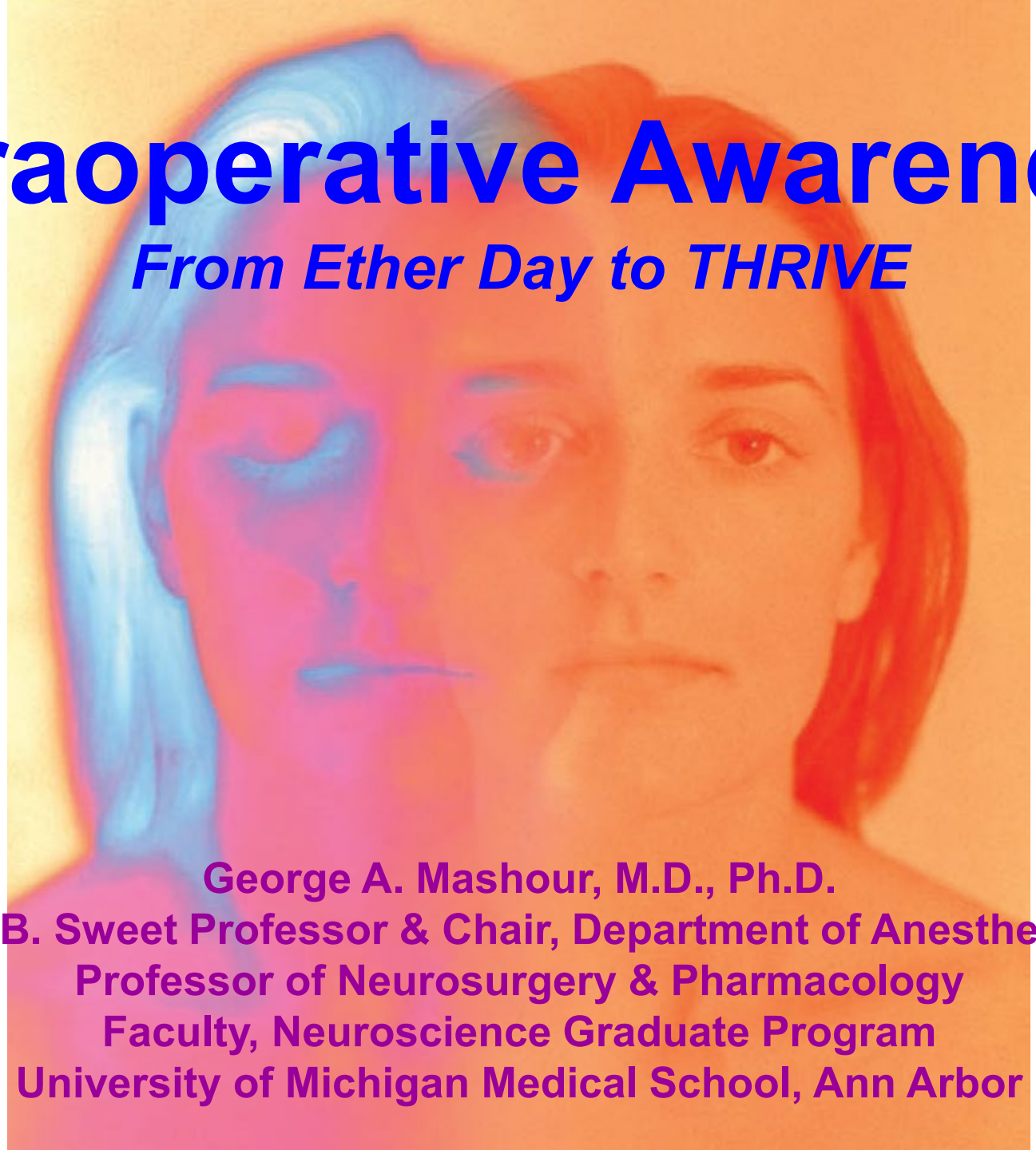
Intraoperative Awareness

From Ether Day to THRIVE



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No conflicts of interest to declare

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"Suffering so great as I underwent cannot be expressed in words. . . but the blank whirlwind of emotion, the horror of great darkness, and the sense of desertion by God and man, which swept through my mind, and overwhelmed my heart, I can never forget."

THE

BOSTON MEDICAL AND SURGICAL JOURNAL.

VOL. XXXV. WEDNESDAY, NOVEMBER 18, 1846. No. 16.

INSENSIBILITY DURING SURGICAL OPERATIONS PRODUCED BY INHALATION.

Read before the Boston Society of Medical Improvement, Nov. 9th, 1846, an abstract having been previously read before the American Academy of Arts and Sciences, Nov. 3d, 1846.

By Henry Jacob Bigelow, M.D., one of the Surgeons of the Massachusetts General Hospital.

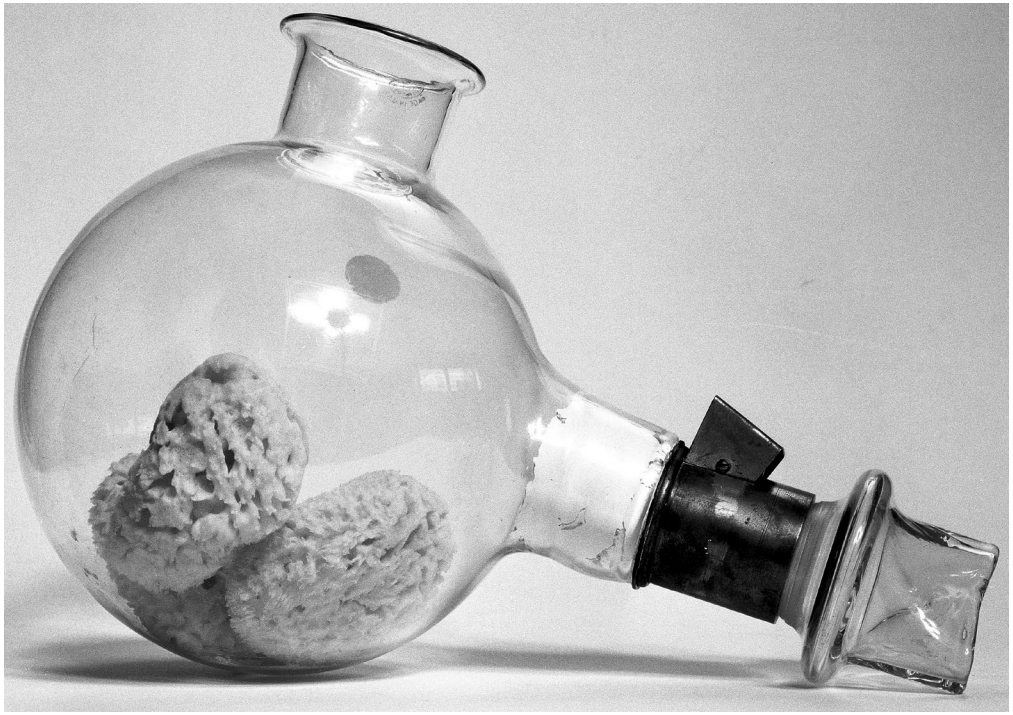
[Communicated for the Boston Medical and Surgical Journal.]

IT has long been an important problem in medical science to devise some method of mitigating the pain of surgical operations. An efficient agent for this purpose has at length been discovered. A patient has been rendered completely insensible during an amputation of the thigh, regaining consciousness after a short interval. Other severe operations have been performed without the knowledge of the patients. So remarkable an occurrence will, it is believed, render the following details relating to the history and character of the process, not uninteresting.

