Medications to Expedite Rehabilitation of the Traumatic Brain Injury Patient

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Primary vs. Secondary Brain Injury
“Neurotransmitter Storm”

Beauchamp et al. (2008)
Neuromodulation with Pharmacootherapy

- Limited level 1 evidence for most medications
- Majority of studies are limited to small RCT’s or case series
- No medication has received approval from U.S. FDA for the treatment of any posttraumatic neuropsychiatric problem, so all such treatments must be considered “off label”
Medications reported to improve cognition after TBI

- **Cholinergic Agents**
  - Physostigmine (not recommended due to systemic effects)
  - Cytidine-5'-diphosphocholine
  - Cholinesterase inhibitors
    - Donepezil, rivastigmine, galantamine

- **Catecholaminergic agents**
  - Psychostimulants (methylphenidate, dextroamphetamine)
  - Amantadine
  - Bromocriptine
  - Levodopa
  - Selegiline

- **Other Agents**
  - TCA’s
  - ?Other antidepressants (SSRIs, SNRIs)
  - ?Atomoxetine (selective norepinephrine reuptake inhibitor)
  - ?Pergolide, pramipexole, ropinirole (dopamine receptor agonists)
  - ?Guanfacine (selective alpha 2a-adrenergic agonist)
  - ?Lamotrigine
  - ?Memantine (N-methyl-D-aspartate receptor antagonist)

=? = potentially useful agents that have very limited or no support within the clinical TBI literature
Amantadine
Amantadine

- Dopamine agonist with weak NMDA antagonistic properties
- Has been shown to accelerate functional recovery and arousal in patients with post-traumatic disorders of consciousness. (Giacino et al, 2012)
  - No reliable data to support the efficacy of pharmacologic intervention in the comatose (Ranchos I) patient
- Dosing: 100-200mg BID at breakfast and lunch, capsule or syrup. Renally dose.
- Timing: Start 3 days – 5 months post-injury
Methylphenidate

- Psychostimulant, used for ADHD
- Dopamine > norepinephrine reuptake inhibitor
- Dosing: 5-15mg po BID at breakfast and lunch
- Randomized, double blind crossover design showed that methylphenidate enhances processing speed and increases attention and concentration (Willmott and Ponsford 2009)
- Greatest medication response was observed in those with more severe head injuries
- Used in patients that have emerged (Ranchos IV – VIII)
Severe TBI (GCS 3-8): Methylphenidate was associated with reductions in ICU and hospital LOS by 23% ($P = 0.06$ for ICU, $P = 0.029$ for hospital stay)

Moderate TBI (GCS 9-12): 26% reduction only in ICU length of stay ($P = 0.05$)
Zolpidem

• GABA potentiator
• Usually used for insomnia
• though generally sedating, GABA potentiators may have a paradoxical effect on severe TBI
• Effective in improving arousal for some severely injured patients (Sara et al, 2009; Whyte and Myers, 2009)
• 4.8% response rate suggested among those with disorders of consciousness (Whyte et al, 2014)
Address Other Factors Affecting Cognition after TBI

- Infection
- Metabolic derangements
- Neuroendocrine dysfunction
- Hypoxia
- Sleep/wake disturbance
  - Sleep hygiene, melatonin, trazodone
- Overmedication/sedation
- Seizures
Seizure prophylaxis

- Given for 7 days after TBI
  - per Evidence Based Guidelines for TBI (Marion 2006)
- Phenytoin and carbamazepine
  - Associated with treatment-related impairments in cognitive and motor function (Dikmen et al. 1991; Smith et al. 1994)
- Levetiracetam
  - better tolerated in TBI in the short and long term when compared with phenytoin (Jones et al. 2008; Szaflarski et al. 2010)
- Valproate
  - relatively benign with respect to effects on cognition and other neurobehavioral functions among persons with TBI (Dikmen et al. 2000)
  - Side effects: hepatic and hematological risks, alopecia, weight gain, polycystic ovarian syndrome

- Important to discontinue seizure prophylaxis at the end of the first week post-TBI, maintain clinical vigilance for the development of post-traumatic seizures thereafter
Potentially Harmful

- Typical antipsychotics (haloperidol)
  - exacerbate cognitive impairments and may prolong posttraumatic amnesia (Stanislav 1997; Rao et al. 1985)
- Benzodiazepines
  - impair memory and other aspects of cognition (Buffett-Jerrott and Stewart 2002)
- Opioids
  - can cause memory impairments in people w/o TBI, and hence can exacerbate cognitive impairments in those with TBI
General Principles

- “start low, go slow”
- Adequate therapeutic trial
  - Employ therapeutic trials of medications
- Continuous reassessment
  - Establish a schedule for the systematic reassessment of the clinical condition for which treatment is prescribed
- Monitor for drug-drug interactions
- Augmentation
  - Consider augmentation of partial responses to medications
- Symptom intensification
  - Discontinue or lower the dose of the most recently prescribed medication if there is a worsening of the treated symptoms soon after the medication has been initiated or increased
- Consider consult other specialists (PM&R, Psychiatry, Neurology)
References

The End

Inadvertently, Roy dooms the entire earth to annihilation when, in an attempt to be friendly, he seizes their leader by the head and shakes vigorously.