TRAUMATIC BRAIN INJURY

Jonathan M. Silver, M.D.
New York University

Stuart C. Yudofsky, M.D.
Baylor College of Medicine

Robert Hales, M.D.
University California, Davis

Outline

- Epidemiology
- Definition
- Pathophysiology
- Neuropsychiatric Sequelae
- Pharmacologic Treatment

1. **Which of the following diseases has the greatest annual incidence?**
    a. **HIV**
    b. **Cerebral vascular accidents**
    c. **Breast cancer**
    d. **Traumatic brain injury**
    e. **Multiple sclerosis**

2. **Which of the following are the minimal criteria for mild traumatic brain injury?**
   a. **loss of consciousness for 5 minutes**
   b. **posttraumatic amnesia for 15 minutes**
   c. **any period of confusion**
   d. **any blow to the head**

3. Which of the following would be most expected with a contusion on the inferior surface of the frontal lobe?
   a. apathy
   b. word finding problems
   c. depression
   d. aggression

4. Which medications have been shown in controlled studies to improve cognition after TBI?

a. cholinesterase inhibitors
b. memantine
c. ginko biloba
d. lamotrigine

5. **Which of the following classes of medications has the strongest support in the literature for the treatment of aggression after TBI?**
   a. **selective serotonin reuptake inhibitors**
   b. **anticonvulsants**
   c. **beta-blockers**
   d. **atypical antipsychotics**

Major Teaching Points

- TBI is one of the most common medical disorders.
- There are several severities of TBI. Mild TBI is the most common, and loss of consciousness is not required for the diagnosis, only an alteration in consciousness.
- There are many processes that occur during a traumatic injury, including structural and neurochemical changes.
- The neuropsychiatric sequelae after a TBI may affect cognition, emotion, and behavior, and can manifest as a "classic" psychiatric disorder.
- Psychopharmacologic treatment focuses on specific symptoms. While there is paucity of controlled clinical trials in this area, medications may be effective.

*

Introduction

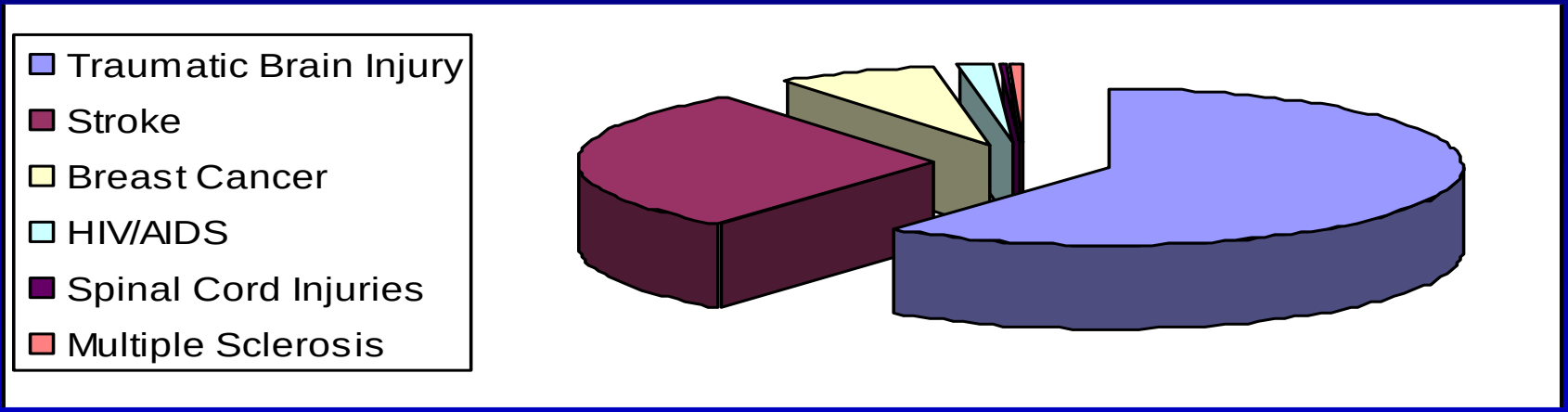
- Two million people sustain a traumatic brain injury (TBI) each year
- Incidence: 120/100,000 population (Kraus,2005)
- 300,000 require hospitalization
- Conservative estimate: 500,000 new TBI per year
  - based on CDC surveillance of TBIs resulting in hospital stay ≥ 24 hours
  - only 1 in 5 patients experiencing a mild TBI are hospitalized ≥ 24 hours
- 5.3 million Americans (~2% of the population) currently live with disabilities resulting from TBI

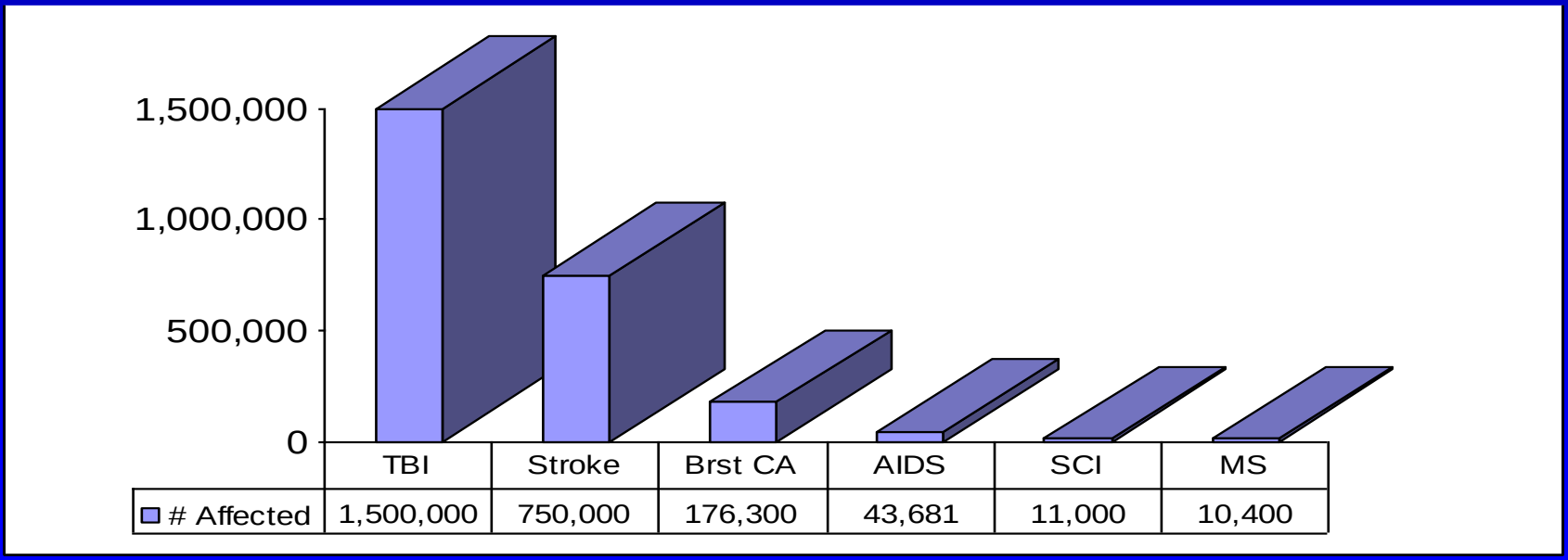
CDC 2001; Silver et al. 1994; Fife 1987; Miller and Pentland 1989; Pentland 1986; Krause and Sorenson, 1994

