Neuropsychiatric Aspects of Traumatic Brain Injury

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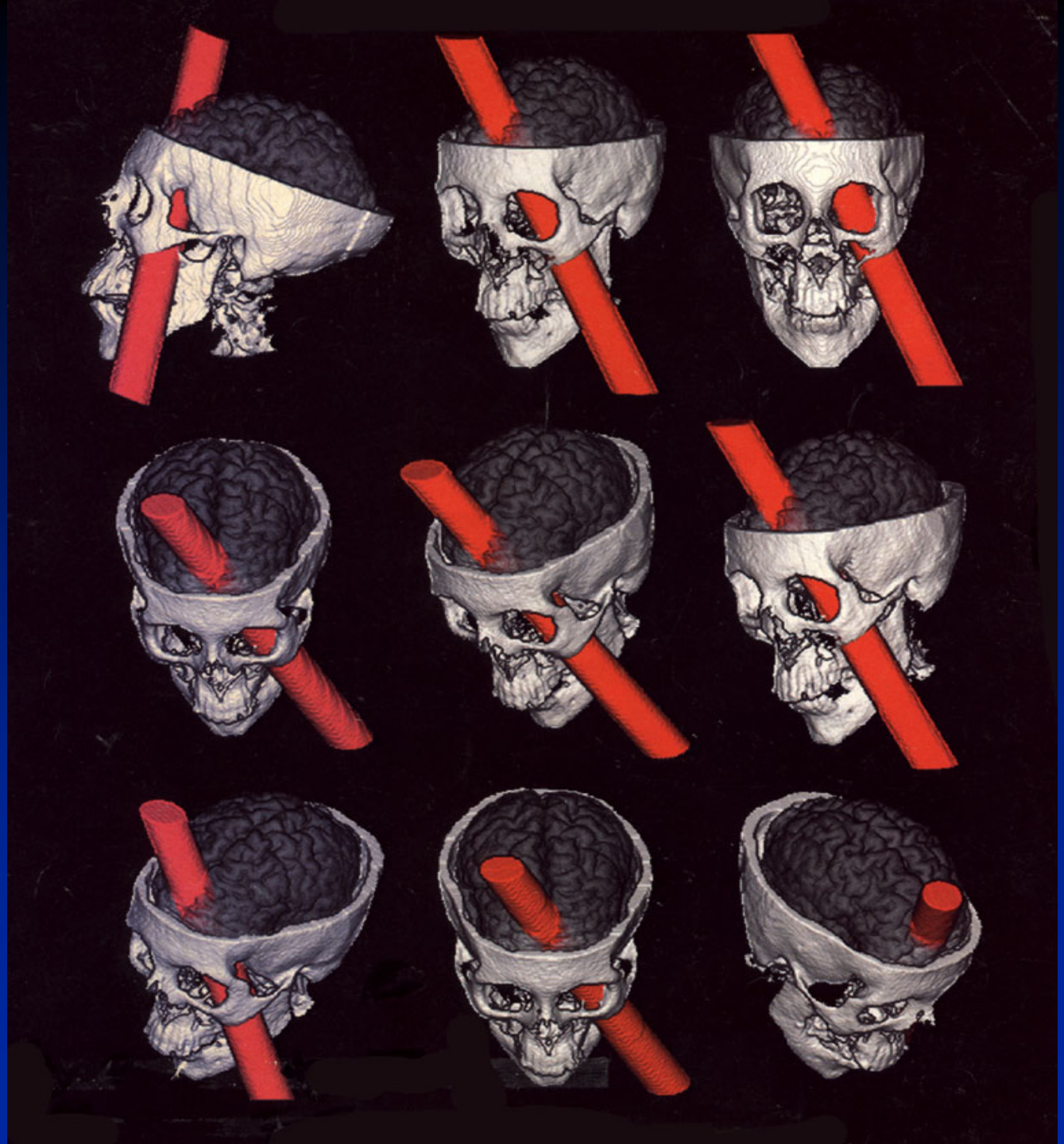


The Washington Times
www.washingtontimes.com

Military seeks test for brain injury

Joyce Howard Price
THE WASHINGTON TIMES

Published March 17, 2003

The Pentagon is funding research to develop a blood test to gauge the severity of head wounds while the victim is still on the battlefield.

"The head is less than 9 percent of the body, yet it gives us 25 percent of the [combat] hits," said Lt. Col. Geoffrey Ling, a physician and director of neuro-intensive care at the Walter Reed Army Medical Center. "What's more, over 50 percent of the soldiers who die [from combat wounds] after reaching medical care have head injuries."

Yet the military has no diagnostic tool to help a combat medic in the field determine if a soldier suffering from a head wound has any chance of survival and should be transported to a hospital.

"If we have a few drops of blood and can use that to determine whether someone [with a head wound] is mildly, severely or moderately injured, that would be a huge contribution to decision-making" by a medic on the battlefield, Col. Ling said Friday in an interview.

The New York Times

Thursday, February 8, 2007

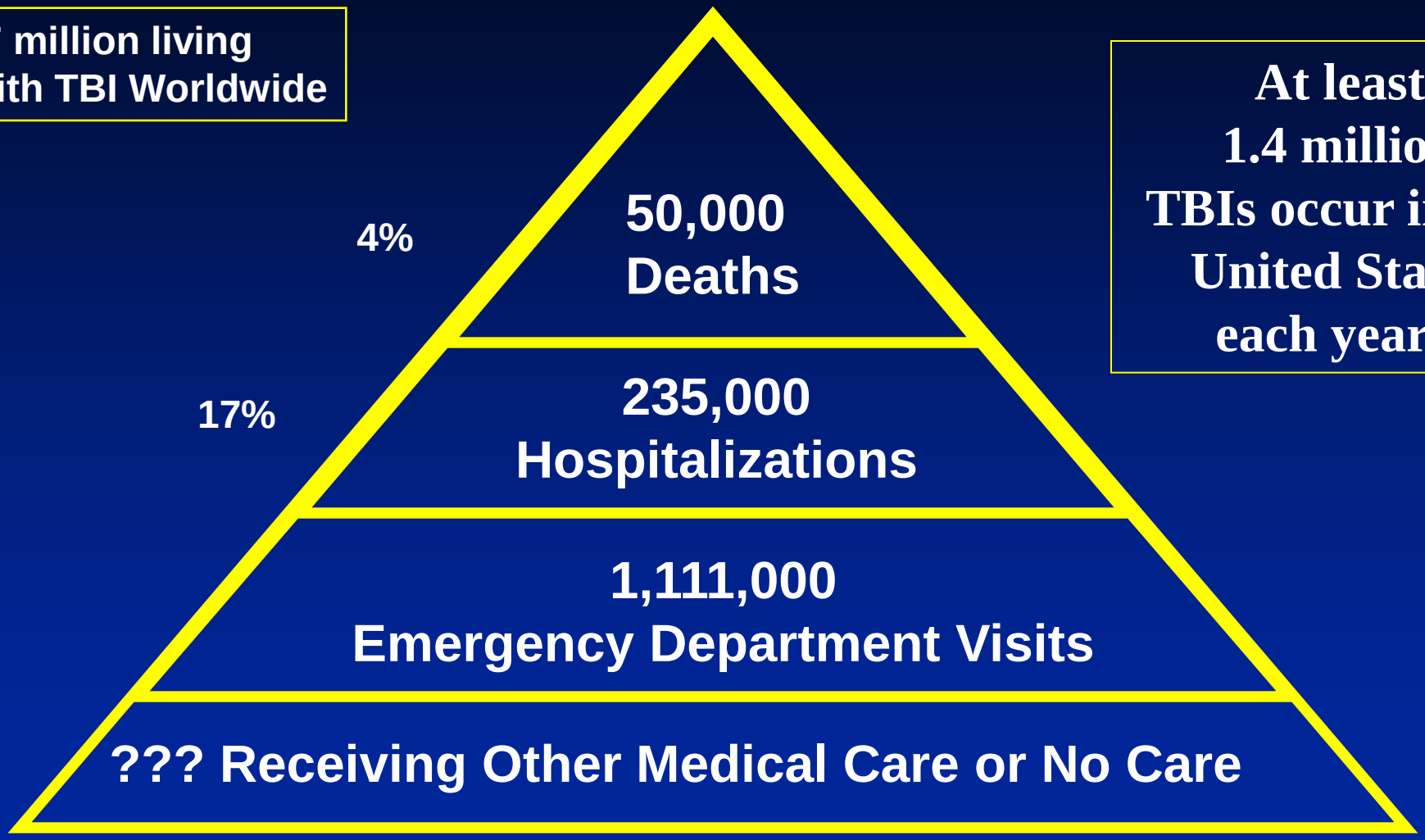
PRO FOOTBALL

Expert Ties Ex-Player's Suicide To Brain Damage From Football

Since the former National Football League player Andre Waters killed himself in November, an explanation for his suicide has remained a mystery. But after examining remains of Mr. Waters's brain, a neuropathologist in Pittsburgh is claiming that Mr. Waters had sustained brain damage from playing football and he says that led to his depression and ultimate death.

