



# Postoperative Delirium

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# Postoperative Delirium

- ◆ **Postoperative delirium (POD) is an acute and fluctuating alteration of mental state**
  - Reduced awareness and disturbance of attention.
  - POD often starts in the PACU and occurs up to 5 days after surgery.
  - Affects 13% to 50% of patients undergoing surgery,
- ◆ **Patients with POD have high in-hospital mortality (4% - 17%) and increased long-term mortality.**
- ◆ **POD increases postoperative morbidity, hospital and ICU length-of-stay, and transfers to skilled nursing facilities**
  - Patients with POD have an increased level of care dependency or limitations in basic activities of daily living up to 12 months postop
- ◆ **POD is distressing to patients and their families**



# Postoperative Delirium (POD)

- ♦ **Delirium can present as hypoactive (decreased alertness, motor activity), as hyperactive (agitated and combative) or as mixed forms**
  - **More common in elderly patients**
  - **It is not uncommon to deal with an agitated patient in the recovery room or ICU**
    - » **Often discounted as secondary to residual anesthesia**
    - » **Agitated delirium only accounts for about 25% of POD.**
  - **Hypoactive delirium is commonly missed because the patient's behavior does not draw attention**
    - » **Associated with higher mortality rates as compared to agitated POD.**



# Causes of POD

- ♦ **There are many risk factors for developing delirium (e.g. infection, dehydration, certain medications). Therefore, one approach to preventing POD is to target these multiple risk factors.**
- ♦ **Some medications have effects on the brain chemicals implicated in developing delirium, and may, therefore, have a role in prevention.**
- ♦ **There are also a number of other interventions that target delirium risk factors related to anesthesia and medical treatment around the time of surgery.**



# Risk Factors – Noncardiac Surgery

- ◆ **Age > 70 years (OR 3.3; CI 1.9 - 5.9)]**
- ◆ **Decreased functional status (< 2 mets) (OR 2.5; CI 1.2 - 5.2)**
- ◆ **Abnormal blood values:**
  - **Sodium (< 130 or > 150 mmol/L)**
  - **Potassium (< 3 or > 6 mmol/L)**
  - **Glucose (> 300 mg/dL)**
- ◆ **Open-aortic surgery (OR 8.3; CI 3.6 - 19.4)**
- ◆ **Thoracic surgery (OR 3.5; CI 1.6 - 7.4)**
- ◆ **Alcohol abuse (OR 3.3; CI 1.4 - 8.3)**
- ◆ **Impaired cognitive function (TICS < 30) (OR 4.2; CI 2.4- 7.3)**



# Additional Risk Factors

- ♦ **Multiple comorbidities**
- ♦ **Taking > 5 medications**
- ♦ **Sensorial deficits (e.g. blind, deaf)**
- ♦ **Frailty**
- ♦ **Emergency procedures**
- ♦ **Patients with 2 or more risk factors should be considered at risk of POD and prevention should be considered**



# Anesthetic Medications Associated with POD

- ♦ **Benzodiazepines:** alprazolam, diazepam, lorazepam, midazolam
- ♦ **Sedative-hypnotics:** zolpidem, zaleplon
- ♦ **Drugs with anticholinergic properties:** scopolamine
- ♦ **Antihistamines:** cyproheptadine, diphenhydramine, hydroxyzine
- ♦ **Antiemetics:** promethazine, droperidol
- ♦ **Corticosteroids:** Methylprednisolone, Prednisone
- ♦ **Long acting agents–** hydromorphone, morphine, meperidine, ketamine
- ♦ **Long acting inhalation agents –** isoflurane, sevoflurane



# Prevention

- ◆ **POD is preventable in almost 40% of patients**
- ◆ **Several classes of medications are associated with increased incidence of POD. In older patients:**
  - **Benzodiazepines increase POD (OR of 3.0 (CI 1.3 - 6.8))**
  - **Meperidine increases POD in patients > 50 years (OR of 2.7 (CI 1.3 - 5.5))**
  - **Diphenhydramine increases POD (OR 2.3 (CI 1.4 - 3.6))**
- ◆ **In older patients avoid agents that increase the incidence of POD unless the benefit outweighs the risks**
  - **Avoid scopolamine patch in older patients**





# Anesthesia Management

- ♦ There is evidence that supports the administration of a lighter depth of anesthesia to decrease the incidence of POD.
- ♦ Specifically, the use of brain function monitoring (i.e. Processed EEG) as a tool to reduce the depth of anesthesia
  - Incidence of **burst suppression** ( $BIS < 20$ ) may be a particular risk factor.



