Delirium Prevention and Treatment: Current Evidence Gaps

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Disclosures

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- NIA
- NHLBI
- AstraZeneca Pharmaceuticals
- American College of Clinical Pharmacy
- CIHR

Delirium

ICU memories

QUALITY OF LIFE

Return to Independence

Depression

Persistent Cognitive Defects

Executive Function

ICU Survival

ICU Survivorship

Family stress

Reduced Functionality

PTSD

Key Points

- Delirium prevalent in hospitalized patients:
  - Acutely ill geriatric
  - Perioperative
  - Critically ill
- Daily risk reduction efforts is the foundation for prevention efforts
- Multimodal protocols using non pharmacologic-based strategies key to delirium prevention and treatment
- Pharmacologic interventions generally have minimal benefit:
  - Reserve for short-term use for select patients with delirium-related symptoms

Delirium Risk Factors

Predisposing Factors
Age
Dementia or pre-existing cognitive impairment
History of delirium
Functional impairment
Sensory impairment: • Vision impairment • Hearing impairment
Comorbidity/severity of illness
Depression
History of transient ischemia/stroke
≥ moderate alcohol use (2 drinks per day)

Inouye SK et al. Lancet 2014

Delirium Risk Factors

Precipitating Factors
Medications: • Psychoactives – particularly sedative-hypnotics and opioids • Anticholinergics • Corticosteroids – higher doses • Metoclopramide
Medication withdrawal
Physical restraints
Bladder catheter
Physiologic and metabolic abnormalities: • Elevated BUN/creatinine ratio – excessive diuresis? • Abnormal sodium, glucose, or potassium • Metabolic acidosis
Infection
Any iatrogenic event
Major surgery
Trauma or urgent admission

Inouye SK et al. Lancet 2014 [6]

Risk Factors – Some additional ICU ones

Question:

Which predisposing and precipitating risk factors are associated with delirium occurrence (ie, incidence, prevalence, or daily transition), delirium duration, or severity in critically ill adults?

Rationale: 68 studies published from 2000-2015

– Evaluated critically ill adults for delirium using multivariable analysis or randomization to evaluate variables as potential risk factors

Ungraded Statement:

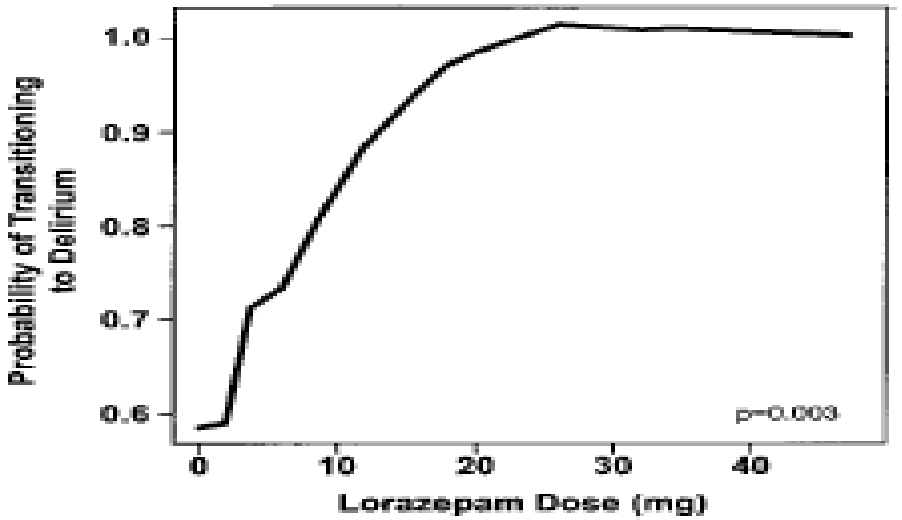
For the following risk factors, **strong evidence** indicates these are associated with delirium in critically ill adults:

Modifiable: **benzodiazepine use, blood transfusions**

Nonmodifiable: greater age, dementia, **prior coma**, pre-ICU emergency surgery or trauma, and **increasing APACHE and ASA scores**

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

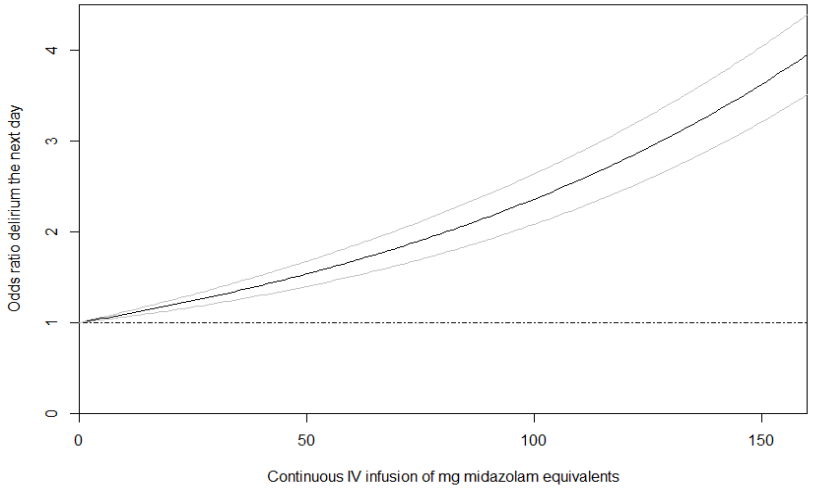
Lorazepam



Pandiharipande P, et al Anesthesiology 2006; 104:21

OR = 1.20 (95% CI 1.1, 1.4)
***per every 1mg of lorazepam**

Midazolam



Zaal I, Devlin JW et al. Intensive Care 2015; 41:2130

OR = 1.04 (95% CI 1.02, 1.05)
***per every 5mg of midazolam**

3 mg/hr = 72mg/24 hours

72/5 = 14.4 x 4% = 57.6% chance of having delirium the next day.

Dr. DRE:

*Important to use a standardized approach to mitigate delirium risk factors on a daily basis during ICU IPT rounds

Diseases	Sepsis CHF COPD New organ dysfunction Hypoxemia
DRug Removal	Sedative down-titration e.g. SATs Stop/Reduce psychoactive meds
Environment	Immobilization Sleep (day/night orientation) Noise Hearing aids/glasses

Nonpharmacologic Strategies

Strategies	Description
Orientation/Therapeutic activities	• Provide lighting, signs, calendars, clocks • Reorient to time, place, person, your role • Cognitively stimulating activities (e.g. reminiscing) • Facilitate regular visits from family, friends
Fluid repletion	• Encourage patients to drink; consider parenteral fluids if necessary • Seek advice regarding fluid balance in patients with comorbidities (heart failure, renal disease)
Early mobilization	• Encourage early post-operative mobilization, regular ambulation. Keep walking aides (canes, walkers) nearby at all times • Encourage active, range-of-motion exercises
Feeding assistance	• Follow general nutrition guidelines and seek advice from dietician as needed • Ensure proper fit of dentures
Vision/Hearing	• Resolve reversible causes of impairment • Ensure working hearing and visual aids are available and used
Sleep enhancement	• Avoid medical/nursing procedures during sleep if possible • Schedule medications to avoid disturbing sleep • Reduce noise at night

Hshieh T, et al. AJGP 2018

Perioperative Older Adults: Strong Recommendations

Strong Recommendations	*Benefits clearly outweigh risks or vice versa*
Multicomponent Non pharmacologic (for Prevention)	• Delivered by interdisciplinary team for at-risk older adults • Includes mobility and walking, avoiding physical restraints, orienting to surroundings, sleep hygiene, adequate oxygen, fluids and nutrition
Educational Programs	• Ongoing, provided for healthcare professionals
Medical Evaluation	• Identify, manage underlying organic contributors to delirium
Pain Management	• Should be optimized, preferably with non-opioid medications

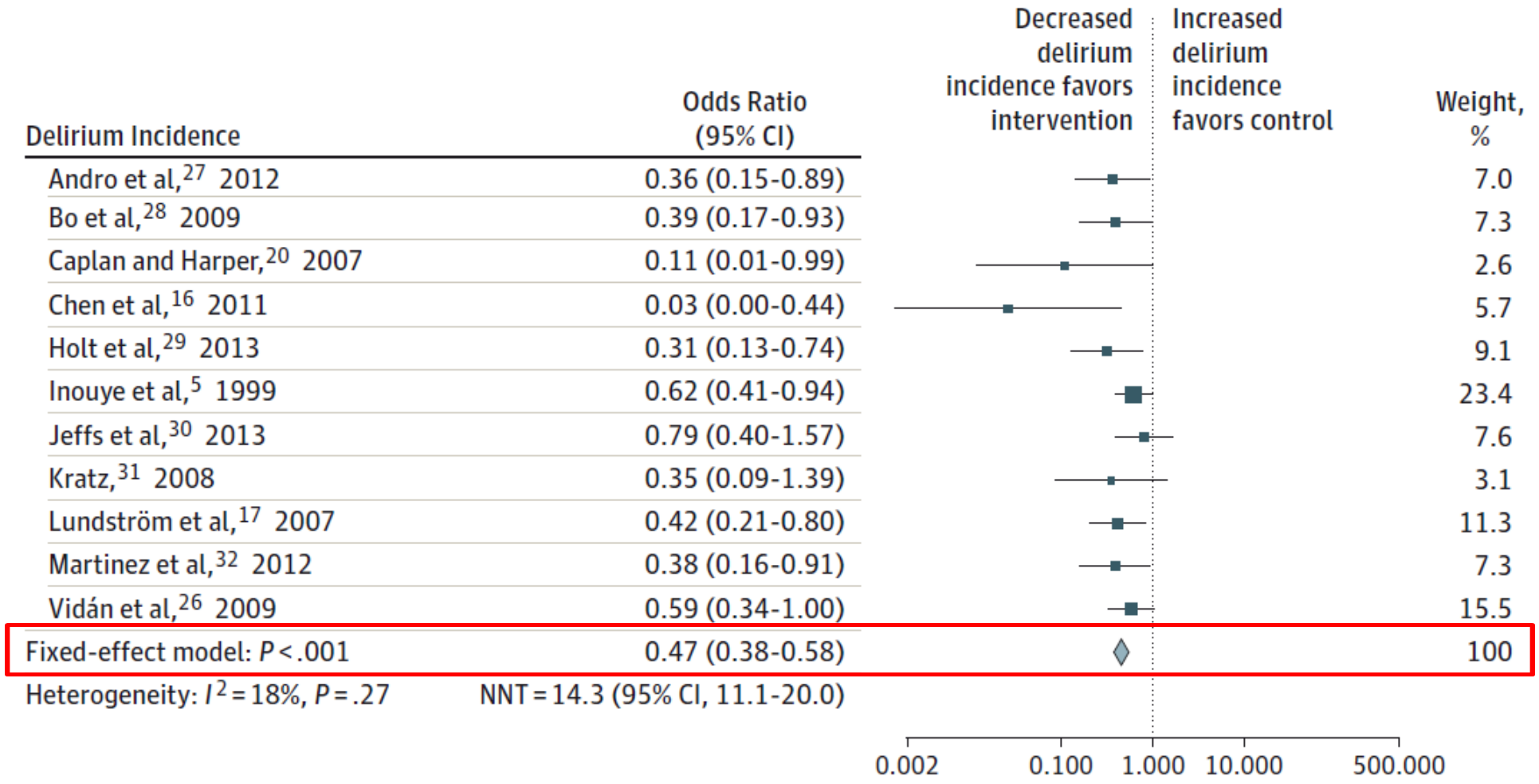
Adapted from: The American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. Clinical Practice Guidelines for Postoperative Delirium in Older Adults. J Am Geriatr Soc. 2014; 63:142-150.

