

Palliative Care Interdisciplinary Curriculum

A Joint Initiative of the
Palliative Medicine Faculty & Staff of



THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER



NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.™

We gratefully acknowledge the support of

Award Number R25CA134309 from the National Cancer Institute

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health

Frontiers in Palliative Medicine

Colorado, November 2017

Agitated Delirium Latest in Symptom Management

Frank D Ferris, MD, FAAHPM, FAACE

Continuing Education Disclosures

- ▶ **Approval Statement:** The University of Colorado College of Nursing is an approved provider of continuing education by the Western Multi-State Division, an accredited approver of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.
 - ▶ Arizona, Colorado, Idaho, Utah Nurses Associations are members of the Western Multi-State Division of the American Nurses Association.
- ▶ **CME Approval:** Community Hospital is an approved category 1 CME provider. This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) and the Council on Osteopathic Continuing Medical Education.
- ▶ **Criteria for successful completion:**
 - ▶ Please sign in and verify contact information and credit choice
 - ▶ Attendance at 90% of activity required
 - ▶ Completed evaluation
- ▶ **Conflicts of Interest:** No individuals in a position to control content for this activity have any relevant financial relationships to declare.
- ▶ **Commercial Support:** There is no commercial support being received for this educational activity.
- ▶ **Joint Provider:** This activity is being jointly provided by the University of Colorado College of Nursing, Western Colorado Area Health Education Center (AHEC), HopeWest, and Community Hospital of Grand Junction Office of CME.

This conference has been made possible by the generosity of these Sponsors

- ▶ Colorado Mesa University
- ▶ Community Hospital
- ▶ COPIC
- ▶ Delta County Memorial Hospital
- ▶ Healthcare Specialties, Inc.
- ▶ Home Care of the Grand Valley
- ▶ HopeWest
- ▶ Juniper Family Medicine
- ▶ Montrose Memorial Hospital
- ▶ One Point Pharmacy
- ▶ Paragon Healthcare
- ▶ Phoenix Home Health Care
- ▶ Primary Care Partners
- ▶ Region X-Area Agency on Aging
- ▶ Region XI-Area Agency on Aging
- ▶ Rocky Mountain Health Plans
- ▶ Senior Community Care PACE
- ▶ St. Mary's Hospital Foundation
- ▶ Technical College of the Rockies
- ▶ Tri-County Health Network
- ▶ Volunteers of America
- ▶ WCAHEC

Objectives

- **Management**
 - Potentially reversible**
 - Irreversible**
 - Pediatrics**
 - ICU**

**How long
would you like to
enjoy delirium ?**

Management...

2013

JOURNAL OF PALLIATIVE MEDICINE
Volume 16, Number 4, 2013
© Mary Ann Liebert, Inc.
DOI: 10.1089/jpm.2012.0319

Palliative Care Reviews

Feature Editor: Vyjeyanthi S. Periyakoil

Clarifying Delirium Management: Practical, Evidenced-Based, Expert Recommendations for Clinical Practice

Scott A. Irwin, MD, PhD, Rosene D. Pirrello, BPharm, RPh, Jeremy M. Hirst, MD, Gary T. Buckholz, MD, and Frank D. Ferris, MD, FAAHPM, FAACE

Abstract

Delirium is highly prevalent in those with serious or advanced medical illnesses. It is associated with many adverse consequences, including significant patient, family, and health care provider distress. This article suggests a novel approach to delirium assessment and management and provides useful, practical guidance for clinicians based on a complete review of the existing literature and the expert clinical opinion of the authors and their colleagues, derived from over a decade of collective bedside experience. Comprehensive assessment includes careful description of observed symptoms, signs, and behaviors; and an understanding of the patient's situation, including primary diagnosis, associated comorbidities, functional status, and prognosis. The importance of incorporating goals of care for the patient and family is discussed. The concepts of potential reversibility versus irreversible delirium and delirium subtype are proffered, with a description of how diagnostic and management strategies follow from these concepts. Pharmacological interventions that provide rapid, effective, and safe relief are presented. Employing both pharmacological and nonpharmacological interventions, including patient and family education, improves symptoms and relieves patient and family distress, whether the delirium is reversible or irreversible, hyperactive or hypoactive. All interventions can be provided in any setting of care, including patients' homes.

General Principles

- **Manage based on:**
 - Potential reversibility**
 - Goals of care**
- **Ensure safety**
- **Address environment**

American Psychiatric Association (1999)

Am J Psychiatry 156: 1 Cook IA (2004)

See <http://bit.ly/29ZrVM4>

Delirium Management Decision Tree

**Context &
Reasonable Goals of Care**

```
graph TD; A[Context & Reasonable Goals of Care] --> B[Potentially Reversible]; A --> C[Irreversible]; C --> D[Dying]; C --> E[Goals of care]; C --> F[Treatment of cause unsuccessful];
```

Potentially Reversible

Irreversible

- Dying
- Goals of care
- Treatment of cause
unsuccessful

Is Patient Actively Dying ?

Signs of the dying process

Neurological Failure

- Altered level of consciousness
- Abnormal breathing patterns
- Loss of swallow / gag
- Oral / tracheal secretions
- Delirium

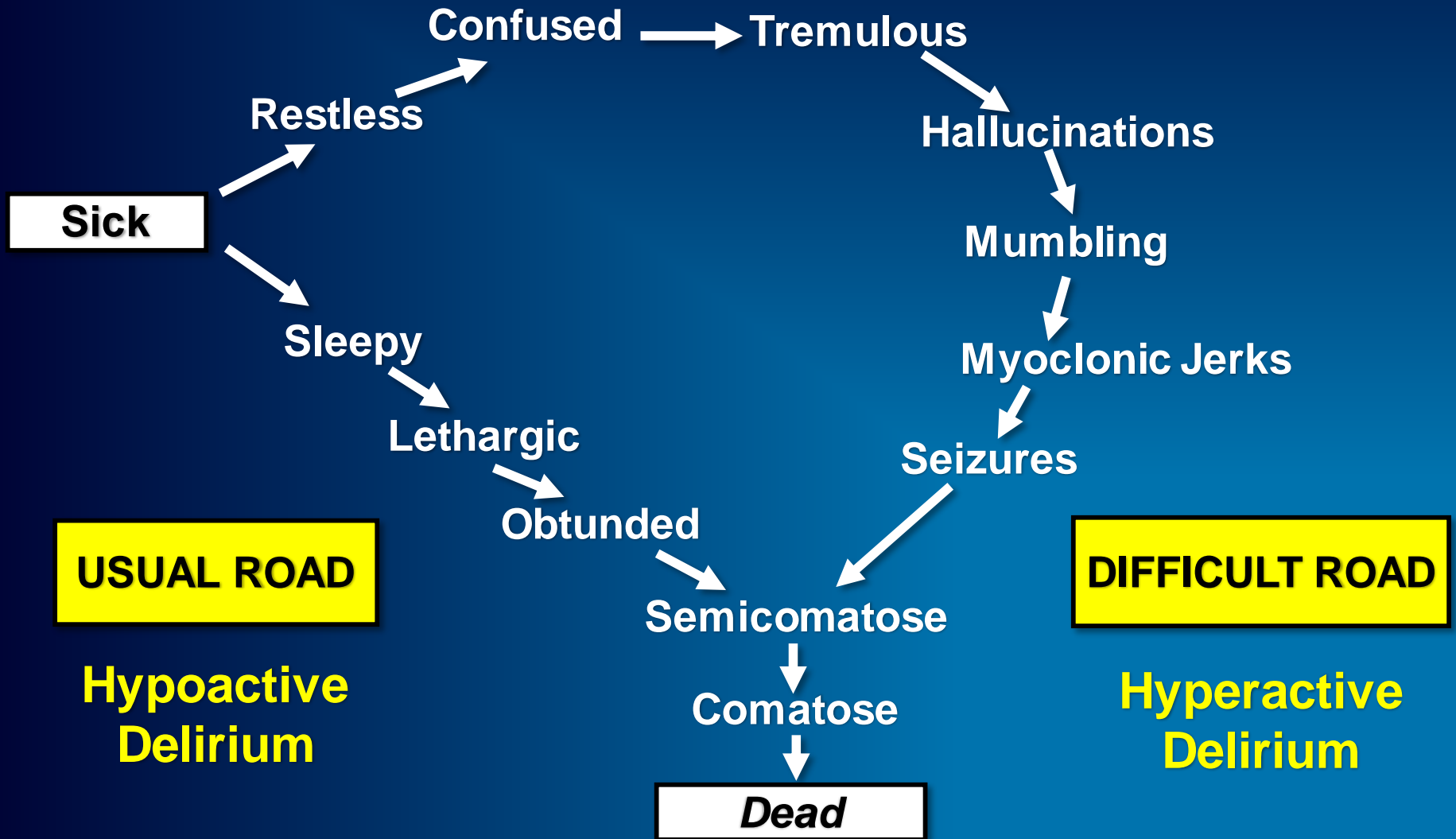
Cardiac Failure

- Tachycardia / hypotension
- Cyanosis
- Peripheral cooling
- Venous pooling / mottling

