Medication and Brain injury

Karl J Sandin MD MPH

Medical Director,

Arroyo Grande Hospital Rehabilitation

Arroyo Grande, CA

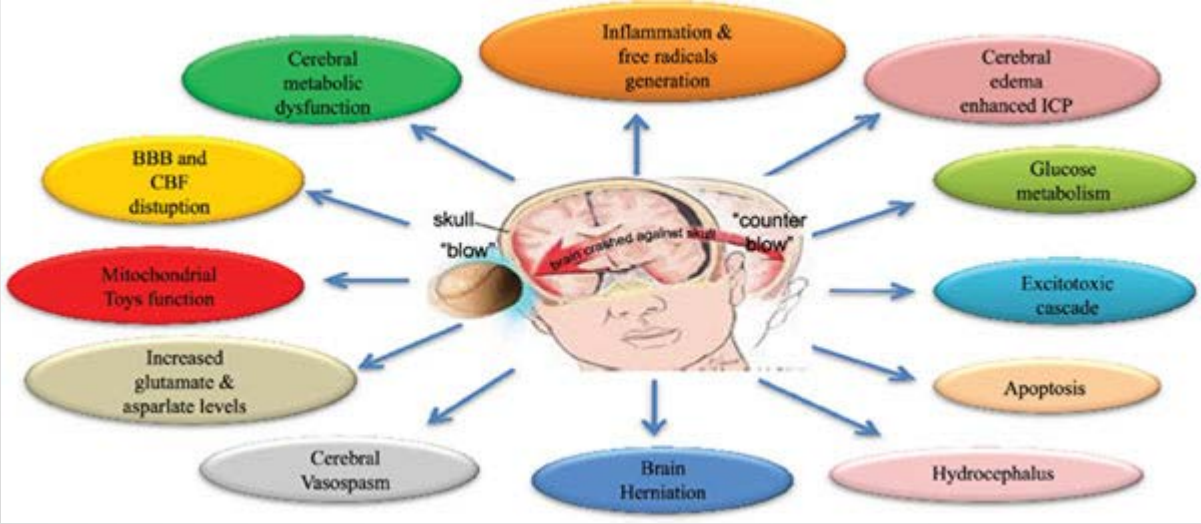
Disclosures

- I will be discussing off label use of medications
- No remuneration except for what I receive from my employer CHI Health Clinic

Educational objectives

- Review medications with beneficial effects on disorders of consciousness, agitation, attention, memory or mood after brain injury
- Compare and contrast pharmaceutical approaches with BI and preexisting or concomitant psychiatric diagnoses
- Learn medications to generally avoid after brain injury

What happens after



Caveats

- Overall very poor research concerning using of medications in acute, rehabilitation, and long-term phases of brain injury recovery
- Basically targeting dopamine, serotonin, and norepinephrine
- Challenges with meaningful outcome measures, extrapolation, experimental design
  - Rancho Scale (8 or 10 level)
  - ACRM or AAN definitions of BI
  - GCS
  - Disability Rating Scale

Medications to avoid

- Haloperidol
  - Antipsychotic, used for agitation typically
  - In humans associated with longer post traumatic amnesia
  - In rodents, associated with irreversible inhibition of synaptogenesis and less synaptic density at autopsy
  - Beloved though because can be given IV, commonly used in mental illness, effective

Pharmacological alternatives

- Valproic acid, antiseizure agent also effective as mood stabilizer
- Intravenous or oral at doses 250-750mg every 8 hours
- Has benefit of effectiveness for seizure prevention

Other agents to avoid, particularly early in ABI

- Clonidine (alpha-2 agonist)
- Trazodone (though commonly used in rehabilitation phase)
- Phenytoin
- Phenobarbital
- Benzodiazpines

Amantadine

- Giacino et.al. NEJM 2013
- 11 sites, n=184
- Nonpenetrating BI in previous 4-16 weeks
- Were receiving inpatient rehabilitation
- DRS (0-29) >11 at enrollment (VS, MCS)
- Inability to follow commands consistently and to engage in functional communication as assessed by coma recovery scale [0-23] (CRS-R)

Amantadine

- 184 started 181 completed
- Treatment group (n=87) amantadine 100-200 BID x 4 weeks, then tapered over 2-3 days
- Placebo group (n=97)
- Both groups with significant improvement
- Treatment group with faster recovery during 4 weeks that plateaud during washout; fewer remained in VS (DRS); more with recovery on CRS-R

