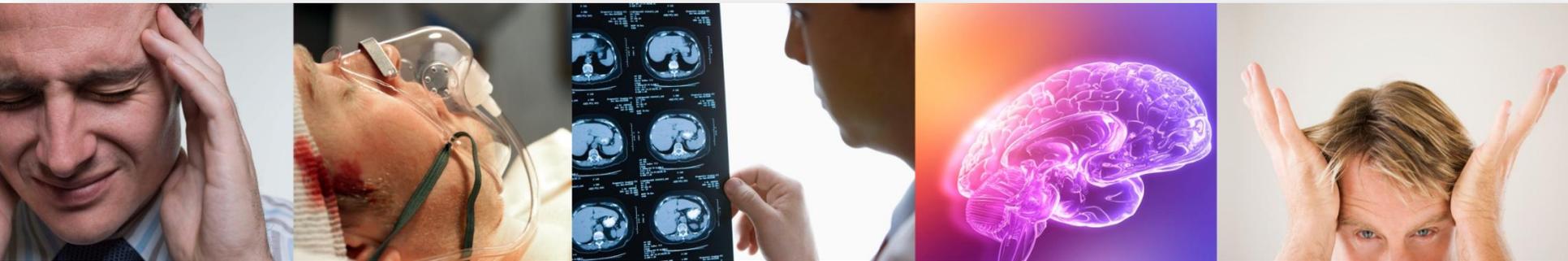


Reducing Severe Traumatic Brain Injury In the United States

- ❑ **Severe TBI in the United States and the Role of Public Health**
Dr. Lisa C. McGuire, Acting Associate Director for Science
Division of Injury Response
National Center for Injury Prevention and Control, CDC
- ❑ **Treatment of Severe TBI**
Dr. David W. Wright, Associate Professor of Emergency Medicine and
Director, Emergency Neurosciences, Department of Emergency Medicine
Emory University School of Medicine
- ❑ **Role of Policy in Reducing TBI and TBI-related Disability**
Dr. Arthur L. Kellermann, Vice President and Director of RAND Health
RAND Corporation

Severe Traumatic Brain Injury in the United States and the Role of Public Health



Lisa C. McGuire, PhD

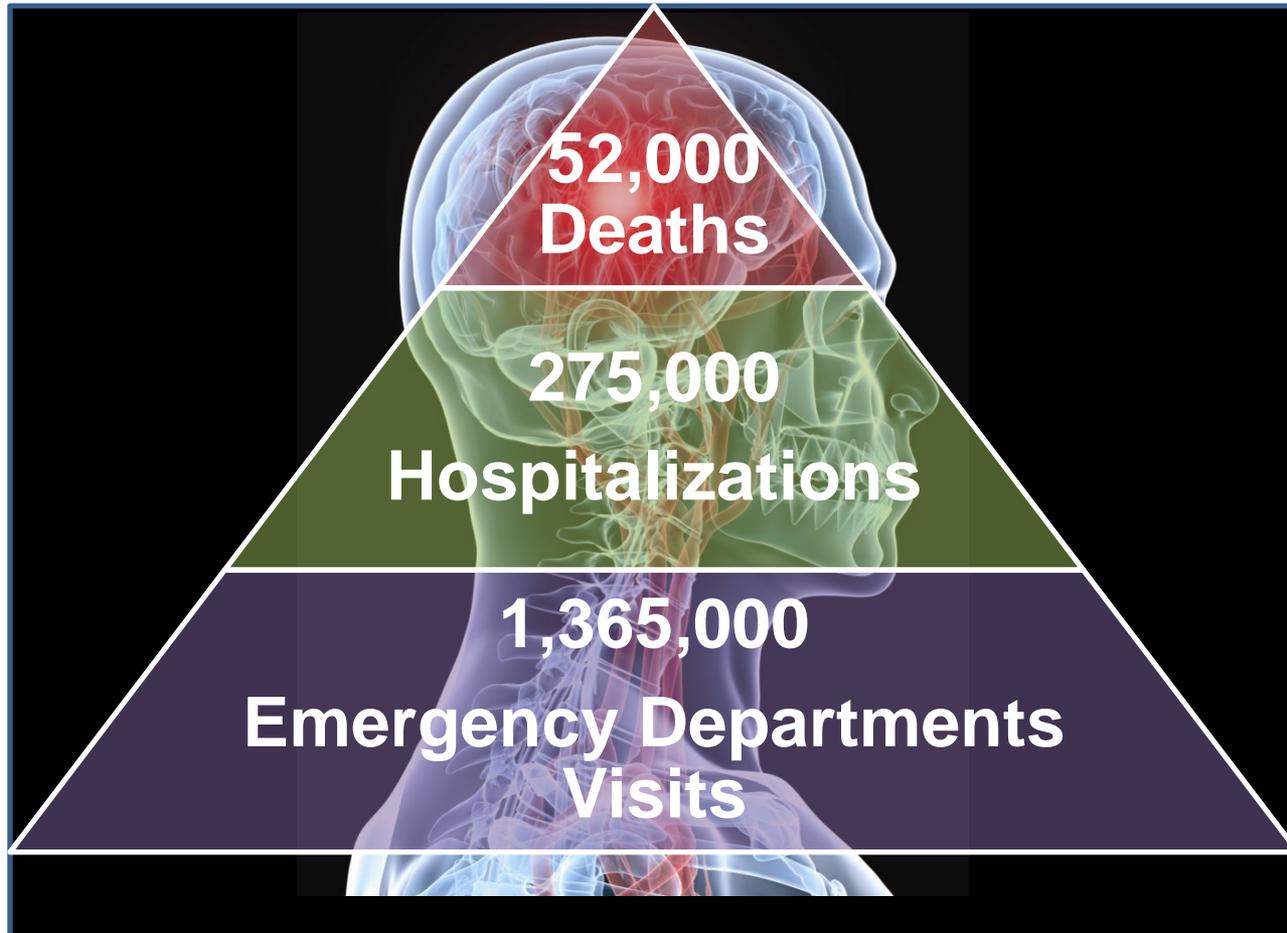
*Acting Associate Director for Science
Division of Injury Response*

National Center for Injury Prevention and Control
Centers for Disease Control and Prevention

What Is a Traumatic Brain Injury (TBI)?

**A TBI is a brain injury
caused by a bump, blow, or jolt to the head,
or a penetrating head injury
that disrupts the normal function of the brain**

Public Health Burden of TBI in the United States: Approximately 1.7M TBIs Annually



Faul, M et al. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2010

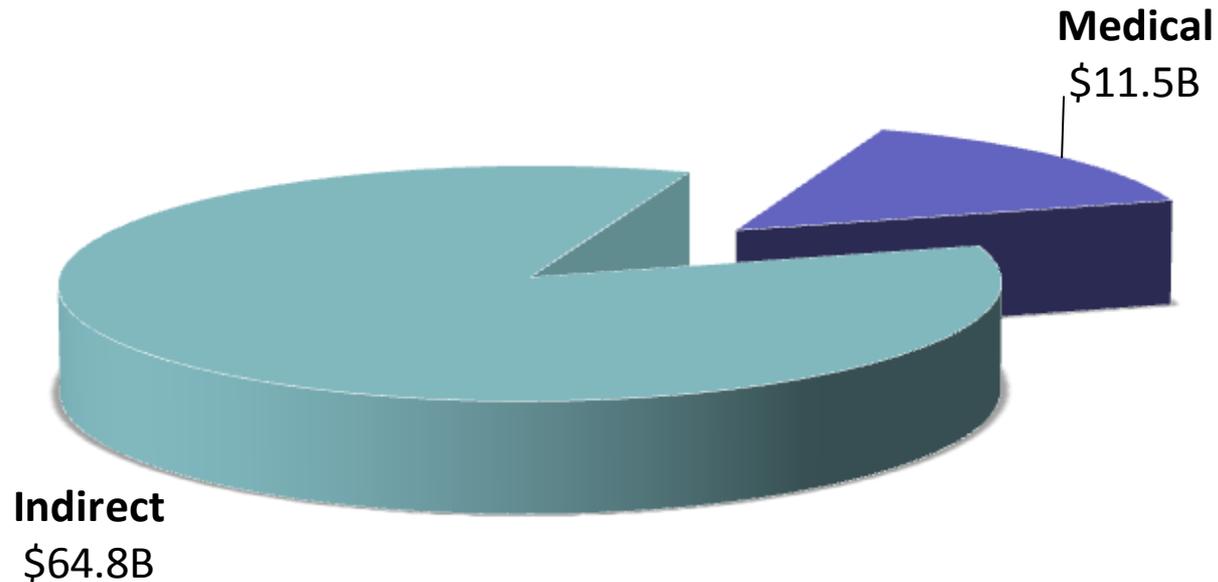
Public Health Burden of TBI in the United States

- ❑ **At least 3 TBIs are sustained every 1 minute**
- ❑ **Males are 3 times more likely to die of TBI than females**
- ❑ **5.3 million people are living with a TBI-related disability**