Renal Failure

- Oliguria / anuria

Two Roads to Death



Delirium Management Decision Tree

Context &
Reasonable Goals of Care

Potentially Reversible

Irreversible

Hyperactive

Hypoactive

Hyperactive

Hypoactive

Medical Rx

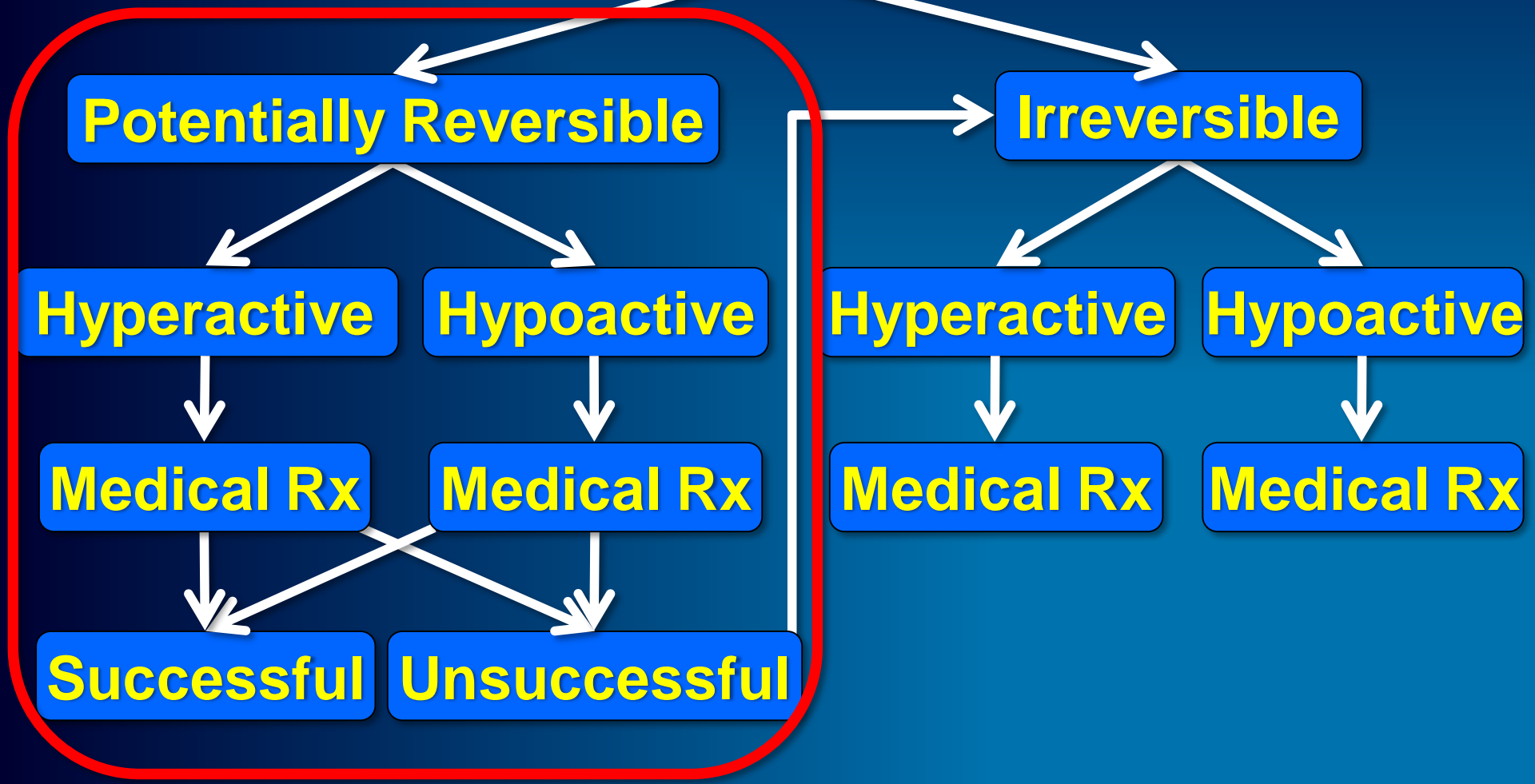
Medical Rx

Medical Rx

Medical Rx

Successful

Unsuccessful



Potentially Reversible...
Treat the Causes...

Treat the Causes

- **Diagnostic workup**
- **Consider treatment**
 - Benefits**
 - Risks**
 - Burdens**
- **Time-limited therapeutic trials**
 - Time to treat**
 - Objective outcome measures**

Treat the Experience...

Prevention of Delirium...

852 patients age > 70 admitted to medicine service

| Target | Treatment |
|----------------------------|--|
| <i>Orientation</i> | Introduce care team / daily schedule each shift, oriented 1 – 3x / day |
| <i>Activity</i> | Cognitive stimulation 3x / day |
| <i>Mobility</i> | Ambulate / range of motion 3x / day |
| <i>Sleep</i> | Non-pharmacological sleep protocol |
| <i>Sensory aids</i> | Glasses, hearing aids |
| <i>Dehydration</i> | Rehydrate as needed |

...Prevention of Delirium

- **In the treatment group**
 - Fewer episodes of delirium**
62 vs. 90 (9.9 % vs. 15 %, p = 0.03)
 - Shorter duration**
105 vs. 161 days (p = 0.02)
- **Followup showed up to an**
89 % reduction of risk of delirium

Inouye SK, et al. (1999) N Engl J Med 340: 669

Inouye SK, et al. (2003) Arch Intern Med 163: 958

NON-PHARMACOLOGICAL INTERVENTIONS

- Frequent orientation/orientation board
- Cognitive exercises
- Dim lighting
- Natural daylight
- Sensory aides, e.g., glasses/hearing aides
- Familiar objects/pictures
- Limit sensory over-stimulation
- Consistent caregivers
- Relaxation techniques
- Daily routine
- Sleep hygiene
- Range of motion or physical activity
- Constant companions or family visitation
- Leisure activities
- Limit immobilization, e.g., catheters, IV's, restraints

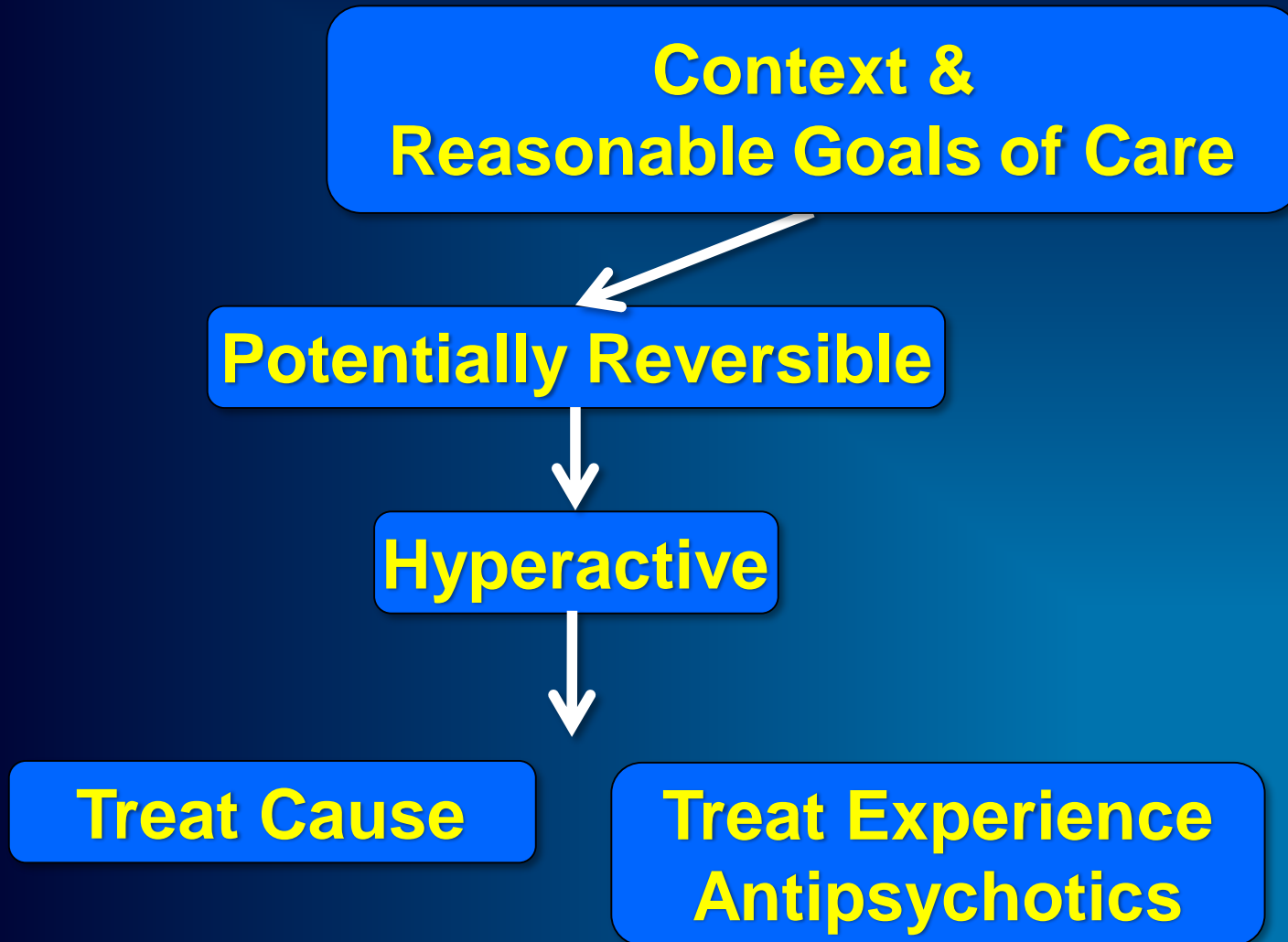
Pharmacological Management

No medication is US FDA approved for the treatment of delirium

Until 2016, no published double-blind, randomized, placebo controlled trials

No consensus among oncologists, geriatricians, psychiatrists, or palliative medicine specialists

Potentially Reversible, Hyperactive



Antipsychotic Indications

| Drug | Indication | Anti - agitation | Sedation | Amnesia | Muscle relaxation | Anti - convulsant |
|----------------|------------|------------------|----------|---------|-------------------|-------------------|
| Haloperidol | | ✓ | ✗ | ✗ | ✗ | ✗ |
| Chlorpromazine | | ✓ | ✓ | ✗ | ✗ | ✗ |
| Risperidone | | ✓ | ✗ | ✗ | ✗ | ✗ |
| Olanzapine | | ✓ | ✓ | ✗ | ✗ | ✗ |
| Quetiapine | | ✓ | ✓ | ✗ | ✗ | ✗ |

