

Agitation, Irritability/Aggression, and Anger after TBI

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General Topic tips:

- Start with a common case presentation(s) that a primary care provider can relate to easily
- Touch on pragmatic differential diagnosis issues that make a primary care provider's job tough
- Weave in interactive yes/no or true/false questions (2-3 to get/keep listeners engaged)
- Sprinkle practical tips throughout and clear easy to understand takeaway points



Talk outline:

1. TITLE - build in a clinical question into the title itself
2. CASE PRESENTATION(S) - quick and brief to frame the clinical scenario you're addressing
3. BACKGROUND - research on the topic - framing it relative to a primary care population (how does the information relate to primary care patients)
 - Include brief takeaway points (what are the new/relevant points that will help them improve practice)
4. PITFALLS - especially with differential diagnoses AND / OR with difficult medication or behavioral intervention choices
 - Include brief takeaway points (what are the basic struggles and what should they be thinking about)
5. TREATMENT - recommendations → offer more practical practice guidance, better if it's actionable (what should they DO, as opposed to what should they KNOW)
 - Include brief takeaway points (what can they do to change/improve their practice)





TBI-BH ECHO

Traumatic Brain Injury - Behavioral Health ECHO
UW Medicine | Psychiatry and Behavioral Sciences

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TBI-BH ECHO

Speaker disclosures

No conflict of interest



TBI-BH ECHO

Objectives

1. Understand definition of agitation, irritability, and anger after TBI
 - Recognize subtypes of agitation
2. Identify evaluation methods:
 - Agitated Behavior Scale
3. Identify treatment tools/plans for agitation, irritability, and anger after TBI



Cases

Case 1 - Agitation

- 30 year-old patient who was found down after a presumed fall
- Head CT demonstrated subarachnoid hemorrhage in bilateral frontal region with skull fracture
- Admitted to the hospital. Initially in coma and unresponsive
- On day 5 of admission, emerged and noted to be agitated

Case 2 - Irritability and Aggression

- 30 year-old patient who was in a motor vehicle collision
- No loss of consciousness
- Noted headache, dizziness, light sensitivity, and fatigue. Discharged home from ED
- Family finds that the patient continues to be short tempered 6 months after the injury



Reminder: TBI Severity Determination

| Criteria | Mild | Moderate | Severe |
|---|----------------|---|--------------------|
| Structural imaging | Normal | Normal or abnormal | Normal or abnormal |
| Loss of consciousness | 0-30 min | >30 min and <24 hours | >24 hours |
| Alteration of consciousness/mental state | Up to 24 hours | >24 hours; severity based on other criteria | |
| Post-traumatic amnesia duration | 0-1 day | >1 and <7 days | >7 days |
| Glasgow Coma Scale (best available score in first 24 hours) | 13-15 | 9-12 | <9 |



Agitation

- Subtype of delirium occurring during the state of posttraumatic amnesia
- Characterized by excesses of behavior:
 - Aggression
 - Akathisia
 - Disinhibition and/or
 - Emotional lability
- 35-96 % exhibit during acute recovery phase

Rosenthal and Mortimer, 2013



TBI-BH ECHO

Reminder: Post-traumatic Amnesia (PTA)

- A loss of memory for events surrounding the injury, disorientation, confusion and significant cognitive impairment
- Resolution: working memory returns
- Multiple assessment tools:
 - Galveston Orientation and Amnesia Test (GOAT)
 - Orientation-log (O-log)
 - Abbreviated Westmead Post Traumatic Amnesia Scale (A-WPTAS)



Irritability and Aggression

- Long-term sequelae of TBI
- Non-specific term

- Irritability: Tendency to be easily upset¹ and poorly controlled brief, external displays of temper
 - Third most commonly reported symptoms
 - 30-35% after mild TBI reported it one year after the injury²

- Aggression:
 - Reflection of irritability
 - Physical and verbal
 - 12-41% after severe TBI reports 1-15 years after the injury³

1. Prigatano, 1992
2. Alderman, 2003
3. Malec, 2018



Risk or Associated Factors

- Major depression
- Frontal lobe lesions
- Poor premorbid social functioning
- Alcohol or substance use disorder



Neuropathology

| Locus | Activity |
|-------------------|---|
| Hypothalamus | Orchestrates neuroendocrine response via sympathetic arousal, monitors internal status |
| Limbic system | Mediates impulses from prefrontal cortex, adds emotional content to cognition |
| Amygdala | Activates and/or suppresses hypothalamus, input from neocortex |
| Temporal cortex | Associated with aggression (also in both ictal and interictal status) |
| Frontal neocortex | Modulates limbic and hypothalamic activity, associated with social judgement aspect of aggression |

