Opioid and delirium

GRG 29 luglio 2011

Simone Franzoni

Outline of the presentation

- Drugs and delirium
- Physiopathology – OIN
- Cancer - opioid – delirium
- Hyperactive delirium
- Postsurgey – opioid - delirium
- ICU - opioid – delirium
- Medical conditions - opioid – delirium
- Prevention
- Therapy

Delirium

Incidence:

6-56% on general hospital units

26-45% on palliative care units

80-90% for patients in intensive care (Balas, 2007; Inouye, 2006)

Many negative outcomes:

- higher mortality rates (10-65%) *(independent factor in predicting short-term survival of patients with advanced cancer)* (Bush, 2011)
- decreased functional ability that often leads to institutionalization (Burns, 2004)
- increased use of physical restraints (Micek, 2005)
- LOS (Inouye, 2006)
- increased hospital expenditures (Milbrandt, 2004)

Drug-induced delirium

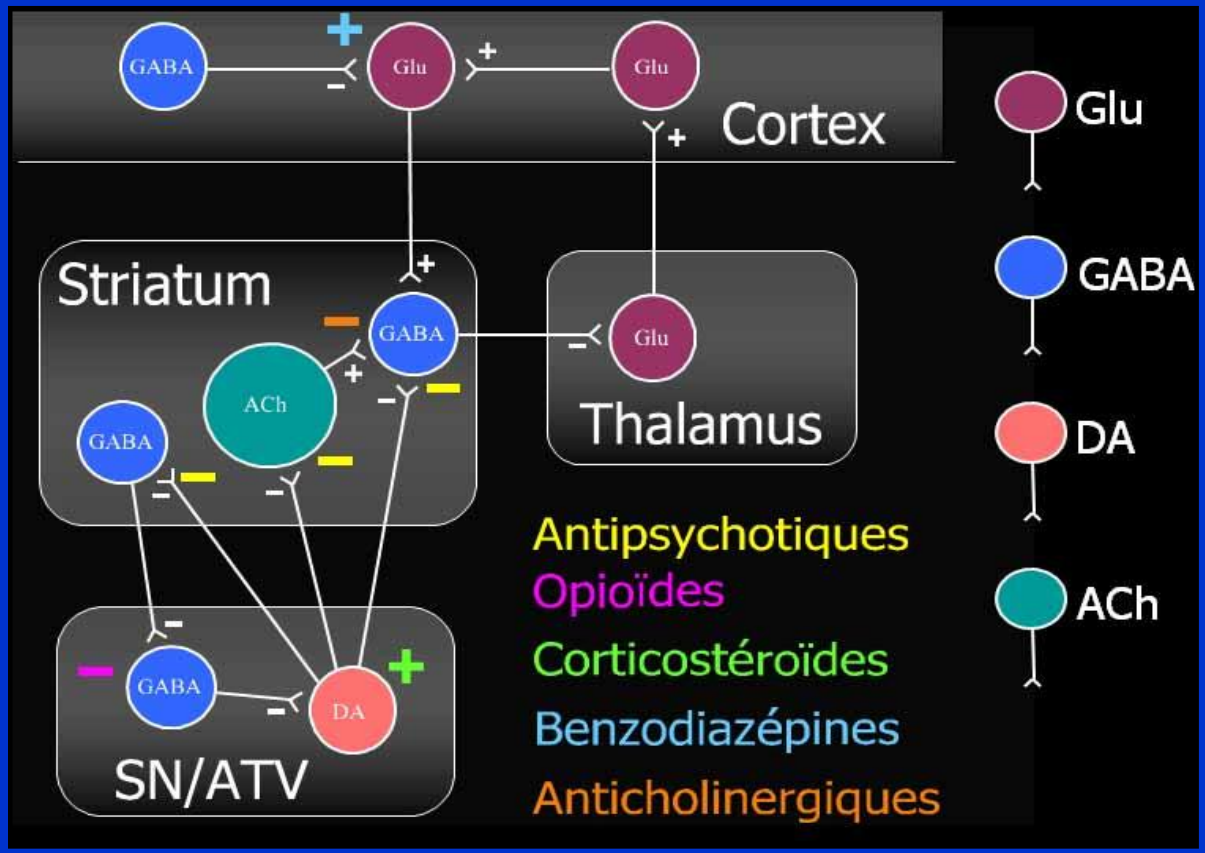
- Psychoactive: opioids, benzodiazepines, anticholinergics, tricyclic antidepressants, SSRI, SNRI, neuroleptics, nonbenzodiazepine hypnotics
- Antineoplastic
- Other: corticosteroids, antihistamines, H2 blockers, antibiotics (quinolones), metoclopramide, anticonvulsants, certain antivirals

Risk factors of opioid delirium

- renal dysfunction
- dehydratated
- infection
- taking other psychoactive drugs

- degree of cognitive impairment
- age
- previous delirium

Pathophysiology of delirium



Opioid-induced neurotoxicity (OIN)

- Syndrome of neuropsychiatric side effects seen with opioid therapy
- Any patient prescribed opioids is at potential risk for developing OIN
- Occur with all known opioid agonists (morphine, hydromorphone, oxycodone, fentanyl, methadone)
- Meperidine produces a high rate of OIN because approximately 60% of it is metabolized to normeperidine

Opioid-induced neurotoxicity (OIN)

- Features: delirium, severe sedation, hallucinations (visual or tactile), cognitive impairment, myoclonus, seizures, hyperalgesia, allodynia
- Symptoms can develop as a single feature or in any combination and order
- Patients with a history of seizures, cerebral metastases, or metabolic abnormalities may have a predisposition to developing tonico-clonic OIN-associated seizures

Phatophysiology opioid-induced delirium

- Cholinergic hypothesis describes a deficiency of acetylcholine and an excess of dopamine
- Other neurotransmitter hypotheses postulate the role of glutamate, serotonin, cortisol, endogenous opioid
- Cytokines is attracting recent interest, especially IL-1, IL-6, IL-8, interferon, TNF
- Transient thalamic dysfunction

Cholinergic hypothesis

In addition to delirium, other features of anticholinergic drug toxicity are

mydriasis,

hyperthermia,

fever with no sweating,

flushed appearance,

dry skin,

urinary retention

1) OIN - anticholinergic action

OIN is related to the anticholinergic actions of opioids, with inhibition of central cholinergic activity in multiple cortical and subcortical regions of the brain,

in addition to an imbalance in CNS cholinergic and dopaminergic systems

2) OIN - toxic opioid metabolites

- Accumulation of toxic opioid metabolites
- Major metabolite (44%–55%), M-3-G, has no MOR-opioid binding and consequently no analgesic properties

