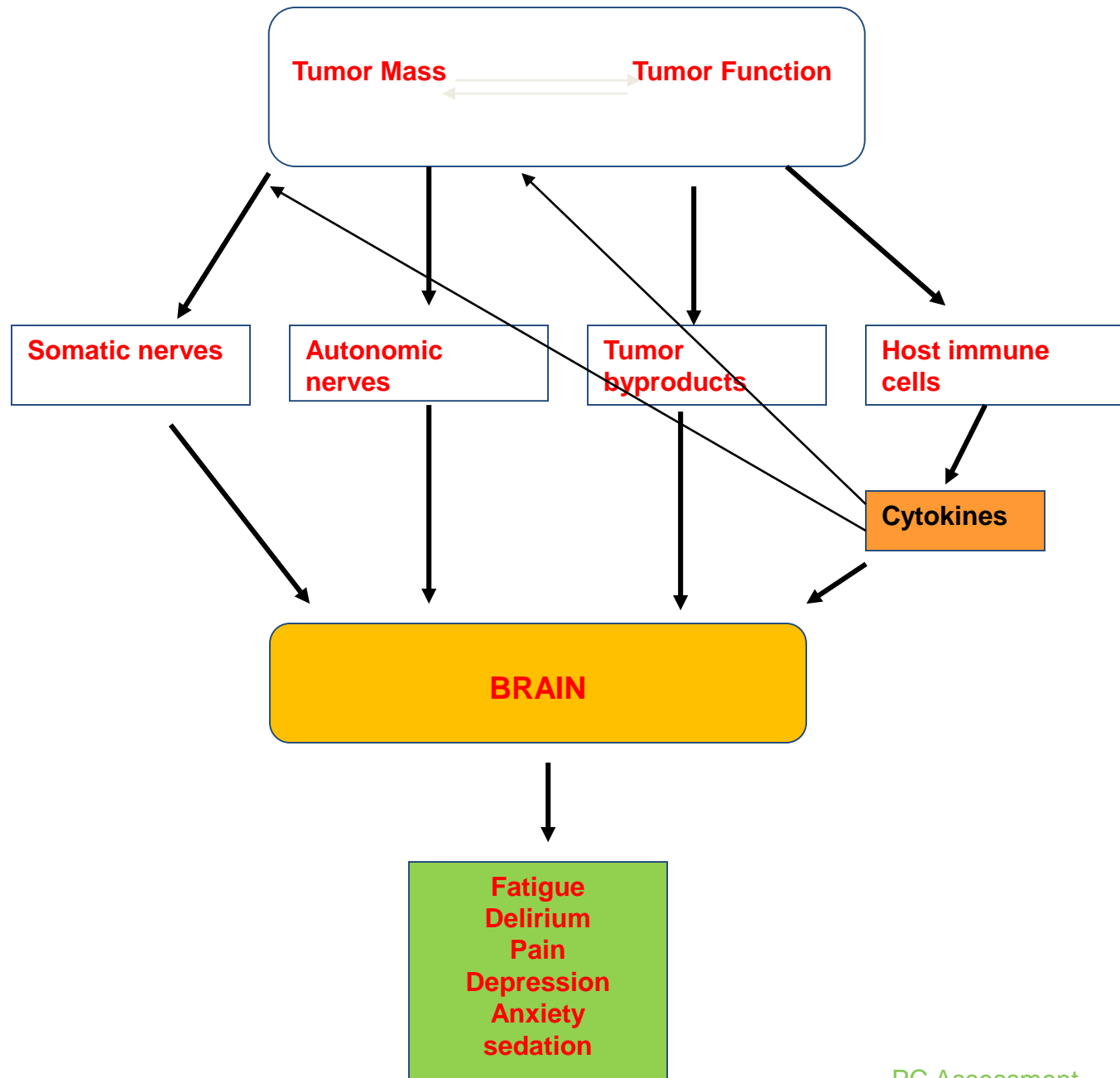# Patient's Problems

- **Pain (80%)**
- **Fatigue (90%)**
- **Weight Loss (80%)**
- **Lack of Appetite (80%)**
- **Nausea, Vomiting (90%)**
- **Anxiety (25%)**
- **Shortness of Breath (50%)**
- **Confusion-Agitation (80%)**

Tumor Mass ⟷ Tumor Function

Somatic nerves

Autonomic nerves

Tumor byproducts

Host immune cells

Cytokines

BRAIN

Fatigue
Delirium
Pain
Depression
Anxiety
sedation

PC Assessment

Delirium

- Global brain failure
- The way most of us here will die

A Big Problem

- Frequent neuro-psychiatric complication

- Distressing to patients and caregivers

- Associated with poor prognosis

- Negative impact on
  - Symptom expression
  - Interventions (e.g. counseling)
  - Communication
  - Decision making

Delirium

- Confusion (time, space, recent memory)
- Hallucinations – tactile!
- Delusions
- Agitation
- Disinhibition: symptoms or emotions!!