# **Postoperative Delirium in a Substudy of Cardiothoracic Surgical Patients**

**Whitlock, EL, Torres BA, et al**

**Washington University, St. Louis, Missouri**

**Anesth Analg. 118(4), 809-817: 2014**



## Methods and Results

- ♦ **2014 subgroup analysis, Whitlock reported a lesser rate of POD in 310 cardiac or thoracic surgery patients randomized to BIS-guided versus end-tidal anesthetic guided anesthesia**
  - **18.1 % versus 28.0 % respectively, (OR 0.06, CI 0.35 – 1.02, P = 0.058)**
- ♦ **Patients with postoperative delirium had**
  - **Longer ICU stays - 8.0 days (CI 7.1 - 8.9) vs. 2.0 days (CI 1.7 – 2.3) (P < 0.001)**
  - **Longer hospital stays - 17.0 days (CI 14.3 – 19.7) vs. 7.0 days (CI 6.4 – 7.6) (P < 0.001)**
  - **Less likely to be alive at last follow-up (P = 0.008)**



# **Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium**

**Fritz BA, Kalarickal PL, et al**

**Washington University, St. Louis Missouri**

***Anesth Analg.* 2016 122(1), 234–242: 2016**



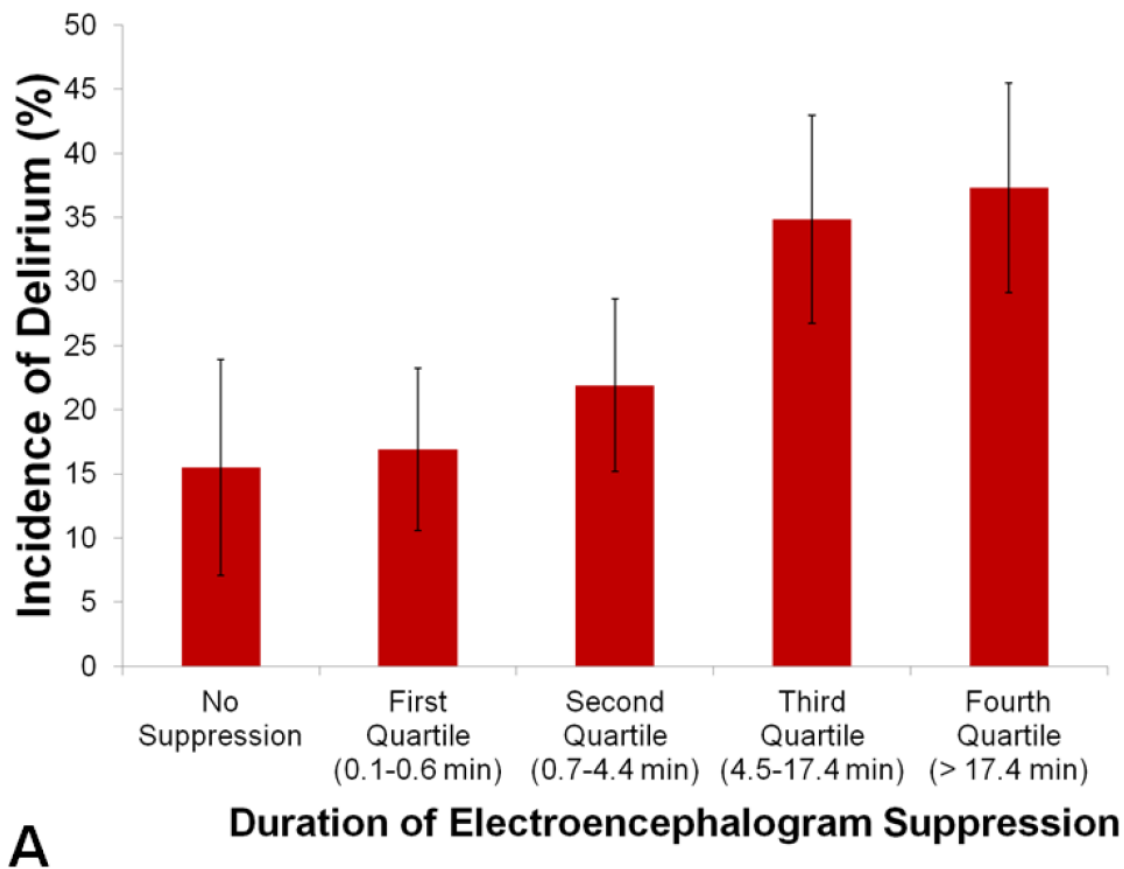
# Methods

- ◆ **727 non-neurosurgical patients with planned ICU admission**
- ◆ **BIS monitoring during surgical procedure**
- ◆ **Delirium was assessed twice daily on postoperative days 1-5 using Confusion Assessment Method of the ICU**
- ◆ **30 days after surgery, quality of life, function independence and cognitive ability were measured.**