- M-3-G may be responsible for the cluster of OIN symptoms (*Evidence for this is conflicting. Gong in 1992, reported that M-3-G did not produce excitatory and antianalgesic effects in rats. Penson in 2001, did not induce neurotoxicity when small i.v. doses of M-3-G were injected into healthy volunteers. Normorphine, another nonopioid-binding neurotoxic metabolite, accounts for only approximately 5% of morphine metabolism)*

- Unknown if M-6-G contributes to OIN

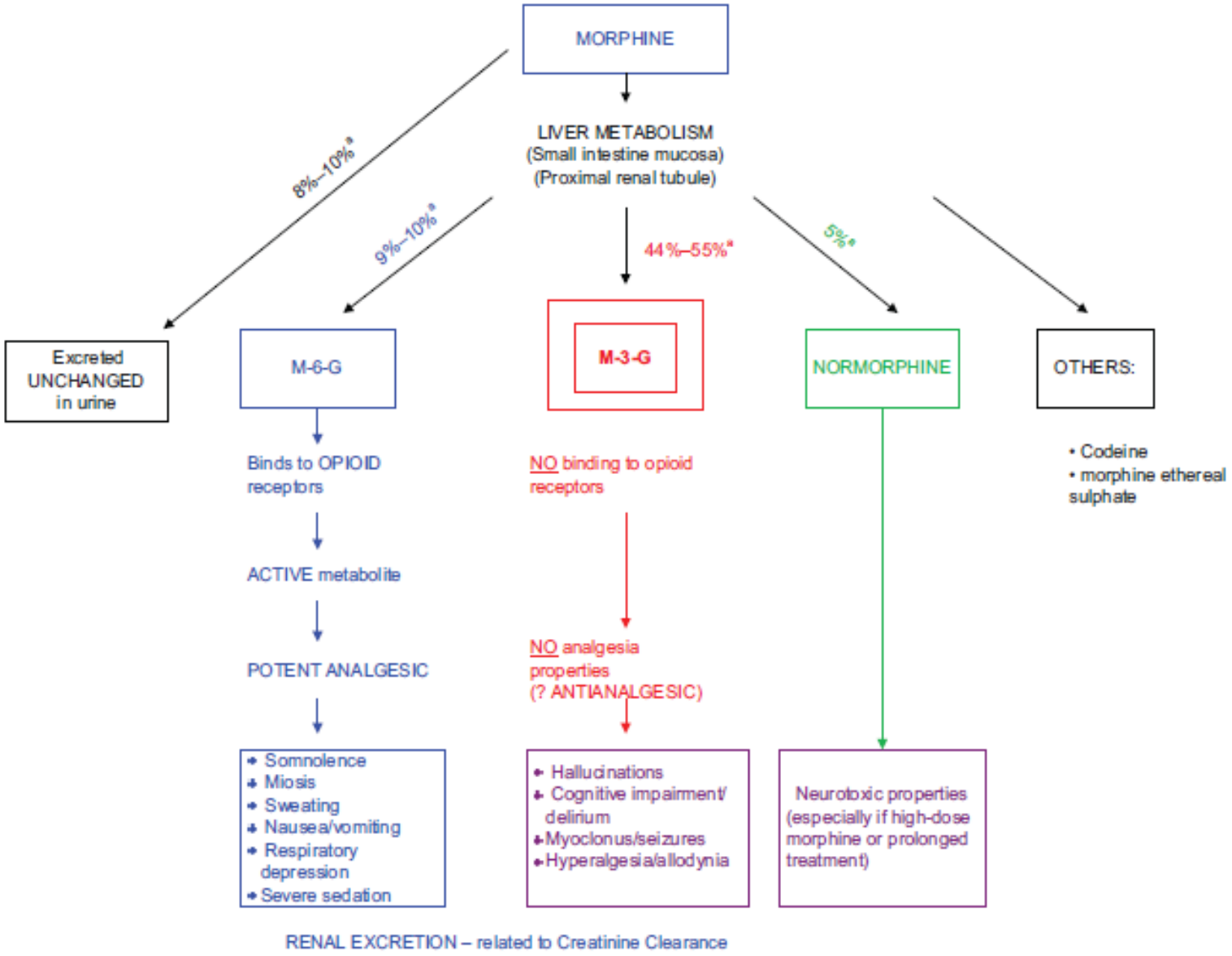


Figure 2. Morphine metabolism [37, 41, 44]. [a]The percentage breakdown of metabolites remains the same for all routes of administration.

Abbreviations: M-3-G, morphine-3-glucuronide; M-6-G, morphine-6-glucuronide.

3) OIN - NMDA

- Involve endocytosis of opioid receptors
- Neurotoxic effect of opioids may occur via a nonopioid receptor–mediated mechanism
  - Activation of N-methyl- D-aspartate (NMDA) receptors, where the neurotransmitter is glutamate
  - Inhibition of glycine in dorsal horn neurons leads to myoclonus and hyperalgesia

Age and Ageing 2011; **40:** 23–29
doi: 10.1093/ageing/afq140
Published electronically 9 November 2010

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Which medications to avoid in people at risk of delirium: a systematic review

Andrew Clegg[1], John B. Young[2]

Moderate quality evidence suggests that opioids are associated with an approximately 2-fold increased risk of delirium in medical and surgical patients

- Meperidine appears to have a higher risk of delirium compared with other opioids. This may be because:
  - Meperidine can accumulate when renal function is impaired
  - Converted to a metabolite with anticholinergic properties (Normeperidine)

- Oxycodone appears to have a favourable profile when compared with other opioids

- Acute severe pain is an important contributing factor for delirium and withholding opioid medications for fear of risk of delirium is clinically inappropriate, but the lowest dose consistent with pain control should be used

- Moderate quality evidence suggest that in situations where acute severe pain is likely (hip fracture), lower doses of opioids may paradoxically be associated with higher risk of delirium

Exposure to opioid analgesia in cognitively impaired and delirious elderly hip fracture patients

n.184 elderly patients with hip fractures undergoing surgical fixation

The amount of morphine equianalgesic dose differed significantly between demented and non-demented patients (7.5±1.8 vs. 14.1±4.9, P<0.001).

Patients with cognitive decline or with delirium received only 53 and 34%, respectively, of the amount of O. that was administered to cognitively intact patients

A significant association was observed between cognitive status, or delirium, and amount of opioid analgesia (P<0.001 and P=0.003, respectively).

