



# Geriatric Emergencies

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# Overview

- What medications convert the older person to the older patient
- What causes falls in the older patient with a focus on medications
- What causes delirium and focus on antipsychotic utilization
  - Delirium prophylaxis
  - Delirium Treatment
- What have we accomplished with dosing of antipsychotics in our older patients
- ADE-Adverse Drug Event, ADL-activities of daily living, BDZ-benzodiazepine, DOACs-Direct Oral Anticoagulants, ED-Emergency Department , IADL-Instrumental Activities of daily living, NTI-Narrow Therapeutic Index, PBA-pseudobulbar affect, PIM-potentially inappropriate medication



# Medication use leading to visits for ADE in the older patient



- ADE cause significant morbidity and mortality and large economic costs (\$30 billion/yr).
- While physicians recognize that medications in older adults require special consideration, nongeriatricians are usually unfamiliar with Beers criteria.
  - Beers criteria prescribing rates are utilized in National Healthcare Quality Report.
  - CMMS incorporated Beers criteria federal safety regulations for long-term-care facilities in 1999.

# American Geriatrics Society 2019 Updated AGS Beers Criteria<sup>®</sup> for Potentially Inappropriate Medication Use in Older Adults

*By the 2019 American Geriatrics Society Beers Criteria<sup>®</sup> Update Expert Panel\**

- Dr Mark Beers first published in 1991
- AGS became stewards in 2011 Updates every 3 years
  - For 2019-17,627 references reviewed from 2015-2018; 377 articles were abstracted into evidence tables, including 67 systematic reviews and/or meta-analyses, 29 controlled clinical trials, and 281 observational studies
- Lists PIMs (to AVOID) by organ system/category/rationale/recommendation and strength of that recommendation/quality of evidence. eg;
  - Anticholinergics-confusion, dry mouth, constipation/ strong recommendation to avoid and moderate evidence (RCT with limitations/well designed controlled trials)
  - Benzodiazepines-cognition impairment, delirium, falls, fractures and motor vehicle crashes. Maybe ok for seizures, alcohol withdrawal, severe GAD. Same recommendations as anticholinergics
- PIM by disease
  - Syncope-Acetylcholinesterase inhibitors, alpha-1 blockers, Tricyclic antidepressants (TCA), antipsychotics (chlorpromazine, olanzapine)
    - Orthostatic hypotension, bradycardia
    - High level of evidence, strong recommendation to avoid TCA and antipsychotics, weak strength to avoid alpha-1 blockers



# American Geriatrics Society 2019 Updated AGS Beers Criteria<sup>®</sup> for Potentially Inappropriate Medication Use in Older Adults

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- PIMS to be used with caution
  - Dextromethorphan/quinidine-limited efficacy in dementia (not PBA), increase risk of falls. Strong recommendation with moderate evidence and Use with caution
- Drug Drug interaction
  - Alpha-1 blocker and loop diuretics-increase risk of urinary incontinence, Avoid with moderate evidence and strong recommendation
- Renal disease modification/cautions-duloxetine, CrCl<30, increased GI side effects (nausea, diarrhea). Weak recommendation to avoid with moderate evidence
- Drugs with anticholinergic properties-Amitriptyline, prochlorperazine and the rest

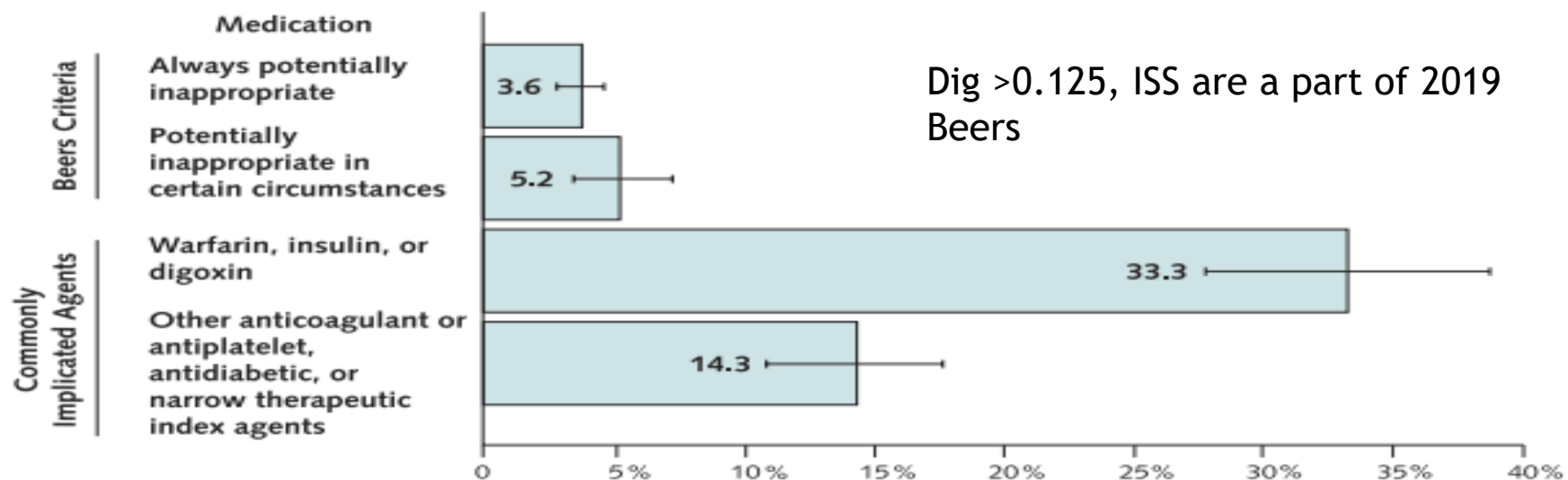
# Medication use leading to ED visits for ADE in the older patient

- Using national ADE (hospital based) database (58 hospitals) from 2 years (2004-2005)-ADE for  $\geq 65$  yo reviewed
  - Allergic reactions, Adverse effects, Unintentional overdose, Secondary effects (eg falls/choking)
- 4492 adverse drug events cases reported and estimated 177,504 ED visits for adverse drug events yearly
- 3.6% (2.8 to 4.5 CI) involved Beers criteria medications
- 33.3% (27.8-38.7) 3 medications-warfarin, insulin, digoxin
  - These 3 medications were 35x risk of “always PIM”
  - Estimated Risk for Insulin, warfarin, Digoxin was 206/100k prescriptions v. 5.6/100k for beers
- 3 classes (anticoagulants/antiplatelets, antidiabetic agents, NTI (digoxin, phenytoin) accounted for 47.5% of ED visits

Most commonly implicated medications†		cases	National Estimate
Warfarin		854	17.3 (12.7–21.9)
Insulin		616	13.0 (9.4–16.6)
Aspirin	Aspirin/clopidogrel not included in “Top 3” as not as severe adverse effect and not as modifiable risk as Warfarin, Insulin, Digoxin	232	5.7 (3.3–8.2)
Clopidogrel		173	4.7 (1.5–7.9)§
Digoxin		130	3.2 (1.6–4.7)
Metformin		103	2.3 (1.4–3.2)
Glyburide		98	2.2 (0.9–3.5)
Acetaminophen–hydrocodone		76	1.7 (1.0–2.5)
Phenytoin		78	1.5 (0.8–2.3)
Glipizide		57	1.5 (0.8–2.1)
Levofloxacin		63	1.4 (1.1–1.8)
Lisinopril		62	1.4 (0.8–2.0)
Trimethoprim–sulfamethoxazole		52	1.3 (0.9–1.7)
Furosemide		48	1.2 (0.6–1.8)

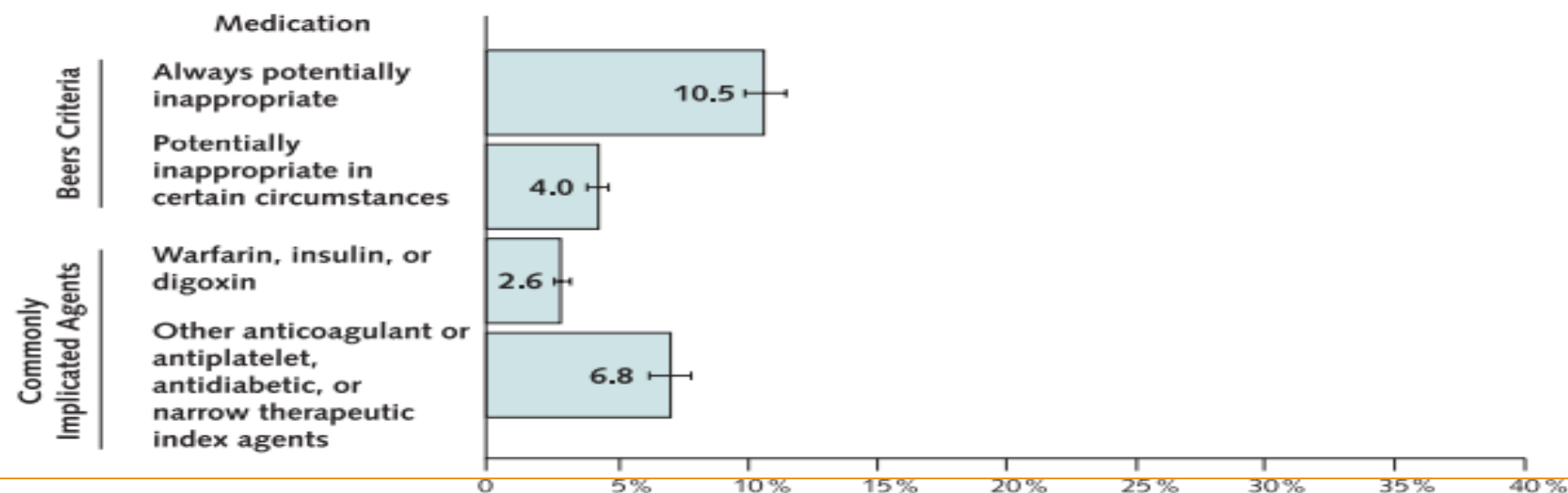


### Estimated ED Visits for ADEs, 2004–2005



Dig >0.125, ISS are a part of 2019 Beers

### Estimated Outpatient Prescription Visits, 2004





# Hospitalization risk from medications in medicare patients

- Cross-sectional analysis of 132 home health agencies in the US
- N=87,780, 79.8 yo
- 2012 Beers criteria Utilized
- At Baseline
  - 57,612 using 0 PIM, 30,168 (34.4%) using  $\geq 1$  PIM, 5969 (6.8%)  $\geq 2$  PIM
- Limitations
  - Not able to assess by indication or disease-not able to collect that data
  - Hospitalization was counted no matter the admitting diagnosis
    - (DID NOT HAVE TO BE DRUG RELATED)