# Results

- ◆ Postoperative delirium was observed in 26% of patients
- ◆ When comparing patients with no EEG suppression, patients with more suppression were more likely to experience postoperative delirium (POD) ( $p < 0.0001$ )
- ◆ This effect remained significant after adjusting for confounders
- ◆ At 30-days postoperatively, EEG suppression associated with reduced functional independence ( $p = 0.02$ )
  - No association with decreased quality of life or cognitive ability
- ◆ **EEG suppression is an independent risk factor for POD**



**Incidence of delirium among patients who experienced no EEG suppression (n=71) and among patients who experience EEG suppression (n=548) divided into quartiles**



# **Monitoring Depth of Anaesthesia in a Randomized Trial Decreases the Rate of Postoperative Delirium**

**Radtke FM, Franck M, et al**

**Dept of Anesth, Campus Charite Mitte  
Berlin, Germany**

**Br. J Anaesth 110(S1): i98–i105 (2013)**





# Methods and Results

- ◆ **2013 study of 1,155 consecutive patients > 60 yo scheduled for surgery expected to last > 1 hour.**
- ◆ **The patients were randomized to either BIS-guided anesthesia or BIS-blinded anesthesia.**
- ◆ **Patients in the BIS-guided group had a lower rate of POD as compared to the BIS-blinded patients (16.7%, CI 13.9 – 20.0% vs. 21.4%, CI 18.3 - 24.9%,  $P = 0.036$ ).**
- ◆ **In a multivariate analysis, **BIS < 20** was associated with POD (OR 1.027; CI 1.008 - 1.046,  $P=0.006$ )**
  - **Duration of surgery (OR 1.008, CI 1.006 – 1.009,  $P < 0.001$ ), and age (OR 1.096, CI 1.065 – 1.127,  $P < 0.001$ ) were also associated with POD.**



# **BIS-Guided Anesthesia Decreases Postoperative Delirium and Cognitive Decline**

**Chan MTV, Cheng BCP, et al**

**University of Hong Kong**

**J Neurosurg Anesthesiol 25:33–42 2013**



# Methods

- ♦ **Study of 921 patients > 60 years old, scheduled for major elective surgery expected to last > 2 hours**
  - Expected hospital stay at least 4 days
  - Exclusion criteria included major psychosis, use of tranquillizers or antidepressants, diseases of the CNS, suspected dementia or memory impairment
- ♦ **Patients were randomized to either BIS-guided anesthesia or BIS-blinded anesthesia.**
  - In the BIS group, anesthetic dosage was adjusted to achieve a BIS value between 40 and 60
  - In the BIS-blinded group, anesthetic drug administration was titrated according to clinical judgment (e.g. HR and BP control)



# Results

- ◆ **Fewer patients with delirium in the BIS-guided group compared with routine care (15.6% vs. 24.1%,  $P=0.01$ )**
  - Multivariable analysis showed that patients in the BIS-guided group had a reduction of POD (OR 0.67, CI 0.32 – 0.98,  $P = 0.025$ )
- ◆ **BIS monitoring reduced:**
  - End-tidal volatile concentration by 29.7% (CI 25.9 - 32.8,  $P < 0.001$ )
  - Propofol effect site concentration by 20.7% (CI, 12.1-31.9,  $P < 0.001$ )
- ◆ **Average BIS value in the BIS-guided group was higher than the routine care group**
  - Time spent with BIS  $< 40$  was lower in the BIS-guided group



# **Sedation Depth During Spinal Anesthesia and the Development of Postoperative Delirium in Elderly Patients Undergoing Hip Fracture Repair**

