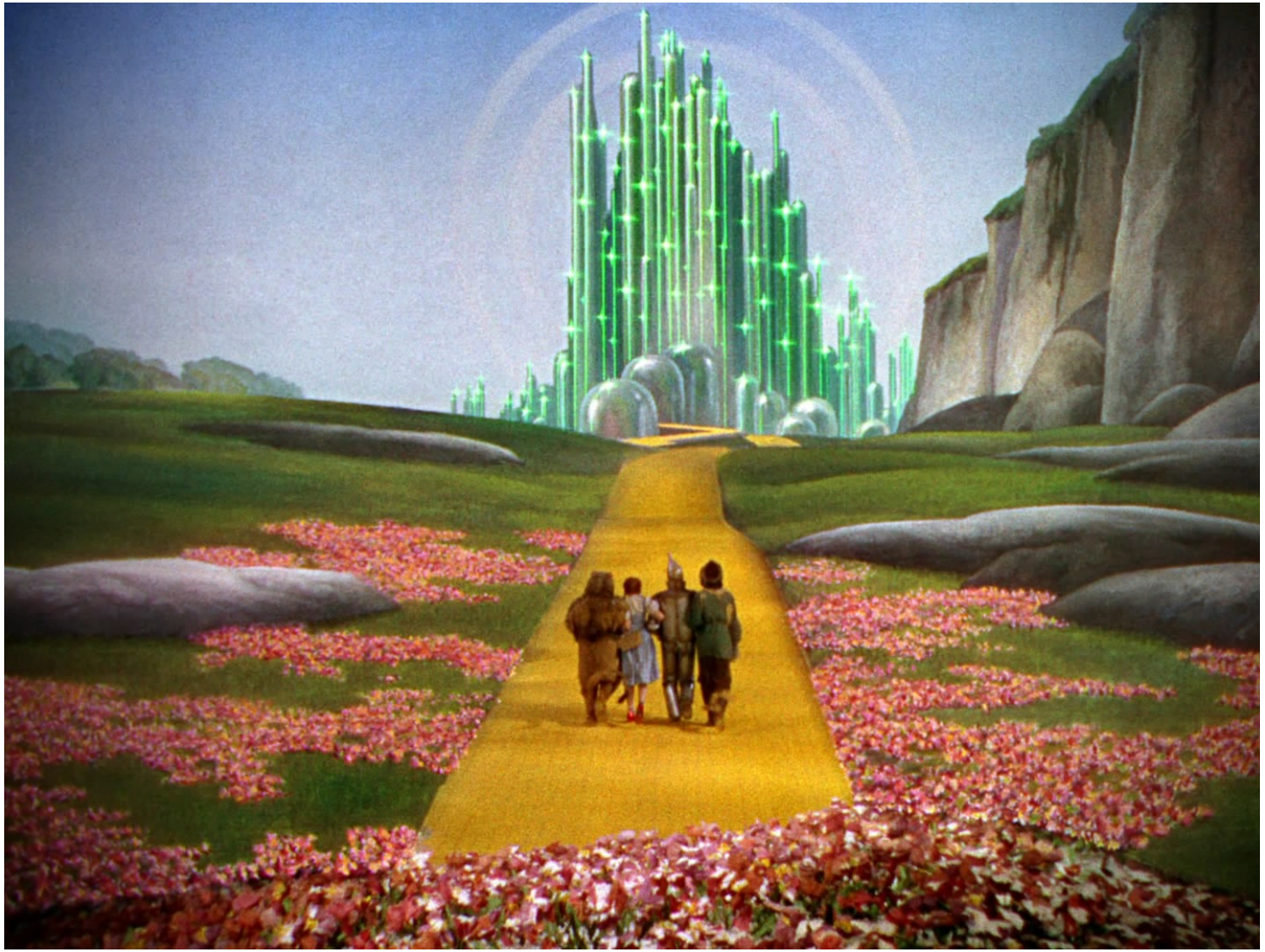
Medications to Maximize Cognitive Rehabilitation After TBI

Davin Quinn, MD



Part 1 **Review the neuroanatomical and neurophysiological effects of TBI**

Part 2 **Review different medications for cognitive deficits after TBI**

UNM HEALTH SCIENCES

Disclosures

- **Co-Investigator**, “Eye Recovery Automation for Post-Injury Dysfunctions (iRAPID).” (PI: Yaramothu) DoD CDMRP
- **Co-Investigator**, “A Prospective Observational Study on Therapeutic and Adverse Effects of Medical Cannabis for Chronic Traumatic Brain Injury.” (PI: Mayer) DoD CDMRP
- **Co-Investigator** for “University of New Mexico (UNM) Center for Brain Recovery and Repair.” (PI: Shuttleworth CW) COBRE NIH/NIGMS 6P20 GM109089-01A1
- **Coordinating Principal Investigator** on “Control Network Neuromodulation to Enhance Cognitive Training in Complex Traumatic Brain Injury (The CONNECT-TBI Trial).” (PI: Quinn) W81XWH-20-1-0928, DoD CDMRP
- **Coordinating Principal Investigator** on “High-Definition Transcranial Direct Current Stimulation for Sensory Deficits in Complex Traumatic Brain Injury.” (PI: Quinn) W81XWH-17-1-0432, DoD CDMRP

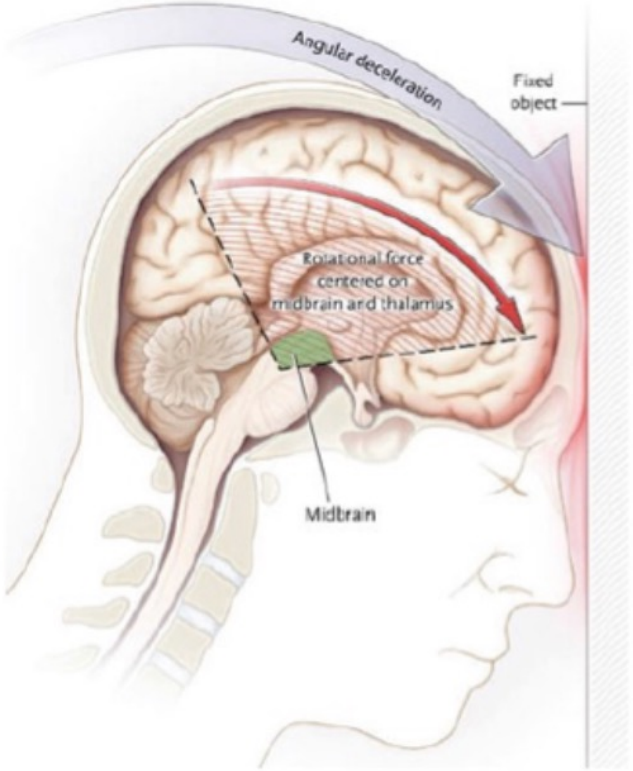
THE UNM CLINICAL NEUROSCIENCE CENTER

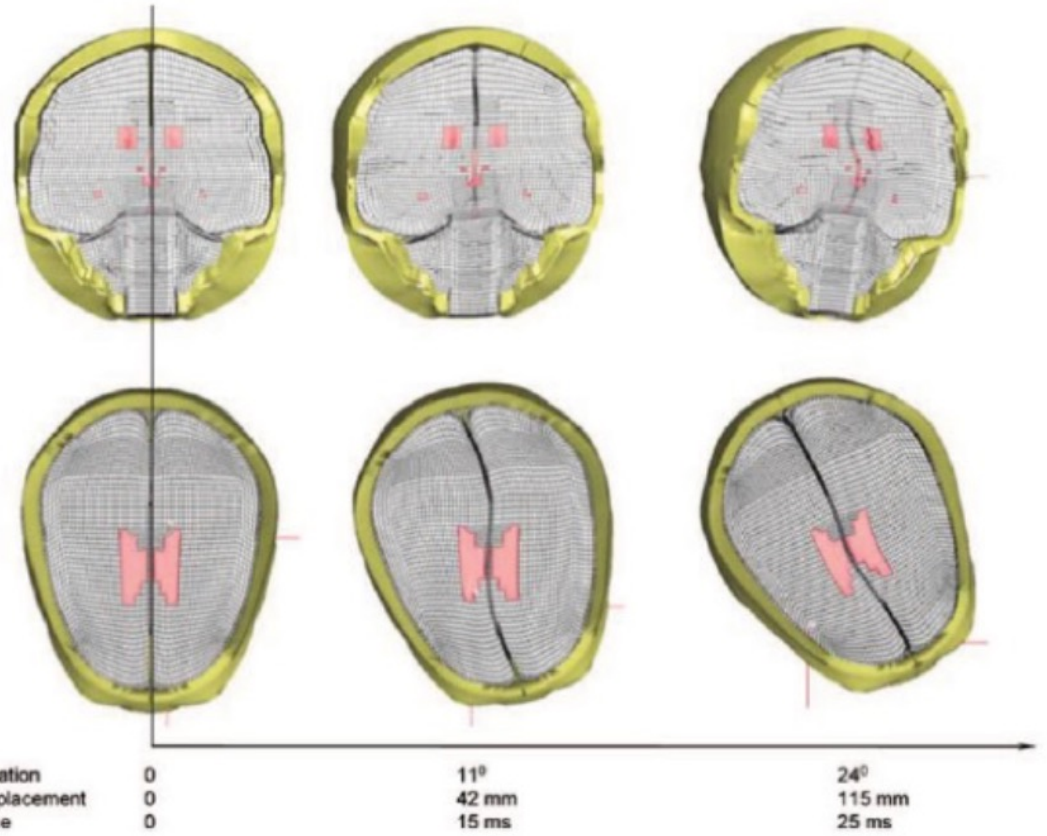
- Admission to UNM ED (< 24 hrs)
- Neurocritical Care/Operative Intervention (< 2 wks)
- Neuroscience Stepdown Unit (< 2 mon)
- Rehabilitation Facility (< 6 mon)
- Outpatient Clinic (> 6 mon)

