Delirium in Advanced Cancer:

An Evidence Based Update

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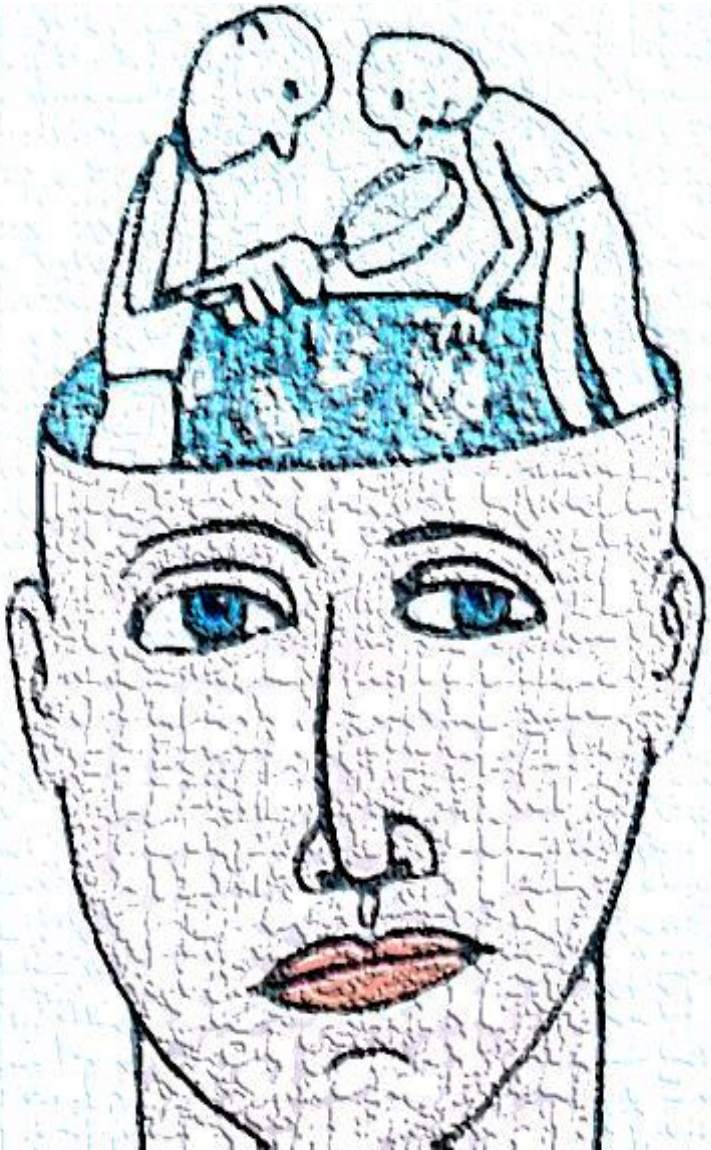


Outline

- Introduction
- Treatment
  - Setting therapeutic goals
  - Treatment of underlying causes
  - Non-pharmacologic approaches
  - Pharmacologic approaches
- Summary

Cardinal Features

DSM-IV Criteria

A. Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.

B. A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.

C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day

D. There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

DSM-5 Criteria

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

B. The disturbance develops over a short period of time (usually hours to a few days), *represents an acute 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).

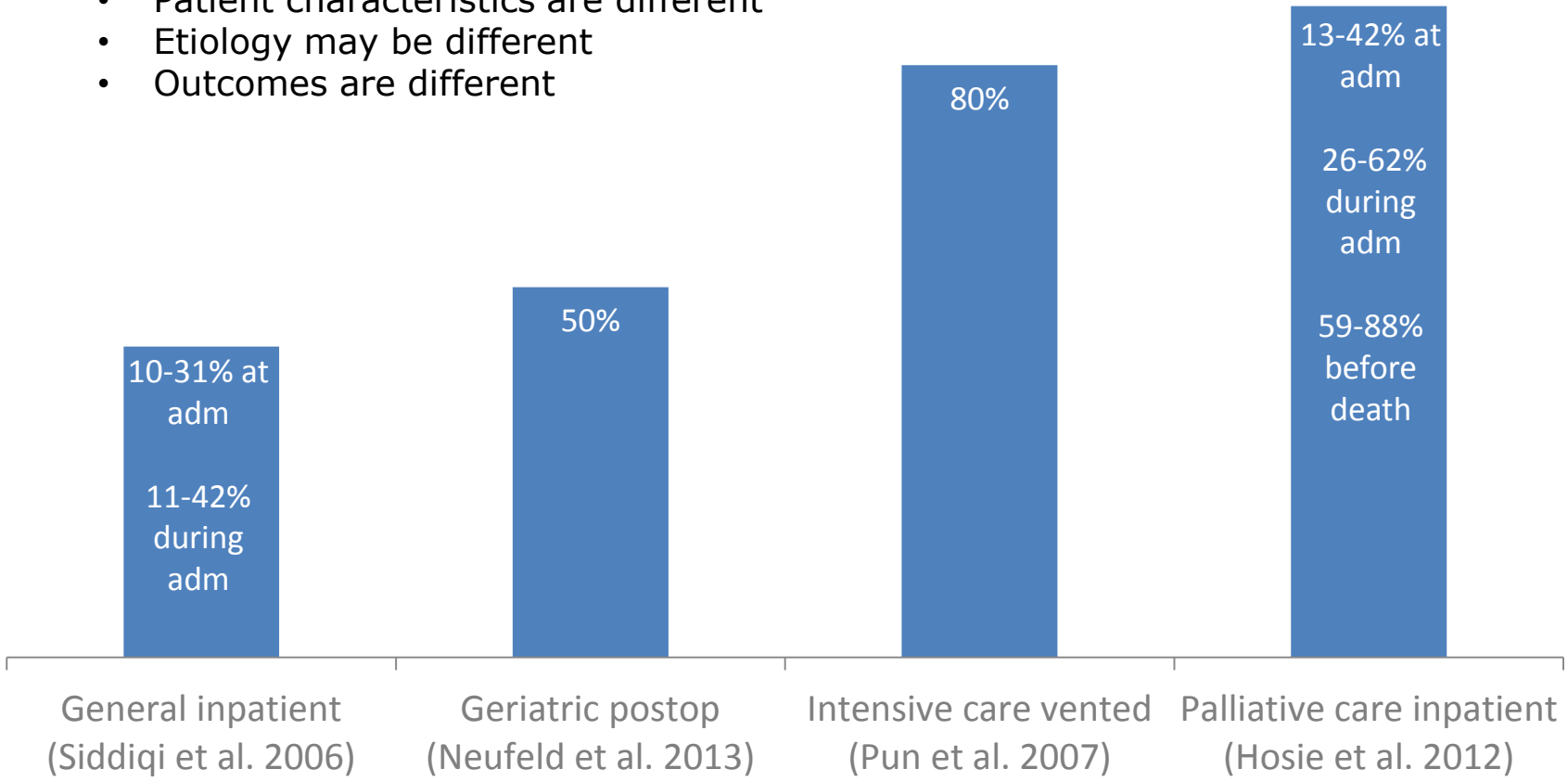
D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and *do not occur in the context of a severely reduced level of arousal such as coma.*

E. There is evidence from the history, physical examination or laboratory findings that the disturbance is *a direct* physiological consequence of another 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.*

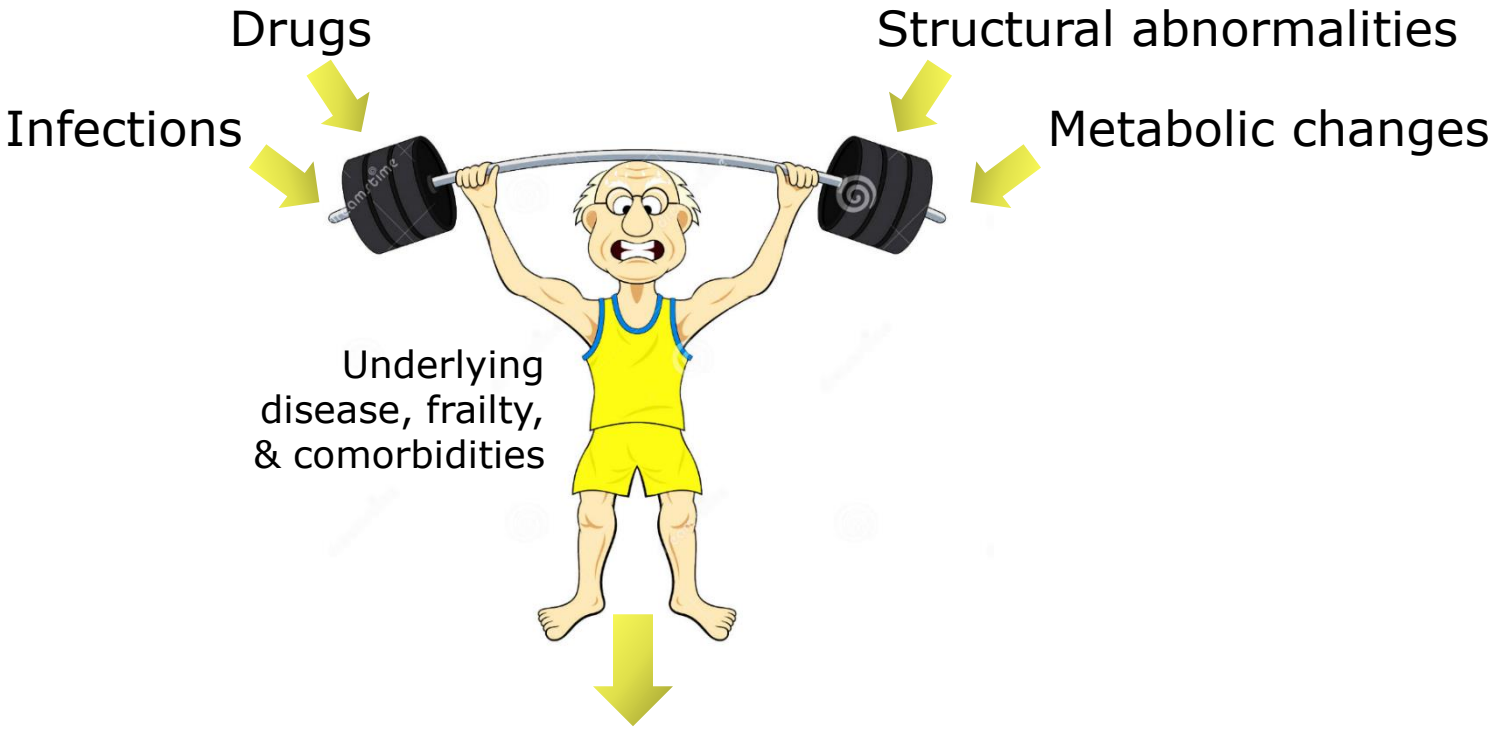
European Delirium Association & American Delirium Association *BMC Medicine* 2014

Delirium is Common

- Patient characteristics are different
- Etiology may be different
- Outcomes are different

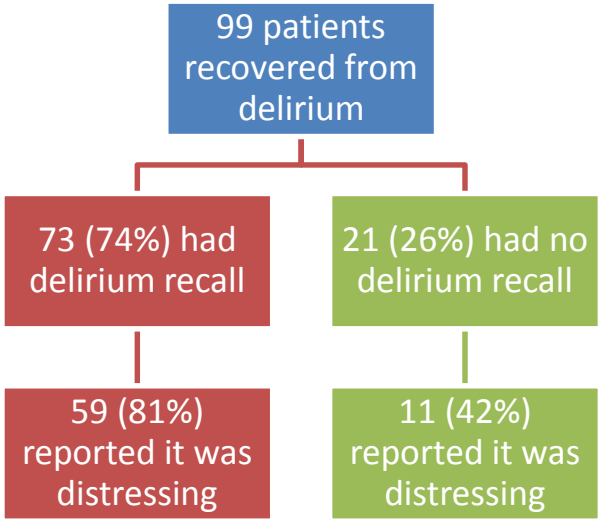


Causes and Outcomes



Associated Complications
Increased morbidity
Increased safety concerns
Increased distress
Increased length of stay
Increased healthcare costs
Increased institutionalization
Increased mortality

Delirium Recall and Related Distress



	Recalled Symptom Frequency					Distress Score				
	Patient		Family Caregiver			Patient		Family Caregiver		
	No.	Median (Q1-Q3)	No.	Median (Q1-Q3)	*P*	No.	Median (Q1-Q3)	No.	Median (Q1-Q3)	*P*
Auditory hallucinations	18	2 (1-2)	30	2 (2-3)	0.14	17	3 (2-3)	29	3 (1-4)	.38
Delusional thoughts	33	2 (1-3)	46	2 (1-3)	0.20	31	3 (1-4)	45	3 (2-4)	.31
Time orientation	57	3 (2-4)	79	3 (2-4)	0.87	56	3 (1-3.5)	77	3 (1-4)	.69
Place orientation	52	2 (1-4)	75	2 (2-4)	0.74	52	3 (1-4)	73	3 (1-4)	.19
Psychomotor agitation	55	2 (2-4)	82	3 (2-4)	0.43	54	3 (2-4)	80	4 (3-4)	.09
Tactile hallucinations	12	2 (1-2.5)	25	2 (1-3)	0.79	12	3.5 (2-4)	23	3 (1-4)	.68
Visual hallucinations	50	2 (1-3)	55	2 (1-3)	0.93	49	2 (1-3)	53	3 (2-4)	.01

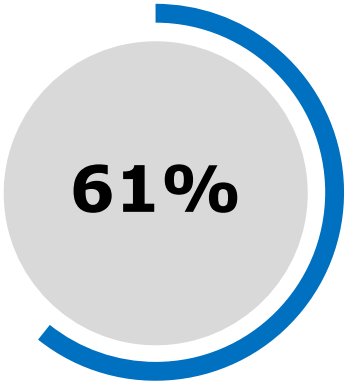
Bruera et al. *Cancer* 2008

"I'VE BEEN HAVING HALLUCINATIONS AGAIN, DOCTOR."

