Medications for Acute Agitation in Traumatic Brain Injury (TBI)

Ethan Beckley MD

Assistant Professor of Psychiatry
Oregon Health & Science University

Disclosures *etc.*

- No financial interests
- This talk **does** discuss "off label" use of medications
  - Not FDA approved for TBI
  - Please be aware
- Comments to: beckleye@ohsu.edu
  - Corrections, additions, questions, suggestions, *etc.*

Objectives

- Describe approaches to medication for TBI agitation including selection, dosing, and timing
- Identify evidence-based medications useful in TBI agitation
- Describe limitations of current evidence in TBI agitation and approach to medications while we wait for better evidence

Reading list

- Williamson *et al.* (2019). "Pharmacological interventions for agitated behaviours in patients with traumatic brain injury: A systematic review." *BMJ Open 9*:e029604

https://pubmed.ncbi.nlm.nih.gov/collections/62098110/?sort=pubdate

shortened URL:
https://bit.ly/3CujXsA

Phases of TBI neuropsychiatric symptoms

- Acute
  - Agitation, altered consciousness
- Subacute
  - Cognitive impairment
- Chronic
  - Mood, anxiety, irritability, apathy, concentration

Agitation

- Often the biggest problem for the hospital
  - Patient injuries
  - Staff injuries
  - Staff morale, fatigue, attrition
  - Preventing other needed care and recovery
  - Preventing discharge
- Challenges
  - Catch-all term
  - One strategy: Standardized scales

RASS (Richmond Agitation Sedation Scale)		
4	Combative	Overtly combative, violent, immediate danger to staff
3	Very agitated	Pulls or removes tubes or catheters; aggressive
2	Agitated	Frequent non-purposeful mvmt, fights ventilator
1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Sustained awakening to voice (≥10sec)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 sec)
-3	Moderate sedation	Movement or eye opening to voice but no eye contact
-4	Deep sedation	No response to voice but movement or eye opening to physical stimulation
-5	Cannot be aroused	No response to voice or physical stimulation

Riker Agitation Scale

Scores	State	Behavior
7	Dangerous agitation	Trying to remove catheters, climbing over bedrail, thrashing side to side, or striking at staff
6	Very agitated	Requiring restraint and frequent verbal reminding of limits
5	Agitated	Anxious or physically agitated and calms to verbal instructions
4	Calm cooperative	Calm, easily arousable, and follows commands
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, and follows simple commands
2	Very sedated	Arouse to physical stimuli but does not communicate or follow commands
1	Unarousable	Minimal or no response to noxious stimuli, and does not communicate or follow commands

Initial medication plan for agitation: A psychiatrist's perspective

- Initial recommendations are rarely final
  - Attempt to treat the patient
  - Gather data about what's working, revise as needed
  - (Only works if the data are collected!)
- Initial recommendations rarely will work in the first day
  - Even if it ends up working later
  - Chance of success goes down if too many changes too quickly
- Initial recommendations rarely involve highest doses
  - Off label meds, serious side effects, black box warnings – good reasons to start low!
  - Trying and failing low doses helps justify higher doses

Approach to medication administration

- Scientific approach
  - Hypothesis
    - Characterize the problem behavior (refer back: standardized scales)
    - Attempt an intervention
    - Assess and document response at rational intervals
  - Review data, revise hypothesis, repeat cycle
- Use as-needed "PRN" medication
  - Establish personalized dose range
  - Identify patterns of agitation
  - Identify "what works" *vs.* doesn't
- Use scheduled medications
  - Get ahead of agitation
  - Dose and timing informed by prior PRN pattern
  - Ongoing adjustment of schedule based on PRN use

Approach to dose and timing

- Low, frequent, early doses
  - Better outcomes
  - Lower total doses, fewer side effects
- Strategies compared:
  - Strategy A: haloperidol 10 mg every 8 hours as needed for severe agitation
  - Strategy B: haloperidol 2 mg every 1 hour as needed for mild agitation
  - Most often: "Strategy B" will result in lower total doses, and less agitation
- Higher rescue doses
  - Sometimes necessary
  - Still try to go back to low, frequent, early doses when feasible

Example case

- Patient with TBI, confused, exiting unit, psychiatry consulted
- Day 1:
  - Rec: haloperidol 1 mg IV twice daily, 5 mg IV every 4 hours as needed
  - That day: receives both scheduled doses, plus 5 mg IV x1 with good effect at 30 minutes
  - Analysis: needs more scheduled haloperidol
- Day 2:
  - Rec: haloperidol 1 mg IV three times daily, 5 mg IV every 4 hours as needed
  - That day: receives all three scheduled doses, no additional dose
  - Analysis: patient can be successful on 3 mg total, but keep PRN available
- Take-home points
  - Initial recommendations are rarely final recommendations
  - Use PRNs to guide scheduled doses
  - Use small, frequent doses to get ahead of agitation
  - Use rescue doses if needed

Medications used in acute TBI: What's even on the table?

