

NEUROLOGIC
OUTCOMES
— *of* —
SURGERY &
ANESTHESIA

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Does the Mind Really Matter?

OXFORD

Department of Anesthesiology

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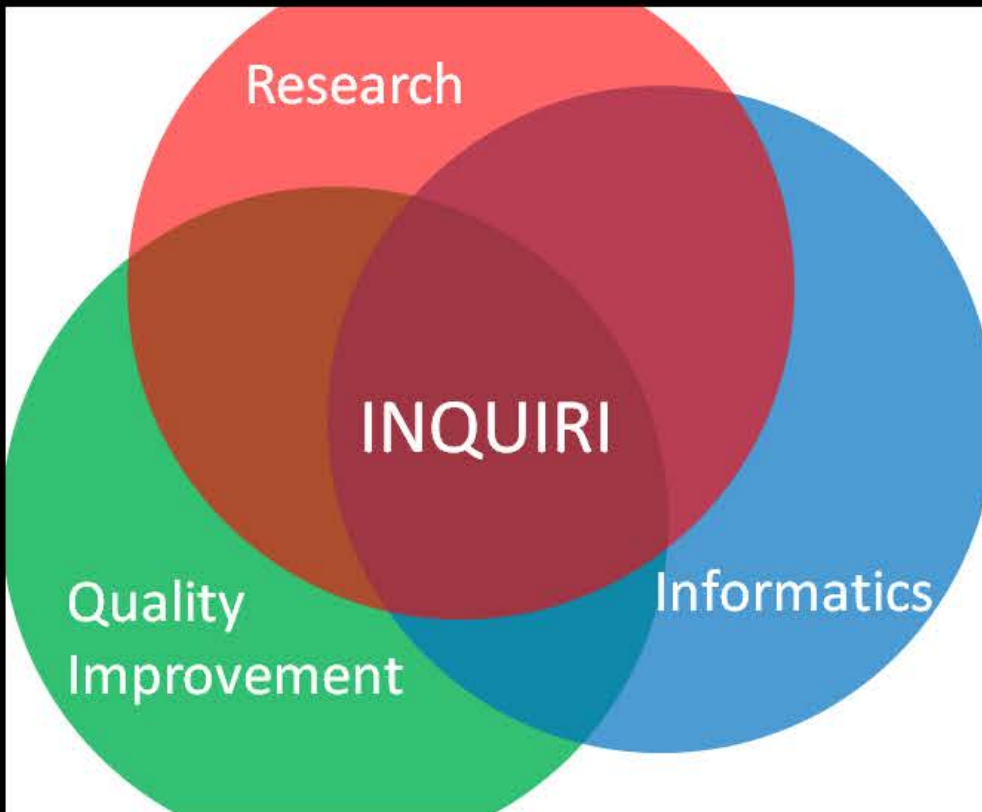
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12 December 2014

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Multicenter Perioperative Outcomes Group





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ABOUT US RESEARCH EDUCATION FACULTY PATIENT CARE HISTORY



STS
National Database
Using data to drive quality



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Conflicts of Interest & Bias

No financial conflicts of interest



Thank You



MSQC

Michigan Surgical Quality Collaborative



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The image shows a presentation slide for the MSQC Conference with the text 'MSQC Conference' and 'The Power of Collaboration' alongside a city skyline. A man in a suit is speaking at a podium with the MSQC logo, addressing an audience.

Transforming Surgical Outcomes Together

Neurological Outcomes: Mind the Mind

- More & persistent pain
- Worse quality of life (mental health)
- Delirium
- Cognitive decline (early)
- Covert & overt stroke
- Falls
- PTSD
- Depression
- Seizures
- Nerve injury
- Spinal cord injury
- Ischemic optic neuropathy
- Cognitive decline (persistent)
- Anesthetic Neurotoxicity

Neurological Outcomes: Positive Paradigm Shift

- Less pain
- Better cognitively
- Better QOL (mental health)

The Scope of this Talk

- Conceptual discussion about tracking outcomes
- Focus on Delirium as an important (orphan) postoperative outcome
- A few words on PTSD
- Tying it all together

A photograph of three surgeons in an operating room, wearing blue scrubs, blue bouffant caps, and white surgical masks. They are looking down at a patient, with their hands visible at the bottom of the frame. The background is slightly blurred, showing medical equipment.

Many people fall under the scalpel

250 000 000 have surgery annually.

40 000 000 have surgery annually in the US.

1% 30-day mortality -> 400,000 deaths per yr

Why do our patients have surgery?

- To cure a condition?
- To decrease pain?
- To improve quality of life?
- **To prolong life?**
- Told by doctor to have surgery?



**Are we in perioperative
medicine fulfilling our mission?**

Perioperative Reality

- By providing world-class healthcare
 - We **cannot know** if we are achieving this as we do not know our patients' perioperative outcomes.
- By continuously improving our practices
 - We **cannot improve** our practices if we do not know what is wrong with them.

How are our surgical patients doing?

- In our hospital?
- When they go home?
- Within the first few months?
- Within the first year?
- Thereafter?

Patient-Reported Outcomes

- 2009 - Incorporated into FDA guidelines
- 2010 - Establishment of PCORI
- 2013 - Major journals call for such data to be collected regularly in clinical settings
 - Basch et al. JAMA 2013; 310:139-140
 - Manary et al. NEJM 2013; 368:201-203

Surgery
Outcomes

```
graph TD; A[Surgery Outcomes] --> B[Positive]; A --> C[Negative];
```

A flowchart with a dark gray rectangular box at the top containing the text "Surgery Outcomes". Two arrows originate from the bottom of this box. A light green arrow points down and to the left towards a large light green rectangular box containing the word "Positive". A light red arrow points down and to the right towards a smaller light red rectangular box containing the word "Negative".

Positive

Negative

Positive
Outcomes

Known

Leaves the
Hospital

Unknown

Feels better
Improved quality of life
Condition is cured
More functional
Less pain
Life is prolonged

Negative Outcomes

Known

- Hospital death
- Hospital medical complication
- Hospital costs (e.g. ICU)

Unknown

- Post hospital death
- Post hospital medical complication
- Feels worse
- Decreased quality of life
- Condition is not cured
- Less functional
- More pain
- Readmission
- Cost to individual & society

Possible
Perception

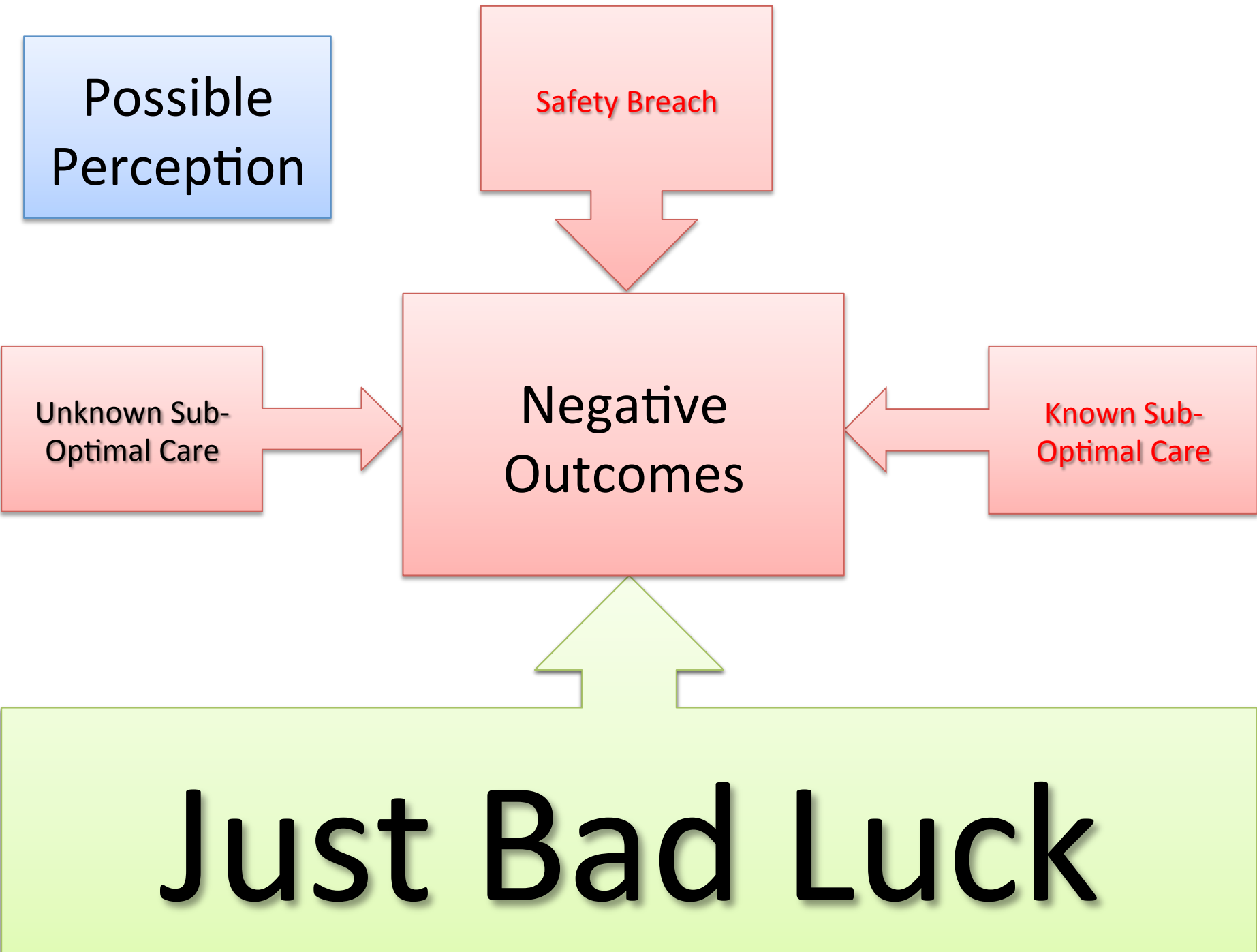
Safety Breach

Unknown Sub-
Optimal Care

Negative
Outcomes

Known Sub-
Optimal Care

Just Bad Luck



Unknown Sub-
Optimal Care

```
graph LR; A[Unknown Sub-Optimal Care] --> C[Negative Outcomes]; B[Safety Breach] --> C; D[Optimal Care] --> C; E[Known Sub-Optimal Care] --> C; F[Alternative Perception] --- E
```

The diagram illustrates a process flow. On the left, a large red box contains the text 'Unknown Sub-Optimal Care'. A large red arrow points from this box to a central red box labeled 'Negative Outcomes'. Above the central box, a smaller red box labeled 'Safety Breach' has a red arrow pointing down to the central box. Below the central box, a green box labeled 'Optimal Care' has a green arrow pointing up to the central box. To the right of the central box, a red box labeled 'Known Sub-Optimal Care' has a red arrow pointing left to the central box. Above this right box is a blue box labeled 'Alternative Perception'.