Delirium Assessment

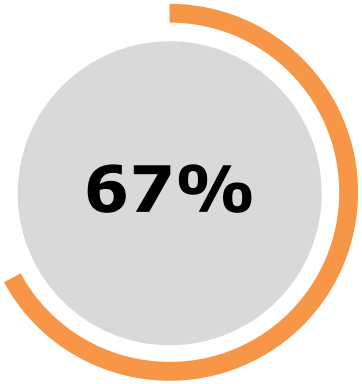
Missed Delirium

Missed Delirium



252/771 (33%) patients who had an inpatient palliative care consult found to have delirium by the palliative care team. 99 (39%) diagnosed with delirium by oncology team

Reversible Delirium



55/82 (67%) patients with reversible delirium had a missed diagnosis initially

Routine screening is key!

De La Cruz et al. *Supp Care Cancer* 2015

Delirium Assessment

Screening Tools

	Burden	Sens	Spc	LR- (95% CI)	LR+ (95% CI)
Confusion Assessment Method (CAM)	4 items <5 min	86%	93%	0.16 (0.09, 0.29)	9.6 (5.8, 16)
Delirium Rating Scale (DRS)	10 items Cutoff ≥10/32	95%	79%	0.07 (0.03, 0.37)	4.3 (2.1, 9.1)
Memorial Delirium Assessment Scale (MDAS)	10 items <10 min Cutoff ≥10/30	92%	92%		12 (2.4, 15.8)
Delirium Observation Screening Scale (DOS/DOSS)	13/25 items <5/<10 min	92%	82%	0.1 (0.03, 0.37)	5.2 (2.7, 9.9)

Greer et al. *VA-ESP Project #09-009* 2011

Outline

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  - Pharmacologic approaches
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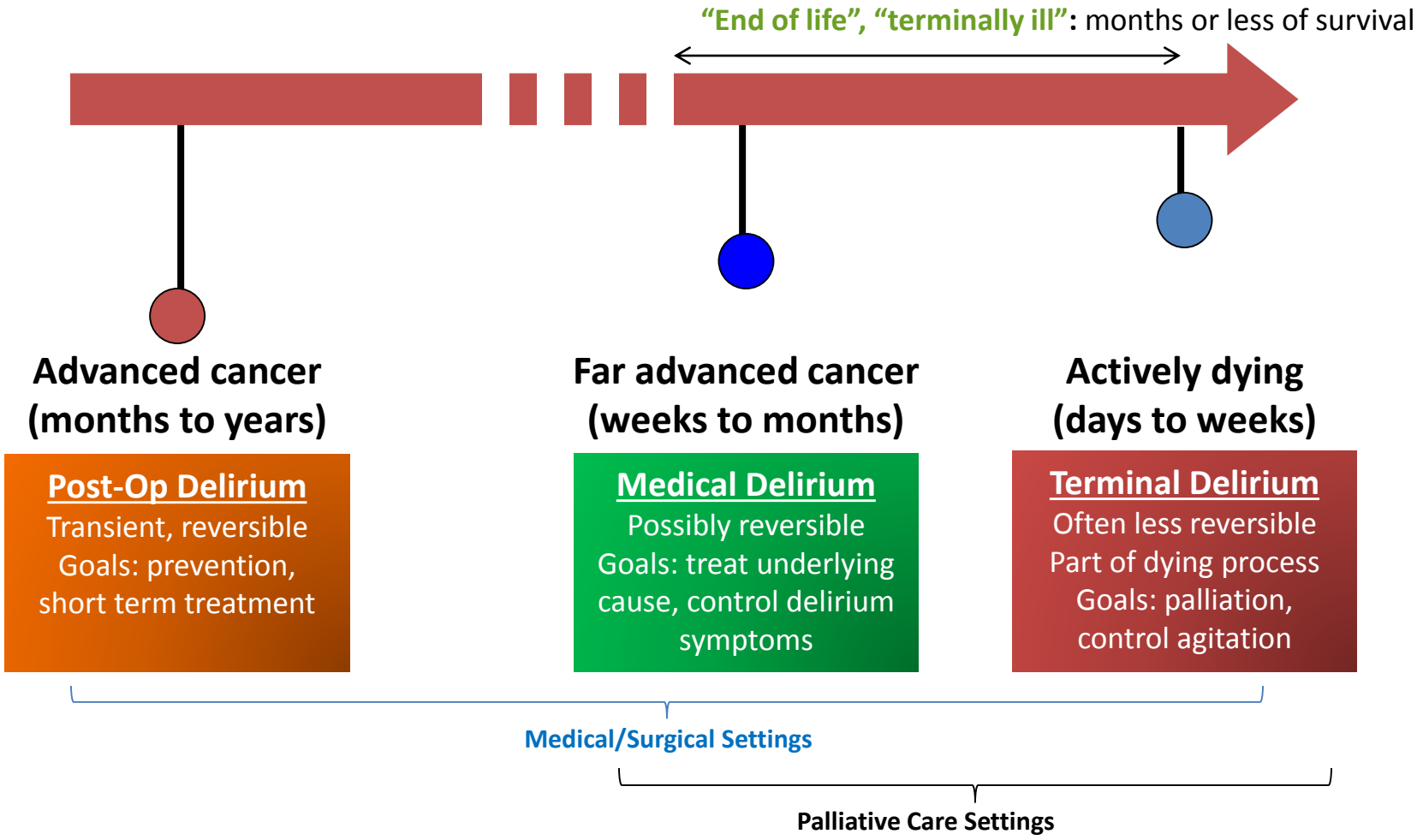
Prognosis-Based Decision Making

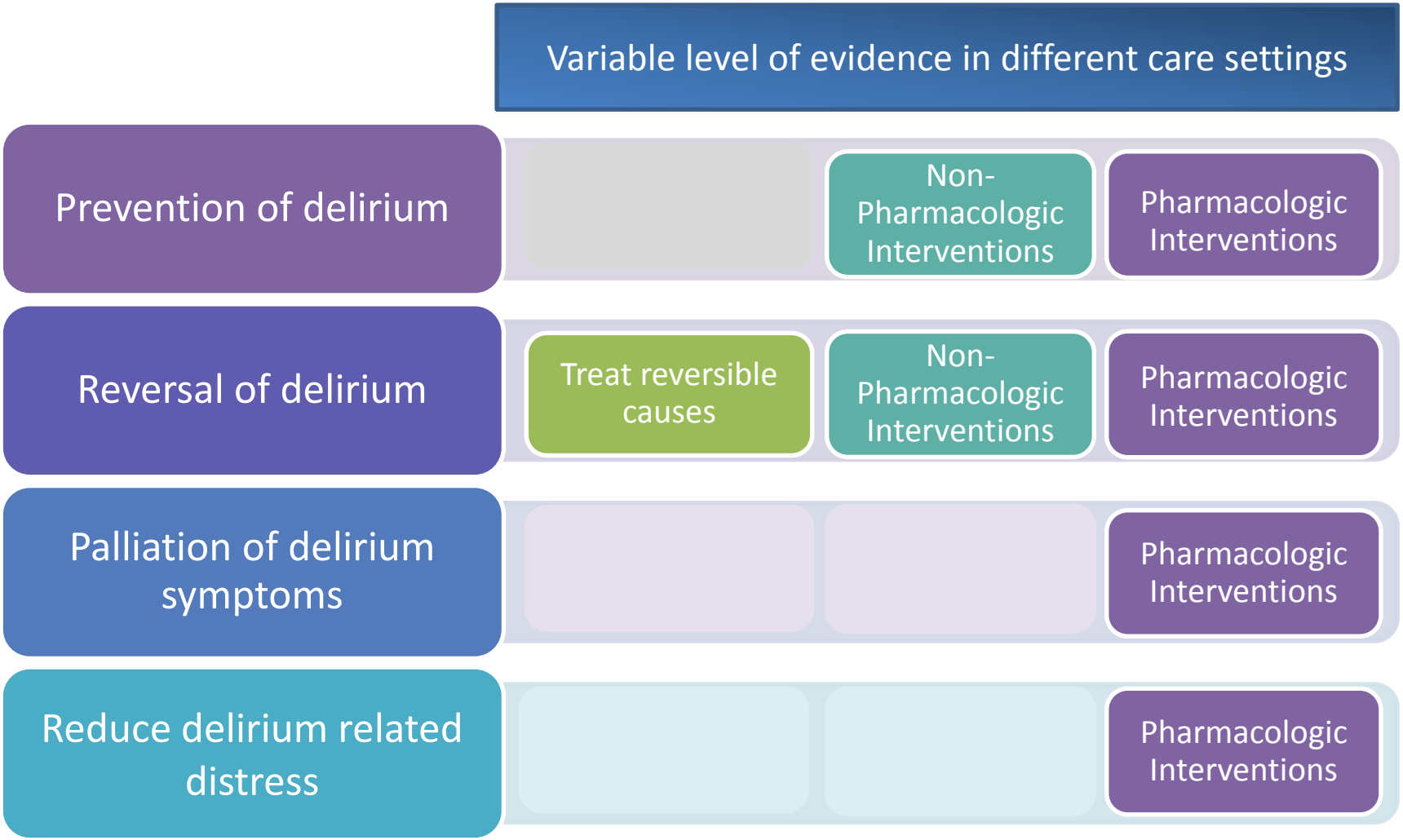
Delirium in Advanced Cancer



Hui et al. *Curr Opin Supp Palliat Care* 2016

Delirium Management

Setting Realistic Goals



Reversibility of Delirium

Palliative Care Setting

- 71 patients with advanced cancer admitted to palliative care developed delirium
  - Reversal in 46/94 (49%) episodes
  - Terminal delirium in 46/52 (88%) APCU deaths
  - Median survival ~25 days

	No. (%) of Episodes		Univariate Analysis			Multivariate Analysis	
Categories†	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* 2001

Reversibility of Delirium

Thiamine Deficiency

- Wernicke encephalopathy diagnosed clinically and treated before lab values confirmed

	Case 1	Case 2	Case 3
Patient	71yo M	66yo F	77yo F
DRS baseline	21	24	24
Onset	Gradual	Gradual	Gradual
Ataxia	Yes	NA	Yes
Ocular	No	No	Yes
Thiamine lvl	18ng/ml	15ng/ml	NA
Reversed after tx	Yes	After 3 days	After 3 days

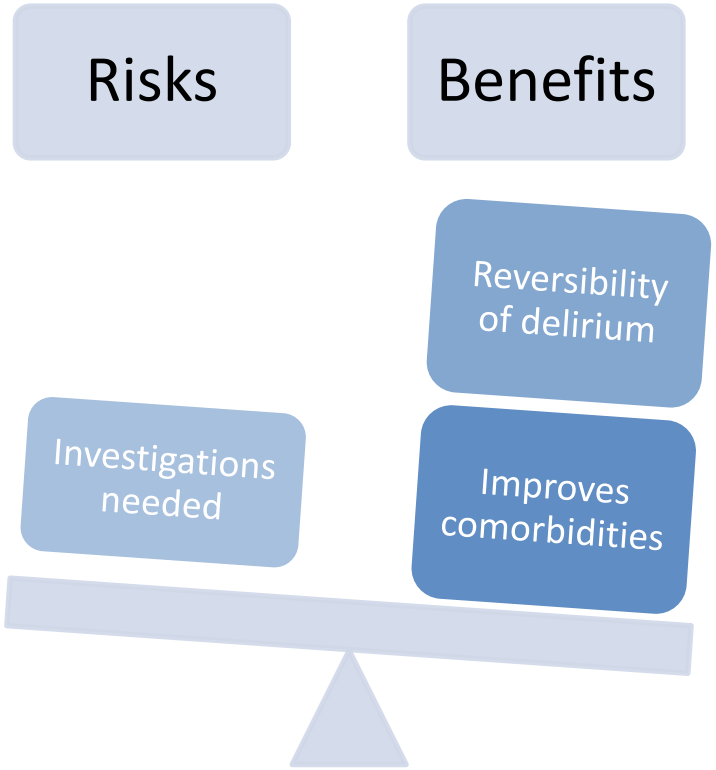
Onishi et al. *Supp Care Cancer* 2004

- 70 year old woman with delirium, disorientation, cognitive impairment but no ocular changes or gait abnormalities
  - Thiamine level 14 (normal 20-50 ng/ml), started IV thiamine 100 mg/day
  - Day 1: DRS 24
  - Day 2: improvement in cognition and insomnia
  - Day 3: able to communicate
  - Day 4: DRS 3. Thiamine level 679 ng/ml
  - Died 10 days later

