TRAUMATIC BRAIN INJURY

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Introduction

- Two million people sustain a traumatic brain injury (TBI) each year
- Incidence: 120/100,000 population (Kraus,2005)
- 300,000 require hospitalization
- 28% of all injury deaths involve TBI (Soshin, 1995)
- 80,000 of the survivors are affected

Kraus and Nourjah, 1994

Epidemiology

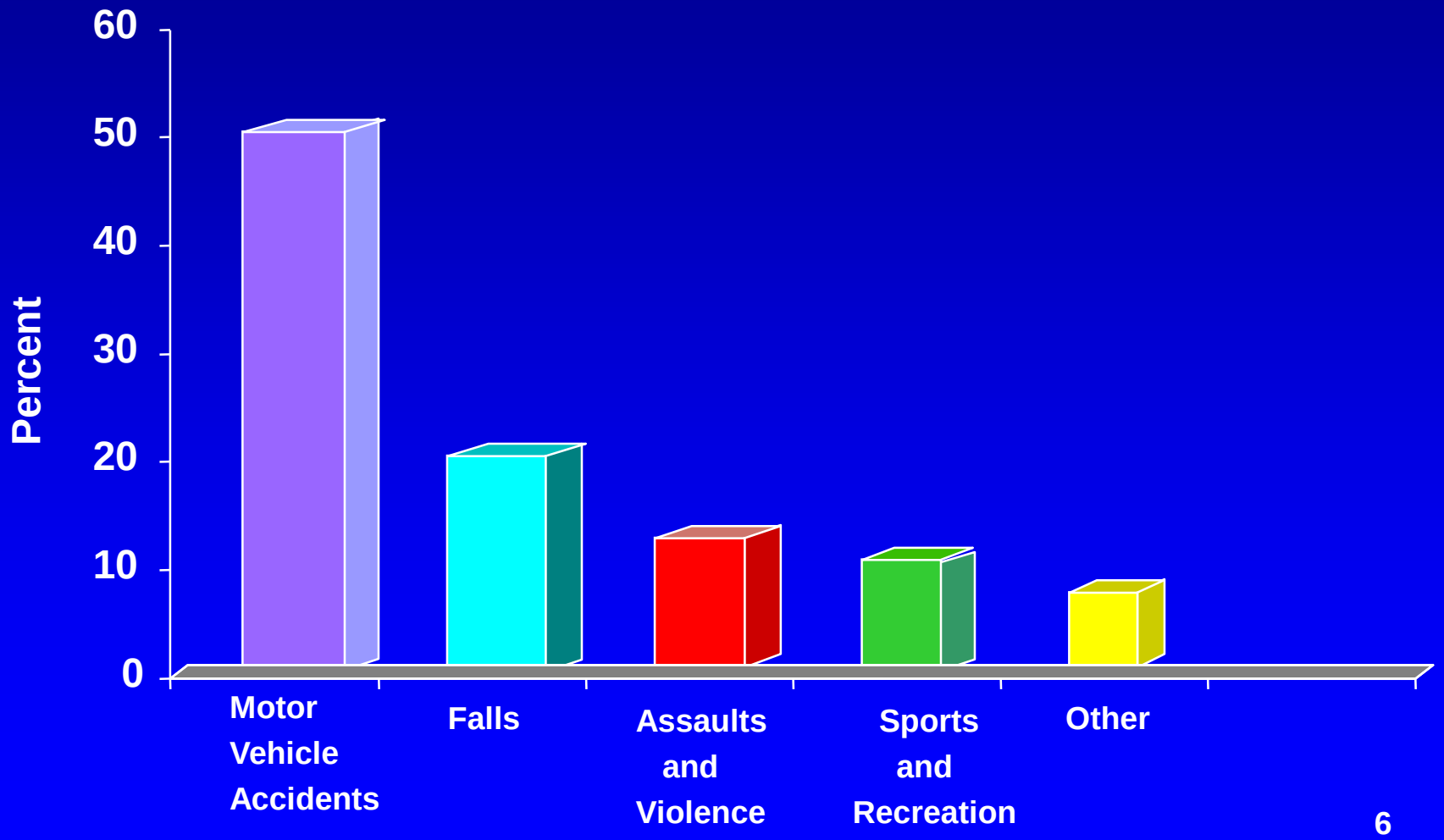
- **#1 Cause of death in persons < 35 is TBI**
- **#2 Cause of death in persons < 35 is suicide**