Safety Breach

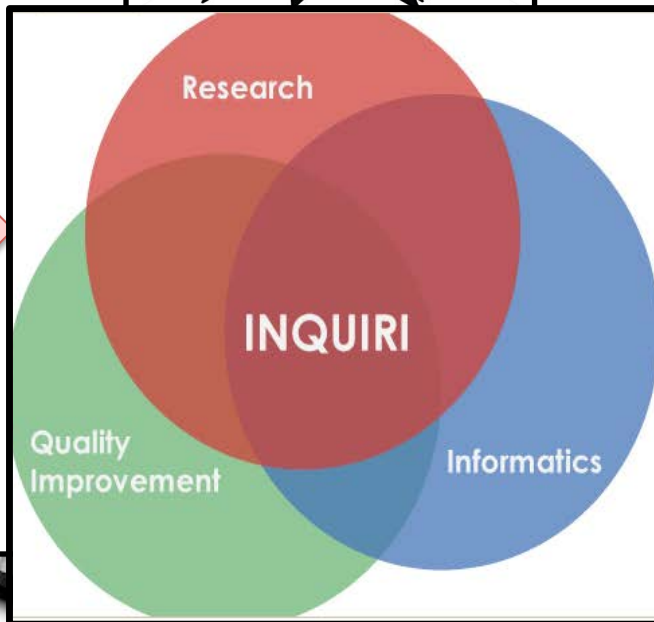
Negative
Outcomes

Optimal Care

Alternative
Perception

Known
Sub-
Optimal
Care

Unknown Sub-
Optimal Care



Alternative
Perception

Known
Sub-
Optimal
Care



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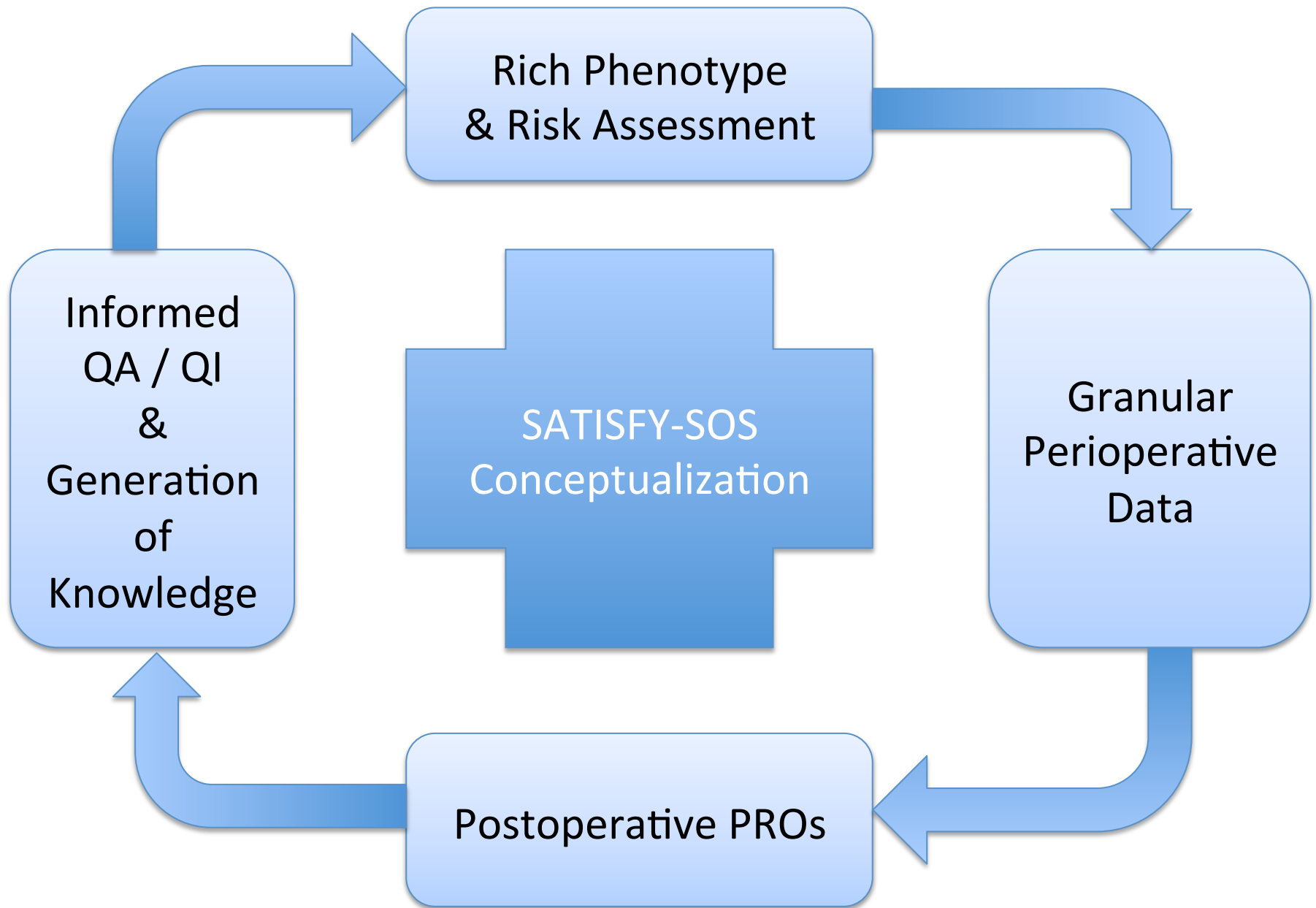
SATISFY