Yae et al. *Palliat Supp Care* 2005

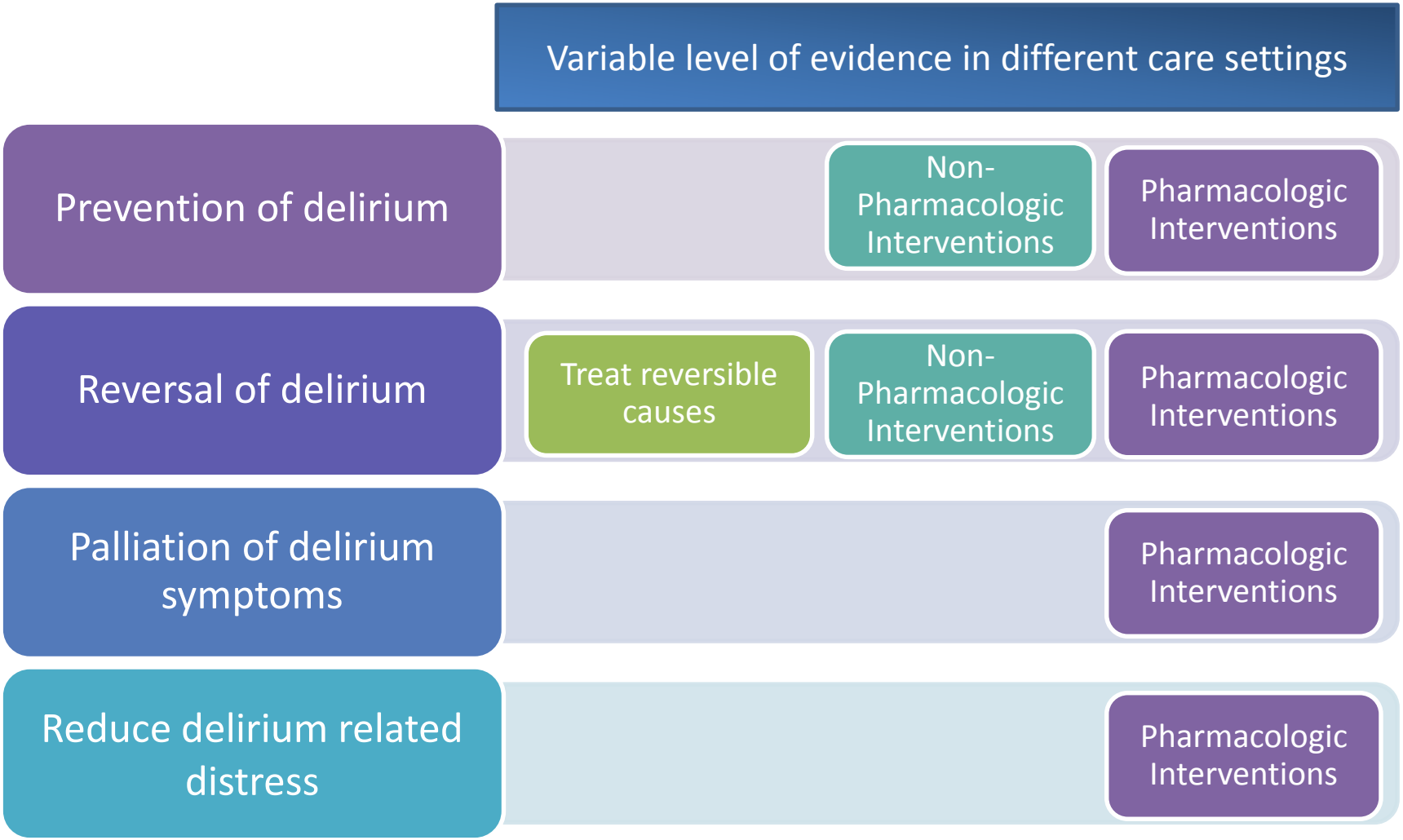
Treat Underlying Cause(s)

Take Home Message



Delirium Management

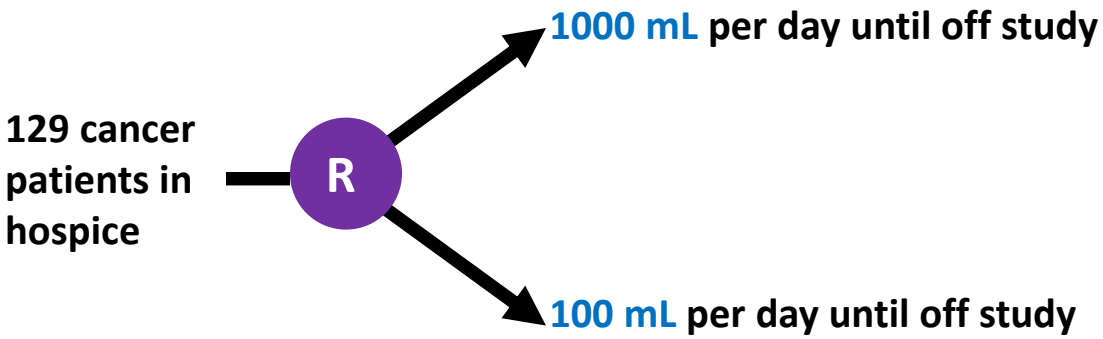
Setting Realistic Goals



Non-Pharmacologic Measures

Hydration for Delirium Prevention

Double blind, randomized controlled trial



Bruera et al. *J Clin Oncol* 2013

Non-Pharmacologic Measures

Hydration for Delirium Prevention

Assessments	Change between Baseline and Day 4			Change between Baseline and Day 7		
	Hydration N=49	Placebo N=51	P-value	Hydration N=44	Placebo N=49	P-value
Composite outcome [fatigue, drowsiness, hallucinations, myoclonus], mean (95% confidence interval)	-3.3 (-1.1, -5.4)	-2.8 (-0.2, -5.3)	0.77	-4.9 (-2.2, -7.7)	-3.8 (-1.1, -6.4)	0.54
MDAS, median (IQR)	1 (-2, 5.8)	3.5 (-0.3, 14.5)	0.08	2 (-2, 10)	2.5 (-1, 14)	0.44
NuDESC , median (SD)						
Day	0 (-1, 1)	0 (-1, 2)	0.13	0 (0, 0)	0 (0, 1)	0.36
Evening	0 (-1, 1)	0 (-1, 2)	0.40	0 (-1, 1)	0 (-1, 3)	0.39
Night	0 (-1, 0)	0 (-1, 2)	0.03	0 (-1, 1)	0 (-1, 1)	0.79

Caveats

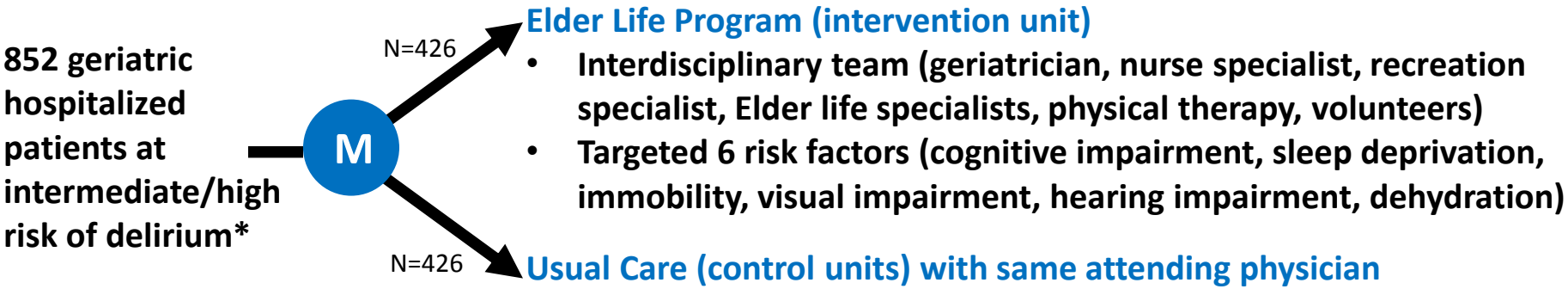
- Only patients with mild-moderate dehydration
- Delirium was a secondary outcome (floor effect)
- Patients with days-weeks of survival
- May need multi-model intervention

Bruera et al. *J Clin Oncol* 2013

Multicomponent Intervention

Delirium Prevention

Open label, matched cohort study



* Four risk factors: visual impairment, severe illness, cognitive impairment, high BUN/Cr
- Intermediate risk: 1-2 risk factors
- High risk: 3-4 risk factors

Inouye et al. *NEJM* 1999

Multicomponent Intervention

Delirium Prevention

Domain	Interventions
Orientation protocol	Board with names of care team members listed, communication to reorient to surroundings Therapeutic activities protocol TID, as tolerated; includes family involvement and structured reminiscence
Sleep protocol	Warm drink at bedtime, relaxation music, unit-wide noise reduction strategies, schedule adjustments to allow sleep (rescheduling of vitals, medications, and procedures)
Mobilization protocol	Physical/occupational therapy assessment, minimal use of immobilizing equipment
Vision protocol	Visual aids (e.g., glasses or magnifying lenses), adaptive equipment (e.g., large illuminated telephone keypads) for patients with visual impairments, reinforcement of their use
Hearing protocol	Portable amplifying devices, special communication techniques for patients with hearing impairments, daily reinforcement of these adaptations
Dehydration protocol	Early recognition of dehydration and volume repletion (e.g., encourage oral intake or parenteral hydration)

Multicomponent Intervention

Delirium Prevention

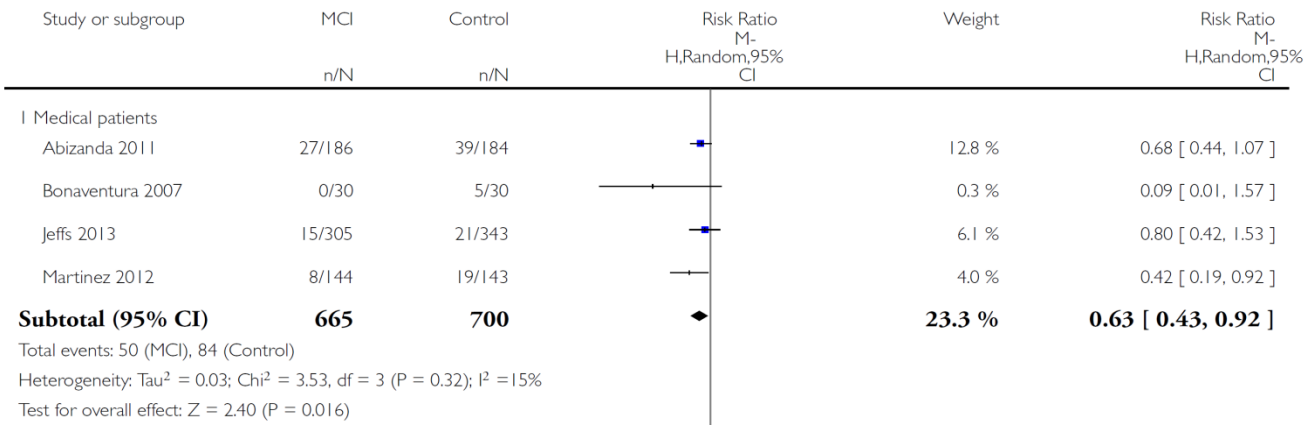
Outcome	Study Group		Statistical Analysis	
	Intervention	Usual Care	Matched	Unmatched
All matched patients (n=852)				
First episode of delirium — no. of patients (%)	42 (9.9)	64 (15.0)	OR, 0.60 (95% CI, 0.39–0.92); P=0.02†	OR, 0.61 (95% CI, 0.40–0.93); P=0.02‡
Total days of delirium§	105	161	P=0.02¶	
No. of episodes of delirium‖	62	90	P=0.03¶	
Patients with delirium (n=106)				
Mean ±SD delirium-severity score	3.85±1.27	3.52±1.44		P=0.25**
Recurrence (two or more episodes) — no. of patients (%)	13 (31.0)	17 (26.6)		P=0.62††

Inouye et al. *NEJM* 1999

Delirium Prevention

Systematic Review and Metaanalysis

- Multicomponent Intervention (RR 0.63, 95% CI 0.43-0.92)



- Pharmacologic therapies (inadequate evidence)
  - Antipsychotics (RR 0.73, 95% CI 0.33-1.59)
    - Haloperidol (RR 1.05, 95% CI 0.69-1.60)
    - Olanzapine (RR 0.36, 95% CI 0.24-0.52)
  - Melatonin (RR 0.41 95% CI 0.09-1.89)
  - Cholinesterase inhibitors (RR 0.68 95% CI 0.17-2.62)

Siddiqi et al. *Cochrane Database* 2016

Multicomponent Intervention

Delirium Treatment

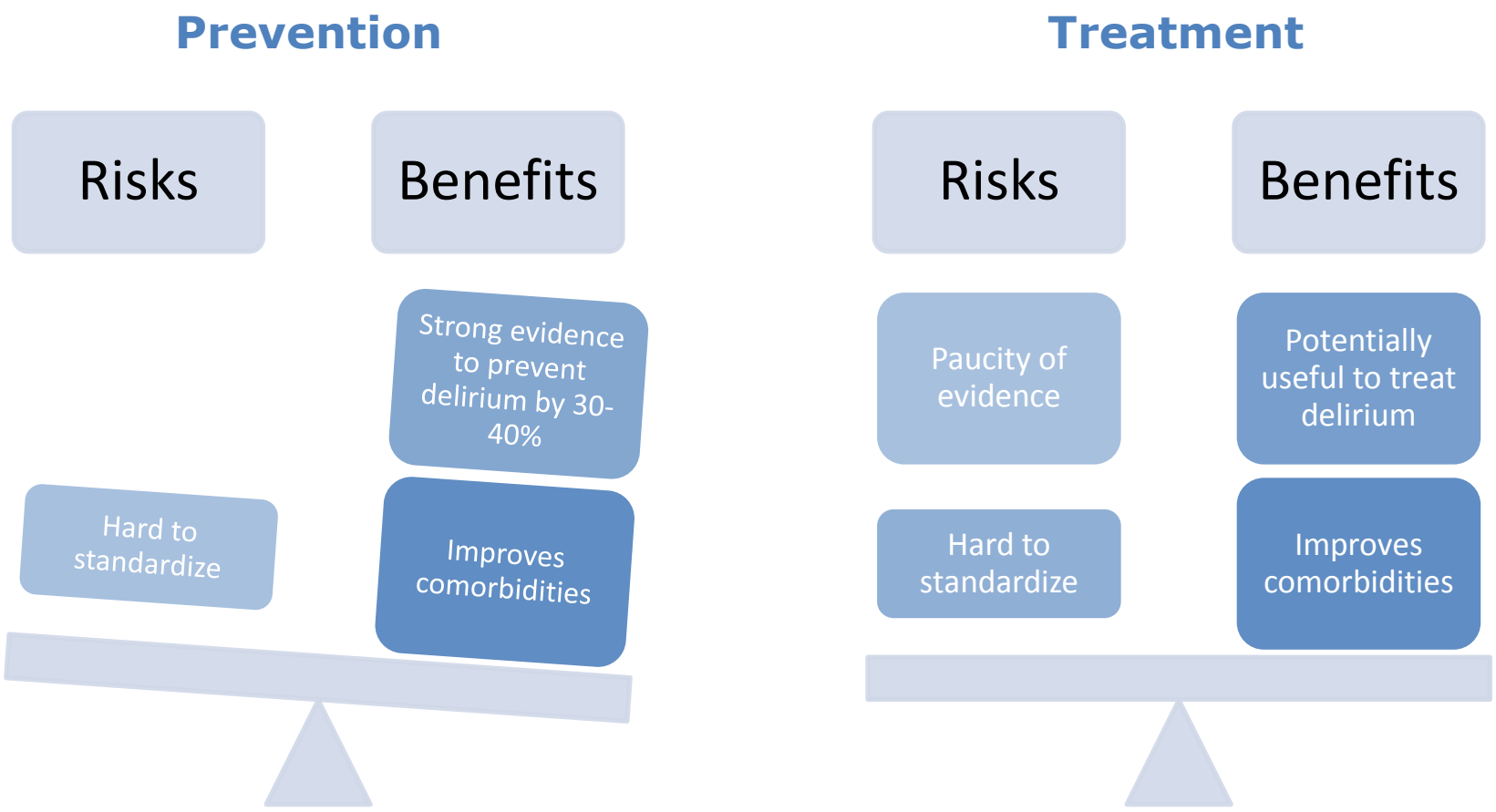
4 geriatric, unblinded randomized controlled trials