TBI in the United States

57 million living
With TBI Worldwide



At least
1.4 million
TBIs occur in the
United States
each year.*

CDC, 2006

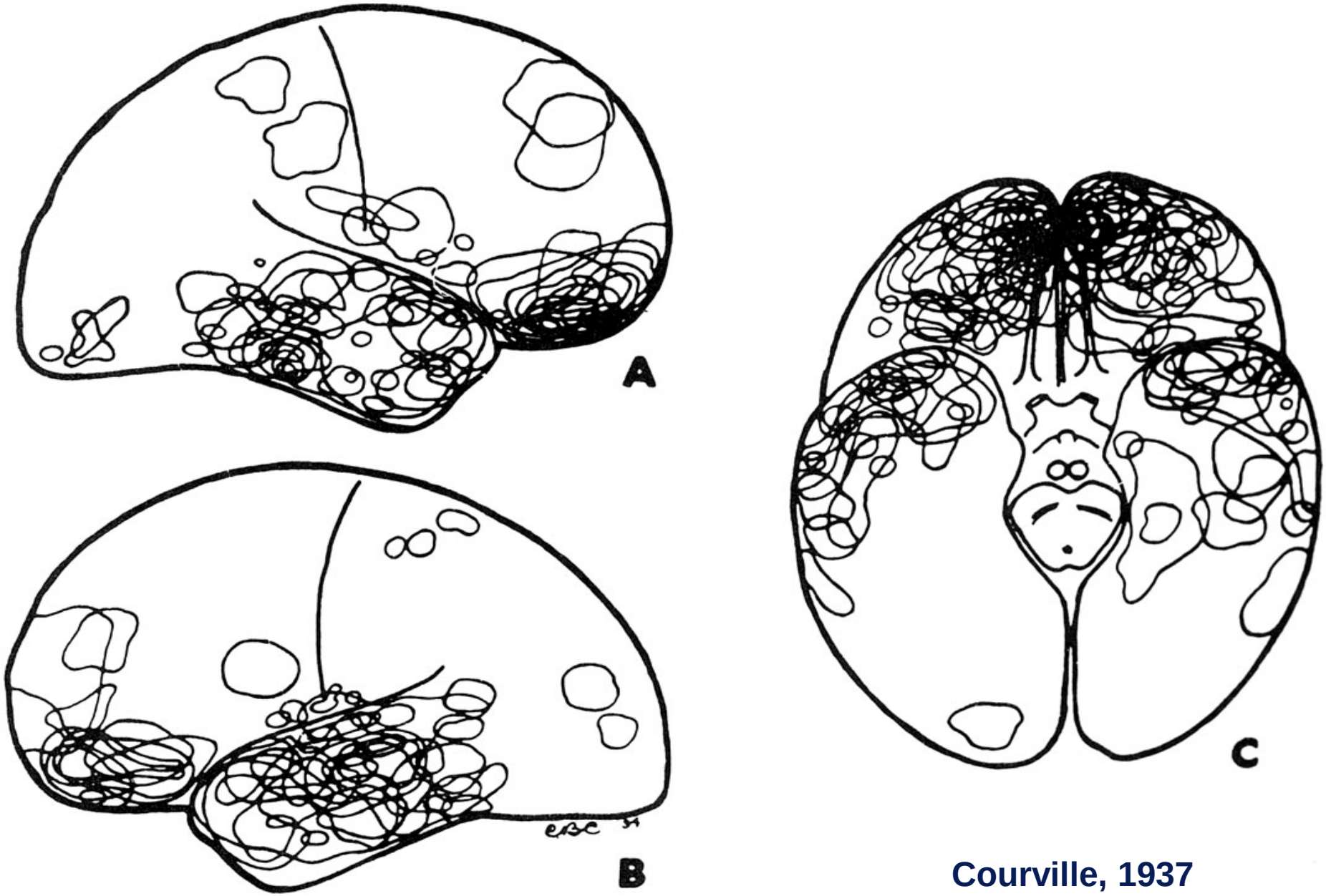
* Average annual numbers, 1995-2001

Traumatic Brain Injury (TBI)

- Neurobiological Injury
- Traumatic Event
- Chronic Medical Illness

TBI as Neurobiological Injury

- **Primary effects of TBI**
  - **Contusions, diffuse axonal injury**
- **Secondary effects of TBI**
  - **Hematomas, edema, hydrocephalus, increased intracranial pressure, infection, hypoxia, neurotoxicity, inflammatory response, protease activation, calcium influx, excitotoxin & free radical release, lipid peroxidation, phospholipase activation**
- **Can affect serotonin, norepinephrine, dopamine, acetylcholine, and GABA systems**



Courville, 1937

Examples of Neuropsychiatric Syndromes Associated with Neuroanatomical Lesions

- **Leteral orbital pre-frontal cortex**
  - Irritability - Impulsivity
  - Mood lability - Mania
- **Anterior cingulate pre-frontal cortex**
  - Apathy - Akinetic mutism
- **Dorsolateral pre-frontal cortex**
  - Poor memory search - Poor set-shifting / maintenance
- **Temporal Lobe**
  - Memory impairment - Mood lability
  - Psychosis - Aggression
- **Hypothalamus**
  - Sexual behavior - Aggression

Neuropathology in TBI and Depression

- Left dorsolateral frontal lesions or left basal ganglia lesions are associated with MDD in acute TBI and stroke (Federoff et al., 1992, Robinson et al., 1985)
- Disruption of frontal lobe - basal ganglia circuits is associated with MDD in TBI (Mayberg, 1994)
- Decreased glucose metabolism in orbital-inferior frontal and anterior temporal cortex is associated with MDD in TBI, CVA, Parkinson's (Mayberg, 1994)
- Serotonergic fibers have been implicated in the pathogenesis of arousal, sleep and depression in both the general population and brain-injured patients
- Frontal lobe damage from TBI is associated with reduced brain serotonergic function (VanWoerkom et al., 1977)
- MDD is associated with reduced left prefrontal gray matter volumes, esp. ventrolateral & dorsolateral regions (Jorge et al., 2004)

TBI as Traumatic Event

- **PTSD Prevalence: 11-27% ***
  - Possibly more prevalent in mild TBI
  - Mediated by implicit memory or conditioned fear response in amnestic patients?
- **PTSD Phenomenology: ****
  - Intrusive memories: 0-19%
  - Emotional reactivity: 96%
  - Intrusive memories, nightmares, emotional reactivity had highest predictive power
- **Anxiety often comorbid with / prolongs depression**

* Warden 1997, Bryant 1995, Flesher 2001, Bombardier 2006

** Warden et al 1997, Bryant et al 2000

TBI as Chronic Illness (the "Silent Epidemic")

- 80,000-90,000 new TBI survivors experience onset of long-term disability annually
- About 1 in 4 adults with TBI is unable to return to work 1 year after injury
- 5.3 million Americans (2% of U.S. population) currently live with TBI-related disabilities
  - Based on hospitalized survivors only
- 65% of costs are accrued among TBI survivors
- Annual acute care and rehab costs of TBI = $9 - $10 billion *
- Estimated annual lifetime costs of TBI survivors in year 2000 = $60 billion **

* NIH Consensus Development Panel on Rehabilitation, 1999

** Finkelstein E, Corso P, Miller T, et al. The Incidence and Economic Burden of Injuries. New York, Oxford Univ Press, 2006

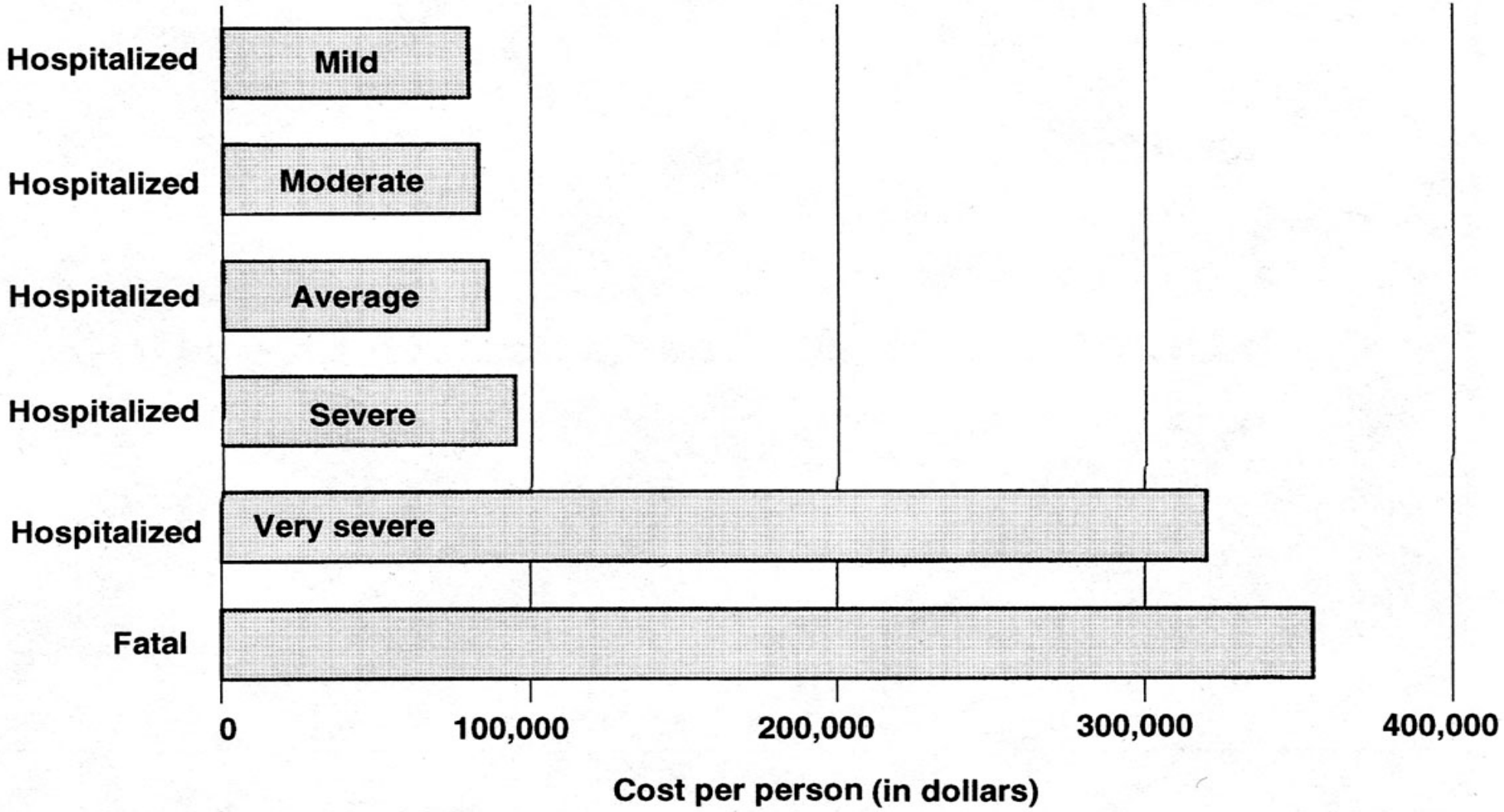


Figure 1–20. Lifetime costs of head injury, 1985 (by severity of injury).
Source. Max et al. 1991.