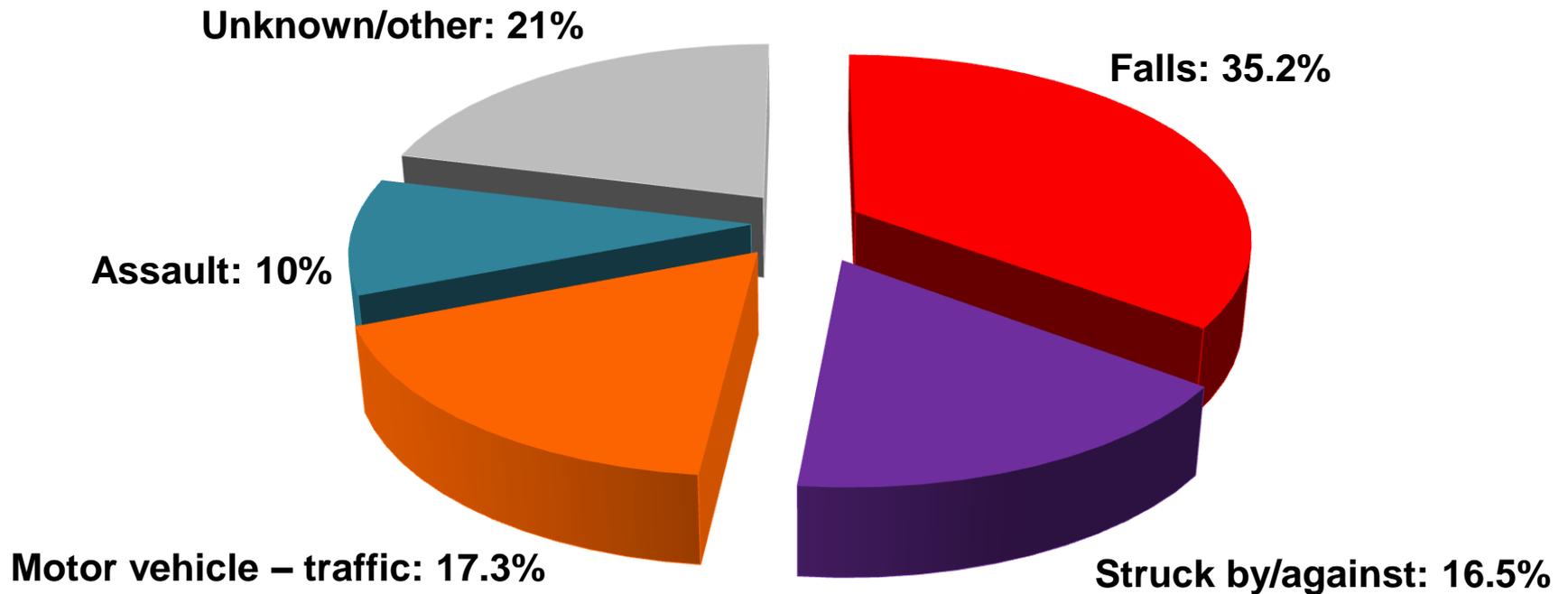
Estimated Economic Costs of TBI

\$76.3 Billion in 2010

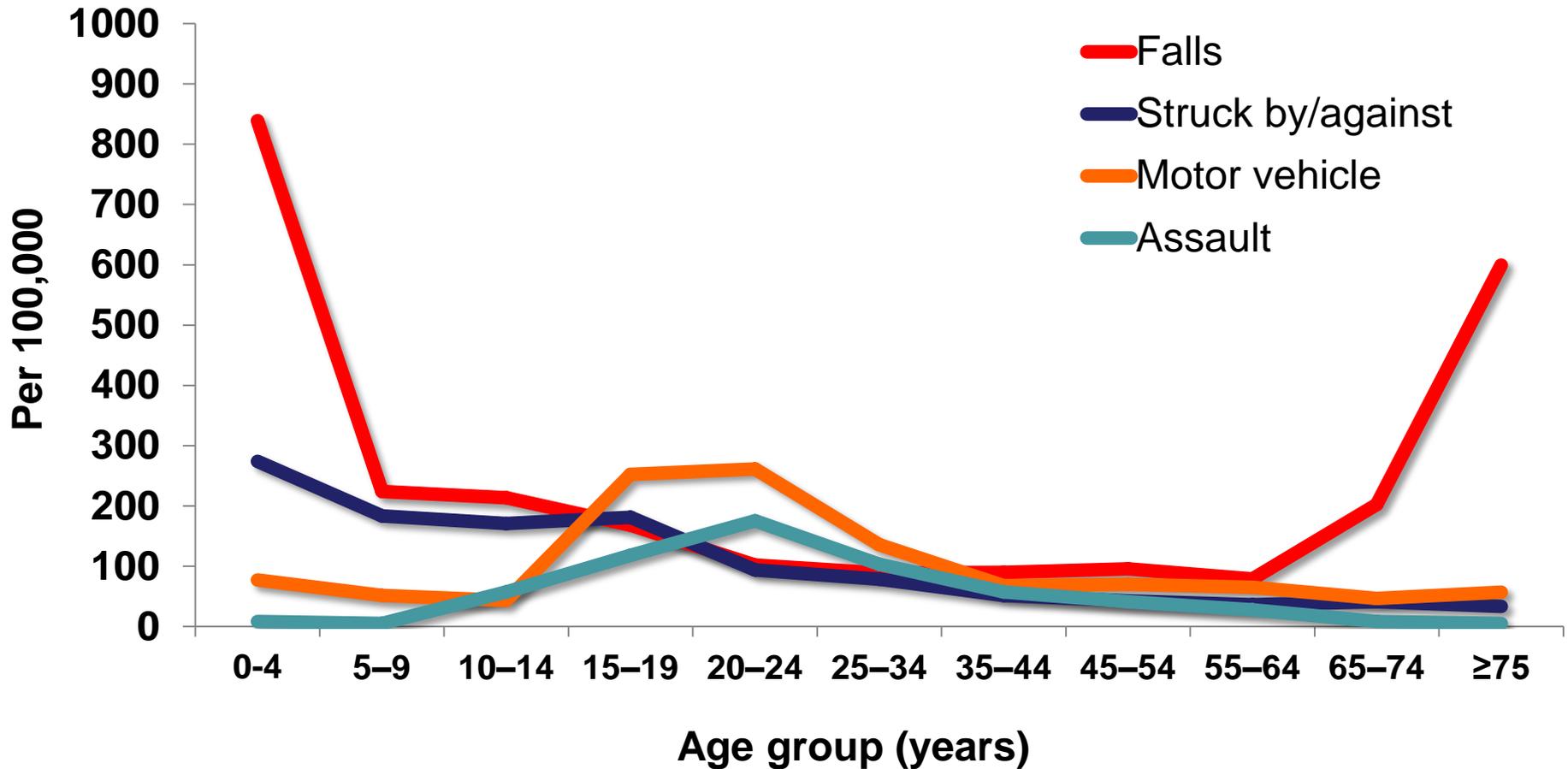


Causes of TBIs

**Estimated Average Percentage of Annual TBI by External Cause
United States, 2002–2006**



Causes of TBIs



Faul, M et al. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2010

Classification of Traumatic Brain Injuries

- ❑ **Currently, there is no general agreement on severity classifications, and several different types of classification are used**
- ❑ **TBI is categorized as mild, moderate, and severe**
- ❑ **Classification may be based on**
 - Level of consciousness (Glasgow Coma Score)
 - Anatomic injury description (Abbreviated Injury Score)
 - Functional outcome after injury (Glasgow Outcome Score)

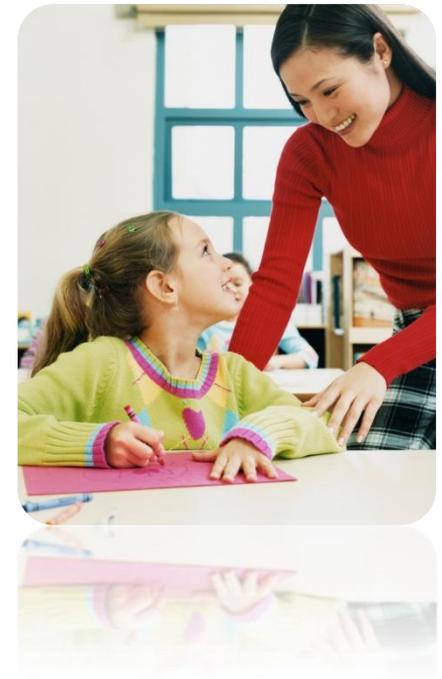
Why Focus on Severe TBI?

- ❑ **Severe TBIs may lead to lifetime disability or death**
 - Estimated 43% of hospitalized TBI survivors (125,000 people) have TBI-related disabilities one year after injury
- ❑ **Major economic impact to society**
 - The cost of fatal TBIs and TBIs requiring hospitalization, many of which can be considered severe, account for ~90% of the total TBI medical costs

Potential Consequences of Non-fatal Severe TBI

Individual

- Cognitive impairment
- Psychological and emotional changes
- Personality changes
- Sensory and/or motor dysfunction
- Seizure disorders



Potential Consequences of Non-fatal Severe TBI

Family, Community, and Society

- Psychological stress
- Economic burden
- Productivity loss
- Need for supportive services



Primary Prevention of Severe TBI

□ Interventions

- Motor vehicle related: Restraints, airbags, vehicle technology
- Sports: Helmets
- Falls: Exercise and balance training
- Shaken baby syndrome: Parent education

□ Challenges

- Dissemination of interventions
- Widespread adoption of interventions, including policy



Early Management of Severe TBI

❑ Guidelines for Field Triage of Injured Patients

- Developed by CDC
- Help EMS providers decide when to transport injured patient to highest level of care within a trauma system

❑ Challenges

- 45 million people in the US are not within 1 hr of a trauma center
- Widespread adoption and implementation of field triage guidelines
- Training of EMS personnel varies across the country



The overall risk of death for patients with serious injury was 25% lower when care was provided at a level I trauma center

Early Management of Severe TBI

❑ Guidelines for Pre-hospital and In-hospital Management of Severe TBI

- Developed by the Brain Trauma Foundation
- Provide health care professionals with evidence-based patient care and treatment recommendations, such as
 - Prevention of hypotension (low blood pressure)
 - Prevention of hypoxemia (low blood oxygen)
 - Monitoring intracranial pressure to guide therapy

❑ Challenges: Widespread adoption of these guidelines

Rehabilitation and Reintegration

A Comprehensive Approach

□ Goals

- Regain function
- Adapt to disabilities
- Return to employment or former role in household and community