Evaluation

- Differential diagnosis:
 - Pain
 - Sleep disorder
 - Medication side effects
 - Delirium
 - Infection
 - Epilepsy
 - Metabolic disorders
 - Drug withdrawal
 - Hypoxia



Agitated Behavior Scale (ABS)

- 14 behaviors are scored
- Each behavior is scored 1 - 4:
 - 1: absent
 - 2: present to slight degree
 - 3: present to moderate degree
 - 4: present to extreme degree
- Excellent test-retest (same day) reliability, interrater reliability, internal consistency, and face validity



ABS - 14 behaviors

1. Short attention span, easy distractibility, inability to concentrate
2. Impulsive, impatient, low tolerance for pain or frustration
3. Uncooperative, resistant to care, demanding
4. Violent and or threatening violence toward people or property
5. Explosive and/or unpredictable anger
6. Rocking, rubbing, moaning or other self-stimulating behavior
7. Pulling at tubes, restraints, etc.
8. Wandering from treatment areas
9. Restlessness, pacing, excessive movement
10. Repetitive behaviors, motor and/or verbal
11. Rapid, loud or excessive talking
12. Sudden changes of mood
13. Easily initiated or excessive crying and/or laughter
14. Self-abusiveness, physical and/or verbal



ABS - Subscale

1. Short attention span, easy distractibility, inability to concentrate
2. Impulsive, impatient, low tolerance for pain or frustration
3. Uncooperative, resistant to care, demanding
4. Violent and or threatening violence toward people or property
5. Explosive and/or unpredictable anger
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Disinhibition: 1, 2, 3, 6, 7, 8, 9, and 10

Aggression: 3, 4, 5, and 14

Lability: 11, 12, and 13



ABS - rating example

8. Restlessness, pacing, excessive movement

Score 2: engages in random movements or fidgets occasionally. The **behavior does not threaten safety and terminates spontaneously.**

Examples:

- a. fidgets in bed but remains in place
- b. occasionally fidgets in the chair but the chair remains stable



ABS - rating example

8. Restlessness, pacing, excessive movement

Score 3: engages in random movements or fidgets frequently. There is **some threat to safety** but the behavior **terminates** with verbal or physical cueing or redirection

Examples:

- a. frequently slips down in bed, needing replacement
- b. fidgets in the chair, threatening stability, stops at least briefly after redirected



ABS - rating example

8. Restlessness, pacing, excessive movement

Score 4: random movements or fidgets frequently, threatening safety. Does **not** terminate with verbal or physical cueing or redirection and must be moved frequently or allowed free movement with **constant supervision**

Examples:

- a. cannot stay in bed, must be moved to wheelchair and allowed to move about
- b. fidgets in the chair, threatening stability. The caregiver must push the chair, move the patient to bed, or allow the patient to walk with assistance



ABS - Scoring

- 14-20: no agitation
- 21-27: mild agitation
- 28-34: moderate agitation
- 35+: severe



Treatment Option - Limitation in Literature

- Literature is limited and **does not discriminate well among behavioral phenotypes** (irritability, verbal or physical aggression, or lability) and research using samples
- Varies on definition of agitation and scales used
- Level of evidence is not strong and often old
- Many treated with **multiple medications**