	Population	Intervention (vs.usual care)	Outcome	Comments
Cole et al. CMAJ 1994	88 pts with delirium Medical unit Age 75 or older	Consultation by geriatrician or psychiatrist and followup by liaison nurse (environment, orientation, familiarity, communication, activities) during admission	Crichton Geriatric Behavioural Rating Scale (-8.1 vs. -3.5, P<0.05) over 8 wks Short Portable Mental Status Questionnaire (-0.5 vs. -0.6, p=0.06) No difference in restraints, length of stay, discharge outcomes or mortality	Non-pharm on delirium; mixed findings and limited improvement
Cole et al. CMAJ 2002	227 pts with delirium Medical units Age 65 or older	Consultation by geriatrician or psychiatrist and followup by liaison nurse (environment, orientation, familiarity, communication, activities) during admission	Time to improvement (HR 1.1, 95% 0.74-1.63) Delirium improvement (48% vs. 45%) No difference in Delirium Index score, Barthel Index score, length of stay, discharge outcomes or survival	Non-pharm on delirium; no improvement
Lundstrom et al. JAGS 2005	125 pts with delirium 275 pts without delirium Medical service Age 70 or older	2 day course in geriatric medicine focusing on delirium Education concerning caregiver-patient interaction Reorganization of nursing care Guidance for nursing staff once a month	Complete remission rate on day 7 (70% vs. 40%, P=0.001) Able to return to home (78% vs. 60%, P=0.05) Length of stay (11 d vs. 21 d) Lower mortality (3% vs. 14%, P=0.03)	Educational/ system change; lots of improvement
Pitkala et al. J Gerontology 2006	174 pts with delirium Medical services Age 69 or older	Comprehensive geriatric assessment at baseline, avoid conventional neuroleptics, orientation, physiotherapy, geriatric interventions (nutrition supplements, calcium, hip protectors), cholinesterase inhibitors	Mortality at 1 year (61% vs. 64%, P=0.64) Days in hospital (126 vs. 140, P=0.69) Delirium MDAS improvement by day 8 (~50% vs. ~20%) MMSE 6 months (8.4 vs. 15.8, P=0.047) Barthel Index 6 months (70.2 vs. 63.8, P=0.14)	Non-pharm; Delirium secondary endpoint and positive

Ahraha et al. *PLOS One* 2015

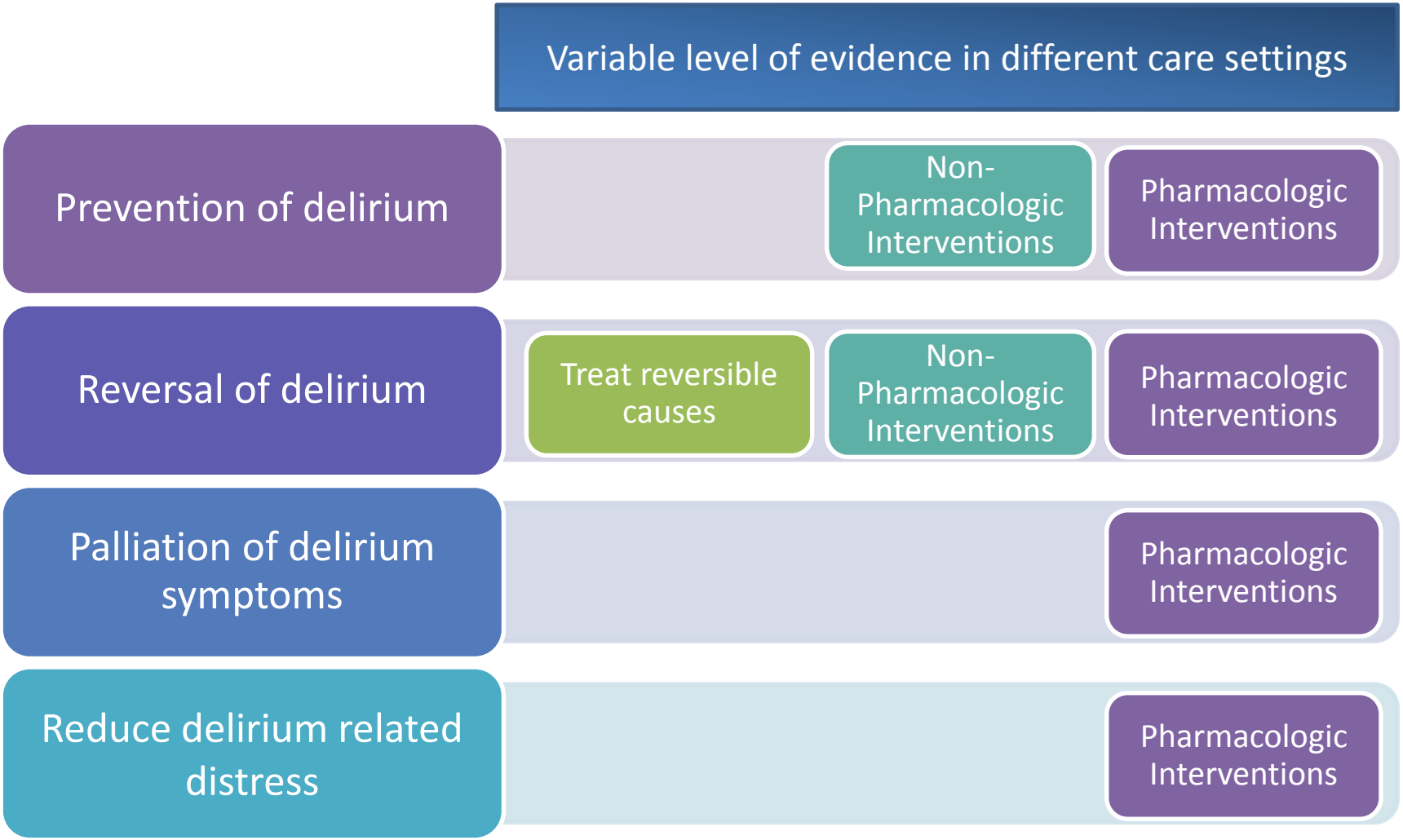
Multicomponent Intervention

Take Home Message



Delirium Management

Setting Realistic Goals



Pharmacologic Interventions

Delirium Prevention

- Antipsychotics (RR 0.73, 95% CI 0.33-1.59)
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Siddiqi et al. *Cochrane Database* 2016

Pharmacologic Interventions

Delirium Prevention

- Antipsychotics for prevention of post-op delirium
  - 2 of 3 haloperidol trials +ve (Kaneko et al. 1999 ICU; Wang et al. 2012 ICU)
  - 2 of 2 risperidone trials +ve (Prakanrattana et al. 2007 ICU; Hakim et al. 2012 ICU)
  - 1 of 1 olanzapine trial +ve (Larsen et al. 2010 Geriatric)

- Cholinesterase inhibitors for prevention of post-op delirium
  - 0 of 3 donepezil trials +ve
  - 0 of 2 rivastigmine trials +ve

Friedman et al. *Am J Psych* 2014

Pharmacologic Interventions

Delirium Treatment

- Antipsychotics for treatment of delirium
  - 0 of 1 haloperidol-placebo trial +ve (Girard et al. 2010 ICU)
  - 0 of 1 ziprasidone-placebo trial +ve (Girard et al. 2010 ICU)
  - 0 of 2 quetiapine-placebo trial +ve (Devlin et al. 2010, Tahir et al. 2010)

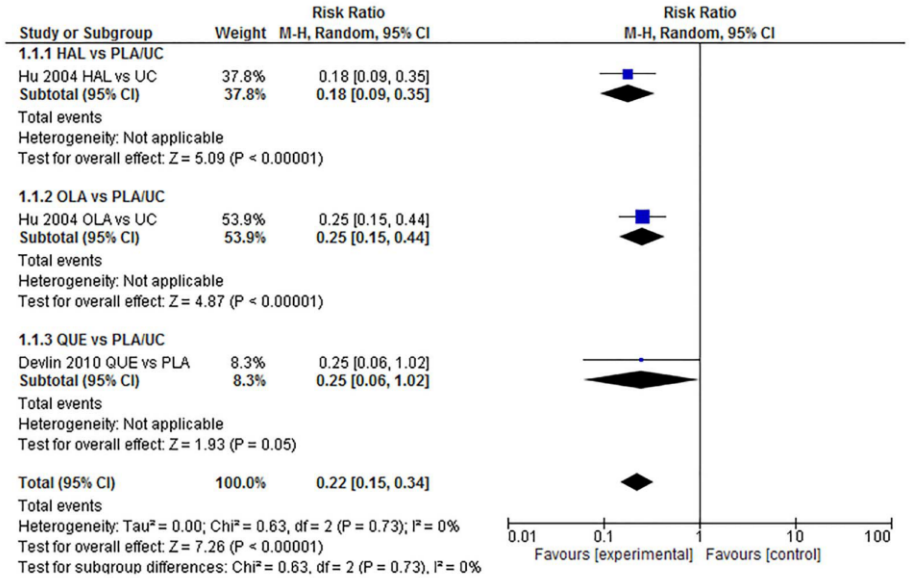
- Miscellaneous treatments
  - 0 of 1 melatonin trial +ve (Al Aama et al. 2011)
  - 0 of 1 ketamine trial +ve (Hudetz et al. 2009)

Friedman et al. *Am J Psych* 2014

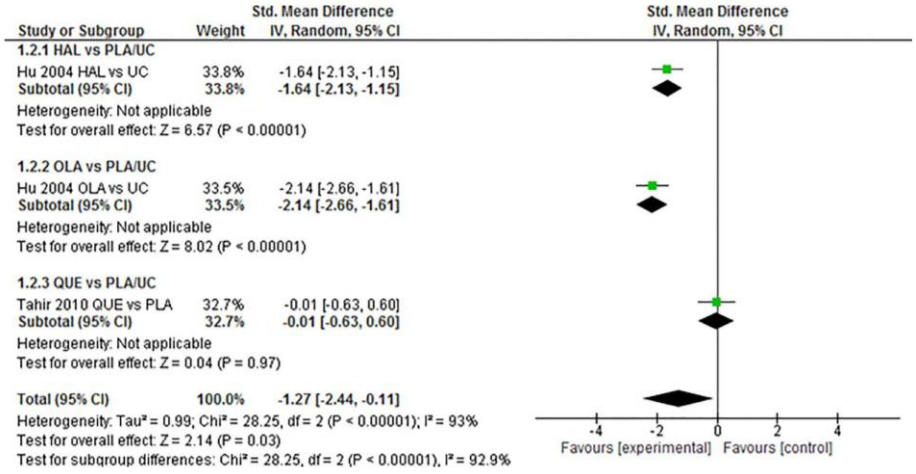
Neuroleptics

Delirium Treatment

Response rate at the study endpoint



Delirium severity scales scores on the endpoint



Conclusion

Our results suggested that antipsychotic medications were superior to PLA/UC in efficacy outcomes. Moreover, SGAs are more beneficial for the treatment of delirium regarding efficacy and safety outcomes compared with haloperidol. However, because the studies included in the meta-analysis were small, further study using larger samples is required.

Kishi et al. *J Neurol Neurosurg Psychiatry* 2016

Neuroleptics

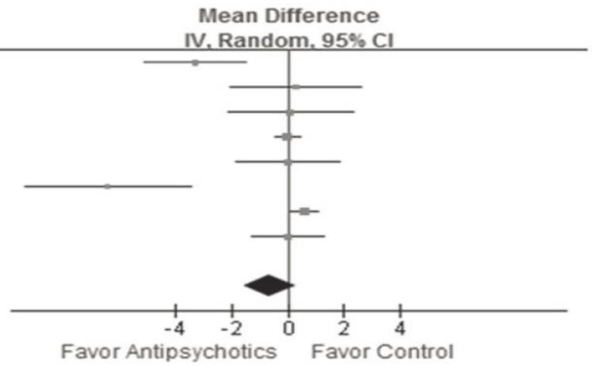
Delirium Prevention and Treatment

12 treatment trials: 10 RCTs, 5 had placebo
7 prevention trials: all post-operative setting

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]**

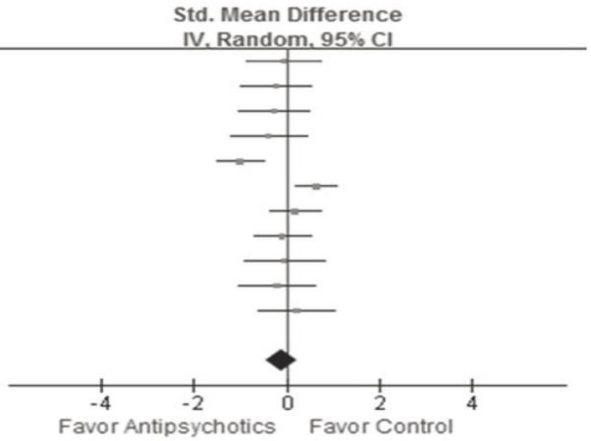
Heterogeneity: $Tau^2 = 1.14$; $Chi^2 = 35.67$, df = 7 ($P < 0.00001$); $I^2 = 80\%$
Test for overall effect: $Z = 1.36$ ($P = 0.17$)



C **Delirium Severity in Hospitalized Patiens**

Study or Subgroup	Antipsychotics Mean	SD	Total	Control Mean	SD	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: $Tau^2 = 0.18$; $Chi^2 = 25.55$, df = 10 ($P = 0.004$); $I^2 = 61\%$
Test for overall effect: $Z = 0.65$ ($P = 0.52$)



Neufeld et al. *JAGS* 2016

Neuroleptics

Terminally Ill 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

Are You Confused Yet?

Delirium Literature

It is Confusing!