SURGICAL OUTCOMES SURVEYS

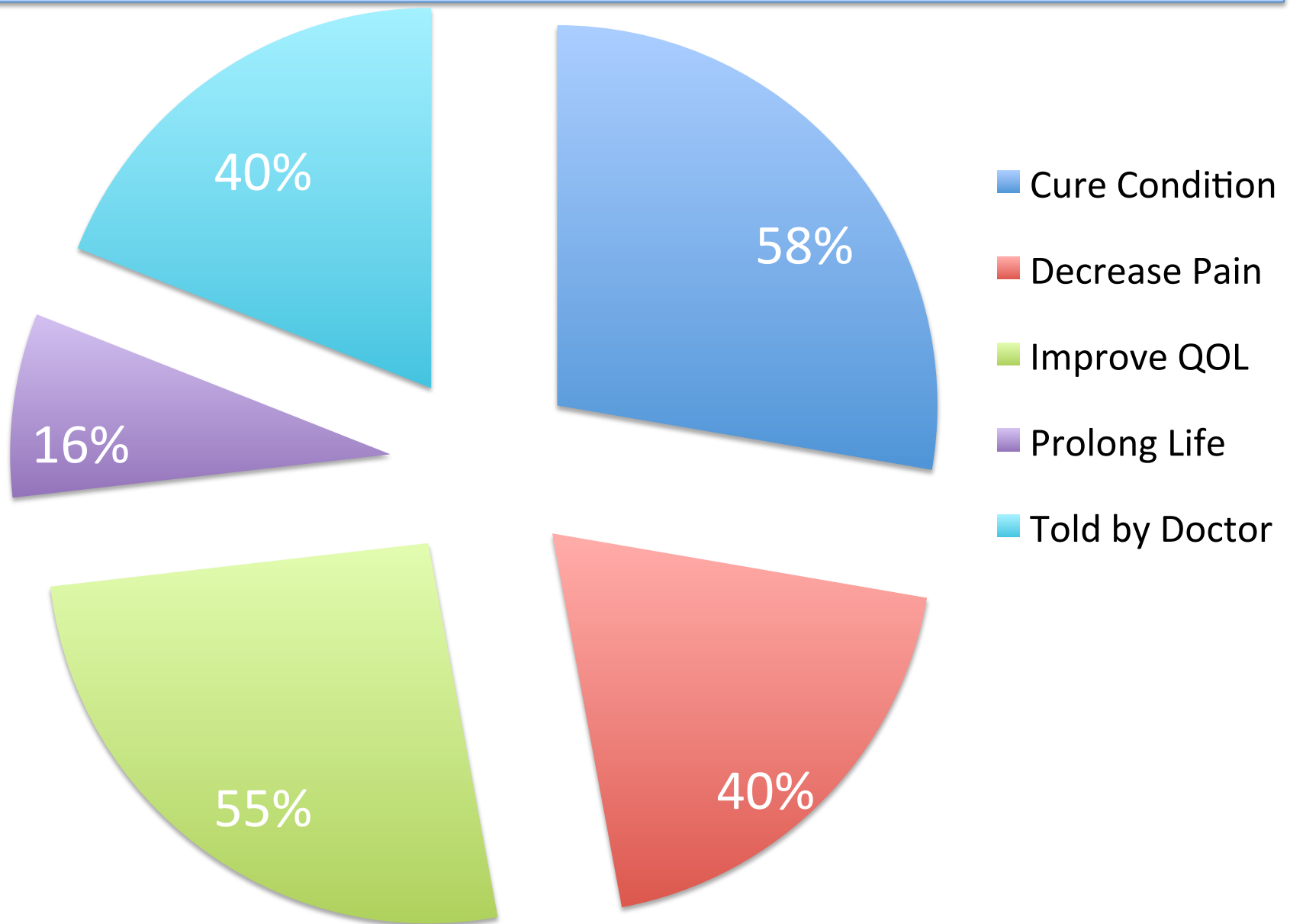
TRACKING YOUR HEALTH & WELL-BEING
AFTER SURGERY



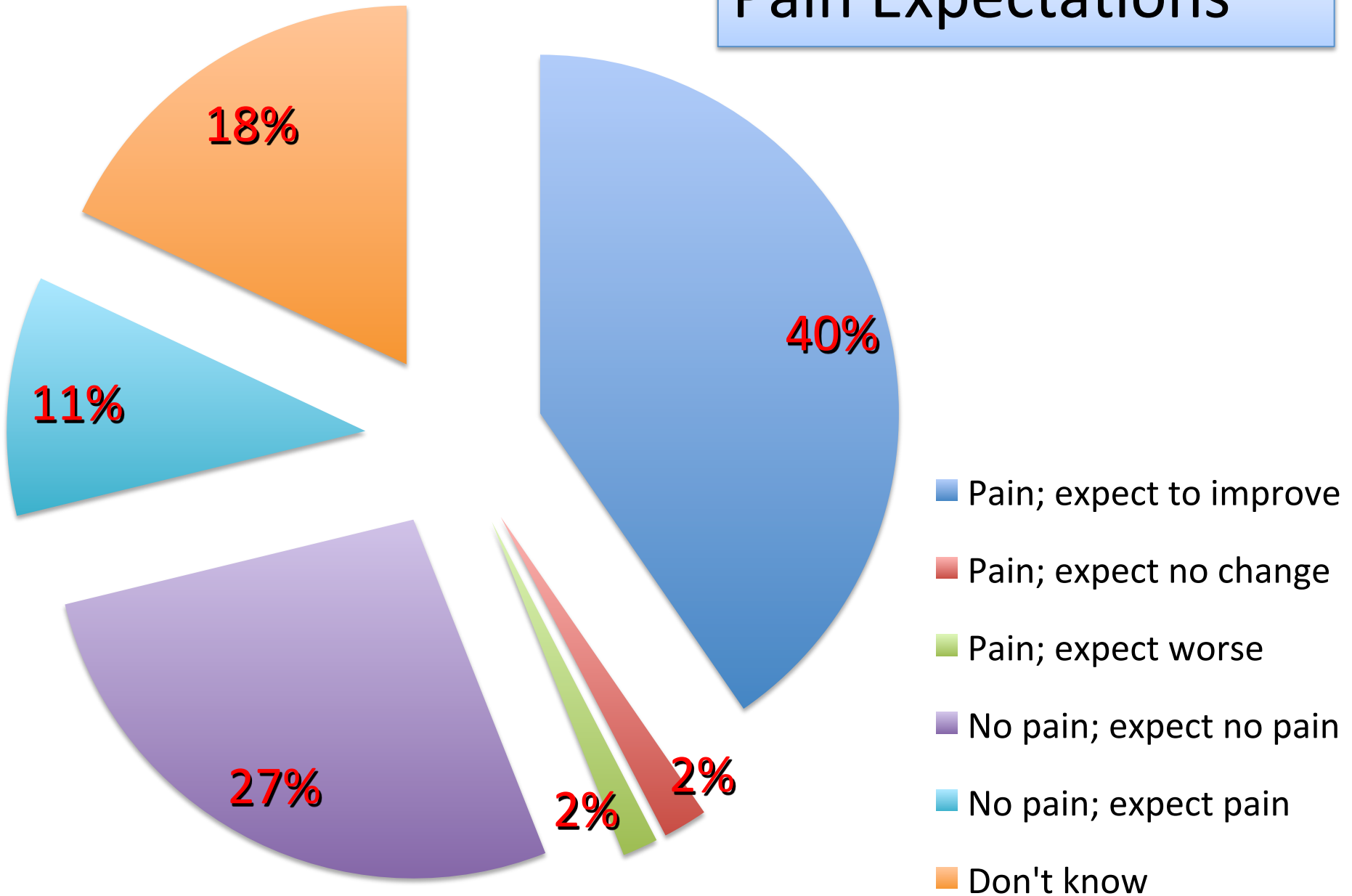
N A T I O N A L L E A D E R S I N M E D I C I N E



Why do our patients have surgery?



Pain Expectations



Positive Outcomes

N~6,000

30-90 Days Postoperative

No Longer Unknown

Feels better

- Physical Health: 54%
- Emotional / Mental Health: 40%

Improved QOL: 62%

Less pain: 15%-65%

Back to work: 70%

Negative Outcomes

N~6,000

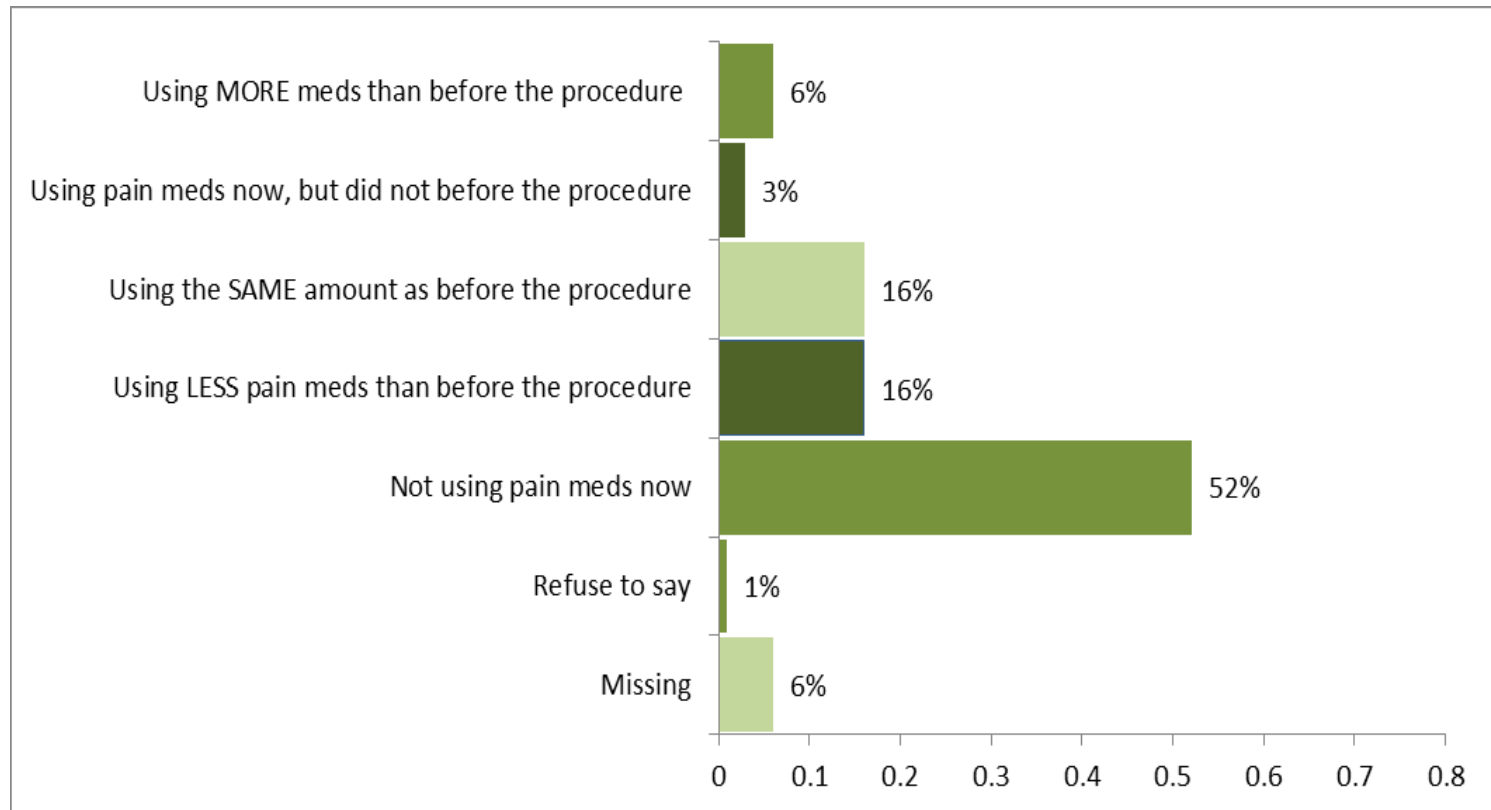
No Longer Unknown

Less Functional

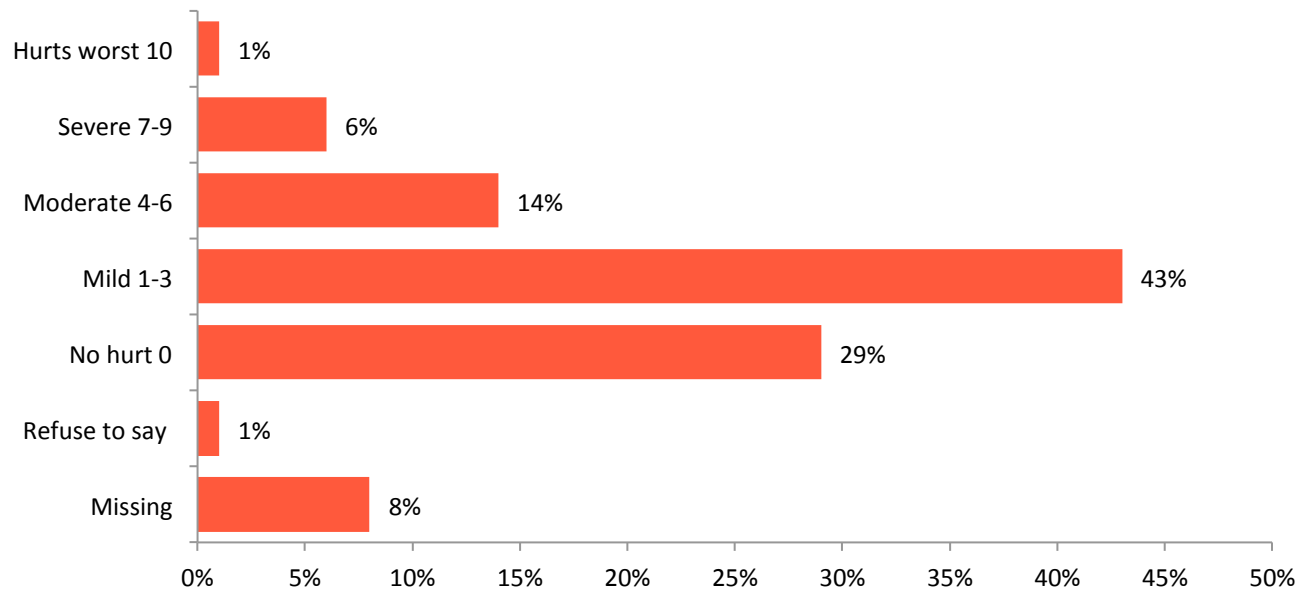
Need Help

Feeding	4%
Bathing	6%
Grooming	4%
Dressing	10%
Bowels	9%
Bladder	16%
Toilet Use	8%
Transfers	4%
Mobility	10%
Stairs	12%

30-day pain medication use



30-day Pain scores



Delirium



My Contentions

- Delirium is one of the **most important postoperative problems**.
- It is generally a **marker** of brain vulnerability.
- Delirium may occur as a **manifestation** of SIRS.
- Delirium can be caused with bad practice, but **cannot always be prevented** with good practice.