# PIM Utilization

Benzodiazepine (BDZ)-alprazolam, lorazepam, oxazepam, clonazepam, diazepam

NSAID-ASA>325mg/day, diclofenac, meloxicam, naproxen, nabumetone

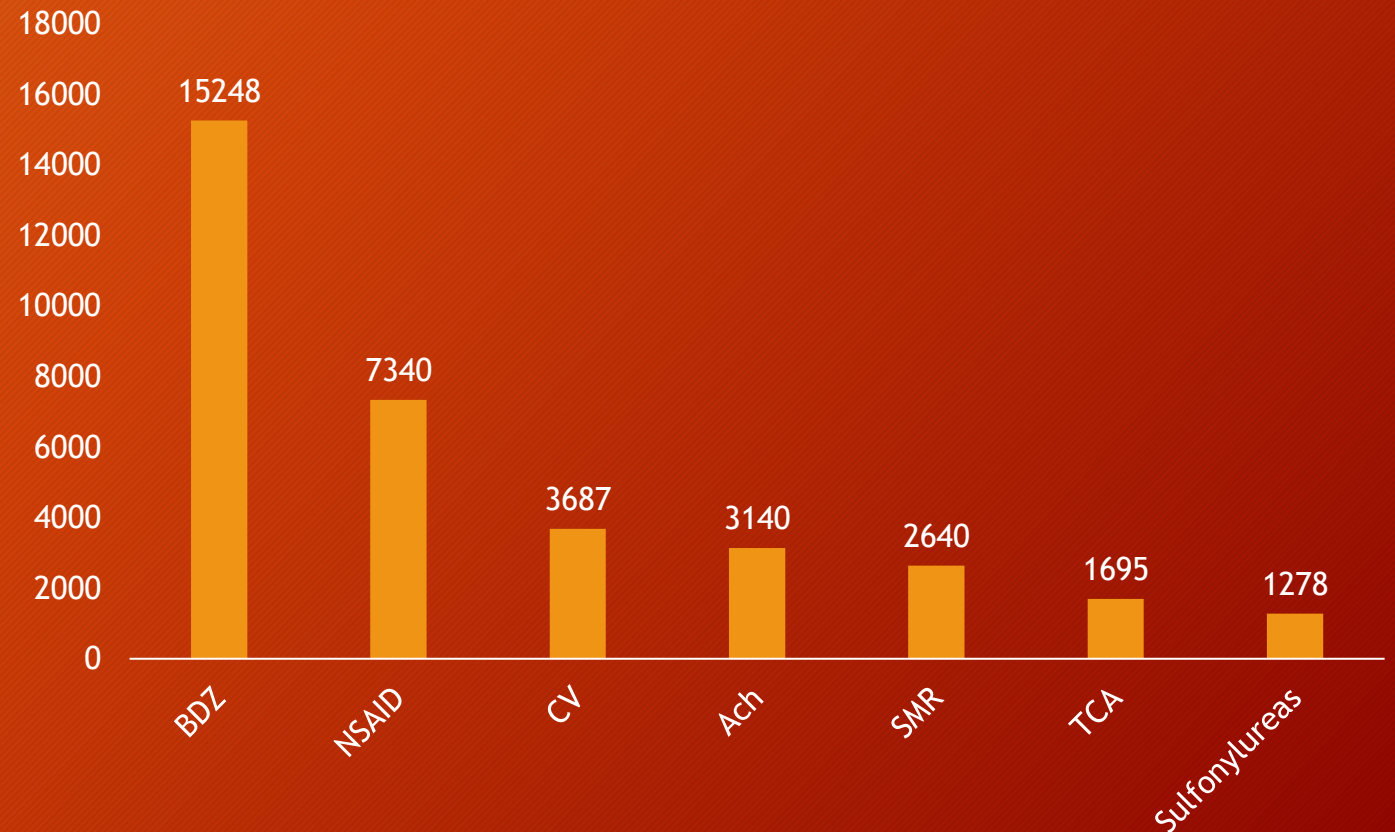
Cardiovascular (CV)-guanabenz, guanfacine, methyldopa, Dig>0.125

Anticholinergics (Ach)-brompheniramine, chlorpheniramine, diphenhydramine, promethazine, benztropine, belladonna alkaloids, clidinium

TCA-amitriptyline, doxepin (>6mg), imipramine

Skeletal muscle relaxants (SMR)-carisoprodol, cyclobenzaprine, methocarbamol, metaxalone

Sulfonylureas-glyburide, chlorpropamide





# Hospitalization risk from medications in medicare patients

- PIM use increased 30-day hospitalization risk from (excluded NSAID)
  - $\geq 1$  PIM 13% greater risk, 1.13 (1.09,1.17) of being hospitalized than 0 PIM
  - $\geq 2$  PIM 21% greater risk, 1.21 (1.12,1.3) “ “
- Anticholinergic PIM 1.13 (1.03,1.23)
- Cardiovascular (CV) PIM 1.2 (1.11,1.29)
- Benzodiazepine PIM 1.17 (1.12,1.22)
- NSAID PIM 0.76 (0.71,0.81)-CV benefit?, used by healthier patients for minor pain

# Discussion/Summary

- 2007 study
  - Warfarin, insulin and digoxin are outpatient medications that often convert the older person to an inpatient
  - Anticoagulation landscape now favoring DOACs over warfarin and somewhat lower adverse effects. (All cause readmissions decreased 0.93 (p=0.003), hospitalization with bleed 0.89 (p=0.009)) JAMA Neurology 2019
  - Limitations-Didn't look at adverse events at PCP, urgent care, Gradual adverse effects not as likely to present at ED
- 2017 study
  - The more PIMs the more likely to be hospitalized.
    - However, more PIMs increase chance of sicker patient
  - Limitation-Hospitalization not necessarily related to the medication



# Will my patient fall?

- 1/3 of community dwelling older adults fall yearly
- 62% of non-fatal injuries in the ED were fall related
- 5 to 10% of falls cause serious injuries
  - Major head trauma, major lacerations, fracture
- Falls predict placement in a skilled nursing facility
- Multi-factorial interventions are effective, reduce fall risk by 12/100 patient months (or 30-40%)



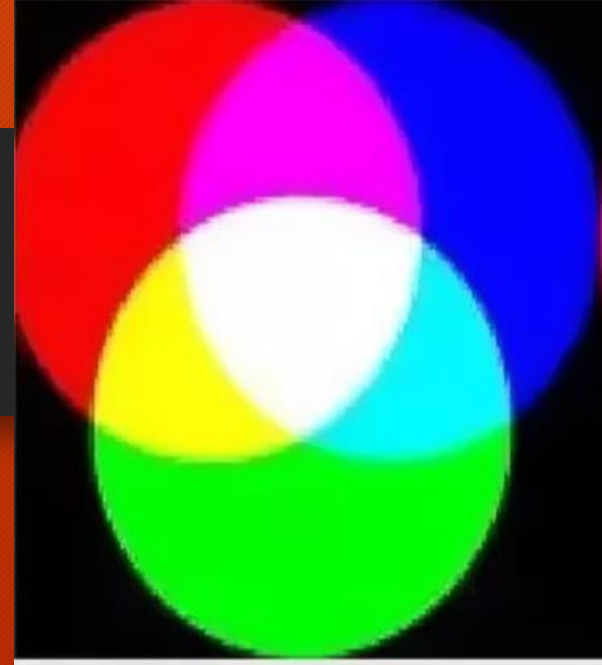
# Multi-factorial interventions

- Assessment of fall risk
  - Medication review-CNS medications (psychotropics, antidepressants, Benzodiazepines, Barbiturates, hydroxyzine, antipsychotics), # of medications
  - ADL and IADL assessment
  - Orthostatic blood pressure-Decrease in SBP/DBP of 20/10 after 1 minute of standing
  - Vision assessment
  - Gait and balance evaluation
  - Cognitive evaluation
  - Environmental hazard assessment



# Multivariate Review

- 18 studies reviewed that provided at least one of the risk factor domains
- Falling in the past year predicts another fall (Likelihood ratio range 2.3-2.8)
- Most Consistent predictor
  - Clinically detected abnormalities of gait or balance (1.7-2.4)
  - Visual impairment, medication variables, decreased activities of daily living, orthostatic hypotension, and impaired cognition were not consistent predictors across studies reviewed.



# Medication Related Falls

- 11 studies reporting medication assessment
- Cambell et al (1 or more falls in 12 months)
  - $\geq 4$  medications 1.9 (1.4-2.5 LR)
  - Taking psychotropic medications 1.7 (1.3-2.2LR)
- Tinetti et al. (1 or more falls in 12 months)
  - Benzodiazepine, phenothiazine or antidepressant 27 (3.6-207 LR)
- Luukinen et al. (2 or more falls in 12 months)
  - Benzodiazepines or antidepressants 1.8 (1.4-2.2 LR)

$$LR = \frac{\text{probability of finding in patients with disease}}{\text{probability of same finding in patients without disease}}$$

- LR >1 argue for the disease of interest; bigger the better
- LRs >0 and <1 argue against the diagnosis of interest
- the closer the LR is to 0, the less likely the disease.
- LRs = 1 lack diagnostic value.



# Heterogeneity (as it pertains to meta-analysis)

- Heterogeneity-Determining similarity between studies
  - $I^2$ -(Inconsistency) =  $100\% \times (Q - df) / Q$ 
    - 0-100% Lower % is ideal (25% (low), 50% (moderate), 75% (high))
  - Cochran's Q - statistical test that is used to determine whether the proportion of “successes” is equal across three or more groups

# Fall Risk Increasing Drugs: systematic review

	Antipsychotics			Antidepressants			Benzodiazepines		
	No.	OR (95% CI)	I <sup>2</sup>	No.	OR (95% CI)	I <sup>2</sup>	No.	OR (95% CI)	I <sup>2</sup>
All studies	16*	1.54 (1.28–1.85)	67%	22	1.57 (1.43–1.74)	76%	14	1.42 (1.22–1.65)	67 %
Outcome									
Any fall	11	1.43 (1.15–1.77)	54%	14	1.35 (1.28–1.42)	0%	12	1.38 (1.17–1.63)	66%
Recurrent fall	5*	1.70 (1.21–2.38)	69%	6	1.90 (1.42–2.54)	52%	3	1.45 (1.20–1.76)	0%
Injurious fall	1	1.66 (0.17–16.21)	N/A	5*	1.72 (1.51–1.96)	72%	1*	1.70 (1.03–2.81)	67%
Population									
Community	4	2.30 (1.24–4.26)	0%	5	1.48 (1.24–1.77)	63%	6*	1.40 (1.18–1.66)	36%
Long term care	6	1.18 (0.97–1.43)	88%	11	1.46 (1.26–1.69)	33%	3	1.11 (0.84–1.47)	0%
Hospital	4	1.57 (1.01–2.43)	67%	2	1.57 (1.43–1.74)	76%	4	1.69 (1.06–2.68)	84%
Other	2*	1.82 (1.10–3.00)	86%	4*	1.75 (1.54–1.99)	73%	1	1.93 (1.24–1.65)	N/A

	Anti-Parkinson		Antiepileptics		Analgesics		Opioids		NSAIDs	
	n	OR (95% CI), I <sup>2</sup>	n	OR (95% CI), I <sup>2</sup>	n	OR (95% CI), I <sup>2</sup>	n	OR (95% CI), I <sup>2</sup>	n	OR (95% CI), I <sup>2</sup>
Unadjusted studies	13	1.52 (0.95–2.43), 77%	16	1.95 (1.65–2.31), 27%	13*	1.16 (0.85–1.60), 70%	14*	1.51 (1.15–1.91), 97%	17*	1.31 (1.11–1.55), 85%
Population										
Community-dwelling	2	4.45 (1.51–13.06), 36%	4	2.55 (1.84–3.52), 4%	3	1.15 (0.41–3.23), 80%	2	1.15 (0.66–2.00), 71%	2	2.02 (0.78–5.24), 67%
Long-term care	2	1.21 (0.32–4.59), 78%	0		7	1.09 (0.72–1.64), 72%	3	1.19 (0.77–1.84), 46%	6	1.39 (0.83–2.34), 55%
In-hospital	6	0.81 (0.33–1.98), 71%	7	1.53 (1.14–2.04), 0%	1	2.17 (0.93–5.07), N/A	6	1.30 (0.96–1.75), 49%	5	1.17 (0.68–1.99), 73%
Other	3	2.83 (2.47–3.23), 0%	4	2.00 (1.48–2.71), 57%	2	1.12 (0.71–1.78), 0%	3*	2.25 (1.37–3.70), 99%	5*	1.27 (1.00–1.61), 94%