On the 16th of Oct., 1846, an operation was performed at the hospital, upon a patient who had inhaled a preparation administered by Dr. Morton, a dentist of this city, with the alleged intention of producing insensibility to pain. Dr. Morton was understood to have extracted teeth under similar circumstances, without the knowledge of the patient. The present operation was performed by Dr. Warren, and though comparatively slight, involved an incision near the lower jaw of some inches in extent. During the operation the patient muttered, as in a semi-conscious state, and afterwards stated that the pain was considerable, though mitigated; in his own words, as though the skin had been scratched with a hoe. There was, probably, in this instance, some defect in the process of inhalation, for on the following day the vapor was administered to another patient with complete success. A fatty tumor of considerable size was removed, by Dr. Hayward, from the arm of a woman near the deltoid muscle. The operation lasted four or five minutes, during which time the patient betrayed occasional marks of uneasiness; but upon subsequently regaining her consciousness, professed not only to have felt no pain, but to have been insensible to surrounding objects, to have known nothing of the operation, being only uneasy about a child left at home. No doubt, I think, existed, in the minds of those who saw this operation, that the unconsciousness was real; nor could the imagination be accused of any share in the production of these remarkable phenomena.

I subsequently undertook a number of experiments, with the view of ascertaining the nature of this new agent, and shall briefly state them,

"During the operation the patient muttered, as in a semi-conscious state, and afterwards stated that the pain was considerable though mitigated... There was, probably, in this instance, some defect in the process of inhalation..."



'Like torture': Man says he was awake, unable to speak or move during surgery

By CNN | 11:04am May 4, 2021

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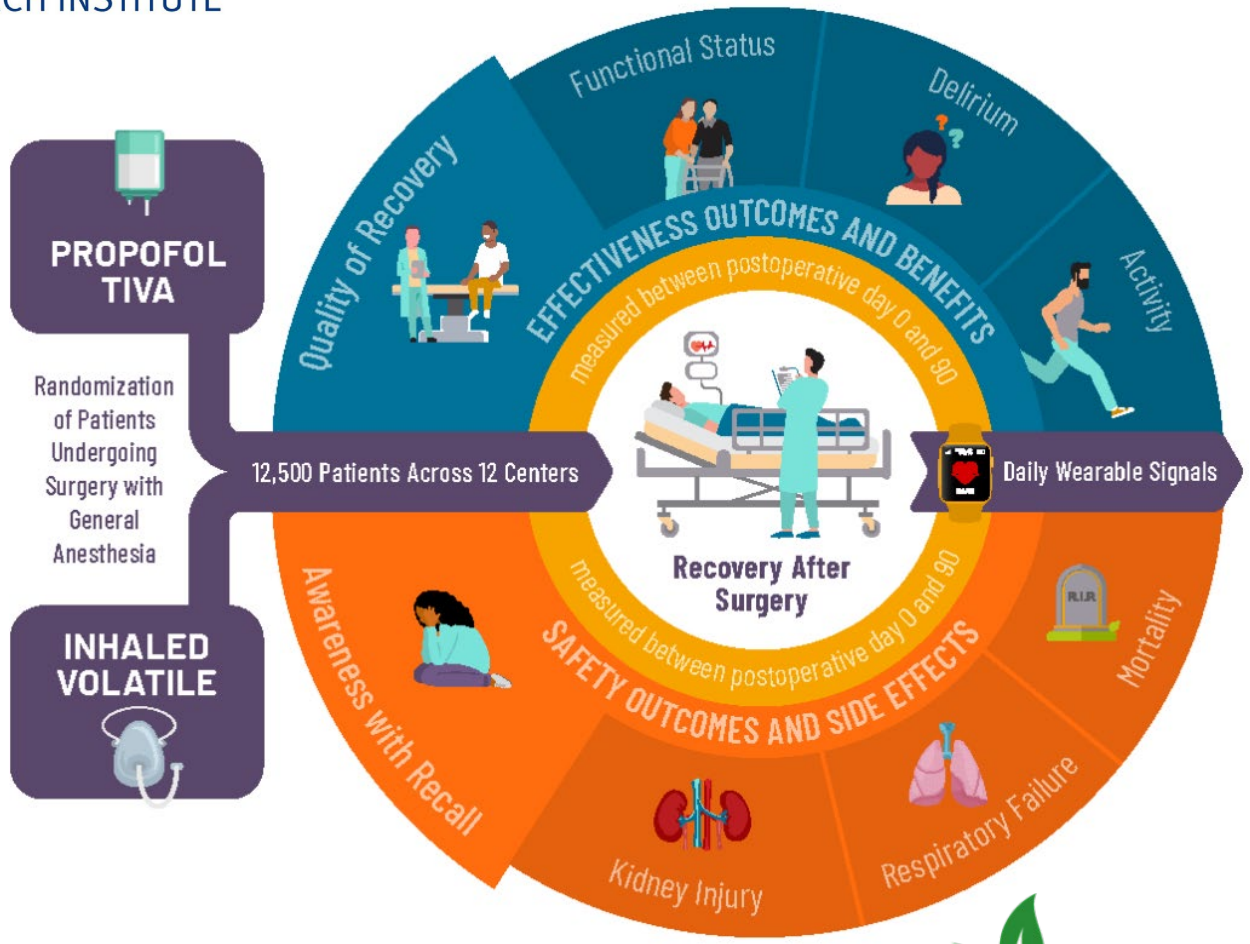


THRIVE

Outline

- Definition
- Incidence & risk factors
- Sequelae
- Prevention

Outline

- **Definition**
- Incidence & risk factors
- Sequelae
- Prevention

Defining the problem

“Awareness”