What is delirium?

Disturbance in consciousness

- Reduced awareness of environment
- Inattention

Change in cognition

- Memory deficit
- Disorientation
- Hallucinations

Short period of time

- Hours to days
- Tends to fluctuate

Medical illness

- Results from the direct physiological consequences of a general medical condition

Which phenotype?

Hyperactive delirium

- Patient is agitated and confused
- Perhaps hallucinations
- May self-extubate or pull out lines



15%

Hypoactive delirium

- Patient appears calm or drowsy
- Disorganized thought
- Recognized by family but often not medical staff



85%

Delirium - Incidence

- Up to 80% of the sickest ICU populations.
- 40%-50% elderly after major surgery.

Rudolph JL. Circulation 2009;119(2):229-36.

Robinson TN. Annals of surgery 2009;249(1):173-8.

Robinson TN. American journal of surgery 2008;196(5):670-4.

Pathophysiology

- Neurotransmitter imbalance
- **Inflammation**
- Impaired oxidative metabolism
- Availability of large neutral amino acids

Girard TD. Critical care 2008;12 Suppl 3:S3.

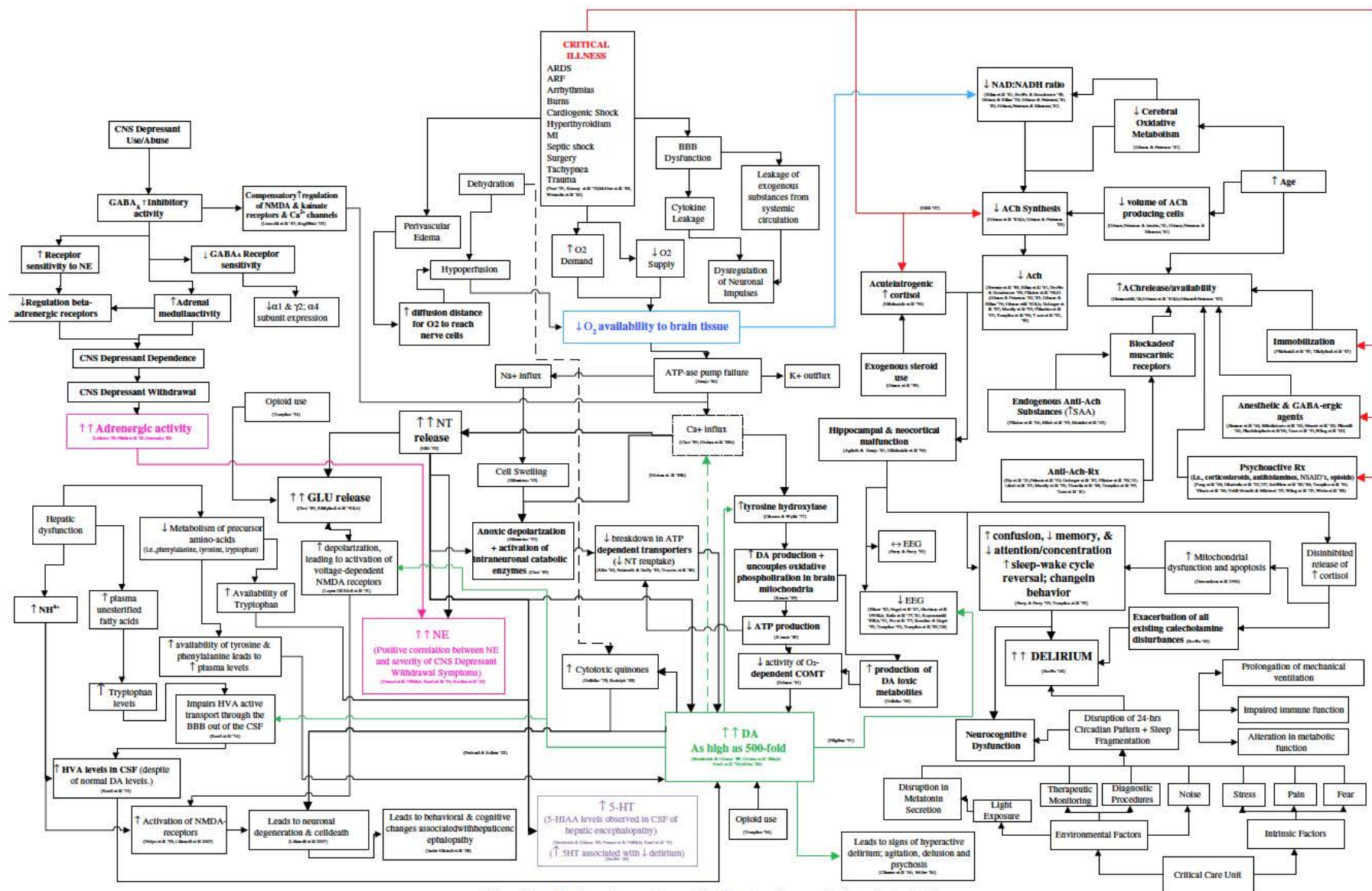


Fig. 1. A basic pathoetiological model of delirium.

Precipitating factors

Pain

Infection

Withdrawal

Sodium, hydrogen, glucose, oxygen, CO₂

Temperature, BP

Benzodiazepines, drugs

Stroke, seizures

Endocrine

Medications cause delirium

Different drugs implicated in different studies

Benzodiazepines (e.g., lorazepam) - dose-related?

Corticosteroids

Morphine

Maybe propofol and fentanyl

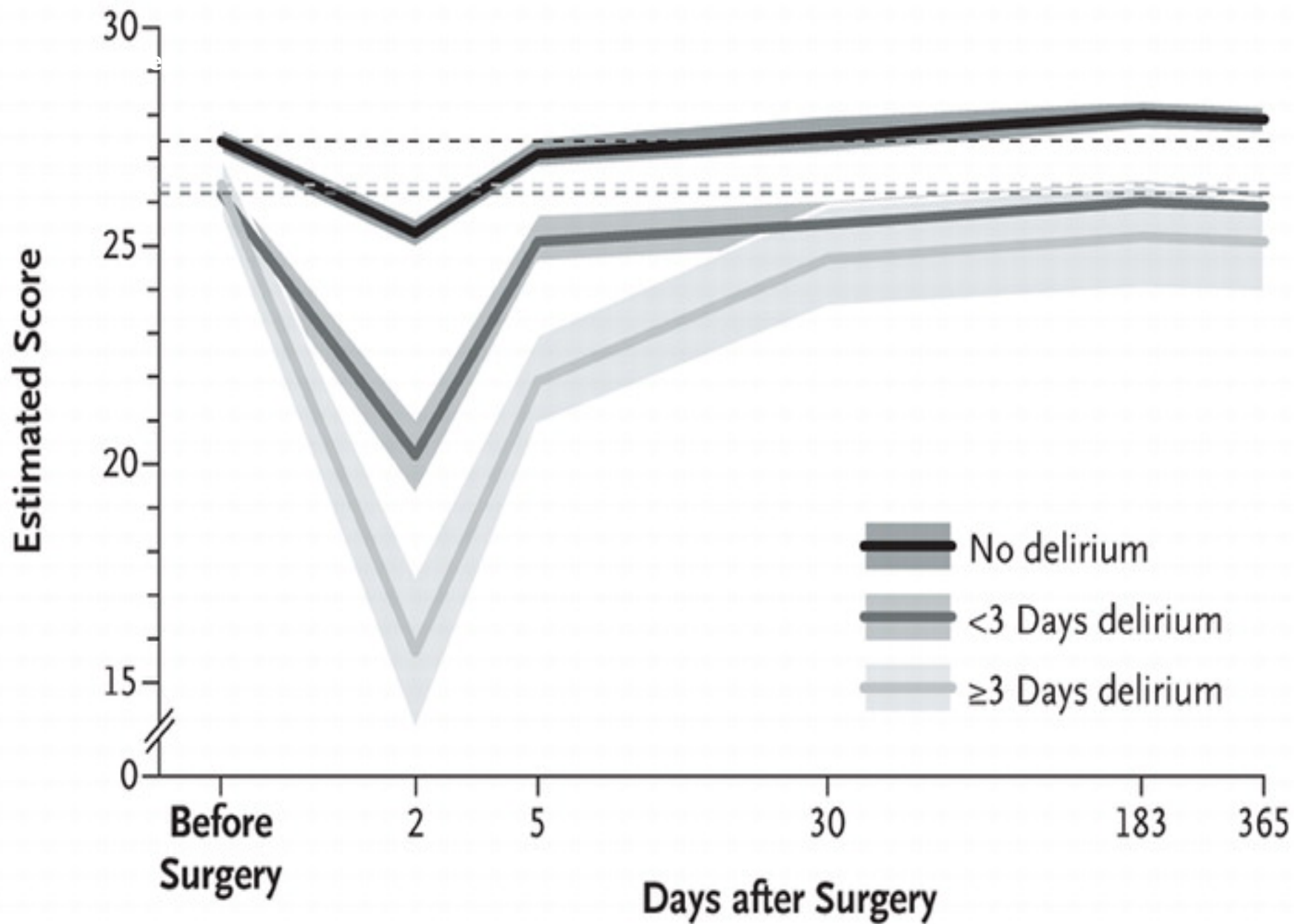
Anticholinergics

Dubois ICM 2001;27:1297-1304,
Marcantonio. JAMA, 1994;272:1518-1522,
Gadreau J of Clin Onc. 23(27):6712-6718
Pandharipande et al. Anesth;104(1):21-26,2006

Does it matter?