2 MAJOR DISORDERS OF COGNITION
DELIRIUM AND DEMENTIA

DELIRIUM: - Usually acute in onset

- Relatively brief in duration

- Fluctuating level of consciousness

- Can be reversible

DEMENTIA: - Intellectual deterioration of protracted & usually
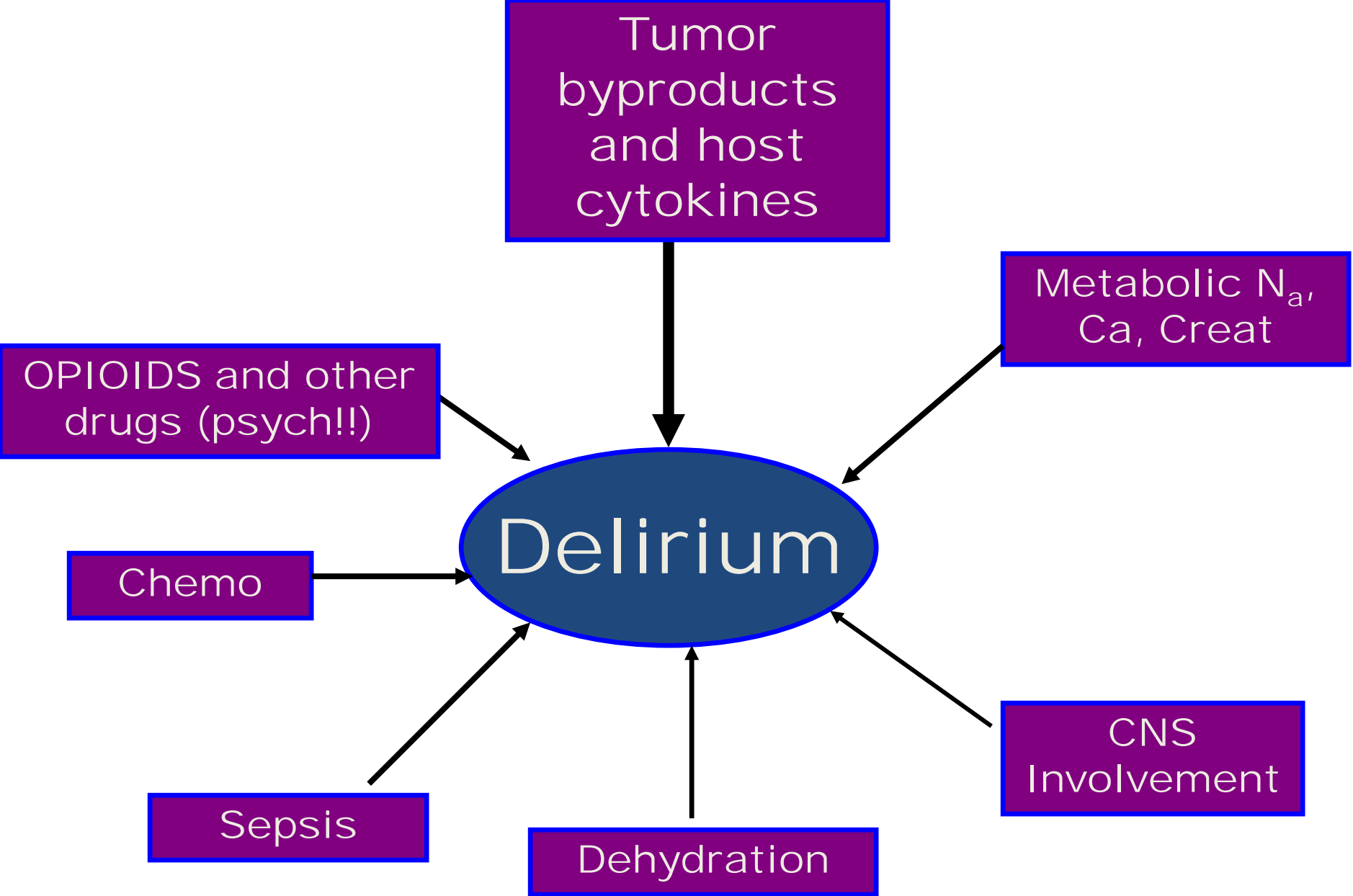
irreversible nature

- Delirium reported to be most common OMS in Cancer PTS
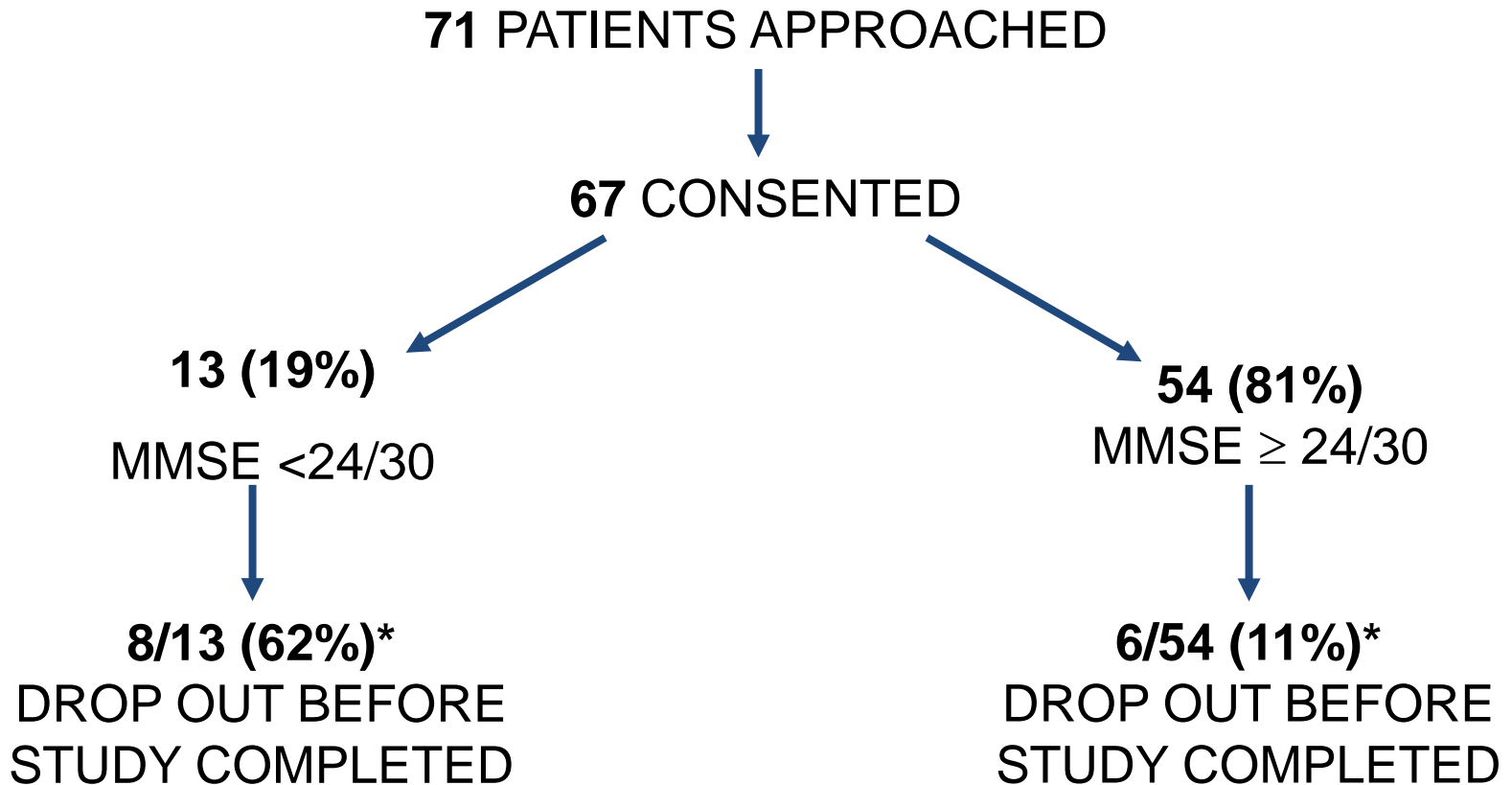
Differential diagnosis

- Dementia (easy from history)
- Sedation (opioids)
- Obstructive sleep apnea (Reddy 2008)
- Depression (60% delirium referrals)
- Anxiety/ manic episode
- Akathisia

Dementia/ nursing home

- Delirium due to multiple causes !!!: MI, fracture, UTI, urinary retention
- Frequent mixed syndromes: delirium + dementia+ depression+ pain.