Traumatic Brain Injury

- 2% of all deaths
- 26% of all injury deaths
- Men ages 15-24 are at highest risk

(Sosin, 1989)

Common Causes Of Traumatic Brain Injury



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

Children Are At High Risk

- 5 million children sustain head injuries each year
- 200,000 are hospitalized
- 50,000 children sustain head injuries from bicycles alone
- 400 die each year from bicycle accidents

Raphaely, 1980; HHS, 1989

Diffuse Axonal Injury

- Refers to mechanical or chemical damage to axons in cerebral white matter
- Axons are stretched, leading to cytoskeleton disruption and impaired axoplasma transport
- Occurs during high velocity accidents when there is twisting and turning of the brain around the brain stem
- Results in loss of consciousness and can occur in minor brain injury or concussion

Cassidy, 1994

Neurochemical Changes Inconsistent Findings Affecting:

- Epi and Norepihinephrine: increase in circulating levels in CNS (McIntosh, 1994; Prasad, 1994)
- Serotonin: increase in circulating levels (Tsuiki, 1995)
- Cytokines: increase in immunocopetent cells in CNS (Fan, 1995)
- Excitatory Amino Acids: marked increase extracellular glutamate and aspartate (Palmer, 1993)
- Acetylcholine: decrease in the binding of cholinergic receptors (Jiang, 1994; Lyeth, 1994)

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, Glascow 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

Rating Scales Commonly Used In Neuropsychiatry

Scale	Indication
Structured Clinical Interview for DSM-IV (SCID)	Evaluate for psychiatric diagnosis
Neurobehavioral Rating Scale (NBRS)	Presence and severity of emotional and cognitive symptoms
Positive and Negative Symptom Scale (PANSS)	
Overt Aggression Scale (OAS)	Frequency and severity of aggressive outbursts
Overt Agitation Severity Scale (OASS)	Frequency and severity of agitation

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

Neuropsychiatric Sequelae Of Traumatic Brain Injury

Intellectual Changes

Dysfunctions in the following:

- Attention and arousal
- Concentration
- Executive functioning
- Memory impairment

Executive Functions

Dysfunctions in the following:

- Setting goals
- Assessing strengths and weaknesses
- Planning and/or directing activity
- Initiating and/or inhibiting behavior
- Monitoring current activity
- Evaluating results

Intellectual Changes

- Can be quite subtle
- Difficult to diagnose on cursory cognitive testing

Neuropsychiatric Sequelae Of Traumatic Brain Injury

- Personality changes
- Mood disorders
- Delirium
- Psychoses
- Post-traumatic Epilepsy
- Anxiety disorders
- Agitation and aggression
- 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
  - 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

- Incidence and severity NOT related to:
  - Duration of LOC
  - Duration of post-traumatic amnesia
  - Presence or absence of skull fractures
- IS related to:
  - Extent of neuropsychological impairment
- More common in:
  - Left anterior frontal regions

Bornstein, 1988 and 1989

Major Depressive Disorder (MDD After TBI)

- 66 hospitalized patients
- 25% diagnosed with MDD at 1, 3, 6, & 12 months following TBI
- 42% developed MDD by one year
- 4.7 months - mean duration (range 1.5-12 months)

Jorge et al. 1993

Suicide

- Occurs more frequently in people with histories of TBI (Oquendo, 2004)

Study:

- 42 patients with severe TBI
- After 1 year
  - 10% suicidal ideation
  - 2% suicide attempts
- After 5 years
  - 155 suicide attempts

Brooks, 1990

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

Frequent Causes Of Delirium In TBI Patients, Cntd.

- Alcohol intoxication or withdrawal
- Reduced hemoperfusion related to multiple trauma
- Fat embolism
- Change pH
- Electrolyte imbalance
- Medications (sedative/hypnotics, steroids, opioids, etc.)