□ Requires multidisciplinary team approach tailored to individual

□ Challenges

- Availability of comprehensive services
- Insurance reimbursement limitations
- Research incorporating growing evidence for neuroplasticity

Public Health Role in Addressing Severe TBI

❑ Reducing severe TBI by providing the best scientific evidence for informing efforts

- To prevent TBI from happening in the first place
- To improve identification of TBI and its management when it happens

❑ Key activities

- Surveillance
- Identification of evidence-based strategies
- Dissemination and implementation of evidence-based strategies

Surveillance

Challenges and Way Forward

❑ Current data sources

- National Electronic Injury Surveillance Systems (NEISS)
- Multiple Cause-of-Death Mortality Data Public Use Data files from the National Center for Health Statistics
- Vital Statistics from all 50 states and the District of Columbia
- National Trauma Data Bank

❑ Way forward

- Development of a standard definition for TBI
- National injury surveillance system
- Population-based longitudinal or follow-up studies

Primary Prevention Challenges and Way Forward

❑ Challenges

- Multiple causes require multiple strategies
- State-based versus national policies and interventions

❑ Way forward

- Tailor and evaluate evidenced-based interventions to high risk populations
- Evaluation of existing primary prevention strategies to strengthen implementation and outcomes
- Fully implement and disseminate evidenced-based strategies
 - Community Guide Recommendations: Seat belts, ignition interlocks
 - Heads Up: Prevention and response to TBI education campaign

Early Management Challenges and Way Forward

❑ Challenges

- Access to trauma care varies among states
- Lack of social and political will for development of trauma systems

❑ Way forward

- Ensure early access to trauma care
- Support the development of trauma systems that are integrated with public health systems across the United States

Rehabilitation and Community Integration Challenges and Way Forward

❑ Challenges

- Regain/maintain health and function
- Insurance reimbursement is fragmented and not comprehensive

❑ Way forward

- Reimbursement mechanisms for comprehensive services
- Build evidence for most effective strategies of a comprehensive rehabilitation program
- Disseminate best practices for linking community services with rehabilitation providers

Public Health Role in Addressing Severe TBI

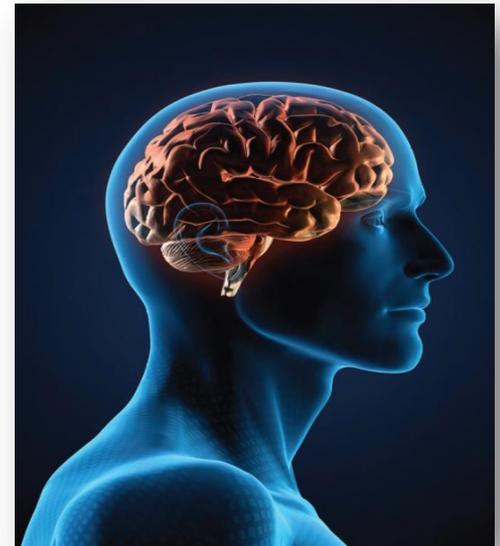
Importance of Partnerships

❑ Building partnerships

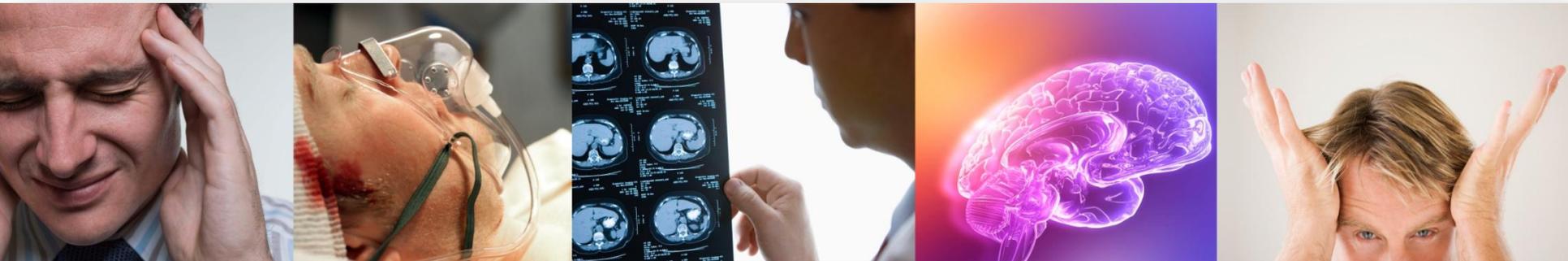
- Close gaps and move forward with effective surveillance
- Develop new interventions
- Promote the widespread adoption of evidence-based prevention and treatment strategies

❑ Partners

- Federal agencies
- State and local health departments
- National and community organizations
- Medical community



Traumatic Brain Injury: From Guidelines to Novel Therapies



David W. Wright, MD

*Associate Professor of Emergency Medicine and
Director, Emergency Neurosciences*

Department of Emergency Medicine, Emory University School of Medicine

Disclaimer: Zenda Technologies[®] Inventor and stockholder, Startup company to further develop the DETECT™ Technology – a novel tool for detecting concussions

BHR Pharma. Inventor of technology licensed from Emory to create path for progesterone technology to consumer. Eligible for Royalties through Emory University

Overview

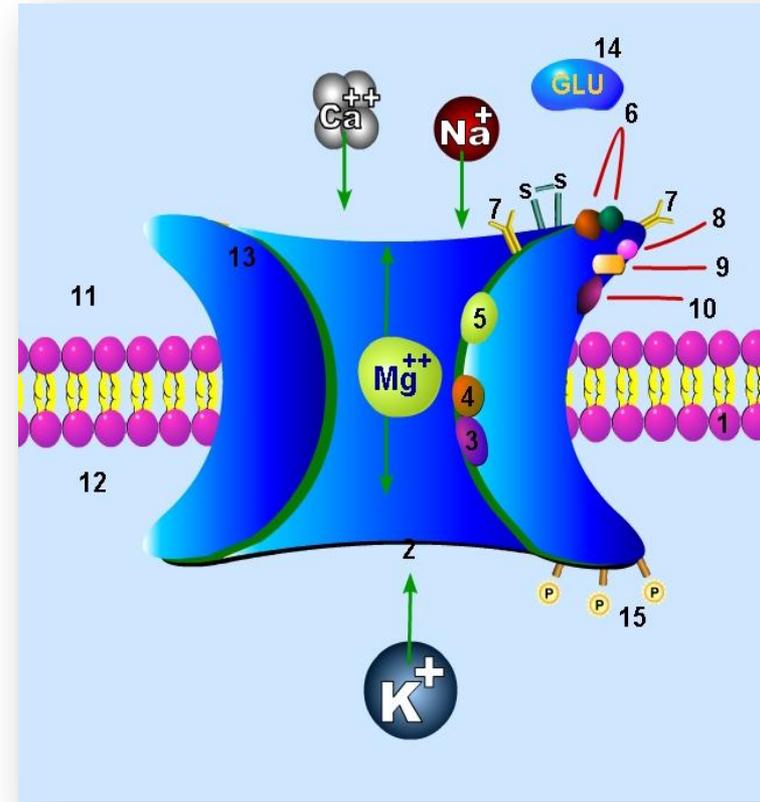
- Review the fundamentals of traumatic brain injury
- Review the current standards of care and guidelines for treatment
- Reflect on the research gaps and opportunities for new interventions
- Discuss a promising new therapy
- Summarize our way forward