American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

The American Geriatrics Society 2012 Beers Criteria Update Expert Panel

Potentially inappropriate medications (PIMs) continue to be prescribed and used as first-line treatment for the most vulnerable of older adults, despite evidence of poor outcomes from the use of PIMs in older adults. PIMs now form an integral part of policy and practice and are incorporated into several quality measures. The specific aim of this project was to update the previous Beers Criteria using a comprehensive, systematic review and grading of the evidence on drug-related problems and adverse drug events (ADEs) in older adults. This was accomplished through the support of The American Geriatrics Society (AGS) and the work of an interdisciplinary panel of 11 experts in geriatric care and pharmacotherapy who applied a modified Delphi method to the systematic review and grading to reach consensus on the updated 2012 AGS Beers Criteria. Fifty-three medications or medication classes encompass the final updated Criteria, which are divided into three categories: potentially inappropriate medications and classes to avoid in older adults, potentially inappropriate

comes. Estimates from past studies in ambulatory and long-term care settings found that 27% of adverse drug events (ADEs) in primary care and 42% of ADEs in long-term care were preventable, with most problems occurring at the ordering and monitoring stages of care.^{1,2} In a study of the 2000/2001 Medical Expenditure Panel Survey, the total estimated healthcare expenditures related to the use of potentially inappropriate medications (PIMs) was \$7.2 billion.³

Avoiding the use of inappropriate and high-risk drugs is an important, simple, and effective strategy in reducing medication-related problems and ADEs in older adults. Methods to address medication-related problems include implicit and explicit criteria. Explicit criteria can identify high-risk drugs using a list of PIMs that have been identified through expert panel review as having an unfavorable balance of risks and benefits by themselves and considering alternative treatments available. A list of PIMs was developed and published by Beers and colleagues for nursing home residents in 1991 and subsequently expanded and

1st Line Pharmacological Treatment

Double-blind RCT of 30 AIDS patients

Haloperidol 0.4 - 3.6 mg daily, n = 11 vs

Chlorpromazine 10 - 80 mg daily, n = 13 vs

Lorazepam 0.5 - 10 mg daily, n = 6

Haloperidol = chlorpromazine >> lorazepam

Lorazepam stopped early due to adverse events

Haloperidol & chlorpromazine minimal side effects

PEARL

- Use 1st generation antipsychotics
- **Do Not Use** Benzodiazepines

Not first-line treatment

Increase confusion, disinhibition, falls

Necessary for alcohol & sedative withdrawal

APA Practice Guidelines 2004

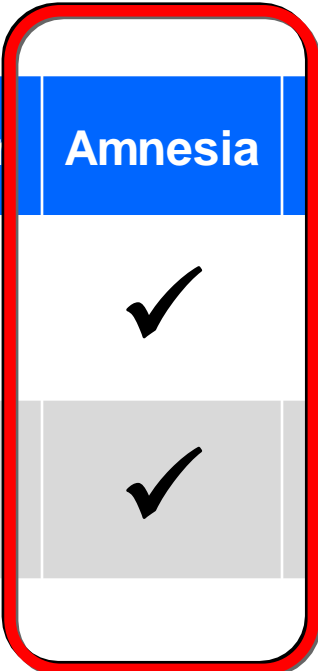
American Psychiatric Association (1999)

Am J Psychiatry 156: 1 Cook IA (2004)

See <http://bit.ly/29ZrVM4>

Why NOT Benzodiazepines for Potentially Reversible Delirium

| Drug \ Indication | Anti - agitation | Sedation | Amnesia | Muscle relaxation | Anti - convulsant |
|-------------------|------------------|----------|---------|-------------------|-------------------|
| Lorazepam | ✓ | ✓ | ✓ | ✓ | ✓ |
| Midazolam | ✓ | ✓ | ✓ | ✓ | ✓ |



**Use Pharmacokinetics to
Guide Dosing and Control
Delirium Rapidly...**

First Order Kinetics

For optimal efficacy & safety

- Titrate to effect or toxicity

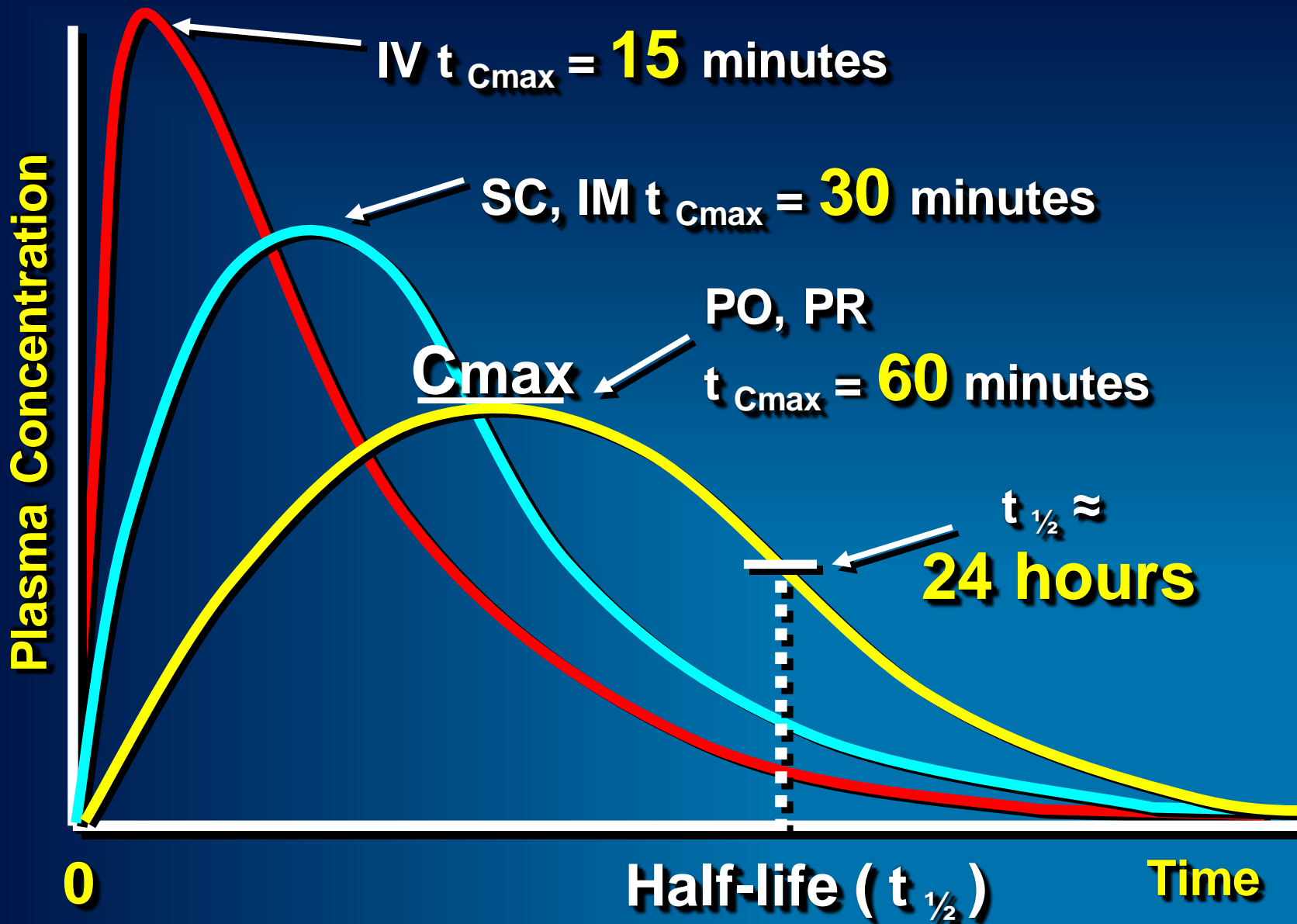
Start low

Dose every t_{Cmax} PRN

“ Catch-up technique ”

- Maintenance dosing, dose every $t_{1/2}$
- Steady state in $5 \times t_{1/2}$
- Elimination in $5 \times t_{1/2}$

Antipsychotic Kinetics



MEDICATION KINETICS

| Generic Name | Time Cmax | Elimination t _{1/2} | Equivalent Dose |
|--|--|--|-----------------|
| ANTIPSYCHOTICS | | | |
| Chlorpromazine (sedating) aka Thorazine | PO: 1 hr SC/IM: 30 min IV: 15 min (6-15) | 24 hrs (23-37) | 100 mg |
| Haloperidol † (non-sedating) aka Haldol | PO: 1 hr SC/IM: 30 min IV: 15 min (6-15) | 21 hrs (10-38) | 2 mg |
| Olanzapine (sedating) aka Zyprexa | PO: 6 hrs IM: 30 min (15-45) | 30 hrs (21-54) | 4 mg |
| Prochlorperazine aka Compazine | PO/PR: 2 hrs (1.5-5) | 8 hrs (6.8-9) | |
| Quetiapine (sedating) aka Seroquel | PO: 1.5 hrs | 6 hrs | 125 mg |
| Risperidone (non-sedating) aka Risperdal | PO: 1 hr (1-2) | PO: 3 hrs Metabolites: 21-30 hrs | 1 mg |

aka = also known as IR = Immediate Release ER = Extended Release

† = Essential medication as defined by WHO: World Health Organization

SC dosing is preferable over IM dosing

Avoid medications with short half-lives in patients with short life expectancy who may experience withdrawal when these medications are stopped at end of life

| Generic Name | Time Cmax | Elimination t _{1/2} | Equivalent Dose |
|---|---|--------------------------------------|-----------------|
| BENZODIAZEPINES | | | |
| Alprazolam aka Xanax | PO: 1 hr | 11 hrs | 0.5 mg |
| Clonazepam aka Klonopin | PO: 2 hrs (1-4) PR: 10-30 min | 30 hrs (19-50) | 0.25 mg |
| Diazepam † aka Valium | PO: 1 hr (0.89-1.32) PR gel: 1.5 hrs IM: 1 hr IV: 8 min | 45 hrs Metabolites: 30-100 hrs | 5 mg |
| Lorazepam aka Ativan | PO: 1 hr SC/IM: 30 min | 12 hrs Metabolites: 12-18 hrs | 1 mg |
| Midazolam † aka Versed | SC/IM: 30 min IV: 15 min (6-15) | 2 hrs (1-3) | |
| Oxazepam aka Serax | PO: 1 hr | 12 hrs (5-15) | 15 mg |
| BENZODIAZEPINES | | | |
| Zolpidem (non-benzo hypnotic) aka Ambien | PO: 1.6 hrs | 2.5 hrs (1.5-7) | 5 mg |