Trzepacz, 1994

Psychotic Disorders

- No standard definition of psychosis in the literature (Andreasen, 2000)
- May occur immediately following brain injury or after a long latency period
- Symptoms may persist despite cognitive improvement
- DSM-IV-TR Diagnosis: Psychotic disorder due to a general medical condition (2000)

Smeltzer, 1994; Nasrallah, 1981

Prevalence Of Psychotic Disorders

- 3.4% of 530 head injury patients followed up to 10 years after injury
- 5.9 year mean latency from TBI to psychosis (Fujii, 1996)
- 26% of 2907 Finnish war veterans developed psychosis *Violon and DeMoi, 1987*

- 14% developed paranoid schizophrenia
  - All had left temporal lobe abnormalities

Buckley, 1993

- 1-15% of inpatients with schizophrenia reviewed between 1917-1964 had histories of brain injury

Davison and Bagley, 1969

Post-traumatic Epilepsy
Risk Factors

- Skull fractures
- Penetrating wounds
- History of chronic alcohol use
- Intracranial hemorrhage
- Increased severity of the injury

Prevalence Of Post-Traumatic Epilepsy

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

Annegees, 1980

Delayed Onset Of Seizures

- 53% of 421 Vietnam veterans had post-traumatic epilepsy
  - 18% had first seizure after 5 years
  - 7% had first seizure after 10 years

Salazar, 1985

Post-traumatic Epilepsy and Psychosis

- 7-8% of TBI patients with epilepsy have persistent psychoses
- Difficult to distinguish from schizophrenia
- DSM-IV diagnosis - Delusional disorder due to traumatic injury

Adverse Effects Of Anticonvulsant Medications

- Phenytoin and carbamazepine may produce negative effects on cognitive performance, esp. motor and speed performance (R/O folate deficiency with phenytoin)

Smith, 1983

- Treatment with more than one anticonvulsant is associated with increased adverse neuropsychiatric reactions.

Reynolds & Trimble, 1986

Adverse Effects Of Anticonvulsant Medications

- Phenytoin and carbamazepine have no prophylactic effect on seizures during the first week following TBI
- May be a role for valproate

Temkin, 1990; Yablon, 1993

Anxiety Disorders Prevalence

- 24% of TBI patients have generalized anxiety disorder after TBI (Fann, 2000); However, many of these had anxiety prior to their injury
- 29% of 1199 patients evaluated between 1942-1990 developed clinical anxiety (Epstein, 1994)

Post-concussion Syndrome

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

Lishman, 1988; Silver, 1990

Post-concussion Syndrome

Neuropsychological Testing Results

- Poorer performance on tests of reasoning, information processing, verbal learning
- Abnormal SPECT, computerized EEG, and brainstem auditory evoked potentials

Leininger, 1990; Hugenholtz, 1988

Post-concussion Syndrome

Laboratory Results

- Normal MRI and CT
- May occur many months after injury

Leininger, 1990; Hugenholtz, 1988

Post-Concussion Syndrome

Other Residual Symptoms

- 22% Decreased energy
- 22% Dizziness
- 47% Headaches
- 47% Memory loss
- 54% Irritability

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

PTSD vs Post-concussive Syndrome

- Sometimes difficult to differentiate between the two (Warden, 2005)
- Post-concussion symptoms usually decrease within 3 months; PTSD persists, untreated
- Patients with amnesia secondary to TBI *can* develop PTSD (McMillen, 1991)

Agitation And Aggression Following Severe TBI

- 34-96% Exhibit Agitation or Aggression (Levin, 1978; Tateno, 2003)
- 40% Exhibit Restlessness (van der Naalt, 2000)
- 34% Exhibit Irritability (Hibbard, 1998)

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

Other Common Neuropsychiatric Causes Of Agitation and Aggression

- Chronic neurological disorders (Huntington's disease, Wilson's disease, Parkinson's disease, multiple sclerosis, systemic lupus erythematosus)
- Brain tumors
- Infectious disease (encephalitis, meningitis, AIDS)

Other Common Neuropsychiatric Causes of Agitation and Aggression, Cntd.