Neurosurgeon
Neuropsychiatrist
Nurse
Medical Technician

Neurology
Neuropsychology
Physiatry
Social Work
PT/OT/SLP

TBI Pathophysiology: Structural Effects





1) Modeling of impact for football player concussed on kick return
2) Maximal structural displacement at 25 ms post impact in medial temporal lobes, hypothalamus
3) Other structures: frontal lobes, long white matter tracts, thalamus, brainstem

Bigler ED. Anterior and middle cranial fossa in traumatic brain injury: neuroanatomy and neuropathology in the study of neuropsychological outcome. Neuropsychology 2007; 21 (5): 515-531. Viano DC et al. Concussion in professional football: brain responses by finite element analysis. Neurosurgery 2005; 57)5: 891-915. Giza CC, Honda DA. The new neurometabolic cascade of concussion. Neurosurgery 2014; 75: S24-S33. Ropper AH, Gorson KC. Clinical practice: Concussion. N Engl J Med 2007; 356: 166-172.

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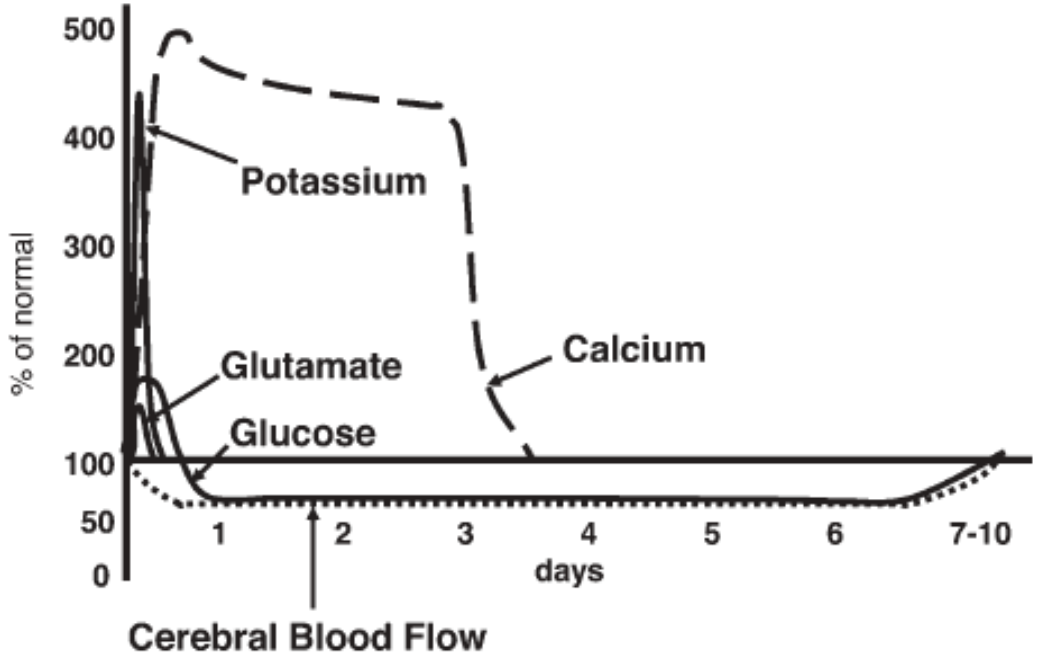
TBI Pathophysiology: Chemical Effects



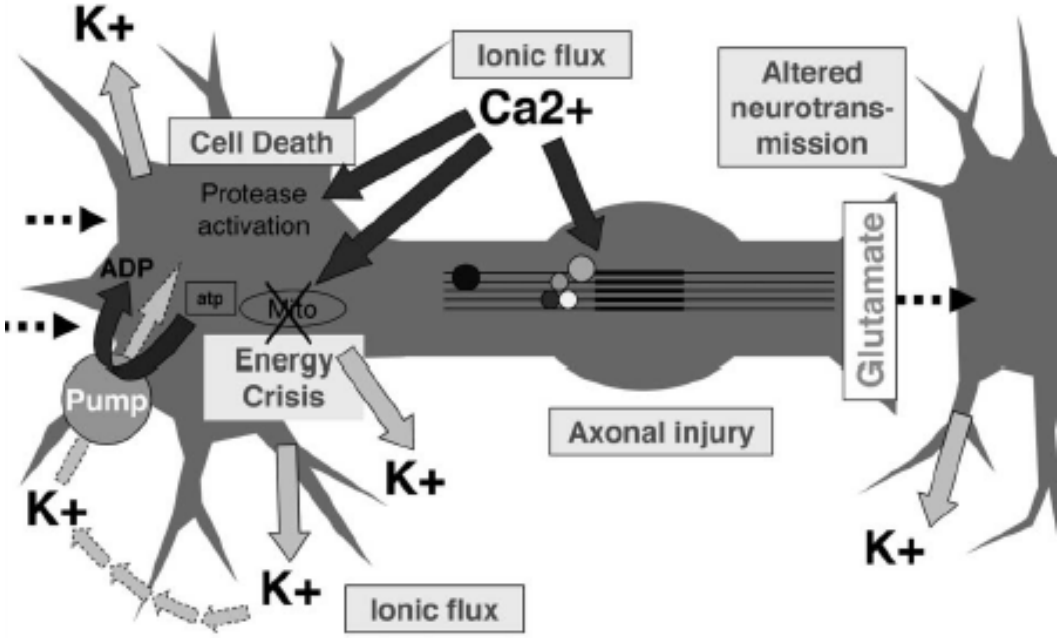
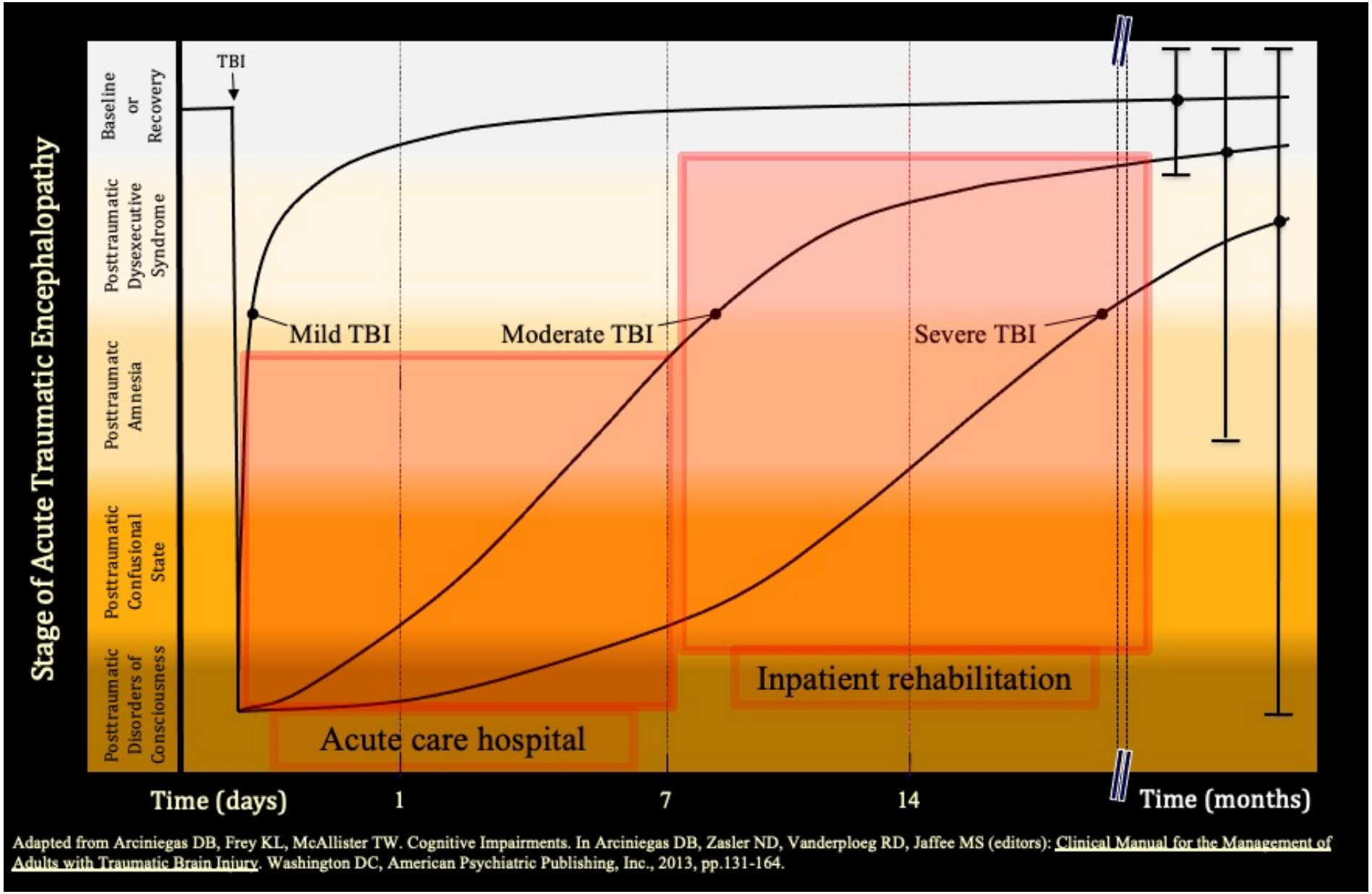