COGNITIVE FAILURE IN CANCER PATIENTS

71 PATIENTS APPROACHED

67 CONSENTED

13 (19%)
MMSE <24/30

54 (81%)
MMSE $\geq$ 24/30

8/13 (62%)*
DROP OUT BEFORE
STUDY COMPLETED

6/54 (11%)*
DROP OUT BEFORE
STUDY COMPLETED

* p,0.01, χ^2 Test

Bruera et al, Lancet, 1993

Cognitive Failure (CF)

- Prospective study, 61 consecutive admissions to PCU
- CF determined by MMSE*
- CF present in 16/47 (83%) before death
- 22/66 (33%) improved with or without treatment
- Physician and nurse missed 15/66 (23%) and 13/66 (20%) of episodes of CF

*Mini Mental State Questionnaire

Bruera et al. J Pain Symptom Manage 1993

Mini-Mental State Exam Results

	All admissions with ≥ 2 MMSEs (n = 240)	Patients who died (n = 160)	Patients discharged (n = 90)	P value
Mean initial MMSE score (± SD)	0.77 (0.26)	0.75 (0.27)	0.81 (0.23)	0.073
Mean final MMSE score (± SD)	0.67 (0.33)	0.59 (0.35)	0.85 (0.14)	0.000
No. of patients with MMSE score < 0.8 on admission (%)	87 (36.1)	65 (40.4)	22 (24.4)	0.05
No. of patients with MMSE score < 0.08 on death or discharge (%)	117 (48.6)	100 (62.5)	17 (18.8)	0.000