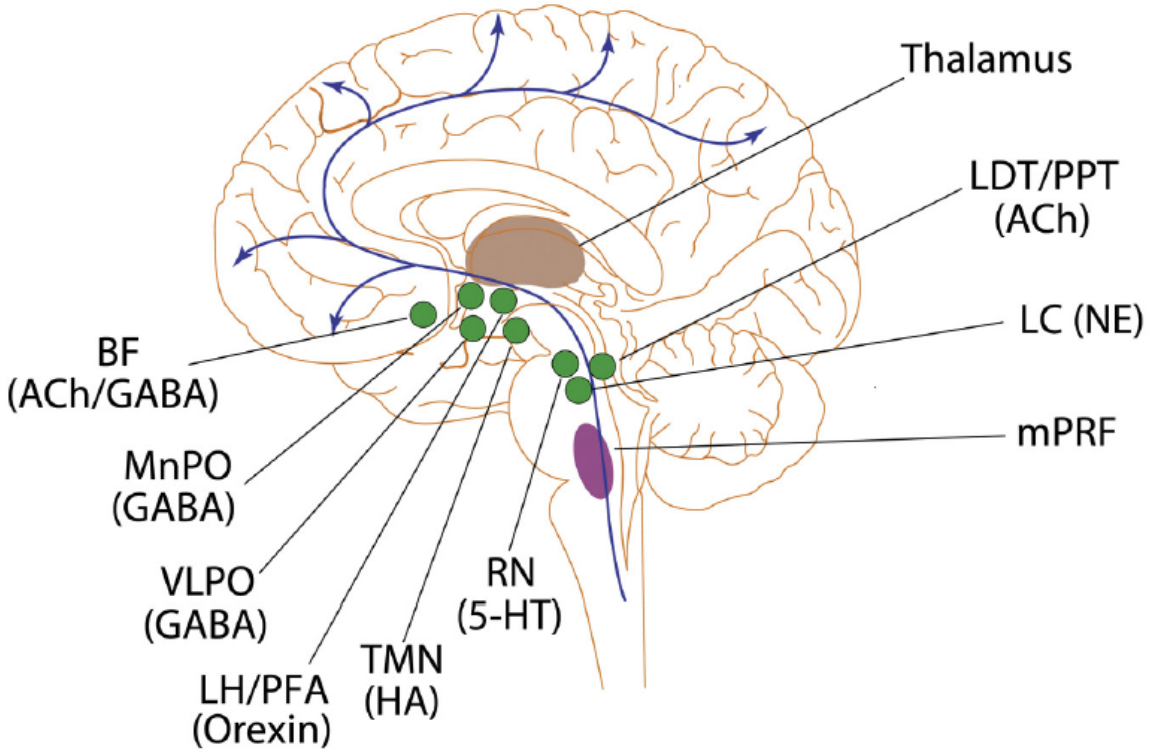
Defining the problem

"Awareness" = Consciousness + Memory

Defining the problem

"Awareness" = Consciousness + Memory

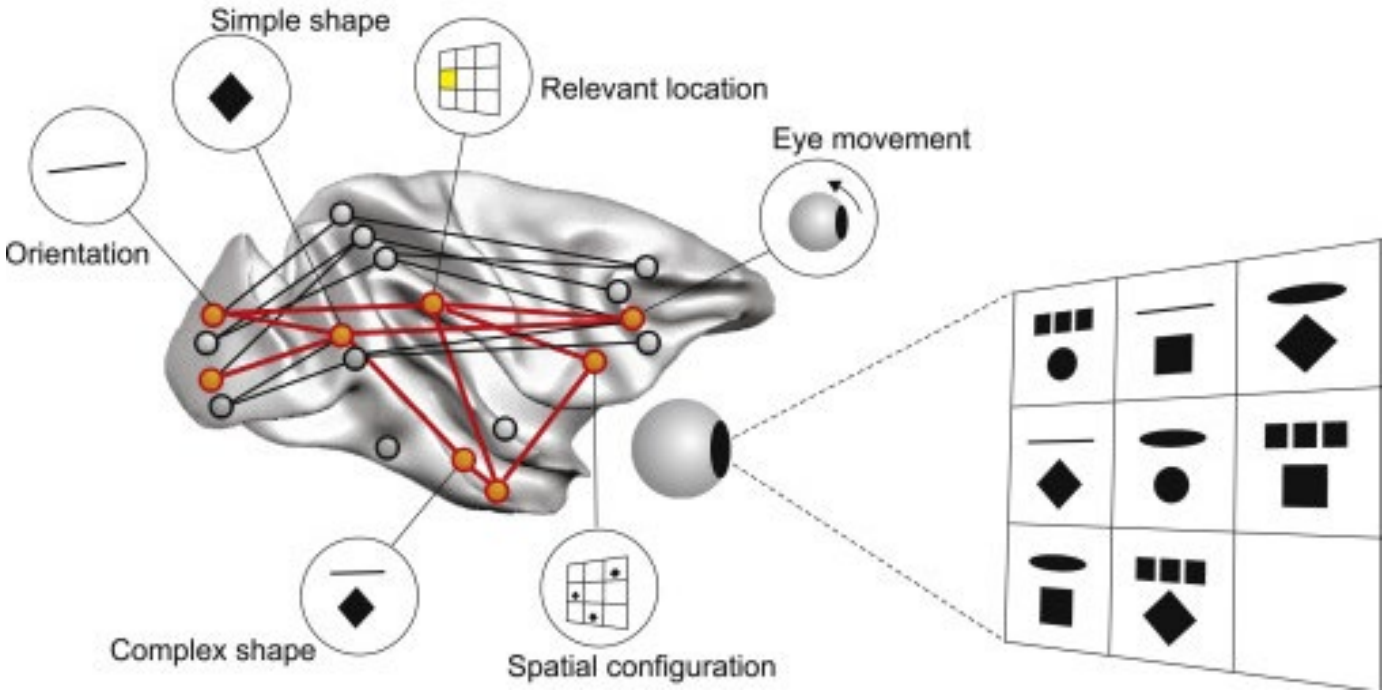
Consciousness = Arousal +



Defining the problem

"Awareness" = Consciousness + Memory

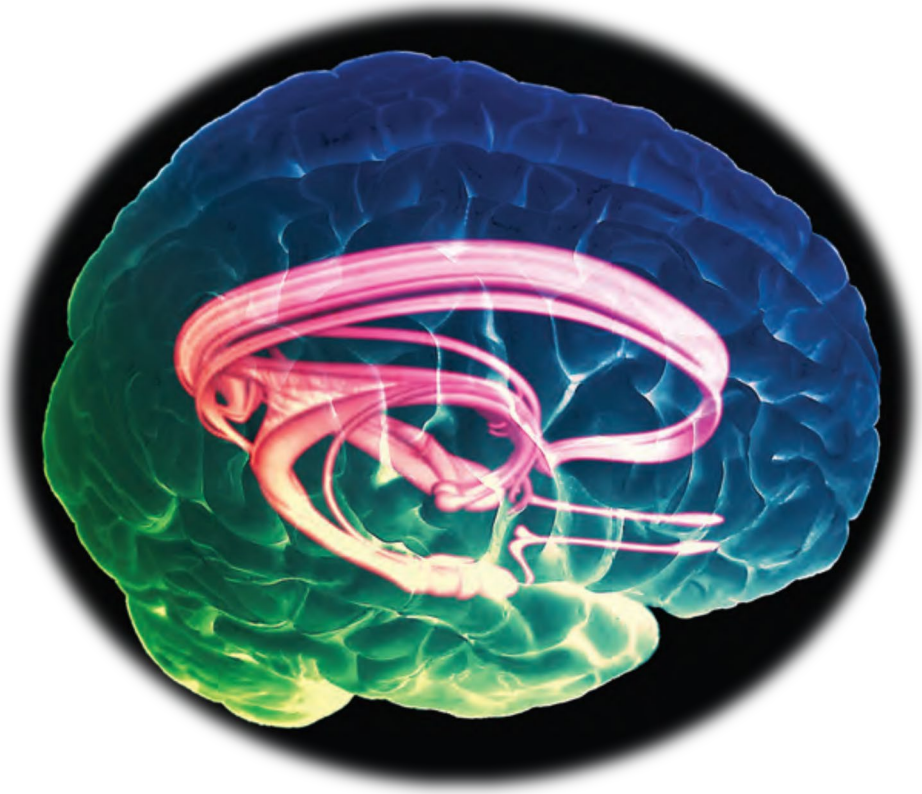
Consciousness = Arousal + Experience



Defining the problem

"Awareness" = Consciousness + Memory

Memory => Explicit Episodic Recall



ANESTHESIOLOGY
The Journal of the American Society of Anesthesiologists, Inc. • anesthesiology.org

Incidence of Connected Consciousness after Tracheal Intubation

A Prospective, International, Multicenter Cohort Study of the Isolated Forearm Technique

Robert D. Sanders, M.B.B.S., Ph.D., F.R.C.A., Amy Gaskell, M.B.Ch.B., F.A.N.Z.C.A., Aeyal Raz, M.D., Ph.D., Joel Winders, B.Sc., Ana Stevanovic, M.D., Rolf Rossaint, M.D., Christina Boncyk, M.D., Aline Defresne, M.D., Gabriel Tran, M.D., Seth Tasbihgou, B.Sc., Sascha Meier, M.D., Phillip E. Vlisides, M.D., Hussein Fardous, B.S., Aaron Hess, M.D., Ph.D., Rebecca M. Bauer, M.D., M.P.H., Anthony Absalom, M.B.Ch.B., M.D., F.R.C.A., George A. Mashour, M.D., Ph.D., Vincent Bonhomme, M.D., Ph.D., Mark Coburn, M.D., Jamie Sleigh, M.B.Ch.B., F.A.N.Z.C.A.