- Naturalistic observation of inpatient rehabilitation:
  - 2,130 TBI patients age ≥14 years in inpatient rehabilitation
    - 8,726 medication orders
    - Mean length of stay 27 days
    - Average patient = 4.067 medications per admission
    - Average patient = 1.062 medications per week
  - Specific medications
    - 88 distinct psycho/neuro-active medications
    - >100 orders for trazodone, opioids, zolpidem, lorazepam, levetiracetam, amantadine, quetiapine, valproic acid, phenytoin, gabapentin, bromocriptine, donepezil, buspirone, risperidone, modafinil
- Conclusion: Everything has been tried!

Hammond *et al.* (2015). Psychotropic medication use during inpatient rehabilitation for traumatic brain injury. *Archives of Physical Medicine & Rehabilitation, 96*(8 Suppl), S256-S273.

Philosophies in medication selection

- "Whatever works" liberal approach
  - Pro: Possible jackpot, patient gets better
  - Con: Possible landmine, patient gets worse
- "Experienced based" moderate approach
  - Pro: Experience may count, help patients despite evidence lack
  - Con: Susceptible to bias
- "Evidence based" conservative approach
  - Pro: Evidence based, theoretically only use proven medications
  - Con: Evidence may not exist, miss out on helpful medications
- Unifying theme: Buy time while the brain heals
  - Primary treatment is time and rehabilitation

"Whatever works" liberal approach

- In general, recommend against this approach
  - Ketamine, benzodiazepines, propofol, opioids, dronabinol—all likely to be one step forward, two steps back
- May be appropriate in rare cases when top priority is immobilization
  - May be acceptable when there is an underlying problem that needs time
- May be appropriate in end-of-life/palliative care situations
  - Surrogate decision maker in agreement
  - Comfort > restoration of function

The Williamson systematic review: Evidence-based medications for agitated behaviors

- High quality systematic review
  - Selected for inclusion in the ABPN ABCC Program (article based continuous certification program) in psychiatry
- Studies must have had >50% of patients with TBI
  - Some prior systematic reviews less strict with inclusion

Williamson *et al.* (2019). Pharmacological interventions for agitated behaviours in patients with a traumatic brain injury: A systematic review. *BMJ Open, 9*, e029604.

The Williamson systematic review: Propranolol

- Drug facts:
  - Name: Propranolol (Inderal, others)
  - Presumed mechanism of action: Nonselective β-blocker
  - Approved uses include: Hypertension, migraine, essential tremor
- Williamson *et al.* findings
  - Take-home: May be beneficial
  - Pros: Reduction in intensity of agitation episodes, use of physical restraints
  - Cons: No reduction in frequency of agitation episodes

Williamson *et al.* (2019). Pharmacological interventions for agitated behaviours in patients with a traumatic brain injury: A systematic review. *BMJ Open, 9*, e029604.

The Williamson systematic review: Amantadine

- Drug facts:
  - Name: Amantadine (Symmetrel, others)
  - Presumed mechanism of action: Weak NMDA antagonist
  - Approved uses include: Parkinsonism, drug-induced parkinsonism, (influenza)
- Williamson *et al.* findings
  - Take-home: Inconsistent findings
  - Pros: Possible reduction in irritability/aggression >6 months after TBI
  - Cons: Poor evidence for any benefit at <6 months after TBI, may increase ICU agitation episodes and length of stay, three studies found no difference in agitated behaviors compared to placebo

Williamson *et al.* (2019). Pharmacological interventions for agitated behaviours in patients with a traumatic brain injury: A systematic review. *BMJ Open, 9*, e029604.

The Williamson systematic review: Olanzapine

- Drug facts:
  - Name: Olanzapine (Zyprexa, Zydis, others)
  - Presumed mechanism of action: Dopamine type-2 receptor antagonist, others
  - Approved uses include: Schizophrenia, bipolar disorder
- Williamson *et al.* findings
  - Take-home: May be beneficial
  - Pros: Reduction of irritability and insomnia at 1-3 weeks after TBI
  - Cons: No reduction in restlessness, not studied in ICU, inadequate statistical comparisons

Williamson *et al.* (2019). Pharmacological interventions for agitated behaviours in patients with a traumatic brain injury: A systematic review. *BMJ Open, 9*, e029604.

The Williamson systematic review: Divalproex

- Drug facts:
  - Name: Divalproex (Depakote, others)
  - Presumed mechanism of action: Increase GABA?, sodium channel inhibitor?
  - Approved uses include: Bipolar disorder, absence seizure, migraine
- Williamson *et al.* findings
  - Take-home: May be beneficial
  - Pros: Significant reduction in agitated behaviors at eight weeks after TBI
  - Cons: Studied in outpatient setting

Williamson *et al.* (2019). Pharmacological interventions for agitated behaviours in patients with a traumatic brain injury: A systematic review. *BMJ Open, 9*, e029604.