MMSE: Mini-Mental State Examination; SD: standard deviation.
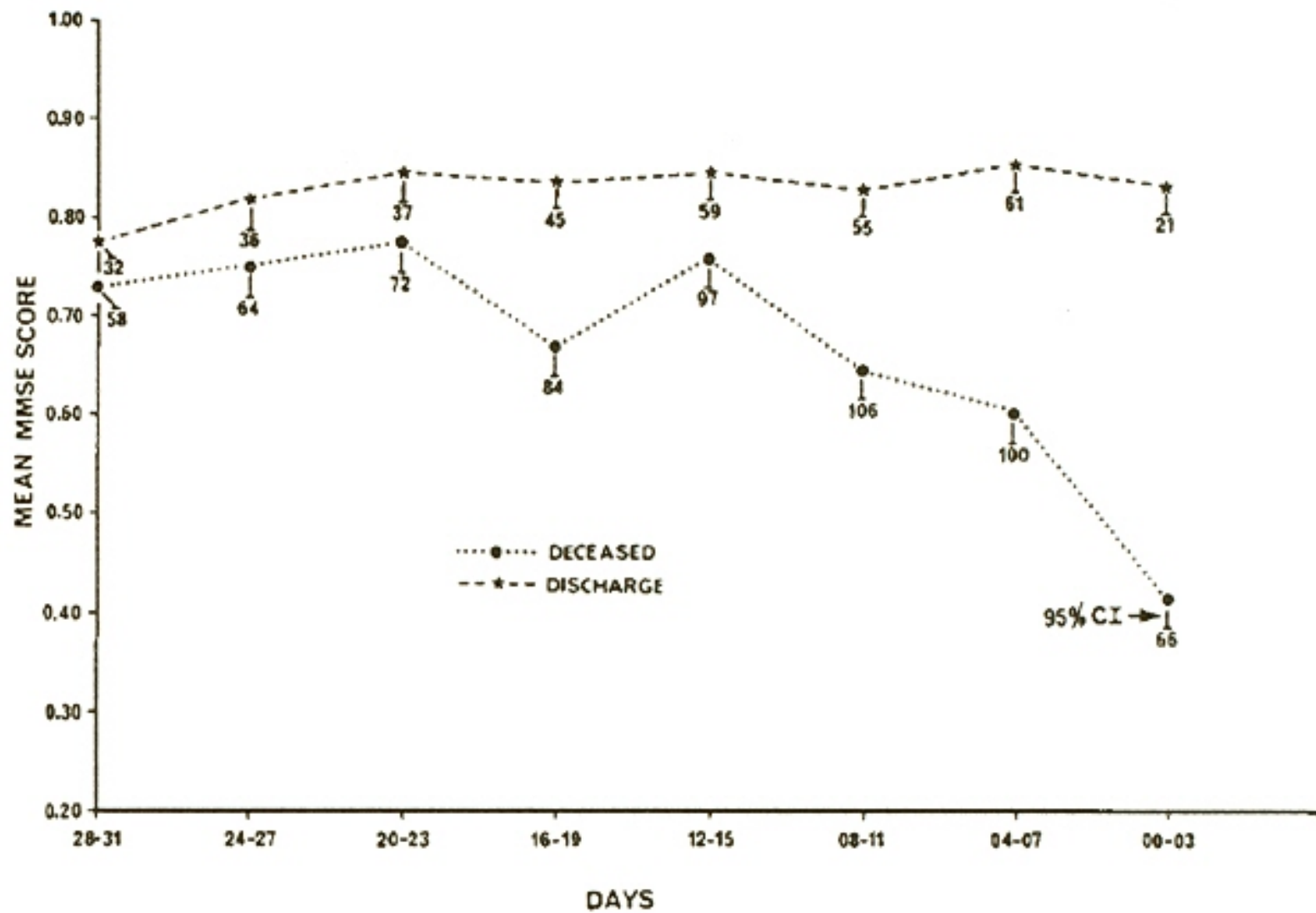
Terminal Delirium
Memorial Delirium Assessment Scale
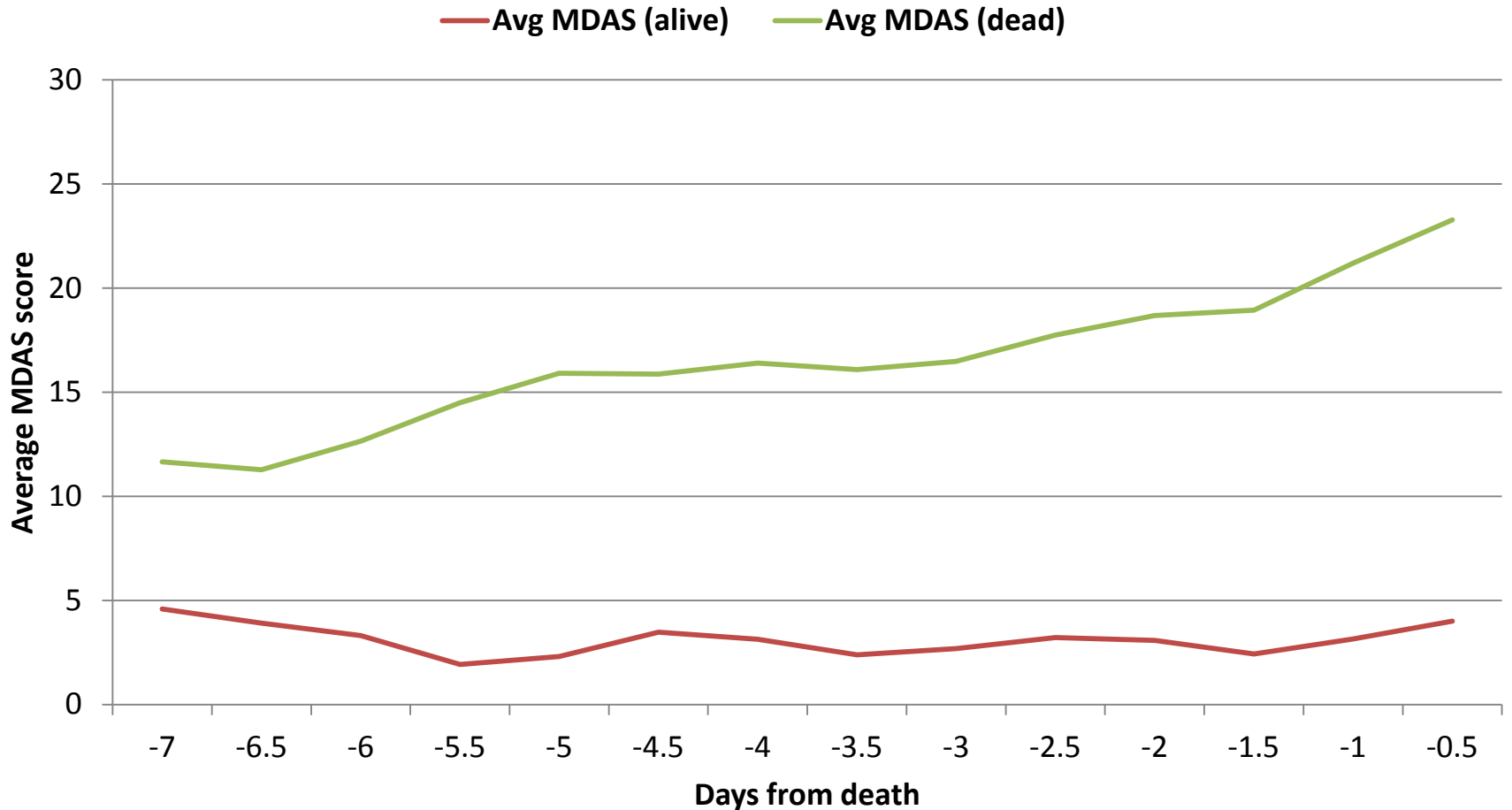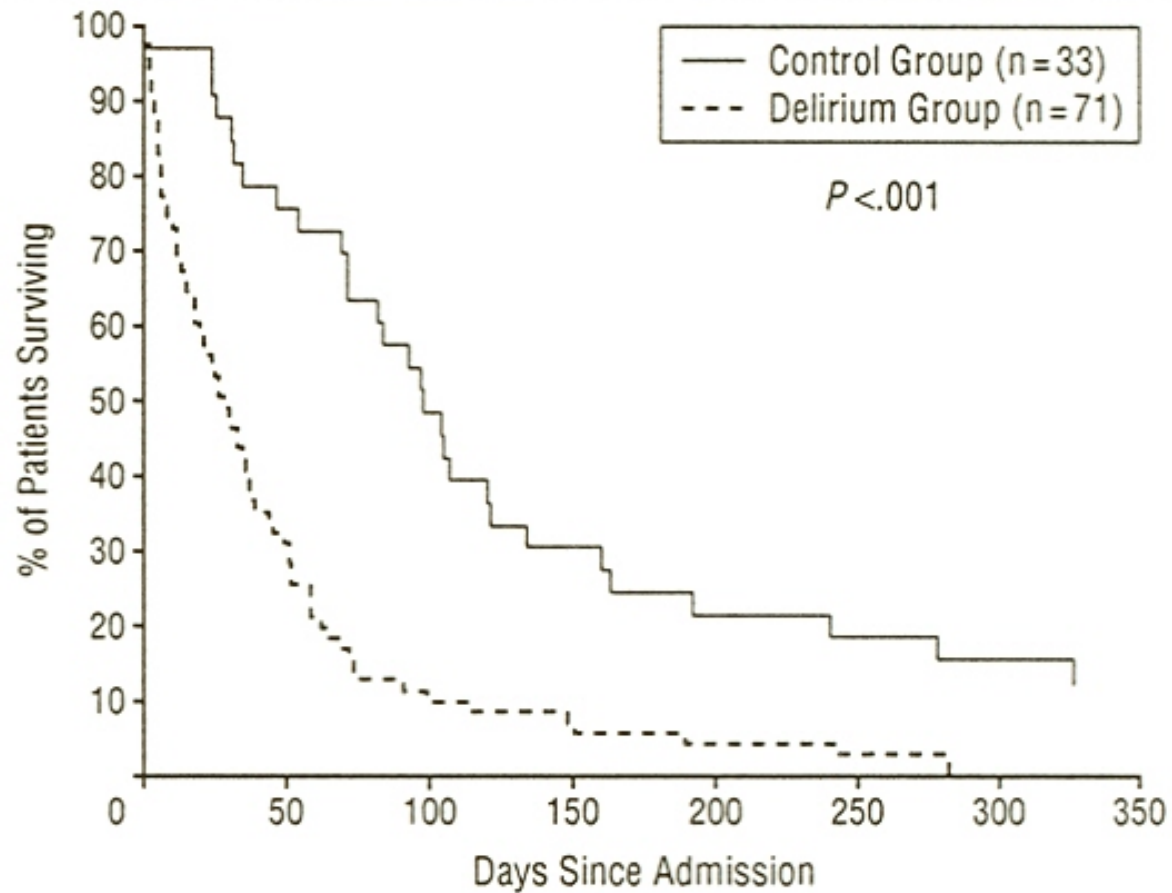
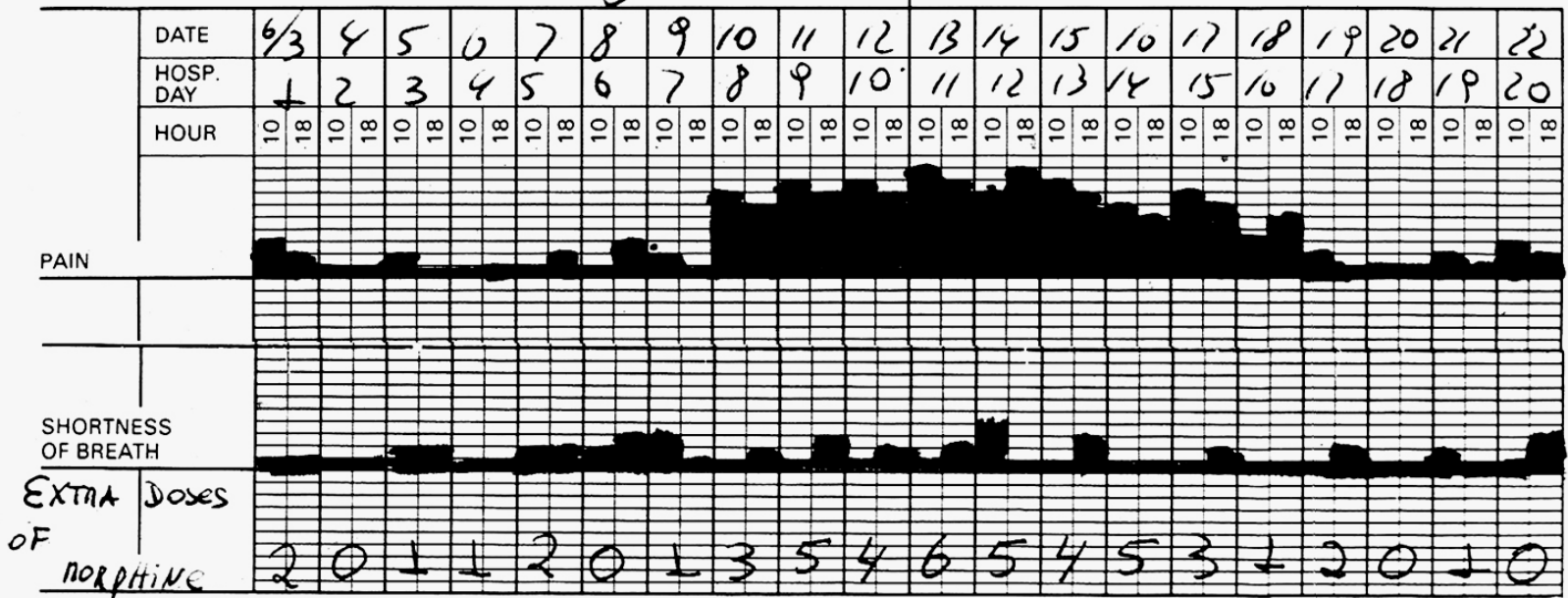|							
Control Group	33	25	16	10	7	6	5	4
Delirium Group	71	22	7	4	3	2	1	1