Abraham Adunsky, Rami Levy, Eliyahu Mizrahi, Marina Arad
Archives of Gerontology and Geriatrics 2002 (Vol. 35, Issue 3: 245-51)

Exposure to opioid analgesia in cognitively impaired and delirious elderly hip fracture patients

The management of pain in older persons with hip fracture surgery is suboptimal with regards to insufficient administration of opioid analgesia in demented and delirious patients (adoption of a standardized protocol for pain control)

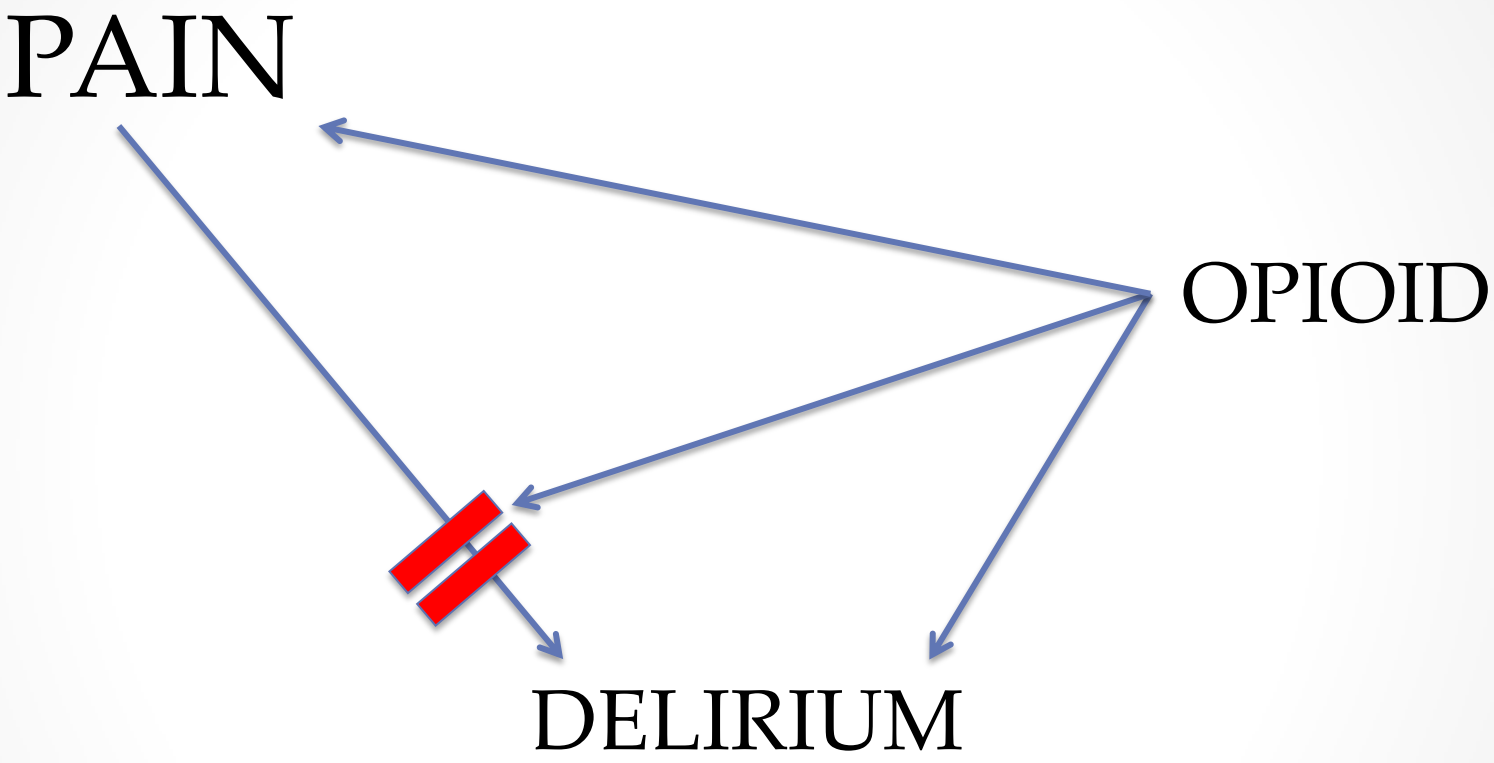
Abraham Adunsky, Rami Levy, Eliyahu Mizrahi, Marina Arad Archives of Gerontology and Geriatrics 2002 (Vol. 35, Issue 3: 245-51)

Undermedication for pain and precipitation of delirium

S.Robinson, C.Vollmer 2008

- The patients who developed delirium received a smaller amount of the total possible analgesic than those who did not develop delirium

- Patients with hip fracture receiving less than 10 mg of morphine in a 24-hour period (a small percentage of what was ordered) were likely to develop delirium ($p<0.001$) *(Morrison 2003)*