Increased ICU LOS	8 vs. 5 days
Increased Hosp. LOS	21 vs. 11 days
Increased time on vent	9 vs. 4 days
Higher costs	\$22 000 vs. \$13 000
3 fold increased risk of death	
Possible long term cognitive impairment	

Ely ICM 2001;27:1892-1900,
Ely JAMA 2004;291:1753-1762,
Lim SM, CCM 2004;32:2254-2259,
Milbrandt E, CCM 2004;32:955-962,
Jackson Neuropsychology Review 2004;14:87-98



Delirium: important prognostic implications

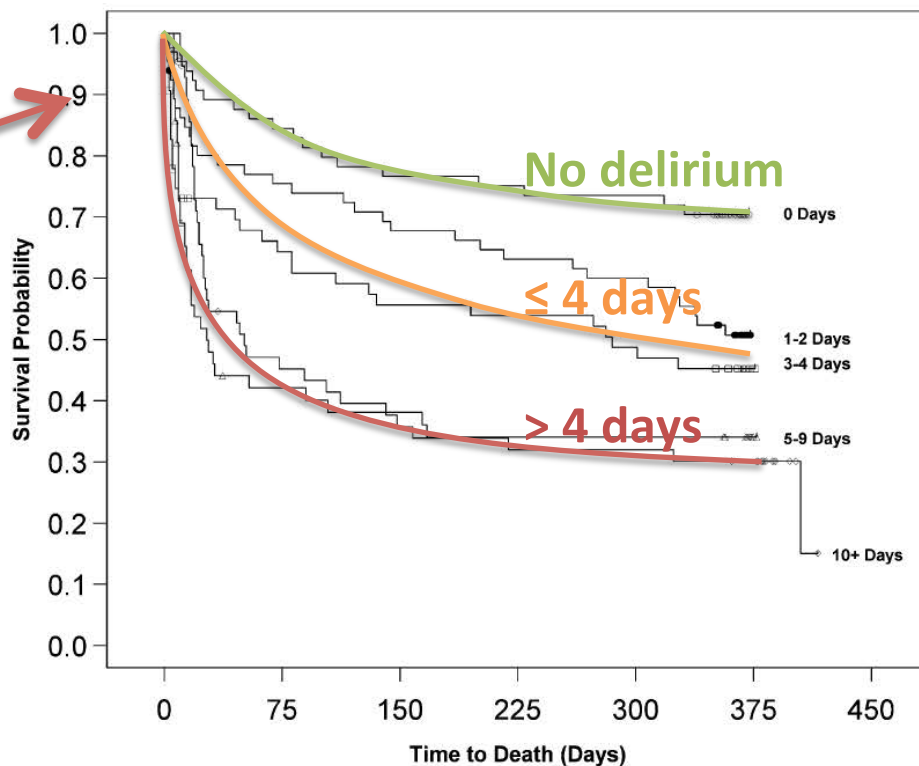
Death: HR 2.0 (1.6 – 2.3)

Institutionalization:

HR 2.4 (1.7 – 3.3)

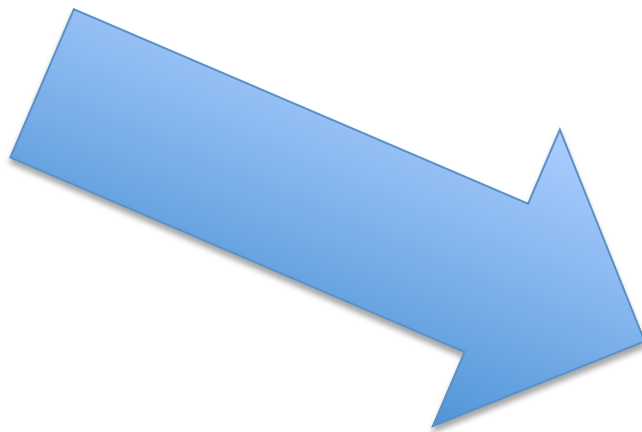
Dementia: HR 10 (3 – 35)

After adjustment for age,
sex, comorbidity, and
baseline dementia.



Longer delirium \rightarrow higher risk
of death (HR 1.1 per day)

delirium



Delirium screening method

- Confusion Assessment Method for the ICU
- Can be performed in intubated patients
- 81% sensitive, 96% specific

Disturbance in
consciousness

- Richmond Agitation and Sedation Scale

Change in
cognition

- Inattention

S A V E A H A A R T

- Disorganized thinking

- Does a stone float on water?
- Are there fish in the sea?

Short period of time

- By history

Medical illness

- By definition

Can Delirium be Prevented?

limited or not modifiable

patient characteristics

age
alcohol
gender
living single at home
smoking

chronic pathology

predisposing cardiac disease
predisposing cognitive impairment
predisposing pulmonary disease

admission via emergency room
admission via transfer
isolation
no clock
no visible daylight
no visit
open intensive care
physical restraints

length of stay
fever
high risk of mortality
internal medicine
no normal food
number of perfusions
psychoactive medication
sedation
TISS 28
tubes and catheters

environment

acute illness

more modifiable

**Non-
Modifiable
Factors**

**Potentially
Modifiable
Factors**

**More
Modifiable
Factors**

Characteristics

- Age >60
- Prior social issues

Chronic Disease

- Cognitive
- Heart disease
- Lung disease

Surgery

- Less invasive

Anesthesia

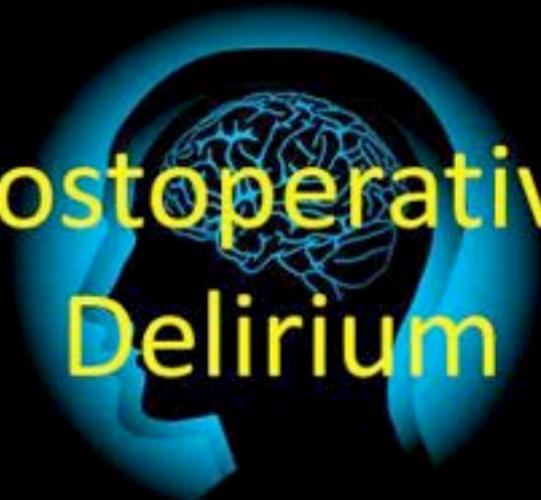
- Less Exposure

Environment

- Noisy
- Uncomfortable
- Unnatural light

Precipitants

- Dehydration
- Infection
- Withdrawal
(alcohol, medicines)



**Postoperative
Delirium**

Management: treat causes & reduce risks

Treat underlying infection and CCF

Correct metabolic disturbance & hypoxia

Frequent reorientation of patient

Goal directed sedation/analgesia &/or daily wakeup.

Stop sedation daily

Spontaneous breathing trial daily

Early mobilisation

Attention to optimising sleep patterns

Can Delirium be Prevented?

Research evidence on effectiveness of interventions to prevent delirium is sparse.

Based on a **single study**, a program of proactive geriatric consultation **may** reduce delirium in hip fracture surgery patients.

Prophylactic low dose haloperidol **may** reduce delirium in hip surgery.

Siddiqi N, Stockdale R, Britton AM, Holmes J.
Interventions for preventing delirium in hospitalised patients.
Cochrane Database Syst Rev. 2007 Apr 18;(2):CD005563.

Delirium epidemiology in critical care (DECCA): an international study

- A 1-day point-prevalence study was undertaken in 104 ICUs from 11 countries in South and North America and Spain.
- The prevalence of delirium was 32.3%.
- Delirium: higher SOFA ($P = 0.004$) and SAPS3 scores ($P < 0.0001$).
- Delirium: increased ICU ($P = 0.002$) and hospital **mortality** ($P = 0.0017$), and longer ICU ($P < 0.0001$) and hospital **LOS**; $P < 0.0001$).
- **Previous use of midazolam** ($P = 0.009$) was more frequent in patients with delirium.

Sedation with dexmedetomidine

- **MENDS:** More days alive without delirium or coma (7.0 vs 3.0; $P = .01$) & a lower prevalence of coma (63% vs 92%; $P < .001$) than lorazepam.
- **SEDCOM:** The prevalence of delirium was **54% (n = 132/244) vs 76.6% (n = 93/122)** in midazolam-treated patients (difference, 22.6% [95% CI, 14% to 33%]; $P < .001$).
- **MIDEX & PRODEX:** Among ICU patients receiving prolonged mechanical ventilation, dexmedetomidine was not inferior to midazolam & propofol in maintaining light to moderate sedation. Reduced duration of mechanical ventilation compared with midazolam & improved patients' ability to communicate pain compared with midazolam & propofol. **More adverse effects were associated with dexmedetomidine.**

Perioperative dexmedetomidine improves outcomes of cardiac surgery

Perioperative dexmedetomidine use was associated with a decrease in postoperative mortality up to 1 year & decreased incidence of postoperative complications and **delirium** in patients undergoing cardiac surgery.

Anesthesia

Ketamine & Delirium

Hudetz JA, Patterson KM, Iqbal Z, Gandhi SD, Byrne AJ, Hudetz AG, Warltier DC, Pagel PS.

Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2009 Oct;23(5):651-7.