Epidemiology

- #1 Cause of death in persons < 35 is TBI
- #2 Cause of death in persons < 35 is suicide

Comparative Annual Incidence of TBI



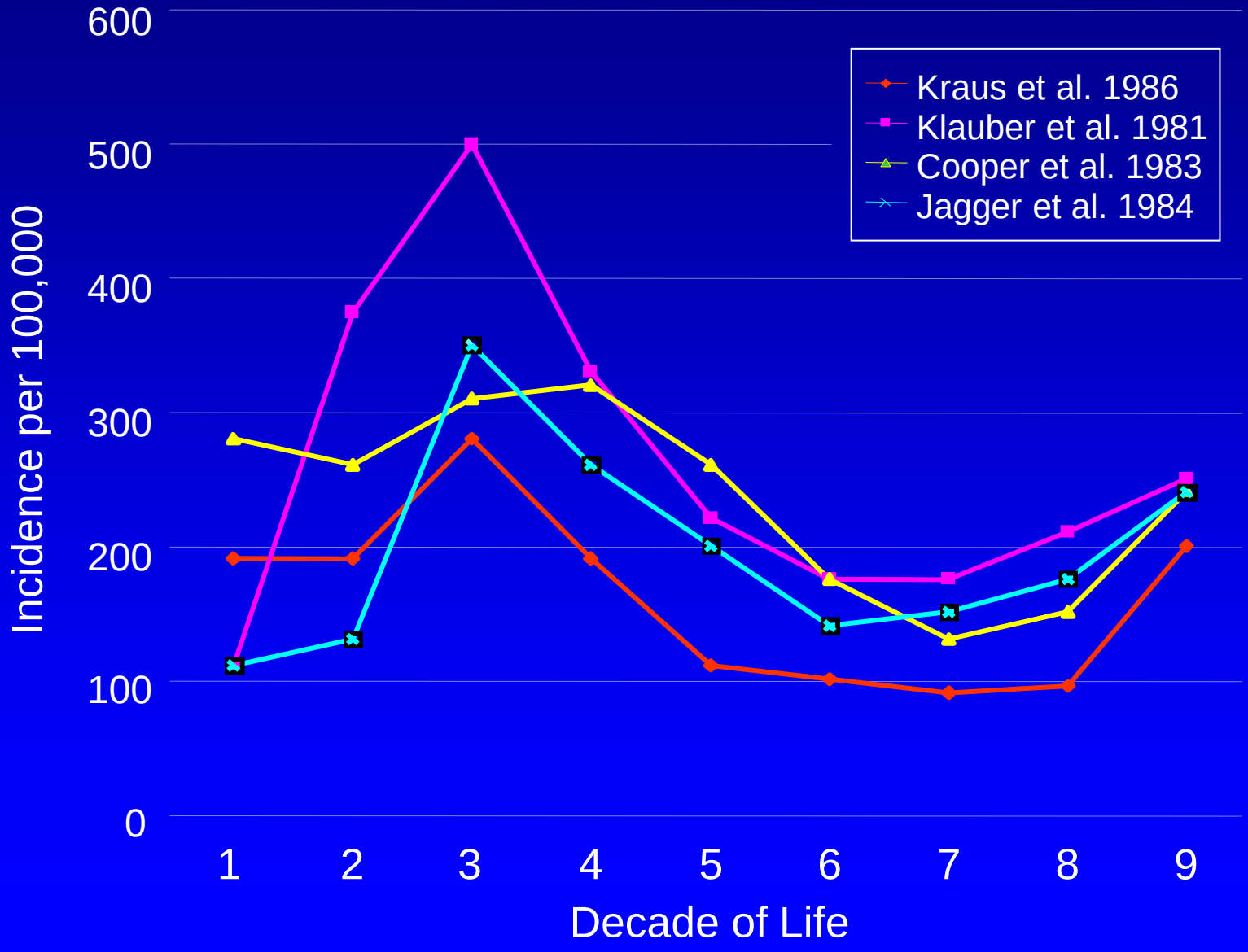


Based on data from the Centers for Disease Control and Prevention, American Cancer Society, American Heart Association, and National Multiple Sclerosis Society. TBI: traumatic brain injury; Brst CA: breast cancer; SCI: spinal cord injury; AIDS: acquired immune deficiency syndrome; MS: multiple sclerosis.