Primary Injury

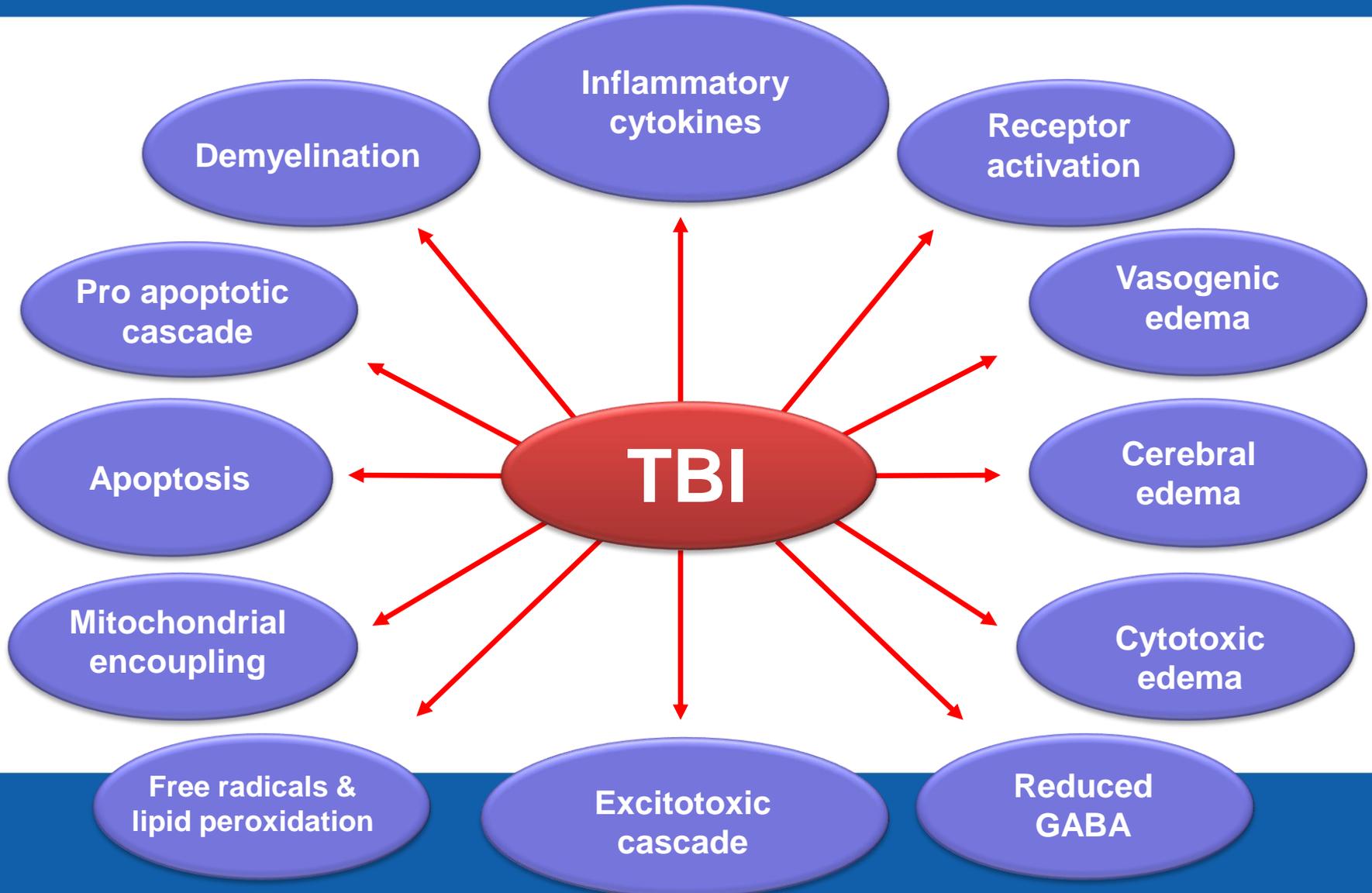


Secondary Injury Neurotoxic Cascade

- ❑ **Begins immediately after the injury and lasts days to months**
- ❑ **Excitatory amino acids**
 - The earliest mechanisms discovered involved an abnormally large release of glutamate (a normal neurotransmitter in the brain)
- ❑ **Critical Ions: Ca, Na, Mg**
 - Ca influx activates multiple intracellular pathways and ultimately leads to cell death and necrosis



Neurotoxic Cascade after TBI



Failure of Past TBI Clinical Trials

- ❑ **None of the available medical therapies provide substantial relief from oedema and raised intracranial pressure, or at best, they are temporizing in most cases**
- ❑ **Hypothermia trials have been inconclusive**
- ❑ **50 compounds in 30 TBI trials over 30 years—all failed**





**At Present There Are
No Effective Drug Treatments
for Traumatic Brain Injury**

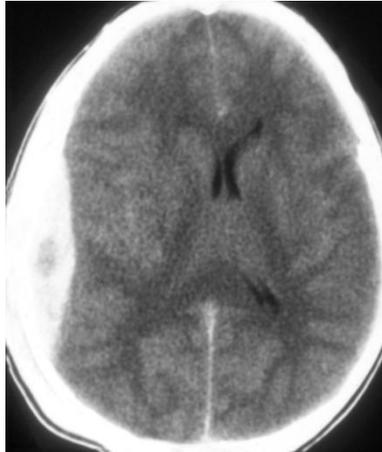
Clinical Research Gaps



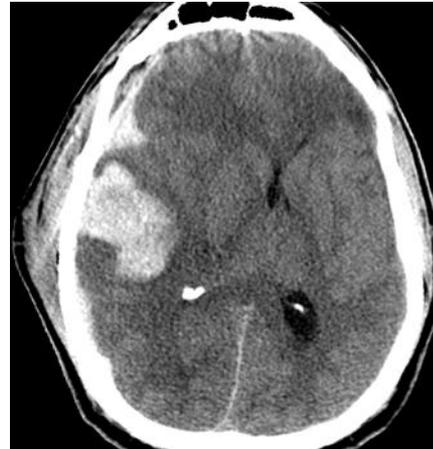
Research Gap: TBI Definition

- ❑ **Lack of a TBI definition based on pathophysiology**
- ❑ **Current approach is based solely on an individual's response to the clinical environment**
 - Patients are categorized based on the Glasgow Coma Scale (GCS) as mild, moderate, or severe
 - Crude
 - Often contaminated by other factors: Alcohol intoxication, sedating drugs, intubation
 - Lacks any pathological link
 - Changes or evolves over time
 - Does disservice to the complexity of the underlying injury

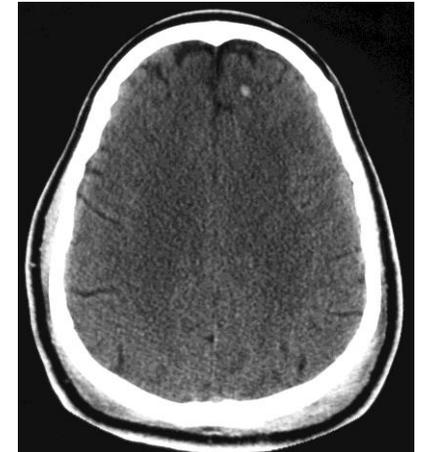
TBI Is a Heterogenous Disease



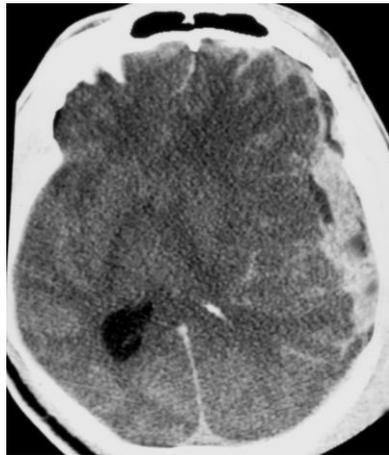
Epidural hematoma



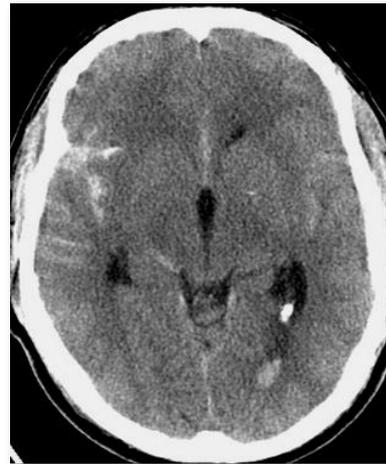
Contusion/Hematoma



Diffuse axonal injury



Subdural hematoma



Subarachnoid hemorrhage

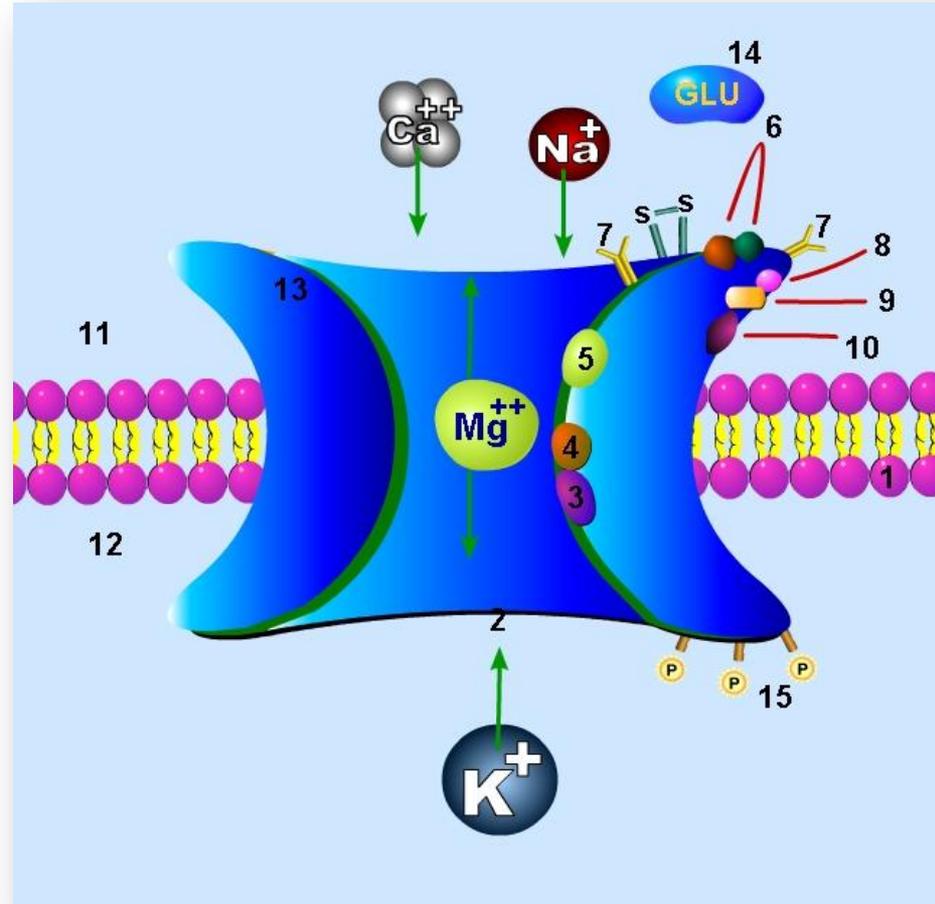


Diffuse swelling

Research Gap: Developing Treatment

- ❑ Mechanistic approach
- ❑ Single target

“The magic bullet”