- Epilepsy (ictal, post-ictal, and inter-ictal)
- Metabolic disorders (hyperthyroidism or hypothyroidism, hypoglycemia, vitamin deficiencies, porphyria)

Categories Of Medications Associated With Agitation And Aggression

Medication	Comment
Sedative-hypnotic agents (including EtOH)	Intoxication and withdrawal
Stimulants (amphetamines, cocaine, caffeine	Manic-like excitement
Steroids (including anabolic)	Therapeutic doses and withdrawal

General Principles Of Psychopharmacologic Treatment

- TBI patients are more sensitive to medication side effects
- Doses must be raised and lowered in small increments over longer periods of time
- Therapeutic doses may be the same as the non-brain injured patient
- Frequent reassessment to determine medication efficacy is important

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

Sinemet (L-DOPA/CARBIDOPA)

- Dosage range - 10/100 - 25/250 mg qid
- Side effects - sedation, nausea, psychosis, HAs, delirium
- Benefits - improved alertness and concentration; increased energy; increased memory, speech, mobility

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

Bromocriptine (Parlodel

- Dosage range - 2.5 mg/d up to 10 mg/d
- Side effects - sedation, nausea, psychosis, HAs, delirium
- Benefits - improved alertness and concentration; increased energy; increased memory, speech, mobility, improvement in nonfluent aphasia, akinetic mutism, and apathy.

  ? Anticholinergic properties

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 Depression after TBI

- Heterocyclic and SSRI Antidepressants are effective in treating depression associated with TBI
- Post-TBI patients are highly sensitive to anticholinergic and parkinsonian side effects of heterocyclics
- All Antidepressants May Increase the Frequency of Seizures in patients after TBI, with: Bupropion and heterocyclics >> SSRIs, Venlafaxine

Somatic Treatment of Major Depression after TBI: ECT

- Underutilized
- Safe and effective
- Nondominant, unilateral preferred
- Fewer treatments (4-6) recommended
- Increased spacing between treatments (2-5 days)
- Use of lowest possible energy for seizure elicitation (at least 20 sec in duration)

Pharmacologic Treatment of Mood Liability In Patients After TBI

Medication	Dose
Fluoxetine (Prozac	40-80 mg
Sertraline (Zoloft)	100-200 mg
Nortriptyline (Pamelor)	100-150 mg

Pharmacologic Treatment of Psychosis in Patients Following TBI: First-Generation Antipsychotic Medications

- High rates of dystonia, akathisia, Parkinsonian side effects
- TBI may make patients more vulnerable to tardive dyskinesia (Kane, 1982)
- May produce hypotension, sedation and confusion
- May impede neuronal recovery
- Should be used sparingly and at low doses
- Start with 33% to 50% of usual dose (McAllister, 1998)
- May have a delayed onset of action

(Stanislav, 1997)

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

Clozapine

- Initial dose 50-100 mg
- Benefits
  - No EPS
  - Positive effect on negative symptoms
- Comments
  - 1% risk of agranulocytosis
  - Weekly blood draws
  - Highly anticholinergic
  - Sedation, hypotension
  - Lowers seizure threshold
    - 1-2% risk <300 mg
    - 5% risk 600-900 mg