- SSRI 2.02 (1.85–2.2) tricyclic antidepressants 1.41 (1.07–1.86)



# Is anticholinergic burden a factor in falls?

- Retrospective (n=132, 97% male, 78.7yo, VA clinics) cohort
  - Older, more cognitive impairment than prospective group
  - 40% falls at baseline
- Prospective (n=117 male patients, 71.5 yo, VA Clinics)
  - 12% falls at baseline
- Peripheral effects
  - Dry Mouth, Dry Eyes, Constipation
- Central Effects
  - Falls, Dizziness, Confusion

# Falls and anticholinergic burden

## Results

- Retrospective group
  - Central Effects (includes falls)
    - 1.5 RR (1.3-1.8)
  - Peripheral Effects
    - 1.6 RR (1.2-2.2)
- Prospective group
  - Central Effects
    - 1.3 RR (0.8-2.1)
  - Peripheral Effects
    - 2.1 RR (1.6-2.8)



# Summary

- Falls are multifactorial
- Some studies show that medications are important factor in falls
  - Psychotropics, Benzodiazepines, anticholinergics
  - Logical contributor-sedation, confusion, orthostatic hypotension
- Why don't more studies find medications as a factor?
  - Perhaps patients are auto-selected as tolerant to those medications that are potentially harmful
    - Patient takes zolpidem once and not tolerable due to excess sedation and confusion and never takes another dose
- Medications are Potentially modifiable factor (or are they?)

# Fall risk reduction through deprescribing

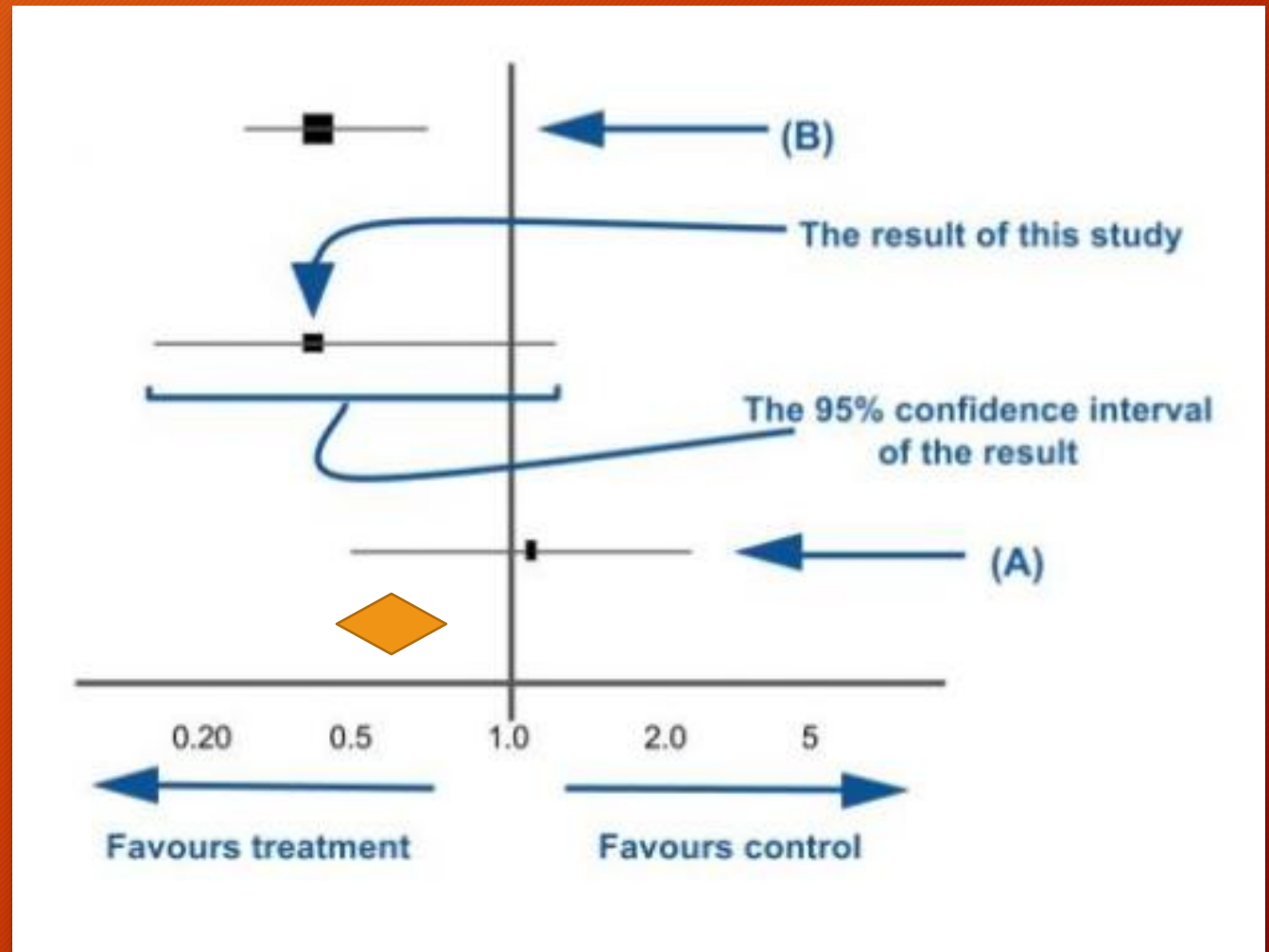
- Deprescribing fall-risk increasing drugs (FRIDs) is common practice
  - Including antihypertensives, antiarrhythmics, anticholinergics, anti-histamines, sedatives, antipsychotics, antidepressants, opioids, NSAIDs
- Meta-analysis of 5 RCT, 3 individual randomized, 2 cluster randomized (by health center or nursing home)
- 1305 patients, 70% female, 79% had falls history





# Forest Plot

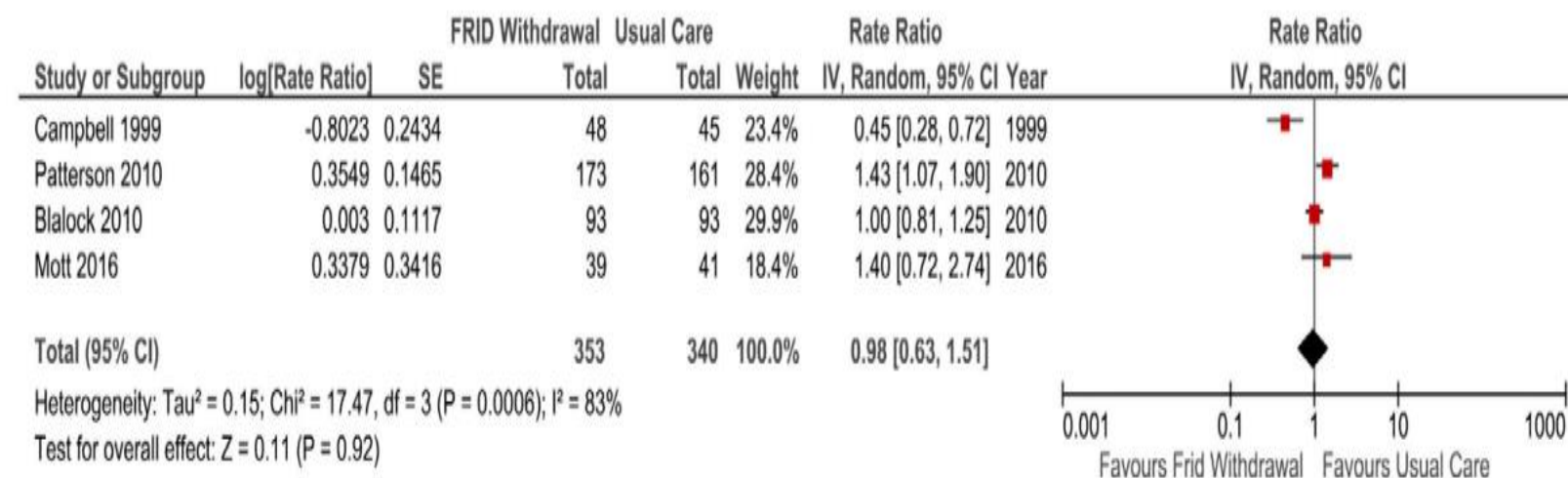
- Takes multiple studies, with a similar variable and statistic (OR, RR, ARR) and lines them up.
- B-line of null effect (“trunk”)
- A-one study added to the plot (“branch”). Box is point estimate and branches are the CI. Box size is sample size
- The diamond (“fruit”) is the summary of all point estimates and CI. The point estimate are the upper and lower parts of the diamond



# Fall risk reduction through deprescribing

- No difference in falls with FRIDs
- Limitations-No Baseline # and types of FRIDs, No Baseline # of medications, No Baseline comorbidities, Completed discontinuation of  $\geq 1$  FRID was **10-40%**, lack of blinding, heterogeneity ( $I^2 > 75\%$ )

## 1.1 Falls Rate



- Lee J. Deprescribing fall-risk increasing drugs (FRIDs) for the prevention of falls and fall-related complications: a systematic review and meta-analysis. *BMJ Open* 2021;11



# Psychotropic medication withdrawal/exercise effect on falls



- $\geq 65$  yo in New Zealand, 4 groups, 44 weeks duration
- Medication withdrawal
  - YES-exercise program (n=24, 76 $\pm$ 7.3 yo)
    - 6.5 meds, BDZ (67%), Antidepressant (33%), Tranquilizer (17%), falls (54%)
  - NO-exercise (n=24, 75 $\pm$ 5.5 yo),
    - 5.0 meds, BDZ (58%), Antidepressant (46%), Tranquilizer (8%), falls (46%)
- Original medication
  - YES-Exercise program (n=21, 73 $\pm$ 6.3 yo)
    - 5.7 meds, BDZ (48%), Antidepressant (67%), Tranquilizer (10%), falls (10%)
  - NO-exercise program (n=24, 75 $\pm$ 5.6yo)
    - 5.6 meds, BDZ (33%), Antidepressant (71%), Tranquilizer (4%), falls (33%)

# Psychotropic medication withdrawal/exercise effect on falls

- Psychotropic (BDZ, hypnotic(non-bdz sleep inducer), antidepressant, major tranquilizer(barbiturates/antipsychotics)) medication withdrawal
  - Original psychotropics were ground up and put into gelatin capsule
  - Active Medication Reduction
    - After 2 weeks-80% of original dose ,After 5 weeks-60% of original dose,After 8 weeks-40% of original dose, After 11 weeks-20% of original dose,After 14 weeks-0% of original dose
- Stopped taking study med. - 45% of medication withdrawal group, 25% of original medication
- Rate of falls
  - Medication withdrawal group (0.52/year) versus Original (1.16/year) (RR of 0.34 (95% CI 0.16-0.74)
  - Exercise group (0.71/year) versus no exercise (0.97/year) (RR of 0.26 (95% CI 0.45-0.97)