See card 46 for Medication Information Sources

NB: These PCIC Reference Guidelines do not replace careful clinical judgment specific to each patient / family situation. PCIC is a collaborative effort of OhioHealth, The Ohio State University Wexner Medical Center, and Nationwide Children's Hospital in Columbus, Ohio, USA. Copyright © Frank D Ferris 2013-2017. All rights reserved. Permission to reproduce any or all of these PCIC Reference Guidelines is granted for non-commercial educational purposes only, provided that the attribution statement and copyright are displayed. To reproduce for all other purposes, contact Frank D. Ferris, Palliative & Hospice Care, OhioHealth, +1-614-533-6299. V7, 2017

Sample Orders for Agitation

Haloperidol – 1 mg SC q 30 min PRN

If 3 doses not effective, call MD

Do not exceed **100 mg in 24 hr**

Schedule today's PRNs tomorrow

1 or 2 x / day + same PRN schedule

Chlorpromazine – 50 mg SC q 30 min PRN

If 3 doses not effective, call MD

Do not exceed **2000 mg in 24 hr**

Schedule today's PRNs tomorrow

1 or 2 x / day + same PRN schedule

Haloperidol

Typical Daily Doses

- Nausea 0.5 – 2.0 mg
- Delirium 2 – 10 mg
- Schizophrenia 5 – 50 mg

Risks

- Q-T Interval
prolongation
- Parkinsonism

Potential Side Effects

Lower doses

- Akathisia
“ ants in your pants ”

Higher doses

- Tardive dyskinesias
- Torticollis

2nd Generation Antipsychotics ?

Haloperidol **EQUAL** to olanzapine and risperidone

1. haloperidol 1 - 28 mg daily n = 45 vs
olanzapine 2.5 - 13.5 mg daily n = 28
2. haloperidol 1.5 - 10 mg daily n = 11 vs
olanzapine 5 - 15 mg daily n = 11
3. haloperidol 1 - 3 mg daily n = 12 vs
risperidone 0.5 - 2 mg daily n = 12

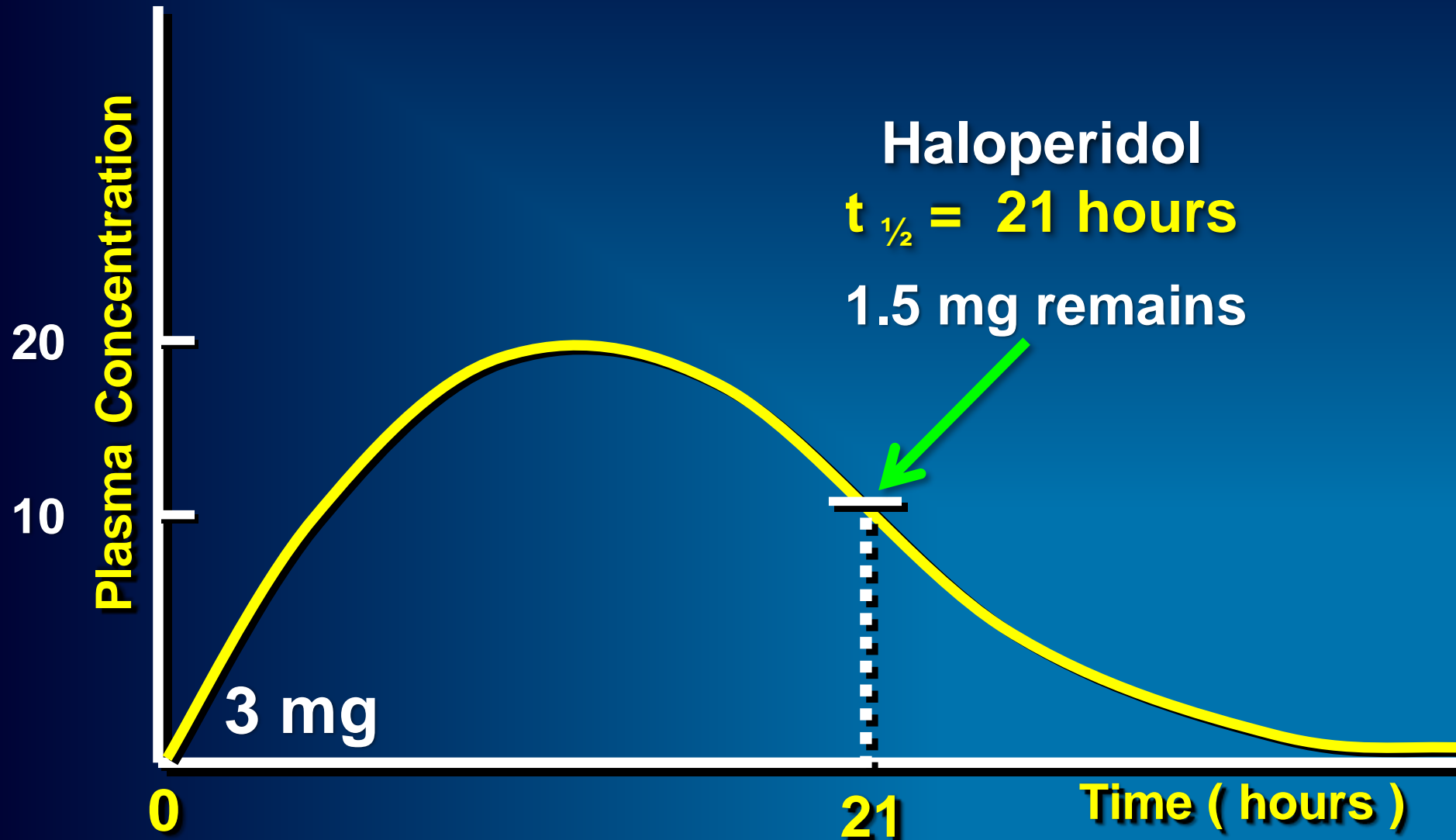
Han CS, Kim YK. (2004) Psychosomatics 45: 297
Skrobik YK, et al. (2004) Intensive Care Med 30: 444

Maintenance Dosing...

85 yo Woman

- Urinary tract infection, fever, Rx Cipro
- Mild delirium, w. confusion, agitation
 - Rx Haloperidol 1mg IV x 3 doses in 1 hour
 - settled, able to eat lunch, communicate normally
- 24 hours later, afebrile, no confusion or agitation
- Use haloperidol PRN if symptoms return

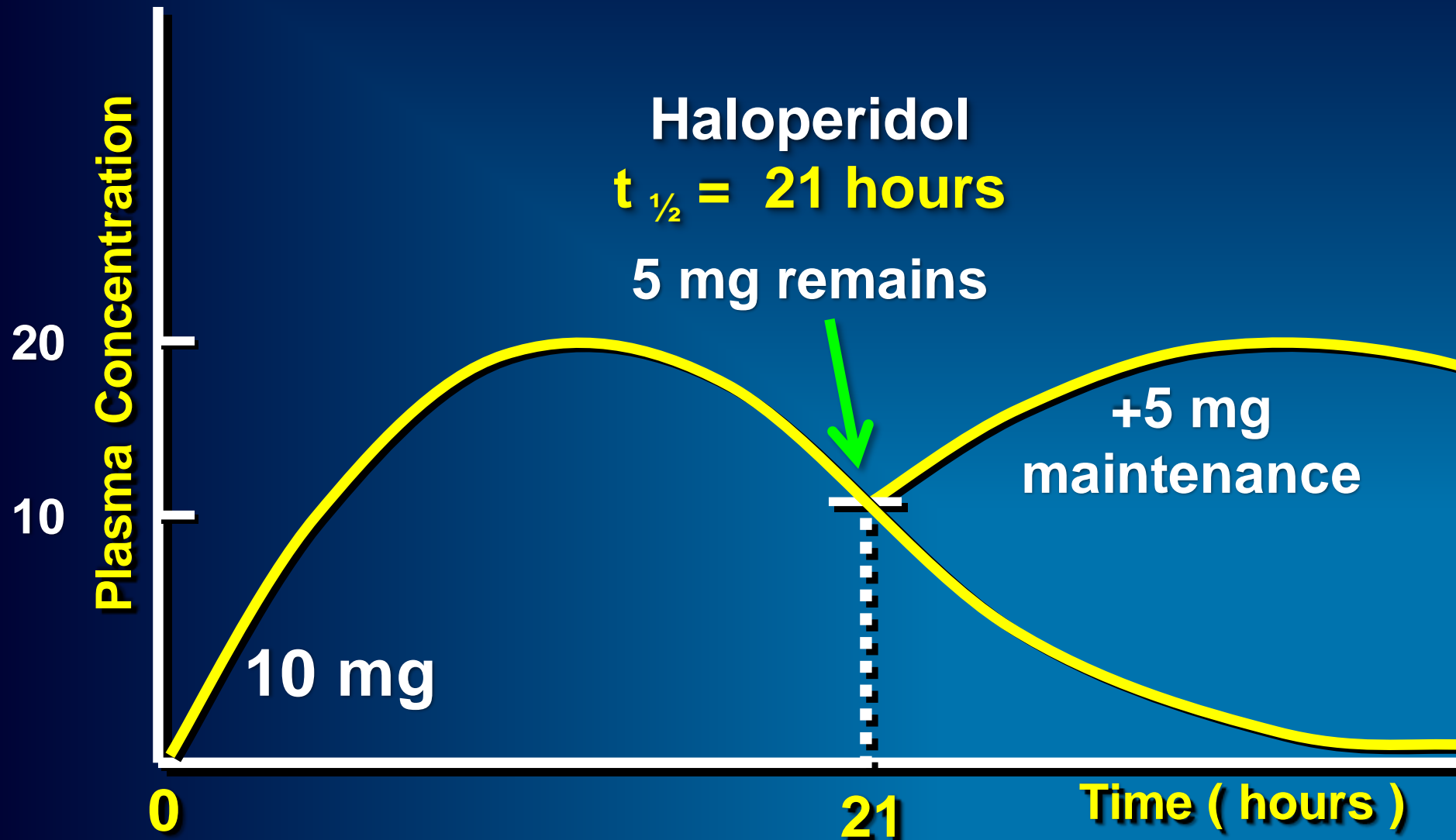
Half-Life ($t_{1/2}$)