Delirium

- 85% cancer pts before death
- Multicausal
- 80% of brain is GABA
- Disinhibition: expression of symptoms and emotions

The General Hospital (Grey Nuns) of Edmonton

SYMPTOM ASSESSMENT GRAPH

C. FAILURE
CHANGE OPIATE.
HALOPERIDOL

DATE	6/3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
HOSP. DAY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
HOUR	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18	10 18

PAIN

SHORTNESS OF BREATH

EXTRA DOSES OF MORPHINE:

2	0	1	1	2	0	1	3	5	4	6	5	4	5	3	1	2	0	1	0

ASSESSED BY: P P P P P P P P P P P P P N N N N N N N N F N W F N N N P P P N P P P N P P

Code   P - Patient   N - Nurse   NA - Nurse Assisted   F - Family

Mini-Mental State Score	30	28	27	19	5	0	16	24	28	27

PSYCHOMOTOR   0   0   0   1   3   3   2   1   0

9 90 5036

Delgado-Guay MO, Yennurajalingam S, Bruera E. JPSM 2008; 36(4): 444
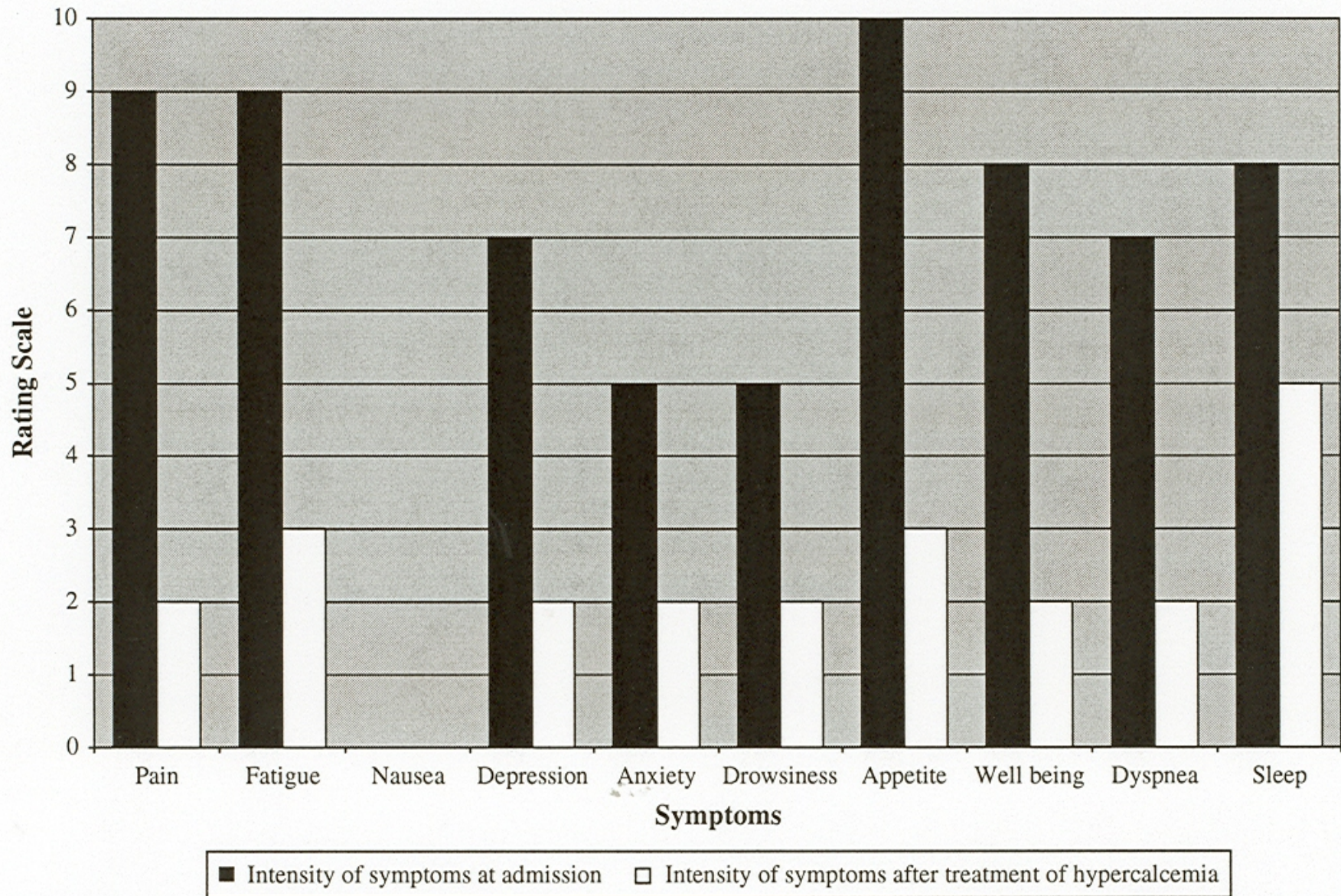
Hematological CA consults more delirium(Fadul, JPM 2008)

- 125 consecutive hematol: 51 delirium (41%)
- 125 consecutive solid: 20 delirium (16%, p<0.001)
- Median interval consult/ death:

Hematol 13 days; solid 46 days (p=001)

- Hematol <pain &>sedation
- Similar symptom distress score

ICU Pall care consults (Delgado-Guay M, Cancer 2009)

- 88/ 1607 Pall care consults were ICU (5%)
- 71/88 pts had delirium (81%)
- 31/71 pts delirium resolved (44%)
- 37/88 consults d/c home (42%)
- 12/ 35 ICU- PCU transfers d/c home (34%)

Frequency and outcome of delirium among cancer patients admitted to the PCU . De La Cruz M et al. The oncologist 2015

- 323/556 (58%) consecutive admissions had delirium (MDAS score >7/30)
- 229(71%) delirium upon admission**(41% of admissions)** and 94 (29% after admission)
- 26% of delirium episodes reversed
- Overall survival of delirium pts shorter
- Delirium **AFTER** admission to PCU: lower reversal and worse survival!!