Multifaceted Approach

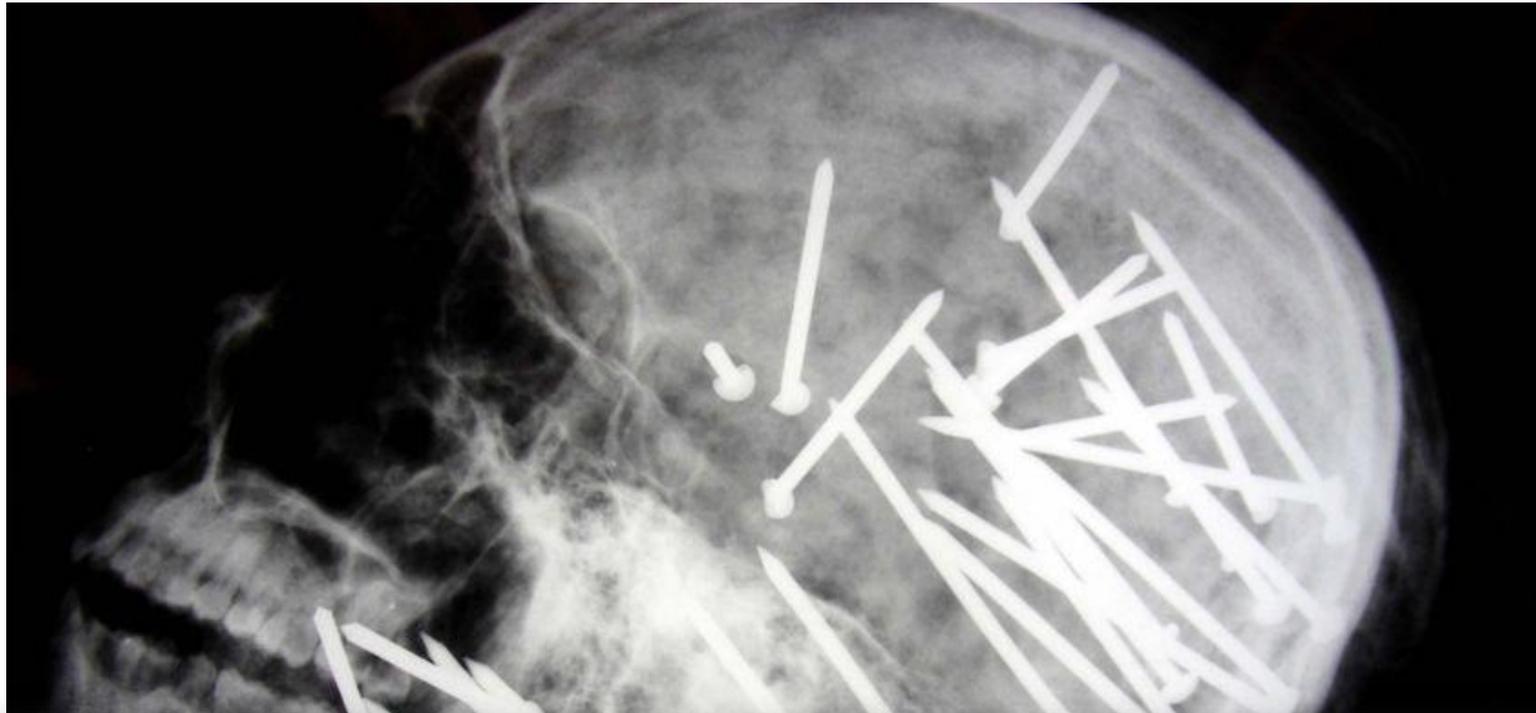
- ❑ Multiple mechanisms
- ❑ Multiple targets
- ❑ Pleiotropic drugs
- ❑ Drug combinations



“The dirty drug...drug cocktail”



Lack of Evidence for Current Approach Results in Treatment Variability

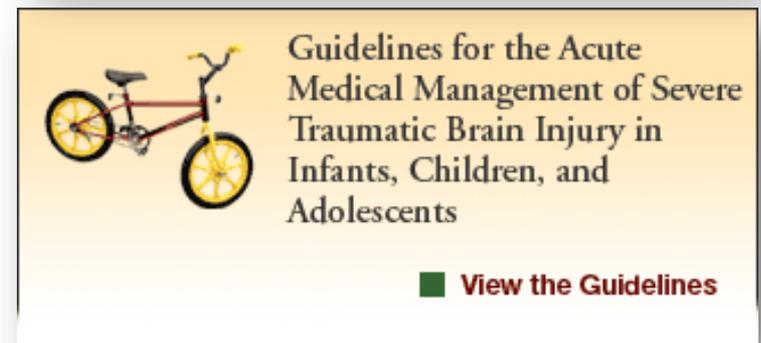
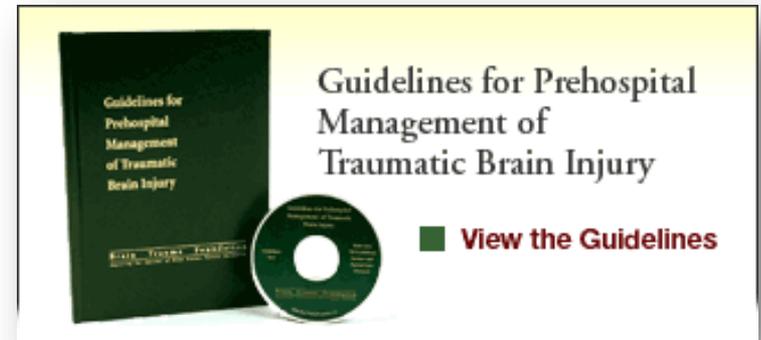
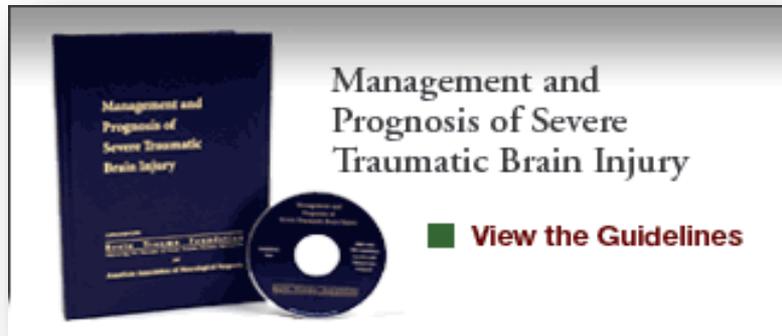


<input type="checkbox"/> Pulse Ox $\geq 90\%$	<input type="checkbox"/> ICP < 20 mmHg	<input type="checkbox"/> Physiologic Na ⁺ 135-145*
<input type="checkbox"/> PaO ₂ ≥ 100 mmHg	<input type="checkbox"/> PbtO ₂ ≥ 15 mmHg	<input type="checkbox"/> INR ≤ 1.4
<input type="checkbox"/> PaCO ₂ 35-45 mmHg	<input type="checkbox"/> CPP ≥ 60 mmHg	<input type="checkbox"/> PLTS $\geq 75 \times 10^3 / \text{mm}^3$
<input type="checkbox"/> SBP ≥ 100 mmHg	<input type="checkbox"/> Temp 36.0-38.1°C	<input type="checkbox"/> Hgb ≥ 8 gm/dl
<input type="checkbox"/> pH 7.35-7.45	<input type="checkbox"/> Glucose 80-180 mg/dL	

*Hypertonic saline therapy: Na⁺ range: 145 mmol/L (minimum) to 160 mmol/L (maximum)

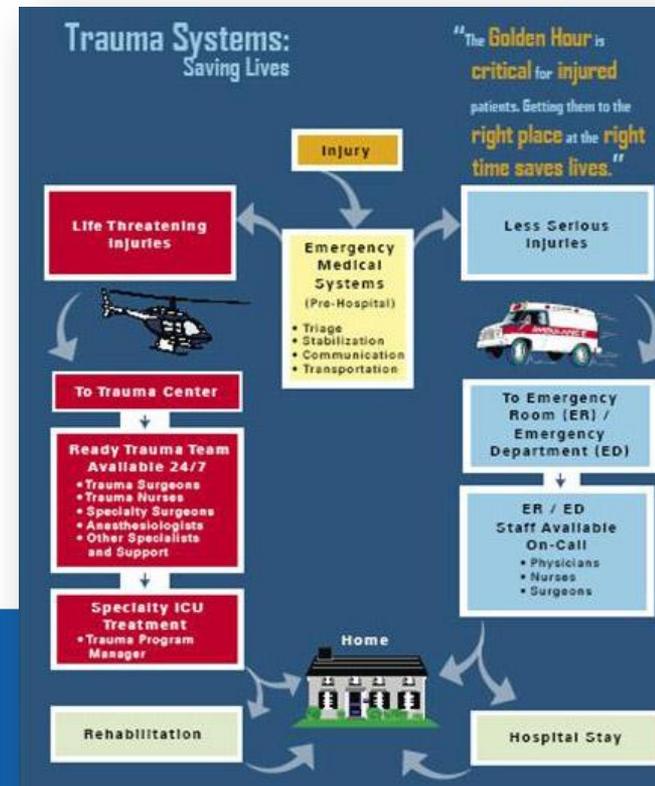
Brain Trauma Foundation Guidelines

- ❑ Evidence-based, first developed in 1996
- ❑ Widely adopted as a way to reduce TBI mortality and morbidity



Brain Trauma Foundation Guidelines

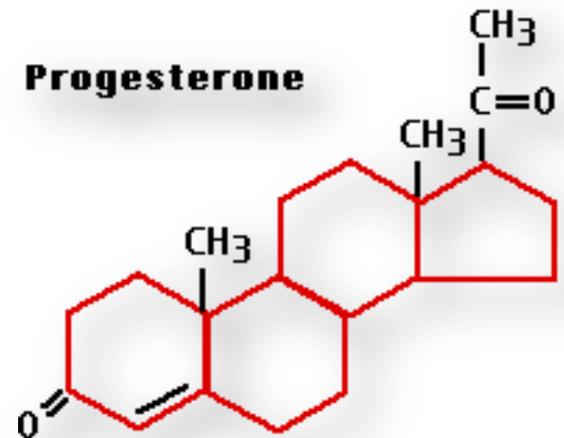
- ❑ Adoption of the guidelines saves lives
- ❑ Current adoption rate is 65%
- ❑ Full adoption of treatment guidelines would result in an estimated annual savings of
 - \$262 million in medical costs
 - \$43 million in rehabilitation costs
 - \$3.84 billion in lifetime societal costs



<http://www.braintrauma.org>

Faul, M et al. J Trauma 2007;63(6):1271-8

Hiding in Plain Sight: Progesterone is a Promising Treatment



Where Would We Be Without CDC?