(1/29 vs. 10/29. Δ (ARR) = **31%**)

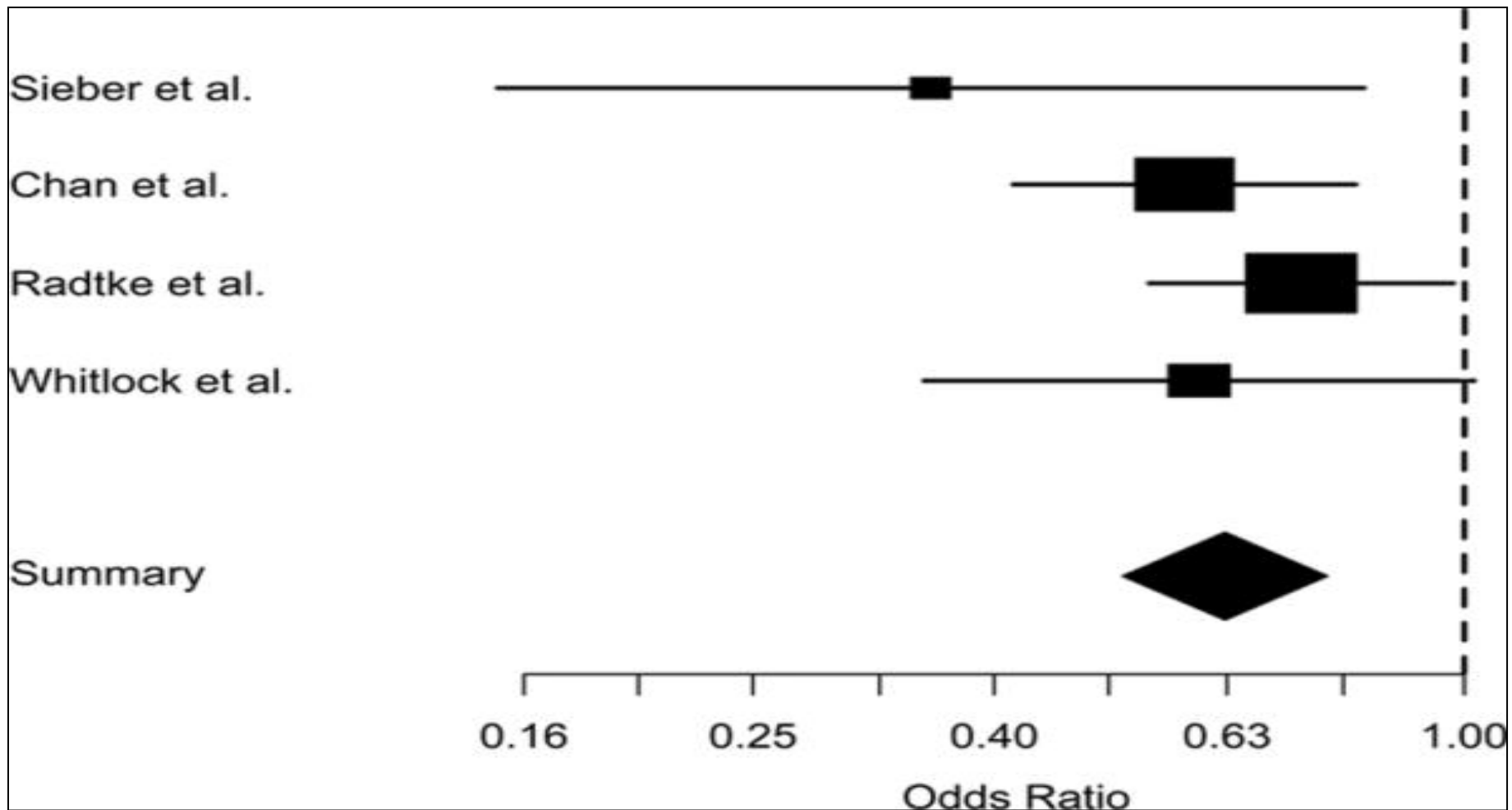
[95% CI, 8.4% to 51.2%]

Deep Sedation -> Delirium

- Spinal anesthesia in combination with light, rather than deep, sedation substantially reduced the incidence of postoperative delirium in elderly patients undergoing hip fracture repair surgery.
- ARR of delirium of 21% (95% confidence interval [CI], 3% to 37%).

BIS-guided Anesthesia Decreases POD & POCD in Non-Cardiac Surgery

- BIS values were lower in the control group, 36 (31 to 49) vs. 53 (48 to 57), $P < 0.001$.
- BIS-guided anesthesia reduced propofol delivery by 21% & volatile anesthetics by 30%.
- Fewer patients with delirium in the BIS group (15.6% vs. 24.1%, $P = 0.01$).
- BIS group had a lower rate of POCD at 3 months (10.2% vs. 14.7%; $P = 0.025$).

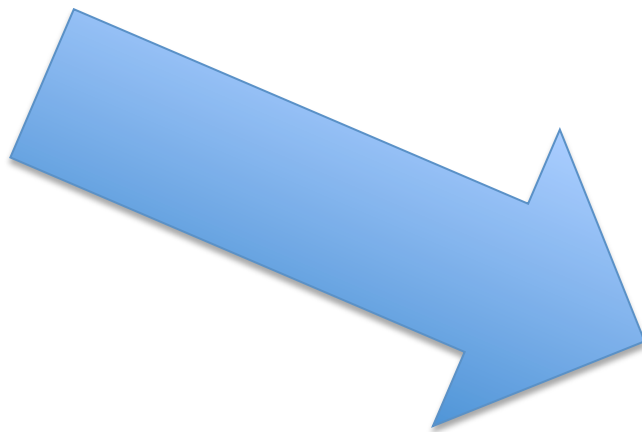


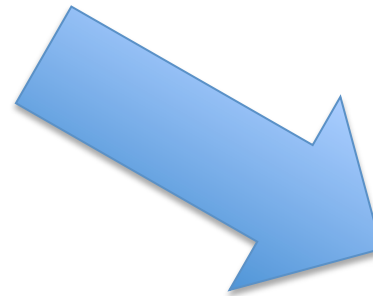
Meta-analysis of randomized controlled trials assessing postoperative delirium with intraoperative Bispectral Index (BIS) guidance of anesthesia compared with an alternative approach (i.e., usual care or an alternative protocol). Odds ratios <1 favor BIS guidance.

Postoperative Delirium in a Substudy of Cardiothoracic Surgical Patients in the BAG-RECALL Clinical Trial.

Whitlock, Elizabeth; MD, MSc; Torres, Brian; Lin, Nan; Helsten, Daniel; Nadelson, Molly; Mashour, George; MD, PhD; Avidan, Michael; MB, BCh
 Anesthesia & Analgesia. 118(4):809-817, April 2014.

delirium





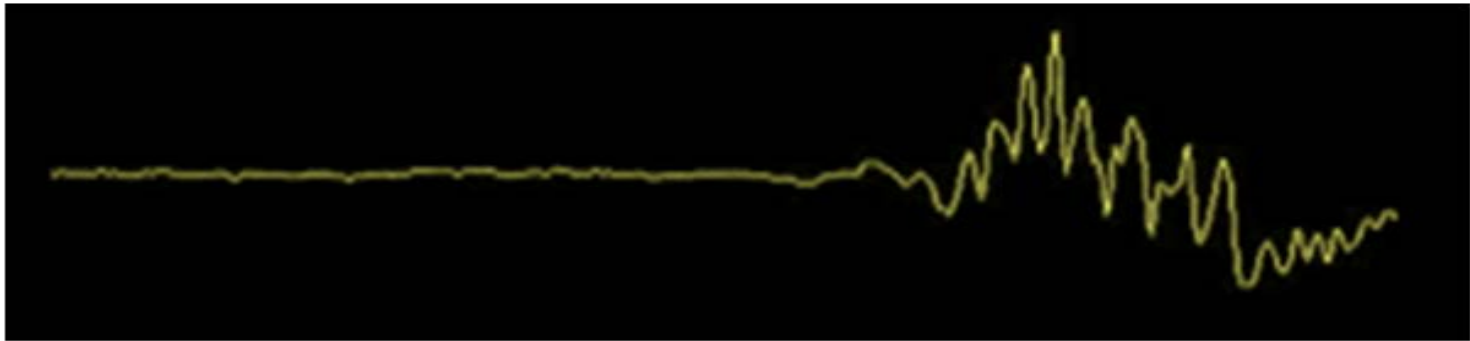
Provocative Hypothesis:
Deep anesthesia causes delirium & death

Association between intraoperative electroencephalographic suppression and postoperative mortality

M. Willingham^{1†}, A. Ben Abdallah¹, S. Gradwohl¹, D. Helsten¹, N. Lin², A. Villafranca³, E. Jacobsohn³,
M. Avidan¹ and H. Kaiser^{1*†}

Burst Suppression

- EEG pattern characterized by periods of suppression alternating with bursts of high amplitude activity



- Seen during anesthesia but not natural sleep
 - Also seen in anoxic brain injury, induced hypothermia, some forms of epilepsy

Association between intraoperative electroencephalographic suppression and postoperative mortality

M. Willingham^{1†}, A. Ben Abdallah¹, S. Gradwohl¹, D. Helsten¹, N. Lin², A. Villafranca³, E. Jacobsohn³, M. Avidan¹ and H. Kaiser^{1*†}

Independent Predictors of Burst Suppression (Two-Part Nonlinear Mixed Effects Model – binary portion)

Risk Factor	Odds Ratio (95% CI)	P value
End-tidal anesthetic (per 0.1 MAC units)	78.67 (64.12 – 96.51)	<0.0001
> 2 mg midazolam eqvts	2.35 (1.69 – 3.28)	<0.0001
> 50 mg morphine eqvts	1.88 (1.35 – 2.63)	0.0002
Nitrous oxide used	0.46 (0.26 – 0.81)	0.0072
Age > 60 yrs	5.31 (3.81 – 7.41)	< 0.0001
Comorbidity index (per 1 unit)	1.48 (1.29 – 1.70)	< 0.0001
COPD	1.65 (1.07 – 2.53)	0.0226
Malignancy	0.61 (0.40 – 0.96)	0.0308
Pre-op alcohol, opiate, or benzo use	0.59 (0.42 – 0.84)	0.0029

Adjusted for gender, ASA physical status, CAD, and CHF

Association between intraoperative electroencephalographic suppression and postoperative mortality