TBI-associated Disability

- “Postconcussive Symptoms”

- Cognitive
- Physical: sensory and motor
- Emotional

- Vocational
- Social
- Family

Neuropsychiatric Sequelae

- Delirium
- Depression / Apathy
- Mania
- Anxiety
- Psychosis
- Cognitive Impairment
- Aggression, Agitation, Impulsivity
- Postconcussive Symptoms

Neuropsychiatric Evaluation and Treatment: Etiologies

Psychiatric	Neurologic/Medical	Social
Premorbid	Neurologic illness	Social, family, vocation
Psych disorders & sxs.	Lesion location, size,	Rehabilitation situation
Personality traits	pathophysiology	and stressors
Coping styles	Other medical illness	Functional impairment
Substance Abuse	Other indirect sequelae	Medicolegal
Medication side effects	(e.g., pain, sleep disturb)	
& interactions	Medication side effects	
Psychodynamic sig.	& interactions	
of neurologic illness		
Family psych. history		

Roy-Byrne P, Fann JR. APA Textbook of Neuropsychiatry, 1997

Neuropsychiatric Evaluation and Treatment: Workup

Psychiatric	Neurologic/Medical	Social
Psychiatric history & examination	Medical history and physical examination	Interview family, friends, caregivers
Neuropsychological testing	Appropriate lab tests e.g., CBC, med blood levels, CT/MRI, EEG	Assess level of care & supervision available
Psychodynamic signif. of neuropsychiatric sxs., disability and treatments	Medication allergies	Assess rehab needs & progress

Neuropsychiatric Evaluation and Treatment: Follow-up

Psychiatric	Neurologic/Medical	Social
Frequent pharmacologic monitoring	Physical signs & sxs.	Rehabilitation
Psychotherapy	Physiologic response (e.g., vital signs)	Maximize support system
Intermittent cognitive assessments	Appropriate lab tests (e.g., CBC, medication blood levels, EEG)	
Support Groups		

Neuropsychiatric History

Psychiatric symptoms may not fit DSM-IV criteria

Focus on functional impairment

Document and rate symptoms

Explore circumstances of trauma

LOC, PTA, hospitalization, medical complications

Subtle symptoms - may fail to associate with trauma

How has life changed since TBI?

Thorough review of medical and psychiatric sxs.

Talk with family, friends, caregivers

Assess level of care and supervision available

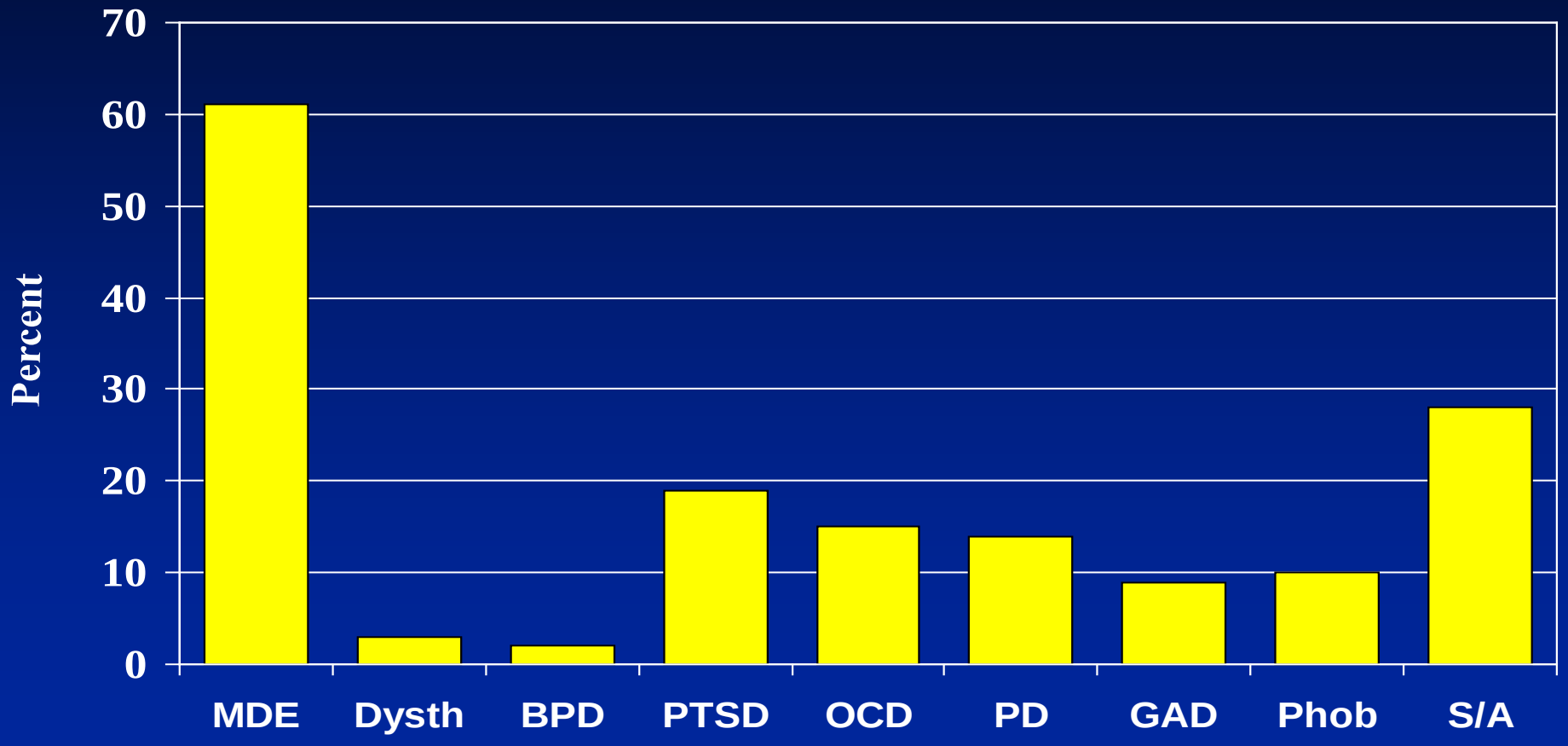
Assess rehabilitation needs and progress

Neuropsychiatric Treatment

- Use Biopsychosocial Model
- Treat maximum signs and symptoms with fewest possible medications
- TBI patients more sensitive to side effects

  START LOW, GO SLOW
- May still need maximum doses
- Therapeutic onset may be latent
- Medications may lower seizure threshold
- Medications may slow cognitive recovery
- Monitor and document outcomes
- Few randomized, controlled trials

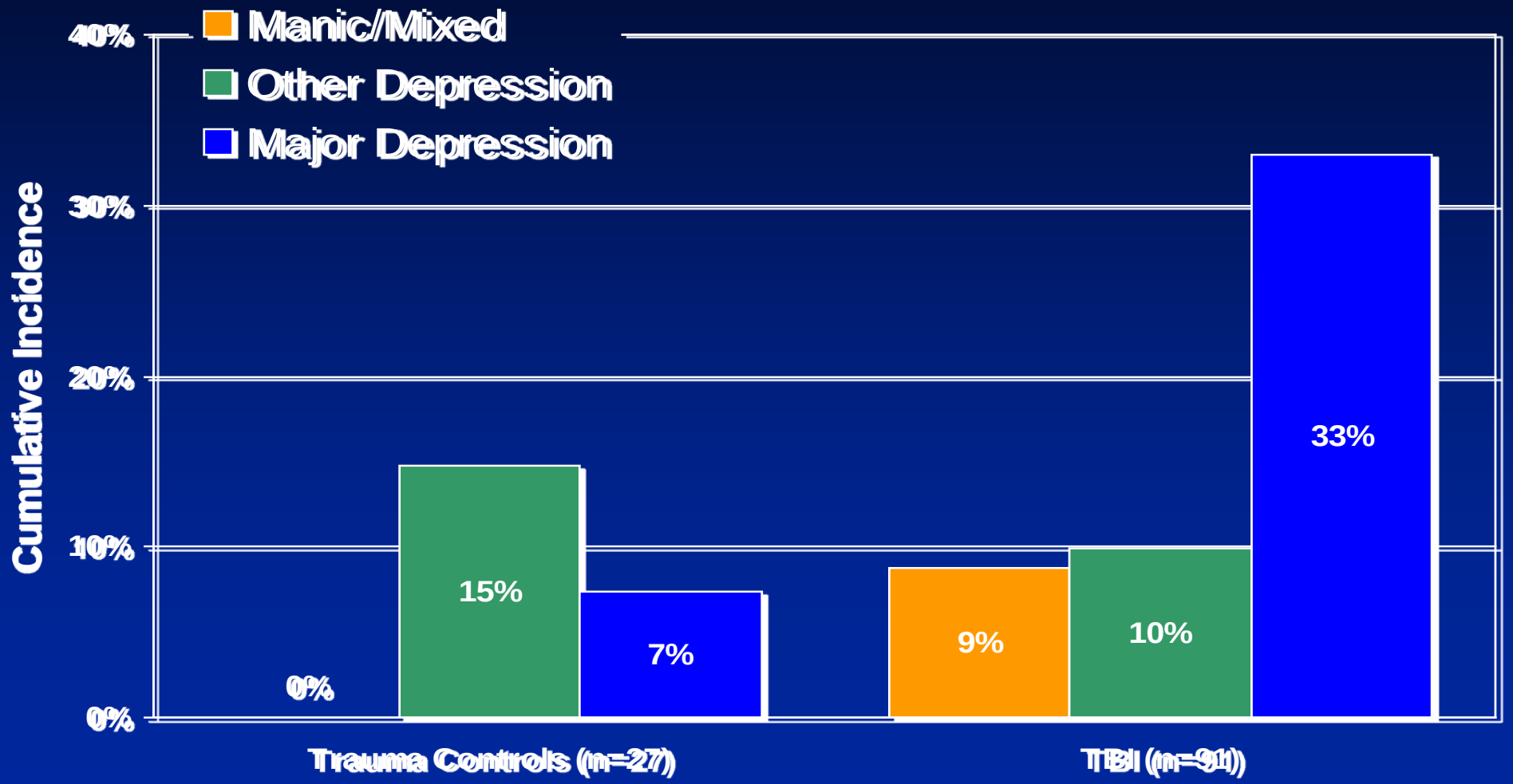
Seven Year Prevalence of SCID* Diagnosed Psychiatric Disorders After TBI