Table 4. Multivariate Cox regression model for survival in patients with delirium vs. those without

Covariate	Effect	HR	95% CI	*p* value
Cancer diagnosis	Hematologic vs solid	1.70	1.17–2.48	.0057
ECOG status	3 vs. 4	0.56	0.38–0.83	.0041
Development of delirium	Yes vs. no	5.42	3.30–8.90	<.0001

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.
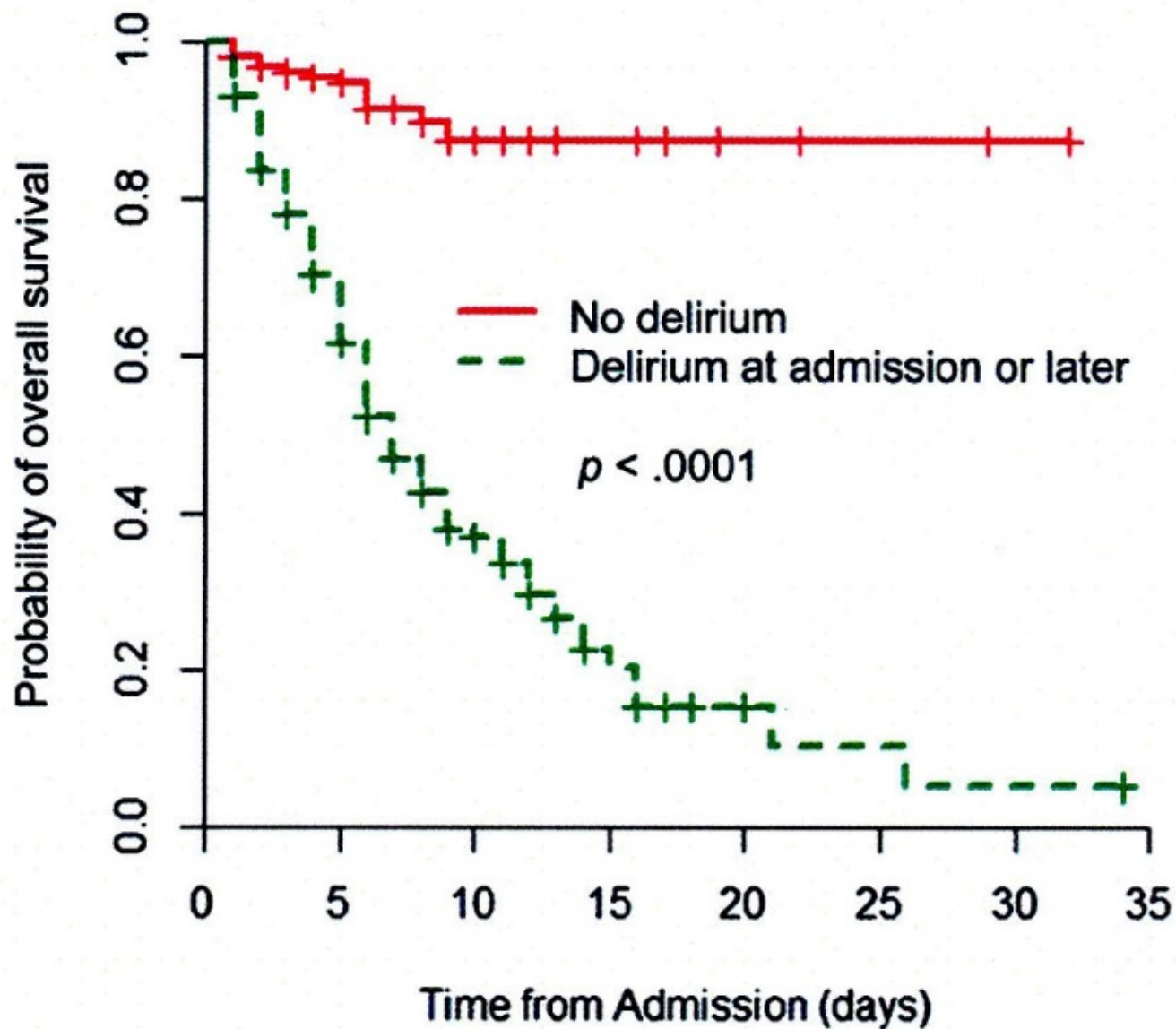
Figure 2. Kaplan-Meier curve of overall survival in patients with delirium on and after admission versus those who did not develop delirium.

Occurrence and Reversibility of Delirium

- Prospective study, admissions to PCU
- 44/104 (42%) delirium on admission
- 71/104 (68%) delirium at some stage
- 46 of 52 who died (88%) had terminal delirium
- 46 of 94 episodes, (49%) reversible
- Reversibility associated with psychoactive medication
- Patients with delirium had poorer survival than controls

Lawlor et al. Arch Intern Med, 2000

Terminal Delirium
Predictors

- **Prospective study of 104 APCU patients**
- **71 (68%) had delirium: 44 on admission, 27 during admission**

Categories†	No. (%) of Episodes		Univariate Analysis			Multivariate Analysis	
	Reversed (n = 40)	Nonreversed (n = 31)	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI
Psychoactive drugs	38 (95)	15 (48)	8.85	2.13-36.7	.003	6.65	1.49-29.6
Dehydration	26 (65)	8 (26)	2.35	1.20-4.62	.01	1.50	0.70-3.20
Miscellaneous other causes	7 (18)	7 (23)	0.69	0.30-1.59	.37	1.10	0.45-2.70
Nonrespiratory infection	10 (25)	8 (26)	0.56	0.26-1.18	.12	0.23	0.08-0.64
Hypoxic encephalopathy	11 (28)	22 (71)	0.39	0.19-0.80	.008	0.32	0.15-0.70
Metabolic	10 (25)	18 (58)	0.44	0.21-0.91	.02	0.46	0.21-1.02
Hematologic	5 (13)	7 (23)	0.58	0.22-1.51	.25	1.21	0.43-3.44

Lawlor et al. *Arch Intern Med* 2000

Delirium among advanced cancer patients assessed at the emergency center (Elsayem A et al, Cancer 2016)

- 22/243 patients prospectively assessed had delirium (CAM +)with median MDAS 14/30
- Delirium was mild in 18 (82%) of patients
- MD detected delirium in 13/22 cases (59%)
- No association with age, but association with PS
- ED great place to make early diagnosis of delirium!