Delirium Prevention: Multicomponent Nonpharmacologic Bundles for Geriatric Inpatients

- Prior studies have found 40% of delirium is preventable
- Multiple successful strategies exist:
  - Hospital Elder Life Program (*Inouye 1999, 2000; Chen 2012*)
    - Cost-effective:
      - Reduces hospital costs by up to $3800
      - Reduces need for long term care
    - Families/volunteers can help deliver
  - Proactive geriatric consultation *(Marcantonio 2001)*
  - Exercise and rehabilitation interventions *(Caplan 2006)*

Use of Multicomponent Non-Pharm Bundles in Geriatric Inpatients

Delirium Incidence

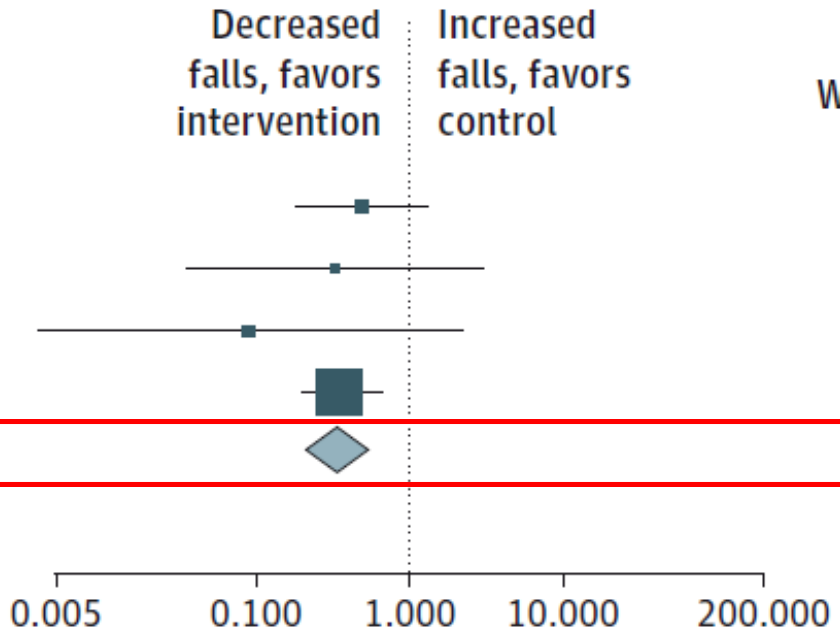


Hshieh T et al. JAMA IM 2015

Use of Multicomponent Non-Pharm Bundles in Geriatric Inpatients

Falls

Falls	Odds Ratio (95% CI)	Weight, %
Babine et al,[14] 2013	0.49 (0.19-1.27)	10.9
Caplan and Harper,[20] 2007	0.33 (0.04-2.93)	2.5
Martinez et al,[32] 2012	0.11 (0.01-2.05)	3.3
Stenvall et al,[18] 2007	0.38 (0.23-0.65)	38.2
Fixed-effect model: $P < .001$	0.38 (0.25-0.60)	100
Heterogeneity: $I^2 = 0\%$, $P = .78$		



Hshieh T et al. JAMA IM 2015

Sleep Disruption

- Poor sleep is a common complaint and a source of distress for many hospitalized patients.
- Sleep disruption can be severe, particularly in the ICU
- Sleep is considered a potentially modifiable risk factor influencing recovery
- The interplay of medications, critical illness, delirium, cerebral perfusion, and sleep is complex, but an important area of current research
- 9 actionable (PICO) questions + 7 descriptive questions

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Use of Noise and Light Reduction Strategies to Improve Sleep

Rationale:

- Two RCTs and two observational studies evaluated the night time use of earplugs (with/without eye shades) in non-sedated ICU pts
  - Improved patient-reported sleep quality
  - Reduced delirium
  - Pooled analysis from 2 observational studies associated earplug use with a 20% increased chance of achieving 4 hrs sleep
- Studies not blinded, some patients refused earplugs and sicker patients not evaluated.
- Earplugs/eyeshades little risk and low cost

Recommendation:

We suggest using noise and light reduction strategies to improve sleep in critically ill adults (conditional recommendation, low quality of evidence).

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Sleep Promoting Protocol

PICO Question		
P	Critically ill adult patients in an ICU	
I	Multicomponent sleep-promoting protocol	
C	No use of a protocol	
O	• Time spent at each sleep stage • Sleep duration • Sleep fragmentation • Circadian rhythm	• Delirium occurrence • Duration of mech-vent • ICU mortality • Patient experience

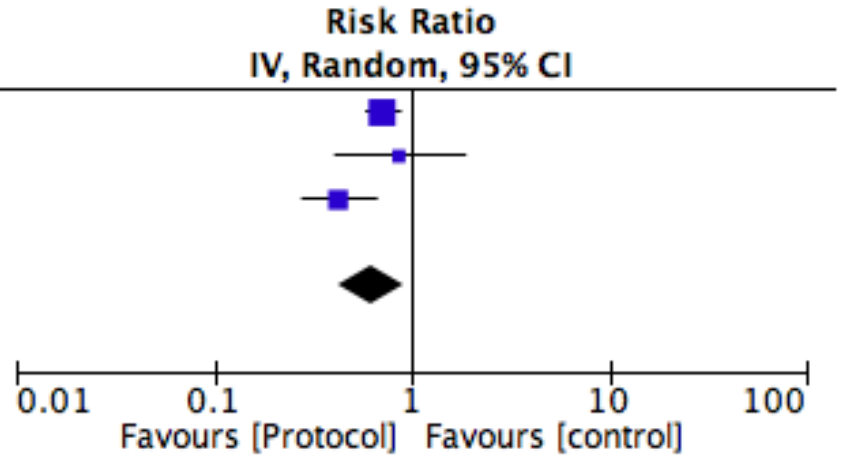
Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Evidence: Sleep Promoting Protocol

Study or Subgroup	Protocol Events	Protocol Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Kamdar 2013	86	175	76	110	49.3%	0.71 [0.58, 0.87]
Lee 2012	6	13	8	15	17.6%	0.87 [0.41, 1.84]
Patel 2014	24	171	55	167	33.0%	0.43 [0.28, 0.65]
Total (95% CI)		**359**		**292**	**100.0%**	**0.62 [0.42, 0.91]**
Total events	116		139			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 5.04$, df = 2 (P = 0.08); $I^2 = 60\%$

Test for overall effect: Z = 2.44 (P = 0.01)

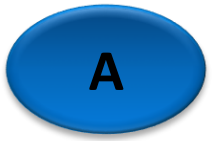


Delirium prevalence: RR: 0.62; 95% CI, 0.42 to 0.91 (for n=3 before-after studies)

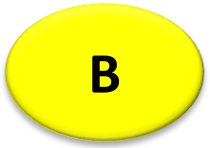
Recommendation:

We suggest using a sleep-promoting, multicomponent protocol in critically ill adults (conditional recommendation, low quality evidence).

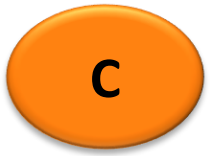
ABCDEF Bundle Elements



Assess, Prevent and manage Pain

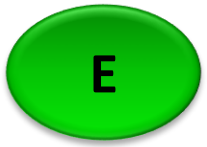


Both SAT and SBT



Choice of Analgesia and Sedation

Delirium: Assess, Prevent and Manage



Early Mobility and Exercise

Family Engagement and Empowerment

New!

Good Sleep

Vasilevskis EE, et al. *Chest*. 2010;138(5):1224-1233.
Davidson JE, et al. *Am Nurse Today*. 2013;8(5):32-38.


Family Member
Intensivist
Advanced Practice Provider
Critical Care Nurse
Critical Care Pharmacist
Respiratory Care Practitioner
Physical and Occupational Therapists
Dietician
Social Worker
Case Manager
Spiritual Care Provider
Nursing Asissant
Non-Intensivist Physician
Speech & Language Pathologist
Patient

Non-Pharmacological Treatment: Multi-component – AF Bundle

ABCDE bundle multi-intervention approach (1 Before-after), 296 pts

- Significantly associated with:
  - Less delirium, 49% vs. 62%, OR=0.55 (95% CI, 0.33 to 0.93)

ABCDEF bundle approach (1 Cohort study), 6064 pts

- Included a focus on "F", Family engagement
- Improvement in bundle compliance significantly associated with:
  - Reduced mortality & more coma/delirium free ICU days

Recommendation:
We ***suggest*** using a multicomponent, non-pharmacologic intervention that is focused on (but not limited to) **reducing modifiable risk factors** for delirium, improving cognition, and optimizing sleep, mobility, hearing, and vision in critically ill adults (conditional recommendation, low quality of evidence)

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults

Brenda T. Pun, DNP, RN, FCCM[1]; Michele C. Balas, PhD, RN, CCRN-K, FCCM, FAAN[2,3]; Mary Ann Barnes-Daly, MS, RN, CCRN-K, DC[4]; Jennifer L. Thompson, MPH[5]; J. Matthew Aldrich, MD[6]; Juliana Barr, MD, FCCM[7,8]; Diane Byrum MSN, RN, CCRN-K, CCNS, FCCM[9]; Shannon S. Carson, MD[10]; John W. Devlin, PharmD, FCCM[11]; Heidi J. Engel, PT, DPT[12]; Cheryl L. Esbrook, OTR/L, BCPR[13]; Ken D. Hargett, MHA, FAARC, FCCM[14]; Lori Harmon, RRT, MBA, CPHQ[15]; Christina Hielsberg, MA[15]; James C. Jackson, PsyD[1]; Tamra L. Kelly, BS, RRT, MHA[4]; Vishakha Kumar, MD, MBA[15]; Lawson Millner, RRT[16]; Alexandra Morse, PharmD[4]; Christiane S. Perme, PT, CCS, FCCM[14]; Patricia J. Posa, BSN, MSA, CCRN-K[17]; Kathleen A. Puntillo, PhD, RN, FCCM, FAAN[18]; William D. Schweickert, MD[19]; Joanna L. Stollings, PharmD, FCCM[20]; Alai Tan, PhD[2]; Lucy D'Agostino McGowan, PhD[21]; E. Wesley Ely, MD, MPH, FCCM[1,22]

Pun, B; Balas, M; Barnes-Daly, MA *Crit Care Med* 2019

ICU Liberation Collaborative - Methods

- **Collaborative Overview**
  - 68 academic, community and VA ICUs
  - 20 months
  - Operationalized the bundle (with flexibility)
  - Operationalized the daily benchmarks for each element
  - Each Site: Interprofessional Executive Team
  - Education and Support Provided:
    - In Person Meetings
    - Coaching Calls
    - Peer Benchmarking
    - Online materials
    - Resource Sharing

Pun B, et al. *Crit Care Med.* 2019; 47:3-14

Bundle Performance

ABCDEF bundle performance (our main exposure) was evaluated in two ways:

1. Complete performance:
- patient received every eligible bundle element on any given day

2. Proportional performance
- percentage of eligible bundle elements performed on any given day

Pun B, et al. *Crit Care Med.* 2019; 47:3-14

Relationship Between Degree of Bundle Performance and Outcomes

We explored the association between complete and proportional ABCDEF bundle performance and the three sets of outcomes:

*All models were adjusted for a minimum of 18 a priori-determined potential confounders.

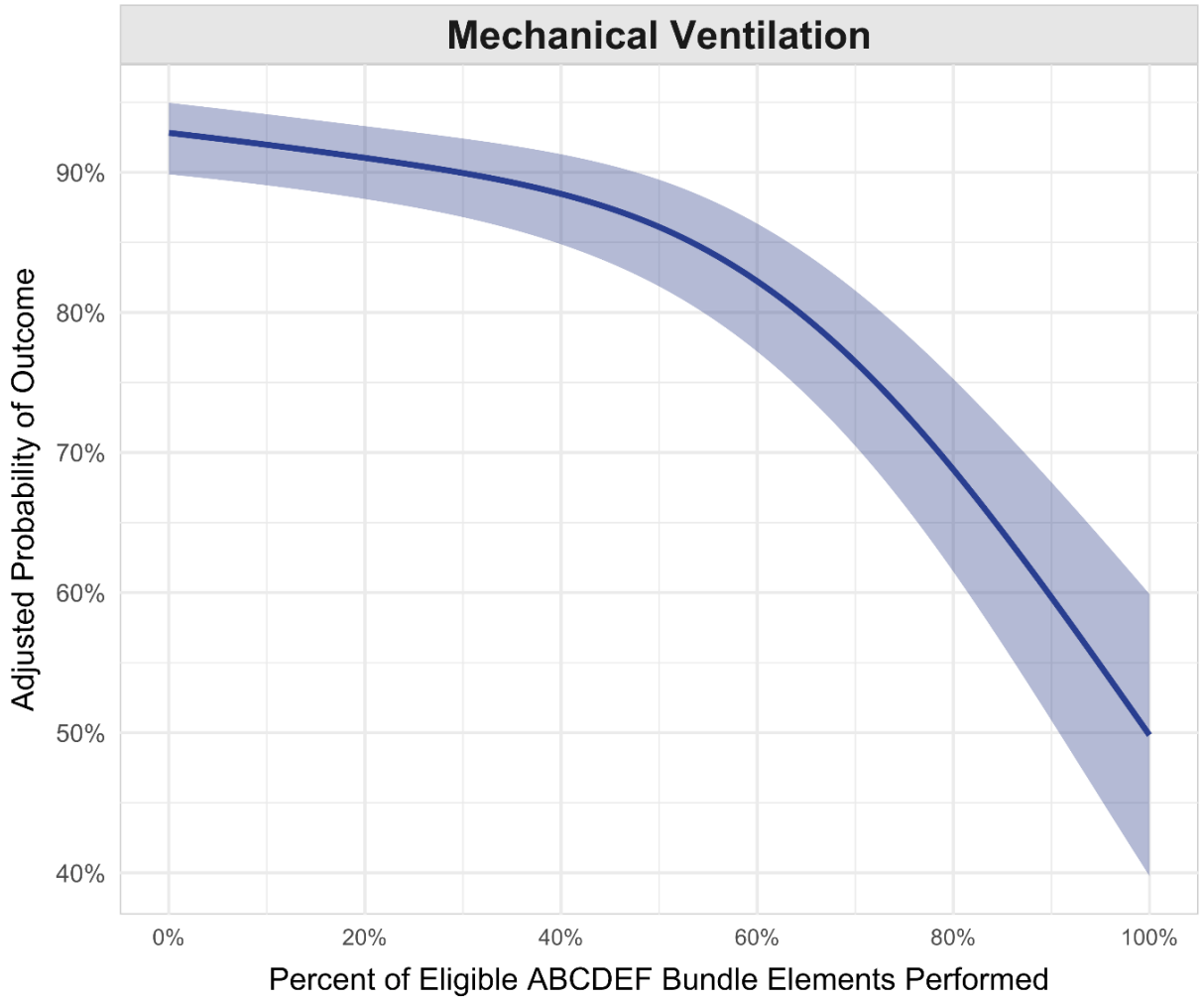
Pun, B; Balas, M; Barnes-Daly, MA et al. *Crit Care Med* 2019