PAIN
OPIOID
DELIRIUM

Models of care with opioid

- **Cancer**
- Post-surgery
- Intensive care unit
- Medical conditions

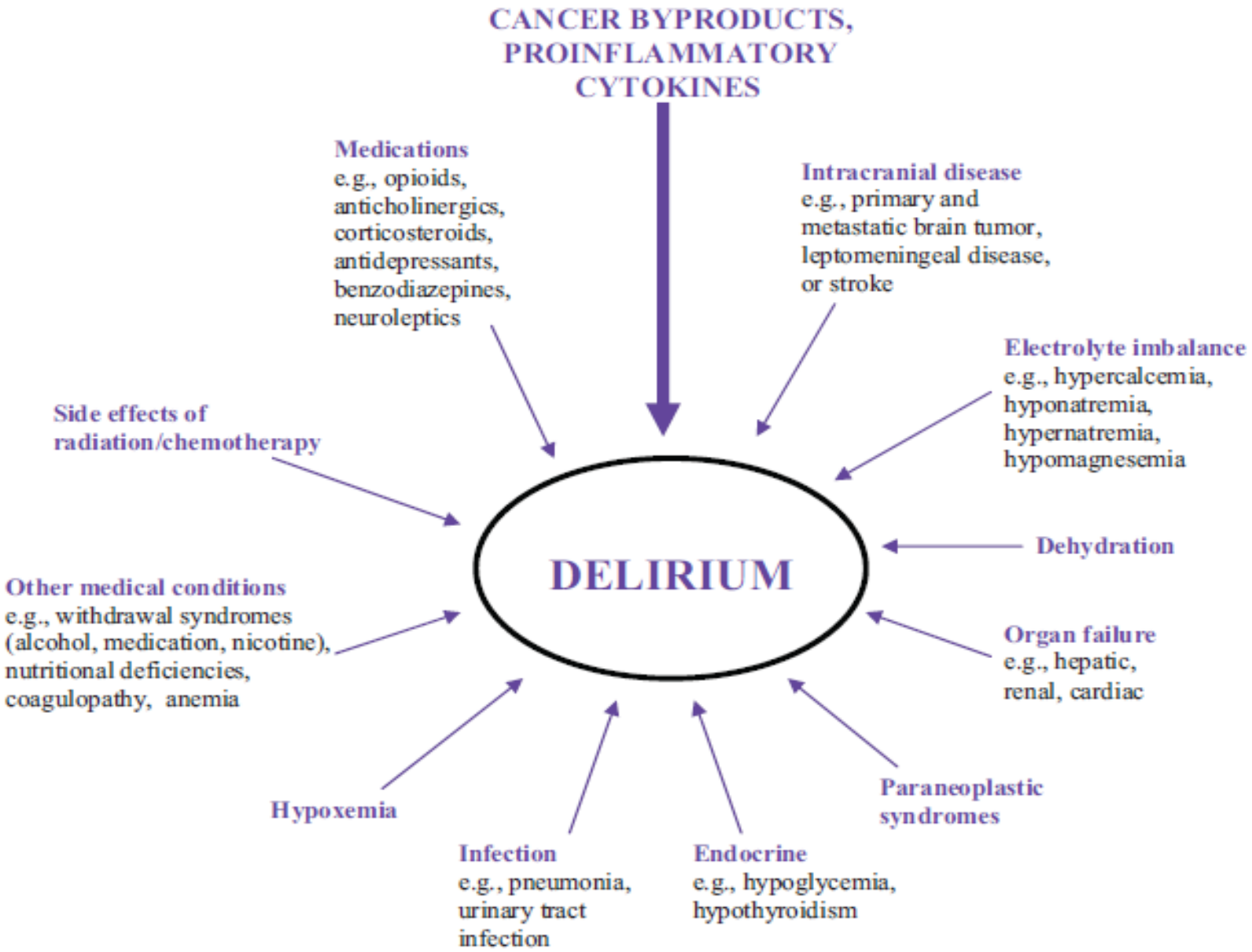
Delirium and cancer

- Delirium is present in 26–44% of advanced cancer patients at the time of admission to an acute care hospital or palliative care unit
- 80% of patients with advanced cancer develop delirium in the last days before death
- Organic etiology of delirium is usually multifactorial, with a median of 3 (range, 1 to 6) precipitants per delirium episode

Delirium and cancer

- Most common and devastating neuropsychiatric complication in patients with advanced cancer
- Causes significant distress to patients and families
- Impairs patient communication, thus challenging the assessment of pain and other symptoms
- Causes significant morbidity, increasing LOS and the risk for falls
- Prognosticates a greater likelihood of death

Reversible in up to 50% of cases



Factors contributing to delirium in cancer patients.

Cause of delirium in cancer patient

- Cancer
- Medical conditions
- Pain
- Opioids (contributing factor in 2/3 of cases)

Type: hyperactive, hypoactive, mixed

Hyperactive delirium

Hyperactive and mixed delirium are highly associated with drug-induced delirium

(hypoactive d. is associated with dehydration and encephalopathies)

Differential diagnosis: opioid delirium

- Hyperactive delirium due to pain
- Hyperactive delirium due to cancer or general medical conditions
- Agitation: increased expression of pain in an agitated patient may be misinterpreted and inappropriately treated as a pain syndrome, with the resulting increased opioid administration exacerbating the delirium severity
- Hyperalgesia

HYPERALGESIA

- Increased pain sensitivity
- This sensitization presents as increasing pain despite increasing doses of opioids
- Long-term use and high doses of opioids may be associated with the development of H., which may be related to
  - opioid metabolites (M3G)
  - opioid-induced cell apoptosis
  - loss of GABA neurons to apoptosis
  - NMDA receptor agonism (glycine)

Differential diagnosis: opioid delirium

HYPERACTIVE DELIRIUM	AGITATION	HYPERALGESIA
PAIN		
CANCER and OTHER CAUSES		
OPIOID		

Disturbance of consciousness

Medication hystory

Psychoactive medications and risk of delirium in hospitalized cancer patients

- 261 hospitalised cancer patients in the hemato-oncology unit at Hôtel-Dieu de Québec Hospital, Canada
- Between January 2002 and December 2003
- Assessment with Nursing Delirium Screening Scale

Gaudreau J-D, Gagnon P, Harel F, Tremblay A, Roy M-A. 2005. J Clin Oncol. 23(27); 6712-8.

Psychoactive medications and risk of delirium in hospitalized cancer patients

Predictor		HR	95% CI	*P* value
Clinical characteristic				
	Sex	0.84	0.46 – 1.55	0.58
	Age	1.007	0.98 – 1.03	0.55
	History of delirium	5.45	2.40 – 12.39	**<.0001**
	Metastases			
	Brain	1.10	0.34 – 3.57	0.87
	Bone	0.77	0.33 – 1.84	0.56
	Liver	1.91	0.96 – 3.78	**0.07**
	Lung	1.59	0.62 – 4.13	0.34
Laboratory data				
	Low sodium	2.19	0.62 – 7.73	0.23
	High sodium	-	-	-
	Low potassium	0.97	0.38 – 2.48	0.94
	High potassium	2.04	0.49 – 8.49	0.33
	Low calcium	1.45	0.76 – 2.78	0.26
	High calcium	1.23	0.17 – 8.99	0.84
	High ALT	0.98	0.37 – 2.58	0.96
	High AST	1.24	0.54 – 2.84	0.61
	High urea	1.39	0.69 – 2.79	0.36
	High creatinine	1.56	0.79 – 3.06	0.20

Gaudreau J-D, Gagnon P, Harel F, Tremblay A, Roy M-A. 2005. J Clin Oncol. 23(27); 6712-8.

Psychoactive medications and risk of delirium in hospitalized cancer patients

- Delirium incidence: 16.5%
- Delirium is associated with
  - > 90mg opioids/day (HR: 2.12; p=0.03)
  - > 2mg benzodiazepines/day (HR: 2.04; p=0.04)
  - > 15mg corticosteroids/day (HR: 2.67; p=0.02)

Predictor	HR (Unadjusted)	95% CI	*P*value	HR (Adjusted)	95% CI	*P*value
Benzodiazepines	1.57	0.84 – 2.93	0.16	2.04	1.05 – 3.97	**0.04**
Corticosteroids	2.62	1.20 – 5.73	0.02	2.67	1.18 – 6.03	**0.02**
Opioids	2.35	1.22 – 4.53	0.01	2.12	1.09 – 4.13	**0.03**
Anticholinergics	1.22	0.65 – 2.30	0.53	1.38	0.73 – 2.60	0.32

Gaudreau J-D, Gagnon P, Harel F, Tremblay A, Roy M-A. 2005. J Clin Oncol. 23(27); 6712-8.