SCID=Structured Clinical Interview for DSM-IV

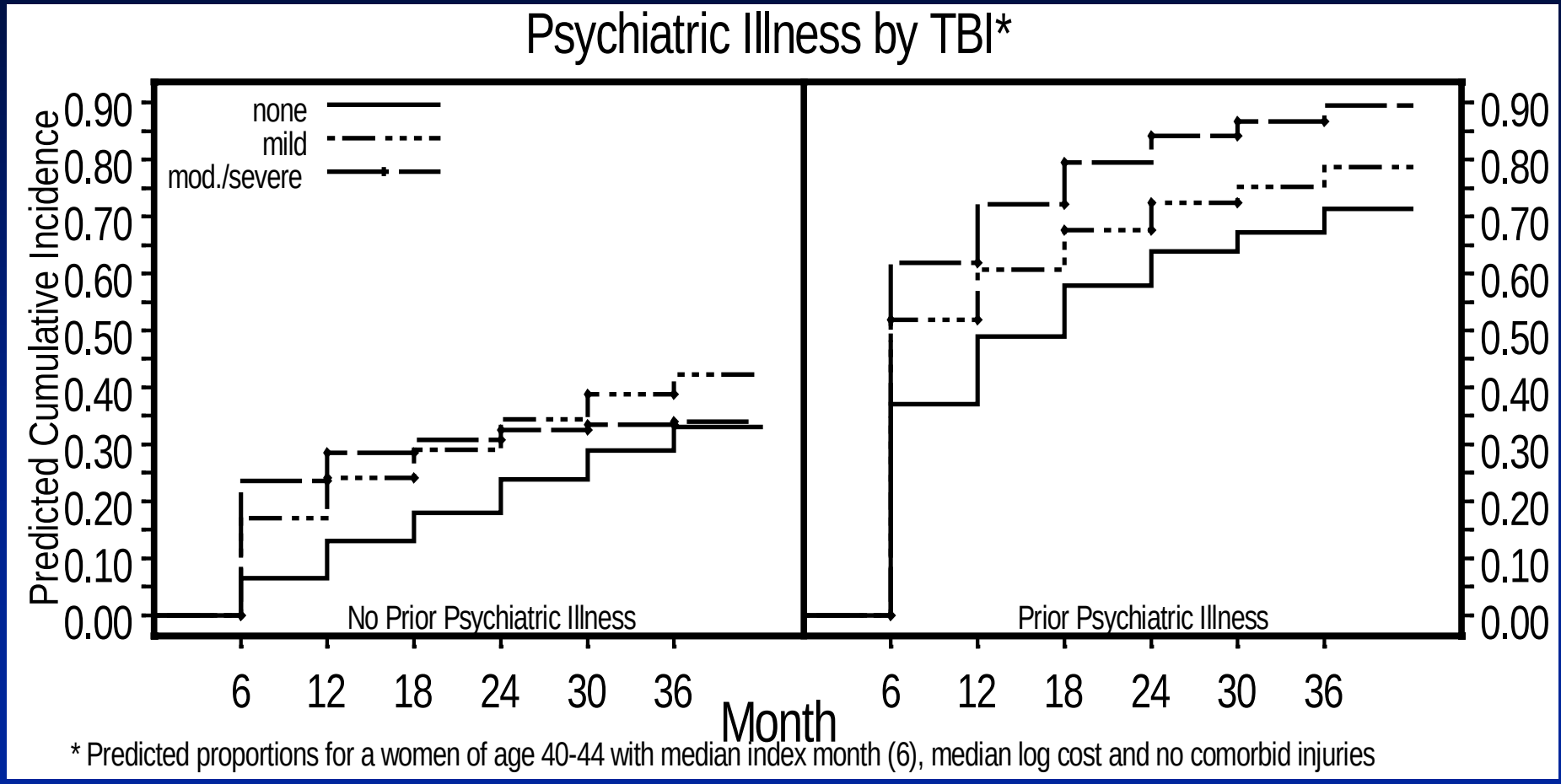
Hibbard et al., 1998

One Year Cumulative Incidence of Mood Disorders After TBI



Jorge et al., 2004

Psychiatric Illness in Adult HMO Enrollees



Fann et al. 2004

Delirium

- Increased risk in patients with TBI
- Undiagnosed in 32-67% of patients
  - Often missed in both inpatient and outpatient settings
- Associated with 10-65% mortality
- Up to 25% of delirious medical patients die during hospitalization and 37% within 1-3 months of onset
- Can lead to self-injurious behavior, decreased self-management, caregiver management problems
- Associated with increased length of hospital stay and increased risk of institutional placement
- Other terms used to denote delirium: acute confusional state, intensive care unit (ICU) psychosis, metabolic encephalopathy organic brain syndrome, sundowning, toxic encephalopathy

Delirium

- **Identify and correct underlying cause**
  - e.g., seizures, hydrocephalus, hygromas, hemorrhage, drug side effect or interactions, endocrine (hypothalamic, pituitary dysfunction)
- **Pharmacologic management**
  - Antipsychotics
    - » haloperidol, droperidol, risperidone, olanzapine, quetiapine
  - Benzodiazepines (combined with antipsychotics)
    - » lorazepam
- **Avoid polypharmacy**
- **Medical management**
  - Frequent monitoring of safety, vital signs, mental status and physical exams
  - Maintain proper nutritional, electrolyte, and fluid balance

Depression / Apathy

- Prevalence of major depression 44.3% *
  - Increased suicide risk
  - Assess pre-injury depression and alcohol use
  - Clinical presentation may vary
  - May occur acutely or post-acutely
  - May be related to neuropsychological impairment and neuroanatomical lesions
  - Associated with increased functional impairment and post-concussive symptoms
- Apathy alone - prevalence 10%
  - disinterest, disengagement, inertia, lack of motivation, lack of emotional responsivity

* van Reekum et al. J Neuropsychiatry Clin Neurosci 2000;12:316-327

Prevalence of MDD after TBI

Outpatient/Referral Cases

- 42% 2.5 years post-TBI (Kreutzer et al, 2001)
- 54% average of 33 months post-TBI (Fann et al, 1995)

Unselected/Consecutive Cases

- 33-42% within 1 yr (Jorge et al, 1993, 2004)
- 13% mostly mild TBI at 1 yr (Deb et al., 1999)
- 17% mild-mod TBI at 3 mos (Levin et al., 2001)
- 27% TBI at 10-126 mos (Seel et al, 2003)
- 11%-27% TBI at 30-50 yrs (Holsinger 2002, Koponen 2002)

Phenomenology (Jorge et al 1993, Kreutzer et al 2001)

- Symptoms may vary depending on time post-TBI (e.g., anxiety, vegetative symptoms early)
- Fatigue, frustration, poor concentration common

Patient Health Questionnaire - 9

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving .around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Spitzer et al. JAMA 1999

Surveillance for Depression After TBI
PHQ-9 to Screen for Depression

- Criterion Validity
- At least 5 symptoms scored at least several days

(≥ 1), at least one cardinal symptom:

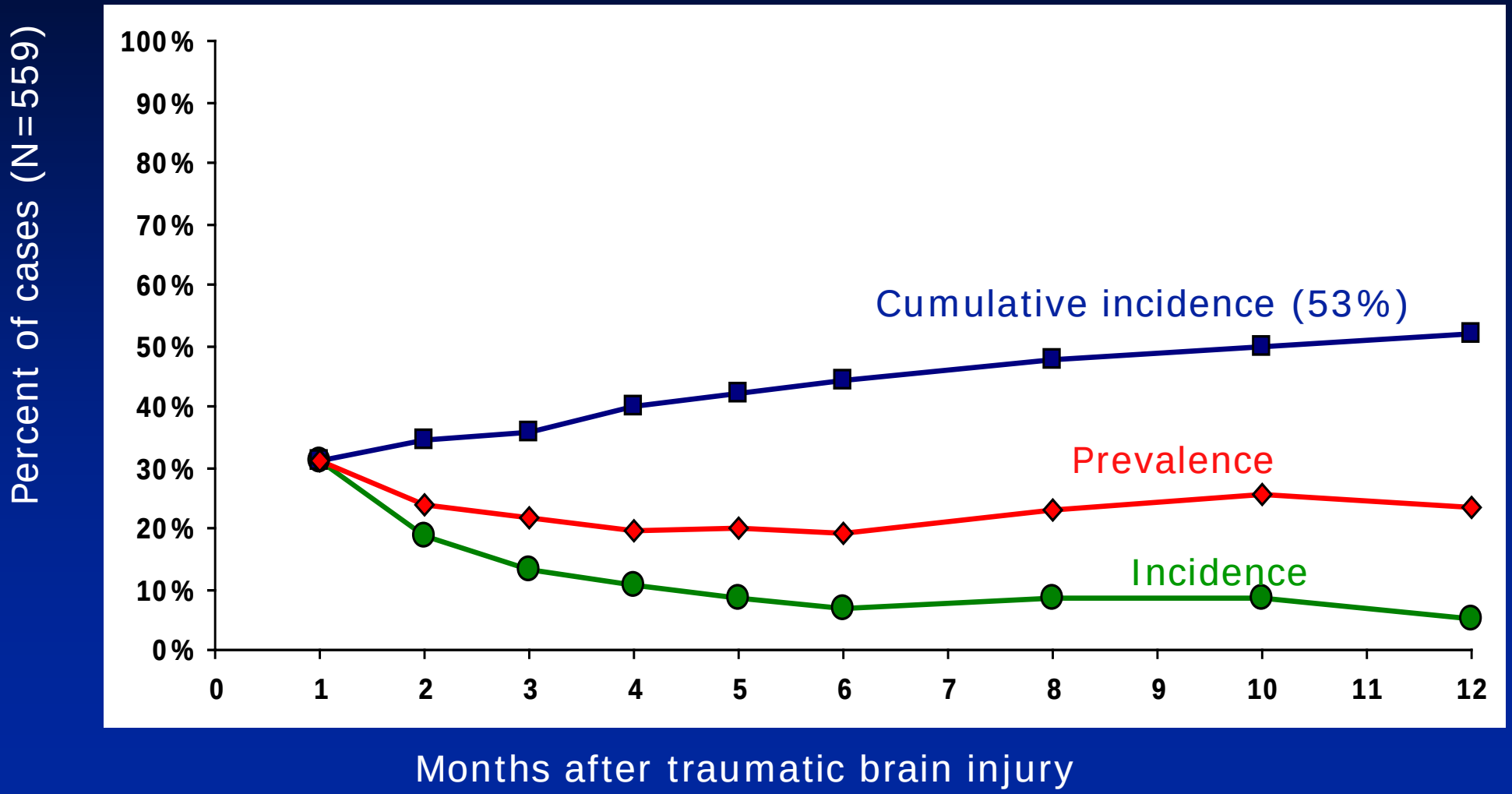
- Overall percent (point prevalence) meeting PHQ-9 screening criteria = 24.1

Sensitivity	.93
Specificity	.89
Positive Predictive Value	.63
Negative Predictive Value	.99

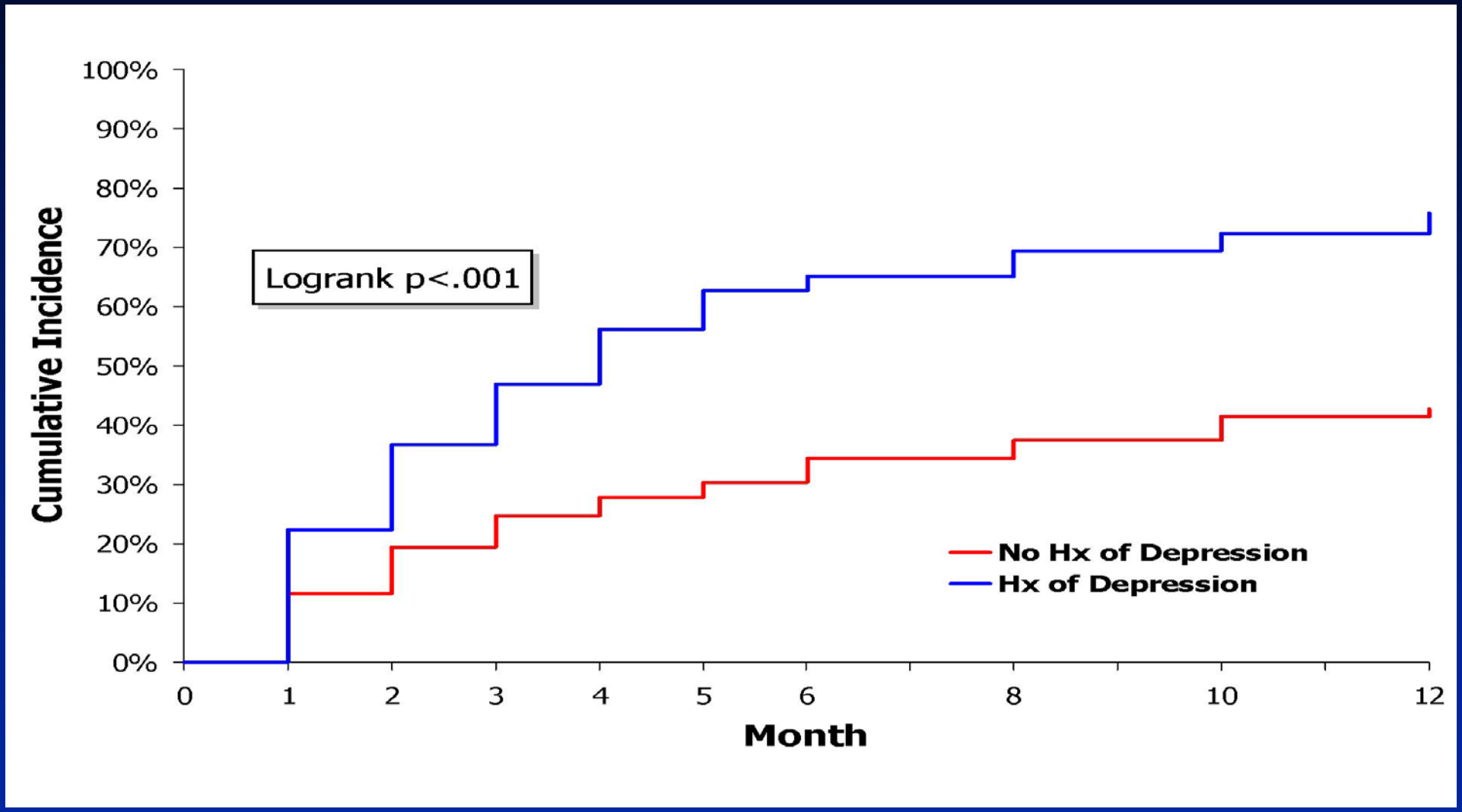
Fann, 2005

Rates of Major Depression after TBI
(N=559)