TABLE 2. Outcomes for Patients With Complete (vs Incomplete) ABCDEF Bundle Performance: Data are Adjusted Hazard Ratios (AHRs) and Adjusted Odds Ratios (AORs)

Outcomes	Complete Bundle Performance	*p* Value
Patient-Related Outcomes	**AHR (95% CI)**	
ICU discharge[a]	1.17 (1.05–1.30)	< 0.004
Hospital discharge[b]	1.19 (1.01–1.40)	< 0.033
Death[c]	0.32 (0.17–0.62)	< 0.001
Symptom-Related Outcomes[d]	**AOR (95%CI)**	
Mechanical ventilation	0.28 (0.22–0.36)	< 0.0001
Coma	0.35 (0.22–0.56)	< 0.0001
Delirium	0.60 (0.49–0.72)	< 0.0001
Significant pain	1.03 (0.88–1.21)	0.7000
Physical restraints	0.37 (0.30–0.46)	< 0.0001
System-Related Outcomes	**Adjusted OR (95%CI)**	
ICU readmission[e]	0.54 (037–0.79)	< 0.001
Discharge destination[f]	0.64 (0.51–0.80)	< 0.001

Pun, B; Balas, M; Barnes-Daly, MA et al. *Crit Care Med* 2019

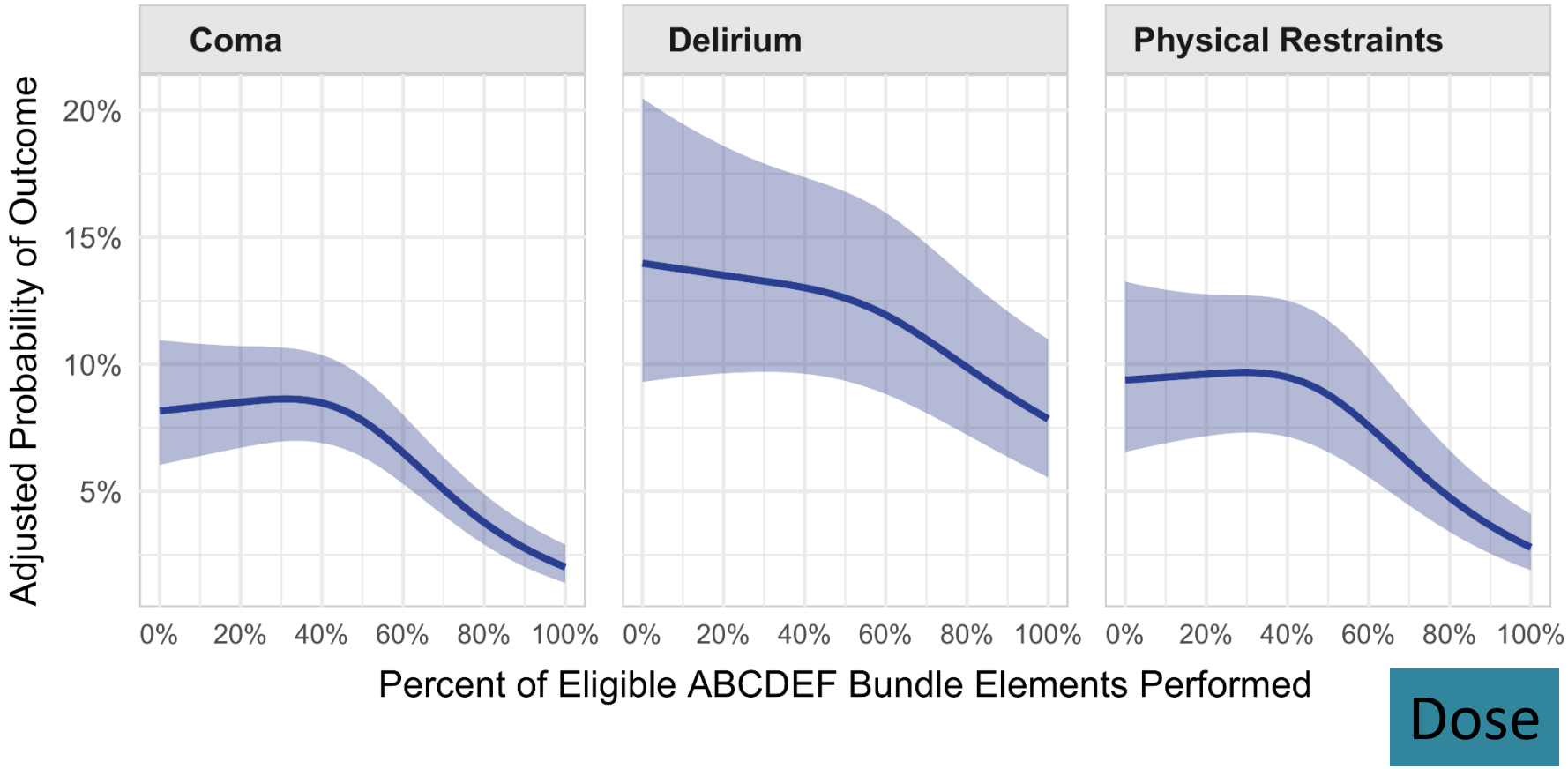
Results: Symptom-Related Outcomes



Dose

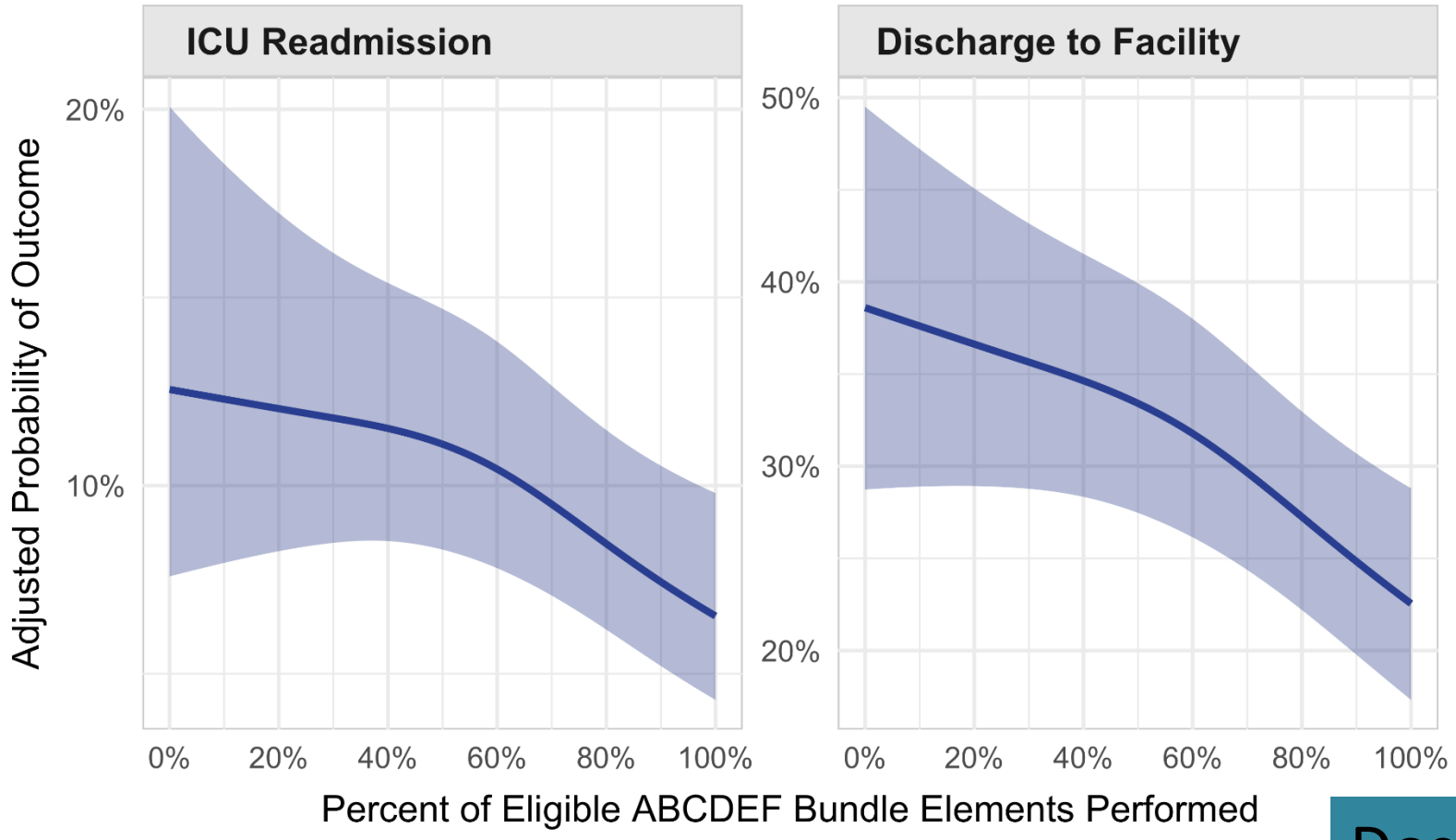
Pun B, et al. *Crit Care Med.* 2019; 47:3-14

Results: Symptom-Related Outcomes



Pun B, et al. *Crit Care Med.* 2019; 47:3-14

Results: System-Related Outcomes



Dose

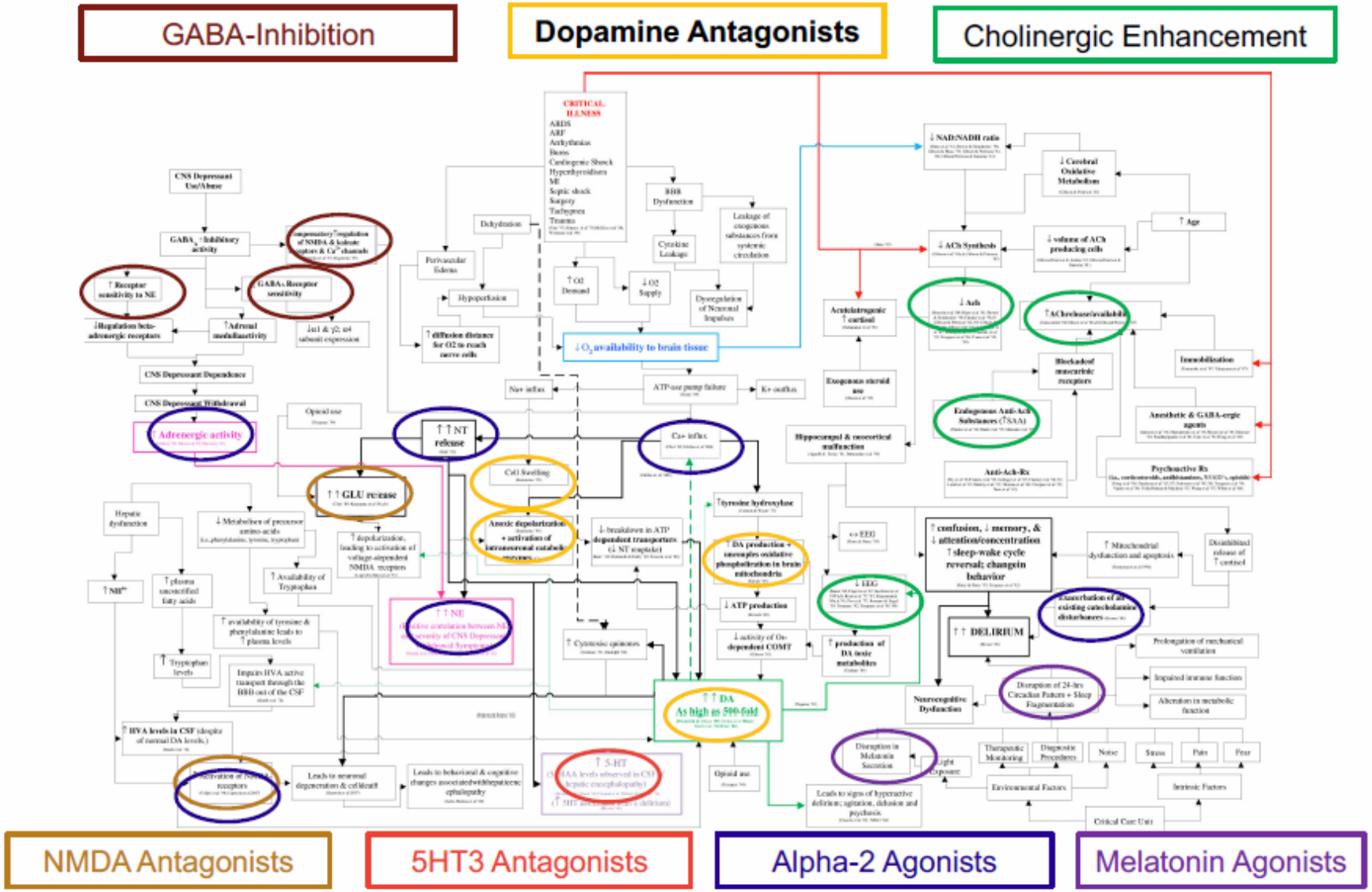
Pun, et al. *Crit Care Med.* 2019; 47:3-14

General Pharmacologic Management Strategies for Preventing or Treating Delirium

- ~~Does the patient have modifiable risk factors for delirium?~~
- ~~Have non-pharmacologic interventions (using a multimodal bundle) been optimized?~~
- No medication is FDA approved for the prevention or treatment of delirium
- All medications have side effects:
  - Dose-related
  - Older adults particularly susceptible
- Medications initiated in the hospital are often continued after discharge
- What is the specific clinical reason to initiate a medication to prevent or treat delirium?

