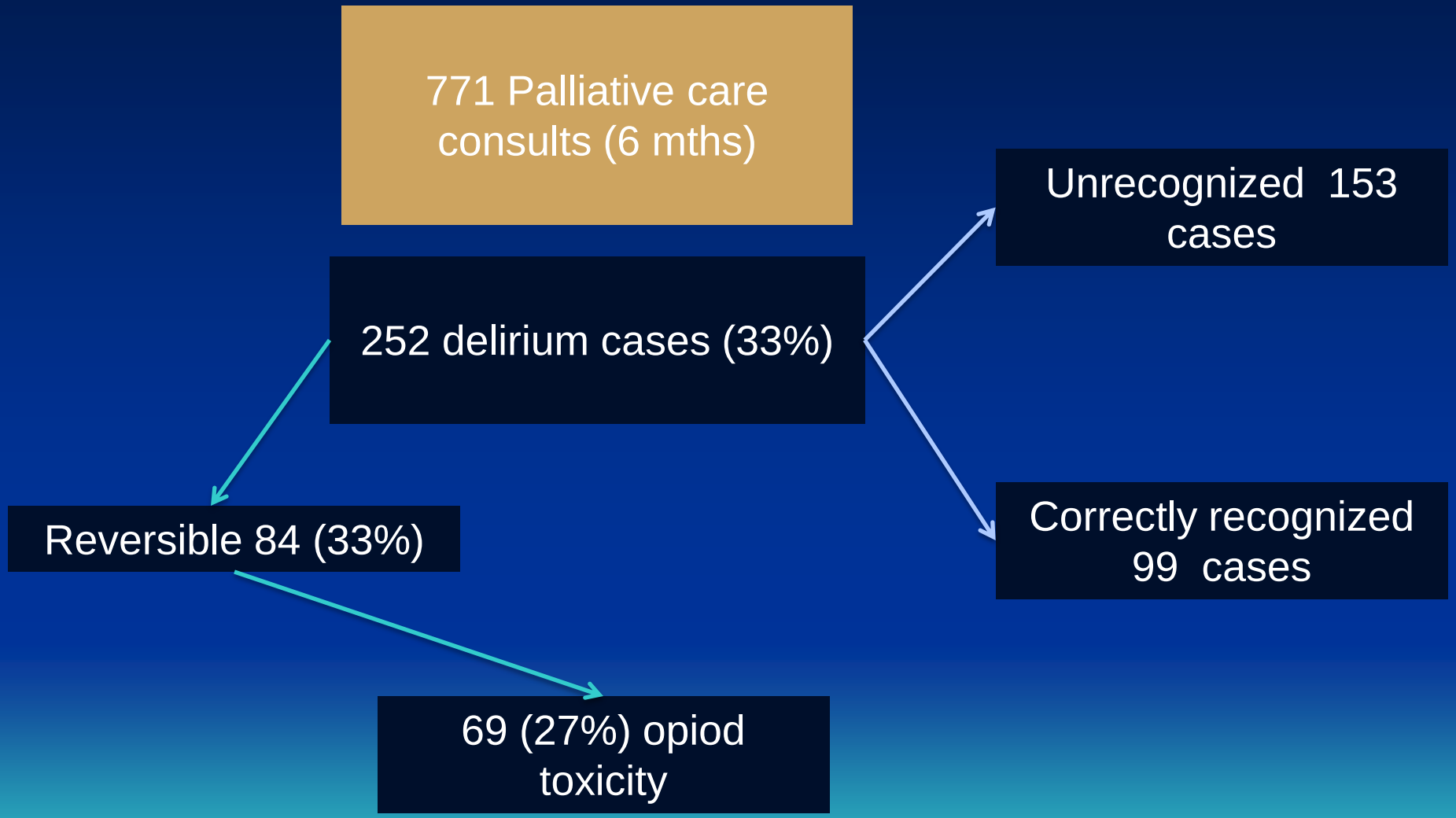
Delirium in the acute palliative care unit

- 556 consecutive patients
  - 58% with delirium
  - 41% at admission
  - 17% during admission

- 26% Acute Delirium episodes recovered
  - Hydration
  - Opiod rotation
  - Antibiotics

De la cruz et al The Oncologist 2015

Delirium and Inpatient Palliative Care Consults



De la cruz et al Supp Care in Cancer 2015

D-PaP Score

- Dsypnea
- Anorexia
- leucocytes and lymphocytes)
- Karnofsky performance status
- Clinical prediction
- Delirium

Scarpi E, Maltoni M, Miceli R, Mariani L, Caraceni A, Amadori D, Nanni O. Survival prediction for terminally ill cancer patients: revision of the palliative prognostic score with incorporation of delirium. Oncologist. 2011;16(12):1793-9. Epub 2011 Oct 31m