TABLE. Physiological Perturbations After Concussion and Proposed Clinical Correlates[a]

Post-TBI Pathophysiology	Acute Symptom/Clinical Correlate
Ionic flux	Migraine headache, photophobia, phonophobia
Energy crisis	Vulnerability to second injury
Axonal injury	Impaired cognition, slowed processing, slowed reaction time
Impaired neurotransmission	Impaired cognition, slowed processing, slowed reaction time
Protease activation, altered cytoskeletal proteins, cell death	Chronic atrophy, development of persistent impairments

Giza CC, Hovda DA. The new neurometabolic cascade of concussion. Neurosurgery. 2014;75(4):S24–33.

TBI Pathophysiology: Trajectory of Recovery



Adapted from Arciniegas DB, Frey KL, McAllister TW. Cognitive Impairments. In Arciniegas DB, Zasler ND, Vanderploeg RD, Jaffee MS (editors): Clinical Manual for the Management of Adults with Traumatic Brain Injury. Washington DC, American Psychiatric Publishing, Inc., 2013, pp.131-164.

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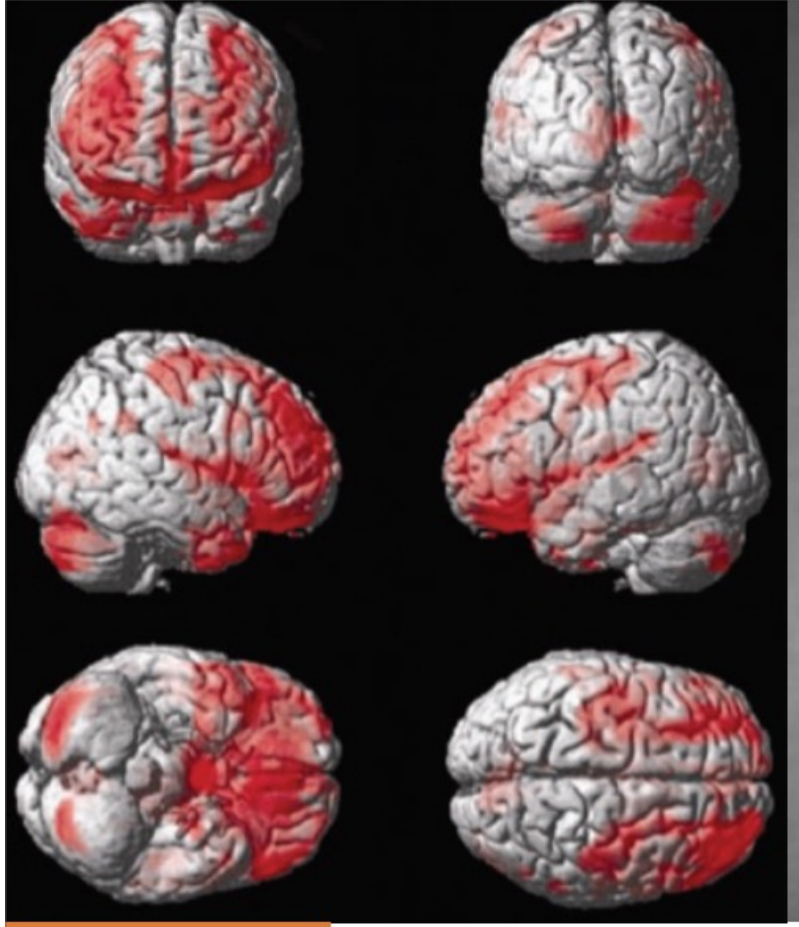
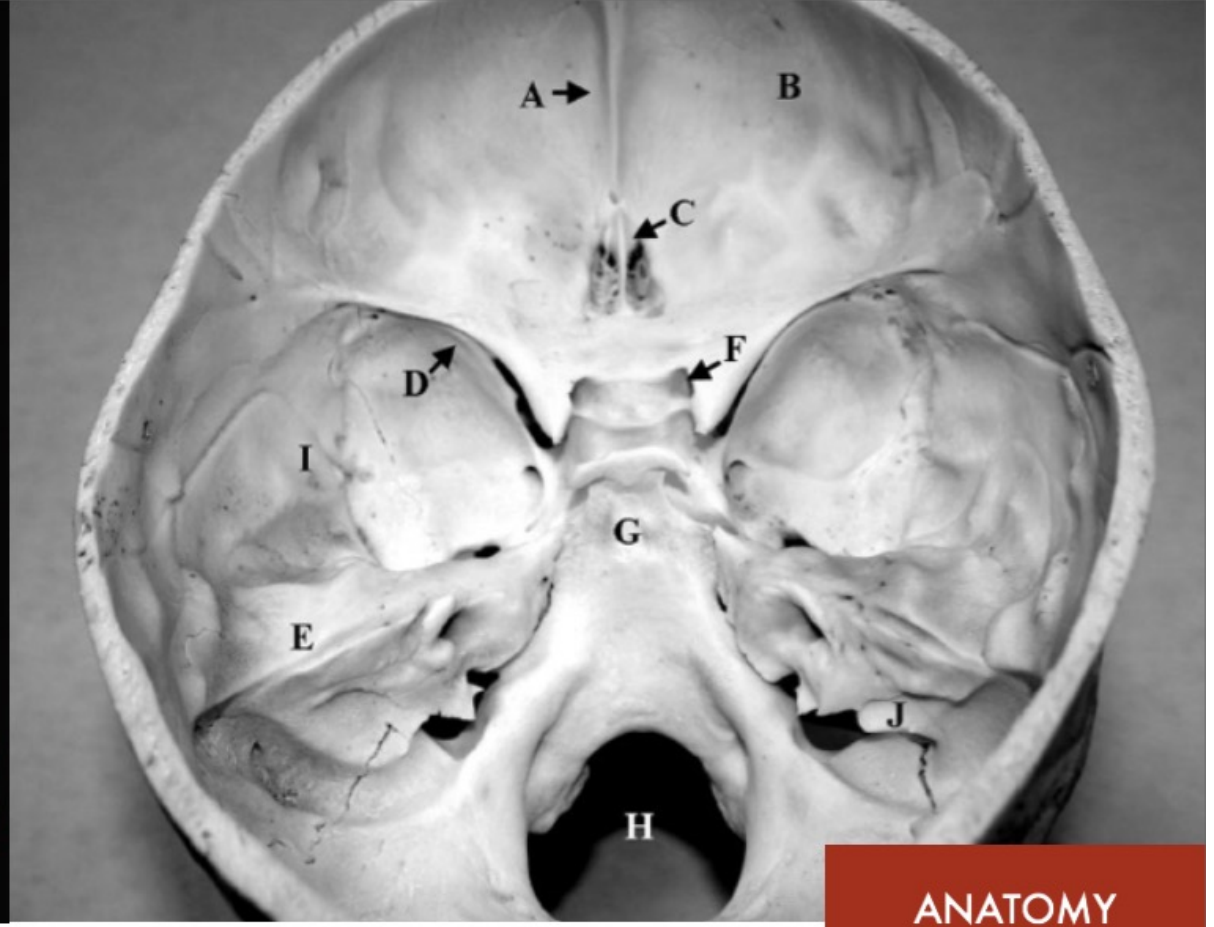
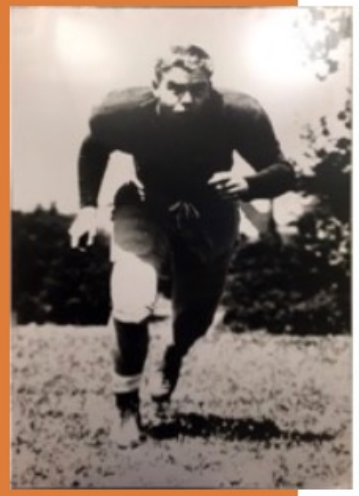