Pharmacologic Intervention

Maldonado, *Crit Care Clin* 2008



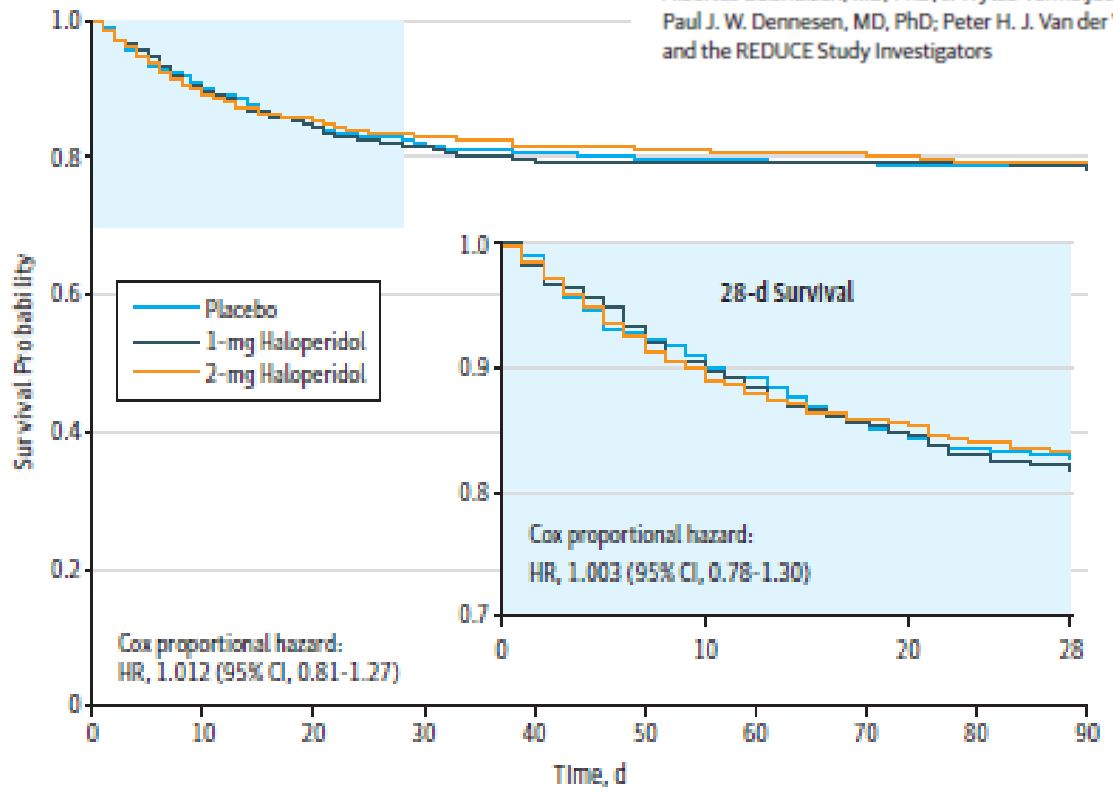
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium

The REDUCE Randomized Clinical Trial

Mark van den Boogaard, PhD; Arjen J. C. Slooter, MD, PhD; Roger J. M. Brüggemann, PharmD, PhD; Lisette Schoonhoven, PhD; Albertus Beishuizen, MD, PhD; J. Wytze Vermeijden, MD, PhD; Danie Pretorius, MD; Jan de Koning, MD; Koen S. Simons, MD; Paul J. W. Dennesen, MD, PhD; Peter H. J. Van der Voort, MD, PhD; Saskia Houterman, PhD; J. G. van der Hoeven, MD, PhD; Peter Pickkers, MD, PhD; and the REDUCE Study Investigators

Figure 2. Survival Analysis at 28 and 90 Days



No. at risk										
Placebo	707	644	600	580	571	565	563	559	557	556
1-mg Haloperidol	350	317	297	285	279	278	278	278	277	276
2-mg Haloperidol	732	658	627	609	599	595	591	589	582	579

For the 28-day end point, follow-up for the 1-mg haloperidol group was a median of 28 days (interquartile range [IQR], 28-28 days); for the 2-mg group, 28 days (IQR, 28-28 days); and for the placebo group, 28 days (IQR, 28-28 days). For the 90-day end point, follow-up for the 1-mg haloperidol group was 90 days (IQR, 90-90 days), for the 2-mg haloperidol group, 90 days (IQR, 90-90 days); and for the placebo group, 90 days (IQR, 90-90 days).

Van den Boorgard M, et al. JAMA 2018; 319(7):680-691

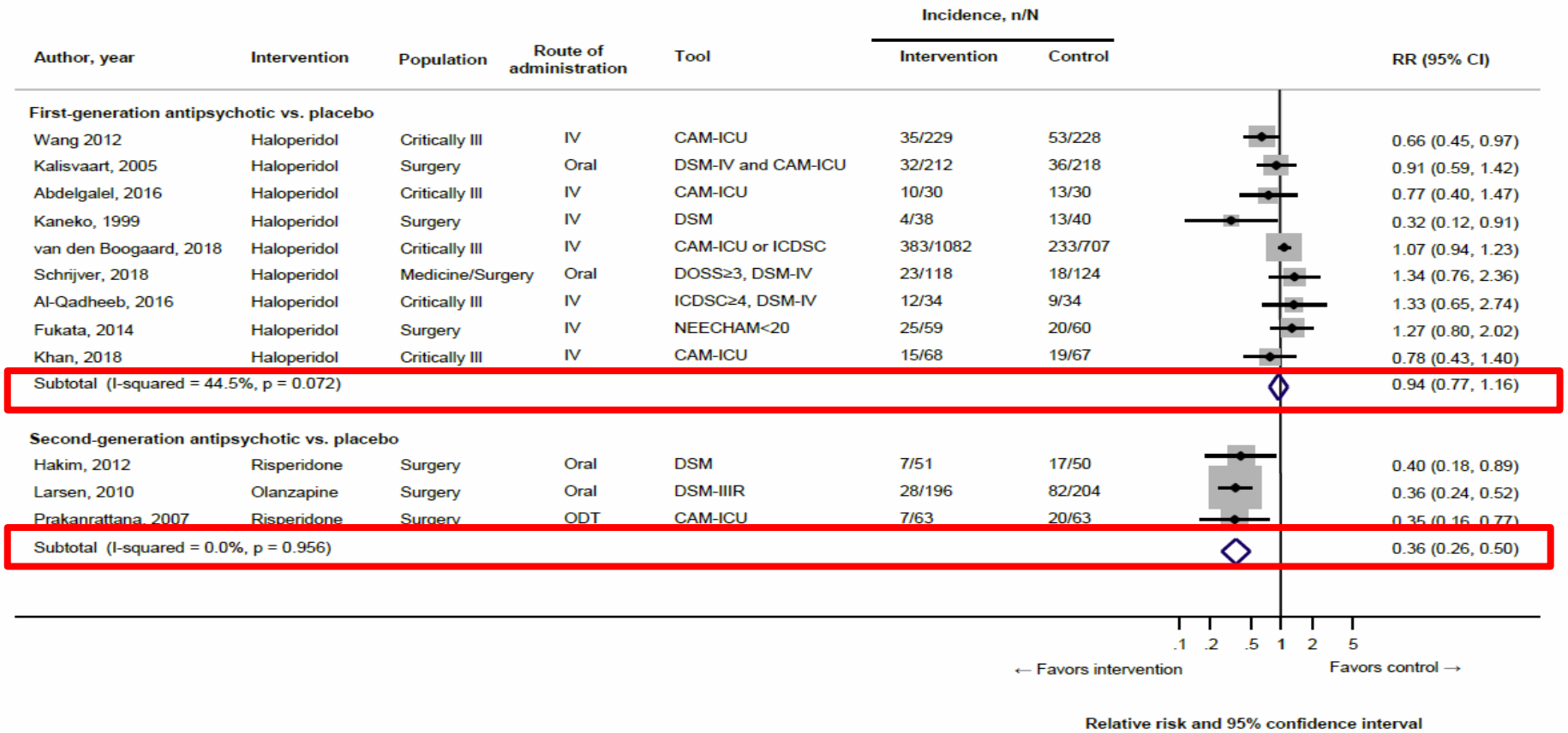
Systematic Review of Haloperidol or Second-generation Antipsychotic for Delirium Prevention in Acutely Hospitalized Adults

- **Search ended July 2019**
- **N=14 RCTs**
  - **9 studies ICU/on-pump cardiac surgery (n=3008 patients)**
  - **5 studies elective surgery (1273 patients)**

Figure 3. Meta-analysis of delirium incidence in trials comparing either haloperidol or second-generation antipsychotics with placebo among patients at risk for delirium.

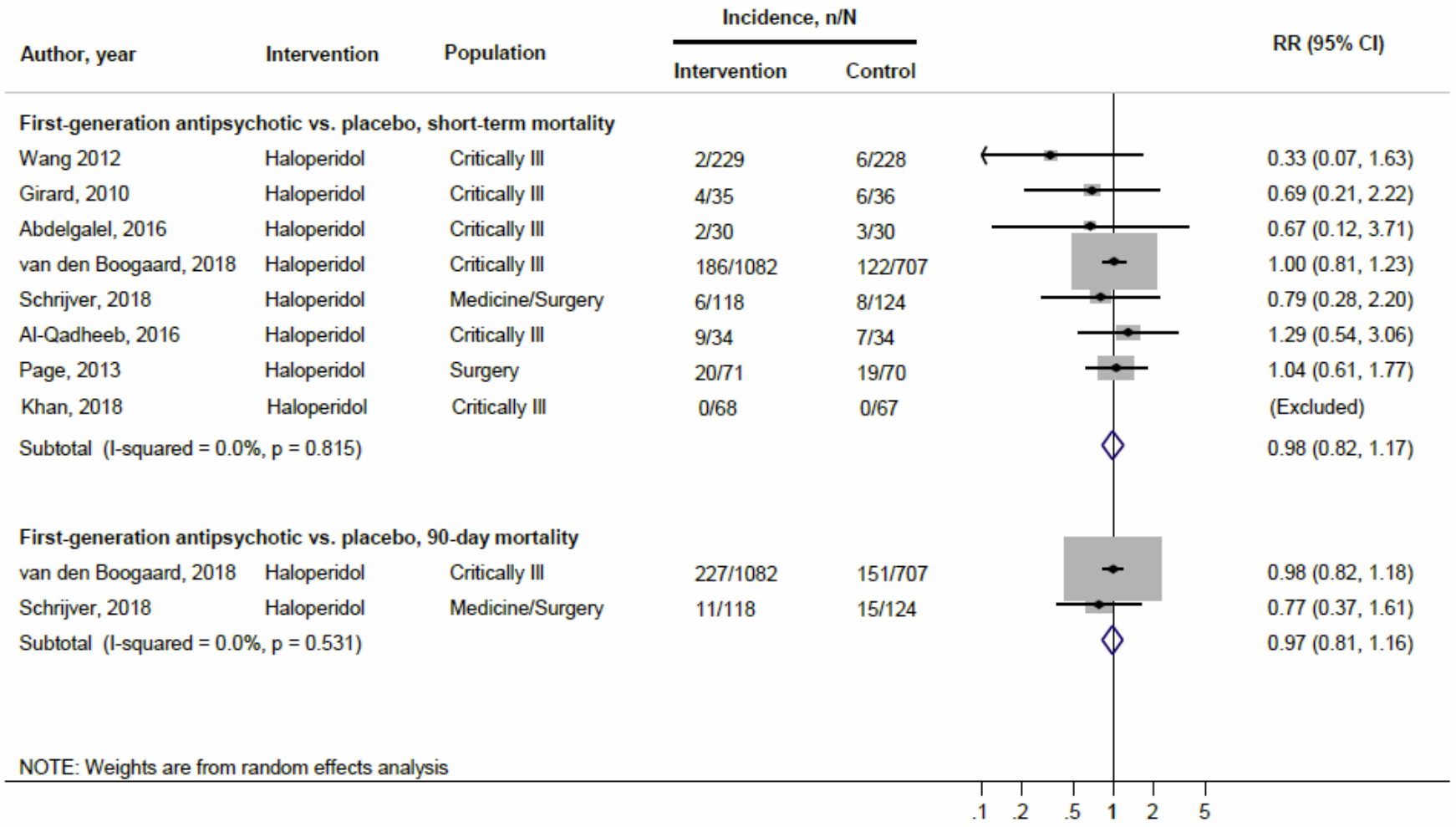
Haloperidol

Second-Gen AP



Oh ES et al. Ann Intern Med 2019

Figure 4. Meta-analysis of mortality in trials comparing haloperidol with placebo in patients at risk for delirium.