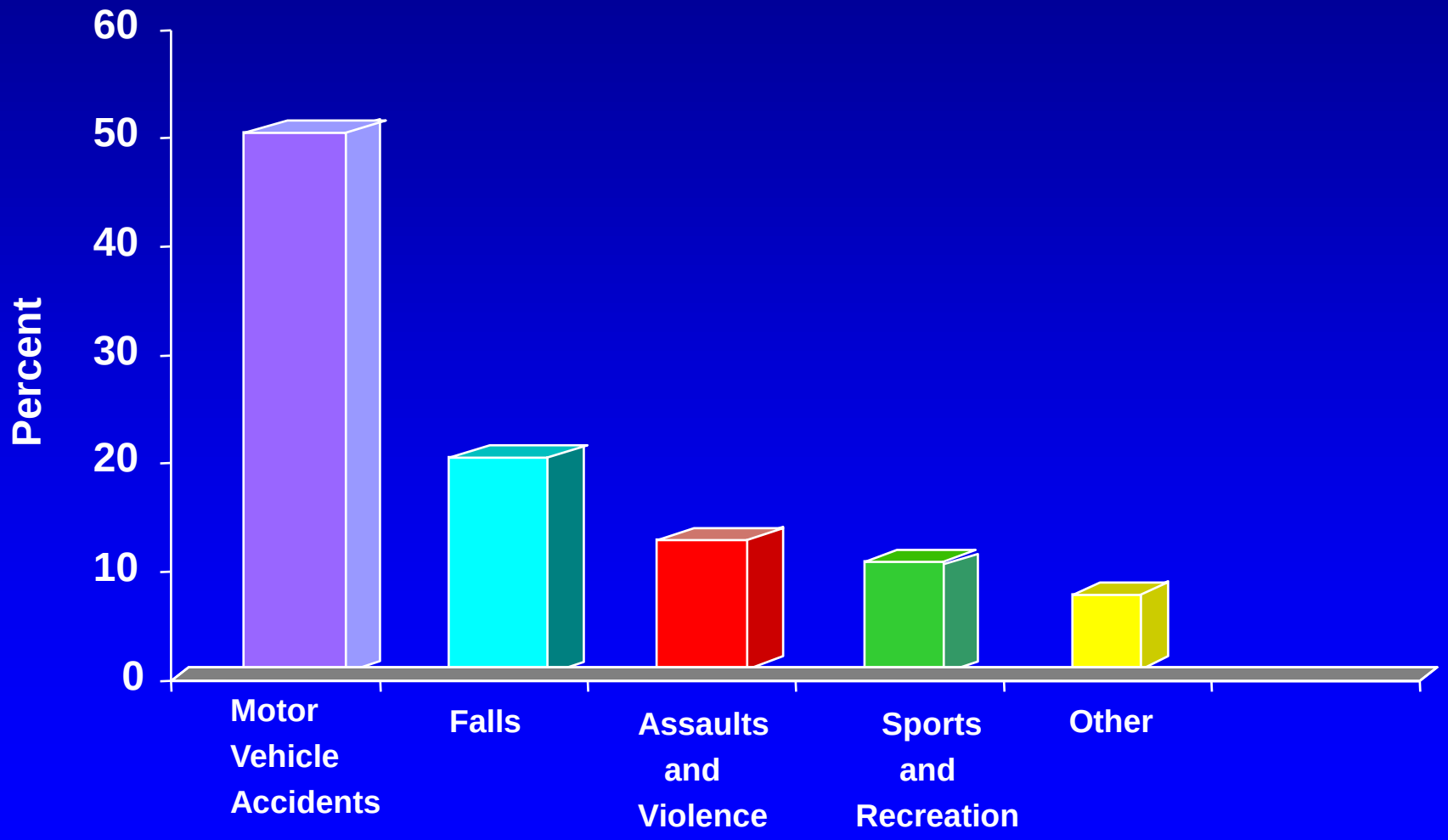
Economic Cost Of Traumatic Brain Injury

- $37.8 billion/year in the U.S. to treat 328,000 victims (Max, 1991)
- $48 billion/year in indirect and direct costs (Lewin, 1992)
- $325,000 is estimated lifetime treatment cost per patient for very severe, non-fatal brain injury

Incidence of TBI by Age



Common Causes Of Traumatic Brain Injury



Defining TBI

- Head injury versus brain injury
  - scalp laceration, dental injury, facial fracture, and even skull fracture may occur without brain injury
- Brain injury may occur without head injury
  - rapid acceleration/deceleration injuries (“shaken baby syndrome”)

Mild Traumatic Brain Injury One of the Following *

- Any period of loss of consciousness
- Any loss of memory immediately before or after accident
- Any alteration of mental state at the time of the accident
- Transient or nontransient focal neurological deficits *with*:
  - Loss of consciousness 30 min or less
  - After 30 min, Glasgow Coma Scale, 13-15
  - Post traumatic amnesia <24 hrs

Am Congress of Rehab Med, 1993

Concussion Rating Scale During Sports

- Grade 1 - No LOC; Confusion without amnesia
- Grade 2 - No LOC: Confusion with amnesia
- Grade 3 - LOC

LOC= Loss of consciousness

Kelly, 1995

Severity of Injury

- Glasgow Coma Scale
- Duration of loss of consciousness
- Post Traumatic Amnesia (PTA)
- Retrograde Amnesia

Definitions of Severity

	Mild	Severe
LOC	<20 min	>1 week
GCS	13-15	<10
PTA	<24 hours	
Hosp	None or brief	Wks-months
Residual def	None or few	prominent