- Different patient populations and settings
- Different doses and dosing schedules
- Different comparison arms
- Different outcome measures (variable degree of validation)

- Different systematic reviews included different studies
- Different quality of studies
- Different languages

Result: Different opinions!

Benzodiazepines

Delirium Treatment

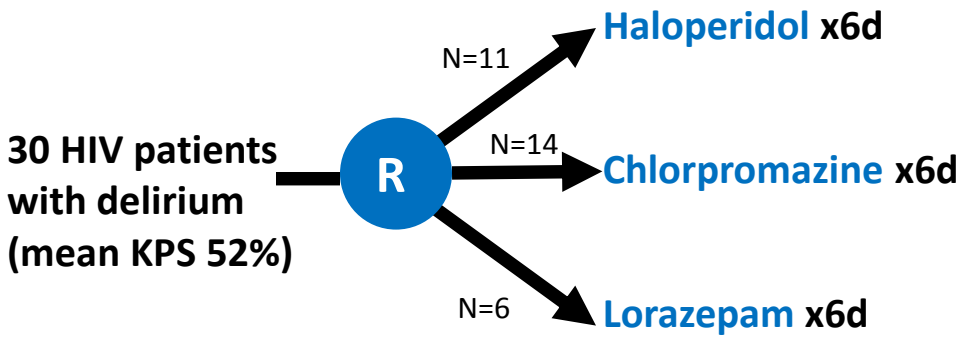
No adequately controlled trials could be found to support the use of benzodiazepines in the treatment of non-alcohol withdrawal related delirium among hospitalised patients, and at this time benzodiazepines cannot be recommended for the control of this condition. Because of the scarcity of trials with randomization of patients, placebo control, and adequate concealment of allocation of subjects, it is clear that further research is required to determine the role of benzodiazepines in the treatment of non-alcohol withdrawal related delirium.

- Pandharipande et al. JAMA 2017
  - Dexmedetomidine vs. lorazepam
  - Only study included in systematic review
- Breitbart et al. Am J Psych 1996
  - Haloperidol vs. chlorpromazine vs. lorazepam
  - Not included as lorazepam arm terminated early
- Christensen et al. JAGS 1998
  - Haloperidol vs. alprazolam
  - Not included because mixed dementia/delirium/amnesic/cognitive disorder

Lonergen et al. *Cochrane* 2009

Haloperidol vs. Chlorpromazine vs. Lorazepam: HIV Patients, Front Line

Double-blind, randomized controlled trial



Outcomes

- Delirium Rating Scale
- Mini-Mental State Examination
- Extrapyramidal Symptom Rating Scale
- Other Side Effects
- Karnofsky Performance Status
- Medical Status Profile

Breitbart et al. *Am J Psychiatry* 1996

Haloperidol vs. Chlorpromazine vs. Lorazepam: HIV Patients, Front Line

TABLE 1. Drug Dosing Protocol for Treatment of Delirium in Hospitalized AIDS Patients

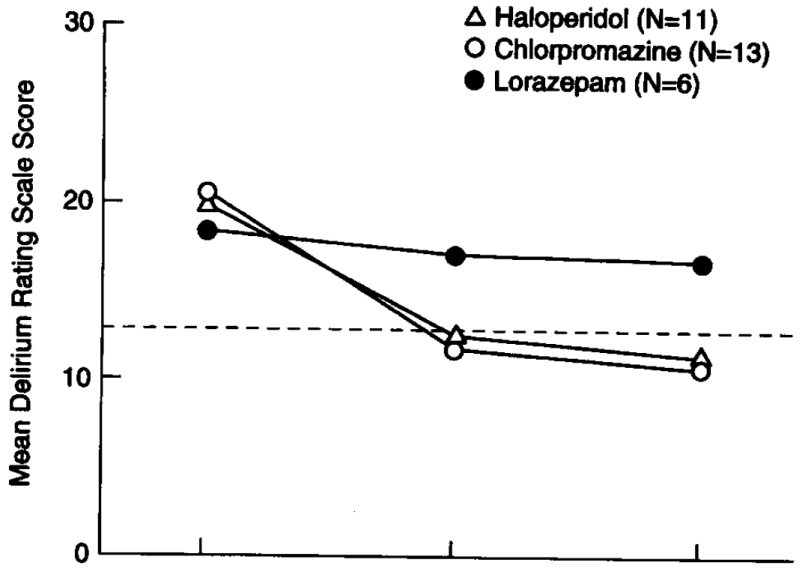
	Dose (mg/hour)					
	Haloperidol		Chlorpromazine		Lorazepam	
Dose Level	Oral	Intramuscular	Oral	Intramuscular	Oral	Intramuscular
1	0.25	0.125	10	5	0.50	0.20
2	0.50	0.50	20	10	1.00	0.50
3	1.00	0.50	40	20	1.50	0.70
4	2.00	1.00	80	40	2.00	1.00
5	2.50	1.50	100	50	2.50	1.25
6	2.50	1.50	100	50	2.50	1.25
7	2.50	1.50	100	50	2.50	1.25
8	5.00	3.00	200	100	4.00	2.00
9	5.00	3.00	200	100	4.00	2.00

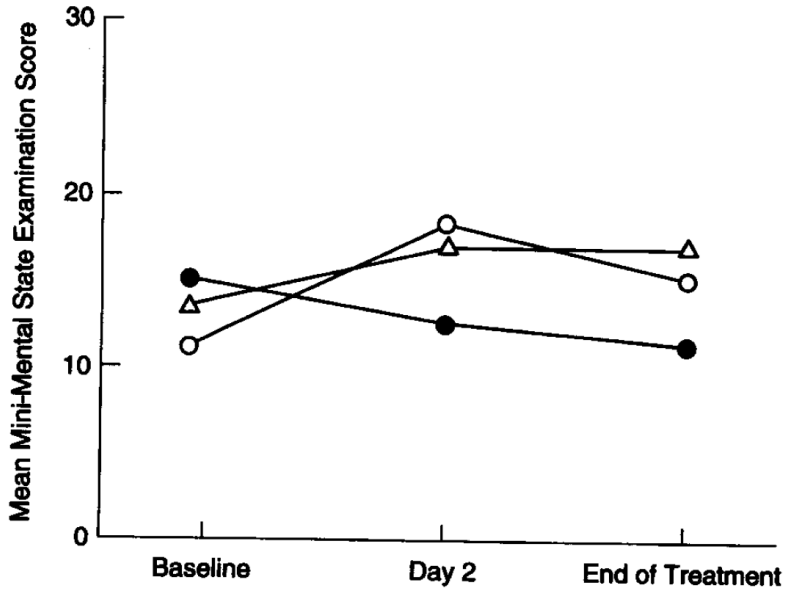
- **Mean drug doses in first 24 h**
  - Haloperidol 3.8 (2.4) mg
  - Chlorpromazine 50 (23.1) mg
  - Lorazepam 3 (3.6) mg
- **Mean maintenance drug doses**
  - Haloperidol 1.4 (1.2) mg
  - Chlorpromazine 36 (18.4) mg
  - Lorazepam 4.6 (4.7) mg

Day 1: Increase dose to next level every hour if DRS >13
Day 2-6: Give total dose from day 1, div BID

Breitbart et al. *Am J Psychiatry* 1996

Haloperidol vs. Chlorpromazine vs. Lorazepam: HIV Patients, Front Line





- Improvement seen within 24 hours of treatment in haloperidol and chlorpromazine arms
- All 6 patients on lorazepam arm developed treatment limiting side effects (sedation, disinhibition, ataxia, increased confusion)

Breitbart et al. *Am J Psychiatry* 1996

Haloperidol vs. Chlorpromazine vs. Lorazepam: HIV Patients, Front Line

- Strengths
  - First delirium study in palliative care setting
  - Rapid titration to identify optimal doses

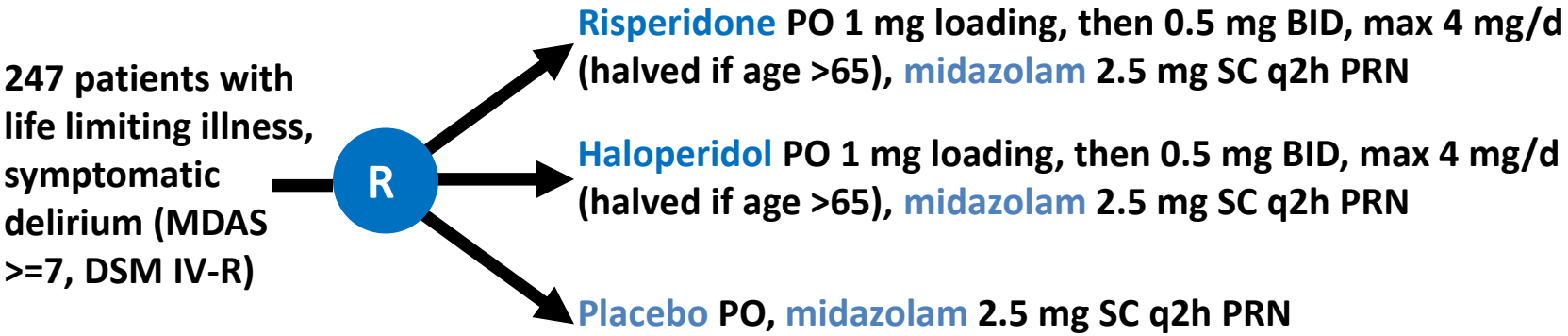
- Limitations
  - No placebo group
  - Small sample size
  - Intensive titration schedule
  - Lorazepam arm terminated early (n=6)

Main implication: Neuroleptics are superior to benzodiazepine for delirium in the palliative care setting

Risperidone vs. Haloperidol vs. Placebo

Palliative Care, Front Line

Double-blind, randomized controlled trial



Outcomes

- Primary: NuDesc inappropriate behaviour, inappropriate communication, illusions/hallucinations at 72 h
- Patient/caregiver/health professional rated distress
- Dosage or length of administration
- Toxicity (extrapyramidal effects, sedation)
- Pathophysiologic correlates (S100B, cytochrome C, caspase 3, neuron specific enolase)

Agar et al. *JAMA Intern Med* 2017

Risperidone vs. Haloperidol vs. Placebo

Palliative Care, Front Line

	Risperidone vs. Placebo		Haloperidol vs. Placebo	
	Effect (95% CI)	P-value	Effect (95% CI)	P-value
Delirium symptoms	0.48 (0.09, 0.86)	0.02	0.24 (0.06, 0.42)	0.009
MDAS scores/day	0.96 (0.16, 1.77)	<0.001	0.76 (-0.03, 1.51)	0.06
RASS/day	-0.05 (-0.19-0.09)	0.52	-0.14 (-0.28, 0)	0.048
Extrapyramidal effects	0.73 (0.09, 1.37)	0.03	0.79 (0.17, 1.41)	0.01
Overall survival (HR)	1.29 (0.91, 1.84)	0.14	1.73 (1.20, 2.50)	0.003
Median survival	17 d vs. 26 d		16 d vs. 26 d	

Agar et al. *JAMA Intern Med* 2017

Risperidone vs. Haloperidol vs. Placebo

Palliative Care, Front Line

- Midazolam use (placebo vs. neuroleptics)
  - Day 1: 13/75 (17%) vs. 50/144 (35%), P=0.007
  - Day 2: 11/68 (17%) vs. 40/121 (33%), P=0.01
  - Day 3: 9/66 (14%) vs. 32/108 (30%), P=0.02
- Midazolam dose/day (among pts who got it)
  - Placebo: median 2.5 mg (2.5-5.0 mg)
  - Risperidone: median 2.5 mg (2.5-5.0 mg)
  - Haloperidol: median 4 mg (2.5-5.0 mg)

Implications:

1. Neuroleptics are inferior to placebo for delirium in the palliative care setting
2. Benzodiazepines alone may be considered for rescue

Agar et al. *JAMA Intern Med* 2017

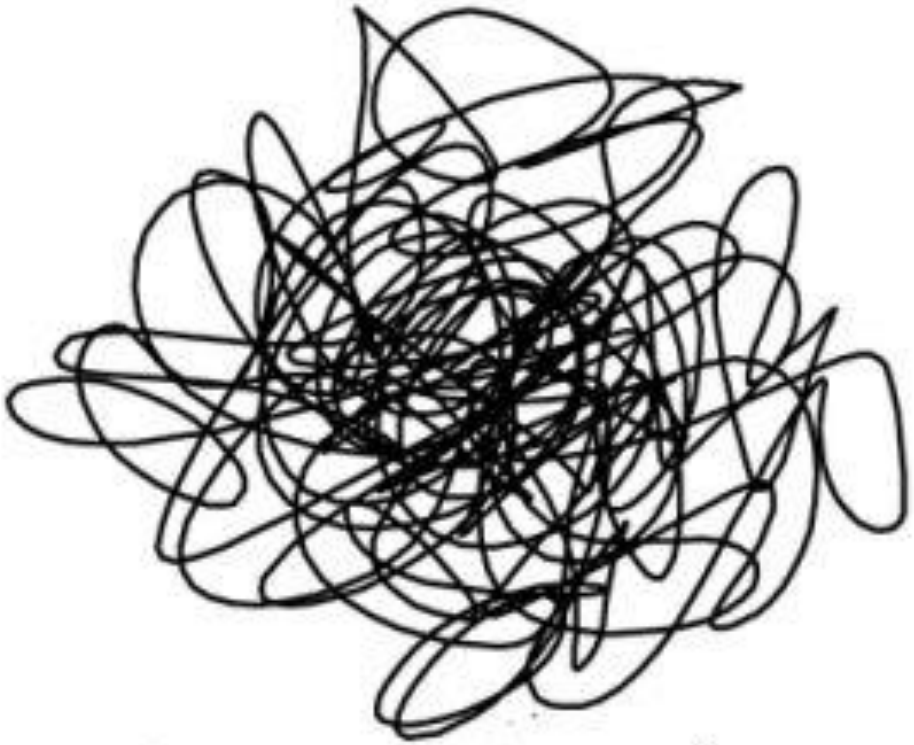
Risperidone vs. Haloperidol vs. Placebo

Palliative Care, Front Line

- Primary outcome
  - Has not been validated
  - Observed difference statistically significant but clinical significant unknown
- Patient population
  - Relatively low MDAS scores (median 13.7-15.1 – placebo best)
  - Did not exclude dementia patients
- Adverse effects
  - Despite very small doses for short duration (72 h)
  - Secondary outcomes = hypothesis generating only