75 yo Man

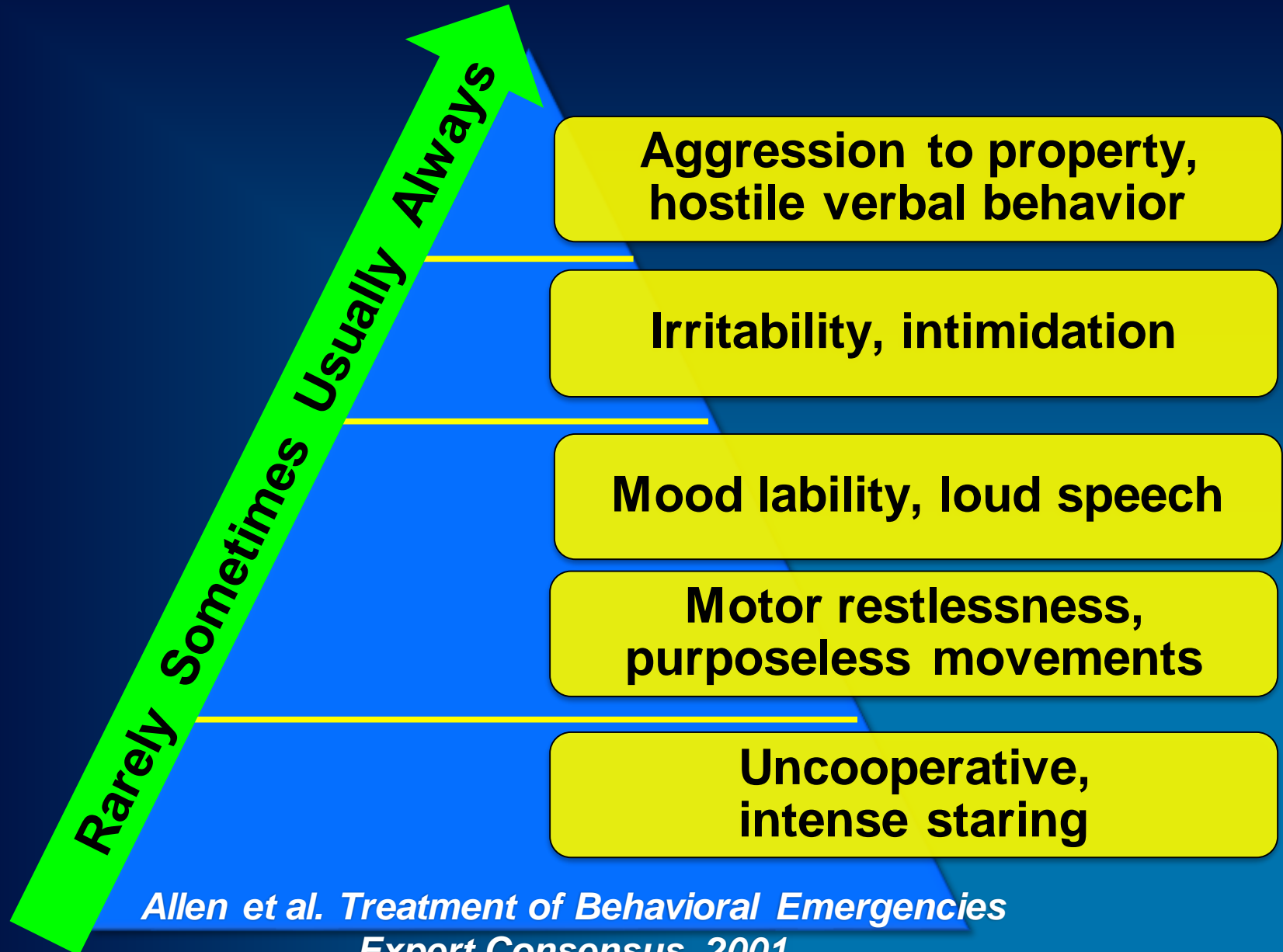
- Heart failure, atrial fibrillation
- Major cerebral infarct
- Moderate ongoing delirium, w. confusion, agitation
 - Rx Haloperidol 2mg SC x 3 doses
+ 4mg x 1 dose in 2 hour → settled
- Next days, mild agitation continues
- Maintenance haloperidol...

Half-Life ($t_{1/2}$)



Management of Severe Agitation...

When is Agitation an Emergency ?



*Allen et al. Treatment of Behavioral Emergencies
Expert Consensus, 2001*

Hierarchy of Treatments

Rarely Sometimes Usually Always

Seclusion and / or Restraint

Emergency Medication

Show of Force

Voluntary Medication

Verbal Intervention

Verbal Intervention

55 yo Man

- Lung cancer, bone, liver mets
- Found to have pneumonia
- Onset of severe agitation, wanting to take off his clothes, striking out at staff
- At risk of harming self / others

Will NEVER be any clinical trials

Severe Agitation...

If imminent risk of harm to self or others

Haloperidol 2 - 5 mg

+ Diphenhydramine* 50 - 100 mg x 1
(protects against EPS & adds sedation)

± Lorazepam 1 - 2 mg (or Midazolam)

In same syringe, mix very slowly in order

Lorazepam ► Haloperidol ► Diphenhydramine

...Severe Agitation Alternatives...

Chlorpromazine 50 - 100 mg SC

Increase dose by 50 mg once every

Time to Maximum Concentration ($t_{C_{max}}$)

until controlled

Up to 2 gm / day

**If SC administration painful, e.g., burning,
consider IV infusion with dexamethasone**

Likely don't need diphenhydramine

± Lorazepam

...Severe Agitation Alternatives

Olanzapine 5 - 10 mg IM

May repeat x 1 in 2 hr

May repeat x 1 again 4 hr later

Up to 30 mg / day (Expensive)

Ziprasidone 10 - 20 mg IM

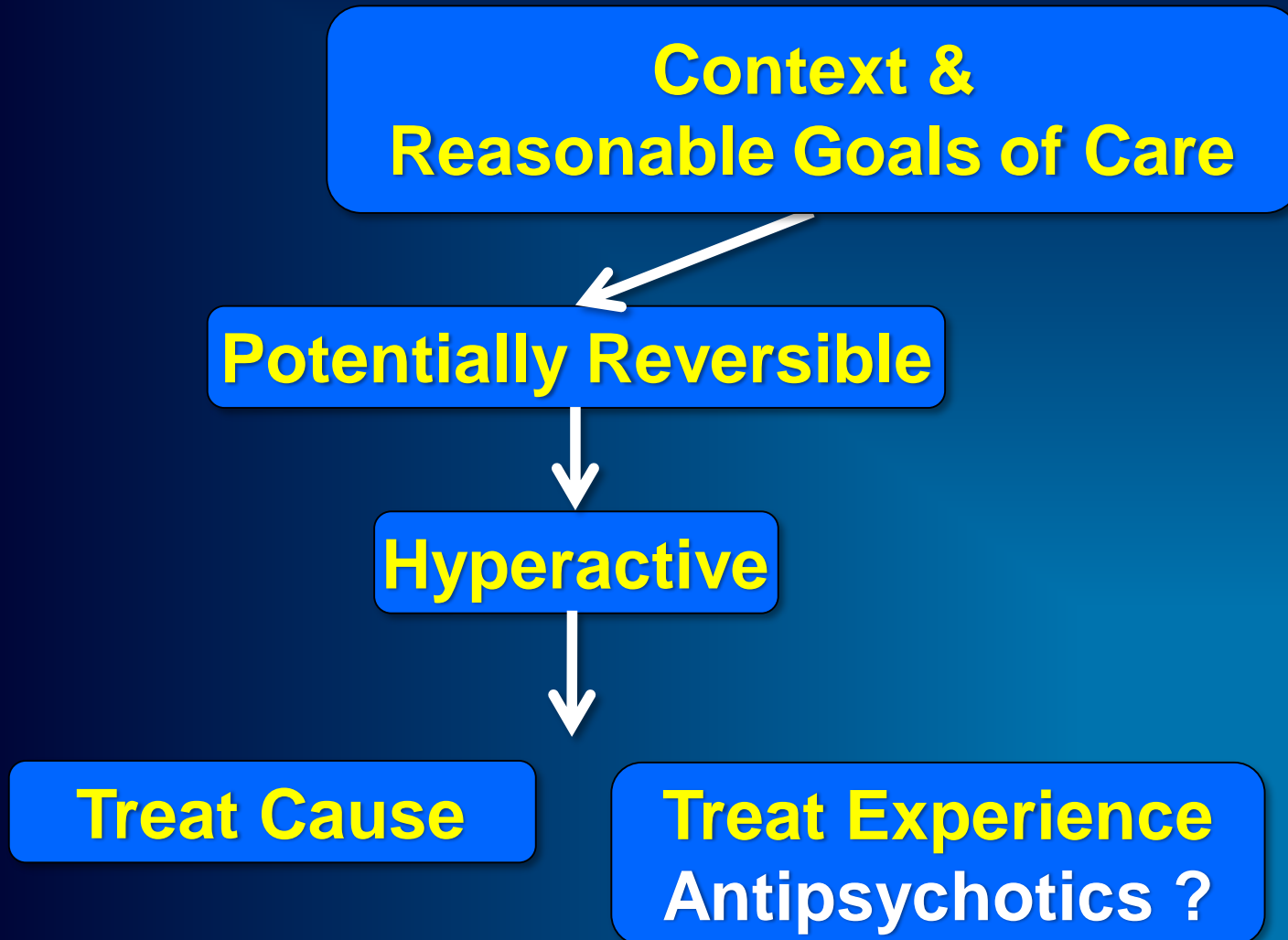
May repeat 10 mg every 2 hr

May repeat 20 mg every 4 hr

Up to 40 mg / day (Expensive)

New Evidence...