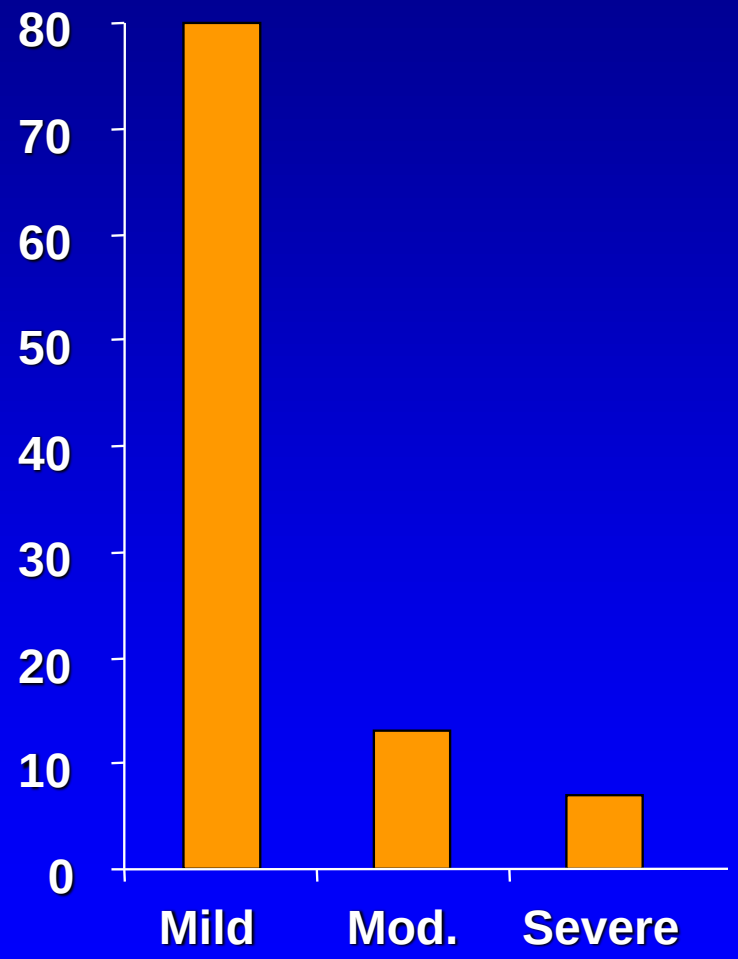
*

Distribution of TBI Severity

Mild injuries = 80%

Moderate = 10-13%

Severe = 7-10%



Kraus and Sorenson. 1994.

Neurobehavioral Symptoms after TBI

Preinjury factors

+

Injury factors

+

Postinjury factors

Factors Influencing Outcome Of Brain Injury

Factor	Comment
Age	Morbidity and mortality increases with age
Psychiatric illness	Usually worsened
Neurological	If previous brain injury, recovery not as good
Behavioral pattern	Worsened
Social Supports	Better support networks are correlated with better recovery

*

Factors Influencing Outcome Of Brain Injury

Factor	Comment
• Type of Injury	Diffuse axonal injury - problems with arousal, attention, & cognitive processing
• Severity	More severe the injury, worse the prognosis.
	The longer the period of post-traumatic amnesia, the worse the cognitive recovery
• Anosmia*	Major vocational problems

*Loss of sense of smell

*

Factors Influencing Outcome Of Brain Injury

Factor	Comment
• Intellectual	Greater preinjury intelligence predicts better recovery
• Substance Abuse	If intoxicated at time of injury, lower level of functioning upon discharge. If history of substance abuse, increased morbidity and mortality
• Neurogenetics	APO E, COMT, other?

Post-injury Factors *

- Untoward medical complications
- Failure to receive timely medical, neurological, psychiatric, or other needed rehabilitative services
  - early engagement in neurorehabilitation is associated with improved functional outcomes
- Lack of education regarding the course of recovery and interpretation of symptoms
- Lack of family, friends, or resources to support recovery
- Premature return to work/school with ensuing failure to perform at expected levels
- Poor adjustment to or coping with disability by injured person or family
- Litigation or other legal entanglements

Injury Factors

- Primary
  - Biomechanical Injury
    - acceleration/deceleration
    - translational/rotational
    - cavitation (“microexplosive”)
    - diffuse axonal injury (DAI)
  - Cytotoxic Injury
    - cytoskeletal & axonal injury
    - disturbance of cell metabolism
    - Ca^{++} and Mg^{++} dysregulation
    - free radical release
    - neurotransmitter excitotoxicity
- Secondary
  - Traumatic Hematomas
  - Cerebral Edema
  - Hydrocephalus
  - Increased Intracranial Pressure (ICP)
  - Systemic Complications
    - hypoxia/hypercapnia
    - anemia
    - electrolyte disturbance
    - infection

(McIntosh et al. 1999; Povlishok 1999; Cassidy 1994)

Injury Factors

- Cortical injury
  - results in a partial or complete loss of function served by the injured cortical area
  - more common in relatively more severe TBIs

- Diffuse axonal injury
  - functions preserved but their use is slow and inefficient
  - contributes to problems with
    - attention
    - speed and efficiency of information processing
    - memory
    - various aspects of frontally-mediated cognition
    - motivation
    - emotional regulation

  - contributes to post-TBI impairments at all levels of severity

Injury Factors: Neurochemistry

Neurotransmitter “storm” at time of TBI

- acute increases in glutamate, acetylcholine, dopamine and norepinephrine, and serotonin
  - these neurotransmitter excesses are functionally disruptive
  - neurotransmitter levels normalize in the days to weeks following TBI

McIntosh 1999 Bullock et al. 1992 Obrenovitch and Urenjak 1997

Injury Factors: Secondary Mechanisms

- Traumatic hematomas
  - A: subdural
  - B: epidural
  - C: subarachnoid
  - D: intraparenchymal
- Immediate evacuation of epidural and subdural hematomas is associated with improved long-term outcome
- Subarachnoid and intraparenchymal hematomas are associated with poor long-term outcome

Neuropsychiatric Sequelae Of TBI

- Cognitive
  - impaired concentration (“distractibility”)
  - impaired memory (learning and retrieval)
  - impaired language (production or comprehension)
  - executive dysfunction
    - poor problem solving
    - poor organizational skills
    - poor task maintenance or task shift
    - impaired executive control of language
    - impaired insight, abstraction, judgment

Neuropsychiatric Sequelae Of TBI

- Personality changes
- Disorders of Mood and Affect
- Delirium
- Psychoses
- Post-traumatic Epilepsy
- Anxiety disorders/PTSD
- Postconcussion syndrome
- Agitation,aggression, and irritability

Behavioral Syndromes Related To Specific Frontal Lobe Damage

*

Frontal Lobe Location	Symptoms
Orbitofrontal	Impulsivity, disinhibition, hyperactivity, distractibility, mood lability
Dorsolateral frontal cortex	Slowness, apathy, perseveration
Inferior orbital surface of frontal lobe (& anterior temporal lobes)	Rage and violent behavior

Differential Diagnosis Of Mood Disorders

- Symptoms secondary to brain injury
  - Mood lability (PBA, IEED)
  - Apathy (decreased motivation)
  - Slowness in thought and cognitive processing

- Premorbid disorders
  - Depression
  - Alcoholism
  - Personality Disorders

Prevalence Of Depression Following TBI

- 2.5 years after injury: 42% (Kreutzer, 2001)
- 8 years after injury: 61% (Hibbard, 1998)