ANATOMY

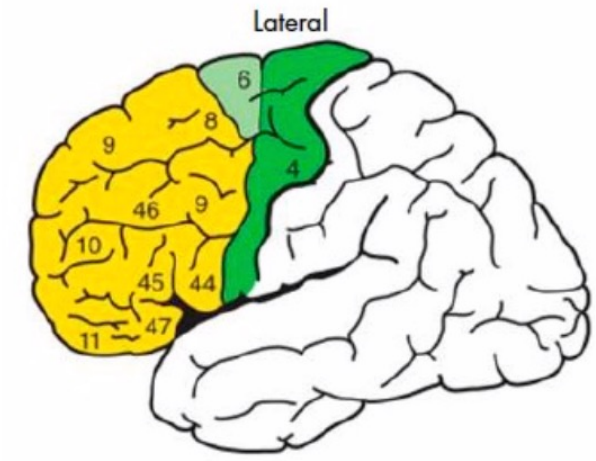


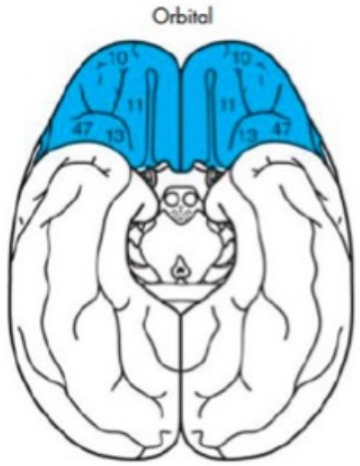
Frontal and Temporal Lobes are Preferentially Injured in TBI

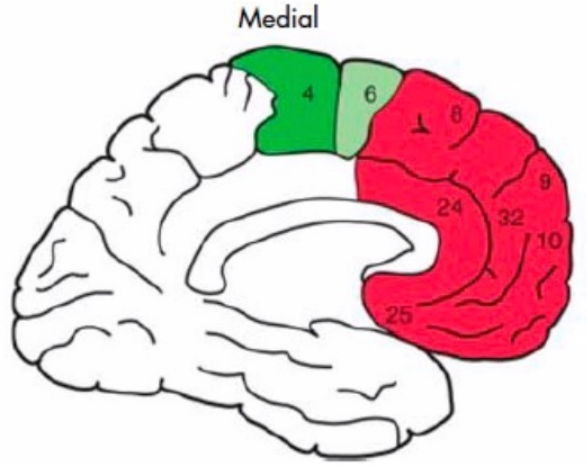
Bigler ED. Anterior and middle cranial fossa in traumatic brain injury: neuroanatomy and neuropathology in the study of neuropsychological outcome. Neuropsychology 2007; 21 (5): 515-531.

HEALTH SCIENCES

Behavioral Symptoms from Injury to Frontal Circuits







Dysexecutive

Poor memory retrieval
Poor planning
Poor abstraction
Poor multitasking
Poor fluency
Poor set-switching
Easily distractible

Disinhibition

Poor impulse control
Poor emotional control
Irritability
Lack of judgment
Socially inappropriate

Apathy

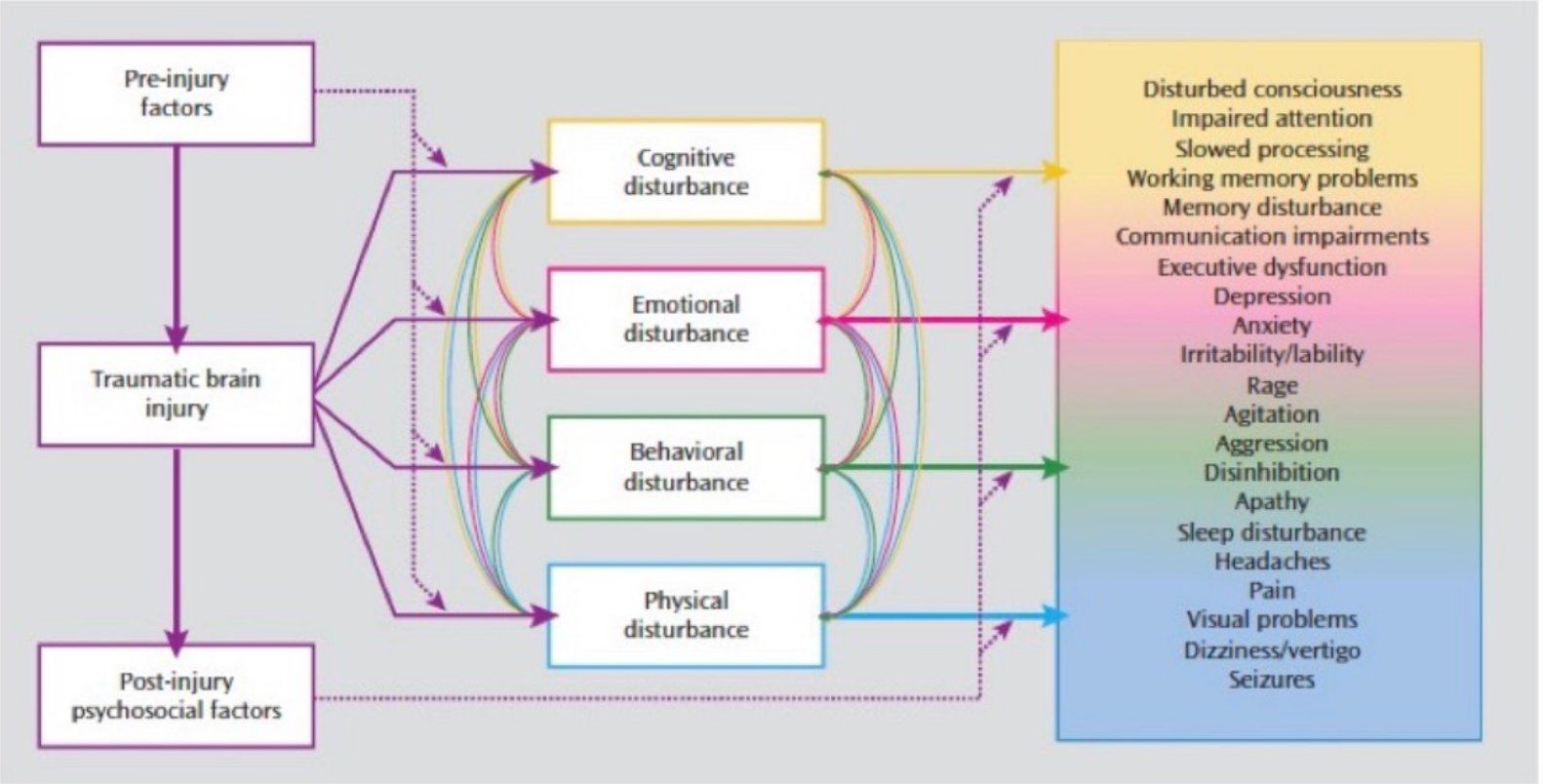
Lack of motivation
Lack of activity
Lack of concern
Indifference to pain, thirst, hunger, etc.

Cummings JL. Frontal subcortical circuits and human behavior. Arch Neurol 1993; 50: 873-880. Quinn DK, Katzman JE. The Wizard of Oz: a depiction of TBI-related neurobehavioral syndromes. Academic Psychiatry 2012; 36(4): 340-344.