Association Between Psychoactive Medications and Delirium in Hospitalized Patients: A Critical Review

n.22 articles included

Non-significant association with the risk of delirium

- Anticholinergics
- Antidepressants
- Antiparkinsonians
- H2 antagonists
- Anticonvulsants
- Antiemetics
- Corticosteroids
- NSAIDs
- Opioids in 8 of 12 studies

Gaudreau J-D, Gagnon P, Roy M-A, Harel F, Tremblay A. 2005. Psychosomatics. 46: 302-316.

Significant association with the risk of delirium

- Antipsychotics and benzodiazepines (1 study each)

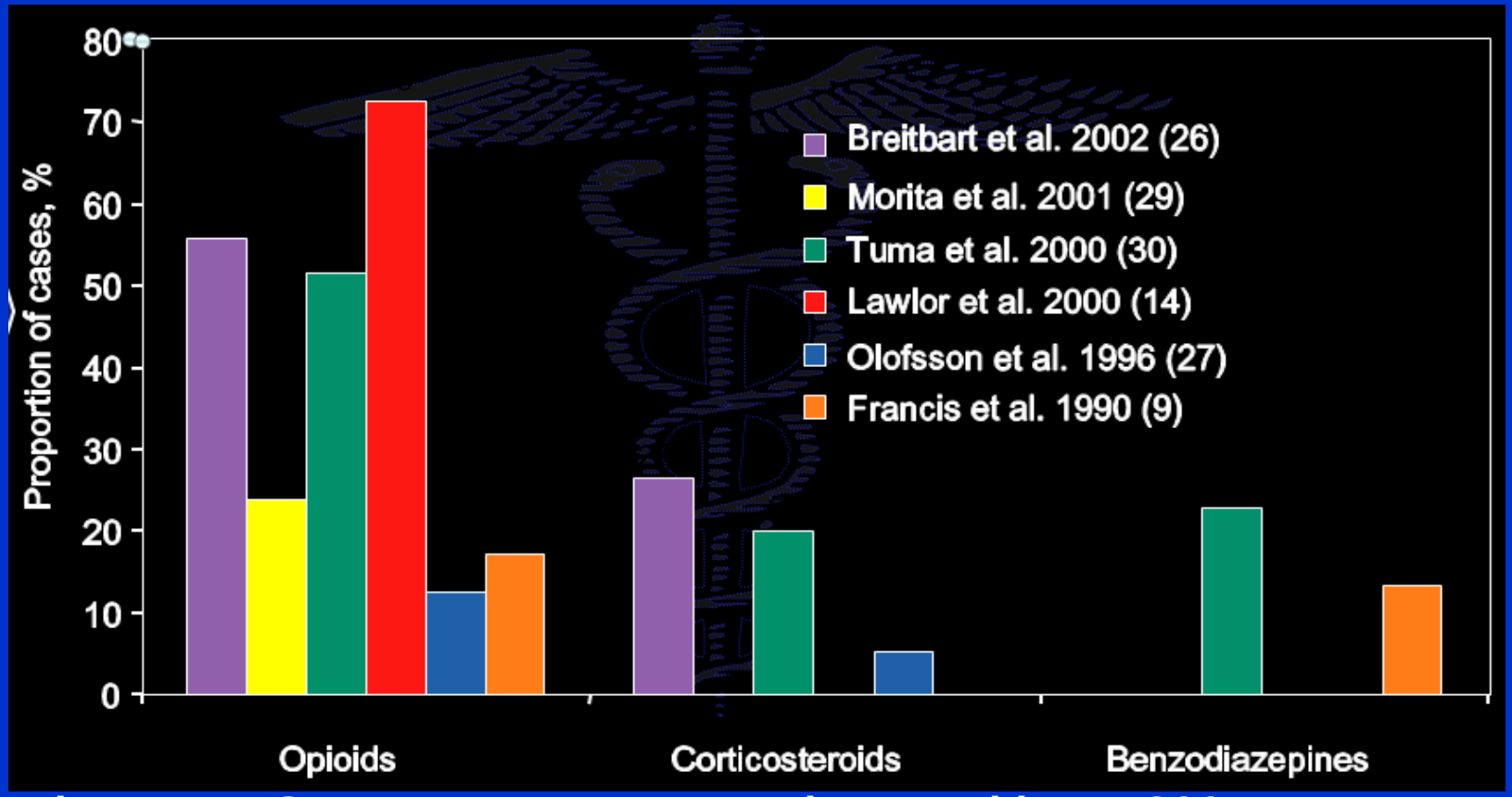
- Studies reveal a 2-9 increase of delirium linked with opioids, but result are inconsistent
- Dubois: > risk if >18.7 mg/day morphine equivalents

- Morrisson: < risk if >30 mg/day compared with <10 mg/day

patients recovering from hip fracture with a substantially increased RR (25.2, 95% CI 1.3–493.3) for lower doses (morphine dose equivalent <10 mg) compared with a lower RR (4.4, 95% CI 0.3–68.6) for higher doses (morphine dose equivalent 10–30 mg) (2003)

Gaudreau J-D, Gagnon P, Roy M-A, Harel F, Tremblay A. 2005. Psychosomatics. 46: 302-316.

Association Between Psychoactive Medications and Delirium in Hospitalized Patients: A Critical Review