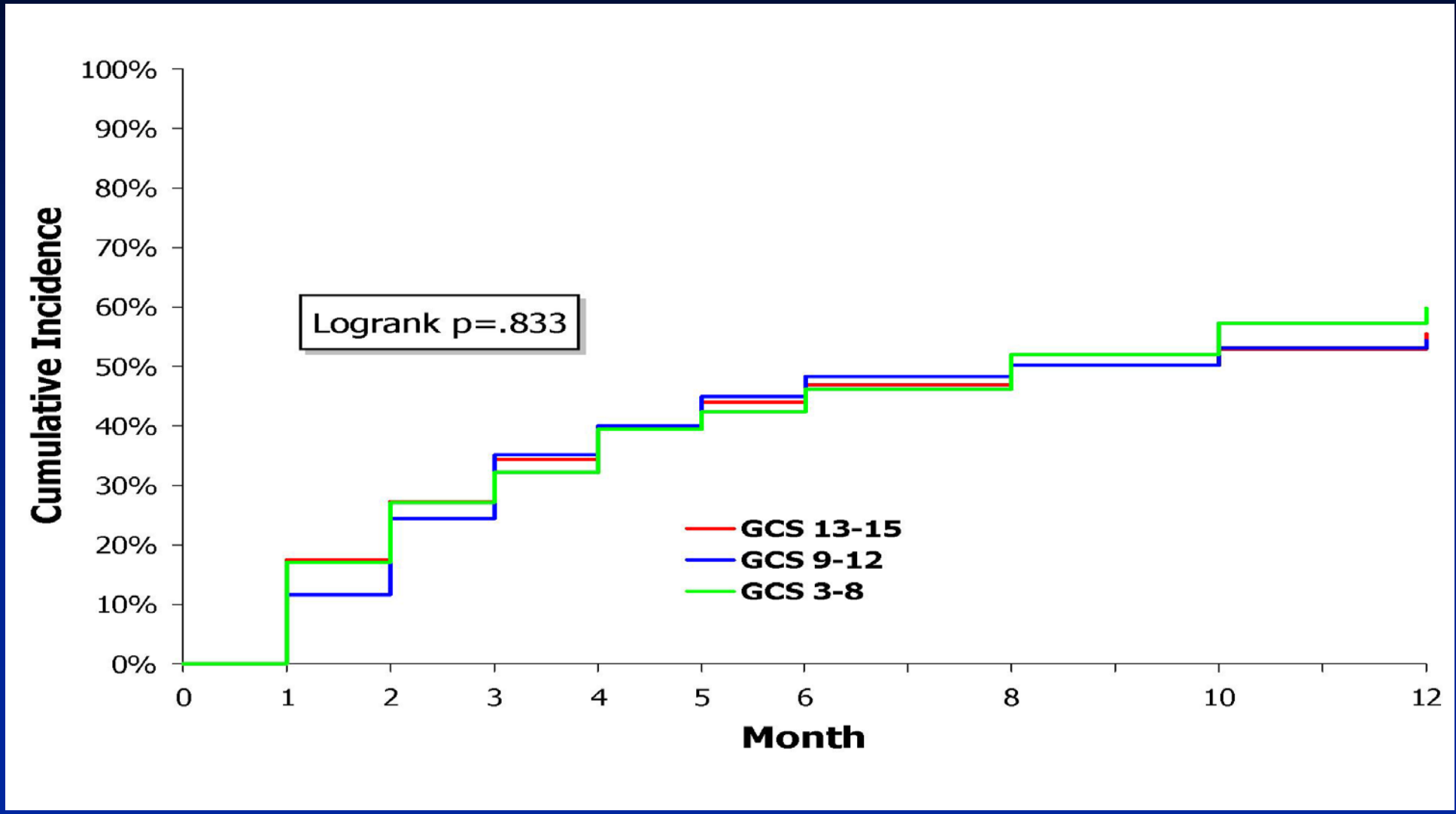
Bombardier, Fann et al, unpublished



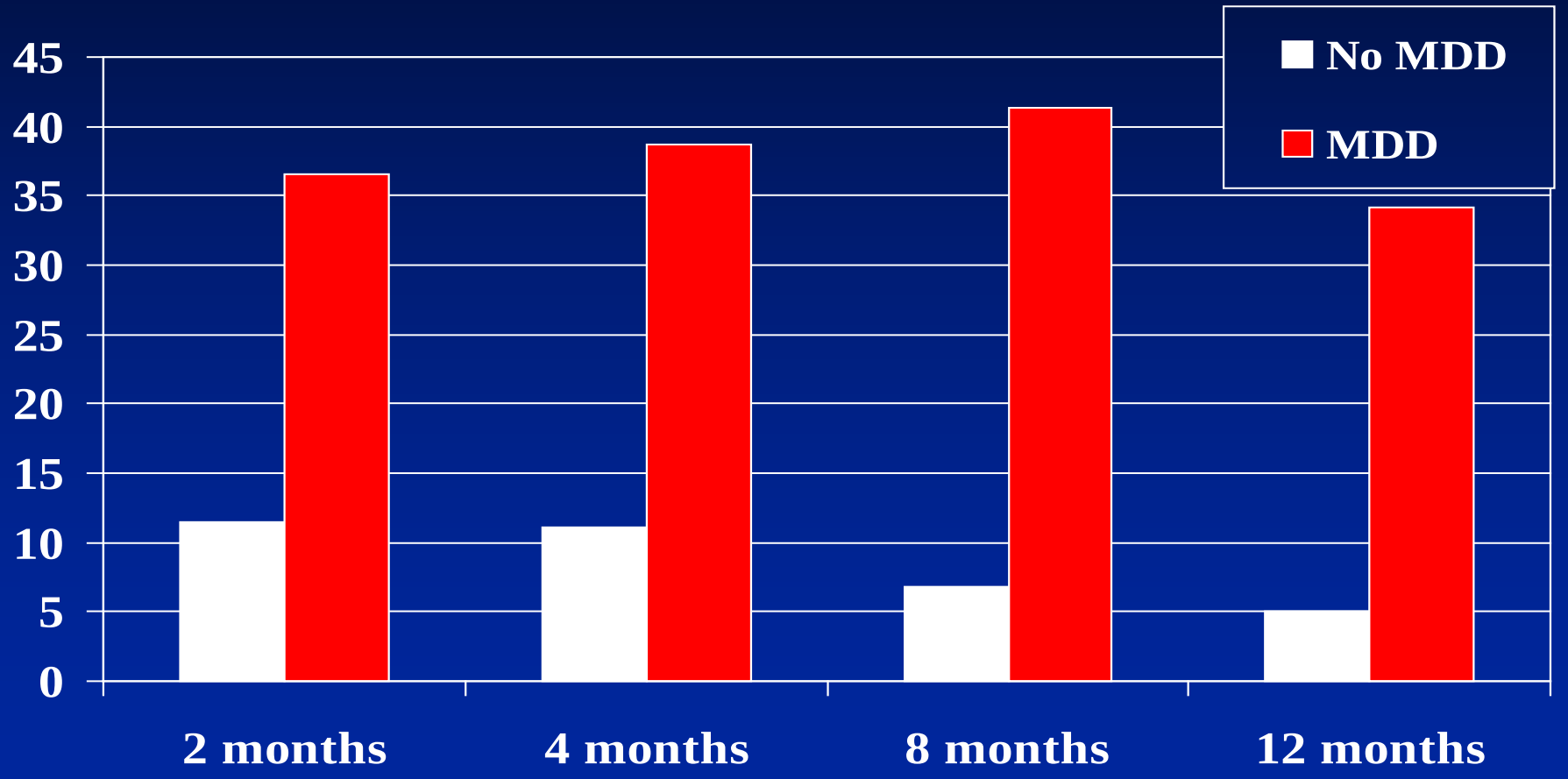
Major Depression by Psychiatric Hx



Major Depression by Coma Severity



Proportion endorsing fair to poor health (SF-1) by MDD status (N=471)



Impact of Depression on Outcomes

Depression after TBI contributes to:

- **Poorer cognitive functioning** (Rappoport et al., 2005)
- **Lower health status and greater functional disability** (Christensen et al., 1994; Levin et al 2001; Fann et al., 1995; Hibbard et al., 2004; Rapoport et al., 2003)
- **Poorer recovery** (Mooney et al., 2005)
- **More post-concussive symptoms** (Fann et al., 1995; Rapoport et al., 2005)

Impact of Depression on Outcomes

Depression after TBI contributes to:

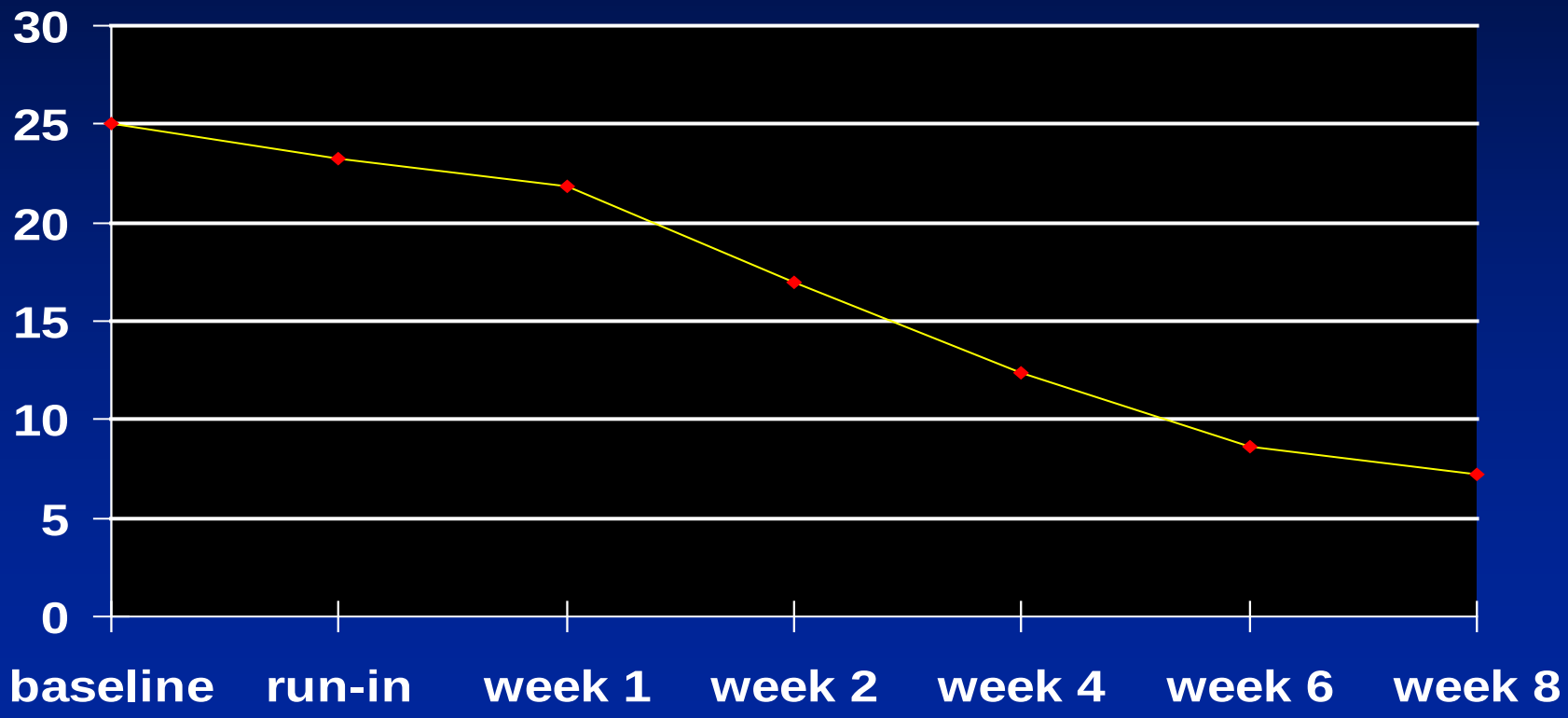
- **increased aggressive behavior and anxiety** (Tateno et al., 2003; Jorge et al., 2004; Fann et al., 1995)
- **significantly higher rates of suicidal plans** (Kishi et al., 2001)
- **8 times more attempts** (Silver et al., 2001)
- **3-4 times more completed suicide than in the general population and non-brain injured controls** (Teasdale and Engberg, 2001)

Depression / Apathy

- Selective serotonin re-uptake inhibitors (SSRIs)
  - sertraline - paroxetine - fluoxetine
  - citalopram - escitalopram
- venlafaxine, duloxetine (may help with pain)
- bupropion (may decrease seizure threshold)
- nefazedone (may be too sedating, liver toxicity)
- mirtazapine (may be too sedating)
- Tricyclics: nortriptyline, desipramine (blood levels)
- methylphenidate, dextroamphetamine
- Electroconvulsive Therapy – consider less frequent, nondominant unilateral