Amantadine

- So now it's everywhere
  - Starting in ICU
  - Continuing longer than 4 weeks
  - Given to people across DRS spectrum
  - Doesn't work for reducing irritability in people with ABI < 6 months out at 200mg/day x 60 days

Other dopamine agonists

Bromocriptine

- 26 patients with mild ABI and 31 controls
- Single dose of bromocriptine 1.25 mg
- Immediate testing of verbal working memory after administration
- Treatment group with improved task performance but not control group

Inhibiting reuptake of DA and NEPI

Methylphenidate

- Favorite on college campuses
- given to 51 ABI patients
  - First 4 weeks no active medication
  - Next 4 weeks methylphenidate 15 mg/day
  - Last 4 weeks methylphenidate 60 mg/day
- Methylphenidate use associated with increased information processing speed, improved SF-36, reduction with mental fatigue

Acetylcholinesterase inhibitors

- Commonly used for dementia
- Donepezil, rivastigmine, tacrine
- Appears helpful in severe BI, not mild
- N=127 patients given rivastigmine for on average 24 weeks; no control group. About 40% got better
- Other study show no improvement

Zolpidem

- Why would a sleeping pill help recovery?
- Du n=165 patients in VS. In some cerebral perfusion and EEG improved.
- Whyte n=84 patients with DOC < 4 months. 5% improved

Sleep disturbance

- Melatonin
- Zolpidem
- Trazodone
- Mirtazapine
- Quetiapine

No clear guidance what to give, but don't give benzodiazpines

SSRI/SNRI

For post traumatic depression as well as neural enhancement

- Citalopram
- Escitalopram
- Paroxetine
- Fluvoxamine
- Sertraline
- Tricyclic antidepressants
- Heterocyclic antidepressants

Lots of failures

- Progesterone (SYNAPSE, PROTECT III)
- Steroids
- Magnetic and direct stimulation of the cortex
- Hyperbaric oxygen
- Stem cells

So what is the prescriber to do

- Do no harm; don't extrapolate
- Start with treatments with lower risk (medications do not fall in this category)
- Understand what condition is being treated (VS, MCS, inattention, behaviors, memory deficit)
- Insist upon strong assessment tools to judge benefit
- Know some medications very well

So what do I tend to do

- Depression likely. Sertraline or duloxetine; 5-HT
- Insomnia common. Trazodone +/- melatonin
- Inattention likely. Methylphenidate (others modafinil)
- Deficit in arousal. Amantadine early
- Anxiety/irritability Buspirone (study recruiting Dr. Hammond Indiana University)

In the absence of good data, I am just a nice guy with a opinion

We can understand better what to do

- Use model of pediatric cancer treatment. 50% of kids ended up in studies
- Keep pressure on state and federal governments for meaningful research and not just within military

References

- Watzlawick R et.al. Neuroprotection after traumatic brain injury. *JAMA Neurology* 73(2):149-150, 2016.
- Ozga JE et .al. Executive (dys)function after traumatic brain injury: special considerations for behavioral pharmacology. *Behavioural Pharmacology* 29(7):617-637, 2018.
- Liepert J: Update on pharmacotherapy for stroke and traumatic brain injury recovery during rehabilitation. *Curr Opin Neurol* 29(6):700-705, 2016.

References (continued)

- Adams SM et.al.: The pharmacogenomics of severe traumatic brain injury. *Pharmacogenomics* 18(15):1427-1440, 2017.
- Diaz-Arrastia R et.al.: Pharmacotherapy of traumatic brain injury: state of the science and the road forward: report of the department of defense neurotrauma pharmacology workgroup. *Journal of Neurotrauma* 31:135-158, 2014.

References (continued)

- Driver S, et.al.: Pharmacological management of sleep after traumatic brain injury, *Neurorehabilitation* 43:347-353, 2018.
- Daniels JP: Traumatic brain injury: choosing drugs to assist recovery. *Current psychiatry* 5(5):57-68, 2006.
- Giacino JT et.al.: Placebo-controlled trial of amantadine for severe traumatic brain injury. *NEJM* 366:819-826, 2012.

For more information:

Email Dr. Sandin:

ksandinmd@gmail.com