Anesthesiology, V 126 • No 2 February 2017

4.6% (12/260 patients) had positive response but no postoperative recall; inhaled anesthetic (after induction, before intubation) appears protective

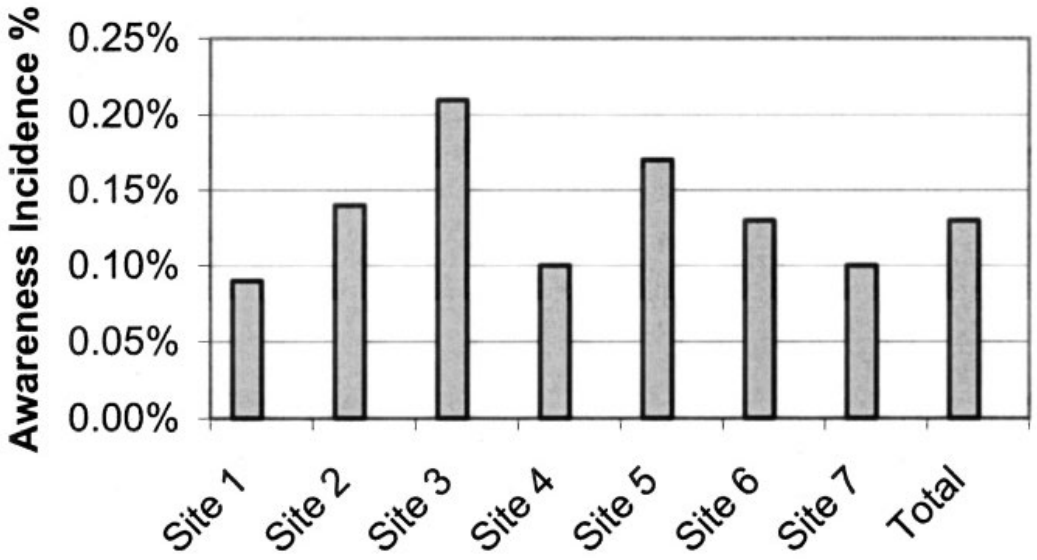
What does this mean for THRIVE?

- **The group randomized to TIVA with no post-induction inhaled agent might be at higher risk of intraoperative awareness without recall**

Outline

- Definition
- **Incidence & risk factors**
- Sequelae
- Prevention

Incidence of the problem in the United States



Incidence of 25/19,575 or 0.13%

Sebel et al, Anesth Analg, 2004;99:833

…consistent with a prospective study in Sweden

	Total (n=11 785)	Patients with awareness (n=19)
Demography		
Age (years)	48 (19)	45 (18)
Height (cm)	170 (9)	170 (9)
Weight (kg)	74 (15)	78 (16)
ASA physical status	1·4 (0·6)	1·4 (0·6)
Male/female	4732/7053	7/12
Surgery		
Duration of anaesthesia (min)	99 (65)	95 (66)
Elective/acute and emergency surgery*	9388/2397	14/5

Incidence of 19/11,785 or 0.16%

Sandin et al, Lancet, 2000;355:707

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Incidence of 19/11,785 or 0.16%

Note that incidence with NMB was higher

Sandin et al, Lancet, 2000;355:707

…not consistent with data from another U.S. study

Facility	Total Cases 2002–2004	CQI Data 2002–2004	Percent CQI Coverage	Excluded Cases*	Total Cases in Study	Recall Cases
1	119,470	108,437	90.76	55,686	52,751	5
2	28,008	16,965	60.75	8,229	8,736	0
3	22,272	17,339	77.85	11,116	6,223	1
4	21,329	19,817	92.9	6,934	12,883	0
5	8,141	6,192	76.06	2,762	3,430	0
6	3,381	2,606	77.08	1,124	1,482	0
7	4,503	3,406	75.64	2,281	1,125	0
8	4,738	2,706	57.11	1,975	731	0
Total	211,842	177,468	83.12	90,107	87,361	6

Incidence of 6/87,381 or 0.0068%

Pollard et al, Anesthesiology 2007:106:269

British Journal of Anaesthesia Page 1 of 9
doi:10.1093/bja/aet016

BJA

A national survey of anaesthetists (NAP5 Baseline) to estimate an annual incidence of accidental awareness during general anaesthesia in the UK

J. J. Pandit[1*], T. M. Cook[2], W. R. Jonker[3] and E. O'Sullivan[4], on behalf of the 5th National Audit Project (NAP5) of the Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain, Ireland

British Journal of Anaesthesia Page 1 of 4
doi:10.1093/bja/aet012

EDITORIAL

The incidence of intraoperative awareness in the UK: under the rate or under the radar?

Michael S. Avidan[1*] and George A. Mashour[2]

Magazine

Waking up under the surgeon's knife

13 February 2017 | Magazine

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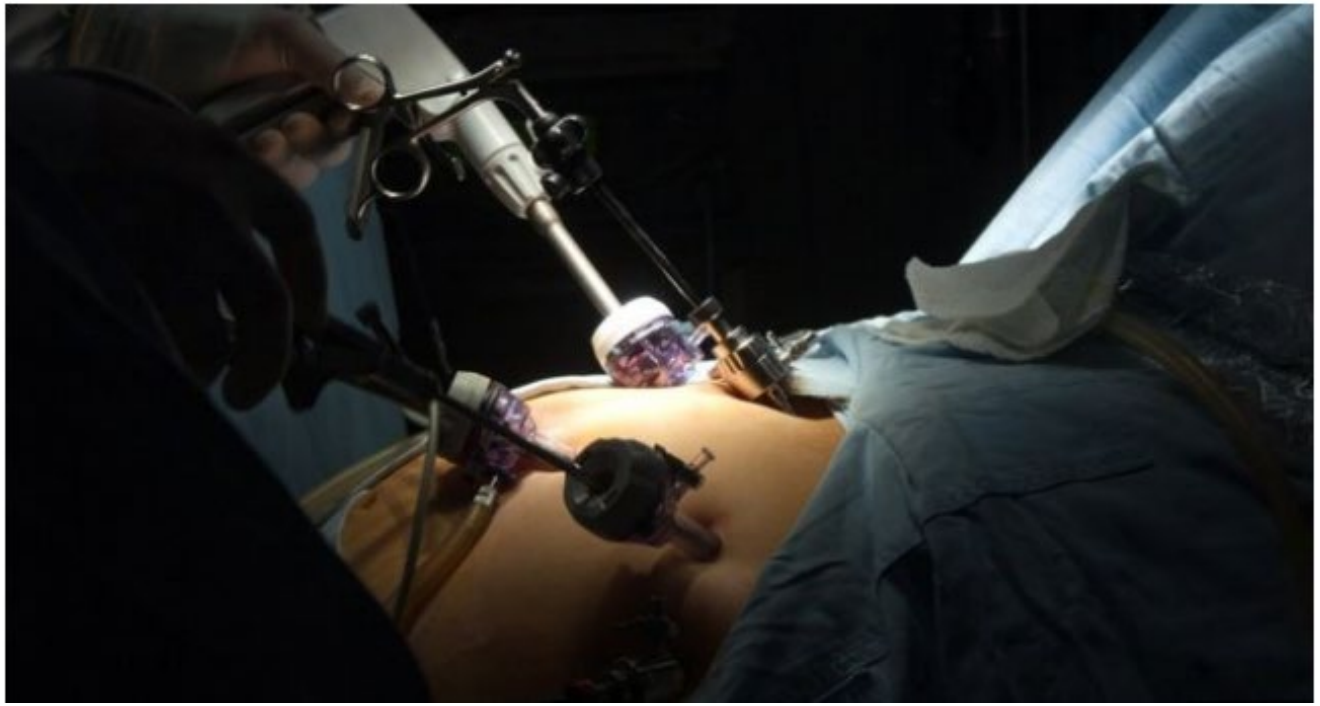