Potentially Reversible, Hyperactive



JAMA Internal Medicine | [Original Investigation](#)

Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care

A Randomized Clinical Trial

Meera R. Agar, PhD; Peter G. Lawlor, MB; Stephen Quinn, PhD; Brian Draper, MD; Gideon A. Caplan, MBBS; Debra Rowett, BPharm; Christine Sanderson, MPH; Janet Hardy, MD; Brian Le, MBBS; Simon Eckermann, PhD; Nicola McCaffrey, PhD; Linda Devilee, MBus; Belinda Fazekas, BN; Mark Hill, PhD; David C Currow, PhD

IMPORTANCE Antipsychotics are widely used for distressing symptoms of delirium, but efficacy has not been established in placebo-controlled trials in palliative care.

OBJECTIVE To determine efficacy of risperidone or haloperidol relative to placebo in relieving target symptoms of delirium associated with distress among patients receiving palliative care.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, parallel-arm, dose-titrated randomized clinical trial was conducted at 11 Australian inpatient hospice or hospital palliative care services between August 13, 2008, and April 2, 2014, among participants with life-limiting illness, delirium, and a delirium symptoms score (sum of Nursing Delirium Screening Scale behavioral, communication, and perceptual items) of 1 or more.

INTERVENTIONS Age-adjusted titrated doses of oral risperidone, haloperidol, or placebo solution were administered every 12 hours for 72 hours, based on symptoms of delirium.

[← Invited Commentary](#)[+ Supplemental content](#)

Risperidone, Haloperidol or Placebo...

- **Double blind, randomized control trial**
Placebo = best nursing care;
non-pharmacological Rx
- **11 Australian inpatient hospice or
hospital palliative care services**
- **6 years**
- **247 participants**
Mean age 74.9; 34 % women; 88.3 % cancer

...82 Risperidone, 81 Haloperidol or 84 Placebo...

- **Delirium symptom scores**

Risperidone > placebo, $p = 0.02$

Haloperidol > placebo, $p = 0.009$

- **Extrapyramidal side effects**

Risperidone > placebo, $p = 0.03$

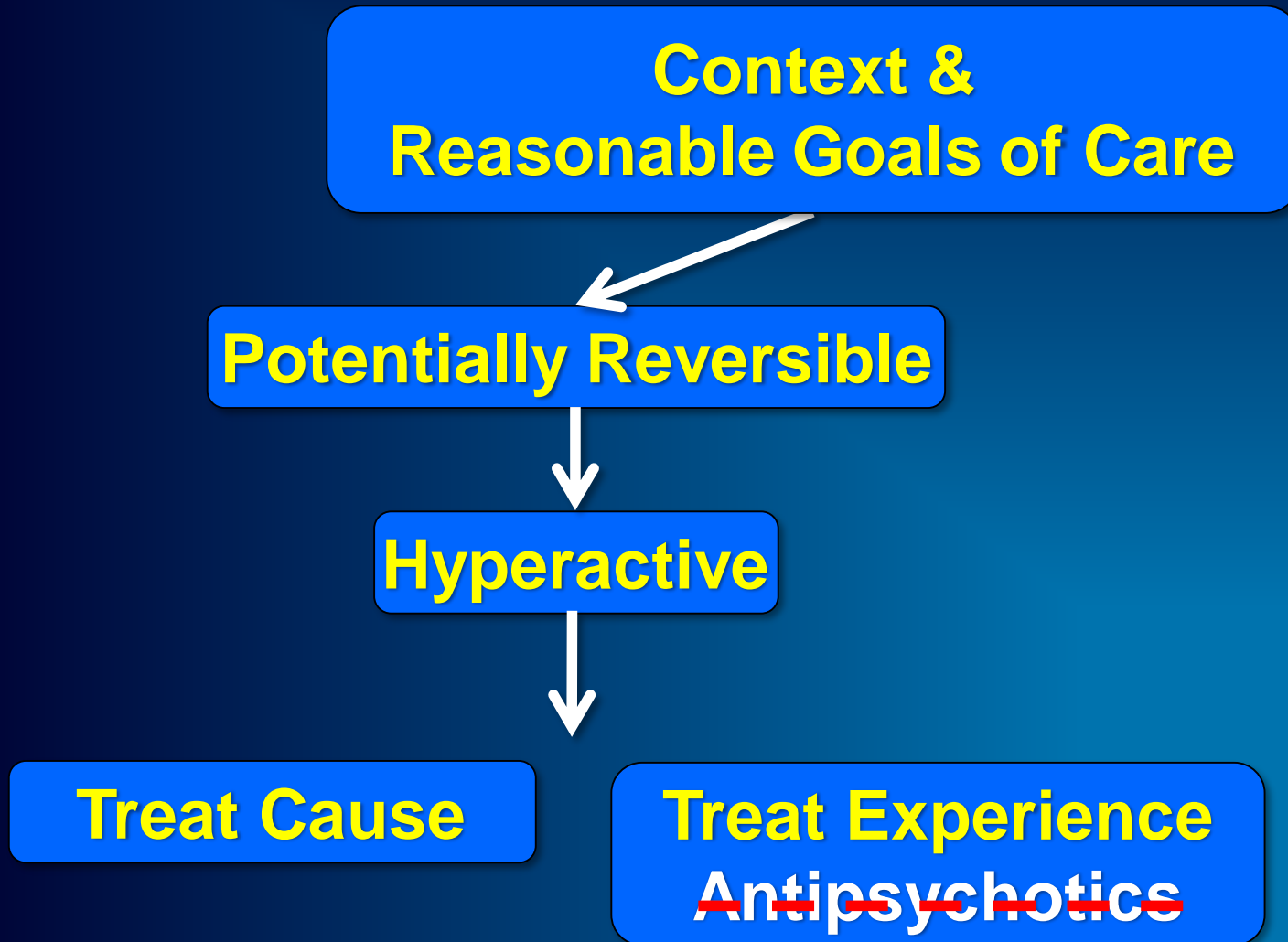
Haloperidol > placebo, $p = 0.01$

- **Overall survival**

Risperidone \approx placebo, $p = 0.14$

Haloperidol < placebo, $p = 0.003$

Potentially Reversible, Hyperactive



...Risperidone, Haloperidol or Placebo Recommendations from the Australian Group

- **Treat underlying cause**
- **Best nursing care**
- **Non-pharmacological Rx**
- **Avoid anti-psychotic medications**
- **For severe agitation / risk of harm**
Rx benzodiazepines to settle patient

Pediatric Delirium: Treatment...

Treatment is similar to adults:

- When able, treat underlying cause of delirium

- Environmental measures

Familiar objects and people at bedside

Frequent re-orientation

Establish and maintain daily routine

...Pediatric Delirium: Treatment

- Re-regulate sleep-wake cycle
- Decrease deliriogenic medications when able
- Use of psychotropic medications if needed



Improving People's Lives Through Innovations in Personalized Health Care

ICU Delirium

Jennica Johns



THE OHIO STATE UNIVERSITY

WEXNER MEDICAL CENTER

ICU Delirium is Common

In a multicenter international study:

- Prevalence of delirium = **32.3%** ⁽⁸⁾
- Incidence of delirium = **45% - 87%** ⁽⁸⁾

Yet we still believe it is frequently underdiagnosed ⁽¹⁾



Morbidity Associated with ICU Delirium

Increased risk of short term and long-term and cognitive dysfunction (1, 8, 17)

- 9-Fold higher incidence of cognitive impairment at discharge (17)
- One study noted **70%** had cognitive impairment at 1-year follow-up (8)



Mortality Associated with ICU Delirium

Increased 30 day all-cause mortality

- 39% for those with 3 days or more of delirium (18)

3.2-fold increase in 6-month mortality (17)

Each additional day an ICU patient spent in delirium was associated with a **10%** increased risk of death (17)



Common Medications for ICU Delirium

| Medication | Onset of Action | Tmax Response | Sedation | Of Note |
|-------------|-------------------------------|---------------|---------------------|--|
| Haldol | 1 hour (PO) 2-5 min (IV) | 4-7 days | Doses >2mg | Avoid in LBD and Parkinsons |
| Thorazine | 30-60 min (PO) 15 min (IV) | 5-14 days | Yes, significant | Avoid in ↓ BP or myelosuppressed Pts |
| Seroquel | 1.5 hours (PO) | 4-7 days | Yes, moderate | Preferred in Parkinsons |
| Risperidone | 1-3 hours (PO) | 4-7 days | Yes, small | 3mg/day is avg effective dose |
| Zyprexa | 6 hours (PO) | 3-7 days | Yes, moderate | Avoid in ↓ BP Least effect on QTc |
| Precedex | <5 minutes | 15-30 min | Yes | Avoid in ↓ BP or ↓ HR Can develop tolerance |



Systematic Review of Prevention and Treatment of Delirium in ICU

Journal of Critical Care Medicine 2015

- 25 articles reviewed, all RCTs
- Only **1 study** with reduced time to delirium resolution
 - Seroquel vs Placebo: 1 day vs. 4.5 days (n = 36)
- Only **1 study** with reduced LOS in ICU
 - Precedex vs. Haldol gtt: 1.5 d vs 6.5 d (n=20)
*Pilot Study
- No difference in mortality in any study



Any changes since that review?

Journal of Critical Care Medicine June 2017

Retrospective analysis of antipsychotic use for delirium in ICU (22)

- **No difference** in time to resolution of delirium
- **No difference** LOS in ICU
- **No difference** in mortality



Where do we go from here?