Oh ES et al. Ann Intern Med 2019

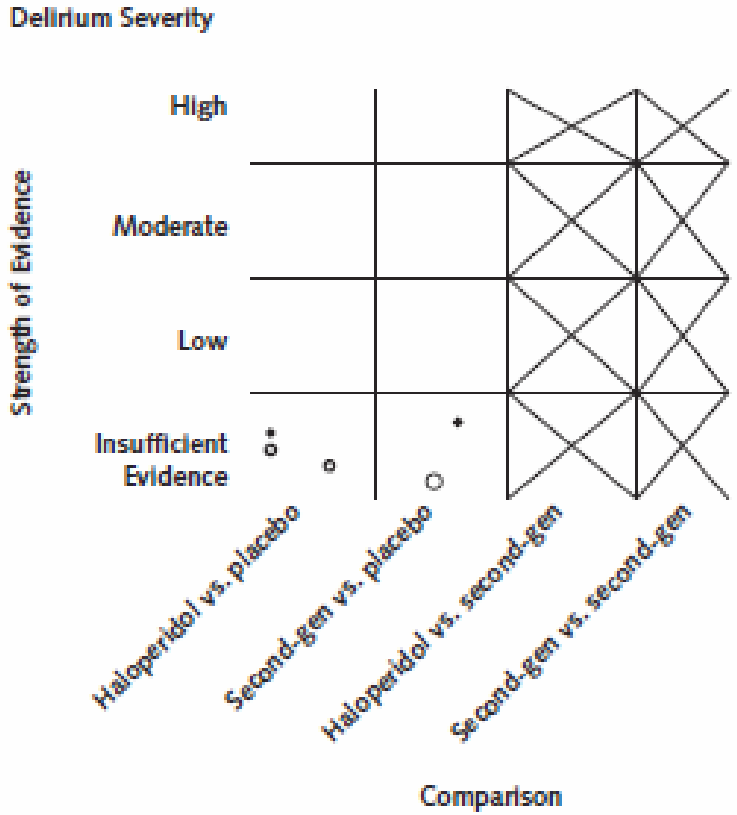
Delirium Duration, Severity and Hospital LOS

Delirium Duration

Haloperidol has no effect on delirium duration (7 trials; low ROB; n = 1238 pts)

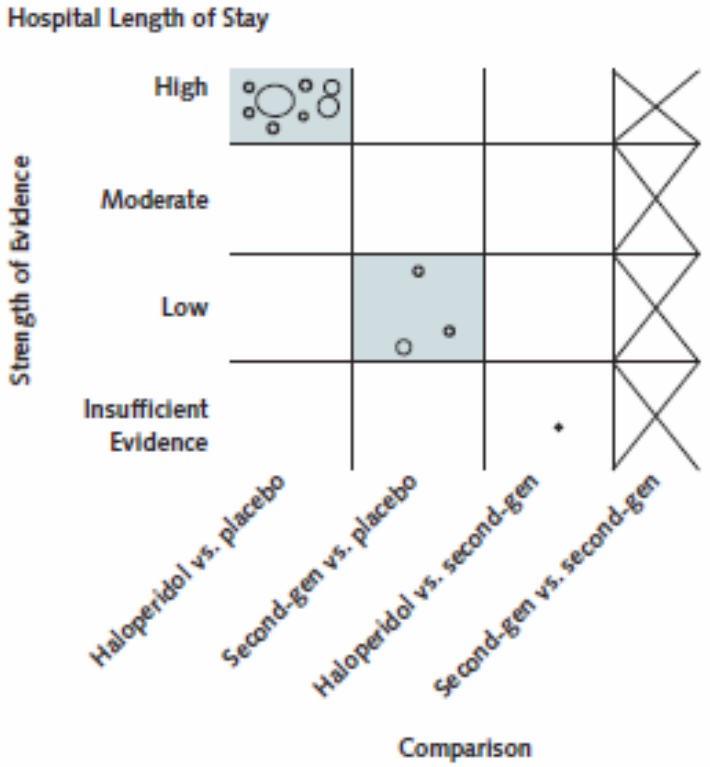
Second generation APs have no effect on delirium duration (3 trials; low ROB; n=602 pts)

Delirium Severity



Inconsistent results and methodological limitations preclude any conclusions

Hospital LOS

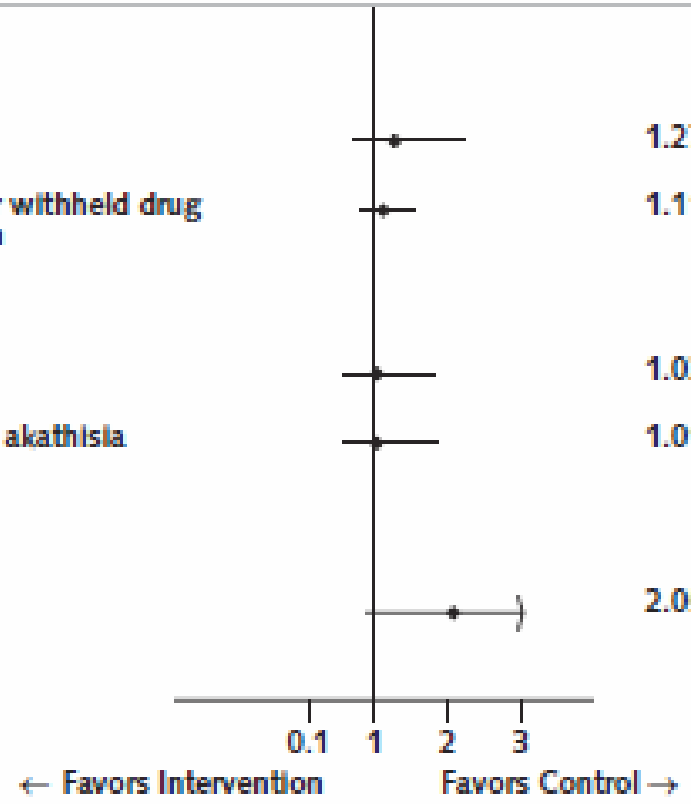


No effect with either haloperidol or second-generation AP on hospital LOS

Oh ES et al. Ann Intern Med 2019

Figure 2. Meta-analysis of difference in the incidence of adverse events in studies evaluating effect of antipsychotics.

Comparison	Studies, *n* (*N*)	Study Population	Outcome	Pooled Meta-analysis	Pooled RR (95% CI)*
Cardiac effects					
Haloperidol vs. placebo	6 (2653)	At risk for delirium	Arrhythmias		1.27 (0.72–2.21)
Haloperidol vs. placebo	7 (2721)	At risk for delirium	QTc prolonged >500 ms or withheld drug owing to QTc prolongation		1.11 (0.80–1.55)
Neurologic effects					
Haloperidol vs. placebo	8 (3276)	At risk for delirium	Extrapyramidal symptoms		1.02 (0.58–1.79)
Haloperidol vs. placebo	4 (2069)	Critically ill patients	Extrapyramidal symptoms, akathisia		1.01 (0.56–1.83)
Sedation					
Haloperidol vs. placebo	4 (881)	At risk for delirium	Somnolence, oversedation		2.05 (0.86–4.85)



RR = relative risk; QTc = corrected QT interval.
* I^2 for all the meta-analysis was 0.0%.

Oh ES et al. Ann Intern Med 2019

Statin Use for Delirium Prevention

- Acute neuroinflammation is a key nidus for delirium development; the pleiotropic effects of statins may reduce delirium
- Cohort studies suggest patient's taking a statin at the time of ICU admission have reduced ICU delirium

Page VJ et al. AJRCCM; 2014: 1898:666
Morandi A et al. Crit Care Med 2014; 42:1899-1909

Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial

Valerie J Page, Annalisa Casarin, E Wesley Ely, Xiao Bei Zhao, Cliona McDowell, Lynn Murphy, Daniel F McAuley

- Simvastatin 80mg daily vs. placebo in critically ill adults with or without delirium
- Days alive with delirium or coma in the 14 days after randomization not different (5.7[5.1](Sim) vs. 6.1[5.2] days, p=0.66)

Paige VJ et al. Lancet Respir Med 2017; 2016; 5:727

Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial

Dale M Needham, Elizabeth Colantuoni, Victor D Dinglas, Catherine L Hough, Amy W Wozniak, James C Jackson, Peter E Morris, Pedro A Mendez-Tellez, E Wesley Ely, Ramona O Hopkins

- Rosuvastatin 20mg daily vs. placebo in critically ill adults with ARDS with or without delirium
- % of ICU days with delirium not different (HR=1.14; 95% CI 0.92,1.41; p=0.22)
- % of patients with cognitive impairment at 6 months not different (HR=0.93; 95% CI 0.39, 2.22; p=0.87)

Needham DM et al. Lancet Respir Med 2016; 4:203

Delirium Pharmacological Prevention

Recommendation:
We suggest **NOT** using haloperidol, an atypical antipsychotic, dexmedetomidine, a statin, or ketamine to ***prevent*** delirium in **all** critically ill adults (Conditional recommendation, very low to low quality of evidence)

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Dexmedetomidine to Improve Sleep

Rationale:

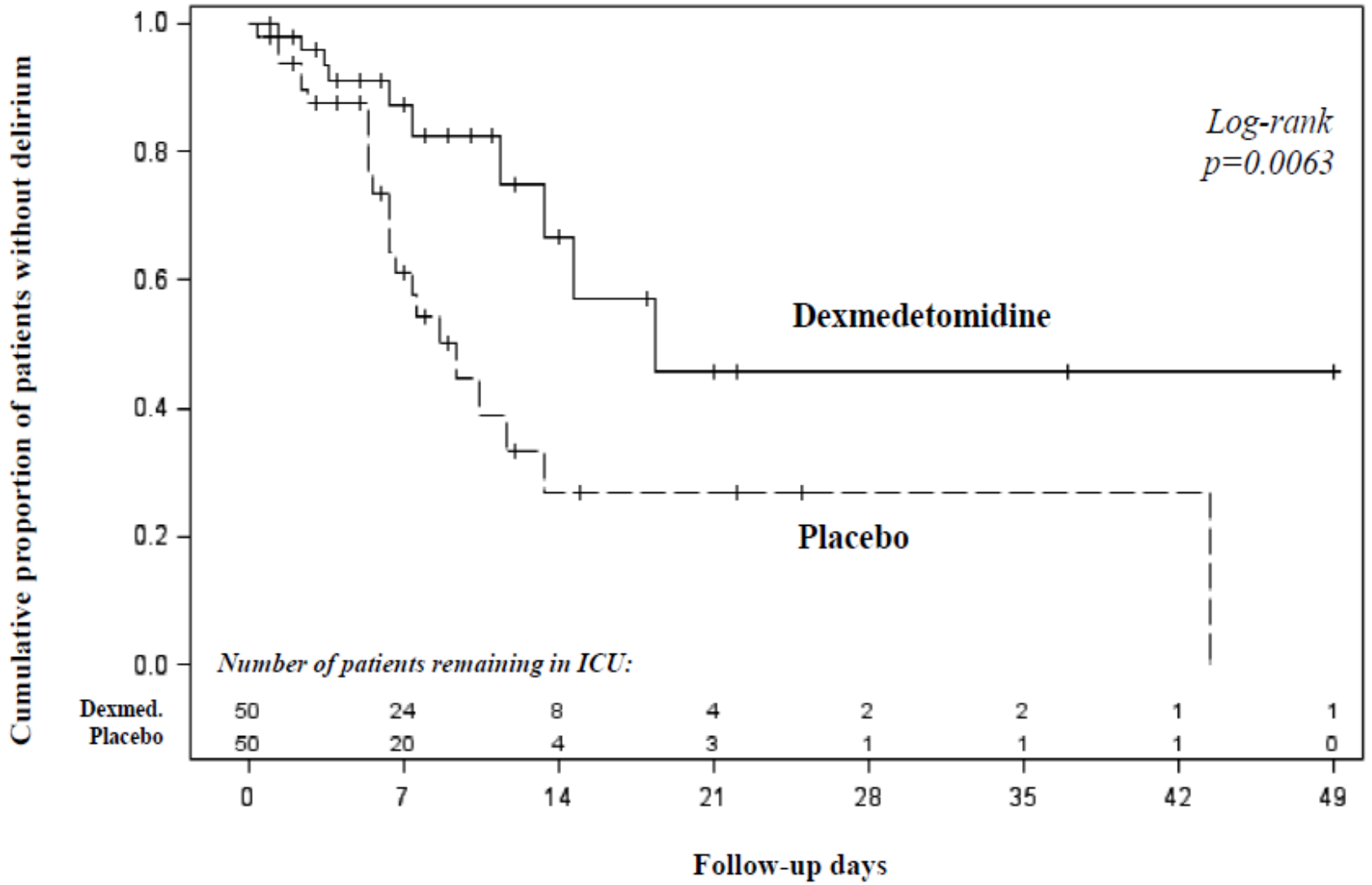
- 2 RCTs (n=74)
  - 1 RCT evaluated MV adults requiring sedation
  - 1 RCT in non-MV adults
- Significant increase in Stage 2 sleep
  - Mean difference = + 47.85% min (95% CI, 24.05-71.64)
- Significant decrease in Stage 1 sleep
  - Mean difference = - 30.37% min (95% CI, -50.01 to -10.73)
- No effect on sleep fragmentation or % time spent in REM sleep
- *Neither delirium, duration of MV, ICU LOS or patient preference evaluated in either RCT
- Concerns about generalizability to all ICU adults, hemodynamic effects, and cost in terms of using dexmedetomidine to ONLY improve sleep (vs. when an IV sedative is needed)