Conscious during surgery

- Accidental awareness during general anaesthesia is reported in around one in 19,000 operations

Comparing Brice interview to quality assurance techniques

Table 1. Modified Brice Interview

1. What was the last thing you remember before anesthesia?
2. What is the first thing you remember after waking up?
3. Do you remember anything between going under anesthesia and waking up?
4. Did you dream during your procedure?
5. What was the worst thing about your operation?

Mashour et al, Anesth Analg, 2013;116:889

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Table 2. Detection of Intraoperative Awareness with Recall

	QA-positive awareness	QA-negative awareness
Brice-positive awareness	3	16
Brice-negative awareness	0	18,817

Mashour et al, Anesth Analg, 2013;116:889

What does this mean for THRIVE?

- **Spontaneous patient reports are not sufficient for an accurate incidence of this outcome**

- **Any MPOG study including intraoperative awareness will likely have to involve enriched, prospective data collection**

Classifying awareness events

Table 1. Michigan Awareness Classification Instrument

Class 0: No awareness
Class 1: Isolated auditory perceptions
Class 2: Tactile perceptions (e.g., surgical manipulation or endotracheal tube)
Class 3: Pain
Class 4: Paralysis (e.g., feeling one cannot move, speak, or breathe)
Class 5: Paralysis and pain

An additional designation of "D" for distress was also included for patient reports of fear, anxiety, suffocation, sense of doom, sense of impending death, etc.

Mashour et al, Anesth Analg, 2010;110:813

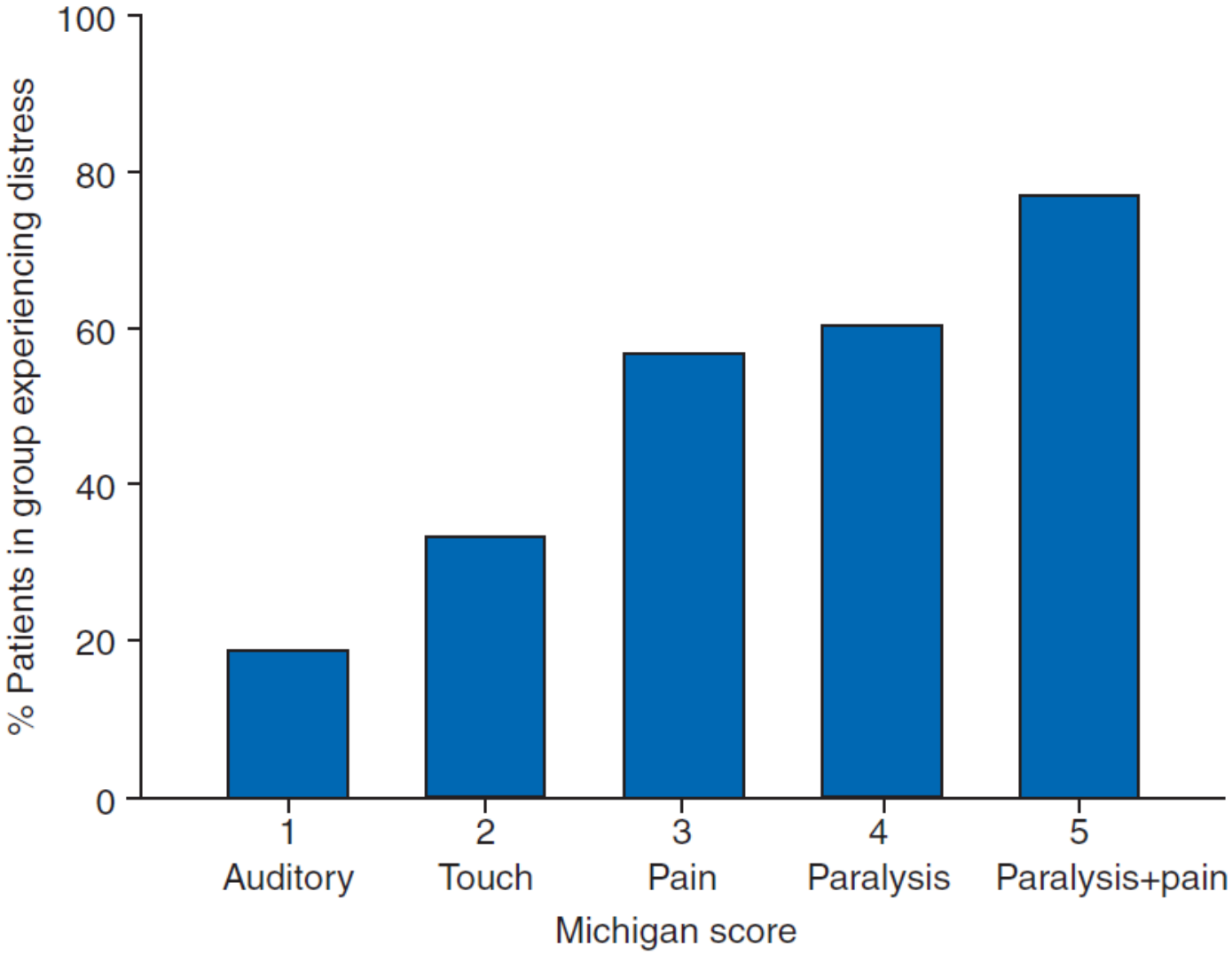
Classifying awareness events

Table 2. Inter-Observer Agreement for the Basic Classification Categories

	Fleiss's kappa value	95% CI	Agreement
Overall classification	0.851	0.847–0.856	Almost perfect
Class 1	0.916	0.907–0.926	Almost perfect
Class 2	0.836	0.827–0.845	Almost perfect
Class 3	0.851	0.842–0.860	Almost perfect
Class 4	0.826	0.817–0.836	Almost perfect
Class 5	0.849	0.839–0.858	Almost perfect

Mashour et al, Anesth Analg, 2010;110:813

Classifying awareness events



Pandit et al, Br J Anaesth, 2014;113:560

High-risk cases

- Cardiac
- Hemorrhagic trauma/surgery
- Cesarean section delivery
- Difficult airway
- Pediatric
- TIVA

High-risk cases

- Cardiac
- Hemorrhagic trauma/surgery
- Cesarean section delivery
- Difficult airway
- Pediatric
- TIVA

What does this mean for THRIVE?