Disinhibition
Syndrome
Orbital


AMOTIVATION
SYNDROME
Medial


DYSEXECUTIVE
SYNDROME
Lateral



Approach

Take care of other problems first, then address cognition

Suggest treating physical, behavioral, emotional dysregulation first before tackling cognitive deficits, given risk of exacerbating these domains.

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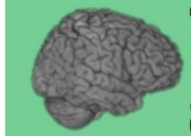
PSYCHOSOCIAL TREATMENTS

Cognitive Rehabilitation

Memory Aids

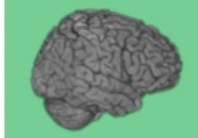
Assistive Devices

Family Counseling



Text messaging websites can help to remind about appointments or treatments

Psychotherapy



"You have thoughts; but you are not your thoughts."

Support Groups

Day Programs

Exercise/Nutrition

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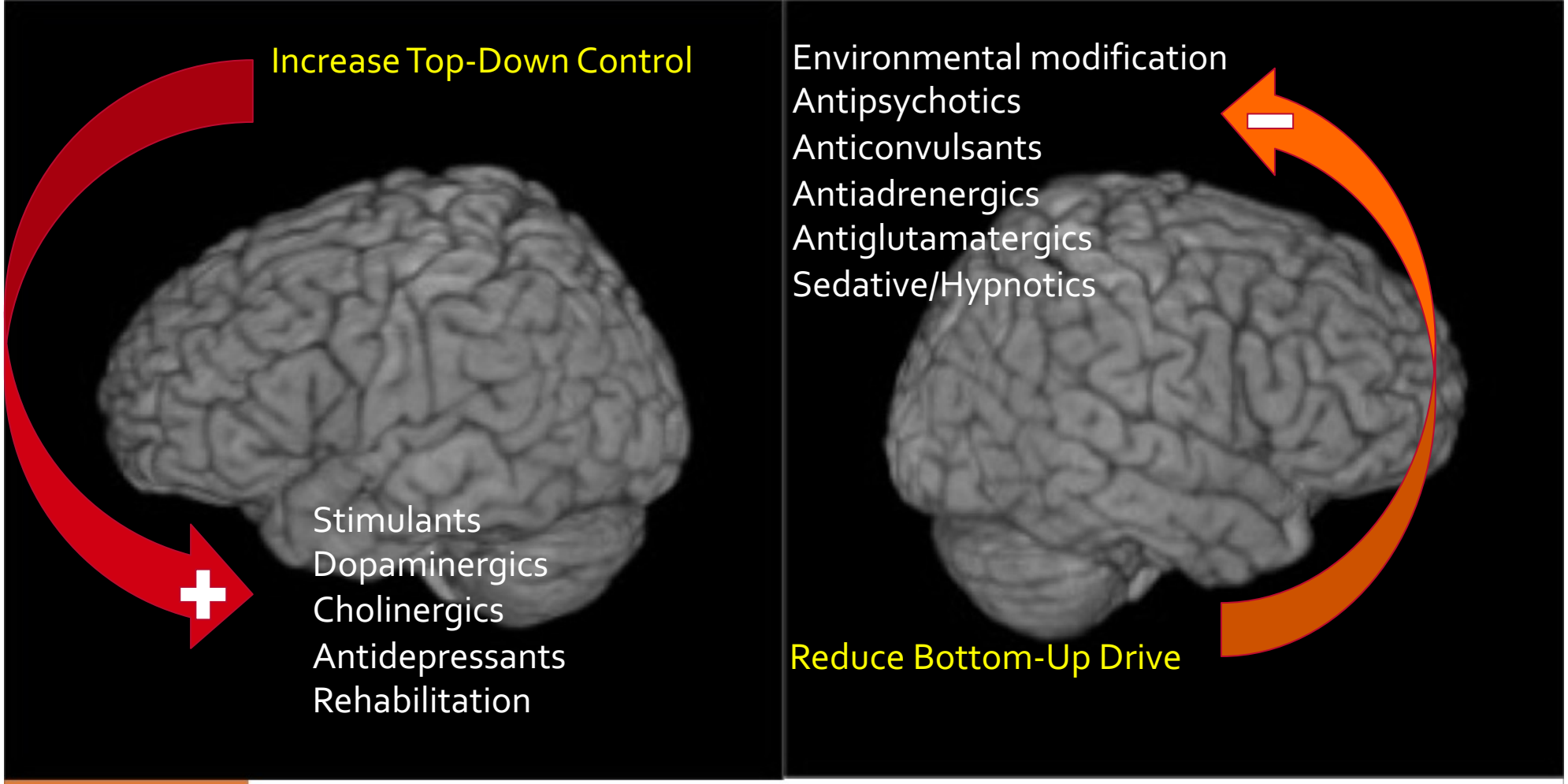
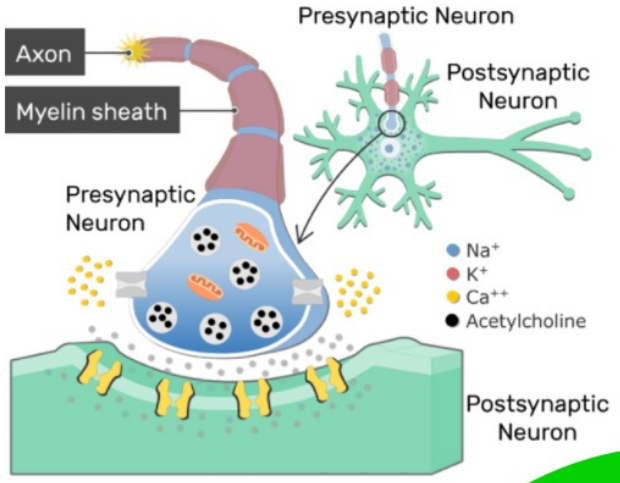
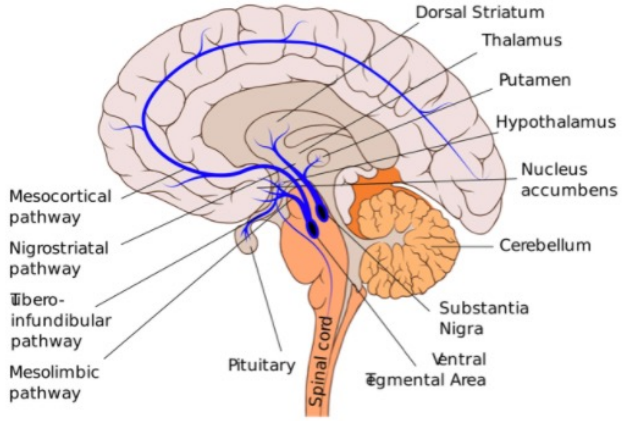
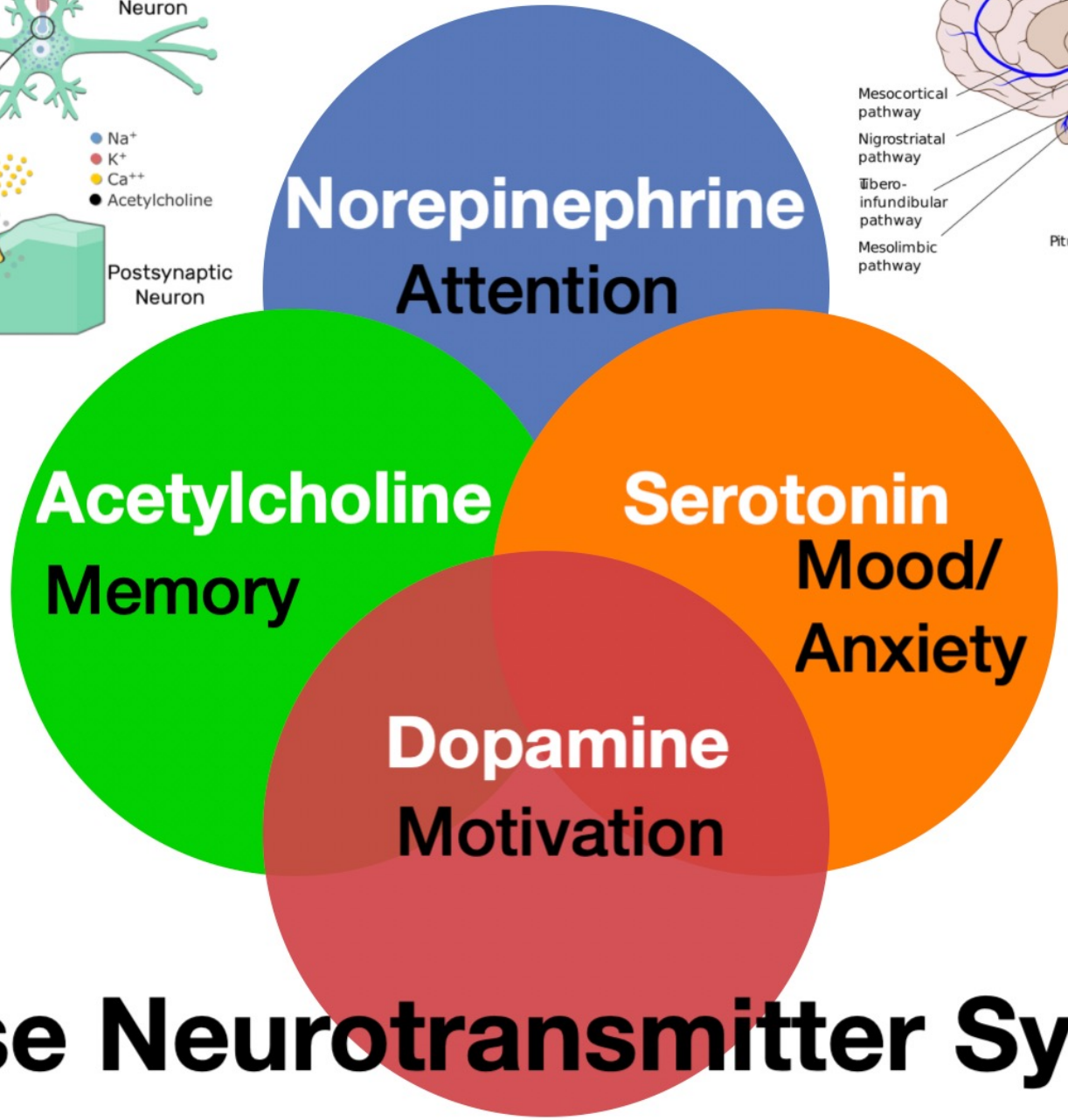


