Topics to be covered

- Common cognitive problems after TBI
- Relevant neuropathology
- Relevant neurotransmitters
- Current state of evidence on drug efficacy
- Recent work from our laboratory
- Potentially useful drugs and how to evaluate them
Common Cognitive Impairments

- Executive function
  - Focal frontal injury, frontal denervation from DAI
- Attention/concentration
  - Diffuse axonal injury, disruption of frontal executive systems
- Memory
  - Excitotoxic hippocampal damage, disruption of frontal executive systems
Importance of Attention & Executive Function

- Critical for all complex tasks!
- Critical for social behavior!
- Critical for inhibiting overlearned habits
  - Have you ever intended to reach into the refrigerator for the orange juice and come out with the milk?
  - How would you like to do that kind of thing repeatedly throughout the day? (If you do, don’t tell us!)
Importance of Memory

- Anterograde memory (hippocampal system) involved in rapid learning of new information. Executive system may be needed for retrieval.
  - Instructions on what to do and how to do it
  - Errors to avoid in the future
- Anterograde memory critical to maintenance of a “sense of self”
- Prospective memory (executive & hippocampal interactions)
  - Remembering to do something in the future
Pathophysiology of TBI

- Diffuse axonal injury
  - Disrupts multiple ascending projections in the reticular formation
- Increased intracranial pressure with brainstem compression
  - Same
- Focal cortical contusions
  - Predominantly anterior frontal, temporal
- Excitotoxicity
  - Hippocampus is particularly vulnerable
Neuroanatomy of Attention & Executive Function

Sustained Attention

2-back Task

$N=12$, cluster-based threshold at $p<.005$ with $k=20$
Structures of the Brain That Play a Role in Memory

- Basal forebrain
- Mediodorsal nucleus
- Prefrontal cortex
- Amygdala
- Rhinal cortex (not visible, on medial surface of temporal lobe)
- Hippocampus
- Inferotemporal cortex
- Cerebellum
Relevant Neurotransmitters

- Dopamine – prefrontal cortex, involved in executive processes, initiation of action
- Norepinephrine – thalamus & diffuse cortical projections, involved in selective attention
- Acetylcholine – diffuse cortical and cortico-cortical projections, involved in memory & attention
- Serotonin – diffuse cortical, involved in regulation of mood, appetite, sleep
- And many others…
What is the evidence for effectiveness of drug treatments?
Guidelines for the Pharmacologic Treatment of Neurobehavioral Sequelae of Traumatic Brain Injury (J Neurotrauma, in press)

- Deborah Warden, MD – Methodology, and task force chair
- Thomas McAllister, MD – Affective, Psychotic, and Anxiety Disorders
- Jon Silver, MD – Aggressive Behavior
- Barry Gordon, MD, PhD - Cognitive Disorders
Funding

- Centers for Disease Control & Prevention
- John Jane Brain Injury Center
- IBIA

(funding for meetings only)
Interdisciplinary Group:

- Neuropsychiatry and Psychiatry
- Neuropsychology
- Neurology
- Physical Medicine and Rehabilitation
- Cognitive Psychology
- Speech and Language Pathology
- Occupational Therapy
- Emergency Medicine
Methodology
Consultants:

- Dr. Beverly Walters, AANS
- Dr. Jess Kraus, Epidemiologist, UCLA
Questions reviewed:

- What are effective somatic (mostly drug) treatments for:
  - Affective disorders, psychotic disorders, and anxiety disorders?
  - Aggressive disorders and irritability?
  - Cognitive disorders?
Methods

In interests of time, will not discuss:

- Importance of clinical problems
- Literature search strategies
- Operational criteria for study quality classification
- Assessment of inter-rater reliability
- Ultimate classification of evidence strength
- Behavioral & psychiatric findings

Will discuss conclusions about cognitive interventions and research limitations
Pharmacotherapy of Cognitive Problems after Traumatic Brain Injury

Cognitive Working Group

Jeff Barth, PhD
Barry Gordon, MD, PhD
Douglas Katz, MD
Laurie Ryan, PhD
John Whyte, MD, PhD
Ashley Zapata, MA, SLP-CCC
Basic Issue

Are there effective pharmacologic treatments for the cognitive disorders that can occur after TBI?
Cognitive domains examined

- Attention
- New Learning (memory)
- Language
- Uncertain/mixed
Evidence by Agent (Class I and II)

- Homeopathy – mild TBI
- Phenytoin, Valproate – general cognition
- Bromocriptine – divided attention
- Methylphenidate – processing speed, attentiveness
- Physostigmine - memory
Current conclusions