"The CDC was the first federal agency willing to take a gamble on what many at the time thought was "pie in the sky" research. Their initial, two-year grant to my team kick-started it all."

Don Stein, PhD

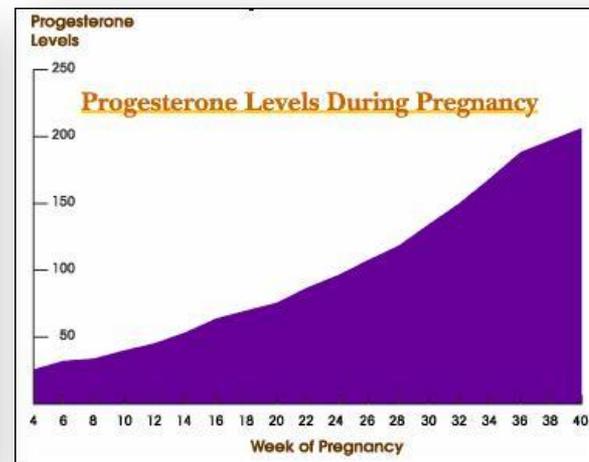


GAME CHANGER

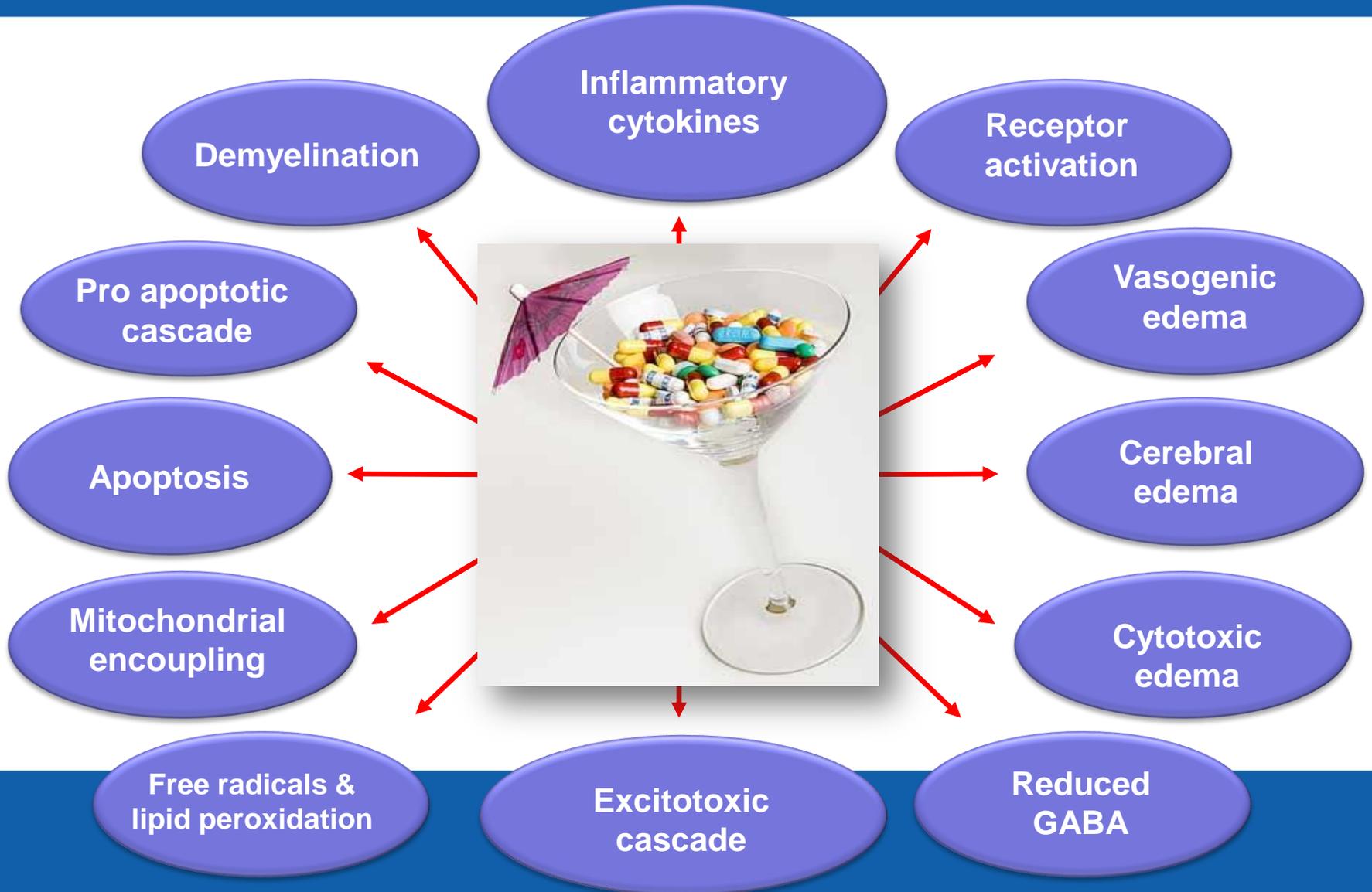
Emory University

Early Observations

- ❑ Hormonal state of female rats at the time of a brain injury affected outcome
- ❑ Animals high in progesterone (e.g., pregnancy) had much better outcomes than male or non-pregnant animals
- ❑ Giving progesterone to animals after injury improved the outcome of both male and female rats



Potential Mechanisms in TBI



Corroborative Research

- ❑ **>180 publications showing positive results with progesterone in neurological injury**
 - 24 different laboratories
 - 4 animal species
 - 22 different animal models



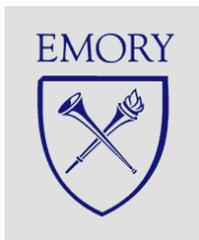
Will Progesterone Work in Humans? Robust in Animal Models, but ...



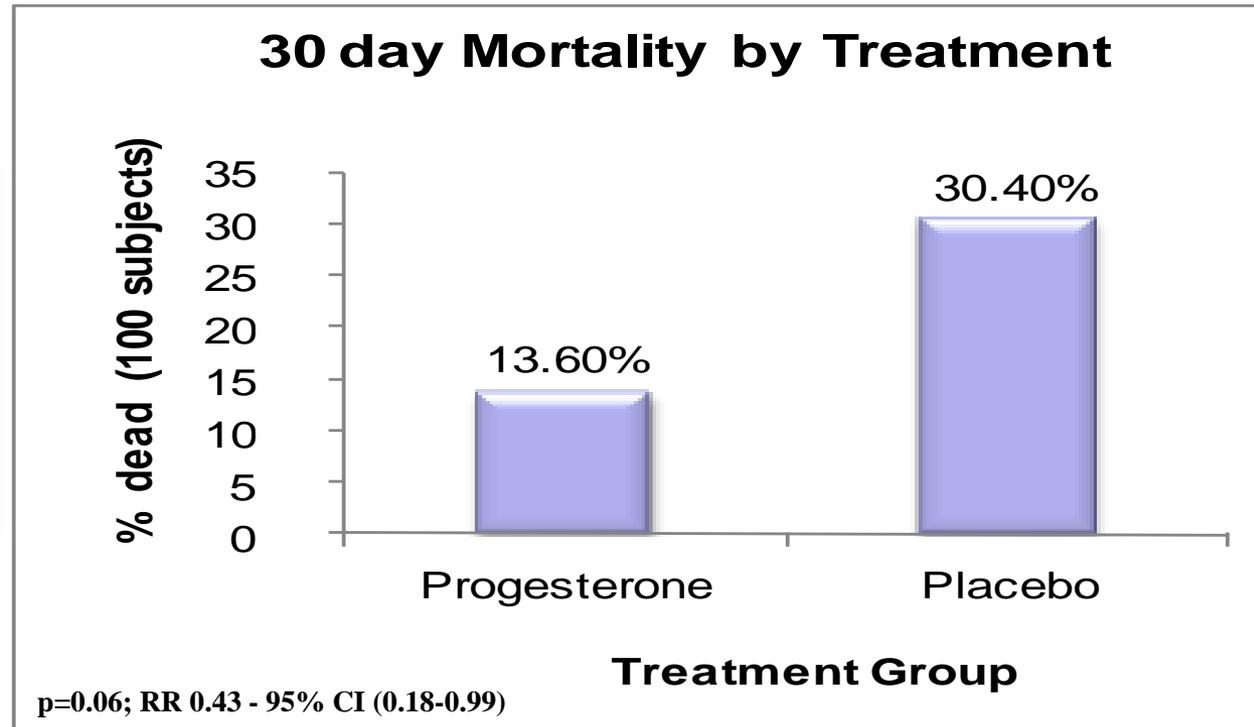


A Randomized Clinical Trial of Progesterone for Acute Traumatic Brain Injury

- ❑ **In 2001, the first human trial of progesterone for TBI was conducted at Grady Memorial Hospital**
 - The Phase II randomized, double blind, placebo controlled study enrolled 100 subjects over 3 years
 - Goal: To verify that progesterone was safe and to determine if any signals of efficacy existed