**Sieber FE, Zakriya KJ, et al  
Johns Hopkins, Baltimore, MD.  
*Mayo Clin Proc* 85(1):18-26 2010**



# Methods and Results

- ◆ **In 2010, a small randomized control trial examining 114 hip fracture patients > 65 years old who had received spinal anesthesia and propofol sedation**
  - **Patients were randomized to be deeply sedated (BIS ~ 50) vs. lightly sedated (BIS ~ 80)**
- ◆ **Patients who were lightly sedated had a lower incidence of POD as compared to deeply sedated (11/57 vs. 23/57,  $P = 0.02$ ).**
- ◆ **Of those with POD, the lightly sedated patients had less days of delirium during their hospitalization ( $0.5 \pm 1.5$  days vs.  $1.4 \pm 4.0$  days,  $P = 0.01$ ).**



# **Cerebral Monitoring of Anaesthesia on Reducing Cognitive Dysfunction and Postoperative Delirium: a systematic review**

**Luo C and Zou W**

**Dept of Neurology, Yongchuan Hospital**

**Chongqing, China**

**Journal of International Medical Research 46(10) 2018**



# Methods

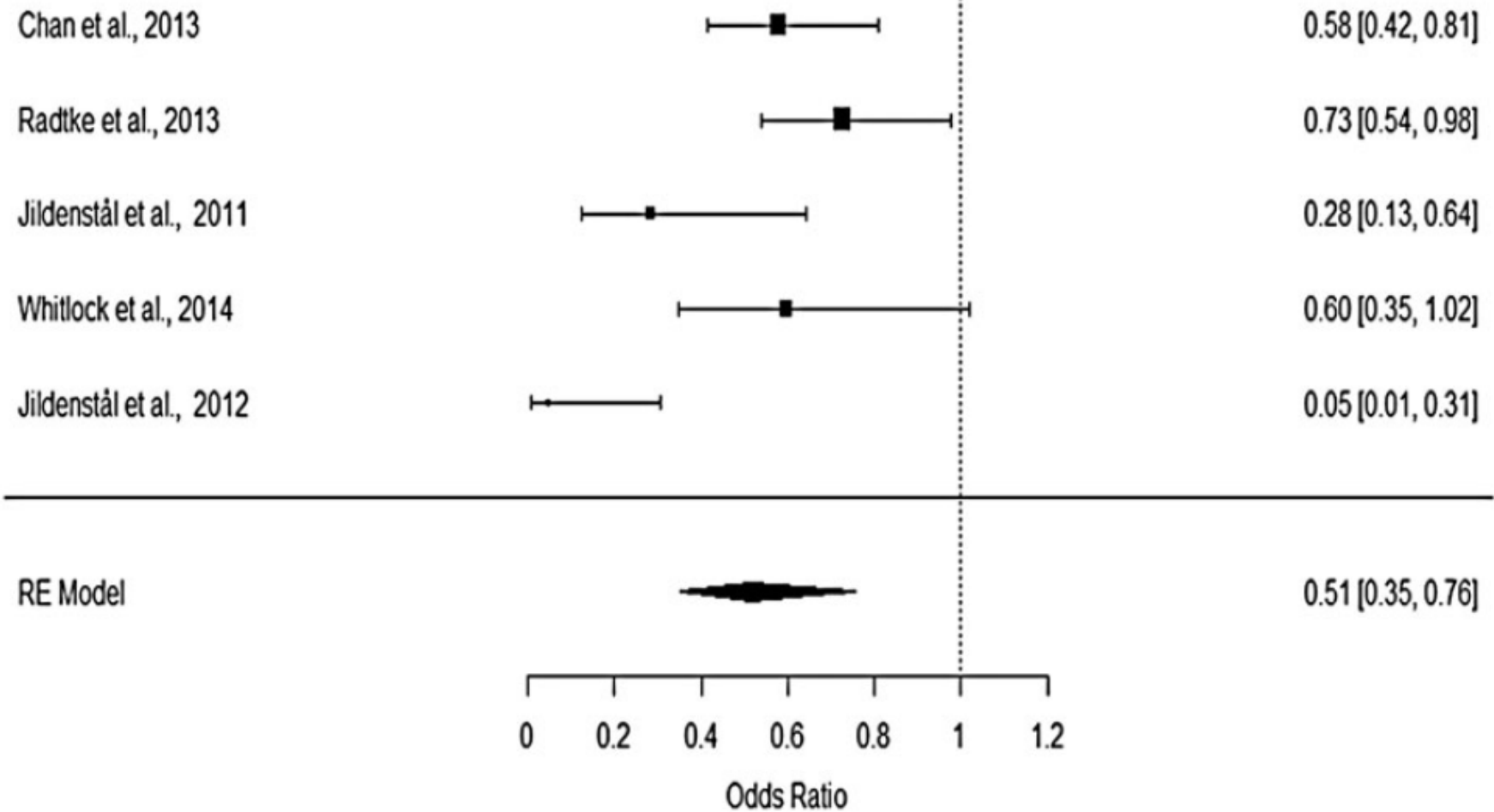
- ◆ **Meta analysis of 5 randomized clinical trials**
  - **Included 2,868 patients**
  - **Bispectral index (BIS) or auditory evoked potential (AEP) as interventions**
  - **Primary outcomes were postoperative delirium (POD) and long-term cognitive dysfunction (LCD)**
  - **Subgroup analysis of intervention type (BIS vs. AEP) and surgery (noncardiac vs. cardiac)**