More Research is Needed

Hui et al. *JAMA Intern Med* 2017 (in press)



How i feel right now

How about agitation…

RASS +1
Restless

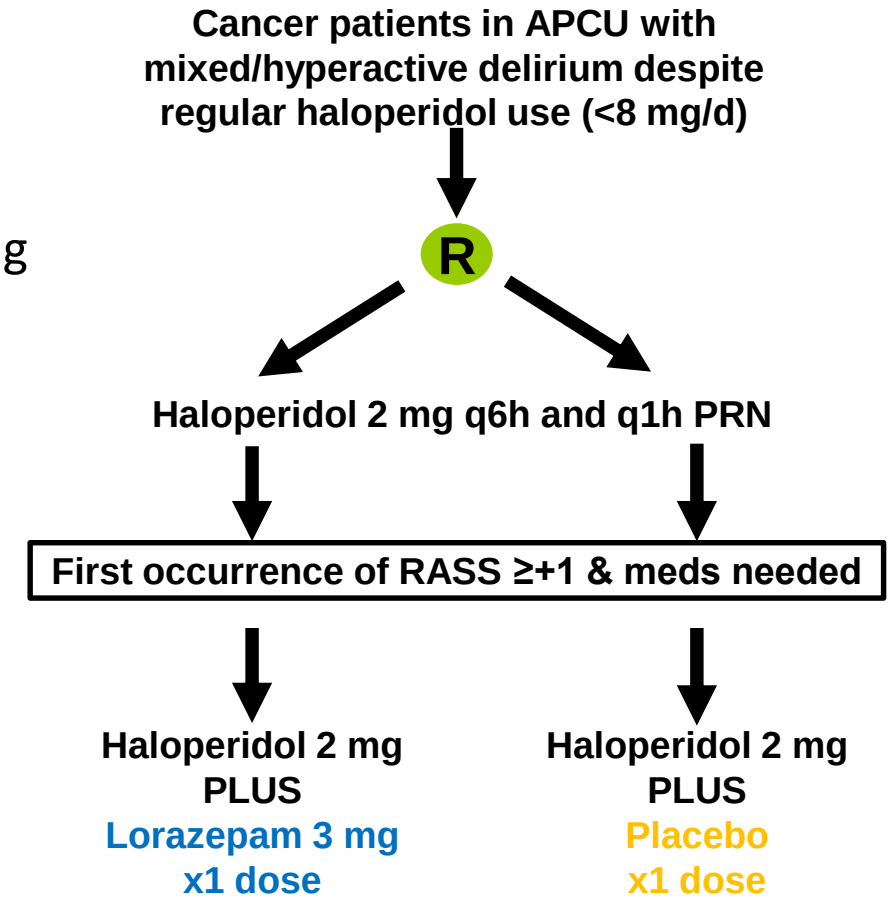
RASS +2
Agitated

RASS +3
Aggressive

Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

- Double-blind, randomized controlled trial
- Single dose instead of repeated dosing
  - Short survival (i.e. hours to days)
  - Uncertain risks associated with lorazepam in a frail population
- Study outcomes:
  - Richmond Agitation Sedation Scale (1°)
  - Use any additional psychotropic agents
  - Perceived patient comfort
  - MDAS, ESAS, DEQ
  - Communication capacity
  - Adverse effects
  - Discharge outcomes, survival

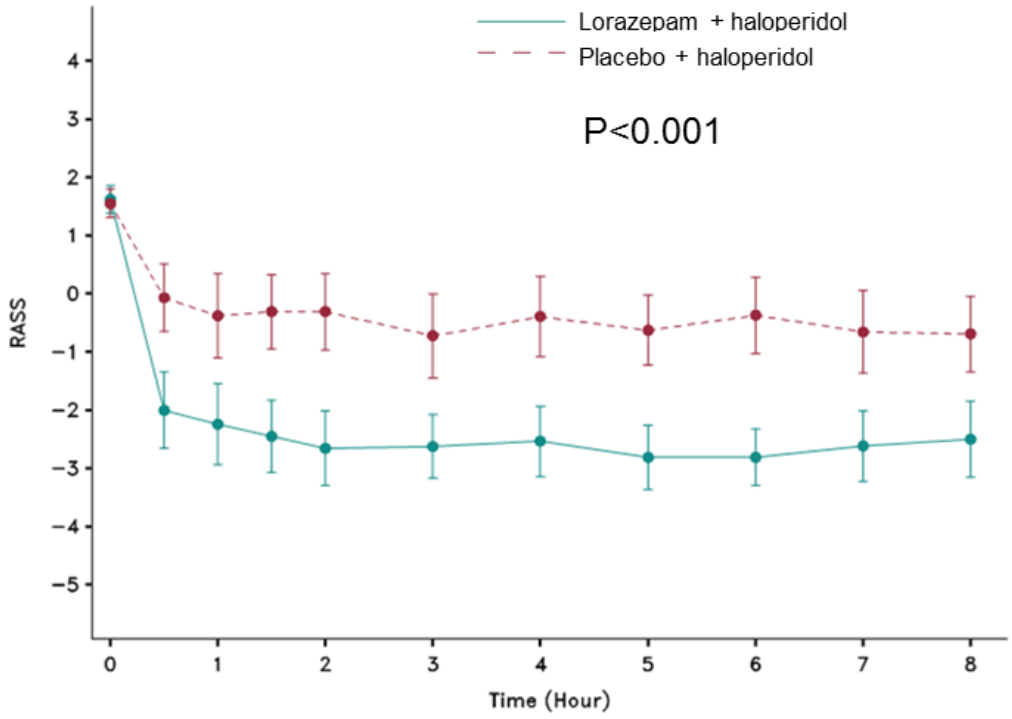


Hui et al. *ASCO* 2017

Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

- Lorazepam/haloperidol was associated with a significantly greater reduction of RASS compared to placebo
  - 0-30 min: mean Δ -2.0, 95% CI -2.9, -1.1, P<0.001
  - 0-8 h: mean Δ -1.9, 95% CI -2.8, -0.9, P<0.001