Depression After TBI

- Jorge et al. Arch Gen Psych 2004
  - 33% of 91 patients during first year post TBI
  - Significantly more than other injury group
  - High rate of co-morbid:
    - Anxiety (75%)
    - Aggression (56%)
    - Reduced executive and social fx
  - Reduced left pre-frontal gray matter

Head Injury and Depression

- WWII veterans: 520 TBI, 1198 no TBI
- F/U 50 years after injury
- Lifetime prevalence: 18.5 v 13.4%
- Current depression: 11.2 v 8.5%
- Risk increased with severity of TBI

Holsinger et al. Arch Gen Psychiatry 2002

Disorders of Affect after TBI *

- **Disorders of the more moment-to-moment regulation of emotion are disorders of *affect*, not *mood***
  - **pathologic laughing and/or crying**
    - **Pseudobulbar affect (PBA)**
    - **Involuntary Emotional Expression Disorder (IEED)**
    - **affective lability**
  - **essential crying**
  - **witzelsucht**
  - **placidity in Klüver-Bucy syndromes**

Pathological Laughing and Crying after TBI

- 92 patients, followed at 3,6, 12 months
- PLC in first year: 10.9% (7 only PC, 2 only PL, 1 PLC)
- Increased h/o substance abuse
- PLC patients: more depressive, anxious, aggressive, and poorer social functioning
- PLC associated with anxiety disorders, but not depressive disorders
- Focal left frontal lesions. (PL- right frontal lobe lesions)
- For those patients treated, there was no relationship between recovery from PLC and change in scores of depression, anxiety, or aggression

  – Tateno et al. J Neuropsychiatry 2004

Affective Lability

…I was not as upset or as sad as my crying would imply, nor as uproariously amused as my uncontrollable laughter would indicate.

You have no idea how terrible it is when the crying is fully triggered and takes hold like a seizure. I can't control any of it. I simply disintegrate and it isn't only emotionally horrible with me, it is physically painful and debilitating.

Lieberman A, Benson DF: Control of emotional expression in pseudobulbar palsy: A personal experience. Archives of Neurology 34:717-719, 1977.

TBI and Schizophrenia

- **Traumatic brain injury accounts for 1% to 17% of all cases of schizophrenia, the most debilitating of all psychotic disorders (Corcoran and Malaspina, 2001)**

Traumatic Brain Injury and Schizophrenia in Members of Schizophrenia and Bipolar Disorder Pedigrees

- **Members of the schizophrenia pedigrees, even those without a schizophrenia diagnosis, had greater exposure to traumatic brain injury compared to members of the bipolar disorder pedigrees.**
- **Within the schizophrenia pedigrees, TBI was associated with a greater risk of schizophrenia, consistent with synergistic effects between genetic vulnerability for schizophrenia and traumatic brain injury.**

Malaspina, Goetz, Friedman, et al: Am J Psychiatry 158:440-446, March 2001

Childhood Head Injury and Expression of Schizophrenia in Multiply Affected Families

- **Comparison of history and severity of TBI in childhood (<10) and adolescence in 67 subjects with schizophrenia and 102 unaffected sibs in 23 families**
- **Families in study of familial schizophrenia with evidence of genetic linkage**
- **TBI almost all mild severity**
- **Individuals with schizophrenia: more likely to have childhood TBI**
- **Younger mean age of onset**
- **Severity of TBI correlated with younger age of onset**

AbdelMali et al. A*rch Gen Psychiatry.* 2003;60:231-236

TBI and Suicide

*

- Suicide attempts may be increased 4 fold in patients with history of TBI (Silver et al. 2001)
- Post-injury 5 years swx attempts: 17.4% (Simpson and Tate, 2002)
- Suicide risk: concussion 3.0; fracture 2.7; contusion 4.1(Teasdale and Engberg, 2001)
- Occurs more frequently in people with histories of TBI, but may be related to pre-TBI aggressivity (Oquendo, 2004)

Delirium

*

- Common in patients emerging from coma
- Prominent symptoms:
  - Restlessness - Disorientation
  - Agitation - Delusions
  - Confusion - Hallucinations
- Frequently termed “post-traumatic amnesia”
- Rancho Los Amigos Scale Level IV (confused, agitated) or V (confused, inappropriate)

Frequent Causes Of Delirium In TBI Patients

- Mechanical effects
- Cerebral edema
- Hemorrhage
- Infection
- Subdural hematoma
- Seizures
- Increased intracranial pressure

Prevalence Of Post-Traumatic Epilepsy

- 12% of severe injury
- 2% of moderate injury
- 1% of mild injury

Annegers, 1980

Prophylaxis of Seizures

- Phenytoin
  - Does not prevent seizures after first week
  - Increases cognitive and emotional symptoms
- Valproate
  - Does not prevent seizures after first week.
  - No effect on cognition and emotional symptoms

  - DO NOT USE ACD FOR SEIZURE PROPHYLAXIS AFTER THE FIRST WEEK

Cognitive Effects of Anticonvulsants

- Phenytoin and carbamazepine compared in patients recovering from TBI
- Both negatively affected cognition, esp. motor and speed performance
- Effects of questionable clinical significance in the group
- Some individuals experienced significant effects
  - (Smith et al. 1993)

PTSD and TBI

- Can occur with both mild and severe TBI
- Symptoms overlap with postconcussive syndrome
- Presence complicates treatment
- Relatively common in returning military population

Ursano et al. 1999; Harvey and Bryant, 2000

Post-concussion Symptoms

Symptom Category	Specific Symptoms
Somatic	Headache, dizziness, fatigue, insomnia
Cognitive	Memory difficulties, impaired concentration
Perceptual	Tinnitus, sensitivity to noise and light
Emotional	Depression, anxiety, irritability

Lishman, 1988; Silver, 1990

Postconcussive Symptoms *

- **“postconcussive” symptoms occur in all degrees of TBI (not synonymous with mild injury)**
- **80-100% describe one or more sxs in the immediate post-injury period (Levin et al 1987)**
- **By 3 months, and certainly 12 months, majority will be free of complaint**

Cognitive Sequelae of Mild Brain Injury

- **Long-term effects:**
  - **More controversial**
  - **Clear minority do suffer persistent deficits**
  - **More likely with prior TBI, >age, assoc. injury**
  - **Usually seen with more difficult tasks, or when performed under stressed**

Is There a Post Concussive Syndrome?