- **TIVA is typically considered a high-risk group for intraoperative awareness with recall**

- **THRIVE will be the first study to compare TIVA to inhaled anesthesia with awareness as an outcome**

Risk factors and causes

	Percentage of case reports
Potential risk factors	
History of awareness	1.6
Absence of volatile anesthetic or propofol during maintenance of anesthesia	23
Cause of awareness	
Overly light anesthesia	87
Increased anesthetic requirement	7
Machine malfunction	5
Misuse of machine	4

Ghoneim et al, Anesth Analg, 2009;108:527

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	Percentage of case reports
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Ghoneim et al, Anesth Analg, 2009;108:527

Are patients with a history of awareness:

Are patients with a history of awareness:

- **At increased risk of awareness?**

Are patients with a history of awareness:

- **At increased risk of awareness?**
- **Cared for differently by anesthesia providers?**

Are patients with a history of awareness:

- At increased risk of awareness?
- Cared for differently by anesthesia providers?
- Less responsive to the effects of general anesthetics?

26,490 patients from three major trials were screened for history of awareness

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 13, 2008 VOL. 358 NO. 11

Anesthesia Awareness and the Bispectral Index

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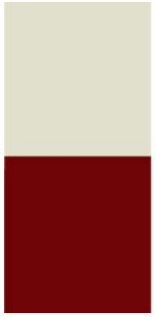
October 2012
Volume 117, Number 4
ISSN 0003-3022



ANESTHESIOLOGY
The Journal of the American Society of Anesthesiologists, Inc. • anesthesiology.org

Prevention of Intraoperative Awareness with Explicit Recall in an Unselected Surgical Population

A Randomized Comparative Effectiveness Trial

George A. Mashour, M.D., Ph.D.,* Amy Shanks, M.S.,†
Kevin K. Tremper, Ph.D., M.D.,‡ Sachin Kheterpal, M.D., M.B.A.,§
Christopher R. Turner, M.D., Ph.D., M.B.A.,‖ Satya Krishna Ramachandran, M.D., F.R.C.A.,§
Paul Picton, M.D., F.R.C.A.,§ Christa Schueller, B.S.,# Michelle Morris, M.S.,**
John C. Vandervest, B.S.,†† Nan Lin, Ph.D.,‡‡ Michael S. Avidan, M.B., B.Ch.§§

26,490 patients from three major trials were screened for history of awareness

Control group

- **Matched 5:1 for**
  - **Age**
  - **ASA physical status**
  - **Comorbid conditions**
  - **Risk factors for awareness**

Increased incidence of awareness with history of awareness

	AWR	No AWR	Total
History of AWR	4 (1.7)	237 (98.3)	241
No history of AWR	4 (0.3)	1,201 (99.7)	1,205

Values are expressed as n (%).

AWR = awareness with explicit recall.

Aranake et al, Anesthesiology, 2013;119:1275

No difference in anesthetic care

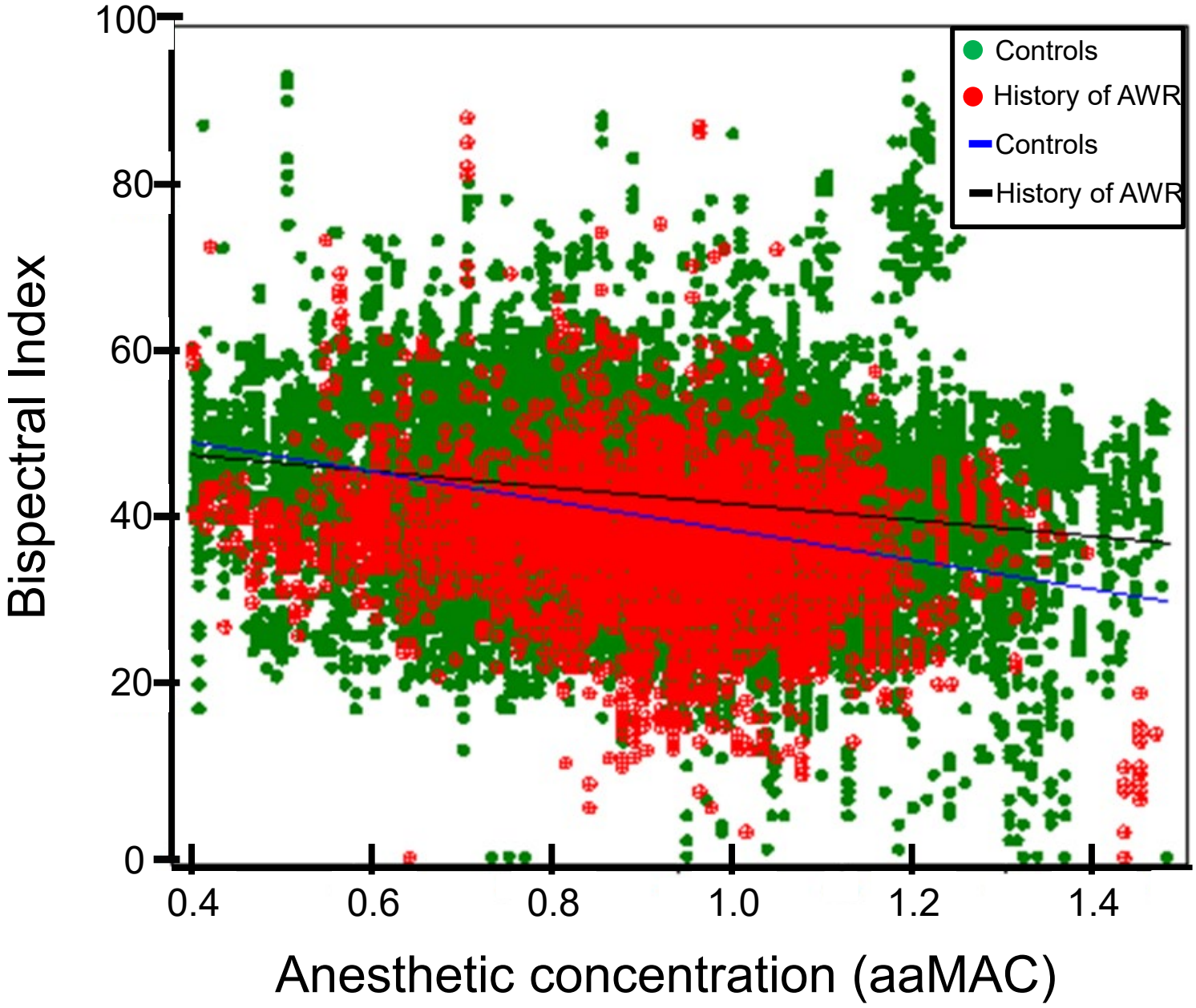
	Hx of AWR (n = 231)	No Hx of AWR (n = 1,151)
Doses		
Midazolam equivalents*	0.04 ± 0.00	0.03 ± 0.00
Propofol equivalents*	3.07 ± 0.12	3.05 ± 0.05
Morphine equivalents*	0.44 ± 0.03	0.44 ± 0.01
Vecuronium equivalents*	0.10 ± 0.01	0.11 ± 0.00
Median aaMAC	0.95 ± 0.01	0.95 ± 0.01

Values are expressed as n (%) or mean ± SEM.

* Doses are reported in mg/kg.

Aranake et al, Anesthesiology, 2013;119:1275

Altered MAC-BIS relationship



What does this mean for THRIVE?