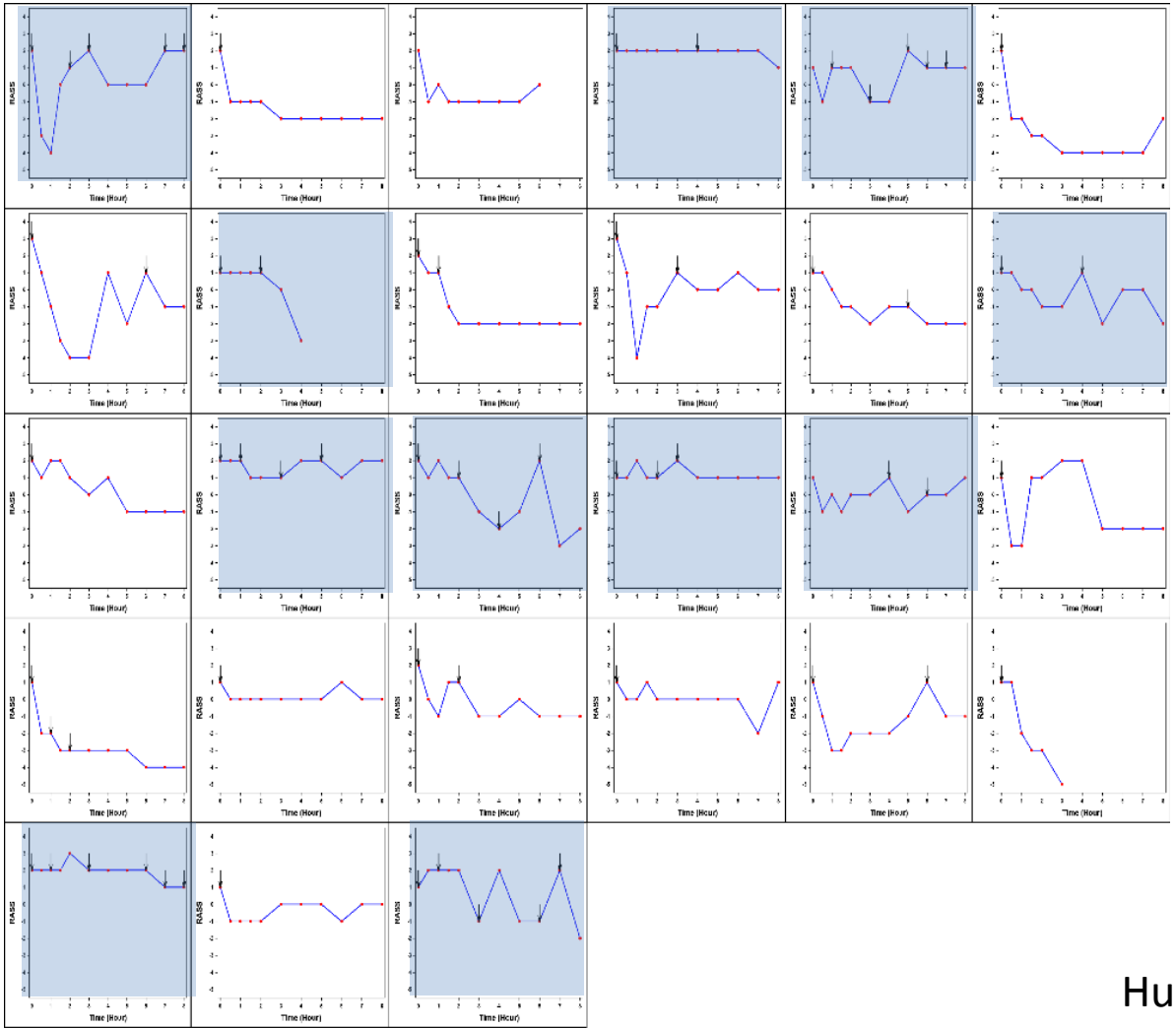


Hui et al. *ASCO* 2017

Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

Placebo + Haloperidol

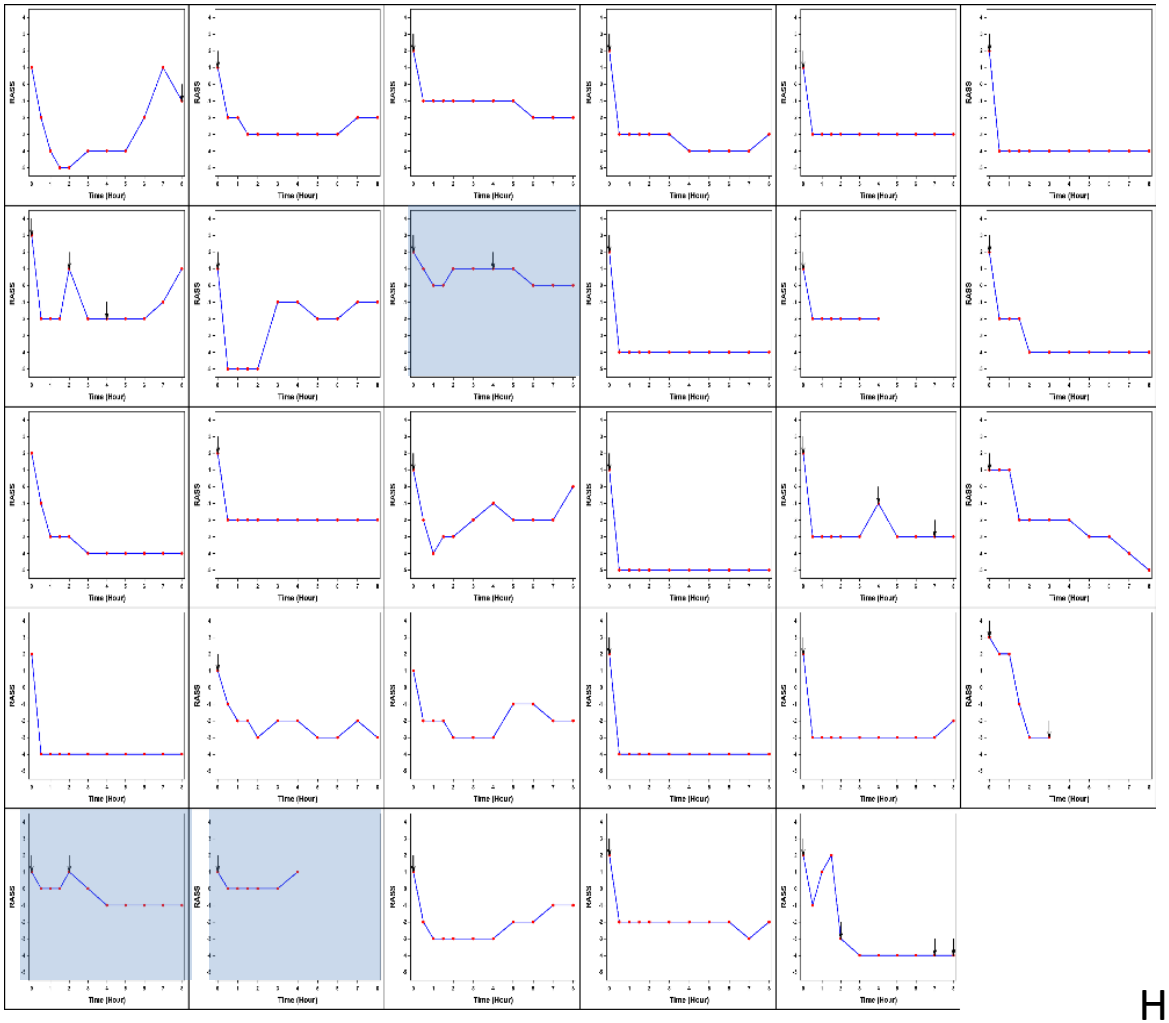


Hui et al. *ASCO* 2017

Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

Lorazepam + Haloperidol



Hui et al. *ASCO* 2017

Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

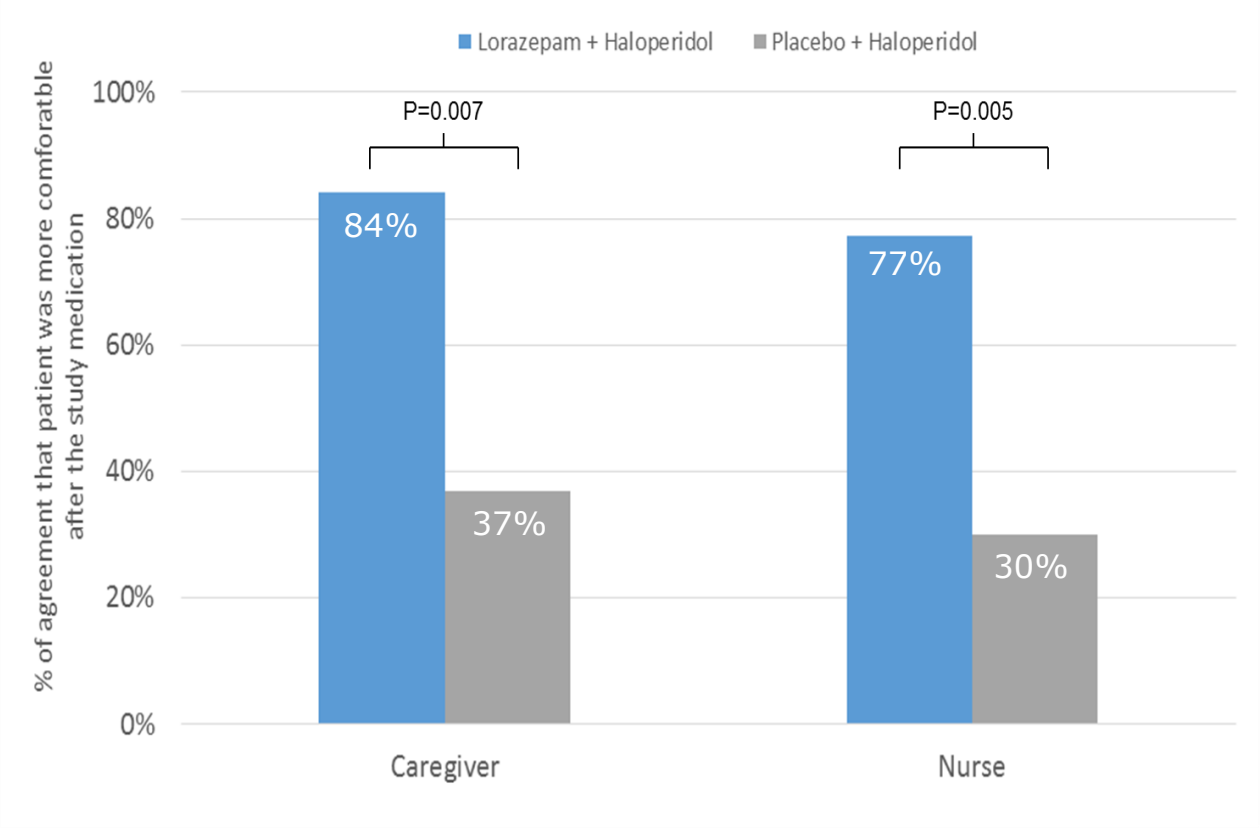
Neuroleptic use during the first 8 hours	Lorazepam + Haloperidol (n=29)	Placebo + Haloperidol (n=29)	Difference between arms (95% CI)	P-value
Scheduled HEDD, median (IQR), mg	2.0 (2.0, 4.0)	2.0 (2.0, 4.0)	-0.1 (-0.9, 0.6)	0.68
Rescue HEDD, median (IQR), mg	2.0 (2.0, 2.0)	4.0 (2.0, 5.0)	-2.2 (-3.8, -0.5)	0.009
Total HEDD, median (IQR), mg	6.0 (4.0, 6.0)	6.0 (4.0, 8.0)	-2.3 (-4.2, -0.5)	0.03
Number of rescue doses, median (IQR), mg	1.0 (1.0, 1.0)	2.0 (1.0, 2.0)	-0.9 (-1.6, -0.2)	0.008
Need for chlorpromazine during first 8 hours, No./total No. of observations (%)	2/29 (6.9%)	4/29 (13.8%)	-0.1 (-0.3, 0.2)	0.67
Change in MDAS, mean (SD)	2.5 (4.5)	0.4 (6.2)	2.1 (-1.0, 5.2)	0.18
Change in Edmonton Symptom Assessment Scale, mean (SD)				
Pain	-2.4 (2.7)	-1.7 (4.2)	-0.7 (-3.6, 2.2)	0.67
Fatigue	0.1 (1.9)	-1.8 (3.2)	1.9 (-0.7, 4.5)	0.23
Nausea	-0.7 (3.4)	-2.7 (3.9)	2.0 (-1.7, 5.7)	0.49
Depression	-1.4 (4.0)	0.2 (2.9)	-1.6 (-5.3, 2.2)	0.56
Anxiety	-3.4 (3.8)	-2.1 (4.7)	-1.3 (-5.0, 2.4)	0.55
Drowsiness	1.9 (3.5)	-2.0 (3.1)	3.9 (0.8, 7.1)	0.03
Shortness of Breath	-1.0 (2.2)	-0.4 (4.5)	-0.6 (-3.3, 2.2)	0.41
Appetite	0.6 (1.6)	2.1 (3.2)	-1.5 (-3.6, 0.6)	0.26
Sleep	-2.9 (3.8)	-2.4 (3.8)	-0.5 (-4.0, 3.1)	0.74
Feeling of Well-being	-2.3 (3.3)	-1.5 (3.3)	-0.8 (-4.2, 2.6)	0.51

Hui et al. *ASCO* 2017

Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

Patients on lorazepam/haloperidol arm were perceived to be more comfortable after the study medication by *blinded* caregivers and nurses

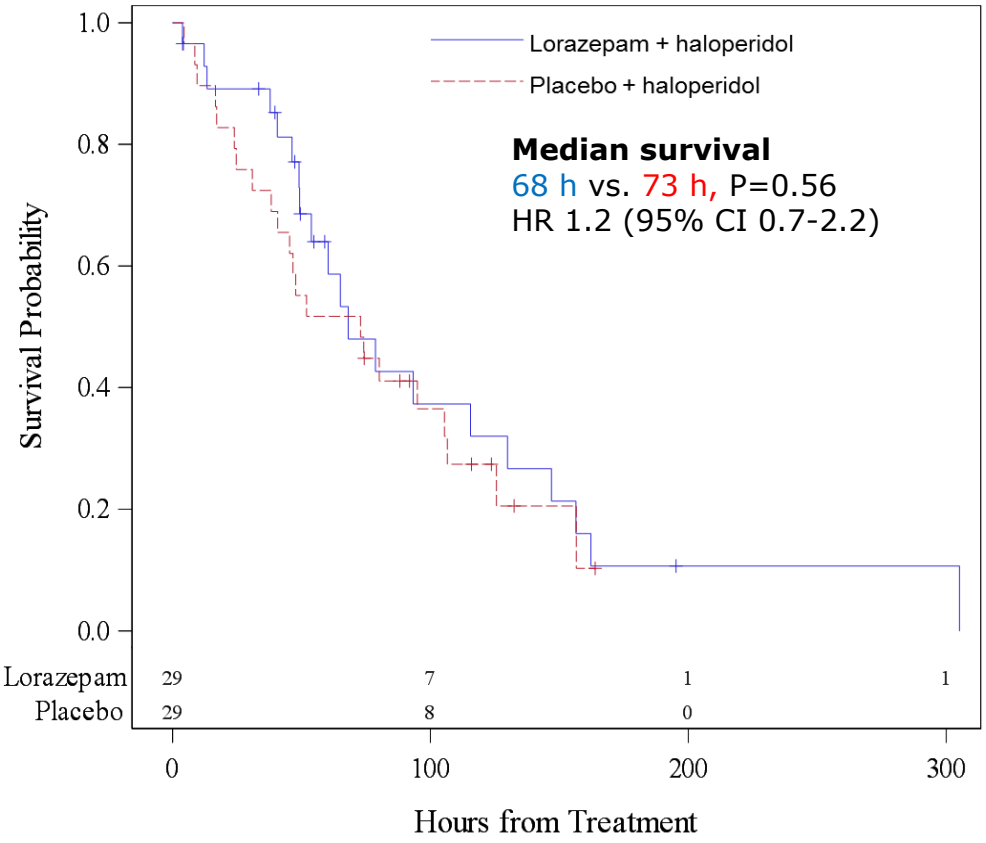


Hui et al. *ASCO* 2017

Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

- No significant difference in
  - Delirium recall
  - Communication capacity
  - Adverse effects
  - Discharge outcomes
  - Overall survival



Hui et al. *ASCO* 2017

Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

- Lorazepam and haloperidol, given to the *right* individuals for the *right* reason at the *right* time, may reduce agitation and improve comfort.

- Limitations:
  - Single center study
  - Small study not powered to examine secondary outcomes
  - Only examined a single dose of lorazepam (3 mg)

More Research is Needed

- Further research is needed to examine the role of benzodiazepines and neuroleptics in delirium management.

Hui et al. *ASCO* 2017

Placebo-Controlled Trials

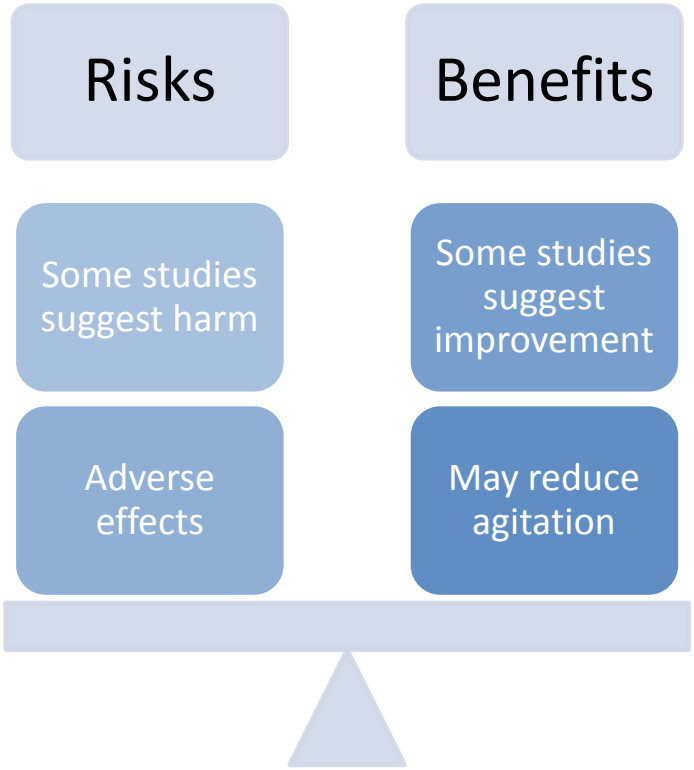
Delirium Treatment

Agents	ICU	Medical/Surgical	Palliative Care
Haloperidol	Girard Crit Care Med 2010		Agar JAMA Intern Med 2017
Risperidone			Agar JAMA Intern Med 2017
Ziprasidone	Girard Crit Care Med 2010		
Quetiapine	Devlin Crit Care Med 2010	Tahir J Psychosom Res 2010	
Olanzapine			
Lorazepam			Hui (submitted)
Midazolam			

Pharmacologic Therapies

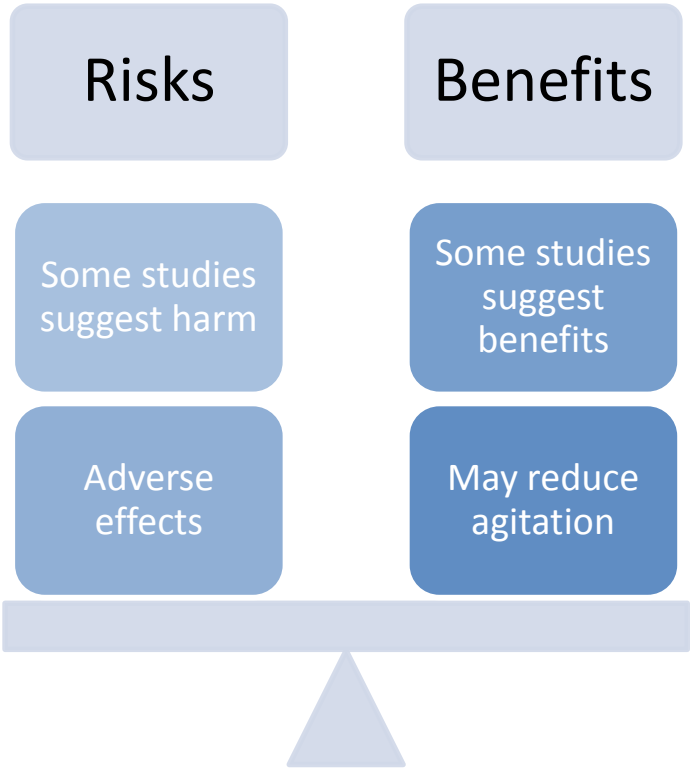
Take Home Message

Neuroleptics



Prevention: Mixed evidence
Treatment: Limited evidence; however, *may be* considered for selected patients given limited options