SCCM published Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium

Meant to be a “road map” to treating ICU delirium based on available evidence

Reads more as **what *not* to do...**
offers no pharmacologic suggestions for treatment

DELIRIUM

Assess delirium Q shift & prn

Preferred delirium assessment tools:

- CAM-ICU (+ or -)
- ICDS (0 to 8)

Delirium present if:

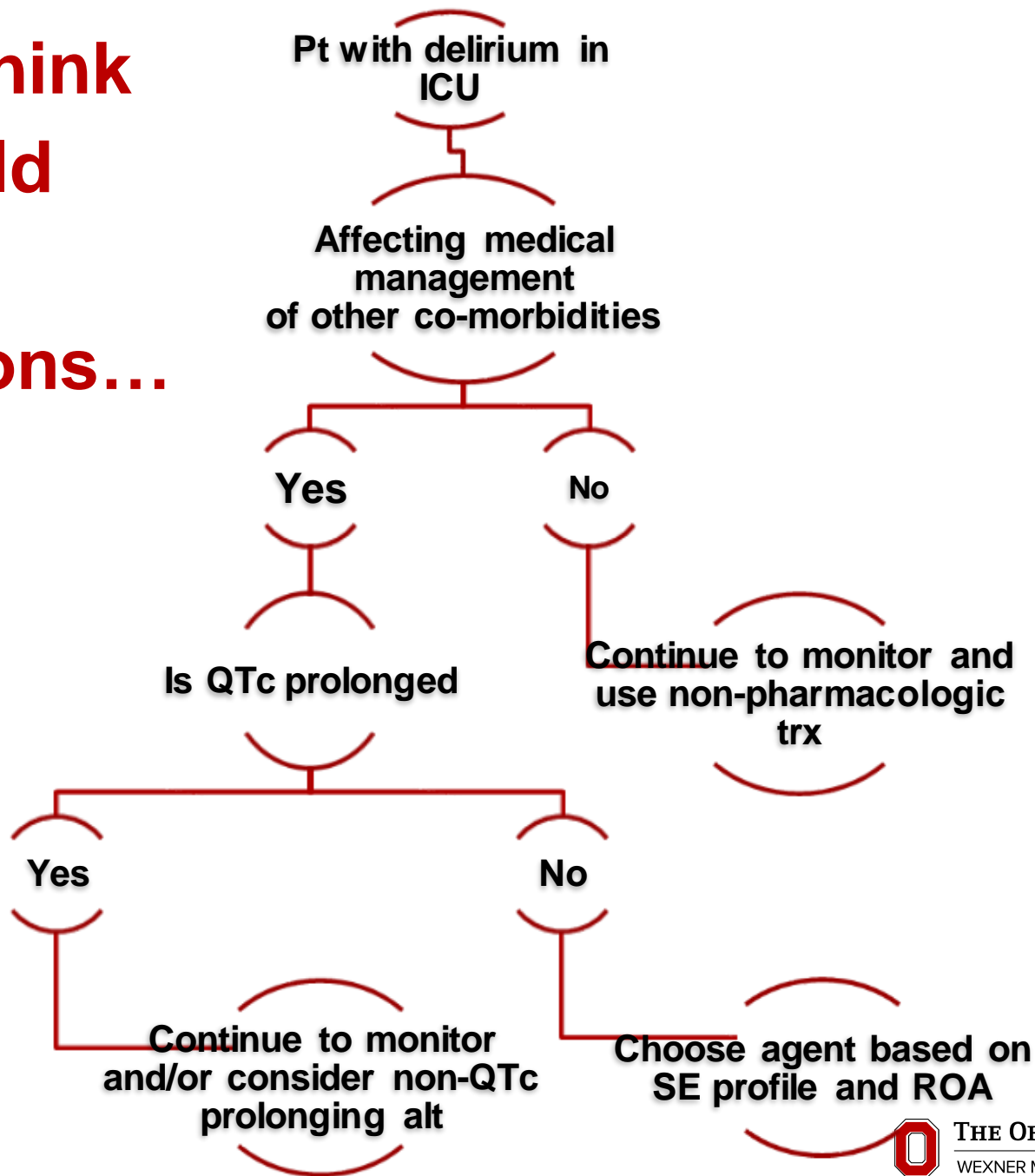
- CAM-ICU is positive
 - ICDS ≥ 4
-

- Treat pain as needed
 - Reorient patients; familiarize surroundings; use patient's eyeglasses, hearing aids if needed
 - Pharmacologic treatment of delirium:
 - Avoid benzodiazepines unless ETOH or benzodiazepine withdrawal is suspected
 - Avoid rivastigmine
 - Avoid antipsychotics if \uparrow risk of Torsades de pointes
-

- Identify delirium risk factors: dementia, HTN, ETOH abuse, high severity of illness, coma, benzodiazepine administration
- Avoid benzodiazepine use in those at \uparrow risk for delirium
- Mobilize and exercise patients early
- Promote sleep (control light, noise; cluster patient care activities; decrease nocturnal stimuli)
- Restart baseline psychiatric meds, if indicated



When I Think We Should Consider Medications...



Summary

ICU delirium is:

- Relatively common
- Associated with high morbidity (short and long term cognitive dysfunction)
- Associated with increased risk of mortality

There is **no evidence** to support anti-psychotic or Precedex use for treatment of delirium in the ICU, BUT we lack alternative treatment options at this time



Summary

- **Treat underlying cause**
- **Best nursing care**
- **Non-pharmacological therapies**
- **If agitation remains mild to moderate, trial of lower dose anti-psychotics**
- **If agitation severe, with risk of harm, Lorazepam + Haloperidol + Benadryl**

Delirium Management Decision Tree

Context &
Reasonable Goals of Care

Potentially Reversible

Hyperactive

Hypoactive

Medical Rx

Medical Rx

Successful

Unsuccessful

Irreversible

Hyperactive

Hypoactive

Medical Rx

Medical Rx

Irreversible Terminal, Hyperactive

Signs of Active Dying

```
graph TD; A[Signs of Active Dying] --> B[Irreversible]; B --> C[Hyperactive]; C --> D["Treat Experience  
Benzodiazepines,  
Barbiturates, Propofol"]; E[Support] --- D;
```

Irreversible

Hyperactive

Support

Treat Experience
Benzodiazepines,
Barbiturates, Propofol

When Irreversible Benzodiazepines Ideal

| Indication Drug | Anti - agitation | Sedation | Amnesia | Muscle relaxation | Anti - convulsant |
|--------------------|---------------------|----------|---------|----------------------|----------------------|
| Lorazepam | ✓ | ✓ | ✓ | ✓ | ✓ |
| Midazolam | ✓ | ✓ | ✓ | ✓ | ✓ |
| Antipsychotics | ✓ | ✓ / x | x | x | - |
| Opioids | x | x | x | x | - |

Sample Orders... For Agitation

With signs of the dying process:

Lorazepam – 1 mg PO q 60 min PRN

If 3 doses not effective, call MD

Do not exceed **40 mg in 24 hr**

Schedule today's PRNs tomorrow

3 x / day + same PRN schedule

Sample Orders... For Agitation

With signs of the dying process:

Midazolam – 0.2 mg / kg SC load

Then 0.1 mg / kg q 30 min x 2 PRN

Maintenance dose / hr =

25 % total dose to sedate

Consider alternative if need > 10 mg / hr

Breitbart W, Strout D. (2000) Clin Geriatr Med 16: 357

Rousseau P. (2004) J Support Oncol 2: 181

Ferris FD. (2004) Clin Geriatr Med 20: 641

Are you Hastening Death ?

- **Lethal Doses in Rats**
 - Lorazepam LD 50 = 4,500 mg / kg
 - Midazolam LD 50 = 215 mg / kg
- **Not concerned about**
 - Amnesia, confusion, restlessness
 - Hypotension
 - Respiratory depression
- **Nigel Sykes 2003**
 - Patients receiving sedation lived longer

When Benzodiazepines Fail

Phenobarbital

10 - 30 mg/kg IV/SC/PO/ PR loading dose then 160 - 800 mg PO/ PR tid or 10 - 100 mg/hrs IV/SC

Propofol

- Start 1 mg/kg/hr
- Titration in 0.5 mg/kg/hr steps within 15-30 min
- Max in palliative medicine literature 6 mg/kg/hr

***Lundström S, et al.
(2005) JPSM 30: 570***

Irreversible, Hyperactive

Goals of Care or
Work-up / Treatment Unsuccessful

```
graph TD; A[Goals of Care or Work-up / Treatment Unsuccessful] --> B[Irreversible]; B --> C[Hyperactive]; C --> D["Treat Experience<br/>Antipsychotics,<br/>Benzodiazepines,<br/>Barbiturates, Propofol"]; E[Support];
```

Irreversible

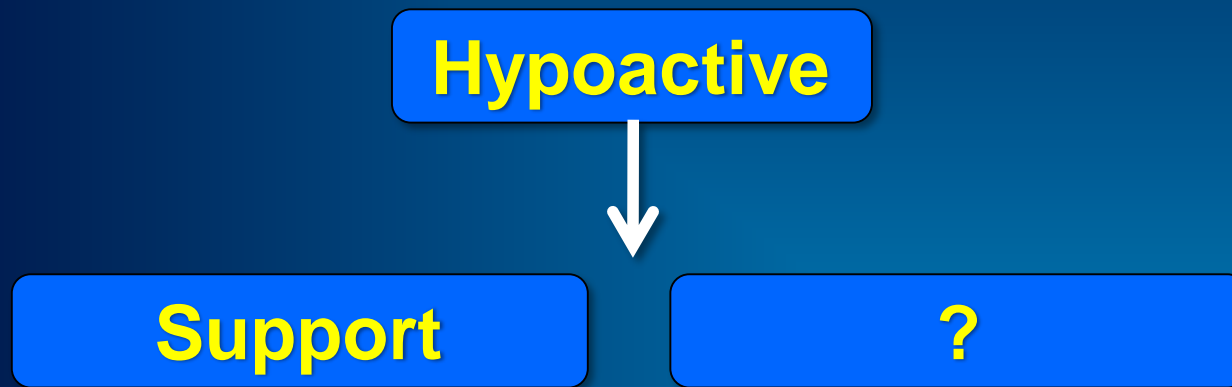
Hyperactive

Support

Treat Experience
Antipsychotics,
Benzodiazepines,
Barbiturates, Propofol

The Challenge

Reversible or Irreversible, Hypoactive



**Treat the Experience...
In Dementia...**

Agitation in Alzheimer's / Vascular / Mixed Dementia

Optimize Existing (if currently prescribed) Medications:

- Acetyl-cholinesterase inhibitors: Donepezil: 10 mg PO qhs
- Rivastigmine: 9.5 mg/24 hr transdermal patch
- NMDA receptor antagonist (memantine: 10 mg PO q12hr)

First Choices:

- Trazodone: 50-100 mg q1 hr prn. Max 600 mg/dose/24 hr. Schedule q8hr based on previous day's prn need.
- Gabapentin: 100 mg q1 hr prn. Schedule q8hr based on previous day's prn need, max does 3600 mg/d
- Propranolol: 5 mg q8hr, titrate by 5 mg tid to effect as tolerated, max dose: 320 mg/day
- Sertraline: 25 mg daily, titrate to effect by 25-50 mg q/wk. Max dose 200 mg.