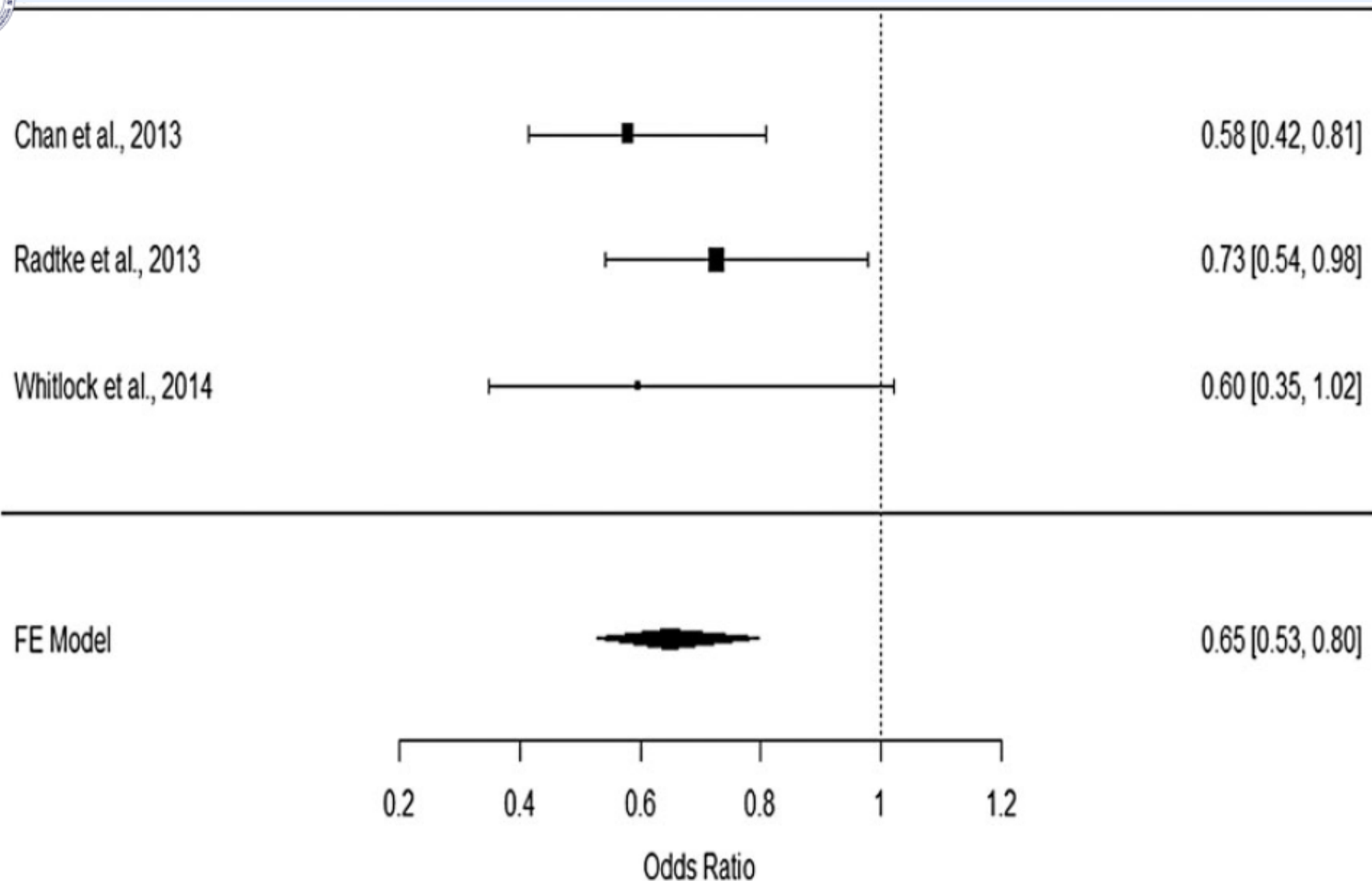
# Results

- ◆ **Odds ratio for postoperative delirium was 0.51 (CI 0.35 – 0.76)**
  - **Long-term cognitive dysfunction was 0.69 (CI 0.49 – 0.97)**
- ◆ **No significant difference between BIS and AEP titration of anesthesia in reducing the risk of POD**
- ◆ **Significant publication bias was found among the POD results**