Recommendation:

We make no recommendation regarding the use of dexmedetomidine to improve sleep in critically ill adults (no recommendation, very low quality of evidence).

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Low-dose Nocturnal Dexmedetomidine Prevents ICU Delirium: A Randomized, Placebo-Controlled trial



No difference in LEEDS Sleep Score between groups

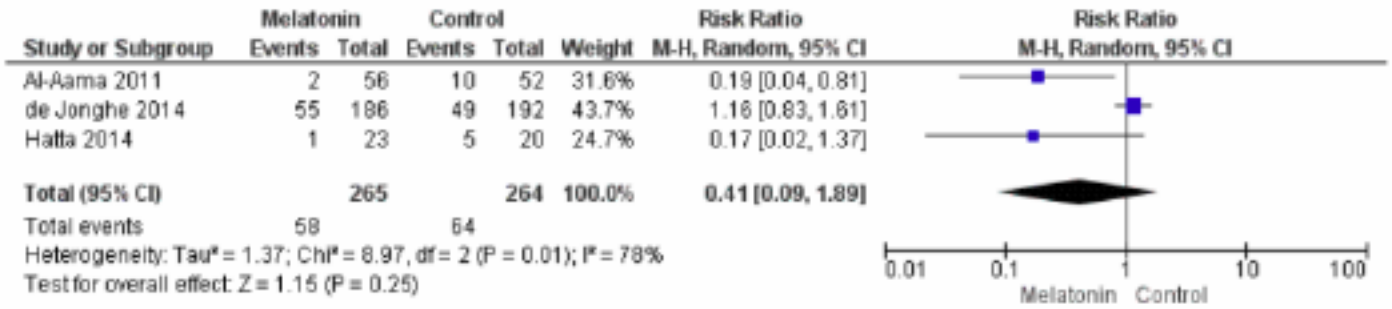
Skrobik Y, Duprey M, Hill NS, Devlin JW. AJRCCM 2018

Melatonin to Improve Sleep

Rationale:

- 3 small RCT (n=60), 3-10 mg HS
- Only evaluated, lower, acuity patients with chronic respiratory failure
- No clear improvements in sleep or reduced delirium

Figure 6. Forest plot of comparison: 4 Prophylactic melatonin versus placebo, outcome: 4.1 Incident delirium.



- While relatively safe and low cost, not FDA regulated.

Recommendation:

We make no recommendation regarding the use of melatonin to improve sleep in critically ill adults (no recommendation, very low quality of evidence).

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Ramelteon to Reduce Delirium?

Results of Three Randomized, Placebo-Controlled Trials

	Population	Dose	Method of delirium assessment	Use of other delirium reduction efforts?	Delirium Incidence		Difference, 95% CI	Comments
					Ramelteon	Placebo		
Hatta et al. JAMA Psych 2014	Delirium-free older medical adults: floor (64%); ICU-not intubated (36%)	8mg ghs	Psych using DSMV daily	Multimodal – non pharm protocol	1/33 (3%)	4/34 (12%)	RR= 0.09; 0.01-0.69	Delirium occurrence primary outcome Results between ICU and floor patients NR
Nishimura M et al. Crit Care Med 2018	Delirium-free critically ill adults (mostly medical; 40% intubated; AP2 score mean=24)	8mg ghs up to 2d after ICU admit	CAM-ICU by bedside nurse q4h	NR	11/45 (24%)	20/43 (47%)	OR=2.69; 1.09, 6.65)	Duration of ICU stay was primary outcome Coma NR Delirium reduction strategies NR
Jaiswal SJ et al. Crit Care Med 2019	Delirium-free adults admitted to the ICU after elective pulmonary thomboendarectomy (average age=57)	8mg qhs starting night before surgery	CAM-ICU twice daily by physician member of research team	Other than daily SAT/SBT NR	22/58 (40%)	19/59 (32%)	RR=0.80; 0.5, 1.4)	No difference in ICU LOS Patients who died assigned outcome of delirium + No difference in delirium occurrence in patient subgroup > 65 yrs

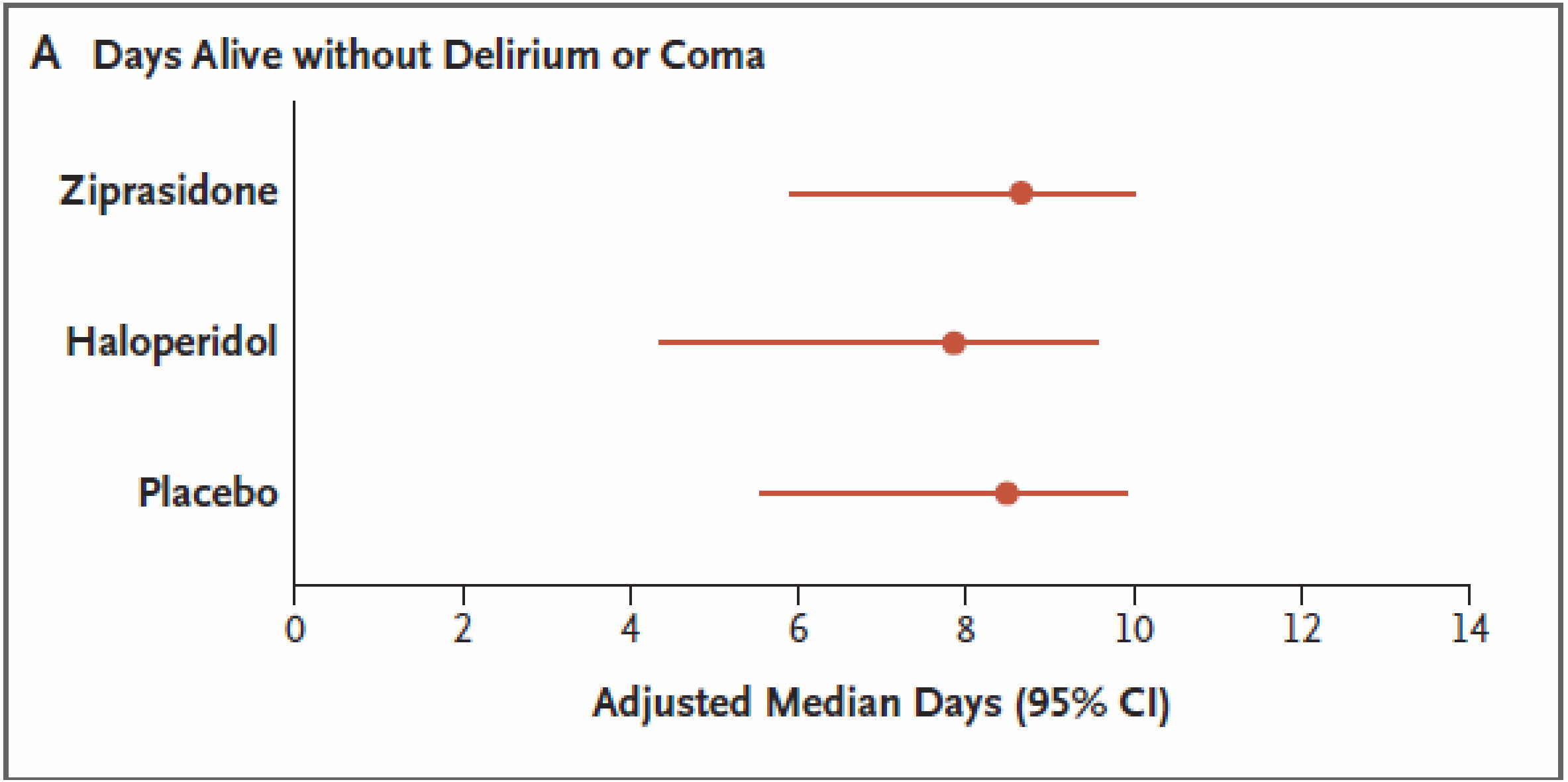
Delirium Pharmacological Treatment

PICO Question		
P	Critically ill adult patients in an ICU	
I	• Haloperidol	• Atypical antipsychotic
	• Statin	• Dexmedetomidine
C	No use of the medication	
O	• Delirium duration	• Duration of mechanical-ventilation
	• ICU LOS	• Mortality

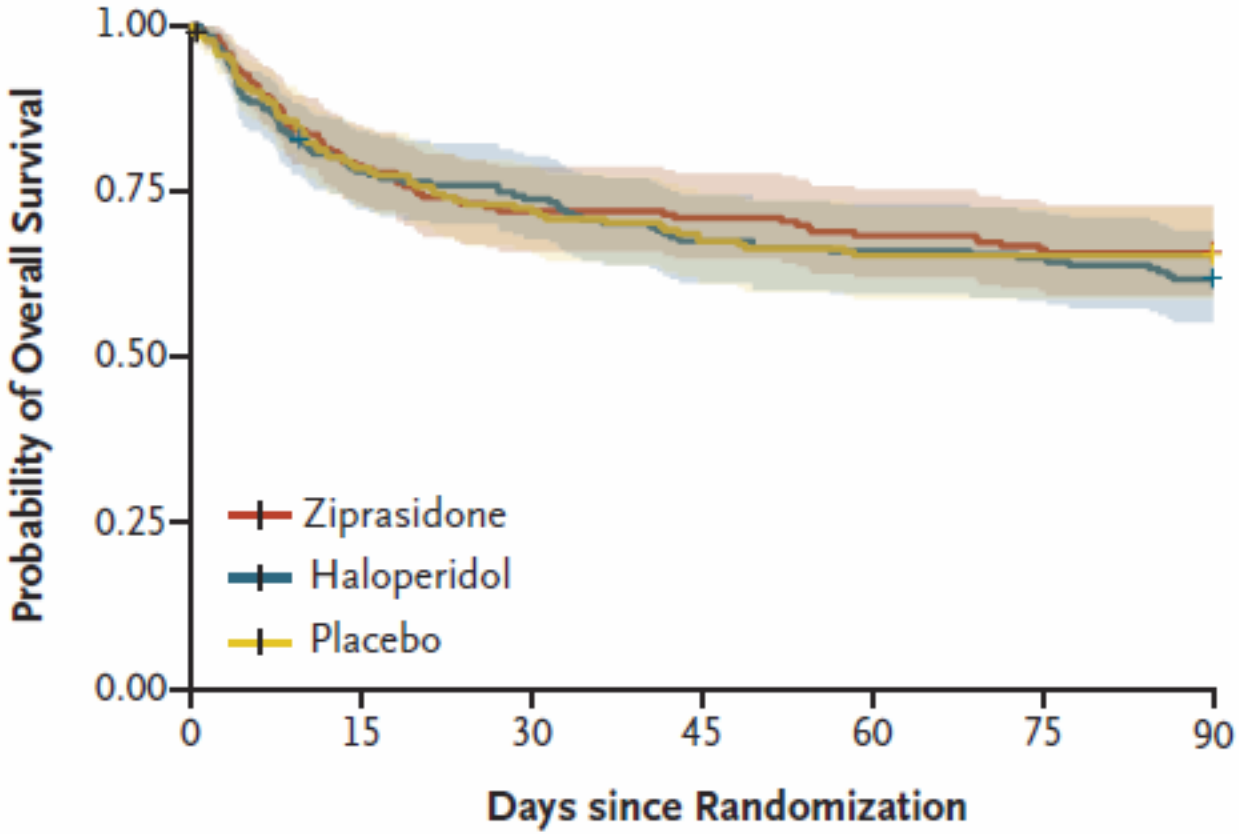
Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

T.D. Girard, M.C. Exline, S.S. Carson, C.L. Hough, P. Rock, M.N. Gong, I.S. Douglas, A. Malhotra, R.L. Owens, D.J. Feinstein, B. Khan, M.A. Pisani, R.C. Hyzy, G.A. Schmidt, W.D. Schweickert, R.D. Hite, D.L. Bowton, A.L. Masica, J.L. Thompson, R. Chandrasekhar, B.T. Pun, C. Strength, L.M. Boehm, J.C. Jackson, P.P. Pandharipande, N.E. Brummel, C.G. Hughes, M.B. Patel, J.L. Stollings, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the MIND-USA Investigators*

Girard TD et al. N Engl J Med 2018; 379:2506



Girard TD et al. N Engl J Med 2018; 379:2506



No. at Risk (cumulative no. of deaths)

Ziprasidone	190 (0)	150 (40)	137 (53)	135 (55)	130 (60)	126 (64)	125 (65)
Haloperidol	192 (0)	149 (42)	141 (50)	129 (62)	126 (65)	124 (67)	118 (73)
Placebo	184 (0)	143 (39)	132 (50)	123 (59)	119 (63)	119 (63)	119 (63)

Figure 3. Effects of Haloperidol, Ziprasidone, and Placebo on 90-Day Survival.