- Strongest evidence is for the efficacy of methylphenidate for certain aspects of cognitive processing related to speed and arousal (guideline)
- Some evidence for bromocriptine effects on dual-task performance (option)
- Suggestive support for homeopathy in mild TBI (option)
Common methodological problems leading to reclassification of class I studies

- Patients frequently not well (or validly) characterized
- Small sample size/low statistical power
- Poor prognostic balance between treatment groups
- Treatment not randomized or blinded
- Lack of valid outcome measurement
- Lack of programmatic research
Important methodologic considerations for studies of drug treatment of cognitive impairments:

The levels of analysis problem
Some possible solutions being explored in our laboratory

- Programmatic research
  - In what ways is attention disturbed in TBI and how can one measure this?
  - Which of the potential measures of the problem are responsive to psychoactive drugs?
  - Dealing with multiple dependent variables
  - Within-subject (crossover) design
  - fMRI component added recently
Research on Methylphenidate Treatment of TBI-related Attention Deficits

- Supported by a grant from NINDS, and NCMRR (both NIH institutes/centers)
- Dose: 0.3 mg/kg, given at breakfast and lunch
Coding of Naturalistic Behavior

- 3 independent visuo-motor tasks
- Suitable for varied ability levels
- Controlled distractions
- Videotaping
Computer Testing Apparatus

- Individualized durations
- Pattern mask
- Simple midline targets/foils
- Most tasks similar with minor variations
Methylphenidate Results

- Processing speed factor
  - $P < .001$, effect sizes: 0 - .48

- Family rating factor
  - $P < .01$, effect sizes: .44 - .50

- Individual inattentiveness factor
  - $P = .06$, $P = .01$, effect sizes: .15 - .62
Research on Bromocriptine Treatment of TBI-related Attention/Executive Deficits

- Supported, as above, by grants from NINDS and NCMRR
- Sharon McDowell, collaborator
- Double-blind placebo-controlled single dose crossover study
- Dose: 2.5 mg, 2 hours prior to testing
Results

- Bromocriptine improved the ability to divide attention (do 2 things at once)
- Did not affect how well each task was performed alone
- Recent research, using a modification of the methylphenidate research design (3 weeks in each phase, single crossover, 10 mg/day) failed to replicate any of the positive results – why?
  - Dose
  - Chronic administration?
How can clinicians practice in the interim?
Potentially useful drugs

- Apathy/lack of initiation
  - Dopaminergic drugs (amantadine, bromocriptine)
  - Psychostimulants (methylphenidate, dextroamphetamine)
- Divided attention, executive deficits
  - Dopaminergic drugs (bromocriptine)
Potentially useful drugs (cont.)

- Inattentiveness, slowness
  - Methylphenidate, other psychostimulants
  - Noradrenergic drugs (atomoxetine, desipramine)?

- Memory impairment
  - Cholinergic drugs (donepezil)
How to deal with the uncertainty about efficacy?

- Seek to join multicenter research systems
- Minimize use of pharmacologic agents in rapidly changing acute patients?
- Single subject, as well as group methods in post-acute patients
Multicenter research systems

The model of oncology practice

- Requires us as a field to improve our labeling and categorization of problems, so we can agree on common treatment protocols
- Requires systematic program organization
- Requires skepticism and a willingness to randomize
Minimize drug treatment acutely

- Variability in the pace of spontaneous recovery makes it virtually impossible to judge whether an agent is effective in resolving the problem.
- Most patients progress without targeted pharmacologic treatment.
- Widespread use of pharmacologic treatment “off-label” builds staff and family resistance to the possibility of placebo treatment in group research.
Single subject methods

- Application of experimental methods to the study of an “n of 1” to arrive at a clinically relevant answer for an individual patient
- Typically does not require IRB approval for a drug that is in widespread clinical use
Three Basic Assessment Designs

- A-B
- A-B-A

(where A = no treatment; B = treatment of interest)
A-B-A Design

TIME (DAYS)

PERFORMANCE
A-B-A-B-A-B Design

PERFORMANCE

TIME (DAYS)
How Successfully Can We Evaluate Treatment Effects?

- A-B: almost never
- A-B-A: rarely done and rarely conclusive
- A-B-A-B-A…: most “trustworthy” design for post-acute drug assessment. But for long-acting drugs, such a design may not be feasible
Summary

What we know a lot about

- The neuropathology of TBI
- The neural networks involved in performance of various cognitive and behavioral functions
- Basic psychopharmacology of drugs
- Efficacy in some other populations

What we know very little about

- What works in TBI and even how to measure what works
Implications

- We must have a greater commitment toward traditional randomized group designs; other approaches have not “delivered”
- For acute patients, safe, rewarding environments for “watchful waiting” may be as good as aggressive drug treatment
- Single subject methods may be of help in post-acute patients
References