TABLE 2. CAM Versus Physician Diagnosis of Delirium

CAM-Diagnosed Delirium	ED Physician Thought Patient Was Delirious		Total
	No	Yes	
No	212	2	214
Yes	9	13	22
Total	221	15	236

Abbreviations: CAM, Confusion Assessment Method; ED, emergency department.

Data were missing for 7 patients.

TABLE 3. Demographic and Clinical Characteristics of ED Patients With Advanced Cancer With and Without Delirium Diagnosed With the CAM Instrument

Category	Subcategory	CAM-Positive Delirium (n = 22), No. (%)	No Delirium (n = 221), No. (%)	P	Missing, No. (%)
Sex	Female	11 (50)	109 (49)		
	Male	11 (50)	112 (51)	1.00	0
Age	<65 y	12 (55)	132 (60)		
	65 y	10 (45)	89 (40)	.68	0
Race/ethnicity	White	13 (59)	154 (71.3)		
	Black, African American	6 (27.3)	32 (14.8)	.40	5 (2.1)
	Hispanic	3 (13.6)	25 (11.57)		
	Other	0 (0.0)	5 (2.31)		
Marital status	Married	18 (81.8)	144 (65.75)		
	Divorced	2 (9.1)	30 (13.7)	.37	2 (0.8)
	Single, separated, widow	2 (9.1)	45 (20.55)		
Employment	Retired/not employed	17 (77.3)	155 (70.45)		
	Employed	5 (22.7)	65 (29.55)	.63	1 (0.4)
ED acuity	Emergent	8 (36.4)	40 (18.2)		
	Urgent	14 (63.6)	173 (78.6)	.14	1 (0.4)
	Nonurgent	0 (0.0)	7 (3.2)		
ECOG performance status	0	0 (0.0)	38 (17.4)		
	1	2 (9.1)	112 (51.4)	<.0001	3 (1.2)
	2	2 (9.1)	23 (10.6)		
	3	13 (59.1)	40 (18.4)		
	4	5 (22.7)	5 (2.3)		

Abbreviations: CAM, Confusion Assessment Method; ECOG, Eastern Cooperative Oncology Group; ED, emergency department.

Delirium Recall (Bruera E et al, Cancer 2009)

- 99 Patients with Complete resolution < 72hs before

- HYPO 20% ; HYPER 13%; MIXED 67%

- 250 Contributing Factors

- **73/99 Patients (74%) Remembered DELIRIUM !!!!**

- 59/73 Recall expressed distress (81%); vs. 11/26 No Recall (42%); p = 0.01

		No. (%)	No. of Evaluable Reports (%)	Median Distress Level (Q1-Q3)	P*
Remember	No	26 (26)	25 (96)	2 (0-4)	.03
	Yes	73 (74)	69 (94)	3 (1-4)	
Delirium subtype	Hypoactive	20 (20)	19 (95)	2 (0-3)	.32
	Hyperactive	13 (13)	13 (100)	2 (2-4)	
	Mixed delirium	66 (67)	62 (94)	3 (1-4)	
Gender	Male	53 (54)	49 (92)	3 (1-4)	.67
	Female	46 (46)	45 (98)	3 (1-4)	
Race	White	76 (77)	74 (97)	2.5 (1-4)	.40
	Nonwhite	23 (23)	20 (86)	3 (2-4)	

*P value reflects comparison in median distress level for each category.

Delirium: Bedside Babel

Symptoms	Patient/ Family Caregiver		Patient/ Nurse		Patient/ PCS		Family Caregiver/ Nurse		Family Caregiver/ PCS		Nurse/ PCS	
	n	WK (P)	n	WK (P)	n	WK (P)	n	WK (P)	n	WK (P)	n	WK (P)
Auditory hallucinations	93	0.38 (<.01)	79	0.19 (<.01)	92	0.2 (.02)	78	0.03 (.52)	93	0.18 (.01)	80	0.26 (<.01)
Delusional thoughts	95	0.29 (<.01)	80	0.15 (.09)	93	0.1 (.26)	79	0.08 (.3)	94	0.07 (.36)	80	0.04 (.63)
Time orientation	91	0.28 (<.01)	74	−0.08 (.4)	87	−0.02 (.79)	79	−0.03 (.73)	94	0.01 (.97)	78	0.19 (.03)
Place orientation	91	0.26 (<.01)	74	−0.01 (.93)	87	0.06 (.43)	80	0.09 (.26)	94	0.01 (.93)	79	0.18 (.03)
Psychomotor agitation	94	0.25 (<.01)	79	0.13 (.12)	90	0.09 (.26)	80	0.13 (.06)	95	0.06 (.4)	80	0.08 (.33)
Tactile hallucinations	93	0.18 (.02)	79	0.09 (.37)	91	−0.003 (.97)	79	0.13 (.12)	94	0.07 (.34)	80	0.13 (.18)
Visual hallucinations	96	0.45 (<.01)	78	0.14 (.01)	91	0.21 (.01)	80	0.18 (<.01)	94	0.24 (<.01)	79	0.05 (.38)

PCS indicates palliative care specialist; n, effective sample size; WK, weighted kappa.

Delirium
Different Settings, Different Patients

- Settings
  - Post-operative
  - Medical-surgical units
  - Critical care
  - Cancer

- Patients
  - Old vs. young
  - Non-cancer vs. cancer
  - Reversible vs. terminal delirium

Delirium management

- Treat reversible causes
  - Drugs
  - Infection
  - Metabolic causes
  - Structural causes

- Palliation
  - Non-pharmacologic measures
  - Pharmacologic measures
    - Neuroleptics—haloperidol, chlorpromazine, olanzapine, risperidone, quetiapine
    - Benzodiazepines?!?
    - Dexmedetomidine

Opioid induced neurotoxicity (OIN)

- severe sedation
- cognitive failure
- hallucinosis/delirium
- myoclonus/grand mal seizures
- hyperalgesia/allodynia

O.I.N. Diagnosis

- ➤ Cognitive Failure
- ➤ Myoclonus
- ➤ Hyperalgesia
- ➤ Tactile hallucinations

History Of:

- ➤ High opioid dose
- ➤ Prolonged time
- ➤ Borderline cognition
- ➤ Decreased glomerular filtration

Risk Factors for OIN

- High opioid dose
- Prolonged opioid exposure
- Pre-existing borderline cognition/delirium
- Dehydration
- Renal failure
- Other psychoactive drugs
- Opioids with mixed agonist/antagonist activity

-

Which drug to choose?

1. Delirium/ Opioid induced neurotoxicity:

All opioids can cause it. Opioid rotation works by eliminating the offending drug.