Top-Down versus Bottom-Up Modulation of Limbic System

Syndromes of irritability, disinhibition, agitation, and aggression can be addressed either by reducing bottom-up drive, or increasing top-down control/inhibition.







Diffuse Neurotransmitter Systems

HEALTH SCIENCES

Limitations of Medications in TBI

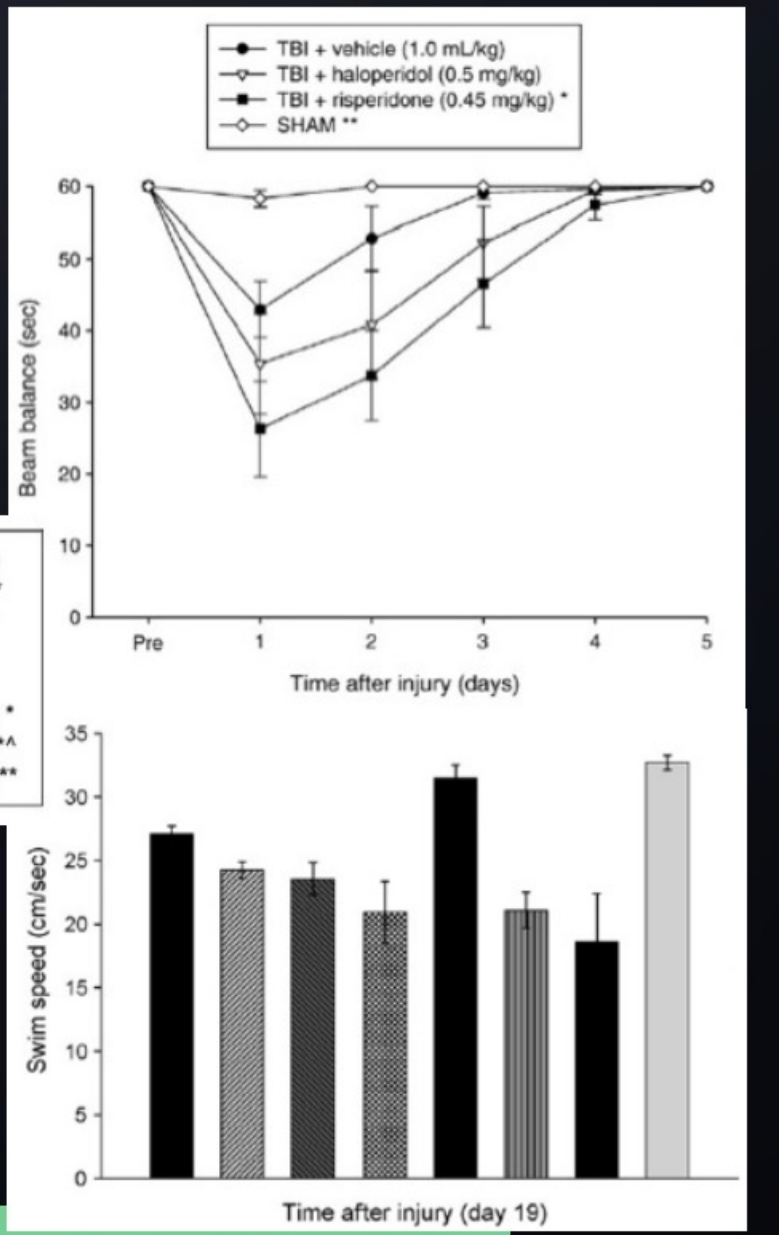
1) Side effects occur early, more frequently in TBI

2) Treatment resistance common

3) Dysexecutive syndrome interferes with administration

4) Drugs for disinhibition (APs, AEDs) may impede cognition/ recovery

5) Drugs for dysexecutive symptoms may exacerbate disinhibition



Hoffman AN et al. Administration of haloperidol and risperidone after neurobehavioral testing hinders the recovery of traumatic brain injury-induced deficits. Life Sciences 2008; 83: 602-607. Kline AE et al. Chronic administration of antipsychotics impede behavioral recovery after experimental traumatic brain injury. Neuroscience Letters 2008; 448: 263-267.

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Cochrane Library

Cochrane Database of Systematic Reviews

Pharmacotherapy for chronic cognitive impairment in traumatic brain injury (Review)

Dougall D, Poole N, Agrawal N

Overview

Cochrane Review: No recommendations possible

In this 2015 systematic review, only 4 RCTs were found, and the quality of evidence was rated as very low. No medications could be recommended and no conclusions could be reached.

UNM HEALTH SCIENCES

Chronic administration of antipsychotics impede behavioral recovery after experimental traumatic brain injury

Anthony E. Kline[a,b,c,d,e,*], Ann N. Hoffman[a,b,1], Jeffrey P. Cheng[a,b], Ross D. Zafonte[f,g,h], Jaime L. Massucci[i]

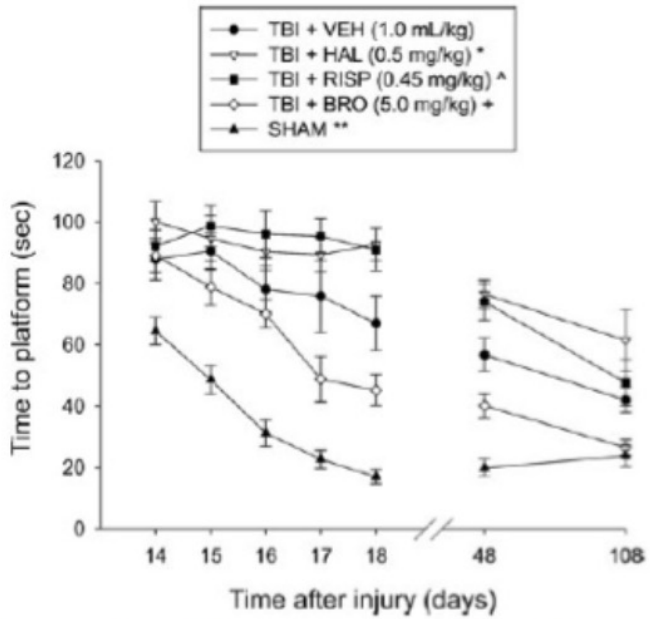
Research report

Intermittent treatment with haloperidol or quetiapine does not disrupt motor and cognitive recovery after experimental brain traum

Jillian J. Weeks[a,b,c], Lauren J. Carlson[a,b], Hannah L. Radabaugh[a,b], Patricia B. de la Tremblaye[a,b], Corina O. Bondi[a,b,c,d], Anthony E. Kline[a,b,c,e,f,g,*]

Divergent Long-Term Consequences of Chronic Treatment with Haloperidol, Risperidone, and Bromocriptine on Traumatic Brain Injury–Induced Cognitive Deficits

Thomas I. Phelps,[1,2] Corina O. Bondi,[1–4] Rashid H. Ahmed,[1,2] Yewande T. Olugbade,[1,2] and Anthony E. Kline[1–6]



Antipsychotics

Drugs to avoid if possible: Antipsychotics prescribed on a standing basis

Avoid using on standing basis or for prolonged periods. Best if used intermittently, prn, avoiding avid dopaminergic blockade when possible.