Girard TD et al. N Engl J Med 2018; 379:2506

Systematic Review of Haloperidol or Second-generation Antipsychotic for Delirium Treatment in Hospitalized Adults

- Search ended July 2019
- N=16 RCTs and N=10 observations studies
- Of the n= 16 RCTs (n=1768)
  - Only 9/16 had a low risk of bias
  - 5 studies ICU (n= 868)
  - 9 studies non-ICU inpatients (n=621)
  - 2 studies hospice/palliative care (n=279)

Delirium Duration:

All patient populations:

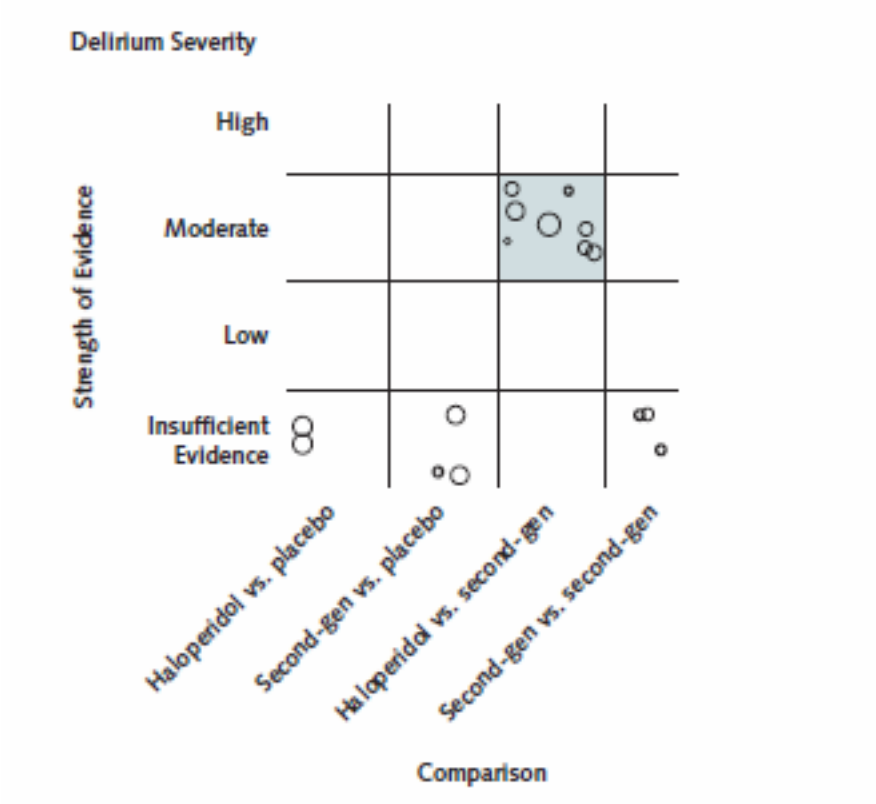
- Haloperidol: 3 RCTs (n=808) reported no difference
- Second generation: 2 RCTs (n=703) reported no difference
- Haloperidol vs. second generation: 6 RCTs (n=905) reported no difference

ICU patients only: No difference with any of the antipsychotic comparators

Roozbeh N et al, Ann Intern Med 2019

Delirium Severity

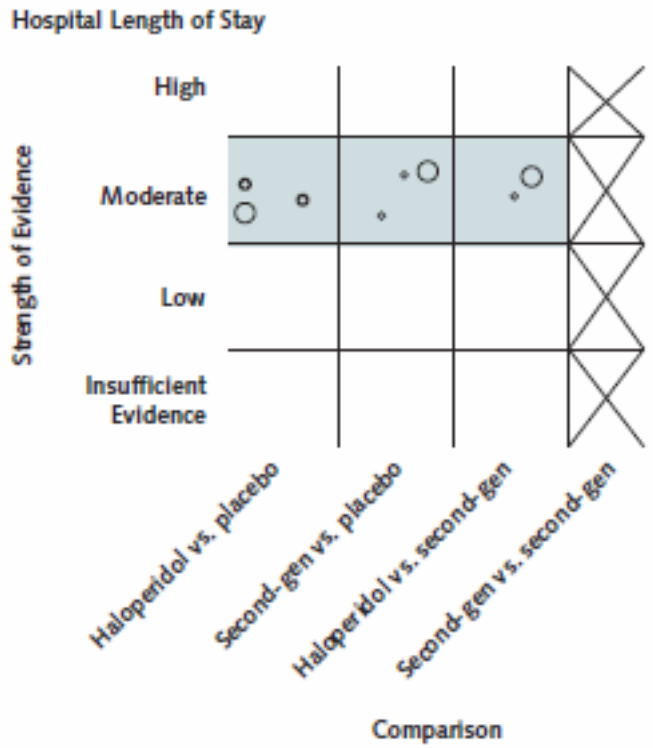
N =12 RCTs (924 pts) primarily non-ICU



Inconsistent results and methodological limitations preclude any conclusions

Hospital Length of Stay

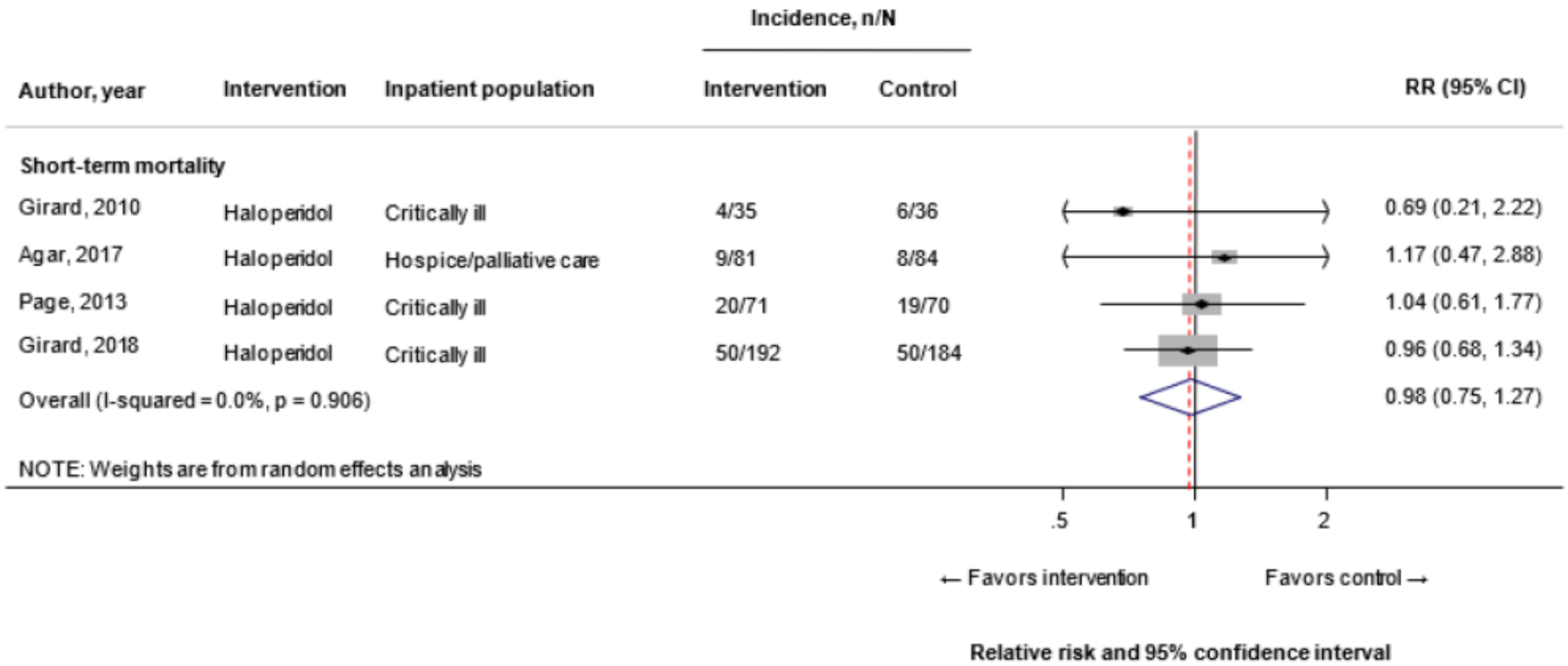
N=7 RCTs (1507 patients



Neither haloperidol nor second-gen AP use associated with reductions in hospital LOS

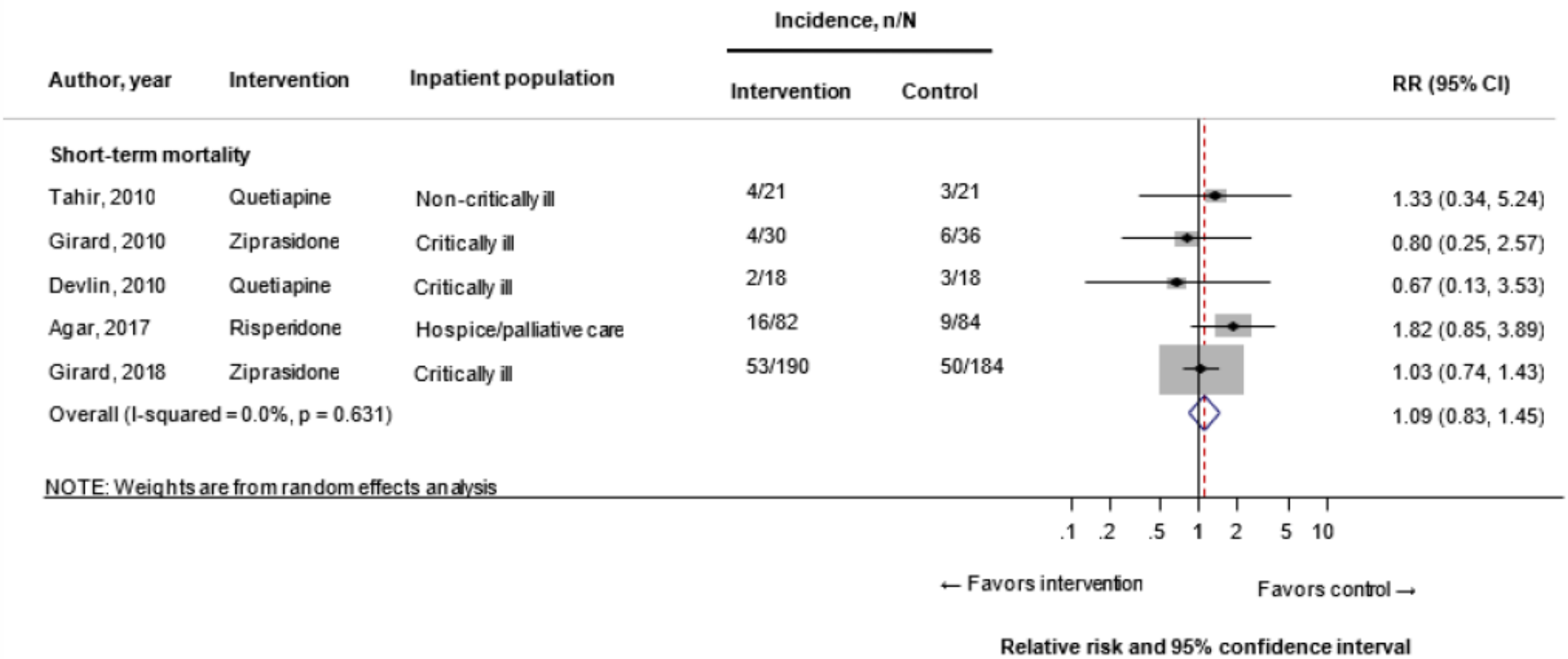
Roozbeh N et al, Ann Intern Med 2019

Figure 6. **Effect of haloperidol versus placebo on mortality***



Roozbeh N et al, Ann Intern Med 2019

Figure 7. **Effect of second-generation antipsychotics versus placebo on mortality***



