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
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  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

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Acting Associate Director for Science
Division of Injury Response
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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.

- 52,000 Deaths
- 275,000 Hospitalizations
- 1,365,000 Emergency Departments Visits

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

Faul, M et al. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2010
Estimated Economic Costs of TBI
$76.3 Billion in 2010

Coronado, VG et al. The epidemiology and prevention of TBI, in press, 2012
Causes of TBIs

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

- Falls: 35.2%
- Motor vehicle – traffic: 17.3%
- Struck by/against: 16.5%
- Assault: 10%
- Unknown/other: 21%
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

References:
Potential Consequences of Non-fatal Severe TBI

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

Coronado, VG et al. The epidemiology and prevention of TBI, in press, 2012
Potential Consequences of Non-fatal Severe TBI

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

Coronado, VG et al. The epidemiology and prevention of TBI, in press, 2012
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

Coronado, VG et al. The epidemiology and prevention of TBI, in press, 2012
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

https://www.braintrauma.org/coma-guidelines
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

Rehabilitation of Persons with Traumatic Brain Injury. Bethesda, MD, September 1999
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

Coronado, VG et al. The Epidemiology and prevention of TBI, in press, 2012
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

http://www.thecommunityguide.org/index.html
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

Heads Up Summary Report, in press, CDC, 2011
http://www.cdc.gov/concussion/clinician.html
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

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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
Secondary Injury
Neurotoxic Cascade

Intracellular Calcium Signaling

Hormones, Neurotransmitters, Growth Factors, Osmolarity

Gene Expression

Hypertrophy

Growth Factors, Osmolarity

ADP-Ribose, Arachidonic Acid, Sphingosine

Depolarization/Voltage

Acetylcholine, Glutamate, Serotonin, ATP
Neurotoxic Cascade after TBI

- Demyelination
- Inflammatory cytokines
- Receptor activation
- Pro apoptotic cascade
- Apoptosis
- Mitochondrial encoupling
- Vasogenic edema
- Cerebral edema
- Cytotoxic edema
- Free radicals & lipid peroxidation
- Reduced GABA
- Excitotoxic cascade
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.

Interagency meeting on TBI, Washington, DC, 2006
At Present There Are No Effective Drug Treatments for Traumatic Brain Injury
Clinical Research Gaps
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
- Pleotropic drugs
- Drug combinations

“The dirty drug…drug cocktail”
Lack of Evidence for Current Approach Results in Treatment Variability

<table>
<thead>
<tr>
<th>Pulses Ox ≥ 90%</th>
<th>ICP &lt; 20 mmHg</th>
<th>Physiologic Na+ 135-145*</th>
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<tbody>
<tr>
<td>PaO2 ≥ 100 mmHg</td>
<td>PbtO2 ≥ 15 mmHg</td>
<td>INR ≤ 1.4</td>
</tr>
<tr>
<td>PaCO2 35-45 mmHg</td>
<td>CPP ≥ 60 mmHg</td>
<td>PLTS ≥ 75 x 10^3 / mm^3</td>
</tr>
<tr>
<td>SBP ≥ 100 mmHg</td>
<td>Temp 36.0-38.1°C</td>
<td>Hgb ≥ 8 gm/dl</td>
</tr>
<tr>
<td>pH 7.35-7.45</td>
<td>Glucose 80-180 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

*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

https://www.braintrauma.org/coma-guidelines
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:
Progestosterone is a Promising Treatment
"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
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

- Demyelination
- Mitochondrial uncoupling
- Excitotoxic cascade
- Receptor activation
- Inflammatory cytokines
- Apoptosis
- Pro apoptotic cascade
- Apoptosis
- Cytotoxic edema
- Vasogenic edema
- Cerebral edema
- Proapoptotic cascade
- Free radicals & lipid peroxidation
- Reduced GABA
- Excitotoxic cascade
>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 …
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

Xiao, G et al. Critical Care 2008;12:R61
**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
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

BTF, Brain Trauma Foundation
http://www.braintrauma.org
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

Countermeasures That Work. NHTSA Office of Behavioral Safety Research, NTI-130. Washington, DC
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

Williams AF and Wells JK. J Safety Res 2004;35:175-180
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
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

http://www.madd.org
Alcohol-Impaired Driving Fatalities: 1982–2008

Proportion of unrestrained occupant fatalities

Proportion of alcohol-impaired driving fatalities

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

Countermeasures That Work. NHTSA Office of Behavioral Safety Research, NTI-130 Washington, DC
www.aaafoundation.org/pdf/NationwideReviewOfGDL.pdf
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
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**

EMS, Emergency medical service
http://www.cdc.gov/fieldtriage
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
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