# Summary

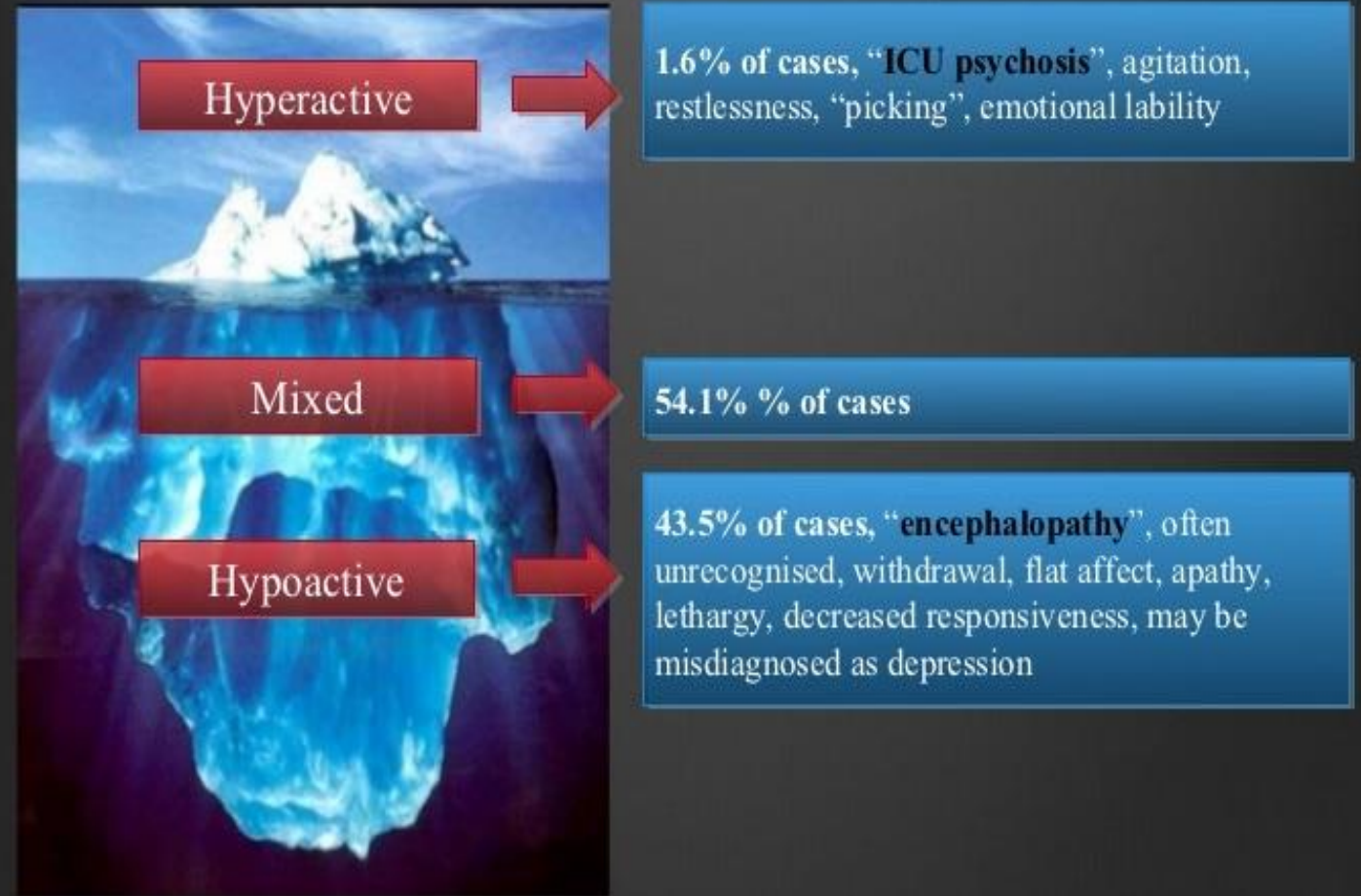
- There is some evidence that falls can be decreased IF medications are withdrawn
  - However, that is easier to describe than it is to execute successfully (even when slow titration and placebo utilized)
- How to avoid beginning PIM medications that could be at risk?

# Delirium

- Reversible, non-specific syndrome of cognitive impairment
  - acute brain dysfunction
  - Acute change in mental status
- ICU patients at high risk
  - 40-60% occurrence



## How is Delirium Categorised?



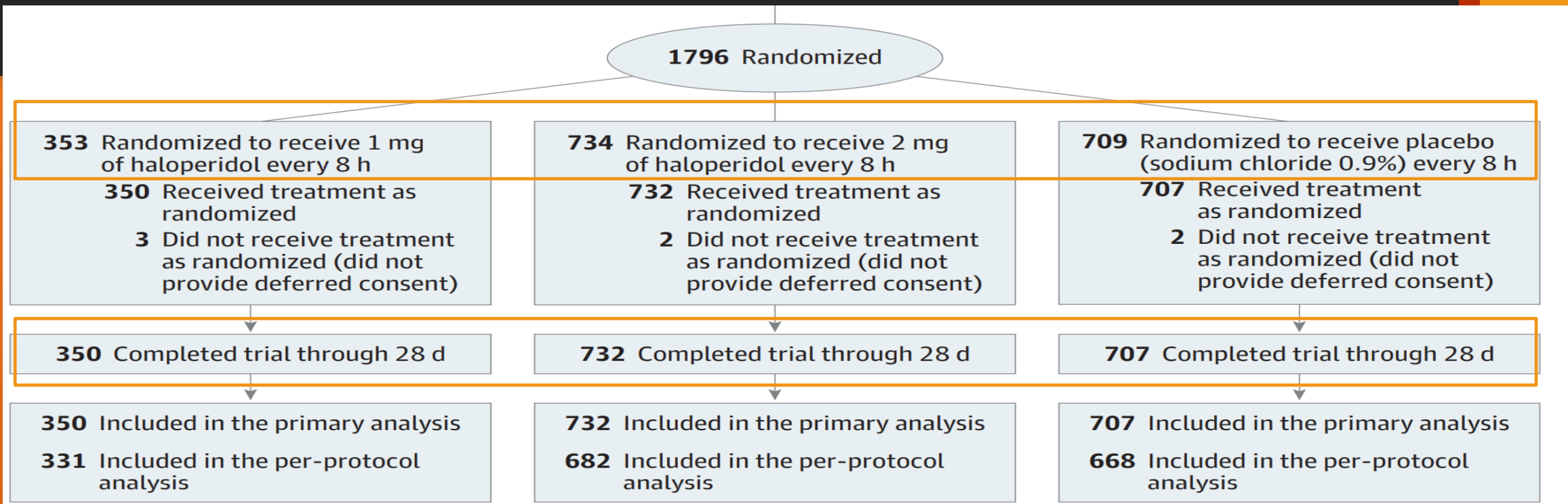


# Delirium Prophylaxis with Haloperidol

- Study Type: Randomized, DB PCB controlled
- Patients Studied
  - 15882 ICU patients  $\geq 2$  LOS days assessed
  - 14086 excluded-5662 (acute neuro), 1207 (already had delirium), 1036 (PD, dementia or alcohol abuse), 706 (taking antipsychotic), 673 (4%) (Prolong QTc or V Tach
  - 1796 randomized, mean age 66.6 yrs
  - Netherlands-(nonpharm intervention\* standard)

\*early mobilization, improving circadian rhythm (sleep improvement protocol), noise reduction strategy, sedation protocol with less sedation (RASS 0/-1), awakening trial protocol, reducing use of benzodiazepines, hearing and visual aids

# Delirium Prophylaxis

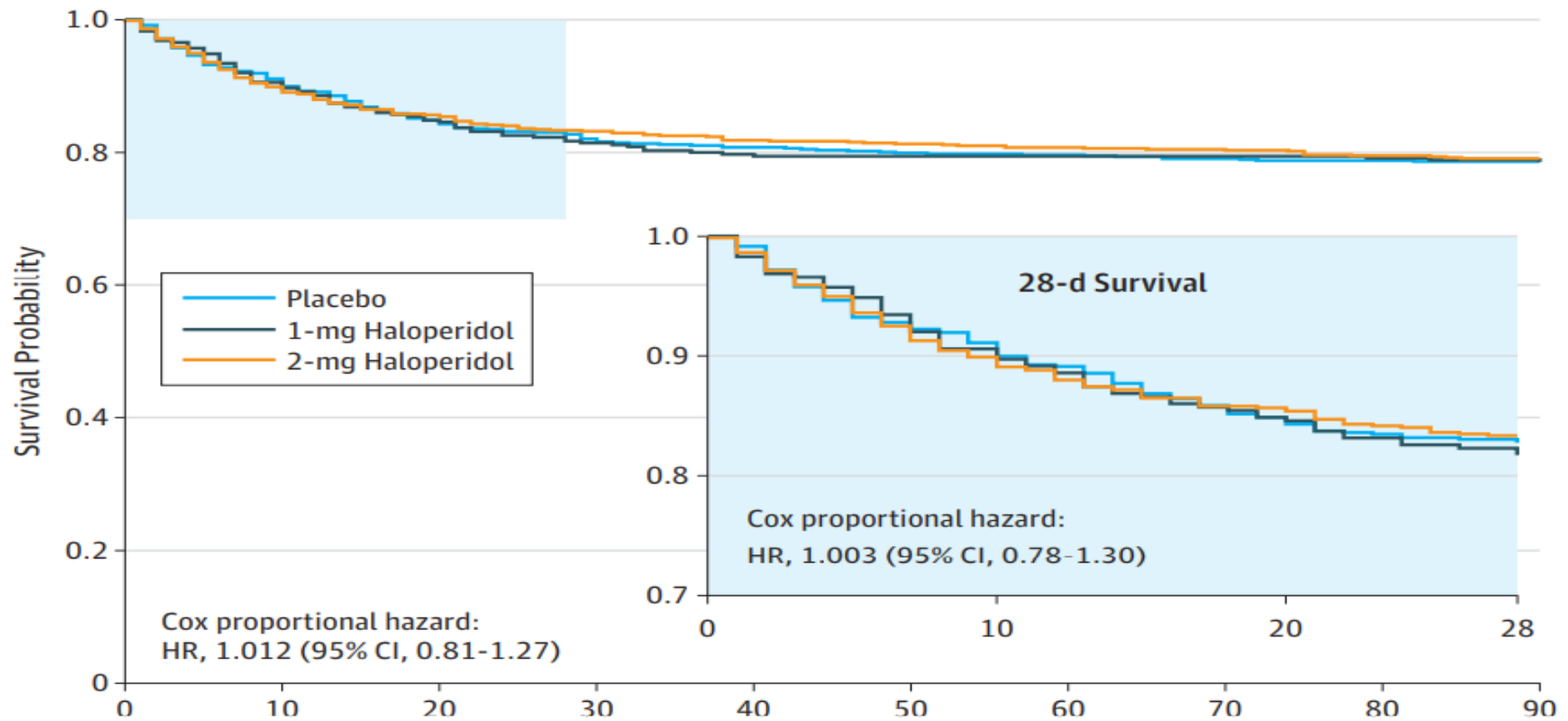


Haloperidol dose reduced 50% → 79yo, <50kg, Bili > 2.9  
Haloperidol continued for 28 days, ICU discharge, or delirium occurred