Roozbeh N et al, Ann Intern Med 2019

Figure 8. **Effect of second-generation antipsychotics versus haloperidol on mortality***

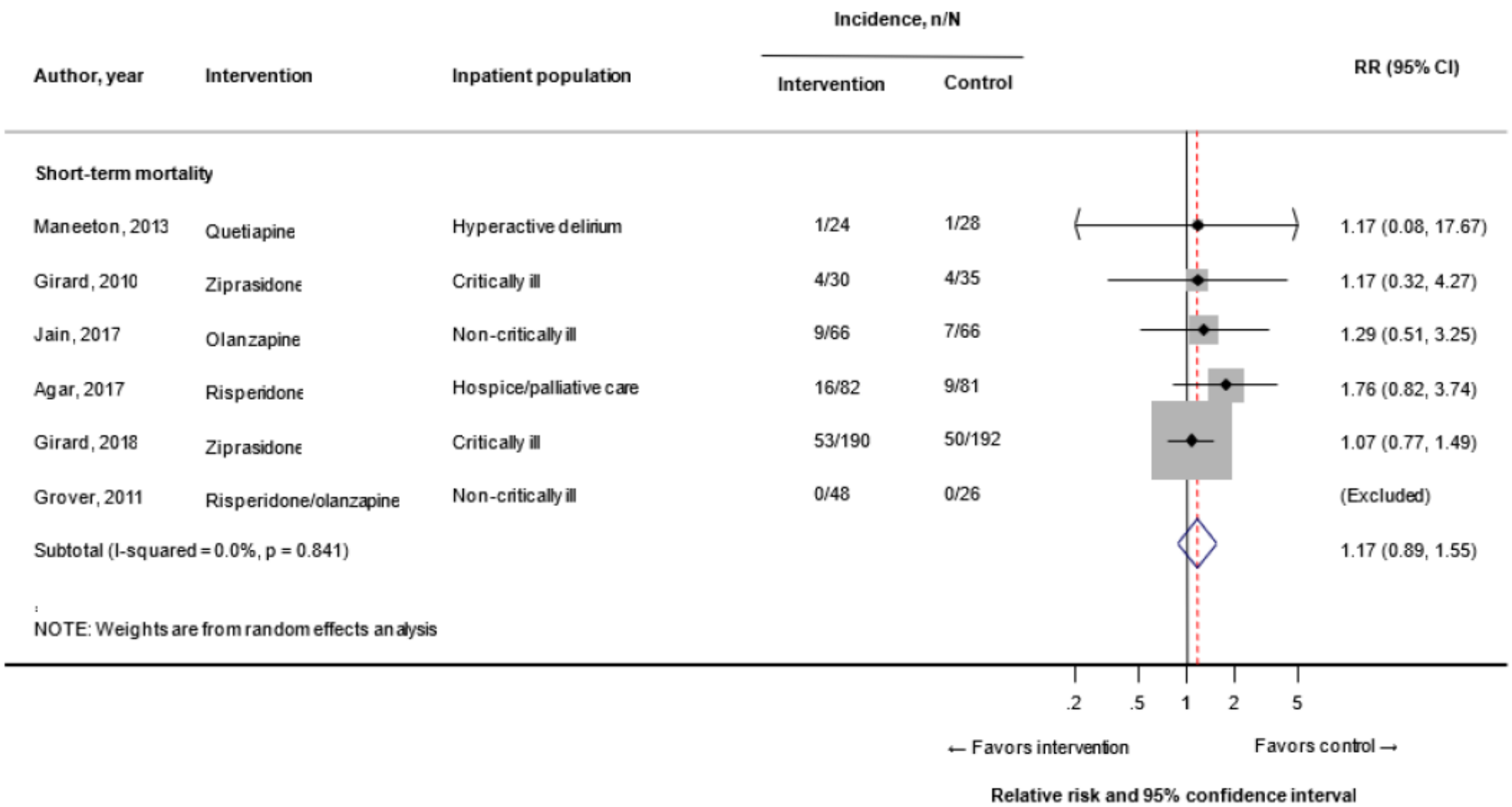


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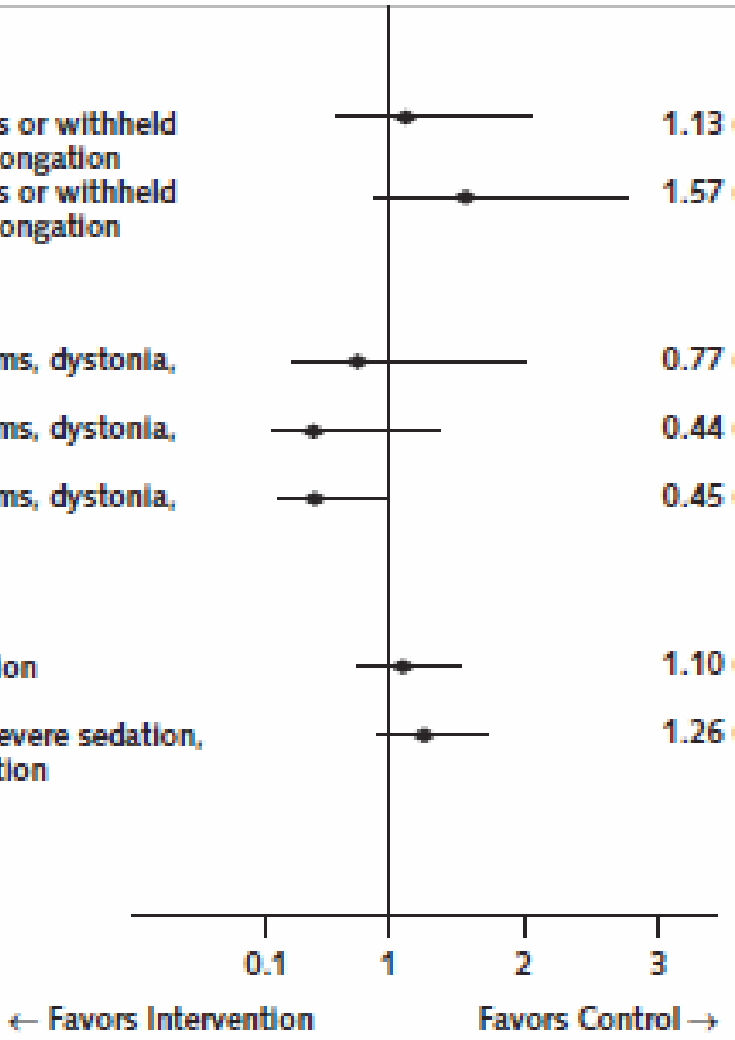
Figure 2. Meta-analysis of trials evaluating the effect of antipsychotics on the incidence of adverse effects.

Comparison	Studies, *n* (*N*)	Study Population	Outcome	Pooled Meta-analysis*	Pooled RR (95% CI)†
Cardiac effects					
Haloperidol vs. placebo	3 (808)	Critically ill patients	QTc prolonged >500 ms or withheld drug owing to QTc prolongation		1.13 (0.62–2.05)
Second-generation‡ vs. placebo	3 (703)	Critically ill patients	QTc prolonged >500 ms or withheld drug owing to QTc prolongation		1.57 (0.90–2.76)
Neurologic effects					
Haloperidol vs. placebo	3 (808)	Critically ill patients	Extrapyramidal symptoms, dystonia, akathisia		0.77 (0.29–2.01)
Second-generation‡ vs. placebo	3 (709)	Inpatients with or without critical illness	Extrapyramidal symptoms, dystonia, akathisia		0.44 (0.14–1.39)
Second-generation§ vs. haloperidol	6 (869)	Inpatients with or without critical illness	Extrapyramidal symptoms, dystonia, akathisia		0.45 (0.20–1.01)
Sedation					
Haloperidol vs. placebo	3 (644)	Inpatients with or without critical illness	Somnolence, oversedation		1.10 (0.78–1.53)
Second-generation‖ vs. haloperidol	6 (872)	Inpatients with or without critical illness	Sleepiness, excessive/severe sedation, hypersomnia, oversedation		1.26 (0.92–1.72)



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Antipsychotic vs. None (Treatment)

Rationale, includes:

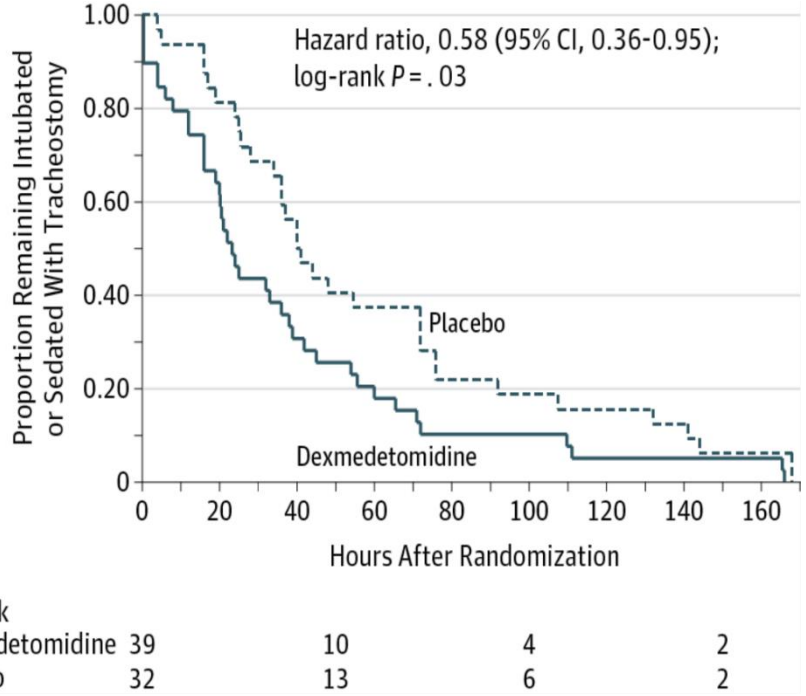
- **No benefit for any critical outcomes**
- **Not Routinely (vs. Never) given that patients with fear, anxiety or agitation not-related to pain may still benefit from a short-course of antipsychotic therapy**
- **Unnecessary continuation causes significant morbidity & cost**

Recommendation:
We ***suggest NOT*** routinely using haloperidol and atypical antipsychotic to treat delirium (conditional recommendation, low quality of evidence).

Dexmedetomidine vs. Placebo (Treatment)

Rationale: 1 RCT (71 pts)

- Significant increase in ventilator-free hours
  - Mean Difference 17 hrs (95% CI, 4 to 33 hrs); very low quality



Important Study Limitations

- 21,500 intubated patients screened to enroll 71
- Alcohol withdrawal patients not excluded
- Study terminated early because lack of funding
- Many patients did not receive opioids
  - was some of the agitation pain-related?
- No effect on ICU/Hospital LOS

Recommendation:

We ***suggest*** using dexmedetomidine for delirium in mechanically ventilated adults **where agitation is precluding weaning/extubation**
(conditional recommendation, low quality of evidence).

Medication Overload: America's Other Drug Problem

How the drive to prescribe is harming older adults

LOWN INSTITUTE

Antipsychotic Continuation Beyond ICU Discharge

Study	Design	Patients Studied	ICU to Floor n (%)	Floor to Discharge n (%)*
Jasiak et al. J Pharm Pract. 2013;26(3):253	Single-center, retrospective	59	28/59 (47)	20/28 (71)
Rowe et al. J Crit Care. 2015;30:1283	Single-center, retrospective	341	n/a	82/341 (24)
Flurie et al. Am J Health-Syst Pharm. 2015;72(suppl 3):S133	Single-center, retrospective	87	23/87 (26)	9/23 (39)
Kram et al. J Crit Care. 2015;30:814	Single-center, retrospective	133	112/133 (84)	38/112 (34)
Gilbert et al. J Intensive Care Med. 2016. DOI: 10.1177/0885066615622424	Single-center, retrospective	161	85/161 (53)	54/85 (64)
Marshall et al. J Crit Care. 2016;33:119	Single-center, retrospective	3,119	n/a	642/3,119 (21)
			248/440 (56%)	**845/3,708 (23%)**

Key Points

- Delirium prevalent in hospitalized patients:
  - Acutely ill geriatric
  - Perioperative
  - Critically ill
- Daily risk reduction efforts is the foundation for prevention efforts
- Multimodal protocols using non pharmacologic-based strategies key to delirium prevention and treatment
- Pharmacologic interventions generally have minimal benefit:
  - Reserve for short-term use for select patients with delirium-related symptoms