## Forest plot for incidence of postoperative delirium

Lou et al, J International Medical Research 46(10); 2018



**Forest plot for BIS-guided titration of anesthesia**



# Summary

- ◆ **BIS and AEP-guided anesthesia is associated with a significant decrease in the risk of POD and LCD**
- ◆ **Significant heterogeneity among studies in patients undergoing cardiac and thoracic surgery but not in noncardiac surgery**
- ◆ **The removal of any trial from the analysis did not alter the outcome of the meta-analysis on POD**
- ◆ **Significant publication bias was identified among the POD data from the 5 clinical trials.**



# **Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery**

**Wildes TS, Mickle AM, et al  
Washington University, St. Louis, MO  
JAMA. 321(5):473-483 2019**



# Methods

- ◆ **Randomized study of 1,232 patients >60 years old, scheduled for major surgery and receiving general anesthesia**
  - **Anesthesiologists were discouraged from using N<sub>2</sub>O and IV hypnotic agents (e.g. midazolam, Propofol, ketamine, dexmedetomidine)**
- ◆ **Patient's were randomized to:**
  - **Usual care group – EEG unavailable**
  - **BIS-guided group – clinicians were encourage to decrease volatile anesthetic based on BIS value, goal to keep BIS > 40**
- ◆ **Primary outcome was delirium incidence on postoperative days 1-5**



# Results

- ♦ **Median end-tidal volatile anesthetic concentration was lower in the BIS-control group 0.69 vs. 0.80 MAC. -0.11 (-0.13 to -0.10)**
- ♦ **Median cumulative time with EEG suppression was less in BIS group; 7 vs 13 minute. -6.0 (-9.9 to -2.1)**
- ♦ **BIS-control group had less exposure to bispectral index < 40 (32 vs. 60 minute). -28 (-38 to -18)**
- ♦ **Median duration of hypotension were not significantly different.**
  - **More phenylephrine was administered in the usual care group (1.37 vs. 2.02 mg). -0.63 (-1.22 to -0.03)**



# Results Continued

- ◆ **POD incidence was 26% in BIS-control group vs. 23% . 3.0 (-2.0 to 8.0)  $P = 0.22$**
- ◆ **30 day mortality was 0.7% in the BIS-control group vs. 3.1% in the usual care group. -2.42 (-4.3 to -0.8)  $P = 0.004$** 
  - **Authors did not offer a hypothesis why the BIS-control group had lower postoperative mortality**





John Abenstein. 11-й Британо-Український Симпозіум. Київ, 2019

# Postoperative Care



# Postoperative Management

- ◆ **Inadequate postoperative pain control is associated with POD**
  - **Multimodal pain management appears to reduce the incidence of POD, while use of opioid-only pain control increases incidence of POD**
- ◆ **Regional nerve blocks are associated with a reduction of POD**
- ◆ **Interventions that improve the postoperative environment such as sensory, cognitive, mobility, and sleep enhancements have been shown to decrease POD by 30-40%**



# Treatment

- ◆ **The initial treatment of POD should be focused on minimizing contributing factors such as pain management and disorientation (reintroduce eye glasses and hearing aids).**
- ◆ **If patient continues to show signs of delirium, pharmacologic intervention may be indicated.**
  - **No evidence of benefit of treating patients with hypoactive delirium.**
  - **Treating patients with acute agitation with the lowest possible dose of an antipsychotic may be beneficial**



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# Recommendations From Professional Societies