- **many studies suggest that relatively few individuals experience persistence of their entire set of multiple symptoms over time, and instead maintain only some subset of those symptoms.**
- **Uncoupling of postconcussive symptoms from one another (some get better while others persist) argues against the concept of a postconcussive syndrome.**

  – **(T McAllister, MD)**

*

Post Concussive Symptoms

- **More accurate to assert that**
  - **common symptoms arise as a result of injury to brain areas commonly affected by TBI**
  - **these symptoms occur to greater or lesser extents in a given individual as a function of the particulars of their individual injury and relevant pre-morbid factors**
  - **most useful to identify specific symptom patterns and to regard such patterns as reflective of the most injured areas of brain in a given individual.**

    - **(T McAllister, MD)**

*

Characteristics of Patients Who Develop Prolonged Post-Concussive Syndrome

- More likely to have been under stress at the time of the injury
- Develop depression or anxiety within a short period
- Experience extensive social disruption
- Exhibit physical symptoms (esp. headaches and dizziness)

Alexander, 1995

Aggression and TBI *

- Acute phase: 35% - 96% of patients exhibit agitated behaviors
- Recovery phase: 31% - 71% of patients with severe TBI and 5% - 70% of patients with mild TBI are agitated or irritable
- 89 patients assessed during the first six months after TBI, aggressive behavior found in 33.7% of TBI patients, compared to 11.5% of patients with multiple trauma but without TBI (Tateno et al)
- Death row inmates: 75% TBI (Freedman et al 2000)
- Irritability increases with more TBI's

Characteristic Features of Neuroaggressive Disorder

*

- Reactive
  - Triggered by modest or trivial stimuli
- Nonreflective
  - Usually does not involve premediation or planning
- Nonpurposeful
  - Aggression serves no obvious long-term aims or goals

Yudofsky et al, 1990

Characteristic Features of Neuroaggressive Disorder *

- Explosive
  - Buildup is NOT gradual
- Periodic
  - Brief outbursts of rage and aggression; punctuated by long periods of relative calm
- Ego-dystonic
  - After outbursts patients are upset, concerned, embarrassed: as opposed to blaming others or justifying behavior

Yudofsky et al, 1990

Principles of TBI Pharmacotherapy *

- Objective evaluation before and during treatment
- Therapeutic trial of all medications
- Start low, go slow
- Monitor side effects
- Ease of use is important
- Monitor drug-drug interactions
- Augment partial treatment responses

Evidence Based Guidelines

J Neurotrauma. 2006 Oct;23(10):1468-501

- Workgroup for Neurobehavioral Consequences of TBI
  - sponsored by IBIA, CDC
- Reviewed current literature
- Class I (randomized, double-blind, placebo controlled)
- Class II (randomized controlled, etc.)
- Class III (case reports, retrospective, etc)

Selecting agents for Cognition

- At present, no medication has received FDA approval for the treatment of impaired cognition following TBI
- At present, there are no widely available clinical tests to facilitate identification of specific neurotransmitter deficits following TBI
- Treatments have, for the most part, been based on those commonly prescribed for persons with similar symptoms due to other neurological problems
  - a more appropriate approach is to derive treatments from the known neurobiology & neurochemistry of TBI and cognition

Selecting agents for Cognition

- In general, patients with diminished arousal, slowed and inefficient information processing, and/or prominent attentional deficits (ie, deceased sustained attention, distractibility) appear to benefit most from psychostimulants
- Those with memory or “sensory gating” deficits may benefit from pro-cholinergic medications
- Some patients benefit from both

Psychostimulants: Methylphenidate

- **In a double-blind, placebo controlled study of patients treated during acute rehabilitation, Whyte et al. (1997) demonstrated improvements in arousal and speed of information processing during treatment with methylphenidate 0.3 mg/kg BID**
  - **no other significant effects were observed on other aspects of attention (ie, distractibility or vigilance, memory) or motor performance**
  - **remains the only Class I study for the use of stimulants for treatment of cognitive impairment following TBI**

(Whyte J et al. 1997)

Cholinergic Augmentation

- Open-label data suggests some improvements in memory during treatment with donepezil HCl
- Double-blind data suggests improvement physiologically with low-dose donepezil
- Multicenter, randomized, double-blind, placebo-controlled study suggest benefit of rivastigmine (Silver et al. 2006)

*

Pharmacologic Treatment of Impairments of Attention and/or Memory after TBI

- Dextroamphetamine
  - Dose: Initial 2.5 mg bid; Maximum 30 mg bid
- Methylphenidate
  - Dose: Initial 5 mg bid; Maximum 30 mg bid
- Side effects for both
  - Paranoia, agitation, irritability, depression
  - Probably no decrease in seizure threshold
- Comments for both
  - Both agents may improve memory and learning attention and behavior

Pharmacologic Treatment of Impairments of Attention and/or Memory after TBI, Cntd.

Amantadine

- Initial dose - 50 mg bid
- Maximum dose - 200 mg bid
- Side effects - confusion, hallucinations, edema, hypotension
- Benefits - Treatment of anergy, abulia (passivity and indifference), mutism, anhedonia

*

Pharmacologic Treatment of Impairments of Attention and/or Memory after TBI, Cntd.