Key Findings: Progesterone Was Safe and Reduced Mortality by >50%



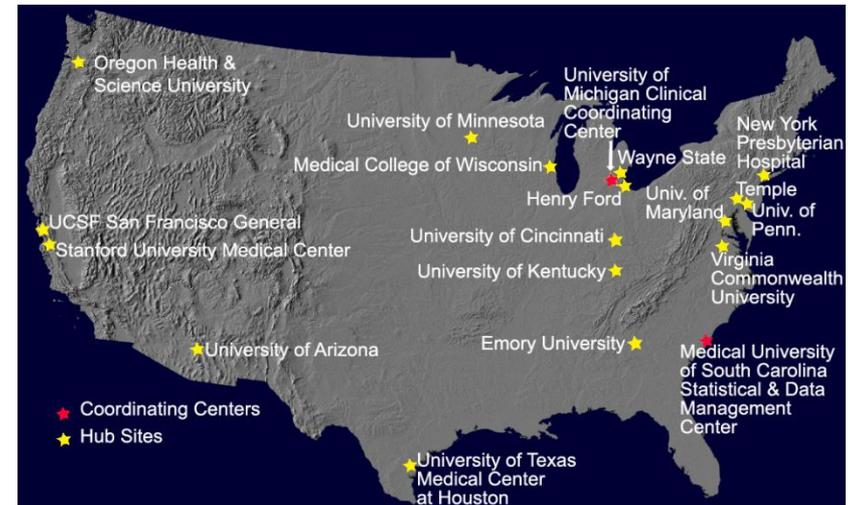
**Similar findings were demonstrated later by Xiao et al in a study of 159 subjects:
Improved functional outcome at 3 and 6 months post injury**

ProTECT™ III

Progesterone for Traumatic Brain Injury

❑ Multicenter Phase III clinical trial

- Funded by NIH
- Conducted through Neurological Emergencies Treatment Trials Network
- 31 level 1 trauma centers



❑ Goal

- Enroll 1,140 patients over 4.5 years
- To date 326 patients enrolled
- Primary outcome is Stratified Glasgow Outcome Scale Extended



Way Forward

- ❑ **Comply with the BTF Guidelines for care**
 - Special attention to standardizing care for clinical trials
- ❑ **Develop a pathophysiological classification system and better biomarkers for targeting therapy and trials**
- ❑ **Keep trying!**
 - Other therapies are being considered or assessed in clinical trials
 - Drugs with pleotropic action or combination therapies are the most likely to be successful
- ❑ **Strengthen partnerships between clinical medicine and public health to improve prevention, public awareness, and outcomes**

Role of Public Policy in Reducing TBI and TBI-Related Disability



Arthur L. Kellermann, MD, MPH

Vice President and Director of RAND Health

RAND Corporation

Santa Monica, CA





“It takes very little energy to scramble an egg, and all our science is incapable of reversing that transaction.”

- Dr. Richard Feynman
Nobel Prize-winning physicist

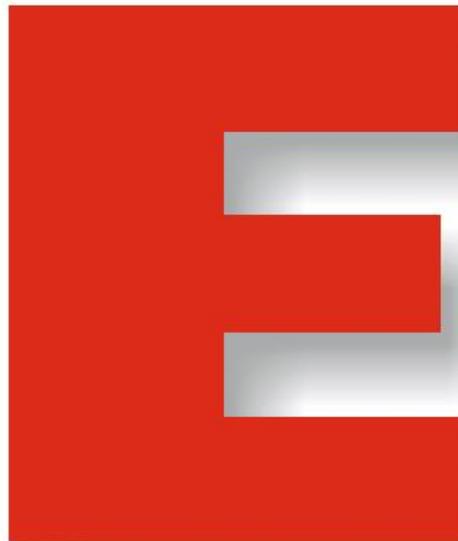
A “Winnable Battle”



<http://www.articlesnatch.com/Article/Seat-Belt-Use-And-Traumatic-Brain-Injury/221375#ixzz1X75nGvuC>

Public Policy Can Advance Prevention

Prevention: The Four E's



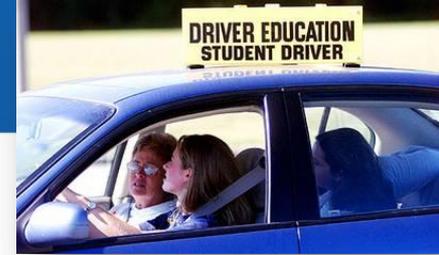
Education & Information

Enforcement & Regulation

Engineering & Technology

Economic Incentives

Driver Education: Ineffective



❑ 3 well-designed national evaluations (United States, Australia, and New Zealand)

- Driver education may paradoxically increase crashes involving teens

❑ DeKalb County, GA, randomized controlled trial

- 3 groups, >16,000 students
 - Standard driver education
 - 80-hr course: Simulation, driving range, on-the-road components
 - Control group: No formal driver education
- Initial analysis: No significant differences in rates of crashes or subsequent traffic violations among the 3 groups
- Follow-up analysis
 - An early and slight reduction only in the standard course group
 - No difference between 80-hr course and control group

Public Education: Largely Ineffective

❑ Safety belts work, but only when used

- Available in all new passenger cars since 1964
- Shoulder belts introduced in 1968
- Integrated lap and shoulder belts in 1972

❑ 1st widespread survey (1982) found low rates of use

- 19 cities; 11% usage by drivers and front-seat passengers

❑ Over the next decade, usage slowly climbed to 66–69%

- Safety belt laws
- Sporadic enforcement
- More public education



High-Visibility Enforcement: Effective



Primary Enforcement: More Effective Than Secondary Enforcement

❑ In “primary enforcement” states

- An officer issues a citation upon observing an unbelted motorist
- Substantially higher levels of enforcement and higher rates of seat belt use

❑ In “secondary enforcement” states

- An officer must stop the vehicle for some other violation before issuing a seat belt citation

❑ Getting seat belt use rates above 83% requires

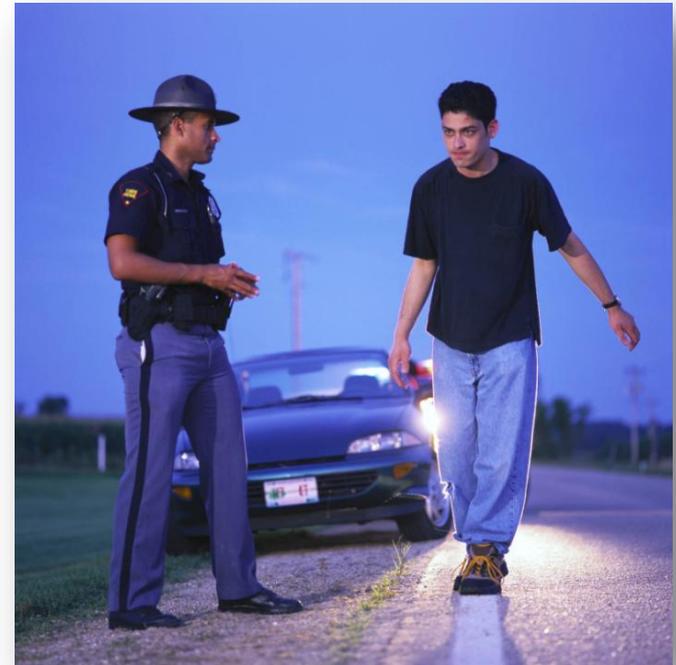
- “Click It or Ticket” type programs aimed at the general population
- Special programs targeting low-use groups such as occupants of pickup trucks, rural residents, and nighttime drivers



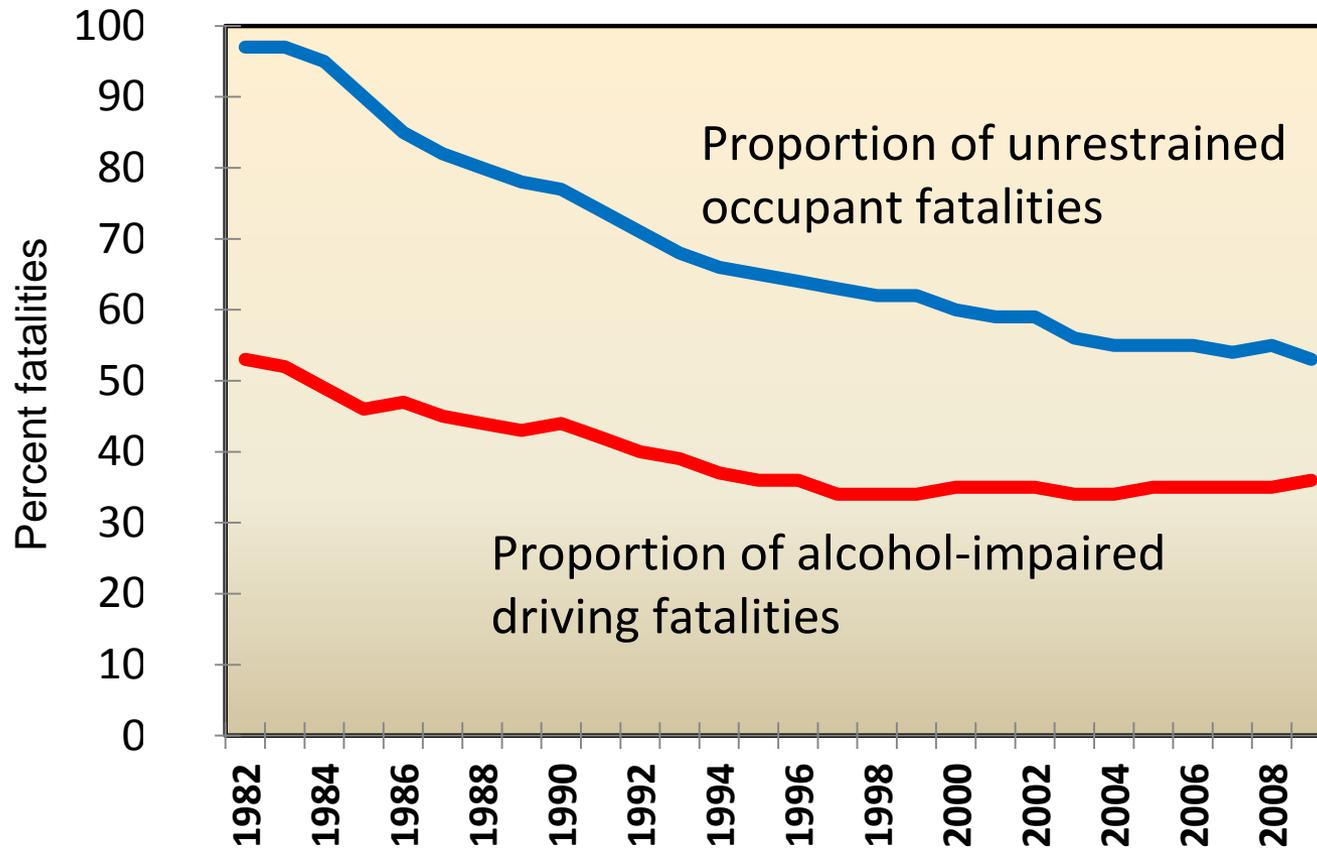
Alcohol-Impaired Driving: An Ongoing Challenge