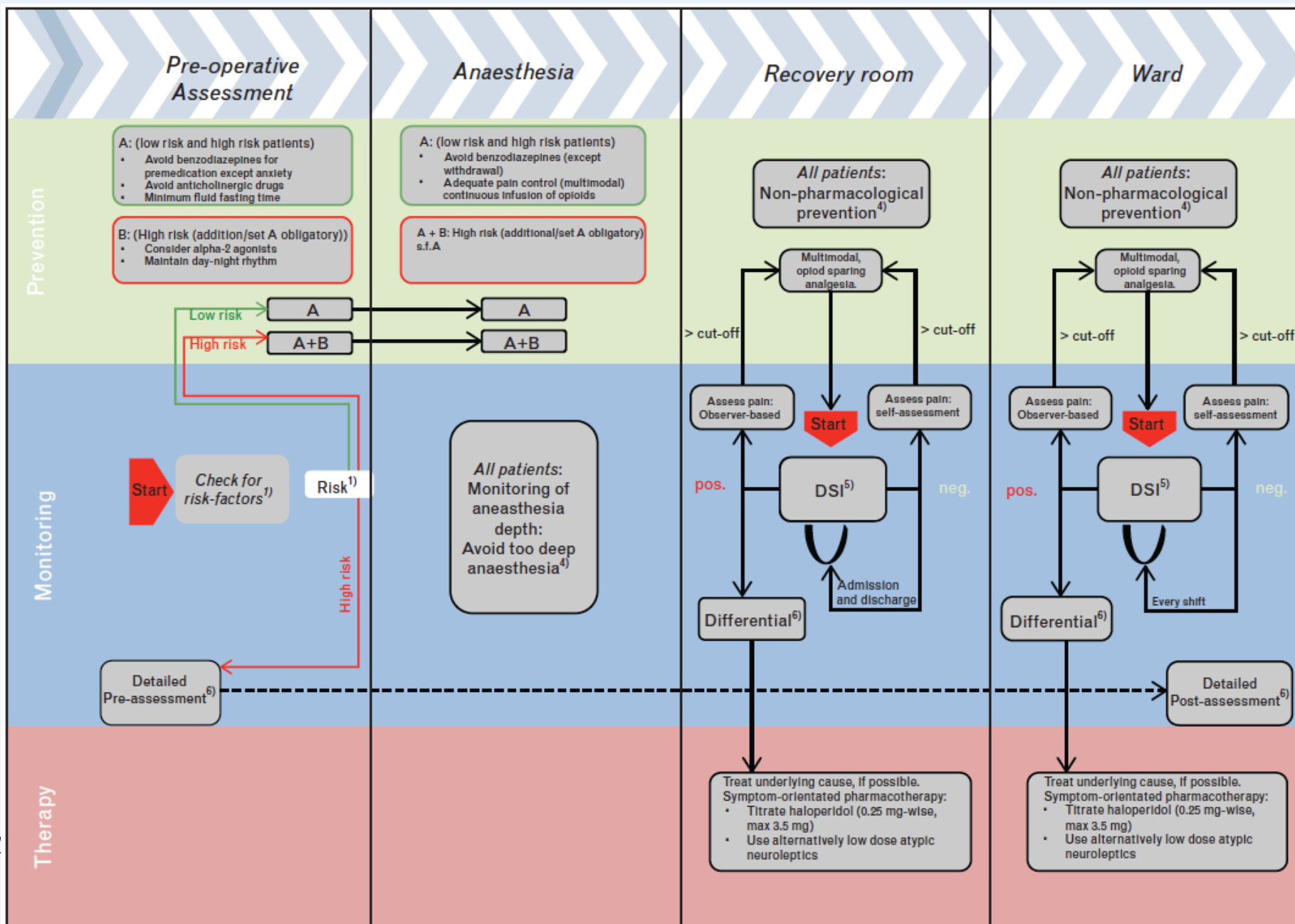
# American Geriatrics Society (2015)

- ◆ **Anesthesia practitioner may use processed EEG monitors of anesthetic depth during IV sedation or general anesthesia in older patients**
- ◆ **Avoid medications that induce POD**
  - **Anticholinergic, sedative-hypnotics particularly benzodiazepines, meperidine, and diphenhydramine considerable increase risk of POD**
- ◆ **Consider regional anesthetic for surgery and postop pain control**
- ◆ **Optimize postop pain control, preferably with nonopioid medications**