- Donepezil: 5 mg for first month, then 10 mg if no change
- Rivastigmine: 1.5 mg bid for first month, then 3 mg bid if no change
- Memantine: no published reports of efficacy

*

Depression: IBIA Evidence Based Review of NBC of TBI

- **1 Class I Study – Wroblewski et al. 1996**
- **2 Class II Studies – Saran 1985; Dinan 1992**
- **19 Class III Studies**
- **Not enough evidence for guideline**
- **Practical recommendation: start with SSRI**

Antidepressant Medication

- SSRI's: Prozac, Zoloft, Paxil, Celexa, Luvox
- TCA's: Pamelor, Norpramin
- "Dual Action": Effexor, Cymbalta
- Atypical antidepressant: Wellbutrin, Remeron
- MAO Inhibitors: Nardil, Parnate
- Stimulants: Ritalin, Dexedrine
- Light therapy
- ECT

Risk of Seizures with Antidepressants

- Records of 68 pts with TBI treated with TCA for 3 months
- Comparison of szs before, during, and after treatment
- 6 Baseline; 16 during TCA Rx; 4 after Rx D/C
- 14 pts had szs shortly after TCA started
- For 12 of these, no sz after Rx D/C

– (Wroblewski et al. 1990)

*

PLC & Affective lability

- Multiple studies in stroke demonstrate efficacy with either low-dose selective serotonin reputake inhibitors or low-dose tricyclic antidepressants
  - response is typically within 1-7 days after initiating treatment
  - the extent to which these findings translate from stroke to TBI is uncertain, given that there may be relevant differences in the neurochemistry and neuroanatomy of these conditions

DM/Q: A Future Treatment Option for Pseudobulbar Affect

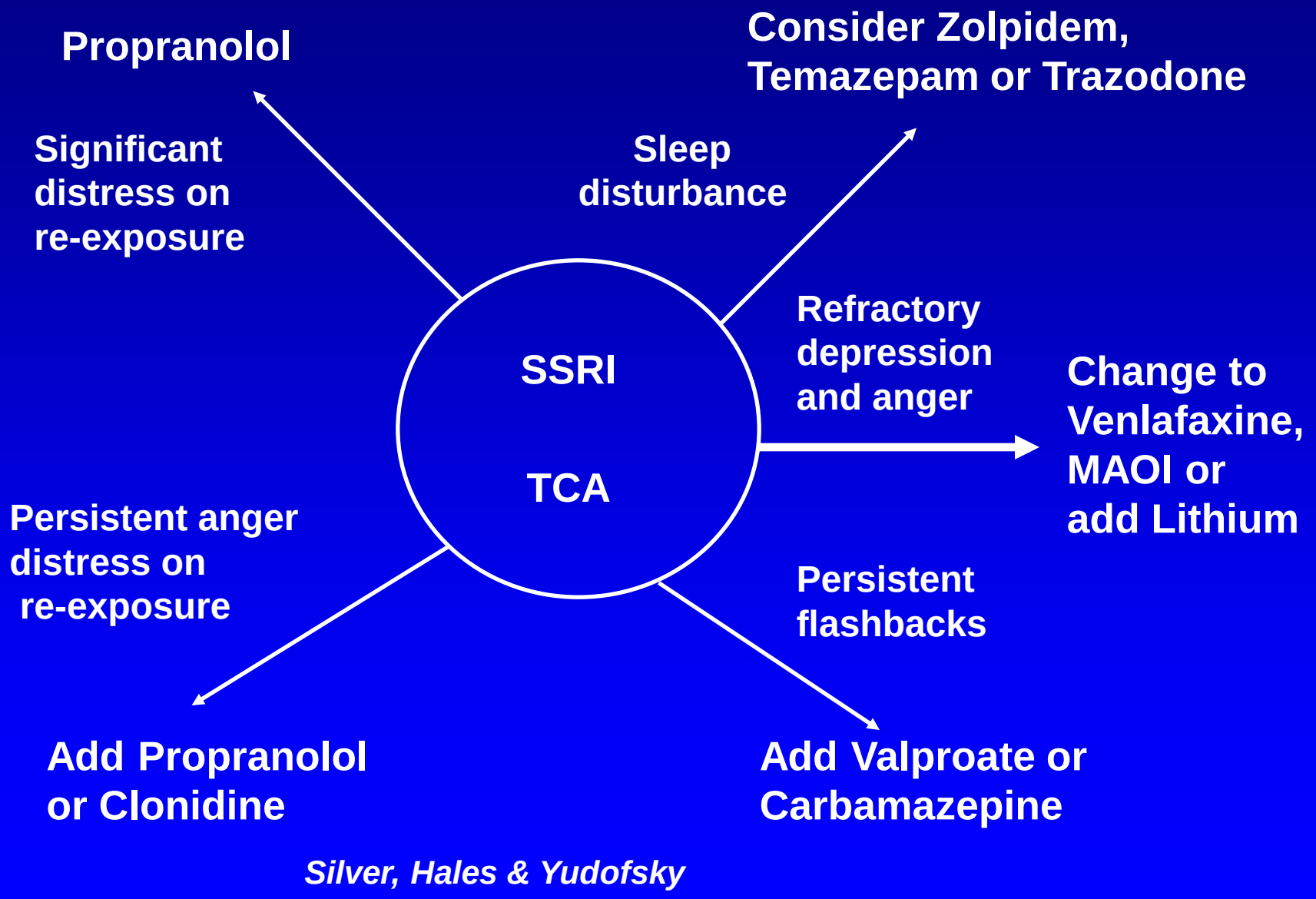
- **DM/Q**
  - **Dextromethorphan 30 mg/quinidine 30 mg**
  - **First agent specifically designed for treatment of PBA**
  - **Demonstrated to be effective in reducing symptoms of PBA in two large-scale studies (ALS and MS)**
  - **Likely to be an effective treatment for PBA, regardless of underlying disease/injury state**

Brooks BR, et al. *Neurology*. 2004;63:1364–1370. Panitch H, et al. 2005. American Academy of Neurology; Abstract S46.001.