Opioid Rotation

- Retrospective Study of 80 Rotations for OIN in PCU
- Symptoms of OIN improved in 58/80 (73% $p<0.01$)
- Pain control improved significantly 4.4 ± 2.3 to 3.6 ± 2.0 $p<0.04$)
- Dose was significantly lower than that thought to be equianalgesic 477 ± 1535 vs. 366 ± 593 ($p<0.04$)

De Stoutz et al. J Pain Symptom Manage; 1995

16 years later…

- Recognized syndrome
- Rotation fully established for management
- Translational research: multiple sub- mu, EAA/ NMDA, active opioid metabolites- all 3!!
- Methadone (better pain, decreased OIN, less cost, billions saved)- orphan drug (all patented ones funding professors to hit it)

Delirium management

1. Screening/ early (or late) diagnosis
2. Look for reversible causes
3. Pharmacological treatment
4. Environmental control
5. Bedside nurse/ referring MD education
6. Family education/ counseling

MDAS

Memorial Delirium Assessment Scale

ITEM 1 – REDUCED LEVEL OF CONSICIOUSNESS (AWARENESS):
- ❑ **0: none**
- ❑ **1: mild**
- ❑ **2: moderate**
- ❑ **3: severe**

ITEM 2 – DISORIENTATION:
- ❑ **0: none**
- ❑ **1: mild**
- ❑ **2: moderate**
- ❑ **3: severe**

ITEM 3 – SHORT-TERM MEMORY IMPAIRMENT:
- ❑ **0: none**
- ❑ **1: mild**
- ❑ **2: moderate**
- ❑ **3: severe**

ITEM 4 – IMPAIRED DIGIT SPAN:
- ❑ **0: none**
- ❑ **1: mild**
- ❑ **2: moderate**
- ❑ **3: severe**

ITEM 5 – REDUCED ABILITY TO MAINTAIN AND SHIFT ATTENTION
- ❑ **0: none**
- ❑ **1: mild**
- ❑ **2: moderate**
- ❑ **3: severe**

ITEM 6 – DISORGANIZED THINKING
- ❑ **0: none**
- ❑ **1: mild**
- ❑ **2: moderate**
- ❑ **3: severe**

ITEM 7 – PERCEPTUAL DISTURBANCE:
- ❑ **0: none**
- ❑ **1: mild**
- ❑ **2: moderate**
- ❑ **3: severe**

ITEM 8 – DELUSIONS:
- ❑ **0: none**
- ❑ **1: mild**
- ❑ **2: moderate**
- ❑ **3: severe**

ITEM 9 – DECREASED OR INCREASED PSYCHOMOTOR ACTIVITY:
- ❑ **0: none**
- ❑ **1: mild**
- ❑ **2: moderate**
- ❑ **3: severe**

ITEM 10 – SLEEP-WAKE CYCLE DISTURBANCE (DISORDER OR AROUSAL):
- ❑ **0: none**
- ❑ **1: mild**
- ❑ **2: moderate**
- ❑ **3: severe**

TOTAL _____

Other tools

- CAM
- DRS
- DSM TN criteria interview

The purpose of drug treatment of delirium

1. Drugs are unable to reverse delirium

2. Eliminate hyperactive features (delusions, hallucinations, psychomotor agitation)

3. Sedation when other measures fail

Delirium
Different Settings, Different Patients

[Intervention Review]

Drug therapy for delirium in terminally ill adult patients

Bridget Candy[1], Kenneth C Jackson[2], Louise Jones[1], Baptiste Leurent[1], Adrian Tookman[1], Michael King[3]

There is limited evidence from clinical trials on the role of drug therapy for the treatment of delirium in terminally ill patients. The key feature of delirium is a decreased level of consciousness (awareness). People may experience impaired memory, thinking and judgement, and become disorientated. They may experience distressing hallucinations or delusions. It occurs frequently in patients with terminal illness, and may be caused by the illness itself or occur as a side effect of drug treatments for symptom management. Our search of the international literature for trials of drug therapies for the treatment of delirium in patients with terminal illness yielded one small study, and therefore it was not possible to assess the effectiveness of drug treatment options. It is hoped that this review will provide an incentive for further research.

Candy et al. *Cochrane Database* 2012

Haloperidol

- Onset: 30- 60 min; dose 0.5- 5 mg, half life 18 hs, metabolized and into urine.

- Time to peak: oral 2-6hs; IM 20 min

- DPM blocker

- Extrapyramidal (less in autonomic neuropathy?), tardive diskynesia, NMS

- Q-T prolongation, more IV

Pharmacological Management

- Haloperidol IV/ SC/ PO. Dose: ???.
- "loading (up to 5 mg/ dose q1h) and maintenance"
- "regular (2mg q 6h, etc) and breakthrough (q1-2h)"
- Wide dose, less extrapyramidal in cancer (autonomic ?)

Should every cancer patient with delirium be on regular haloperidol?

- Hyperactive and mixed YES

- In cancer 80 % are MIXED

- In PURE hypo no evidence, prn needed in case of change to mixed

Shin, HS et al. Frequency and outcome of neuroleptic rotation in patients with advanced cancer. Cancer Res treat 2014

- 167/266 consecutive PCU admissions (63%) delirium treated with haloperidol 1st line
- 128 (77%) only haloperidol (71% discharged alive)
- 39 (23%) required neuroleptic rotation (41% discharged alive)
- Median (IQR) H dose: 5 (3-7) mg/day

Then benzo story

- Most common drugs !!!
- Breitbart RCT worsened delirium
- Add to haloperidol en severe agitation (VS change to chlorpromazine, methotrimeprazine)- on a temporary basis
- Palliative sedation

Environment control

1. Excessive or NO light
2. Loud noises (TV, sitter on cell phone)
3. Stimulation (visitors, consultants, family)
4. Large clock/ calendar
5. Familiar objects, sounds smells
6. Do not ask for consent/ debate

Bedside RN/ referring MD

- Diagnosis (frequently made by PC team)
- Need to search for reversible causes
- MAJOR med changes needed!!
- Disinhibition!! "patient in a lot of pain", decision making
- NOT always opioid-induced, haloperidol best drug (no, not akathisia, running from taxpayers with AIG bonus pay)
- Bedside RN support!! (distress) mainly with education and good patient/ family care!!

Family

- Global brain dysfunction (blood products, poor quality fuel)
- Very common and poor prognosis
- Disinhibition of symptoms and emotions
- Environmental control
- Expressive/ supportive counseling!!! High distress

COUNSELING

1. Patient
   - Brief conversations
   - Avoid Confrontation – Avoid stimulation (hyperactivity)
   - Reassurance: familiar objects, people and sounds

2. Family
   - Monitor behavior regularly
   - Explain the mechanism of delirium
   - Reassure regarding physical suffering
   - Major cause of conflict!!

3. Staff
   - Difference between pain and agitated delirium
   - Aggressive behavior by patient
   - Family distress and dissatisfaction
   - Importance of ———— consistent behavior!
                        team approach!

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Conclusions

- Delirium will develop in more than 80% of palliative care patients
- It is s source of distress and conflict
- It is severely underdiagnosed by HCPs
- The best management is to eliminate precipitating factors
- Haloperidol remains the main drug
- Communication/ education is a major intervention