The Williamson systematic review: Methylphenidate

- Drug facts:
  - Name: Methylphenidate (Ritalin, others)
  - Presumed mechanism of action: Blocks norepinephrine, dopamine reuptake?
  - Approved uses include: Attention deficit/hyperactivity disorder, narcolepsy
- Williamson *et al.* findings
  - Take-home: Inconsistent findings
  - Pros: After 6 weeks patients had reduced anger scores on standardized scale (first study)
  - Cons: Long time to onset?, unclear benefit beyond anger as symptom (first study); no effect on irritability/aggression in a second study

Williamson *et al.* (2019). Pharmacological interventions for agitated behaviours in patients with a traumatic brain injury: A systematic review. *BMJ Open, 9*, e029604.

The Williamson systematic review: Sertraline

- Drug facts:
  - Name: Sertraline (Zoloft)
  - Presumed mechanism of action: Selective serotonin reuptake inhibitor
  - Approved uses include: Major depressive disorder, panic disorder, others
- Williamson *et al.* findings
  - Take-home: May be harmful
  - Pros: Not demonstrated
  - Cons: No effect on agitation, anger, or aggression in three studies, and possibly more restlessness/agitation in one study

Williamson *et al.* (2019). Pharmacological interventions for agitated behaviours in patients with a traumatic brain injury: A systematic review. *BMJ Open, 9*, e029604.

The Williamson systematic review: Amphetamine type stimulants

- Drug facts:
  - Name: Dextroamphetamine (Dexedrine), lisdexamfetamine (Vyvanse)
  - Presumed mechanism of action: Blocks norepinephrine, dopamine reuptake?
  - Approved uses include: ADHD, narcolepsy, binge eating disorder
- Williamson *et al.* findings
  - Take-home: May be harmful
  - Pros: Not demonstrated
  - Cons: Dextroamphetamine increased agitation

Williamson *et al.* (2019). Pharmacological interventions for agitated behaviours in patients with a traumatic brain injury: A systematic review. *BMJ Open, 9*, e029604.

The Williamson systematic review: Summary

- May be helpful:
  - Propranolol, olanzapine, divalproex
- Inconsistent findings:
  - Amantadine, methylphenidate
- May be harmful:
  - Sertraline, amphetamine-type stimulants

Williamson *et al.* (2019). Pharmacological interventions for agitated behaviours in patients with a traumatic brain injury: A systematic review. *BMJ Open, 9*, e029604.

The Williamson systematic review: Problems

- Studies evaluated
  - Mostly sub-acute patients, likely milder injury
- Evidence limited for agitation among TBI patients, especially for:
  - Most acute timing
  - Most severe injury
  - Most serious agitation

"Experience based" moderate approach

The Williamson systematic review: Summary

- May be helpful:
  - Propranolol, olanzapine, divalproex
- Inconsistent findings:
  - Amantadine, methylphenidate
- May be harmful:
  - Sertraline, amphetamine-type stimulants

Williamson *et al.* (2019). Pharmacological interventions for agitated behaviours in patients with a traumatic brain injury: A systematic review. *BMJ Open, 9*, e029604.

<u>Williams *et al.* review</u>

- May be helpful:
  - Propranolol, olanzapine, divalproex
- Inconsistent findings:
  - Amantadine, methylphenidate
- May be harmful:
  - Sertraline, amphetamine-type stimulants

<u>By extrapolation</u>

- May be helpful:
  - β-blockers, antipsychotics, some mood stabilizers… α_2-agonists?
- May not be helpful:
  - Stimulants, antidepressants, cognitive enhancers

"Experience based" moderate approach

- Haloperidol
  - PO, IM, IV routes
  - Many decades of safe use
  - Few contraindications
  - Not sedating
- Olanzapine
  - PO and IM routes, ODT
  - Helpful when sedation is required
- Risperidone
  - PO and ODT
- Quetiapine
  - Gentle in older patients, low EPS
  - Relatively safe in Parkinson disorder
- Divalproex and other valproates
  - May be helpful with mood lability or impulsivity
  - Augmentation for patients refractory to antipsychotics
- Propranolol, clonidine, dexmedetomidine
  - Emerging
  - Some evidence, some roles

Objectives

- Describe approaches to medication for TBI agitation including selection, dosing, and timing
  - Liberal, moderate, and conservative approaches to selection have different trade-offs (risks *vs.* benefits)
  - Low, frequent, early doses usually more effective, fewer side effects
  - Use scheduled medications to get ahead of agitation with PRN medications to augment
  - Use scientific approach, define problem behavior, attempt intervention, assess and adjust as needed

Objectives

- Identify evidence-based medications useful in TBI agitation
  - Propranolol, olanzapine, and divalproex had the best evidence in a recent, high-quality systematic review
  - Cognitive enhancers and antidepressants were not well supported

Objectives

- Describe limitations of current evidence in TBI agitation and approach to medications while we wait for better evidence
  - Relatively little research on TBI agitation
  - Existing research may be skewed toward sub-acute settings and milder injury
  - Haloperidol and other antipsychotic medications have extensive track record for safety and effectiveness, multiple routes of administration