Second Choices: Antipsychotics

- Haloperidol: 1 mg q30min SC prn (q60min PO). Max 10 mg/dose 100 mg/day
- Risperidone: 0.25 mg PO q1 hr prn. Max 6 mg/day
- Chlorpromazine: 50mg SC q30min prn (q60min PO/PR). Max 200 mg/dose 2000 mg/day

Note: Use lower, slower titrations in the elderly, frail, demented patient as safety allows.

PEARL

- Treat agitation like a breakthrough symptom, e.g., pain
- Provide breakthrough (PRN) doses on the **Time to maximum concentration (T_{Cmax})**
 - If 3 doses not effective, call MD (time-limited trials)
- Provide routine / maintenance doses once every **Half-life ($t_{1/2}$)**

Summary – It takes a team !

Assess potential reversibility

Treat the cause

**Use pharmacokinetics to guide dosing &
treat the experience rapidly**

Frontiers in Palliative Medicine

October 2017

Gandhi... You need to be the change you want to see in the world...



Palliative Care Interdisciplinary Curriculum

A Joint Initiative of the
Palliative Medicine Faculty & Staff of



THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER



NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.™

We gratefully acknowledge the support of

Award Number R25CA134309 from the National Cancer Institute

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health

Acknowledgements

The principals of the Palliative Care Interdisciplinary Curriculum gratefully acknowledge the support of

Award Number R25CA134309 from the National Cancer Institute

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Acknowledgment and appreciation are extended to faculty and staff of OhioHealth, the Ohio State University Wexner Medical Center, Nationwide Children's Hospital, the OhioHealth Research Institute, the Institute for Palliative Medicine at San Diego Hospice and the consultants who provided the inspiration and assisted in the development of this curriculum.

Attribution & Permission to Use

Attribution: Ferris FD, Humphrey L, Johns J. Delirium Management.

ISBN: 978-1-945872-93-8.

In Ferris FD, Gustin J, Humphrey L (eds). Palliative Care Interdisciplinary Curriculum. Copyright © 2017 Frank D Ferris. PCIC ISBN: 978-0-9884318-1-2

Permission to use, reproduce or adapt any presentations and other content within the **Palliative Care Interdisciplinary Curriculum (PCIC)** is granted for non-commercial educational purposes only, provided that the above attribution statement and copyright are displayed.

Commercial entities presenting not-for-profit educational programs based on the PCIC Curriculum must not use the PCIC materials with products, images or logos from the commercial entity.

Commercial entities presenting for-profit educational programs using any part of the PCIC Curriculum, must only do so with written permission from Drs. Frank D. Ferris, Jillian Gustin or Lisa Humphrey, Principals, PCIC.

Contact the PCIC Principals...

Frank D. Ferris, MD

**Executive Director, Palliative Medicine,
Research & Education**

Kobacker House, OhioHealth

800 McConnell Dr

Columbus, OH, USA 43214-3463

Phone: +1 (614) 533-6299

Fax: +1 (614) 533-6200

Frank.Ferris@OhioHealth.com

Jillian Gustin, MD

**Fellowship Program Director,
Hospice and Palliative Medicine
Fellowship**

Division of Palliative Medicine

Ohio State University Medical Center

5th Floor McCampbell Hall

1581 Dodd Dr

Columbus, OH, USA 43210

Phone: +1 (614) 293-2957

Fax: +1 (614) 688-3700

Jillian.Gustin@osumc.edu

...Contact the PCIC Principals

Lisa Humphrey, MD

Director, Hospice and Palliative Medicine

Nationwide Children's Hospital

700 Children's Drive, A1061

Columbus, OH 43205

Phone: +1 (614) 722- 5139

Fax:+1 (614) 355- 2878

Lisa.Humphrey@NationwideChildrens.org

References for ICU Delirium

- 1) Pandharipande, P. P., Patel, M. B., & Barr, J. (2014). Management of pain, agitation, and delirium in critically ill patients. *Polish Archives of Internal Medicine*, 124(3), 114-123. doi:10.20452/pamw.2136
- 2) Dubois MJ, Bergeron N, Dumont M, et al. Delirium in an intensive care unit: a study of risk factors. *Intensive Care Med*. 2001; 27: 1297-1304
- 3) Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med*. 2001; 27: 1892-1900.
- 4) Pisani MA, Murphy TE, Van Ness PH, et al. Characteristics associated with delirium in older patients in a medical intensive care unit. *Arch Intern Med*. 2007; 167: 1629-1634.
- 5) Pisani MA, Kong SYJ, Kasl SV, et al. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med*. 2009; 180: 1092-1097.
- 6) Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004; 291: 1753-1762.
- 7) Barr J, Fraser GL, Puntillo K, et al. Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit. *Crit Care Med*. 2013; 41: 278-280.
- 8) Cavallazzi R, Saad M, Marik PE. Delirium in the ICU: an overview. *Ann Intensive Care*. 2012;2(1):49. doi: 10.1186/2110-5820-2-49.
- 9) Trogrlić Z, van der Jagt M, Bakker J, Balas MC, Ely EW, van der Voort PH, et al. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. *Crit Care*. 2015;19:157. doi: 10.1186/s13054-015-0886-9.



10. Martinez FE, Anstey M, Ford A, et al. Prophylactic Melatonin for Delirium in Intensive Care (Pro-MEDIC): study protocol for a randomised controlled trial. *Trials*. 2017;18:4. doi:10.1186/s13063-016-1751-0.
11. Litton, E., Carnegie, V., Elliott, R., & Webb, S. A. (2016). The Efficacy of Earplugs as a Sleep Hygiene Strategy for Reducing Delirium in the ICU. *Critical Care Medicine*, 44(5), 992-999. doi:10.1097/ccm.0000000000001557
12. Serafim, R. B., Bozza, F. A., Soares, M., Brasil, P. E., Tura, B. R., Ely, E. W., & Salluh, J. I. (2015). Pharmacologic prevention and treatment of delirium in intensive care patients: A systematic review. *Journal of Critical Care*, 30(4), 799-807. doi:10.1016/j.jcrc.2015.04.005
13. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)
14. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R: Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001,286(21):2703–2710.
15. van Eijk MM, van Marum RJ, Klijn IA, de Wit N, Kesecioglu J, Slooter AJ: Comparison of delirium assessment tools in a mixed intensive care unit. *Crit Care Med* 2009, 37(6):1881–1885.
16. Gusmao-Flores D, Salluh JI, Chalhub RA, et al. *The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies*. *Crit Care* 2012;16:R115. [doi:10.1186/cc11407](https://doi.org/10.1186/cc11407)
17. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS: Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004, 291(14):1753–1762.
18. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW, SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group: Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit Care Med* 2010, 38(12):2311–2318.



19. Nitchingham, A., Kumar, V., Shenkin, S., Ferguson, K. J., & Caplan, G. A. (2017). A systematic review of neuroimaging in delirium: predictors, correlates and consequences. *International Journal of Geriatric Psychiatry*. doi:10.1002/gps.4724
20. Pol, I. V., Iterson, M. V., & Maaskant, J. (2017). Effect of nocturnal sound reduction on the incidence of delirium in intensive care unit patients: An interrupted time series analysis. *Intensive and Critical Care Nursing*. doi:10.1016/j.iccn.2017.01.008
21. Matsumoto-Miyazaki, J., Ushikoshi, H., Miyata, S., Miyazaki, N., Nawa, T., Okada, H., . . . Minatoguchi, S. (2017). Acupuncture and Traditional Herbal Medicine Therapy Prevent Delirium in Patients with Cardiovascular Disease in Intensive Care Units. *The American Journal of Chinese Medicine*, 45(02), 255-268. doi:10.1142/s0192415x17500161
22. Weaver, C. B., Kane-Gill, S. L., Gunn, S. R., Kirisci, L., & Smithburger, P. L. (2017). A retrospective analysis of the effectiveness of antipsychotics in the treatment of ICU delirium. *Journal of Critical Care*. doi:10.1016/j.jcrc.2017.05.034
23. Coyle, N., Breitbart, W., Weaver, S., & Portenoy, R. (1994). Delirium as a contributing factor to “crescendo” pain: Three case reports. *Journal of Pain and Symptom Management*, 9(1), 44-47. doi:10.1016/0885-3924(94)90146-5
24. Santos, E., Cardoso, D., Apóstolo, J., Neves, H., Cunha, M., & Rodrigues, M. (2015). Effectiveness of haloperidol prophylaxis in critically ill patients with a high risk for delirium: a systematic review of quantitative evidence protocol. *The JBI Database of Systematic Reviews and Implementation Reports*, 13(7), 83. doi:10.11124/jbisrir-2015-2301
25. Pun, B. T., & Ely, E. W. (2007). The Importance of Diagnosing and Managing ICU Delirium. *Chest*, 132(2), 624-636. doi:10.1378/chest.06-1795