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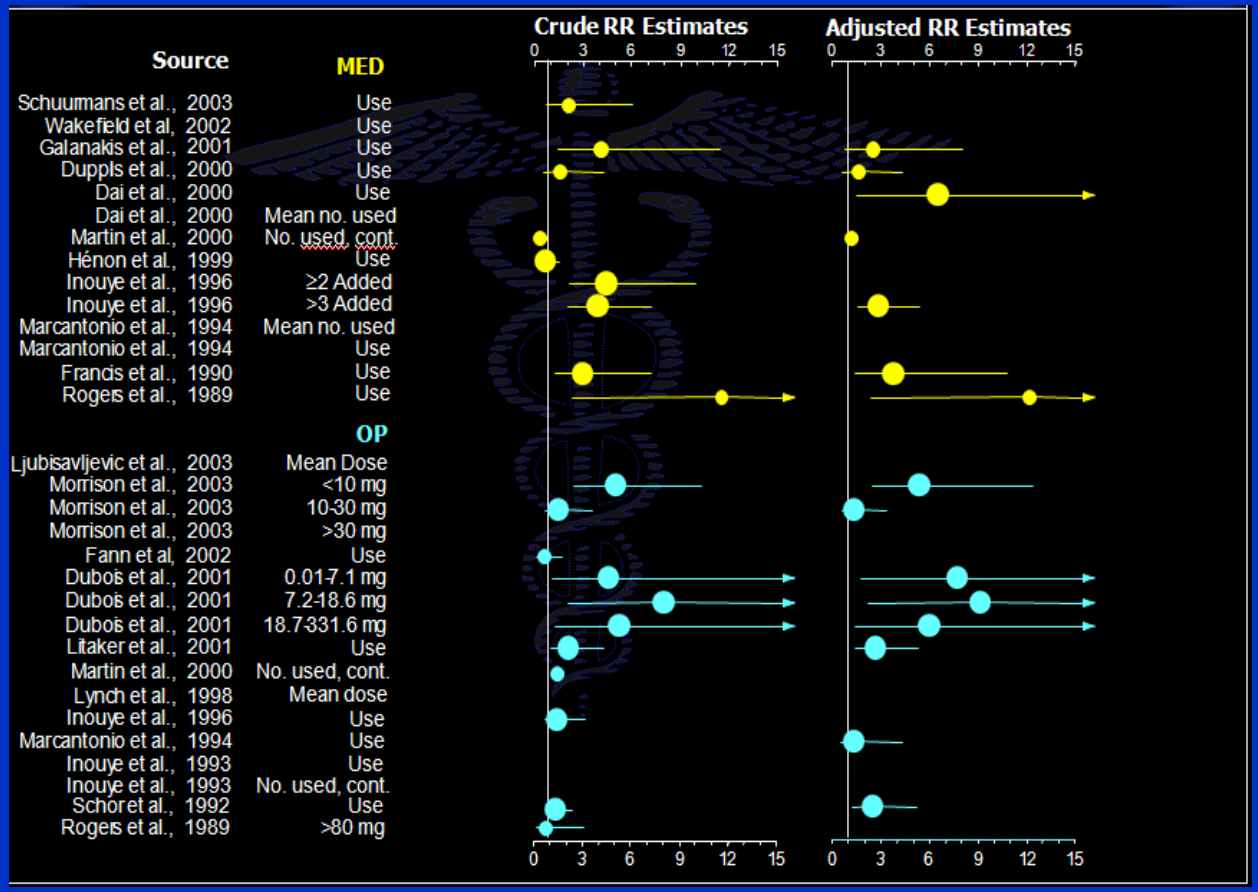


Gaudreau J-D, Gagnon P, Roy M-A, Harel F, Tremblay A. 2005. Psychosomatics. 46: 302-316.

Association of delirium symptoms with medication in terminal cancer

Methods:

- 1516 patients admitted for terminal cancer
  - 7 palliative care units in Canada
  - Survived longer than 48 hours
- Delirium rating with the Confusion Rating Scale (CRS)

Gagnon P, Allard P, Gagnon B, Mérette C, Tardif F, Émond C, Jomphe V. 2007. Poster presentation. APA.

Association of delirium symptoms with medication in terminal cancer

Results:

- Comparison of medication taken 48h before delirium symptoms to the overall delirium-free population
- Prevalence of delirium on admission (CRS ≥2) : 20% (n = 507)
- Incidence during stay : 46% (n = 701)
- Associated with a past history of delirium

Gagnon P, Allard P, Gagnon B, Mérette C, Tardif F, Émond C, Jomphe V. 2007. Poster presentation. APA.

Association of delirium symptoms with medication in terminal cancer

Delirium was associated with:

- Higher dosage of opioids (>90 mg daily; OR=1.451; p=0.0045)
- More frequent prescription of co-analgesics (OR=1.59, p=0.0022).

- Non significant relation with corticosteroids
  - OR=1.022; p=0.8652
- Inverse correlation with higher benzodiazepine dosage
  - ≥2mg daily; OR=0.679; p=0.0077

Gagnon P, Allard P, Gagnon B, Mérette C, Tardif F, Émond C, Jomphe V. 2007. Poster presentation. APA.

Association of delirium symptoms with medication in terminal cancer

- Association with opioids and co-analgesics
- Surprising inverse correlation with benzodiazepines
  - Related to confounding variables ?
  - Hypoactive delirium not detected with the CRS?

Gagnon P, Allard P, Gagnon B, Mérette C, Tardif F, Émond C, Jomphe V. 2007. Poster presentation. APA.

Models of care with opioid

- Cancer
- **Post-surgery**
- Intensive care unit
- Medical conditions

Med Hypotheses. 2005;65(5):972-82.

Drugs of anesthesia acting on central cholinergic system may cause post-operative cognitive dysfunction and delirium

Praticò C, Quattrone D, Lucanto T, Amato A, Penna O, Roscitano C, Fodale V.

….multiple interactions of

drugs of anesthesia

and central muscarinic cholinergic system

- General anesthesia affects brain function at all levels, including neuronal membranes, receptors, ion channels, neurotransmitters, cerebral blood flow and metabolism

- The functional equivalents of these impairments involve mood, memory, and motor function behavioural changes

- These dysfunctions are much more evident in the occurrence of stress-regulating transmission and in the alteration of
  - intra-cellular signal transduction systems
  - neurotransmitter synthesis and release
  - intra-neuronal signal transduction and second messenger system

Hypothesis:

inhibition of muscarinic cholinergic receptors could have a pivotal role in the pathogenesis not only of post-operative delirium but also the more complex phenomena of post-operative cognitive dysfunction

The Role of Postoperative Analgesia in Delirium and Cognitive Decline in Elderly Patients: A Systematic Review

Harold K. Fong, Laura P. Sands, Jacqueline M. Leung

Incidence of delirium ranges after

- noncardiac surgery 10%–60%
- cardiac surgery 3%– 47%

The varied incidence rates are likely a result of differences in study methodology and patient population characteristics (age)

(Anesth Analg 2006;102:1255–66)

The Role of Postoperative Analgesia in Delirium and Cognitive Decline in Elderly Patients: A Systematic Review

Harold K. Fong, Laura P. Sands, Jacqueline M. Leung

- Meperidine was consistently associated with an increased risk of delirium in elderly surgical patients
- No significant difference in postoperative delirium among other postoperative opioids (morphine, fentanyl, or hydromorphone)
- IV or epidural techniques do not influence cognitive function differently

(Anesth Analg 2006;102:1255–66)

Does Postoperative Delirium Limit the Use of Patient Controlled Analgesia in Older Surgical Patients?