# Delirium Prophylaxis

Figure 2. Survival Analysis at 28 and 90 Days



# Delirium Prophylaxis

Third column  
is difference  
between the  
medians

28-Day end points	2mg H	PCB	2mg H v.PCB	1mg H
Incidence of delirium, No. (%)	244 (33.3)	233 (33.0)	0.4 (-4.6 to 5.4)	139 (39.7)
No. of delirium- and coma-free, median (IQR), d <sup>b</sup>	26 (17 to 28)	26 (19 to 28)	0.0 (0 to 0) <sup>a</sup>	26 (17 to 28)
No. of delirium-free, median (IQR), d <sup>b</sup>	28 (22 to 28)	28 (23 to 28)	0.0 (0 to 0) <sup>a</sup>	28 (21 to 28)
No. of coma-free, median (IQR), d <sup>b</sup>	27 (22 to 28)	27 (23 to 28)	0.0 (0 to 0) <sup>a</sup>	27 (21 to 28)
No. of days to occurrence of delirium, median (IQR) <sup>b</sup>	3 (2 to 6)	3 (2 to 6)	0.0 (0 to 0) <sup>a</sup>	4 (2 to 6)
Duration of mechanical ventilation, median (IQR), d	2 (0 to 6)	2 (0 to 5)	0.0 (0 to 0) <sup>a</sup>	2 (0.3 to 7)
Length of stay, median (IQR), d				
ICU	5 (2 to 9)	4 (2 to 9)	0 (-0.0 to 1.0) <sup>a</sup>	4 (2 to 9)
Survivors	4 (2 to 4)	4 (2 to 8)	0 (0 to 1.0) <sup>a</sup>	4 (2 to 9)
Nonsurvivors	17 (10 to 32)	16 (10 to 30)	0 (-1.0 to 1.0) <sup>a</sup>	18 (9 to 34)
Hospital	15 (9 to 28)	15 (9 to 26)	1.0 (0 to 2.0) <sup>a</sup>	16 (9 to 31)
Survivors	6 (2 to 9)	5 (2 to 10)	1.0 (0 to 2.0) <sup>a</sup>	7 (2 to 11)
Nonsurvivors	9 (5 to 15)	10 (4 to 17)		11 (6 to 22)
Incidence, No. (%)				
ICU readmission, No. (%)	65 (8.9)	68 (9.6)	0.7 (-3.4 to 2.4)	36 (10.3)
Physical restraints, No. (%)	191 (27.0)	169 (24.8)	2.2 (-2.4 to 6.8)	102 (30.0)
Unplanned removal of tubes or catheters, No. (%)	81 (11.1)	73 (10.3)	0.7 (-2.5 to 4.1)	42 (12.0)
Reintubation, No. (%)	71 (9.7)	62 (8.8)	0.9 (-0.2 to 4.1)	32 (9.1)
No. of days treated with open-label haloperidol, median (IQR)	2.0 (1.0 to 5.0)	2.0 (1.0 to 5.0)	0 (0 to 0) <sup>a</sup>	2.0 (1.0 to 5.0)
Open-label haloperidol dose, median (IQR), mg/d	3.0 (2.0 to 4.6)	3.0 (3.0-4.6)	0 (-0.4 to 0.3) <sup>a</sup>	3.0 (2.0 to 4.3)

Boogaard M Effect of haloperidol on survival among critically ill adults with a high risk of delirium. JAMA 2018;319:680-691



# Delirium Treatment

## Haloperidol v. Ziprasidone v. PCB

- Study Type: Randomized, DB PCB controlled
- Patients Studied
  - 21k assessed
  - 1183 patients with acute respiratory failure/shock enrolled
  - 566 developed delirium
    - 11% hyper
    - **89% hypoactive**
  - 184 PCB, 192 haloperidol, 190 Ziprasidone

# Delirium Treatment

## Haloperidol v. Ziprasidone v. PCB

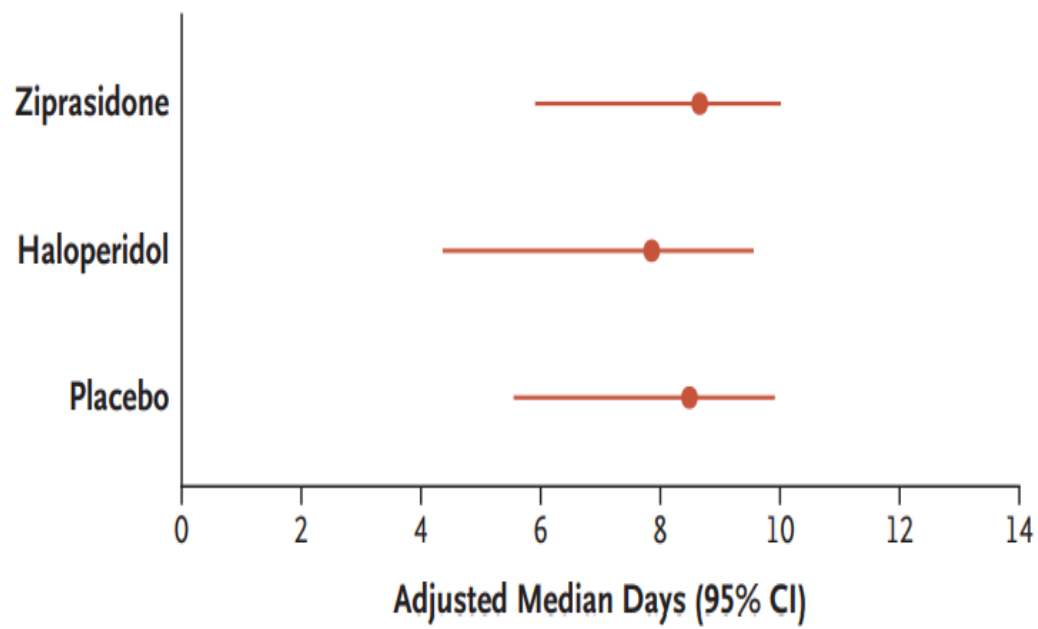
- Treatments:
  - Haloperidol IV start dose <70 2.5mg >70 1.25mg and give q12h.
  - Ziprasidone IV start dose <70 5mg, >70 2.5mg and give q12h
  - Dose doubled if delirium continued up to 10mg, 20mg daily MAX (haloperidol) or 20mg, 40mg daily MAX (ziprasidone)
  - Dose halved if no delirium (per CAM-ICU) x 2 and D/C if no delirium x4 or Safety issue
- Outcomes: # days alive without delirium/coma during 2 weeks of intervention; 30d/90d survival, freedom from mechanical ventilation, discharge
- Results:



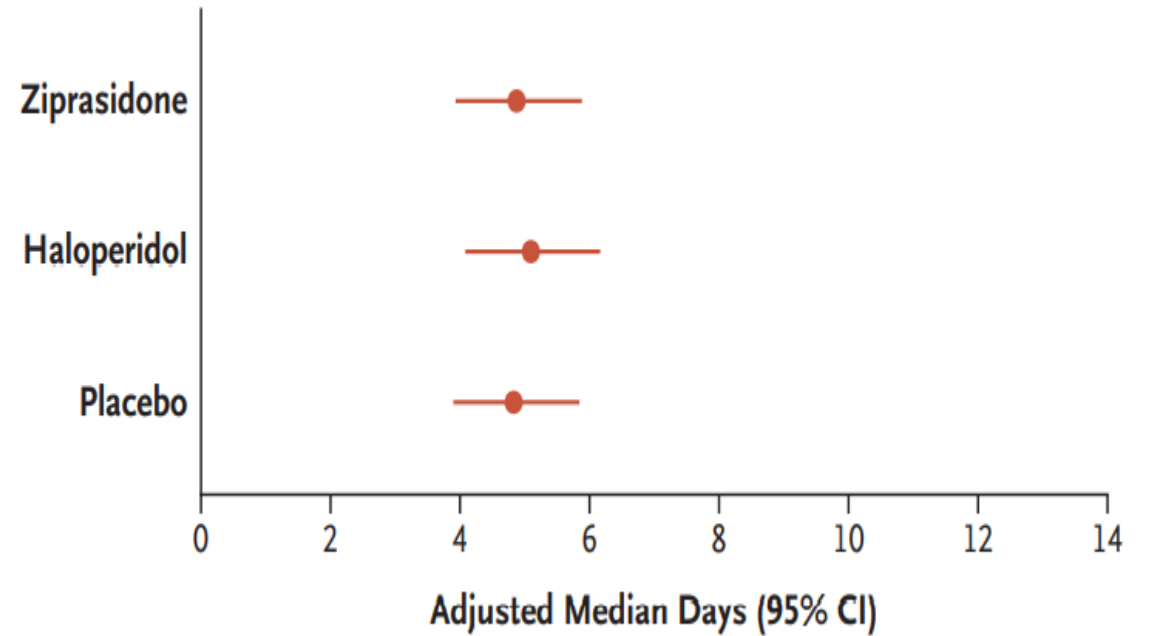
# Delirium Treatment

## Haloperidol v. Ziprasidone v. PCB

A Days Alive without Delirium or Coma



B Days with Delirium

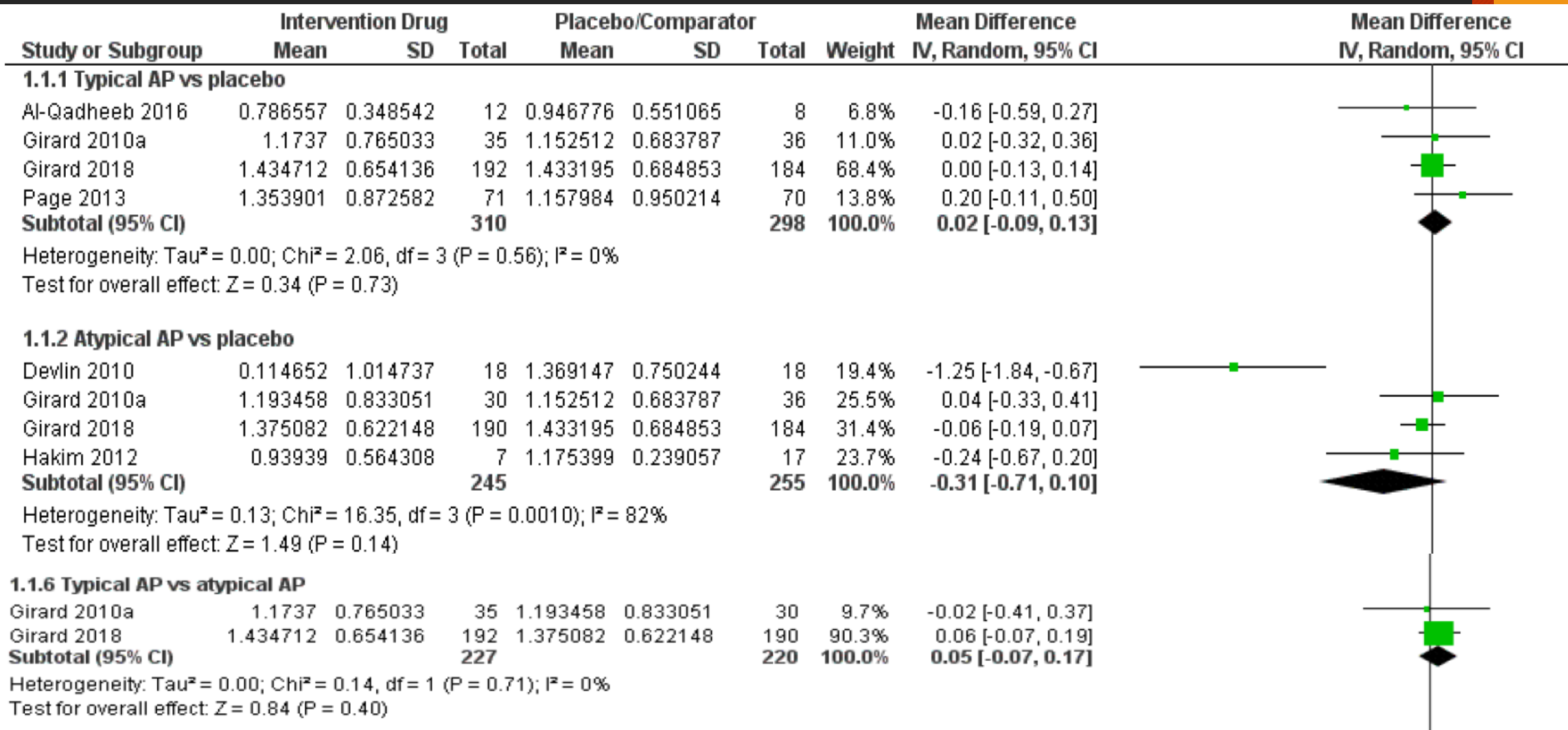


# Delirium Treatment Cochrane Analysis

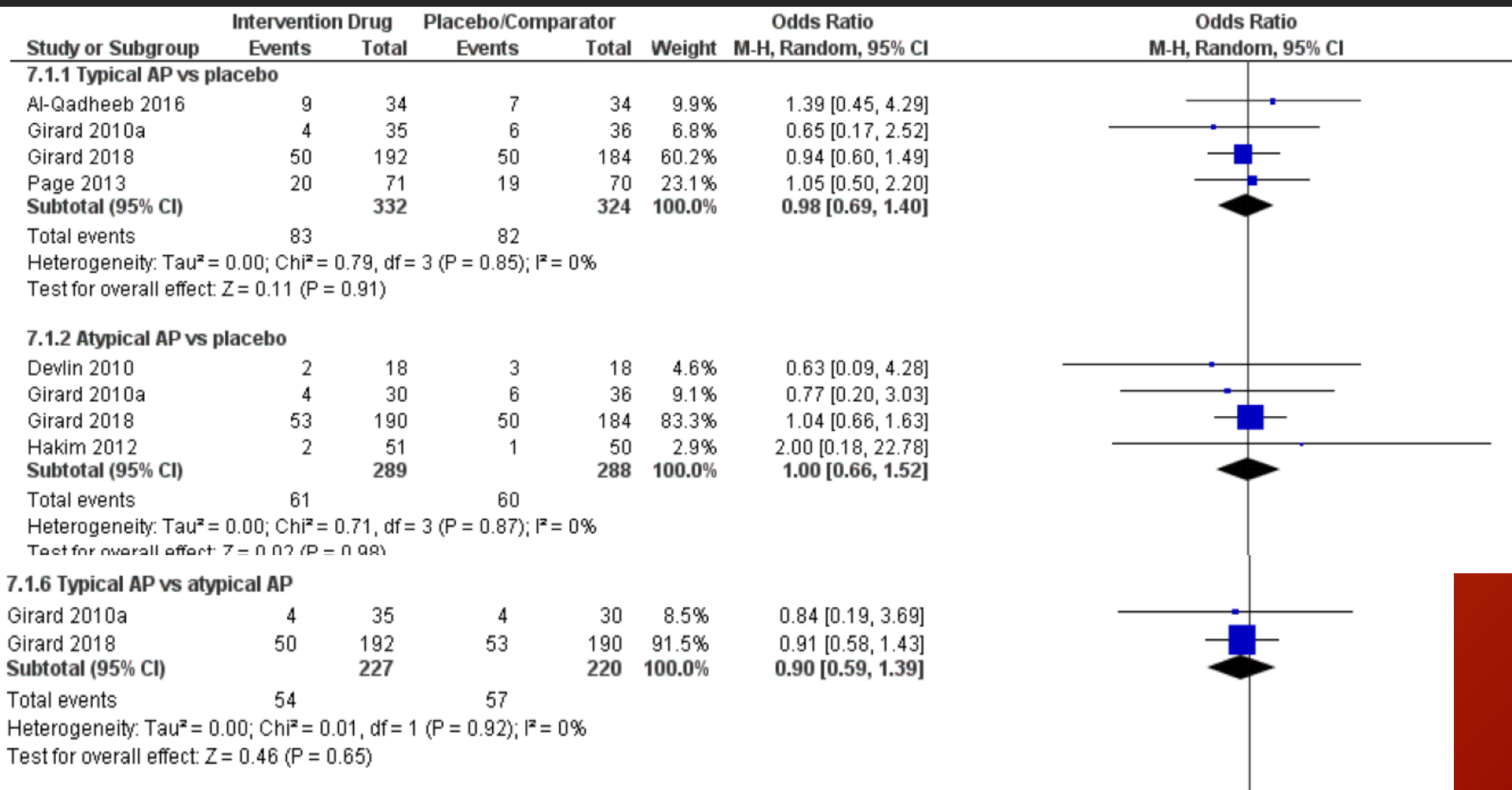
- 10 authors, 2 pharmacists
- 121 pages
- 7674 citations, 14 trials with n=1844 met inclusion criteria
- RCT's evaluating pharmacological interventions for treatment of delirium in critically ill adults (ICU stay)



# Duration of Delirium



# Mortality

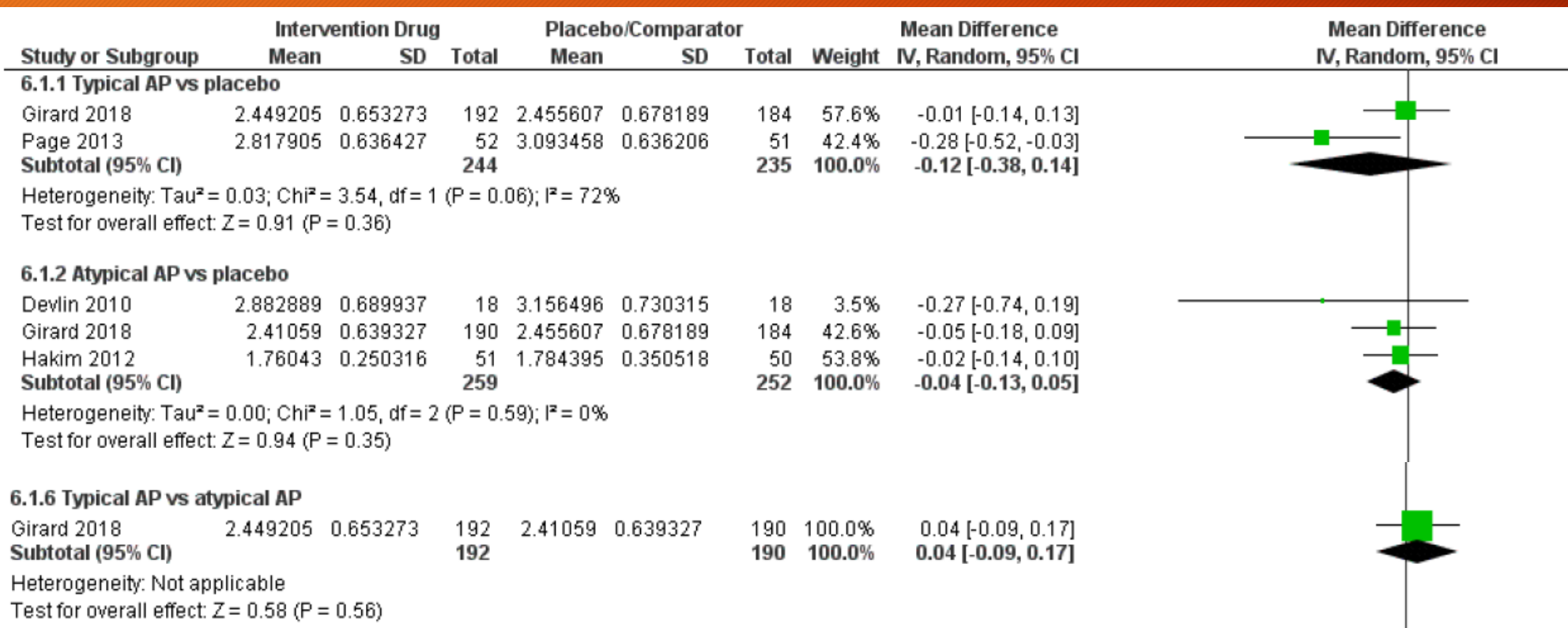




# QTc Prolongation

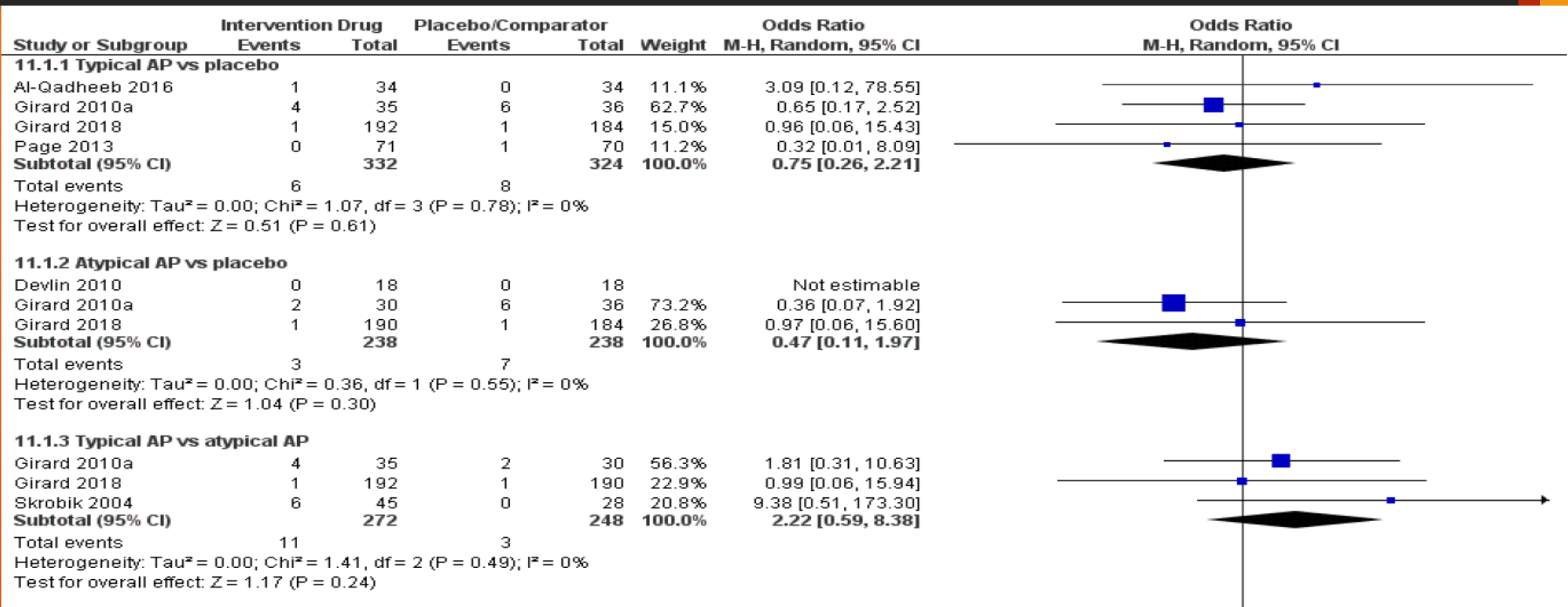
Comparisons	Illustrative comparative risks* (95% CI)		Relative effect OR (95% CI)	Absolute effect (auto calculation using GRADEpro GDT)	Number of participants (studies)	Quality of the evi- dence (GRADE)
	Assumed risk	Corresponding risk				
	Place- bo/Compara- tor	Intervention drug				
Typical antipsychotic vs placebo	62 per 1000	78 per 1000	1.26 (0.68 to 2.34) $I^2 = 0\%$	15 more per 1000 (from 19 fewer to 72 more)	656 (4 studies)	⊕⊕⊕⊕ High
Atypical antipsychotic vs placebo	90 per 1000	118 per 1000	1.28 (0.45 to 3.66) $I^2 = 56\%$	22 more per 1000 (from 48 fewer to 176 more)	577 (4 studies)	⊕⊕⊕⊖ Moder- ate <sup>a</sup>