□ 1982 to the mid-90s: Progress made

- Grassroots organizations like Mothers Against Drunk Driving (MADD)
- High-visibility enforcement
- Intense publicity of fatal crashes
- Public policy
 - 0.08 blood alcohol level
 - License revocation for driving under influence
 - Minimum drinking age laws



Alcohol-Impaired Driving Fatalities: 1982–2008



**Impaired driving
still causes
one-third of
fatal crashes**

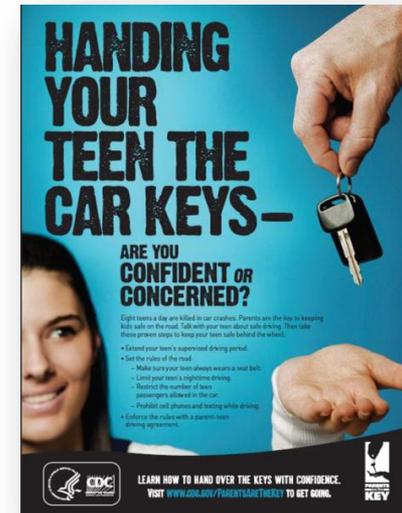
Graduated Drivers Licensing (GDL) Laws: Effective

❑ A 3-phase system for beginning drivers

- Learner's permit: Allows driving only while supervised by a fully licensed driver
- Intermediate license: Unsupervised driving allowed, but only with certain restrictions
- Unrestricted license after intermediate phase

❑ Among 16-year old drivers, the most stringent GDL laws are associated with

- 38% reduction in fatal crashes
- 40% reduction in injury crashes



Motorcycle Helmet Laws: Effective



□ History of universal helmet laws

- 1966: The 1st law enacted
- By 1975: Laws in effect in 47 states and the District of Columbia
- 1975: Federal penalties eliminated for states failing to have a universal law; about half the states repealed their laws

□ Cochrane review of 61 studies

- Helmets reduce risk of death in a crash by 42%
- Helmets decrease the risk of head injury by 69%

□ Mandatory helmet use laws are highly effective

- Adopting states quickly achieve helmet use rates of >90%
- Repealing states see usage rates plummet to 50%

Safety Engineering: Effective



Built to Protect...

❑ Key design features

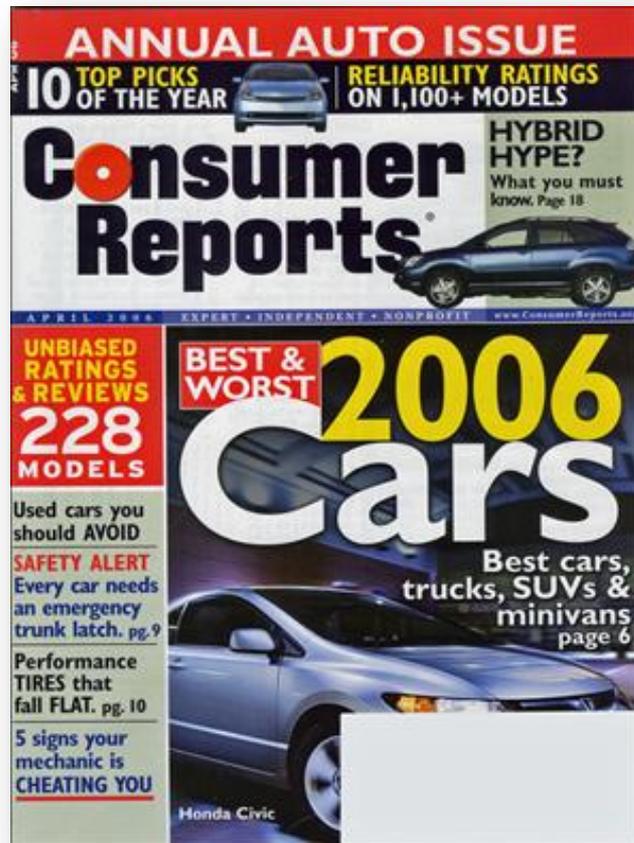
- Strong occupant compartment (safety cage)
- Crumple zones to absorb the force of a serious crash
- Side elements and a strong roof support protect against intrusion
- Safety belts, pre-tensioners, and frontal and supplemental (side and curtain) airbags absorb energy in a crash

❑ Mandatory safety testing

- Based on dynamic testing, new vehicles earn a “crashworthiness rating”



Economic Incentives: Effective



Policy Challenges in Acute Care and Rehabilitation

❑ Prehospital (EMS) care

- CDC trauma triage guidelines

❑ Regionalized trauma systems

- “Get the right patient to right hospital at the right time”

❑ Acute care at trauma centers

❑ Optimal rehabilitation



Policy Gaps

- ❑ **Sports-related concussions are a large and growing concern**
- ❑ **Access to trauma and rehabilitation care is inadequate in many parts of the US**
 - **What can be done about it?**
- ❑ **Reimbursement policies affect access to and the quality of rehabilitation services**
 - **How should they be changed?**



Policy Challenges

❑ Values

- Concern about “personal freedom” could trump robust evidence of the benefit of helmet and seatbelt laws, product safety regulations, and even policies that deter impaired driving

❑ Funding

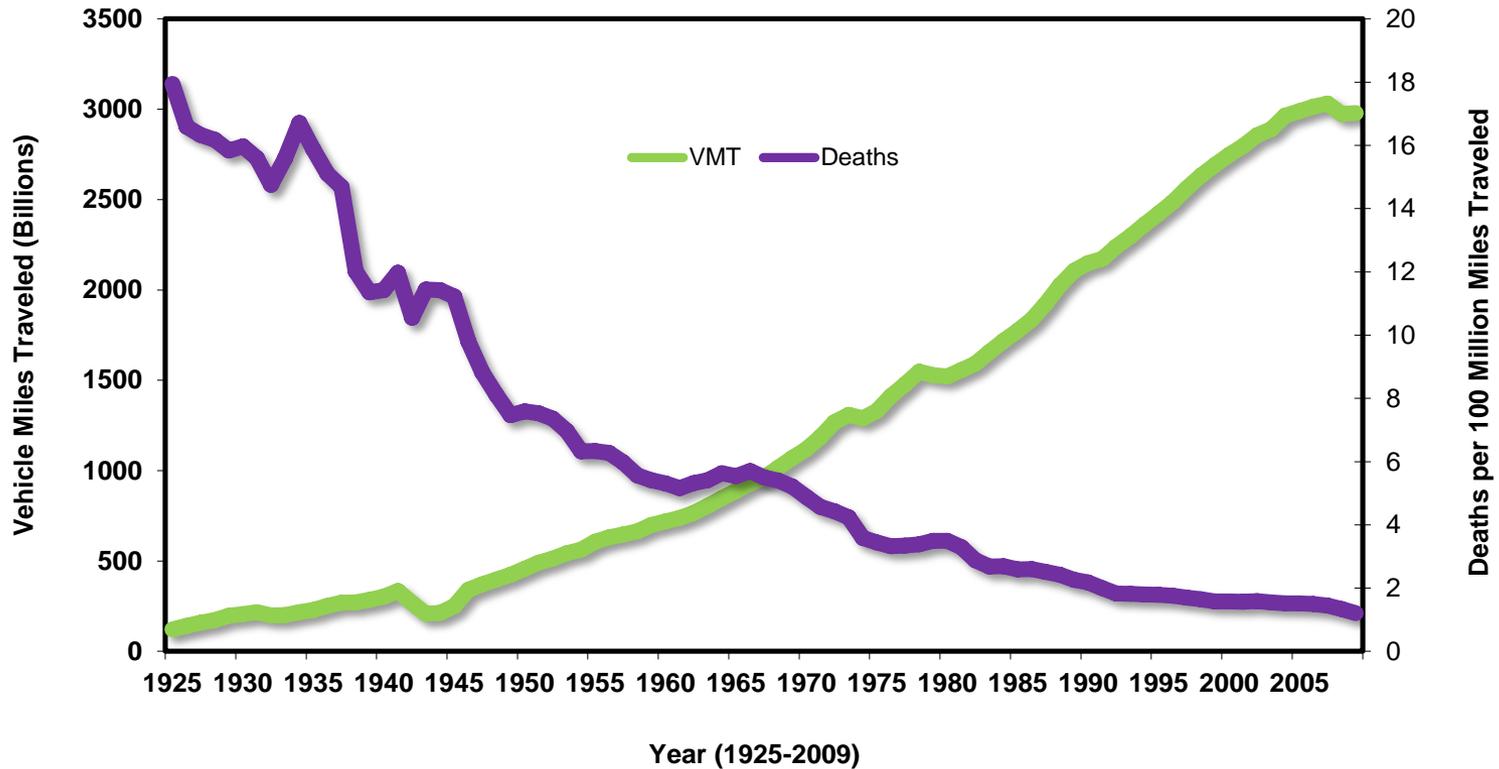
- Convincing policy-makers to allocate sufficient money to trauma care and rehabilitation



The Chronicle / Michael Macor

We Are Winning This Battle!

Annual Vehicle Miles Traveled and Motor Vehicle-Related Deaths
United States 1925-2009



VMT, Vehicle miles traveled
MMWR, May 14, 1999;48(18);369-374
Data source: National Safety Council, Injury Facts, 2011