Lieberman, 1989; Burke, 1999

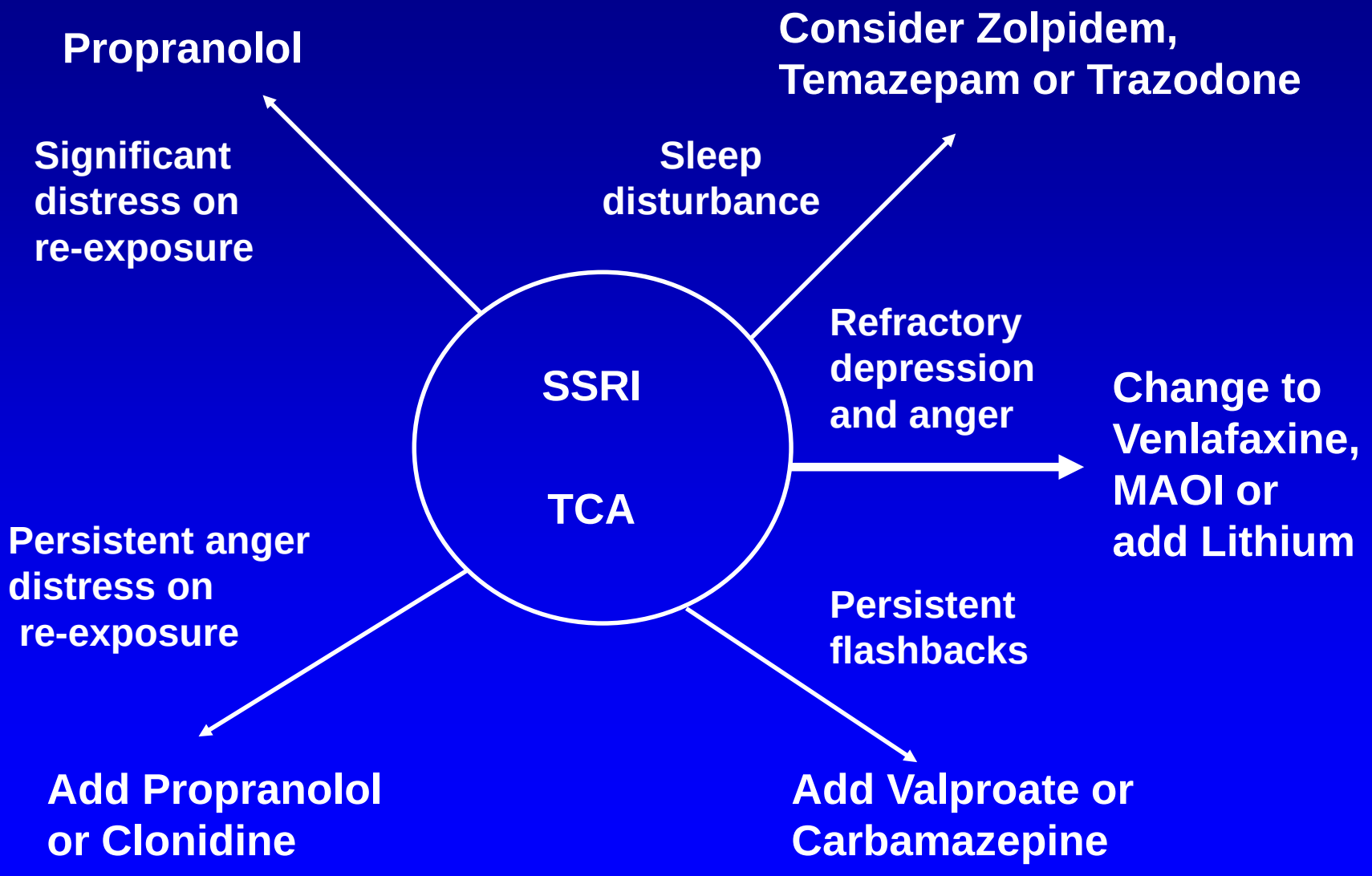
Pharmacologic Treatment of Generalized Anxiety Disorder Associated with TBI

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

General Principles
Psychopharmacology Treatment of PTSD Associated with TBI

- Positive symptoms (re-experiencing the event, increased arousal) improve with medication
- Negative symptoms (avoidance and withdrawal) respond poorly to medication

Psychopharmacologic Treatment Of PTSD Associated with TBI



Silver, Hales & Yudoksky

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

Use of Haloperidol in the Treatment of Acute Agitation or Aggression Associated with TBI

- Initiate haloperidol - 1 mg po or 0.5 mg IM or IV, q1h
- Increase dose by 0.5-1 mg q1h until agitation or aggression is controlled
- Maintain at a maximum dose of 2 mg po or 1 mg IV or IM bid-tid (i.e., 3-4 mg qd)

Use of Haloperidol in the Treatment of Acute Agitation or Aggression Associated with TBI

- When patient is not agitated or violent for a period of 48 hrs, taper daily at a rate of 25% of highest total daily dose
- If agitation reemerges upon tapering drug, reassess etiology and consider changing to a more specific medication
- Do not maintain patient on haloperidol for >6 weeks - except for agitation or aggression secondary to psychosis

Use Of Lorazepam In The Treatment Of Acute Agitation Or Aggression Associated with TBI

- Initiate lorazepam - 1-2 mg po, IM or IV
- Repeat q1h until control of agitation or aggression is achieved
- If IV dose must be given, push slowly! Do not exceed 2 mg (1 ml) per min to avoid respiratory depression and laryngospasm; may be repeated in 30 min if required
- Maintain at a max dose of 2 mg po, IM or IV tid-qid (i.e., 8 mg qd)

Use of Lorazepam in the Treatment of Acute Agitation or Aggression Associated With TBI, cntd.

- When patient is not agitated or violent for 48 hours, taper daily at 10% of highest total daily dose
- If agitation reemerges upon tapering drug, reassess etiology and consider changing to a more specific medication
- Do not maintain patient on lorazapem for >6 wks - except for agitation or aggression secondary to generalized anxiety disorder

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

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