Pharmacologic Treatment of Generalized Anxiety Disorder Associated with TBI *

Agent	Dose	Benefits	Risks
Buspirone	10-30 mg bid	No motor incoordination, dependence or tolerance	Delayed onset of action; sedation, dizziness, less effective in recent benzo. users
Lorazepam	0.5-2 mg tid-qid	Fast onset of action, sedation	Motor incoordination, memory disturbance, dependence, tolerance, ataxia, sedation
Clonazepam	0.5-2 mg bid tid	As above Longer half-life	As above More sedation

Psychopharmacologic Treatment Of PTSD Associated with TBI *



Silver, Hales & Yudofsky

*

Common Sleep Problems in TBI Patients

- Impaired REM
- Multiple nocturnal awakenings
- Hypersomnia is more common with missile injury (Castriotta, 2001; Masel, 2001)--usually resolves < 1 yr
- Insomnia is common following coma and diffuse CNS injury has more chronic course
- Daytime fatigue is a common problem (Rao, 2005)

Clinical Challenges of Pharmacologic Treatment of Insomnia in Patients After TBI

Medications to Avoid	Reasons
Barbiturates	Interfere with REM, sleep stages
Benzodiazepines (esp. long acting)	Motor incoordination, confusion decreased memory, tolerance, dependence
OTC Preparations	Anticholinergic side effects

Buysse and Reynolds, 1990

Pharmacologic Treatment Of Insomnia In TBI Patients

Medications to Consider	Problems/Side Effects
Trazodone 50-100 mg	Hypotension, daytime sedation
Zolpidem; zalepon; 5-10 mg	Cost, short half-life

Buysse, 1990; Rao, 2005

Pharmacologic Treatment of Acute Agitation Or Aggression Associated with TBI: General Principles *

- No FDA approved medication
- Using (mis-using) sedative side effects to treat aggression or agitation
- Patients develop tolerance to sedation from neuroleptics and benzodiazepines
- Medications may impair arousal and cognitive function

Common Causes of Chronic Agitation and Aggression Associated with CNS Impairments

- Traumatic brain injury
- Stroke and other cerebrovascular disease
- Medications, alcohol and other abused substances, over-the-counter drugs
- Delirium (hypoxia, electrolyte imbalance, anesthesia and surgery, uremia, etc.)
- Alzheimer's disease

Categories of Medications Associated with Agitation and Aggression In Patients with TBI

Medication	Comment
Analgesics (opiates & other narcotic analogs)	Intoxication and withdrawal
Anticholinergic agents	Including OCT meds
Antidepressants	Esp. in early stages of Rx
Antipsychotics	Esp. high potency agents
Hallucinogens (LSD, PCP, etc.)	Intoxication

Aggression: IBIA Evidence Based Review of NBC of TBI

- **Insufficient rigorous evidence**
- **Use of medications is a “guideline” (beta blockers-most evidence)**
- **?other medications as “option”**

Overall Strategies: Time Frame of Intervention

- Acute
  - rapid symptom control
  - one time to a few weeks
- Long-term
  - continuous treatment
  - a few weeks or more

Pharmacotherapy of Agitation

- Acute Agitation
  - antipsychotic drugs
  - benzodiazepines
- Chronic Agitation
  - atypical antipsychotics
  - anticonvulsants (VPA, CBZ, OXC, ?Gabapentin)
  - serotonergic antidepressants (SSRI, trazodone)
  - buspirone
  - beta blockers

Acute Agitation

- Antipsychotic medications
- Benzodiazepines

- These are used to “put out the fire”
- Try to avoid long-term (weeks).

Distinct Syndromes Associated with Agitation in Brain Injury

*

- Psychosis-atypical
- Depression-SSRI
- Anxiety-buspirone
- Insomnia-trazodone
- Aggression without other cause-beta blocker, VPA, CBZ,OXC

β- Blockers in the Treatment of Chronic Aggression Associated With CNS Lesions

*

- First reported in 1981 to treat chronic aggression in adults and children with organic brain syndromes and adults with Korsakoff's psychosis (Yudofsky, 1981, 1984)
- More than 35 papers published since 1981 related to treatment of chronic aggression or agitation in patients with CNS lesions (Silver, 2005)

Key Characteristics Of Propranolol

- Peripheral beta receptors are saturated at 300-400 mg/d (i.e., no further ¬ BP or ¬ HR)
- Often a latency of 6-8 weeks
- Depression is an uncommon side effect (~9%)
- Increase plasma levels of neuroleptics
- Avoid combination with thioridazine (Mellaril) because of Mellaril's 800 mg absolute dosage ceiling

Psychosis: IBIA Evidence Based Review of NBC of TBI

- **There were no Class I, or II studies found which addressed the treatment of psychotic syndromes**
- **Some Class III studies addressed these patient populations, many of these had such methodological flaws that they were not useable in establishing treatment guidelines.**

Pharmacologic Treatment of Psychosis in Patients Following TBI: Second-Generation (Atypical) Antipsychotic Medications *

- First-line medication for treatment of psychosis associated with TBI (Corcoran, 2005)
- Well-tolerated for psychoses following TBI
- Far fewer Parkinsonian side effects and less emergence of tardive dyskinesia
- In treatment of chronic psychosis associated with TBI, be alert for emergence of metabolic syndrome

Antipsychotic Medications

- Conventional neuroleptics
  - High potency: haloperidol
  - Low potency: thioridazine/chlorpromazine
- Atypical neuroleptics
  - Risperidone (Risperdal)
  - Olanzapine (Zyprexa)
  - Quetiapine (Seroquel)
  - Aripiprazole (Abilify)
  - Ziprazadone (Geodon)
  - Clozapine (Clozaril)

Education: The Role of Medication

- Caregivers can burn out; “TLC” not always enough
- Medication is not a restraint or punishment
  - treats a medical disorder that is affecting the brain
- Goals:
  - relieve suffering
  - improve communication
  - avoid sedation
- Target specific causes; may need trial and error
- Keep doctor informed of other drugs, diseases

1. **Which of the following diseases has the greatest annual incidence?**
    a. **HIV**
    b. **Cerebral vascular accidents**
    c. **Breast cancer**
    d. **Traumatic brain injury**
    e. **Multiple sclerosis**

2. **Which of the following are the minimal criteria for mild traumatic brain injury?**
   a. **loss of consciousness for 5 minutes**
   b. **posttraumatic amnesia for 15 minutes**
   c. **any period of confusion**
   d. **any blow to the head**

3. Which of the following would be most expected with a contusion on the inferior surface of the frontal lobe?
   a. apathy
   b. word finding problems
   c. depression
   d. aggression

4. Which medications have been shown in controlled studies to improve cognition after TBI?

a. cholinesterase inhibitors
b. memantine
c. ginko biloba
d. lamotrigine

5. **Which of the following classes of medications has the strongest support in the literature for the treatment of aggression after TBI?**
   a. **selective serotonin reuptake inhibitors**
   b. **anticonvulsants**
   c. **beta-blockers**
   d. **atypical antipsychotics**

Answers

1. d
2. c
3. d
4. a
5. c