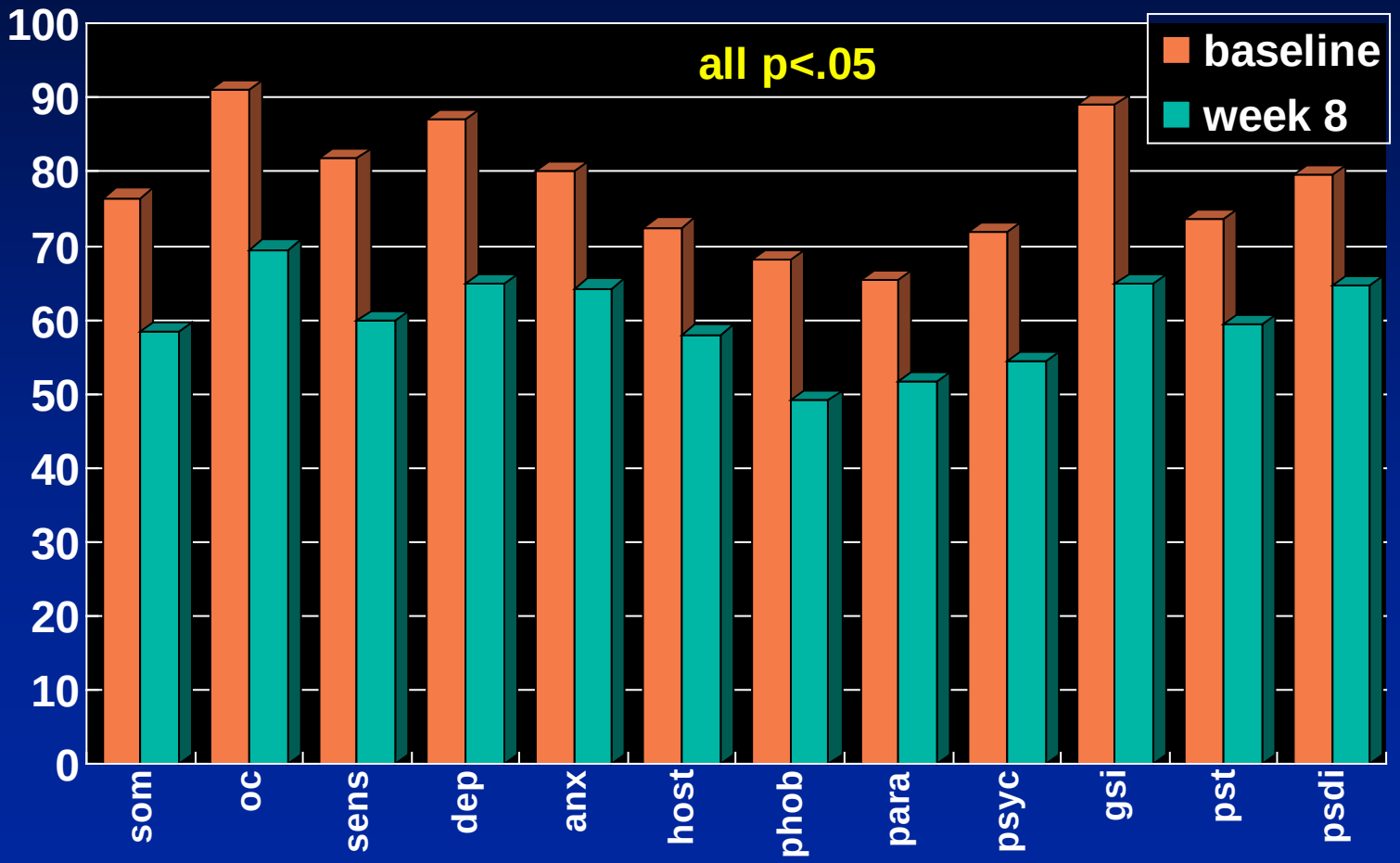
- Apathy: Dopaminergic agents - methylpyhenidate, pemoline, bupropion, amantadine, bromocriptine, modafinil

Pilot study of sertraline (N=15)
(Hamilton Depression Scale-17 item)



Fann et al. 2000

Hopkins Symptom Checklist
(SCL-90-R)



Mania

- Prevalence of Bipolar Disorder 4.2% *
- High rate of irritability, “emotional incontinence”
- May be associated with epileptiform activity
- Potential interaction of genetic loading, right hemisphere lesions, and anterior subcortical atrophy

* van Reekum et al. J Neuropsychiatry Clin Neurosci 2000;12:316-327

Mania

- Acute
  - Benzodiazepines
  - Antipsychotics
    - » olanzapine, risperidone, clozapine, others
  - Anticonvulsants
    - » valproate
  - Electroconvulsive Therapy
- Chronic
  - valproate
  - carbamazepine
  - lamotrigine
  - lithium carbonate (neurotoxicity)
  - gabapentin, topiramate (adjunctive treatments)

Anxiety

- Often comorbid with and prolongs course of depression
- Posttraumatic Stress Disorder: Prevalence 14.1% *
  - Reexperience, Avoidance, Hyperarousal
  - > 1 month, causes significant distress or impairment
  - Possibly more prevalent in mild TBI
- Panic Disorder: Prevalence 9.2% *
- Generalized Anxiety Disorder: Prevalence 9.1% *
- Obsessive-Compulsive Disorder: Prevalence 6.4% *

* van Reekum et al. J Neuropsychiatry Clin Neurosci 2000;12:316-327

Anxiety

- Benzodiazepines:
  - e.g., clonazepam, lorazepam, alprazolam
  - Watch for cognitive impairment, dependence
- Buspirone (for Generalized Anxiety Disorder)
- Antidepressants
  - SSRIs, venlafaxine, nefazedone, mirtazapine, TCAs
- Beta-blockers, verapamil, clonidine
- Anticonvulsants: valproate & gabapentin have some anxiolytic effects
- Psychosocial
  - Individual, couples, family, group

Psychosis

- Immediate or latent onset
- Symptoms may resemble schizophrenia: prevalence 0.7% *
- Schizophrenics have increased risk of TBI pre-dating psychosis
- Patients developing schizophrenic-like psychosis over 15-20 years is 0.7-9.8%
- Look for epileptiform activity and temporal lobe lesions

* van Reekum et al. J Neuropsychiatry Clin Neurosci 2000;12:316-327

Psychosis

- Antipsychotics
  - First generation: e.g. haloperidol, chlorpromazine
  - Second generation: e.g., risperidone
  - Third generation: e.g., olanzapine, quetiapine, ziprasidone, aripiprazole, clozapine (seizures)
- Start with low doses
- TBI pts have high risk of anticholinergic and extrapyramidal side effects
- May cause QTc prolongation
- Use sparingly - may impede neuronal recovery acutely (from animal data)

Cognitive Impairment

- Common problems
  - Concentration and attention
  - Memory
  - Speed of information processing
  - Mental flexibility
  - Executive functioning
  - Neurolinguistic
- Association with Alzheimer's Disease suggested
- May be associated with other psychiatric syndromes (e.g., depression, anxiety, psychosis) – treating these may improve cognition

Cognitive Impairment

May accelerate recovery

amphetamine
Norepinephrine (TCAs)
gangliosides
methylphenidate, dextroamphetamine
amantadine
L-dopa/carbidopa
bromocriptine
pergolide
physostigmine
donepezil
selegiline
apomorphine
caffeine
phenylpropanolamine
Naltrexone
atomoxetine

May impede recovery

haloperidol
phenothiazines
prazosin
clonidine
phenoxybenzamine
GABA
benzodiazepines
phenytoin
phenobarbital
idazoxan

Aggression, Irritability, Impulsivity

- Up to 70% within 1 year of TBI
- May last over 10-15 years
- Interview family and caregivers
- Characteristic features
  - Reactive - Explosive
  - Non-reflective - Periodic
  - Non-purposeful - Ego-dystonic
- Treat other underlying etiologies (e.g., bipolar)
- Also use behavioral interventions

Manifestations of Impulsivity and Aggression

- Emotional lability
- Pathologic laughing and crying
- Rage and aggression
- Altered sexual behavior
- Lack of concern over consequences of actions
- Social indifference
- Inappropriate joking and punning
- Superficiality of emotions

Aggression, Agitation, Impulsivity
(none FDA approved for this indication)

- **Acute**

  Antipsychotics

  Benzodiazepines

- **Chronic**

  ***Beta-blockers (e.g. propranolol, pindolol, nadolol)**
  ***valproate, carbamazepine, gabapentin**

  Lithium (narrow therapeutic window)

  buspirone

  Serotonergic antidepressants (e.g., SSRIs, trazodone)

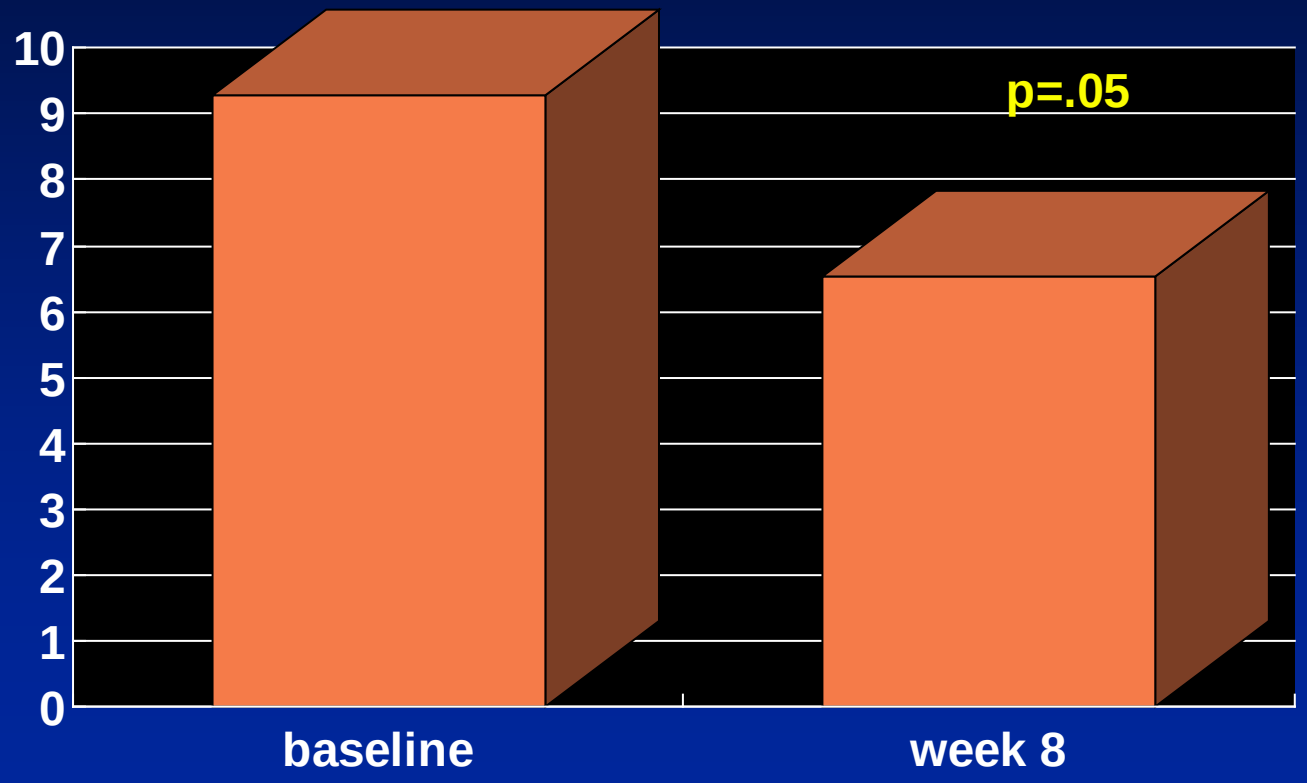
  Antipsychotics (esp. second and third generation)