UNM HEALTH SCIENCES

The Effect of Sleep Medications on Cognitive Recovery From Traumatic Brain Injury

Eric B. Larson, PhD; Felise S. Zollman, MD

The impact of acute care medications on rehabilitation outcome after traumatic brain injury

W. Jerry Mysiw, Jennifer A. Bogner, John D. Corrigan, Lisa P. Fugate, Daniel M. Clinchot & Vivek Kadyan

Spontaneous recovery of traumatic brain injury-induced functional deficits is not hindered by daily administration of lorazepam

Jeffrey P. Cheng[a,b], Jacob B. Leary[a,b], Darik A. O'Neil[a,b], Elizabeth A. Meyer[a,b], Kristin E. Free[a,b], Corina O. Bondi[a,c,d], Anthony E. Kline[a,b,d,e,f,g,*]

Benzodiazepines

Drugs to avoid if possible: Benzodiazepines and Sedatives

Avoid using on standing basis or for prolonged periods. Best if used intermittently, prn, avoiding oversedation when possible.

UNM HEALTH SCIENCES

Randomized Placebo-Controlled Trial of Methylphenidate or Galantamine for Persistent Emotional and Cognitive Symptoms Associated with PTSD and/or Traumatic Brain Injury

Thomas W McAllister[*,1,12], Ross Zafonte[2,12], Sonia Jain[3], Laura A Flashman[4], Mark S George[5], Gerald A Grant[6], Feng He[3], James B Lohr[7], Norberto Andaluz[8], Lanier Summerall[9], Martin P Paulus[10], Rema Raman[3] and Murray B Stein[11]

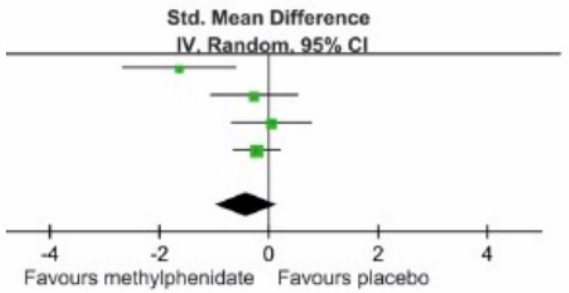
Methylphenidate and Memory and Attention Adaptation Training for Persistent Cognitive Symptoms after Traumatic Brain Injury: A Randomized, Placebo-Controlled Trial

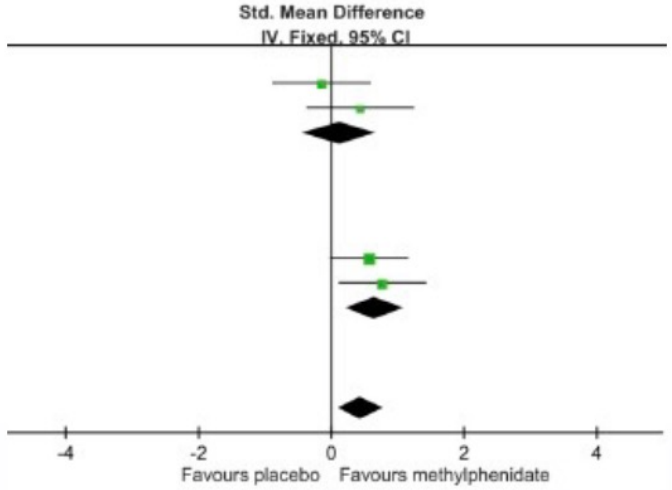
Brenna C McDonald[1,2,3], Laura A Flashman[4], David B Arciniegas[5,6], Robert J Ferguson[7], Li Xing[8,9], Jaroslaw Harezlak[8,9], Gwen C Sprehn[2], Flora M Hammond[10], Arthur C Maerlender[11], Carrie L Kruck[4], Karen L Gillock[4], Kim Frey[12], Rachel N Wall[3], Andrew J Saykin[1,2,3,13] and Thomas W McAllister[*,3]

272 *Current Neuropharmacology*, 2016, *14*, 272-281

Methylphenidate on Cognitive Improvement in Patients with Traumatic Brain Injury: A Meta-Analysis

Chi-Hsien Huang[1,2], Chia-Chen Huang[3], Cheuk-Kwan Sun[4,5], Gong-Hong Lin[6] and Wen-Hsuan Hou[7,8,9,*]





Methylphenidate

Methylphenidate can improve attention, and possibly memory and processing speed

10 RCTs of methylphenidate demonstrate moderate effects on attention, working memory, processing speed

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RESEARCH ARTICLE

WILEY

Effects of dextroamphetamine in subacute traumatic brain injury: A randomized, placebo-controlled pilot study

Tessa Hart[1] | John Whyte[1] | Thomas Watanabe[2] | Inna Chervoneva[3]

Traumatic brain injury-related attention deficits: Treatment outcomes with lisdexamfetamine dimesylate (Vyvanse)

Michael G. Tramontana, Ronald L. Cowan, David Zald, Jonathan W. Prokop & Oscar Guillamondegui

Amphetamines

Amphetamines may improve attention and processing speed, but have drawbacks

Mostly open series and case reports, with several negative studies, issues with tolerability

HEALTH SCIENCES

Amantadine Did Not Positively Impact Cognition in Chronic Traumatic Brain Injury: A Multi-Site, Randomized, Controlled Trial

Flora M. Hammond,[1–3] Mark Sherer,[4] James F. Malec,[1,2] Ross D. Zafonte,[5] Sureyya Dikmen,[6] Jennifer Bogner,[7] Kathleen R. Bell,[6,8] Jason Barber,[9] and Nancy Temkin[9,10]

The NEW ENGLAND JOURNAL of MEDICINE

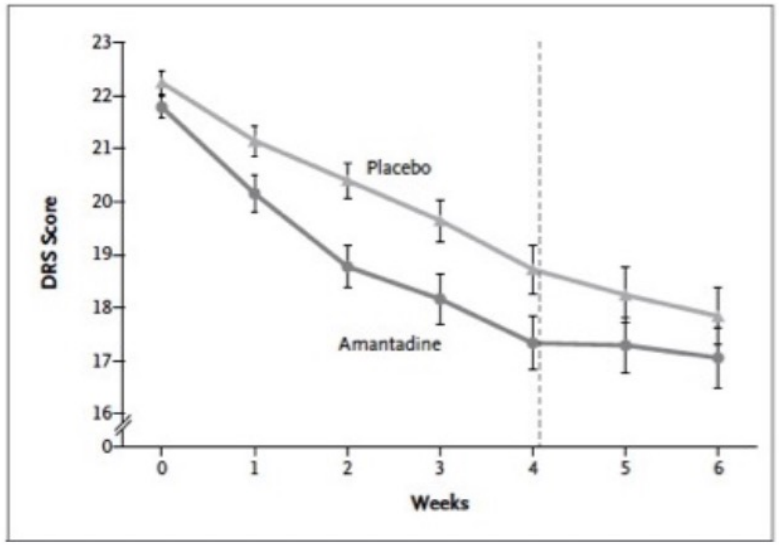
The effects of amantadine on traumatic brain injury outcome: a double-blind, randomized, controlled, clinical trial

Hossein Ghalaenovi, Arash Fattahi, Jalil Koohpayehzadeh, Mahmoud Khodadost, Neda Fatahi, Morteza Taheri, Alireza Azimi, Sadra Rohani & Hessam Rahatlou

ORIGINAL ARTICLE

Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury

Joseph T. Giacino, Ph.D., John Whyte, M.D., Ph.D., Emilia Bagiella, Ph.D., Kathleen Kalmar, Ph.D., Nancy Childs, M.D., Allen Khademi, M.D., Bernd Eifert, M.D., David Long, M.D., Douglas I. Katz, M.D., Sooja Cho, M.D., Stuart A. Yablon, M.D., Marianne Luther, M.D., Flora M. Hammond, M.D., Annette Nordenbo, M.D., Paul Novak, O.T.R., Walt Mercer, Ph.D., Petra Maurer-Karattup, Dr.Rer.Nat., and Mark Sherer, Ph.D.



Amantadine

Amantadine is not really helpful for memory and cognition, but is more helpful for arousal and agitation

Originally widely used in the rehabilitation literature, now shone mostly effective in early post-acute phase for arousal, motivation, but not cognition.