- Drug toxicity

Antineoplastic agents

Antiblastic

- Paclitaxel
- Vincristine
- Ifosfamide
- Cytosine Arabinoside
- Cisplatin
- Methotrexate
- Thiotepa
- Etoposide
- Nitrosurea
-

Other agents

- Bevacizumab
- Rituximab

Serotonergic Syndrome

- Fluoxetine other SSRIs
- Venlafaxine
- Trazodone
- Tramadol
- Mirtazapine
- Risperidone
- Citalopram
- TCAs

Clinically significant drug interactions

CYP2D6 Inhibitors	Drugs metabolized by CYP2D6
Cimetidine	Oxycodone
Desimipramine	Tramadol
Fluoxetine	Haloperidol
Paroxetine	Risperidone
Haloperidol	Fluoxetine
Sertraline	Paroxetine
	Venlafaxine
	Duloxetine
	Desimipramine

Clinically significant drug interactions

CYP3A4 Inhibitors	Drugs metabolized by CYP3A4
All imidazole antifungine	Fentanyl, Alfentanyl
Fluoxetine	Methadone
Norfloxacine	Alprazolam, Midazolam
Erythromicine	
Grapefruit juice	

Therapeutic interventions

- Reduce overall risk
- Treat reversible causes
- Non pharmacological management
- Family counselling
- Drug therapy

A geriatric model of risk modification

- Orientation protocol
- Non pharmacological protocol for night sleep mannagement
- Mobilization
- Visual and auditory aids
- Hydration

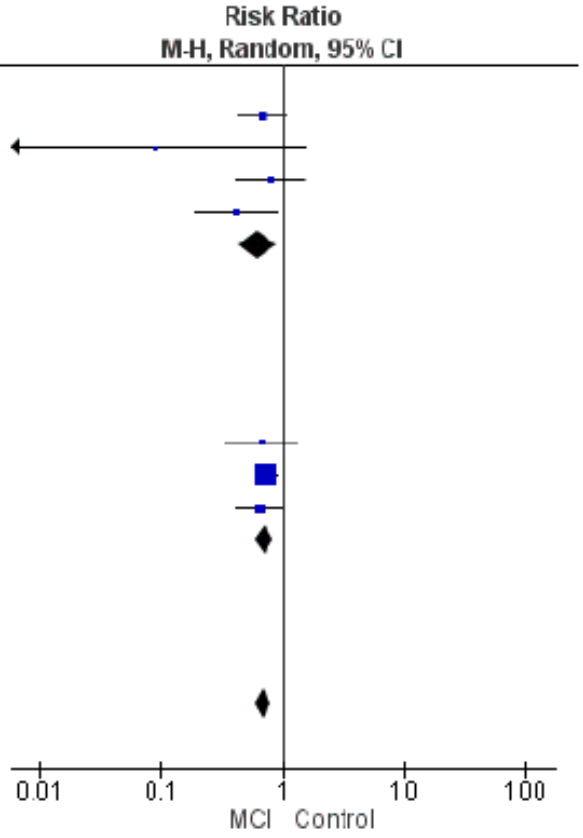
Inouye et al 1999

New England Journal of Medicine

Reduction of delirium incidence from 15 to 9 %.in patients ≥ 70 years of age

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%						



Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, Simpkins SA. Interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD005563.

Opioid-induced delirium

- Oversedation - hypoactive delirium
- Cognitive impairment
- Hyperactive delirium

Opioid-induced delirium

- Dose reduction
- Switch opioid
- Switch route
- Haloperidol
- Psychostimulants

Winegarden J et al Pain Medicine 2015 epub ahead of print. Ketamine for opiod-induced neurotoxicity

Evidenceson delirium pharmacological therapies

- Lonergan E Cochrane review 2007
- Lonergan E Cochrane review 2009
- Seitz D J Clin Psychiatry 2007
- Lacasse H Ann Pharmacother 2006
- Jackson Cochrane terminal delirium review 2004 updated Candy et al 2012
  - Only 1 RCT Breitbart et al