- **A proportion of patients screened for THRIVE will have a substantially higher risk of awareness**

- **Clinicians are unlikely to change practice as a result of that risk factor**

Outline

- Definition
- Incidence & risk factors
- **Sequelae**
- Prevention

Post-traumatic stress disorder

- **Elevated autonomic arousal and generalized anxiety**
- **Intrusive and distressing thoughts or images recalling the trauma**
- **Behavioral avoidance of physical cues that prompt memory of the trauma**

Incidence of post-awareness PTSD

Table 1. Past Studies of the Psychological Consequences of Intraoperative Awareness

Study	Year	Recruitment method	No. of awareness patients studied	Patients with PTSD (*N*)	Patients with postoperative psychological sequelae (may be inclusive of PTSD)
Moerman et al.[1]	1993	Referral	26	ND	69% (described as "after effects")
Schwender et al.[2]	1998	Advertising and referral	45	7% (3)	49% (described as "after effects")
Ranta et al.[3]	1998	Secondary outcome of a prospective awareness study	5[a]	0	20% (described as "sleep disturbances")
Domino et al.[4]	1999	Closed claims	61[b]	10% (6)	84% (described as "temporary emotional distress")
Osterman et al.[5]	2001	Advertising and referral	16	56% (9)	ND (range of CAPS score for non-PTSD awareness patients was 7–41)
Lennmarken et al.[6]	2002	Secondary outcome of a prospective awareness study[19]	9[c]	44% (4)	78%
Samuelsson et al.[7]	2007	Consecutive enrollment of patients who had previously experienced awareness	46	2% (1)[d]	33%
Leslie et al.[8]	2010	Secondary outcome of a prospective awareness study[9]	7[e]	71% (5)	ND (all patients met at least some criteria for PTSD)

Mashour, Anesth Analg, 2010;110:668

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PTSD in 71%

Mashour, Anesth Analg, 2010;110:668

Psychological Sequelae of Surgery (Psych SOS) study

- **Awareness patients and matched controls taken from B-Unaware, BAG-RECALL and MACS trials**
- **PCL-S self-report administered**
- **43% with awareness met a screening threshold for PTSD**
- **Dissociation appeared to be a mediating factor**

Whitlock et al, Anesth Analg, 2015;120:87

What does this mean for THRIVE?

- **Trial participants reporting awareness should be made aware of the risk for syndromal or subsyndromal PTSD**

Outline

- Definition
- Incidence & risk factors
- Sequelae
- **Prevention**

Major randomized controlled trials

- B-Aware trial (2004)
- B-Unaware trial (2008)
- BAG-RECALL trial (2011)
- BIS-TIVA trial (2011)
- MACS (2012)

THE LANCET

ARTICLES

Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial

*P S Myles, K Leslie, J McNeil, A Forbes, M T V Chan, for the B-Aware trial group**

Lancet 2004; **363:** 1757–63

B-Aware trial

- High-risk population, multicenter
- Randomized to routine care or BIS 40-60
- Confirmed awareness 0.17% (n=2) in BIS compared to 0.91% (n=11) in control (p=0.02)

Myles et al, Lancet, 2004;363:1757

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B-Unaware trial

- High-risk population, single center
- Compared BIS 40-60 to MAC 0.7-1.3
- 2 cases of definite awareness in each group (overall incidence of 0.21%)

Avidan et al, NEJM, 2008;358:1097

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BAG-RECALL trial

- High-risk population, multicenter
- Elimination of “minor criteria”
- Compared BIS 40-60 to age-adjusted MAC 0.7-1.3

Avidan et al, NEJM, 2011;365:591

Outcomes

Table 3. Between-Group Comparison of Awareness Experiences.*

Outcome	BIS Group (N = 2861)	ETAC Group (N = 2852)	P Value†	Difference, BIS–ETAC
	no. (%)			*percentage points (95% CI)*
Definite awareness: primary outcome	7 (0.24)	2 (0.07)	0.98	0.17 (–0.03 to 0.38)
Definite or possible awareness: pre-specified secondary outcome	19 (0.66)	8 (0.28)	0.99	0.38 (0.03 to 0.74)
Distressing experience of awareness: post hoc secondary outcome	8 (0.28)	1 (0.04)	0.99	0.24 (0.04 to 0.45)

Avidan et al, NEJM, 2011;365:591

Chin Med J 2011;124(22):3664-3669

Original article

Bispectral index monitoring prevent awareness during total intravenous anesthesia: a prospective, randomized, double-blinded, multi-center controlled trial

ZHANG Chen, XU Liang, MA Ya-qun, SUN Yan-xia, LI Yan-hong, ZHANG Liang, FENG Chun-sheng, LUO Bing, ZHAO Zhen-long, GUO Jian-rong, JIN Yao-jun, WU Gang, YUAN Wei, YUAN Zhi-guo and YUE Yun

BIS-TIVA trial

- High-risk population, multicenter
- 2919 TIVA cases randomized to BIS 40-60, 2309 TIVA cases randomized to routine care
- Confirmed awareness 0.14% (n=4) in BIS compared to 0.65% (n=15) in control (p=0.002)

Zhang et al, Chin Med J, 2011;124:3664

October 2012
Volume 117, Number 4
ISSN 0003-3022

ANESTHESIOLOGY
The Journal of the American Society of Anesthesiologists, Inc. • anesthesiology.org

Prevention of Intraoperative Awareness with Explicit Recall in an Unselected Surgical Population

A Randomized Comparative Effectiveness Trial

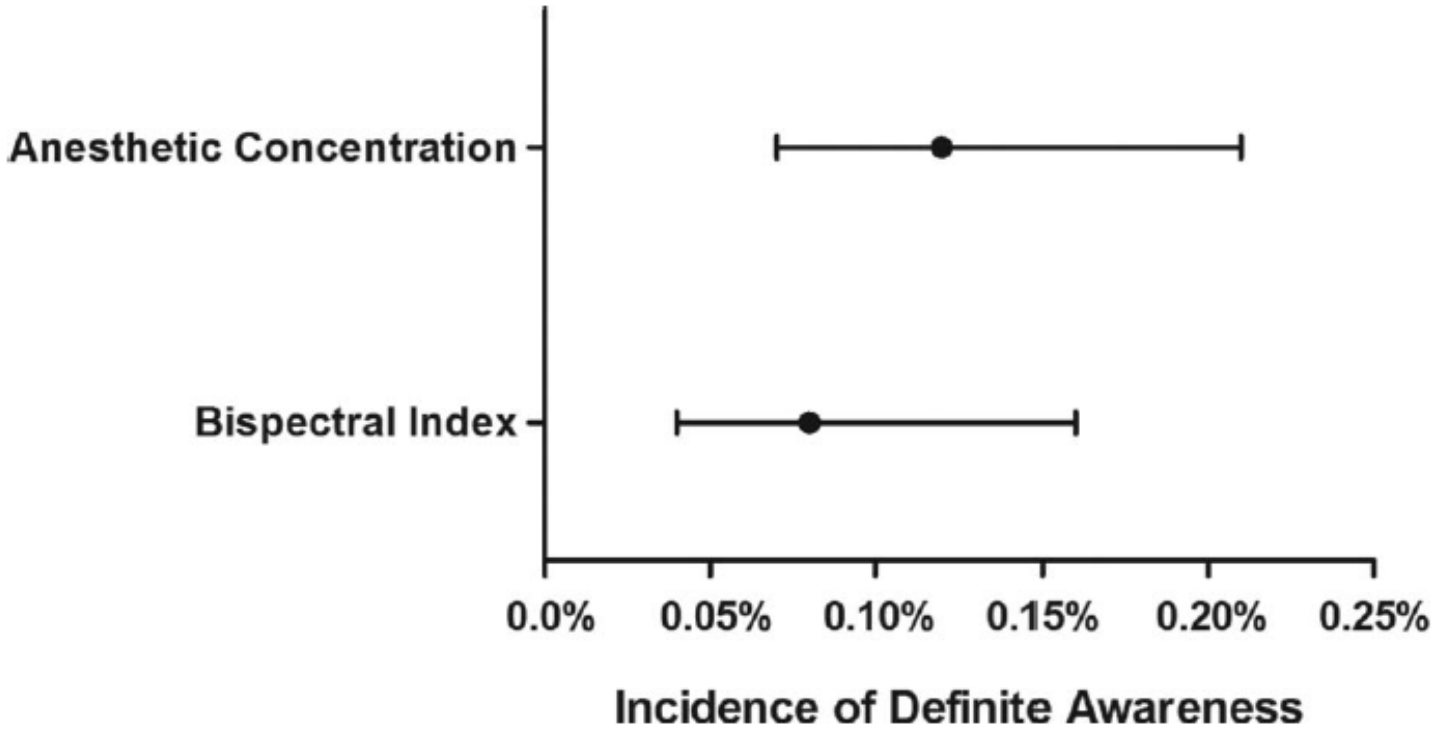
George A. Mashour, M.D., Ph.D.,* Amy Shanks, M.S.,†
Kevin K. Tremper, Ph.D., M.D.,‡ Sachin Kheterpal, M.D., M.B.A.,§
Christopher R. Turner, M.D., Ph.D., M.B.A.,‖ Satya Krishna Ramachandran, M.D., F.R.C.A.,§
Paul Picton, M.D., F.R.C.A.,§ Christa Schueller, B.S.,# Michelle Morris, M.S.,**
John C. Vandervest, B.S.,†† Nan Lin, Ph.D.,‡‡ Michael S. Avidan, M.B., B.Ch.§§