UNM HEALTH SCIENCES

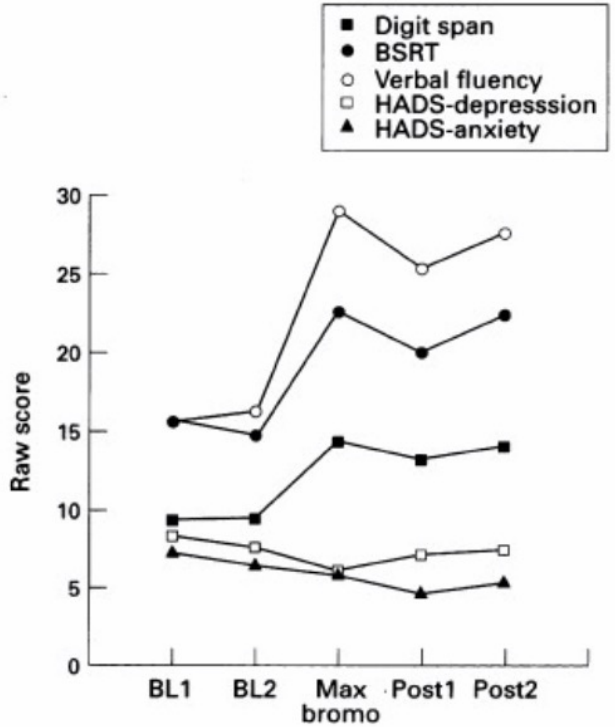
ORIGINAL RESEARCH ARTICLE

The Effects of Bromocriptine on Attention Deficits After Traumatic Brain Injury

A Placebo-Controlled Pilot Study

ABSTRACT

Whyte J, Vaccaro M, Grieb-Neff P, Hart T, Polansky M, Coslett HB: The effects of bromocriptine on attention deficits after traumatic brain injury: a placebo-controlled pilot study. Am J Phys Med Rehabil 2008;87:85–99.



Motivational deficits after brain injury: effects of bromocriptine in 11 patients

J H Powell, S Al-Adawi, J Morgan, R J Greenwood

Dopamine Agonists

Other dopamine agonists are effective for arousal, but not necessarily cognition, after TBI

Bromocriptine, cabergoline, lisuride, pramipexole.
Mostly small series and case reports. More side effects with older generation DAs.

HEALTH SCIENCES

The effect of donepezil on the cognitive ability early in the course of recovery from traumatic brain injury

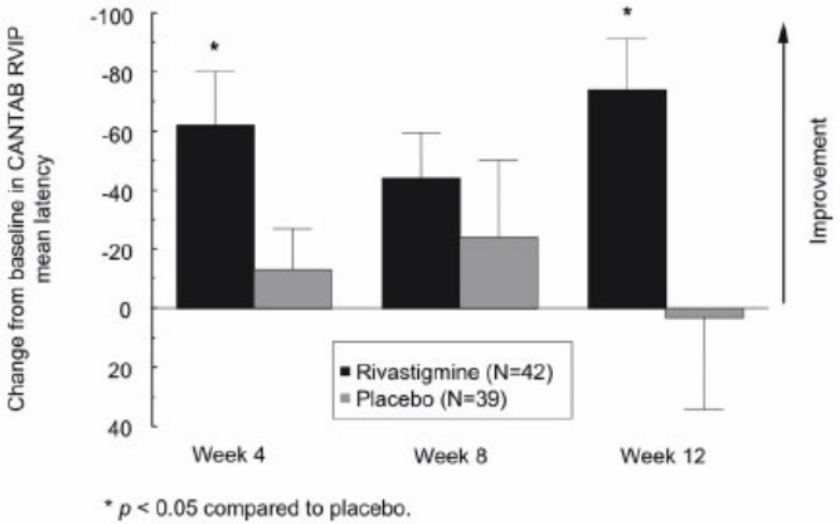
Kelsey A. Campbell[a], Richard E. Kennedy[b], Robert C. Brunner[c], Sean D. Hollis[c], Ross A. Lumsden[c], and Thomas A. Novack[c]

EFFECTS OF ACETYLCHOLINESTERASE INHIBITORS ON COGNITIVE FUNCTION IN PATIENTS WITH CHRONIC TRAUMATIC BRAIN INJURY: A SYSTEMATIC REVIEW

Marita Bengtsson, MD[1] and Alison K. Godbolt, MD, MRCP[1,2]

Effects of rivastigmine on cognitive function in patients with traumatic brain injury

J.M. Silver, MD; B. Koumaras, BA; M. Chen, PhD; D. Mirski, MD; S.G. Potkin, MD; P. Reyes, MD; D. Warden, MD; P.D. Harvey, PhD; D. Arciniegas, MD; D.I. Katz, MD; and I. Gunay, MD



* $p < 0.05$ compared to placebo.

Cholinesterase Inhibitors

Cholinesterase Inhibitors are mildly helpful for improving memory and cognition

Several large RCTs with different AChIs have been performed with variable effects. GI side effects.

HEALTH SCIENCES

The Journal of Neuropsychiatry and Clinical Neurosciences

Multicenter Evaluation of Memory Remediation in Traumatic Brain Injury with Donepezil (the MEMRI-TBI-D Study): A Randomized Controlled Trial

Results: Seventy-five participants were randomized to treatment (donepezil n=37, placebo n=38). Both the mITT and per protocol analyses demonstrated donepezil efficacy on the primary outcome (HVLT-R Total Trials 1-3) (p=0.034, d= 0.44, and p=0.036, d=0.45, respectively). Donepezil and placebo response rates were 42% and 18%, respectively (p=0.027, NNT = 3.5). Among donepezil responders, delayed recall and processing speed also improved significantly. Treatment-emergent adverse event rates to donepezil and placebo were 46% and 8%, respectively. The majority (85%) of treatment-emergent adverse events to donepezil were mild or moderate; only diarrhea and nausea were significantly more common in the donepezil group.

Cholinesterase Inhibitors

Cholinesterase Inhibitors are mildly helpful for improving memory and cognition

Several large RCTs with different AChIs have been performed with variable effects. GI side effects.

HEALTH SCIENCES

Effect of Memantine on Serum Levels of Neuron-Specific Enolase and on the Glasgow Coma Scale in Patients With Moderate Traumatic Brain Injury

Ann Nucl Med (2010) 24:363–369
DOI 10.1007/s12149-010-0360-3

ORIGINAL ARTICLE

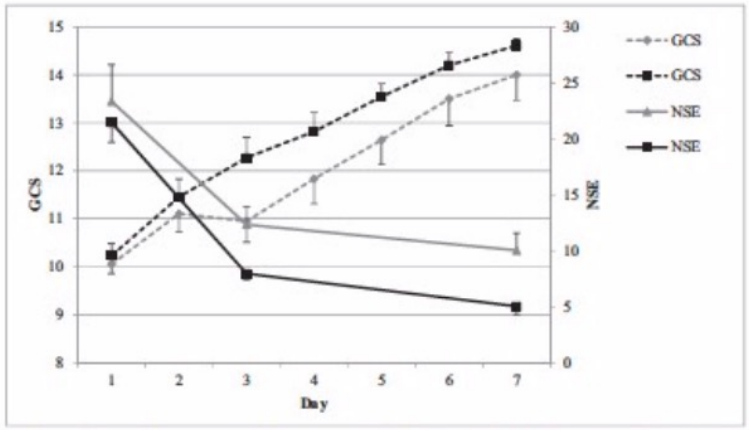
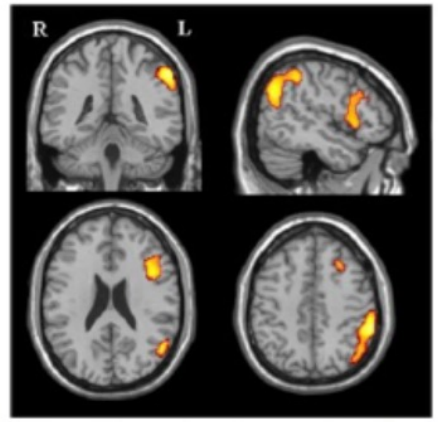


Figure 3. Neuron-specific enolase (NSE) level and Glasgow Coma Scale (GCS) score in memantine and control groups.

Changes in cerebral glucose metabolism in patients with posttraumatic cognitive impairment after memantine therapy: a preliminary study

Yong Wook Kim · Ji-Cheol Shin · Young-sil An



Memantine

Memantine: promise for neuroprotection in TBI?

Less studied than amantadine, potentially very helpful for TBI neuroprotection, but recently shown ineffective in Alzheimer's dementia

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Questions?

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