Research

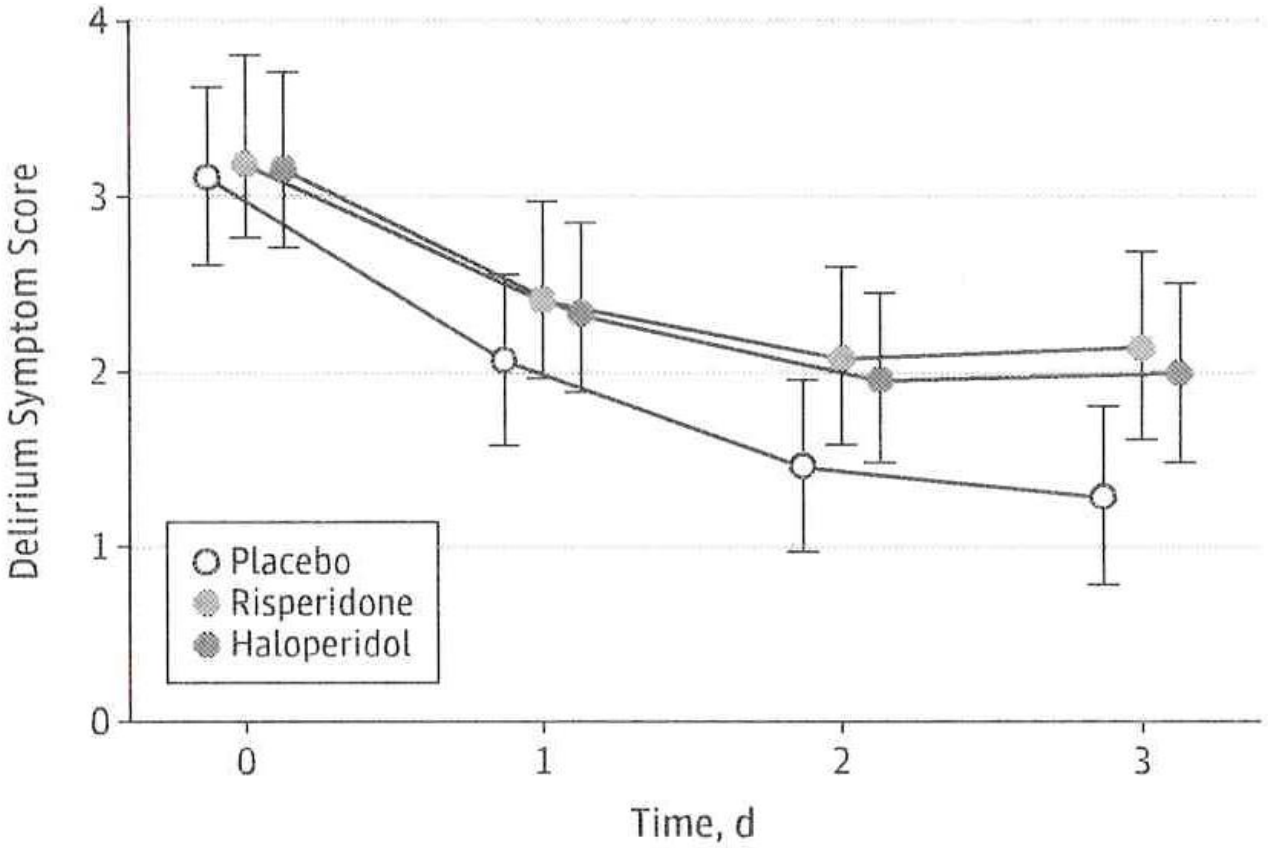
JAMA Internal Medicine | Original Investigation

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

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

Delirium therapy

	oral	parenteral
• Haloperidol	+	+
• Risperidone	+	
• Olanzapine	+	+
• Ziprasidone	+	+
• Quetiapine	+	

with or without Lorazepam ?

Lonergan et al Antipsychotics for delirium (Review) Cochrane database of systematic reviews 2007, Issue 2. http://www.cochranelibrary.com

Drug therapy

- Haloperidol
- Phenotiazine neuroleptics
- Atypical neuroleptics
- Sedation
  - Anthistamine
  - Clonidine (alpha-2 agonists)
  - Benzodiazepines

Therapeutic strategy

- First step tranquilization
  - Control agitation, hallucination , delusion
  - Improve sleep at night
  - Preserve consciousness
- Second step sedation
  - Controlled sedation

First step

- Haloperidol individual titration
- Alternative neuroleptics
  - Olanzapine
  - Ziprasidone
  - Quetiapine
- Antihistamine for nigh time sleep
  - Prometazine

Other neuroleptics

Drug	dose	T/2
Droperidolo	1-10 mg	2-3 ore
Chlorpromazine	25-50 mg	16-30 ore
Promazine	25 mg	15-30 ore
Metotrimeprazine (levomepromazine)	25-50 mg	16-78 ore

Second step sedation required

- Add prometazine
- More sedating neuroleptics
  - Quetiapine at bedtime
  - Chlorpromazine
- Benzodiazepines for continuous sedation
  - Midazolam, lorazepam
- Alpha-2-agonist agents
  - Clonidine
  - Dexmedetomidine