MACS

- All risk levels, multihospital, single center
- Randomized to real-time decision support with alarms for BIS>60 or “effective” MAC<0.5
- Study terminated for futility after interim analysis and recruitment of >20,000 patients

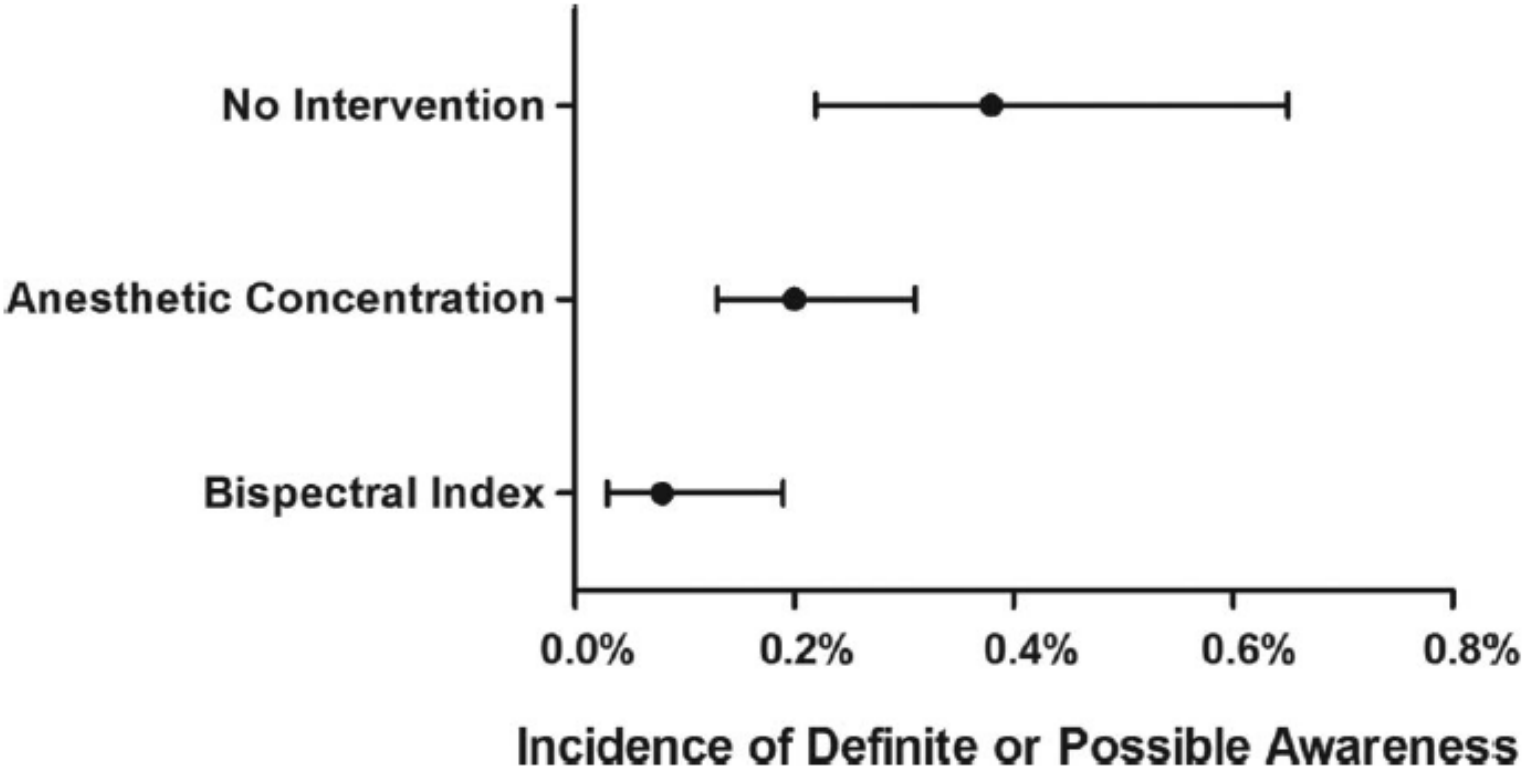
Mashour et al, Anesthesiology;2012:117:717

Primary outcome



Mashour et al, Anesthesiology;2012:117:717

Secondary outcome



Mashour et al, Anesthesiology;2012:117:717

Synthesizing the Trials

- **BIS is effective in reducing awareness compared to routine care and in patients receiving TIVA (B-Aware, 2004; Zhang-TIVA trial, 2011; MACS, 2012)**

- **BIS not superior compared to a MAC-guided protocol (B-Unaware, 2008; BAG-RECALL, 2011; MACS 2012)**

Avidan & Mashour, Anesthesiology, 2013;118:449
Mashour & Avidan, Br J Anaesth, 2015;115:i20

Cochrane Library

Cochrane Database of Systematic Reviews

2014, 2019

Bispectral index for improving intraoperative awareness and early postoperative recovery in adults (Review)

Lewis SR, Pritchard MW, Fawcett LJ, Punjasawadwong Y

What does this mean for THRIVE?

- **Patients randomized to the TIVA group would likely benefit from intraoperative EEG monitoring to reduce risk of intraoperative awareness with recall**

Summary

- **“Awareness” refers to arousal, experience, and explicit episodic recall**
- **Awareness occurs in approximately 1-2 cases/1000**
- **Risk factors include high-risk anesthetics and a history of awareness**
- **PTSD occurs in a significant proportion of patients experiencing awareness**

Summary

- **BIS monitor is likely effective in reducing awareness compared to routine care and during TIVA**

- **MAC protocol is a cost-effective alternative in patients receiving volatile anesthetics**

Current Directions

- Neural inertia
- Emergence trajectories
- EEG oscillations
- Coherence, cross-frequency coupling, connectivity
- Cortical dynamics

Acknowledgments