J.M. Leung,, L.P. Sands, S.Paul, T.Joseph, S.Kinjo, T.Tsai

Anesthesiology 2009; 111(3): 625–31

Opioid "gold standard" for the treatment of acute postoperative pain despite the important side effects

- Opioid
- Severity of postoperative pain

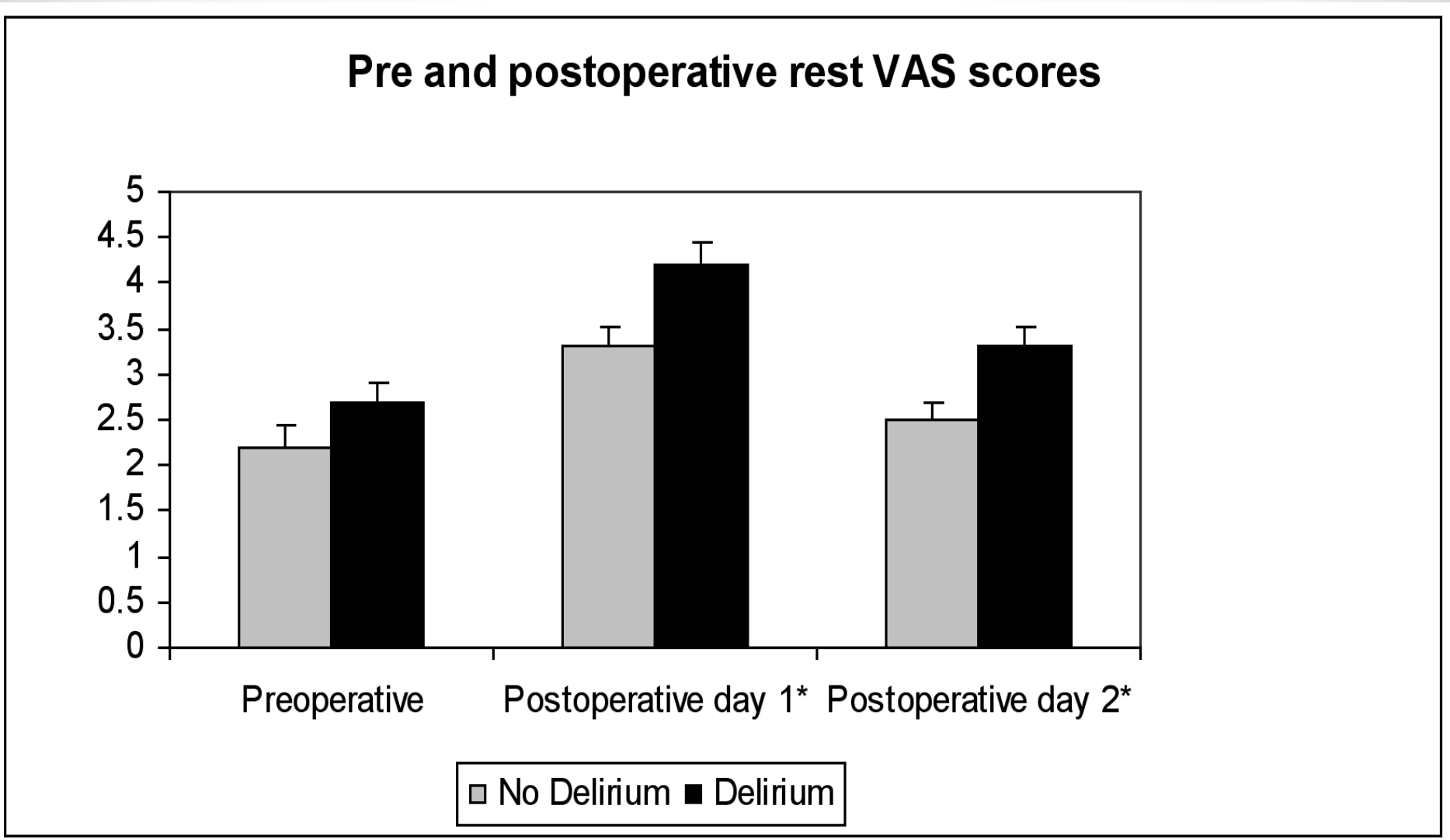
both independently increase the occurrence of postoperative delirium

Does Postoperative Delirium Limit the Use of Patient Controlled Analgesia in Older Surgical Patients?

Anesthesiology 2009, 111(3): 625–31

- N.335 orthopedic surgery patients
- 74 y
- 32% postoperative delirium
- PCA

	D +	D -
VAS 1° day	4.2	3.3
HYDROMORPHONE daily	2.2 mg	1.2 mg


Pre and postoperative rest VAS scores
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Preoperative
Postoperative day 1*
Postoperative day 2*
No Delirium
Delirium

Does Postoperative Delirium Limit the Use of Patient Controlled Analgesia in Older Surgical Patients?

Anesthesiology 2009, 111(3): 625–31

- Postoperative delirium DOES NOT limit the patient's use of on-demand patient controlled analgesia
- Alternative to opioid in patients at risk of postoperative delirium and with postoperative delirium: opioid-sparing
  - NSAID ?
  - adjuvant nonopioid analgesics
  - regional techniques such (peripheral nerve blocks or epidural analgesia)

Does femoral nerve analgesia impact the development of postoperative delirium in the elderly? A retrospective investigation

N.99 patients were retrospectively investigated for delirium following hip fracture repair in 1 year

Group 1 received patient-controlled femoral nerve analgesia (PCAF)

Group 2 were treated with iv analgesia

- The incidence of postoperative delirium was lower in the PCAF group than those treated with conventional analgesia (8.2% and 42%, respectively)
- PCAF technique in hip fracture repair improves the quality of postoperative analgesia, without needing rescue opioid analgesia (no morphine rescue medication in contrast to 28% of those of Group 2; $p<0.001$)

E.Del Rosario, N.Esteve, M.J. Sernandez, C. Batet, J.L. Aguilar Acute Pain 2008 (Vol. 10, Issue 2: 59-64)

Models of care with opioid

- Cancer
- Post-surgery
- **Intensive care unit**
- Medical conditions

Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population

M.A. Pisani, T.E. Murphy, K.L.B. Araujo, P.Slattum, P.H. Van Ness, S.K. Inouye

Crit Care Med 2009; 37:177–83

- Reducing delirium duration may improve patient outcomes by reducing days on mechanical ventilation, length of ICU and hospital stay, hospital morbidity related to falls and unnecessary restraint use