# **European Society of Anesthesiologists - ALL Patients (4/2017)**

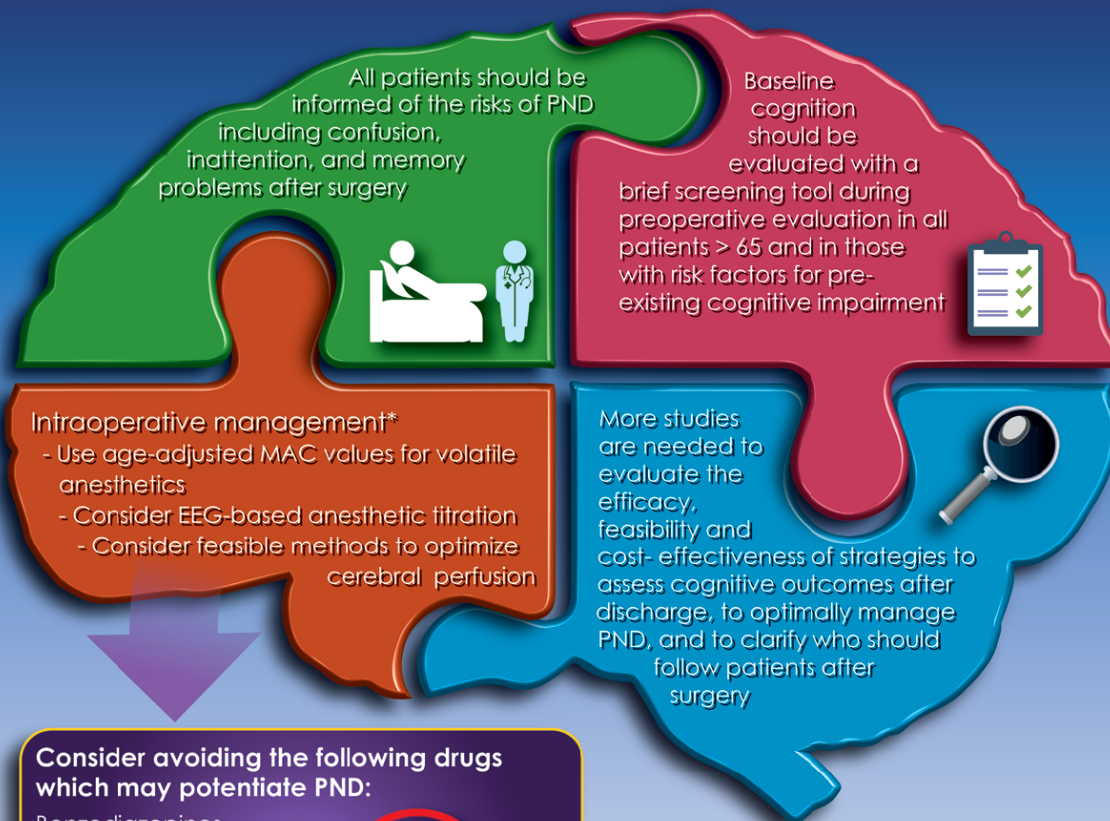
- **Avoid use of anticholinergics and benzodiazepines**
- **Reduce surgical stress - continuous intraoperative analgesia regimen**
- **Organ-protective intraoperative management**
  - » i.e. Avoid hypotension
- **Brain function monitoring to avoid excessively deep anesthesia**
  - » Avoid overdosage
- **Adequate pain assessment and treatment**





## Brain Protection Beyond the OR: *Consensus Statement on Perioperative Neurocognitive Disorders (PND)*

The 5th International Perioperative Neurotoxicity Workshop convened in 2016 to discuss best practices for optimizing perioperative brain health in older adults (> 65 years). A summary of their consensus statements is illustrated below.<sup>1</sup>



### Consider avoiding the following drugs which may potentiate PND:

- Benzodiazepines
- Corticosteroids
- Meperidine
- Metoclopramide
- H2 antagonists
- All drugs with significant anticholinergic effects



The American Society of Anesthesiology Brain Health Initiative strives to understand, optimize and manage brain function in the perioperative period. Further studies are needed to advance this endeavor.

<sup>1</sup> For an in depth understanding of the principles underlying these recommendations, the reader is encouraged to explore the full review article in this issue.





# Conclusion

- ◆ **Postoperative Delirium is a serious complication with long term implications.**
  - **Risk factors include age, co-morbidities, major surgical intervention**
  - **Increases episode-of-care cost and increases length of stay**
  - **Associated with deep anesthesia, POD increases with exposure to BIS < 40 and the amount of time with BIS < 40 further increases POD.**
    - » **Etiology may be burst suppression, which occurs with BIS < 20**
  - **Avoid medications associated with POD**
  - **Use short acting anesthetics**



# Questions

<https://youtu.be/ZWaTGB-BDDA>