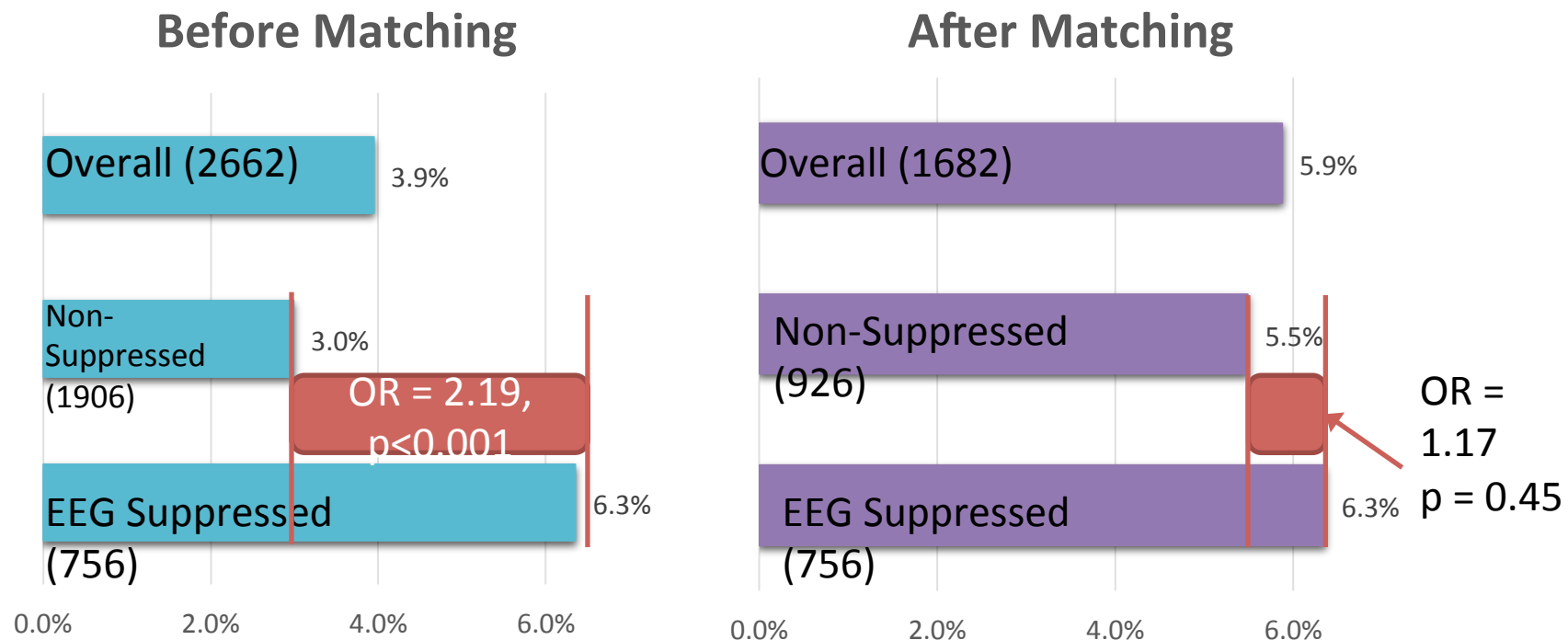
M. Willingham^{1†}, A. Ben Abdallah¹, S. Gradwohl¹, D. Helsten¹, N. Lin², A. Villafranca³, E. Jacobsohn³, M. Avidan¹ and H. Kaiser^{1*†}

Independent Predictors of Higher Suppression Ratio (Two-Part Nonlinear Mixed Effects Model – gamma portion)

Risk Factor	Gamma Coefficient (95% CI)	P value
End-tidal anesthetic (per 0.1 MAC units)	2.19 (2.08 – 2.31)	<0.0001
> 2 mg midazolam eqvts	0.23 (0.10 – 0.36)	0.0004
> 50 mg morphine eqvts	0.31 (0.19 – 0.44)	<0.0001
Nitrous oxide used	-0.49 (-0.70 – -0.27)	<0.0001
Male gender	0.06 (0.01 – 0.26)	0.0307
Age > 60 yrs	0.43 (0.30 – 0.56)	< 0.0001
Comorbidity index (per 1 unit)	0.10 (0.04 – 0.15)	0.0004
COPD	0.19 (0.03 – 0.36)	0.0229
Malignancy	-0.27 (-0.44 - -0.10)	0.0018

Adjusted for ASA physical status, CAD, CHF, and pre-op alcohol, opiate, or benzo use

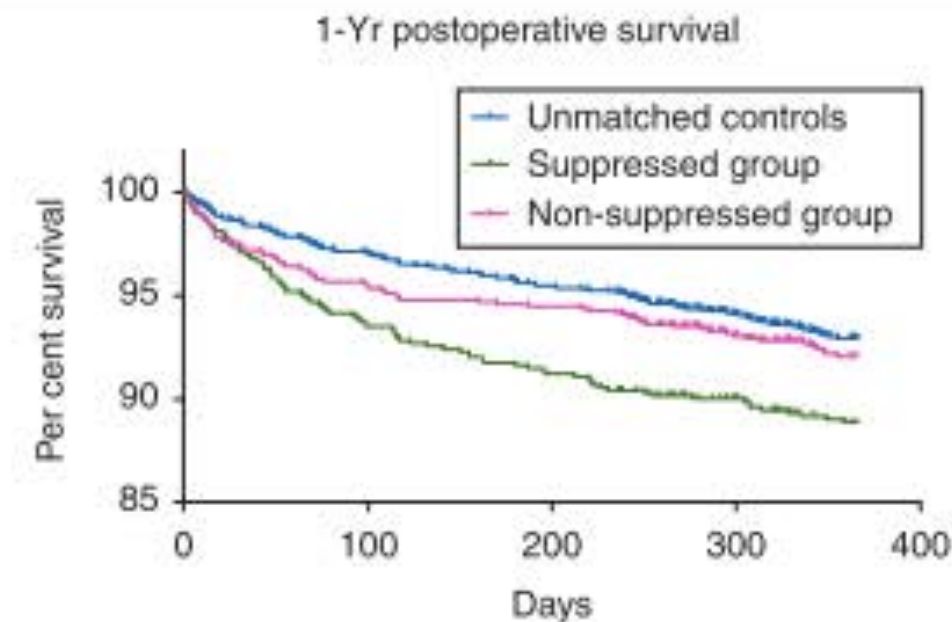
Results: 90-day mortality



Association between intraoperative electroencephalographic suppression and postoperative mortality

M. Willingham^{1†}, A. Ben Abdallah¹, S. Gradwohl¹, D. Helsten¹, N. Lin², A. Villafranca³, E. Jacobsohn³, M. Avidan¹ and H. Kaiser^{1*†}

Time to Mortality (up to 1 yr follow-up) (Log-Rank Tests)



All patients (prior to matching):

Green curve vs blue curve

Shorter time to death:

Log-Rank $\chi^2(1) = 14.09$, $p < 0.001$

Matched cohorts:

Green curve vs pink curve

No difference:

Log-Rank $\chi^2(1) = 2.13$, $p = 0.14$

Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium



Institute of Clinical and
Translational Sciences

**Bradley A Fritz, Philip Kalarickal MD, Hannah R Maybrier,
Maxwell R Muench, Douglas Dearth MD, Yulong Chen, Arbi Ben Abdallah PhD, Michael S Avidan MBBCh**

Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium



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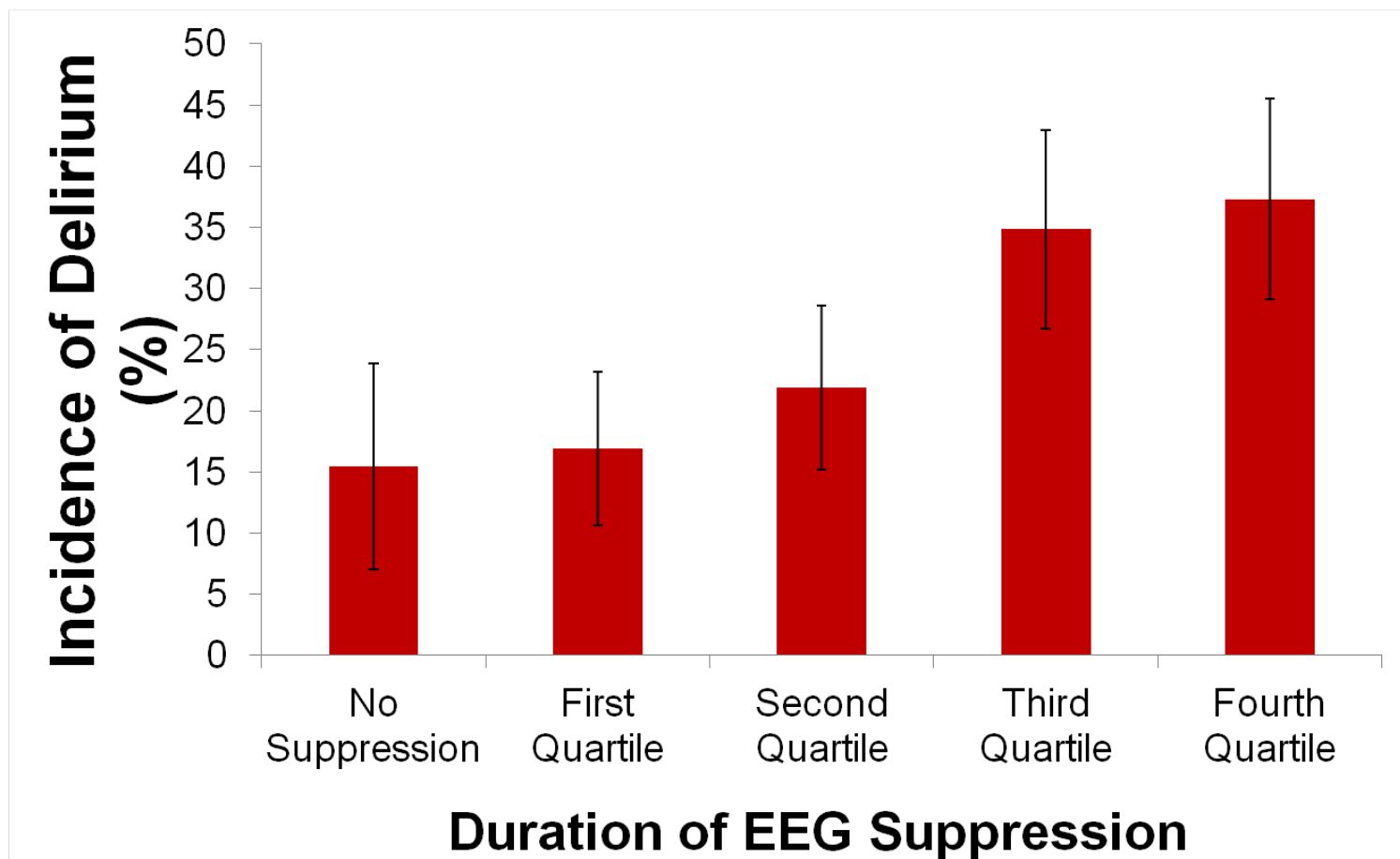
- *Patients* (N = 775)
 - Adult cardiac and non-cardiac surgery
 - Planned ICU admission
- *Outcome Definition - Delirium*
 - Positive CAM-ICU assessment at any point during postoperative days 1-5

Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium

 Washington
University in St. Louis
SCHOOL OF MEDICINE



Bradley A Fritz, Philip Kalarickal MD, Hannah R Maybrier,
Maxwell R Muench, Douglas Dearth MD, Yulong Chen, Arbi Ben Abdallah PhD, Michael S Avidan MBBCh



Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium



Bradley A Fritz, Philip Kalarickal MD, Hannah R Maybrier,
Maxwell R Muench, Douglas Dearth MD, Yulong Chen, Arbi Ben Abdallah PhD, Michael S Avidan MBBCh

Independent Predictors of Postoperative Delirium (Logistic Regression, N = 619)

Risk Factor	Odds Ratio (95% CI)	P value
Duration of EEG suppression (per 5 min)	1.05 (1.01 – 1.09)	<0.01
Blood transfusion (per unit)	1.31 (1.20 – 1.42)	<0.01
Mean end-tidal anesthetic (per 0.1 MAC unit)	0.65 (0.53 – 0.81)	<0.01

Adjusted for age, sex, ASA class, age-adjusted Charlson index, sensory impairment, alcohol use, surgery type (non-cardiac/CABG/open cardiac), and intraoperative opiate dose

Psychological sequelae of surgery in a cohort of patients from three intraoperative awareness prevention trials

Elizabeth L Whitlock, MD, MSc

Thomas L Rodebaugh, PhD, Afton Hassett, PhD, Eric Jacobsohn, MBChB, George A
Mashour, MD, PhD,* Michael S Avidan,* MBBCh

* These authors contributed equally to the abstract.



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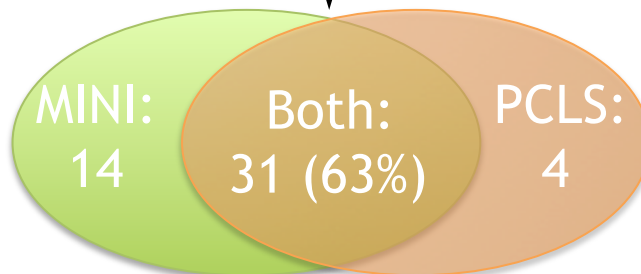


Study measurements

Mini Int'l Neuropsych Interview (MINI)

- PTSD section only
- Depression, social support, mental health questions
- Given by telephone

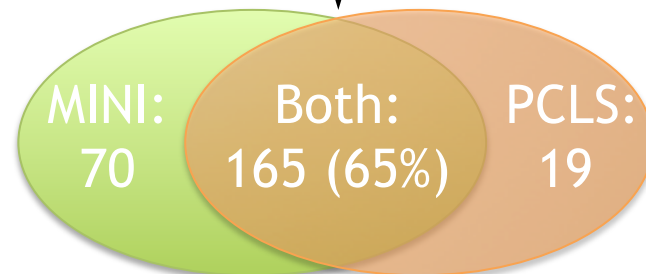
Aware: 49



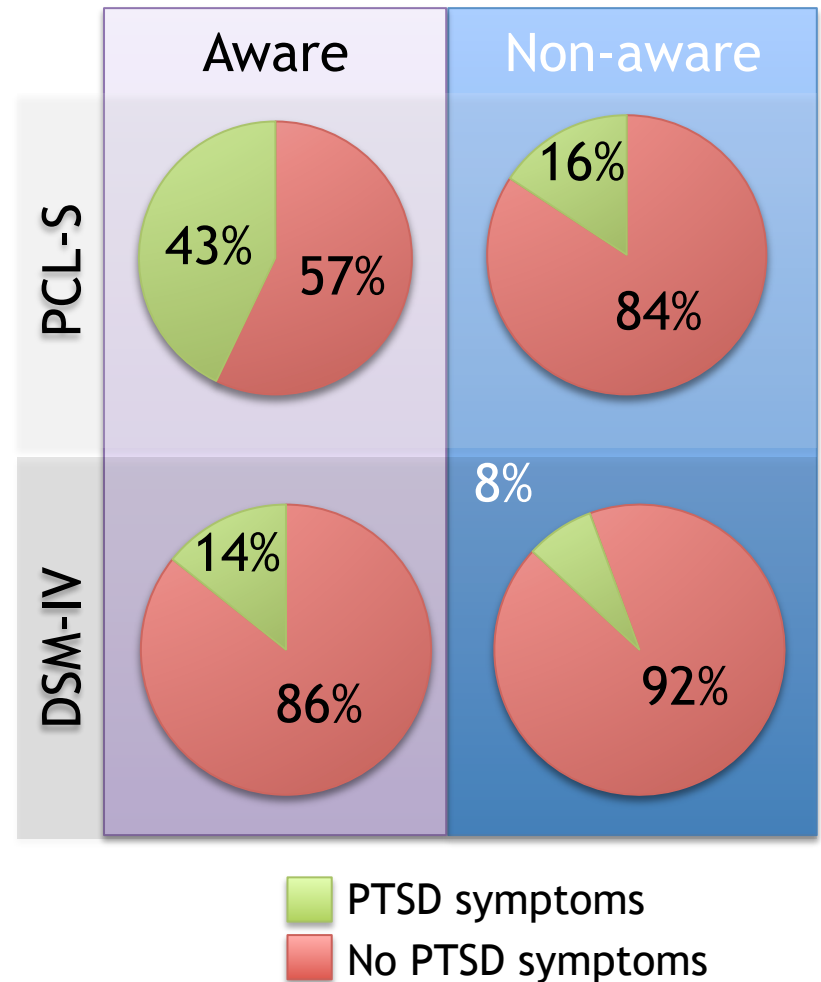
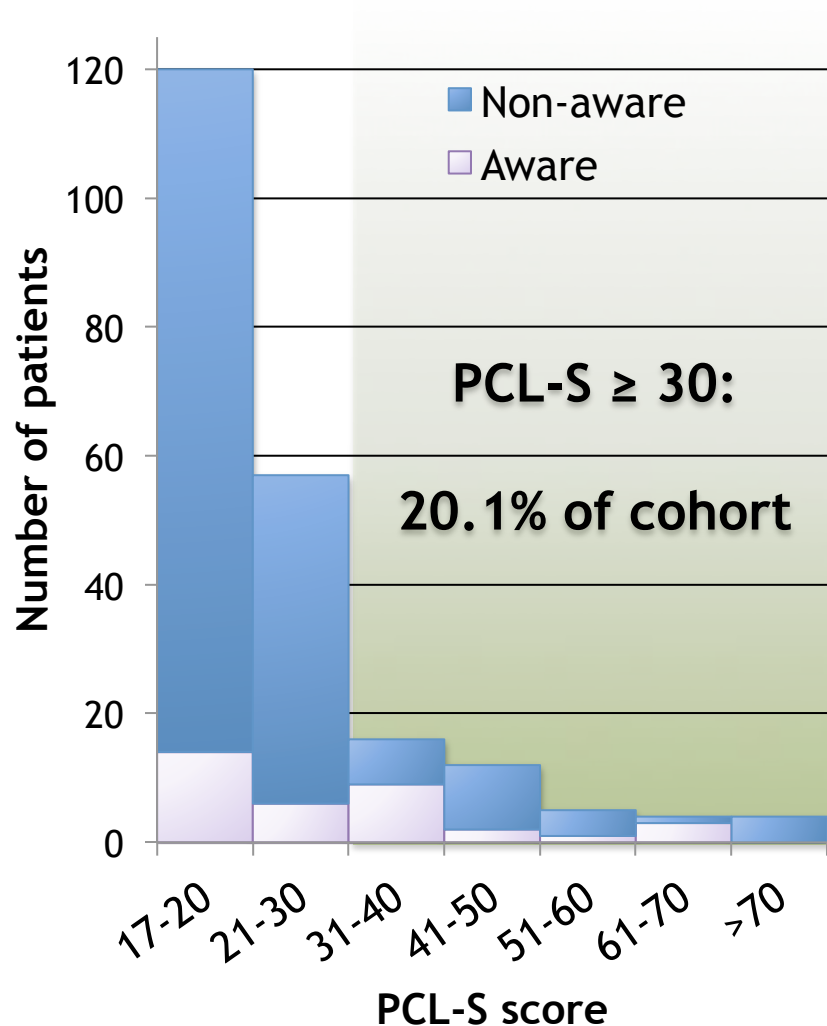
PTSD Checklist - Specific (PCL-S)

- Developed by VA
- Likert scale
- Defined incident (e.g. surgery)

Non-aware: 254



Results: PCL-S & MINI



Results: Confirmatory factor analysis

Significant variables	P-value
Dissociation at time of surgery	<0.001
Perceived threat to life at time of surgery	0.002
Past PTSD-complex symptoms	0.003
Poor perceived social support	0.006
Intraoperative awareness	0.014
Prior mental health treatment	0.017

Previously described
for other PTSD triggers

Nonsignificant factors			
Cardiac surgery	0.09	ICU care	0.40
Age	0.21	Gender	0.49

Tying it all together...

- Elective surgery is a **predictable major life stressor**.
- It is associated with **pain, inflammation and medical complications**.
- **Most patients improve** following successful recovery.
- Many **patients suffer complications** and get worse.
- It is likely that **neurological complications occur commonly** and are not appreciated by us.

Neurological Outcomes:

Mind the Mind

- More & persistent pain >10%
- Worse quality of life (mental health) >15%
- Delirium >20%
- Cognitive decline (early)
- Covert & overt stroke
- Falls >10%
- PTSD >5%
- Depression
- Seizures
- Nerve injury
- Spinal cord injury
- Ischemic optic neuropathy
- Cognitive decline (persistent)
- Anesthetic Neurotoxicity



"And hast thou slain the Jabberwock?
Come to my arms, my beamish boy!
O frabjous day! Callooh! Callay!"
He chortled in his joy.

QUESTIONS