  amantadine, bromocriptine, bupropion

  clonidine, methylphenidate, naltrexone, estrogen

*** Has most evidence for efficacy**

Pilot study of sertraline (N=15)
Brief Anger / Aggression Questionnaire (BAAQ)

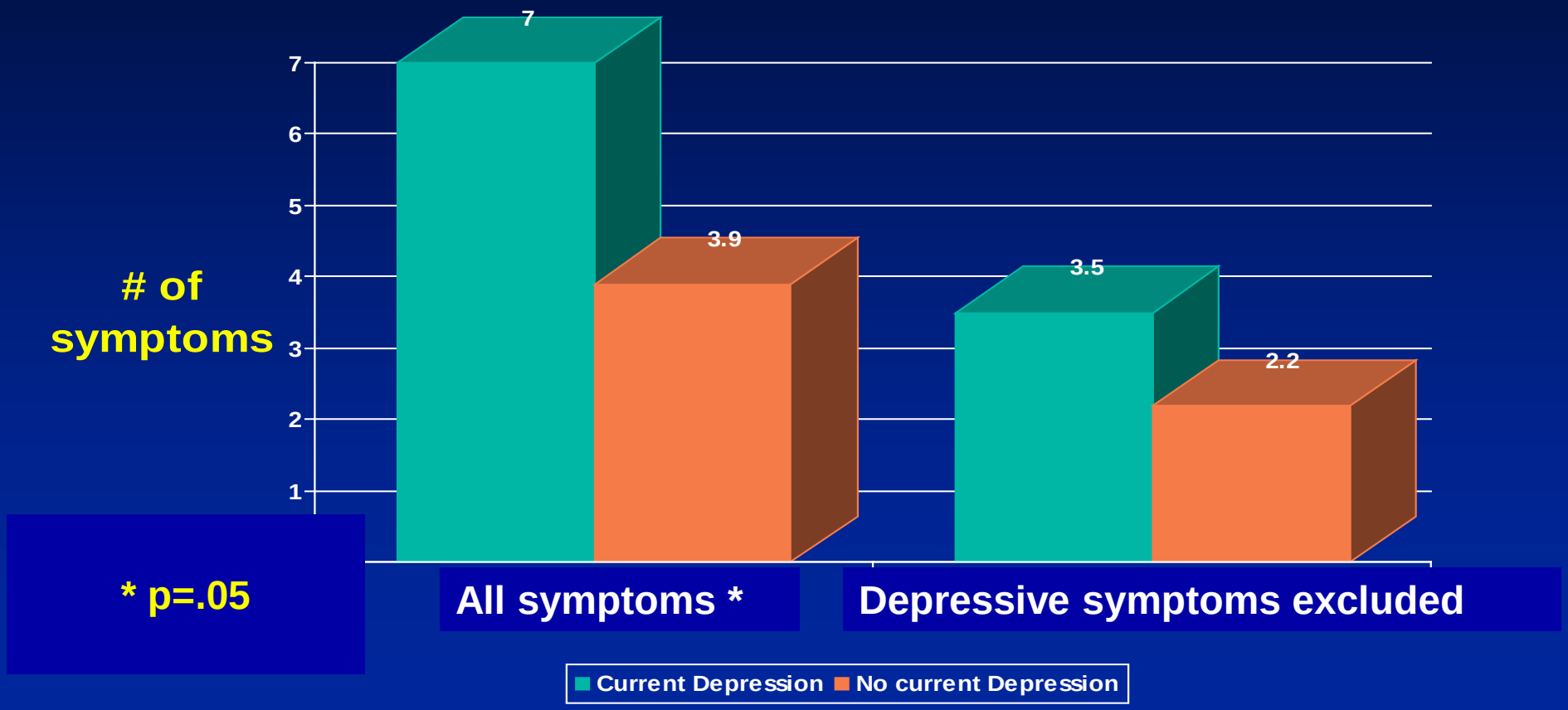


Fann et al. Psychosomatics 2001; 42:48-54

Postconcussive Symptoms

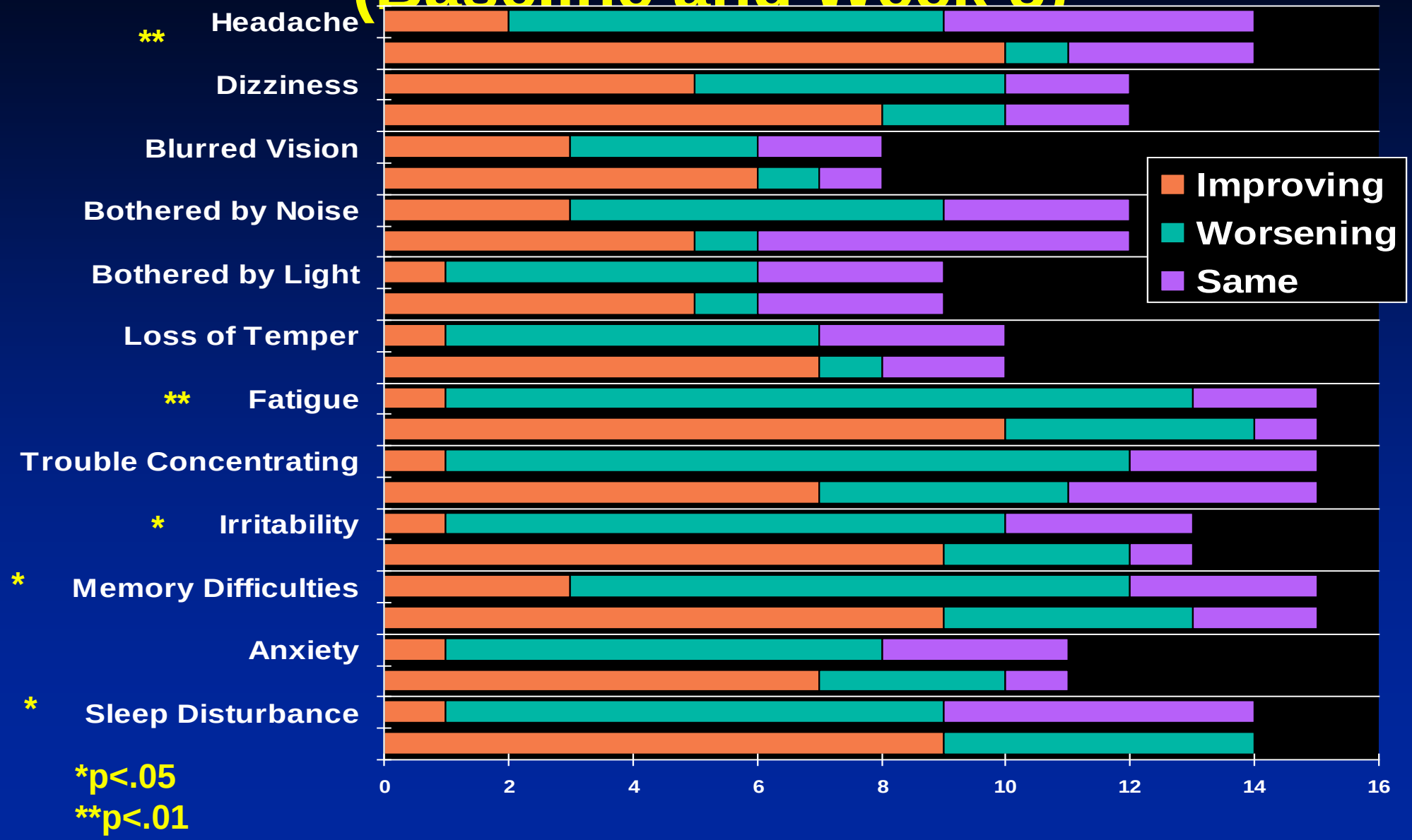
	Depressed (n=10)	Non-depressed (n=22)
Headache	50%	27%
Dizziness	40	32
Blurred Vision	40	27
Bothered by Noise	50	32
Bothered by Light	30	18
Loss of Temper Easily	70	32
Memory Difficulties	70	55
Fatigue	60	32
Trouble Concentrating	60	41
Irritability	80	32
Anxiety	90	32
Sleep Disturbance	60	27

Number of Postconcussive Symptoms



* p=.05

PCS – Depression Study (Baseline and Week 8)



*p<.05
**p<.01

Conclusions

- Neuropsychiatric syndromes are common after TBI
- They can present in many different ways
- They can significantly increase distress, disability, and health care utilization
- Use biopsychosocial and multidisciplinary approach
- Treat as many symptoms with as few medications as possible
- Monitor systematically and longitudinally

Proposed Model