# Length of Hospital Stay





# Extrapyramidal Symptoms



# Summary of Prophylaxis and Treatment of Delirium with antipsychotics

- Prophylaxis of delirium with haloperidol is not effective
- For treatment of delirium
  - Antipsychotics (haloperidol/ziprasidone) were not better than placebo in patients with acute respiratory failure and delirium (hypo or hyper)
    - Days alive with delirium
    - Days alive without delirium or coma
- Patients with hyperactive delirium (in Girard study) were not analyzed due to small sample size
- Antipsychotics have adverse effects (EPS, QTc prolongation)

Girard TD. Haloperidol and Ziprasidone for treatment of delirium in critical illness NEJM 2018;379:2506-16

Boogaard M Effect of haloperidol on survival among critically ill adults with a high risk of delirium. JAMA 2018;319:680-691

Burry L. Pharmacologic intervention for the treatment of delirium in critically ill adults. Cochrane Database. Issue 9, 2019



# Use of Haloperidol in Emergencies at CC

- GEM X initiative to use a more appropriate dose of haloperidol (0.5mg injectable in the antipsychotic naive older patient)
  - Initially failed
- How to improve on a quality improvement project
- Evidence for use of haloperidol 0.5mg as an effective dose



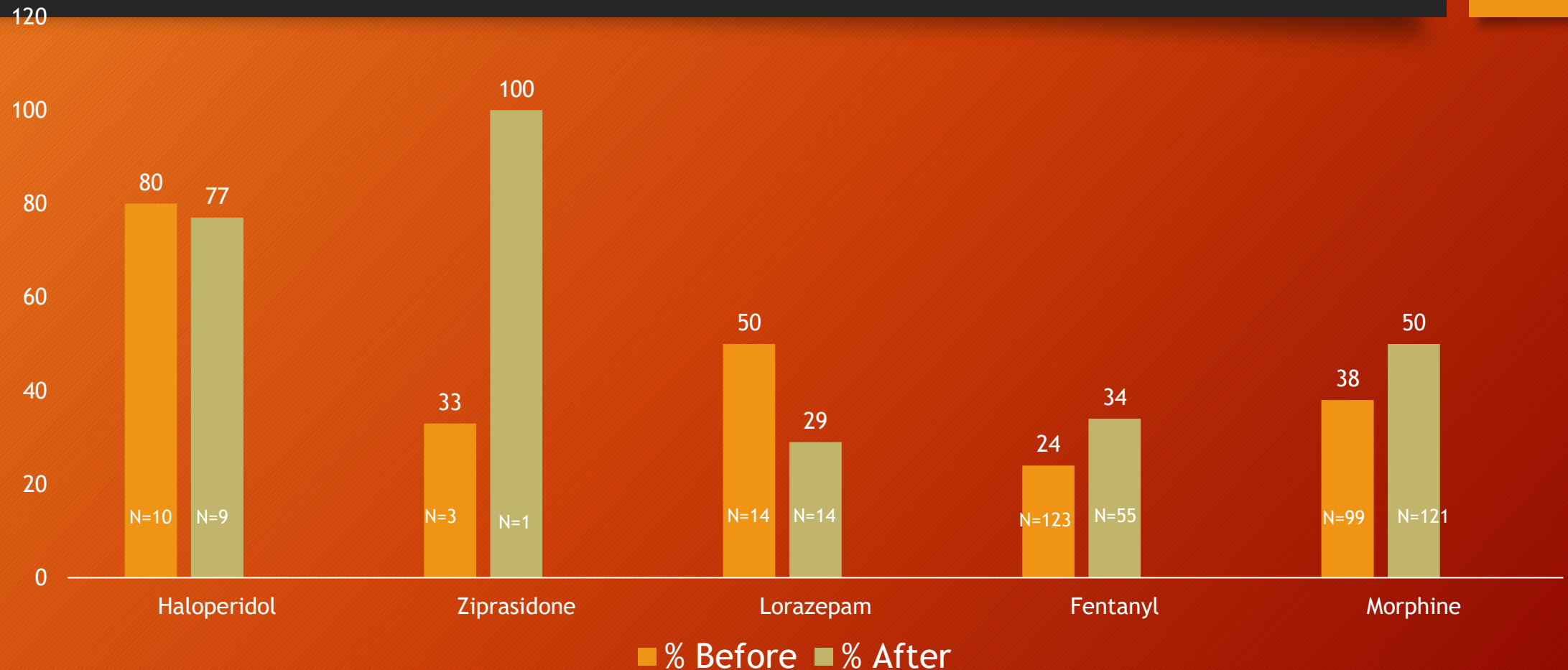
# GEM X

## Geriatric Emergency Medicine maXimum dose protocol

- Protocol Established (October 2020) for pharmacist review of high doses administered in the ED for 5 potentially harmful medications in Older Adults ( $\geq 65$  yo)
  - Haloperidol Inj ( $>0.5\text{mg}$ ), Ziprasidone Inj ( $>5\text{mg}$ ), Lorazepam inj ( $>0.5\text{mg}$ ), Fentanyl ( $>25\text{mcg}$ ), Morphine inj ( $>2\text{mg}$ )
- Rollout included
  - Development of a written protocol that was distributed to all pharmacists
  - Communication with ED providers through email establishing maximum doses and that pharmacist would be contacting them when high doses ordered
  - Inservice to nursing staff about GEM X
- Initial Review showed little change in prescribing, so restarted with emphasis on Haloperidol and Ziprasidone in January and Lorazepam in April 2021.



# Percentage of Doses above the Recommended Dose Before and After Protocol (Jan 2021)



# What next?

- Restrospective evaluation (by myself) of each order conducted monthly
  - Pharmacist contacted IF No contact was made when appropriate
  - Overall “scores” published with anonymity
- Geriatrician spoke directly with ED Staff Meeting about use of haloperidol at January staff meeting
- Presentation Developed for ED clinicians on appropriateness of haloperidol injection at 0.5mg
- Chart review of haloperidol dosing in our older inpatients
- EPIC “fix”



# Haloperidol Administration in the CC ED

Variable	Baseline-Jan to Jun 2020 (6 months)	Post Implementation February to May 2021 (4 months)	Per Month Change
Number Patients (per month)	12 (2)	6 (1.5)	25% reduction
Number Doses (per month)	16 (2.7)	8 (2)	26% reduction
Number Doses >0.5mg (per month)	15 (2.5)	4 (1)	60% reduction
Number Doses >0.5mg in <b>NAÏVE Patients</b>	12 (2)	0 (0)	<b>100% reduction</b>

Why do I have to  
use 0.5mg  
haloperidol?



# General Principles of Medication Administration and Dosing in the older patient

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Higher concentrations of water soluble and free (unbound) drugs

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Longer half-life for lipophilic drugs

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Slower phase I metabolism

---

Impaired excretion

---

Increased susceptibility to adverse effects

# General Principles of Medication Administration and Dosing in the older patient

- Start with a low dose and increase gradually
  - Start LOW, go SLOW
- Start one medication at a time
- Monitor for response
- Monitor and anticipate adverse effects



# APA practice guidelines for use of antipsychotics in Dementia Patients (2016)

- Only use when agitation and psychosis symptoms are severe, are dangerous and/or cause significant distress to the patient.
- Response to non-drug interventions not effective
- Assess risks and benefits and discuss with the patient and the patient's surrogate decision maker, with input from the family.
- Treatment should be initiated at a low dose and eased up to the minimum effective dose.


<https://www.psychiatry.org/newsroom/news-releases/apa-releases-new-practice-guidelines-on-the-use-of-antipsychotics-in-patients-with-dementia>



# Delirium in Older Persons-Review Article\*

The NEW ENGLAND JOURNAL of MEDICINE

**Table 4. Pharmacologic Treatment of Delirium.**

Class and Drug	Dose	Adverse Effects	Comments
Antipsychotic Haloperidol	0.5–1.0 mg twice daily orally, with additional doses every 4 hr as needed (peak effect, 4–6 hr)  0.5–1.0 mg intramuscularly; observe after 30–60 min and repeat if needed (peak effect, 20–40 min)	Extrapyramidal symptoms, especially if dose is >3 mg per day Prolonged corrected QT interval on electrocardiogram Avoid in patients with withdrawal syndrome, hepatic insufficiency, neuroleptic malignant syndrome	Usually agent of choice Effectiveness demonstrated in randomized, controlled trials <sup>20,37</sup> Avoid intravenous use because of short duration of action
Atypical antipsychotic Risperidone Olanzapine Quetiapine	0.5 mg twice daily 2.5–5.0 mg once daily 25 mg twice daily	Extrapyramidal effects equivalent to or slightly less than those with haloperidol Prolonged corrected QT interval on electrocardiogram	Tested only in small uncontrolled studies Associated with increased mortality rate among older patients with dementia
Benzodiazepine Lorazepam	0.5–1.0 mg orally, with additional doses every 4 hr as needed*	Paradoxical excitation, respiratory depression, oversedation	Second-line agent Associated with prolongation and worsening of delirium symptoms demonstrated in clinical trial <sup>37</sup> Reserve for use in patients undergoing sedative and alcohol withdrawal, those with Parkinson's disease, and those with neuroleptic malignant syndrome

\*part of course curriculum in Blackboard “Geriatric course for the emergency department”

Inouye. N Engl J Med 2006;354:1157-65

# Managing Delirium and Agitation in the Older Emergency Department Patient: The ADEPT Tool

**Table 4.** Summary of low-, intermediate-, and high-risk interventions, as well as risks or contraindications of certain medications, and interventions to avoid.