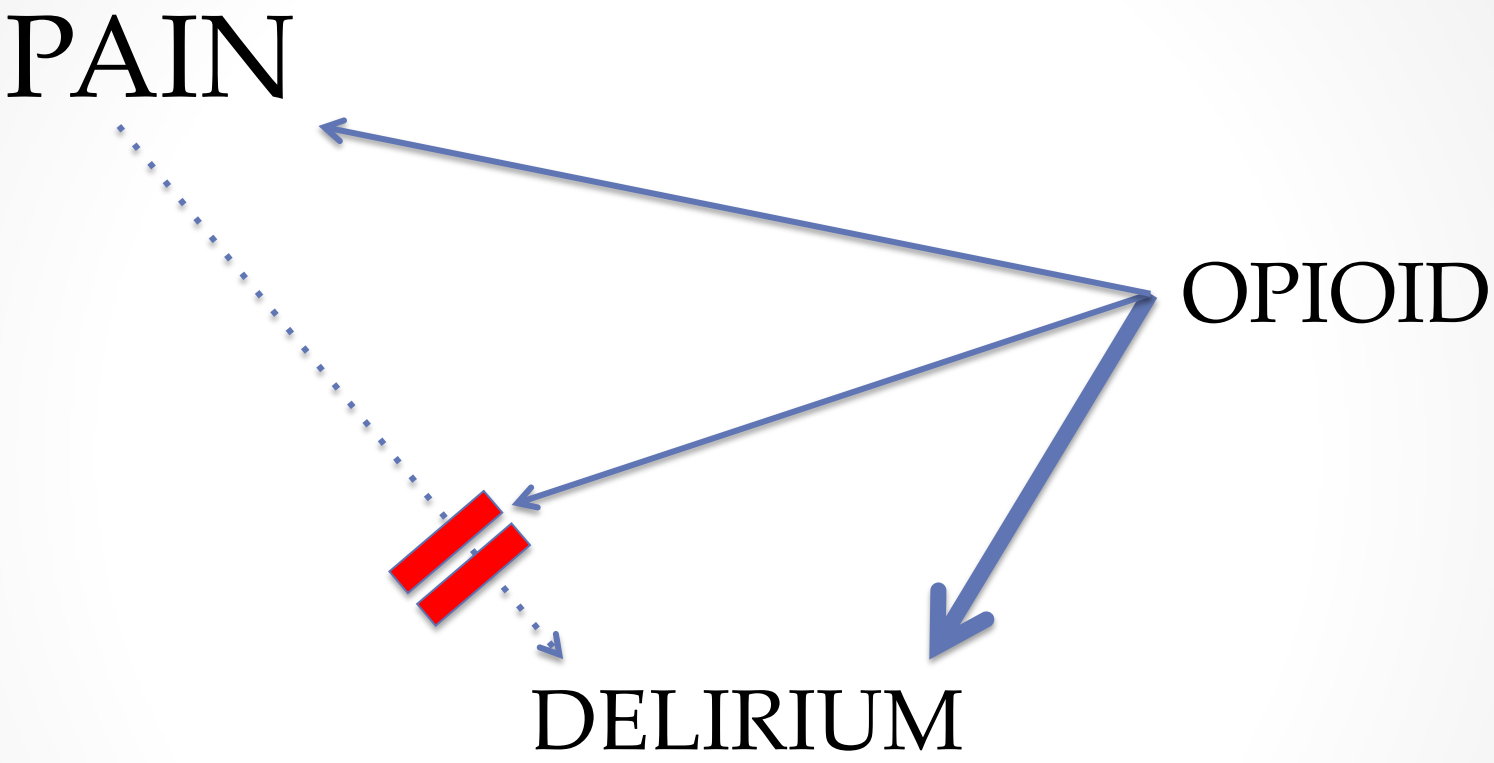
- N.304 patient 74y 79% delirium prevalence

- Patients who received opioids had an average ICU delirium duration of 5.8 vs 3.1 days for patients who did not receive opioids (RR 1.6, 95%CI 1.3–2.1)

- Haloperidol did not short delirium duration in patients receiving opioids
- May treat symptoms of delirium (such as agitation) without reducing duration of delirium

Models of care with opioid

- Cancer
- Post-surgery
- Intensive care unit
- **Medical conditions**


PAIN
OPIOID
DELIRIUM

Prevention of opioid - delirium

There is limited research evidence from clinical trials, so this review reports current best practice

Prevention of opioid - delirium

- Initial opioid selection (avoid opioids with active metabolites in patients with known renal failure)

- Route of administration and lipophilicity of the opioid may cause a more rapid receptor occupancy and increases the probability of delirium

Prevention of opioid - delirium

- Exposure to opioid medications was kept as **"low"** as possible
- Critical threshold of daily exposure to opioid medications (90 mg of morphine/day) above which the risk of delirium significantly increases (40%)
- Extended treatment time, rapid dose escalation and withdrawal (reduced nociceptive input) should be avoided
- Opioid doses should be reduced by 25% if analgesia is satisfactory

Clinical management of opioid - delirium

- Because 50% of delirium episodes in advanced cancer are reversible, ALL possible contributors to delirium should be appropriately treated
- 75%–80% of episodes of drug-induced delirium resolve by action of opioid rotation and discontinuation of other drugs
- Most effects of OIN resolve within 3–5 days of introduction of opioid rotation and hydration

Management of OIN

- Opioid should be discontinued

  or if cessation of the implicated medication is not possible
  - dose reduction (equianalgesic dose of the new opioid should be reduced by 30%–50%)
  - opioid switch / rotation
  - change in opioid route to the intraspinal route
- Stop contributing drugs (hypnotics)
- Nonessential, centrally active medications should be discontinued
- Symptomatic treatment with neuroleptics (haloperidol)
- Benzodiazepine for myoclonus (clonazepam), but in some patients may paradoxically exacerbate delirium

Many clinicians immediately assume opioids are the cause of delirium in a patient with pain, and their first response may be to discontinue the opioids

Antipsychotic

- When rotation fails or is impractical, and when other causes have been excluded, neuropleptics are often administered to patients with "agitated" delirium (or mioclono and seizure)
- Potent dopamine D2 receptor antagonist with few anticholinergic side effects
- Limited randomized controlled trial evidence for its use in the management of delirium
- [Antipsychotic prophylaxis is one of the most promising research directions in pharmacologic delirium prevention

N.Slatkin, M.Rhiner. J Pain Symptom Manage 27:268–73, 2004

Haloperidol

H. at dose of <3.5 mg/day, risperidone, and olanzapine were equally effective

Lonergan E, Britton AM, Luxenberg J. Antipsychotics for delirium. Cochrane Database Syst Rev 2007

Advantage of versatile routes of administration:

oral, s.c., i.m., i.v.

It is rarely sedating

Average oral bioavailability of haloperidol is approximately 60%, parenteral doses are about 2 as potent as oral doses

Case report:

acetylcholinesterase inhibitors

Describing successful treatment with acetylcholinesterase inhibitors, such as donepezil and physostigmine, suggest that delirium may be precipitated via an opioid-induced disorder of central cholinergic neurotransmission

Care comorbidity

- Sepsis, metabolic derangement, and/or tumor in the central nervous system should be excluded
- Hydration (oral/parenteral: i.v. or s.c.)

Palliative sedation

Monitored use of proportionate sedative medication to reduce the patient's awareness of intractable and refractory symptoms near the end of life when other interventions have failed to control them

Conclusion

- Opioids cause delirium
- Risk of opioid delirium is