Benzodiazepines

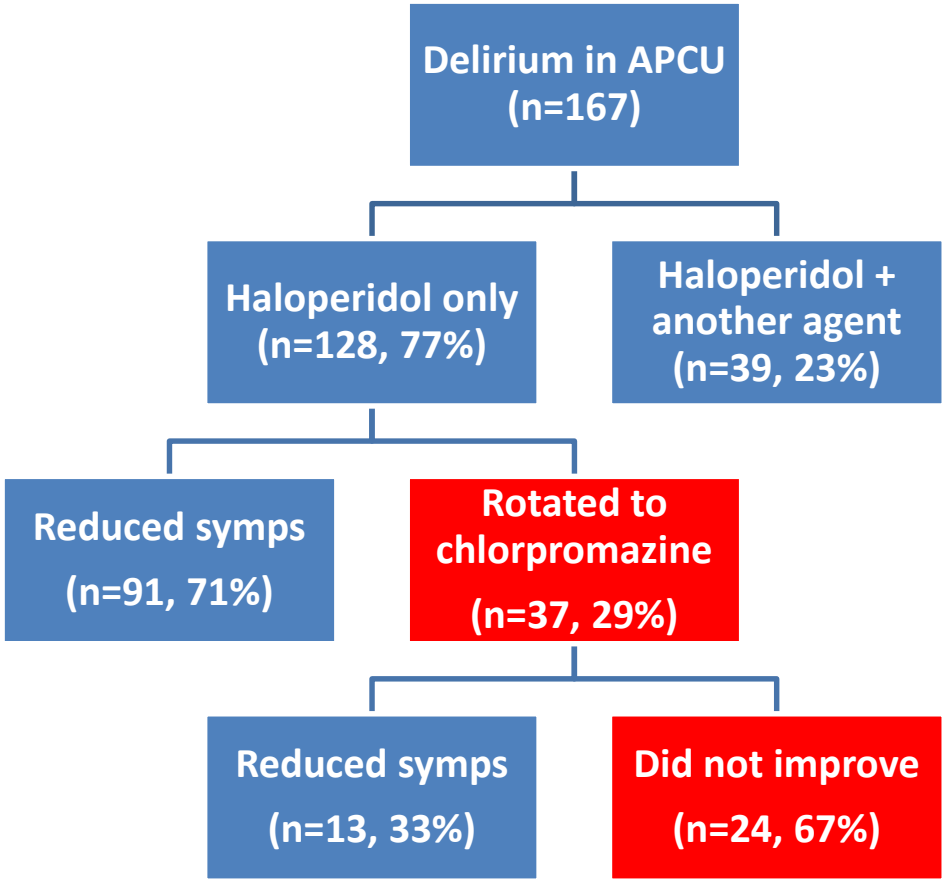


Prevention: No evidence
Treatment: Some evidence for agitation control; use with great caution

Neuroleptic Rotation

Palliative Care, Persistent Agitation

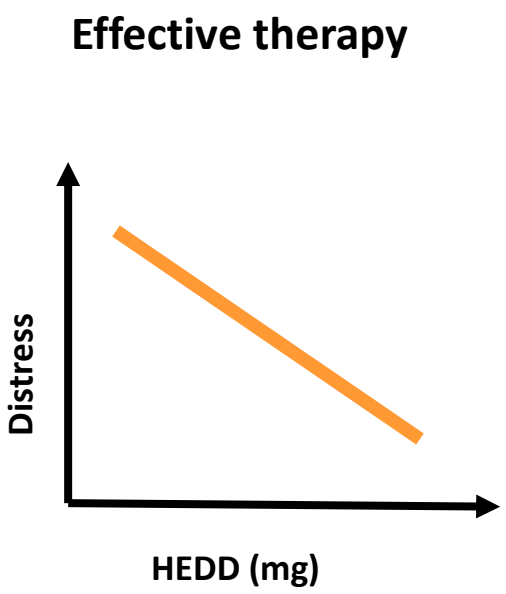
- Haloperidol use
  - Initial doses 5 (3-7) mg
  - Median duration 5 (3-7) days
- Chlorpromazine use
  - Initial dose 150 (100-150) mg
  - Median duration 3 (2-6) days



Shin et al. *Cancer Treat Res* 2015

Neuroleptics

Impact on Delirium Recall and Related Distress



Neuroleptics

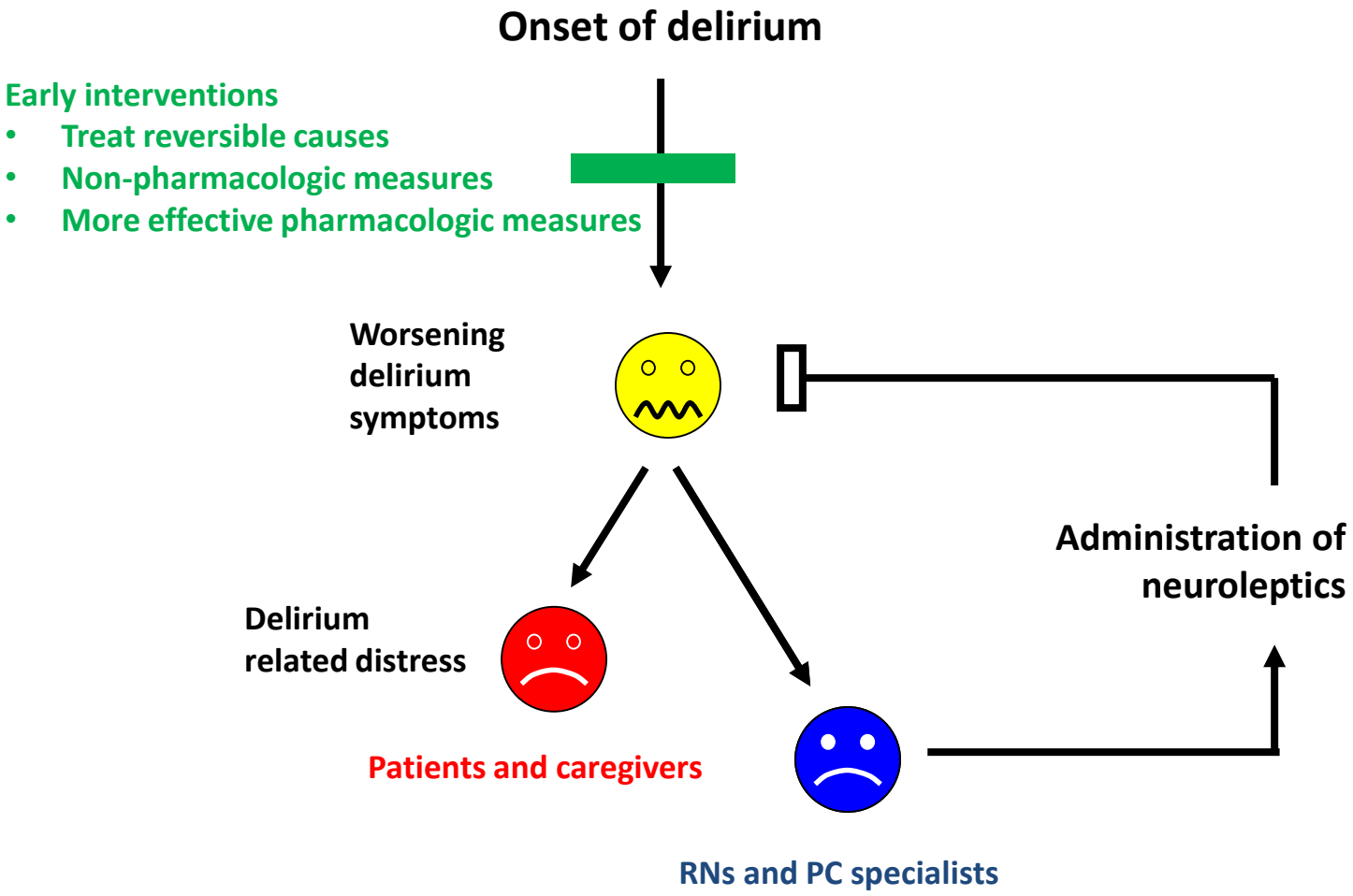
Impact on Delirium-Related Distress

		Patients	Caregivers	Nurses	PC specialists
Disorientation to place	H L	2.6 (N=36) 1.8 (N=48) p=0.48	2.0 (N=55) 2.8 (N=35) p=0.24	7.0 (N=8) 2.5 (N=65) p=0.002	3.3 (N=13) 2.0 (N=76) p=0.32
Disorientation to time	H L	2.5 (N=40) 2.7 (N=45) p=0.94	1.8 (N=52) 3.0 (N=41) p=0.54	7.0 (N=6) 2.5 (N=69) p=0.008	3.7 (N=16) 2.0 (N=75) p=0.18
Hallucinations	H L	3.5 (N=33) 2.0 (N=47) p=0.30	3.2 (N=47) 1.7 (N=43) p=0.14	4.6 (N=6) 2.5 (N=63) p=0.20	7.5 (N=10) 2.0 (N=79) p=0.006
Delusions	H L	2.5 (N=23) 2.5 (N=57) p=0.90	1.8 (N=36) 2.8 (N=49) p=0.52	4.3 (N=7) 2.3 (N=64) p=0.041	4.0 (N=9) 2.0 (N=80) p=0.75
Agitation	H L	2.5 (N=45) 1.8 (N=40) p=0.27	2.5 (N=69) 1.6 (N=22) p=0.36	6 (N=11) 1.9 (N=62) p<0.001	4.3 (N=23) 1.9 (N=69) p=0.006

Hui et al. *J Pain Symp Manage* 2010

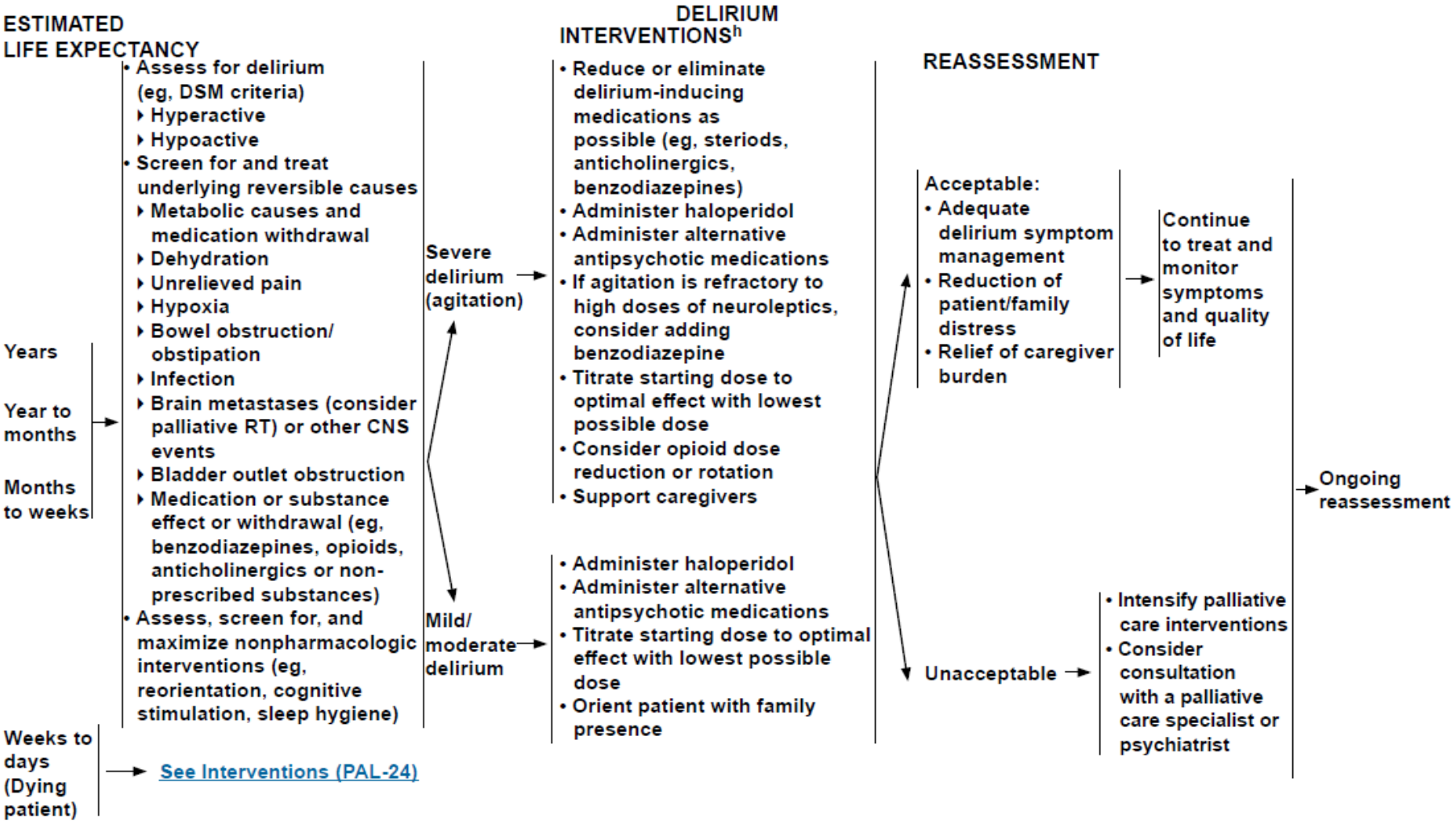
Delirium Treatment

Implications



Treatment of Delirium

NCCN Clinical Practice Guideline



Dans et al. *NCCN Palliative Care* v1.2017

Delirium Literature

More Research is Needed

- Better understanding of pathophysiology
  - Classify subtypes
  - Identify novel interventions
- More validated outcomes are needed
  - Appropriate outcome based on goals of care
  - Minimal clinically important difference
- Interventions
  - Dose-finding studies
  - Multimodal interventions
- Control arms
  - Placebos are needed
- More adequately powered studies needed
  - Homogeneous populations
  - We need funding and collaborations

Hui et al. *J Palliat Care* 2014

Summary

- Think Delirium!
  - Routine screening
  - Match setting with goals of care
- Prevention
  - Treat potential contributors of delirium (if any)
  - Multicomponent intervention – high quality evidence in most settings
  - Pharmacologic therapy – nothing definitive yet!
- Treatment
  - Treat reversible causes (up to 50% even in palliative care setting)
  - Non-pharmacologic approaches – limited evidence but limited harm
  - Neuroleptics – consider for agitation, optimal dose undefined
  - Benzodiazepines – consider for agitation, optimal dose undefined
  - Dexmedetomidine – limited to intensive care

Summary

Delirium Management by Setting

	Post-Op (months-years)	**Medical** (weeks-months)	**Palliative Care** (days-weeks)
Prevention of delirium	Multi-component	Multi-component	?Multi-component
Reversal of delirium	Treat etiology	Treat etiology	Treat etiology
Palliation of delirium symptoms (agitation)		?Neuroleptics	?Neuroleptics ?Benzos
Reduce delirium related distress			??Neuroleptics ??Benzos

ありがとうございます

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  - Cardiology (Dr. Juan Lepez-Mattei, Dr. Kara Thompson)
  - Leukemia (Dr. Jorge Cortes)
  - PROSPR (Dr. Basen Engquist, Carol Harrison)
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- Acute Palliative Care Unit Nursing
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