Intervention Risk Category	Intervention Details
Low-risk interventions or activities: for all patients	Treat underlying conditions and symptoms, restart home medications if possible. Follow prevention steps. Transfer to hospital-style bed or chair/recliner instead of gurney, which limits mobility/independence and may increase falls risk. Verbal de-escalation if actively agitated.
Medium-risk interventions: for moderate agitation or patient at risk of harming self or staff	Step 1: PO medications. If the patient is prescribed an antipsychotic at home, administer this. Other options include the following: Risperidone $\leq 1$ mg. Caution in frail or volume-depleted patients; may cause orthostatic hypotension. Olanzapine 2.5–5 mg. Contraindications/risks: Caution in intoxicated or volume-depleted patients; may cause orthostatic hypotension or sedation. Quetiapine 25–50 mg at night. May cause orthostatic hypotension and somnolence. Haloperidol 1–2 mg PO. May have more extrapyramidal adverse effects than the atypical antipsychotics. Step 2: IM or IV medications if patients are not cooperative with PO medications or are at risk of harming themselves or staff: Ziprasidone 10–20 mg IM. Caution in uncontrolled heart failure or cardiac disease, intoxicated patients, or volume-depleted/orthostatic patients. Olanzapine 2.5–5 mg IM. Caution in intoxicated or volume-depleted patients; may cause orthostatic hypotension or sedation. Haloperidol 0.5–1 mg IM. Higher risk for extrapyramidal adverse effects than the atypical antipsychotics. Higher risk with IV, so IM is preferred. Can redose if needed, but avoid doses of 5–10 mg haloperidol because it may cause prolonged effects/sedation, EPS, or other adverse effects. Use caution or avoid IV haloperidol because of adverse effects.

# Haloperidol Overdosing in the Treatment of Agitated Hospitalized Older People with Delirium

- Review of haloperidol 0.5mg versus 1mg in treating acute agitation in hospitalized older patients
- Outcome-sedation and agitation and length of stay
- N=56 (75% female), ~83yo
- 35.7% received 0.5mg (the recommended dose at this institution), 26.8% received 1mg, 37.5% receive  $\geq 1$ mg



# Haloperidol Overdosing in the Treatment of Agitated Hospitalized Older People with Delirium-RESULTS

	Group	
	Low dose	High dose
Hospital stay (days)	8.7 ( $\pm 4.4$ )	14.3 ( $\pm 14.6$ )
Days of agitation	3.6 ( $\pm 1.7$ )	6.1 ( $\pm 7.4$ )
Days restrained	1.6 ( $\pm 2.9$ )	3.5 ( $\pm 7.1$ )
Complications (oversedation)	3 (10.3 %)	11 (40.7 %) **
24 h haloperidol dose (mg)	0.8 ( $\pm 0.2$ )	3.3 ( $\pm 3.1$ ) ***
Initial haloperidol dose (mg)	0.7 ( $\pm 0.3$ )	2.2 ( $\pm 1.1$ ) ***

# Conclusions

- Higher than recommended initial doses of haloperidol were frequently used in the treatment of delirium with acute agitation
- No evidence to suggest that higher dosages were more effective in decreasing the duration of agitation or the length of hospital stay.
- Low dose haloperidol appears to be as effective as and safer than higher doses in the treatment of acute agitation in this older population.

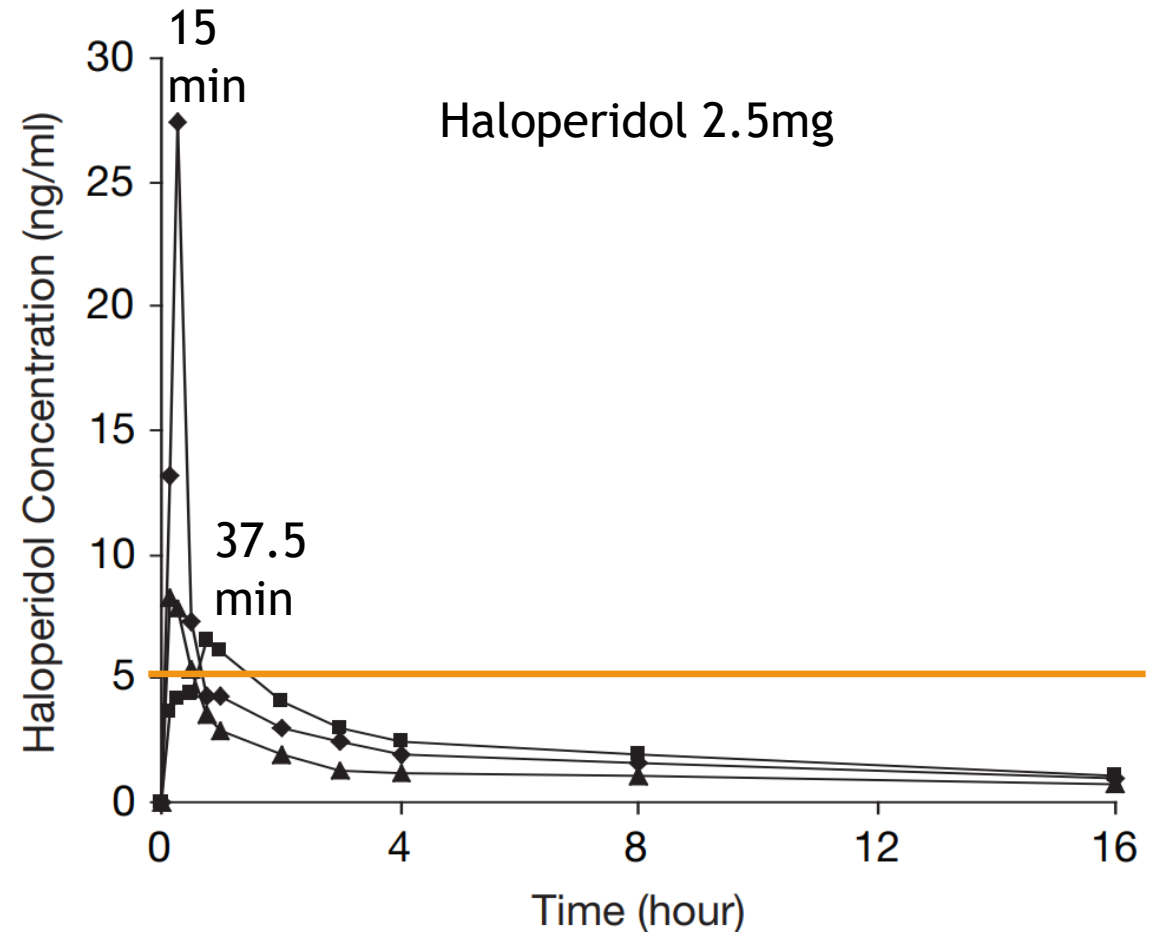
# Haloperidol dosing assessment in the older patient. Upstate Chart review

- Antipsychotic naive (at admission) patients  $\geq 65$  yo receiving haloperidol injectable at 3 different doses
  - 87 patients reviewed, 30 excluded (28-antipsychotic PTA, 2-alcohol withdrawal order set)
  - Low dose  $\leq 0.5\text{mg}$  (n=15), age  $\sim 84 \pm 9$  years
  - Medium dose  $> 0.5\text{mg}$  &  $\leq 1\text{mg}$  (n=23), age  $\sim 80 \pm 8$  years
  - High Dose  $> 1\text{mg}$  (n=19), age  $\sim 83 \pm 10$  years
- Did patient require additional antipsychotic after haloperidol dose within 4 hours?



# Haloperidol Injectable PK/PD

- T<sub>max</sub>; IV-15min, IM-37.5 min
- T<sub>1/2</sub> 17h-20h
- Pharmacodynamics (dose dependent)
  - Peak sedation 30 minutes (lexi)
  - Duration 2hrs IM, 3-24hrs IV (lexi)
- Agitation/aggression/psychosis dosing
  - repeat dose every  $\geq 15$  minutes until acute symptoms are controlled (lexi)



Miller JL. Comparison of intranasal administration of haloperidol with intravenous and intramuscular administration. *Pharmacotherapy* 2008;28:875 N=4, 24-37 yo, 63-82kg

# Baseline Demographics

Characteristic	Low dose (n = 15)	Medium dose (n = 23)	High dose (n = 19)	P-Value
Age (years); mean (SD)	84.3 (+/-8.5)	80.1 (+/-8.2)	82.9 (+/-9.8)	0.073
Female Gender, n (%)	6 (40)	13 (56.5)	9 (47.4)	0.90
Weight (kg) (SD)	72.07 (+/-14.0)	77.2 (+/-18.8)	71.8 (+/- 18.0)	0.81
BMI, mean (SD)	25.5 (+/- 4.0)	28.7 (+/- 6.8)	28.6 (+/- 8.4)	0.40
Creatinine Clearance, mean (SD)	62.9 (+/- 32.0)	43.9 (+/- 19.3)	49.8 (+/-19.8)	0.29
Psychiatric past medical history (yes) (%)	6 (40)	10 (43.5)	8 (42.1)	0.77
On benzodiazepine prior to admission (yes) (%)	2 (13.3)	3 (13)	2 (10.5)	0.70

Going to add; delirium screen, LACE (readmission risk), EWS (early warning score-change in status), BIMS (similar to MMSE)

# Results

Characteristic	Low dose (n=15)	Medium dose (n=23)	High dose (n = 19)	P-Value
Required additional haloperidol dose <4 hours post initial haloperidol dose	0 (0)	1 (4.3)	1 (5.3)	0.94
Required additional antipsychotic, other than haloperidol, < 4 hours post initial haloperidol dose	1 (6.7)	6 (26.1)	5 (26.3)	0.83
Required additional benzodiazepine <4 hours post initial haloperidol dose	1 (6.7)	0 (0)	3 (15.8)	0.04
Length of stay	7.1 (+/- 6.8)	8.2 (+/- 5.6)	13.1 (+/- 18.6)	0.01
Restraints utilized	1 (6.7)	5 (21.7)	4 (21.1)	0.04



# Conclusions

- Our results are similar to Zirker
- Higher than recommended initial doses of haloperidol were frequently used in the treatment of delirium with acute agitation
- No evidence to suggest that higher dosages were more effective in decreasing agitation (restraint use) or the length of hospital stay.
- Low dose haloperidol appears to be as effective as higher doses in the treatment of acute agitation in this older population.

# EPIC “Fixes”

haloperidol lactate (HALDOL) injection 0.5 mg ✓ Accept ✗ Cancel


Administer Dose: 0.5 mg  
Administer Amount: 0.1 mL


Route:

Frequency:


Starting:    At:


First Dose: **Today 0800** Number of doses: **1**


Scheduled Times   
12/24/21 0800

Admin. Inst.:  [Add Administration Instructions](#)

Prod. Admin. Inst.: (none)



Note to Pharmacy:  [Add Note to Pharmacy \(F6\)](#)

 Was this patient on haloperidol or other antipsychotic prior to this order?

 Is this patient a danger to themselves/others or active psychosis?

Priority:

Dispense: Dispense from:  First doses from:

Product: HALOPERIDOL LACTATE 5 MG/ML IJ SOLN [3584] Package:   

# Conclusion

- Medications are problematic and cause admissions to ED and falls in the older patient
- Reducing medications in the older patient is challenging
- Delirium prophylaxis with antipsychotics is not warranted
- Delirium treatment with antipsychotics has little evidence to support
- Haloperidol dosing by clinicians in our older patient can be guided towards lower dosing with education and practice reminders