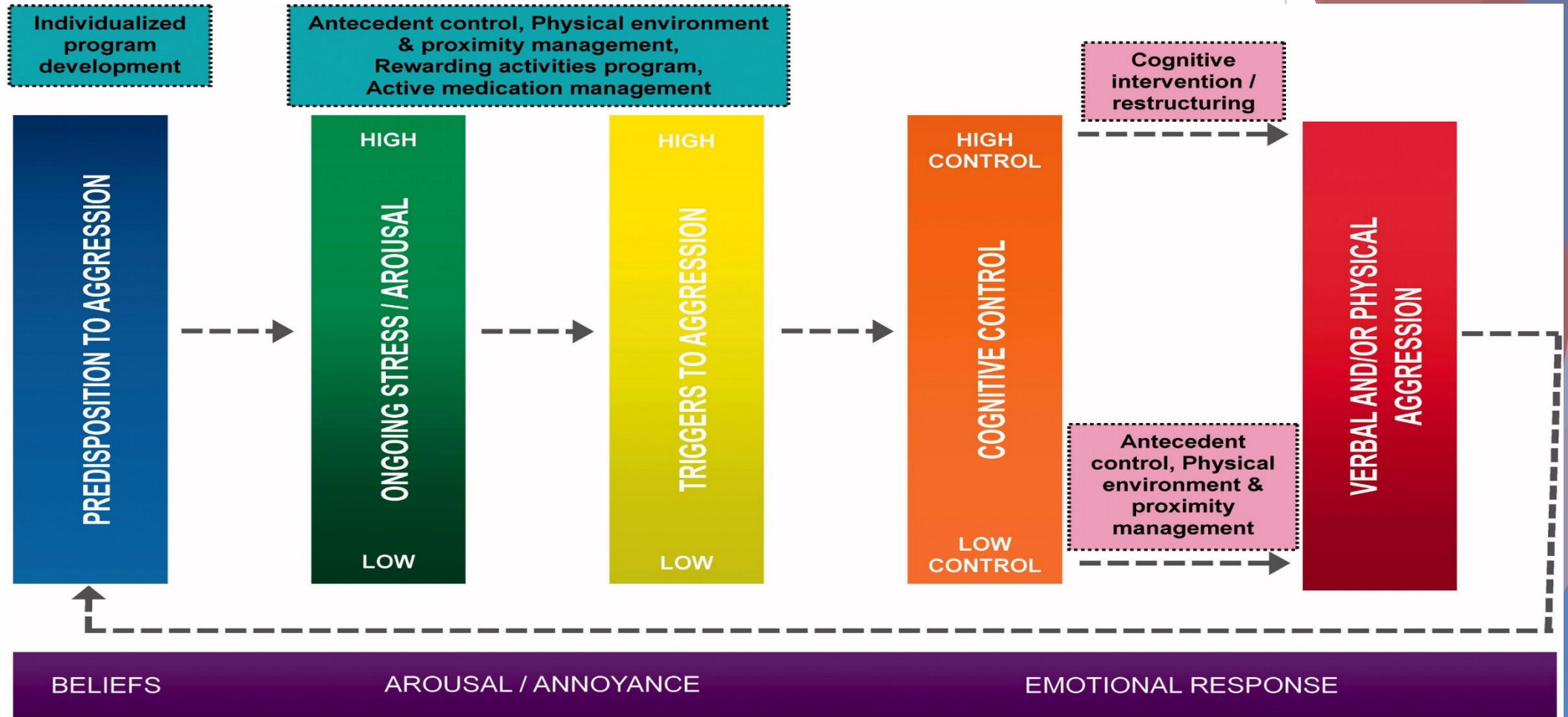


Environmental Management - Agitation

- **First line treatment**
- Safe, structured, low-stimulus environment
 - Consistent staff
 - Beds: floor beds or enclosure beds
- Restraints only if danger to self or others
- Reduce stimulation
- Reduce cognitive confusion
- Tolerate restlessness when possible



Neurobehavioral Approach





Nonpharmacological Management of Agitation and Anger after TBI

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Acknowledgement

Some materials for this talk were drawn from:

- ▶ Anger Self-Management Training for People with TBI by Hart, Maiuro, Brockway and Vaccaro (undated, unpublished)
- ▶ Understanding and Coping With Irritability, Anger, and Aggression After TBI by Neuman, Miles, Sander, Greenwald <https://www.msktc.org/tbi/factsheets>



Anger

- ▶ Anger is a normal, healthy human emotion
- ▶ Anger has survival benefit i.e., fight or flight in response to threats
- ▶ Helps us get what we want, source of motivation
- ▶ Helps us say no to what we don't want; self-protective function
- ▶ Managing anger constructively can lead to closer, more cooperative relationships i.e., being honest about what you want and don't want
- ▶ Understanding anger can lead to greater self-knowledge and emotional growth; what are my common anger triggers?



Anger as a Second Feeling

▶ Anger often arises secondarily from another emotional response being triggered; helpful to identify and deal with

- ▶ Fear
- ▶ Offended
- ▶ Vulnerable
- ▶ Ashamed
- ▶ Disrespected
- ▶ Overwhelmed
- ▶ Trapped
- ▶ Pressured

Note that for minoritized individuals, anger also may be an understandable response to systemic racism, microaggressions, and distrust of healthcare providers based on historical and current disparities in healthcare and outcomes.

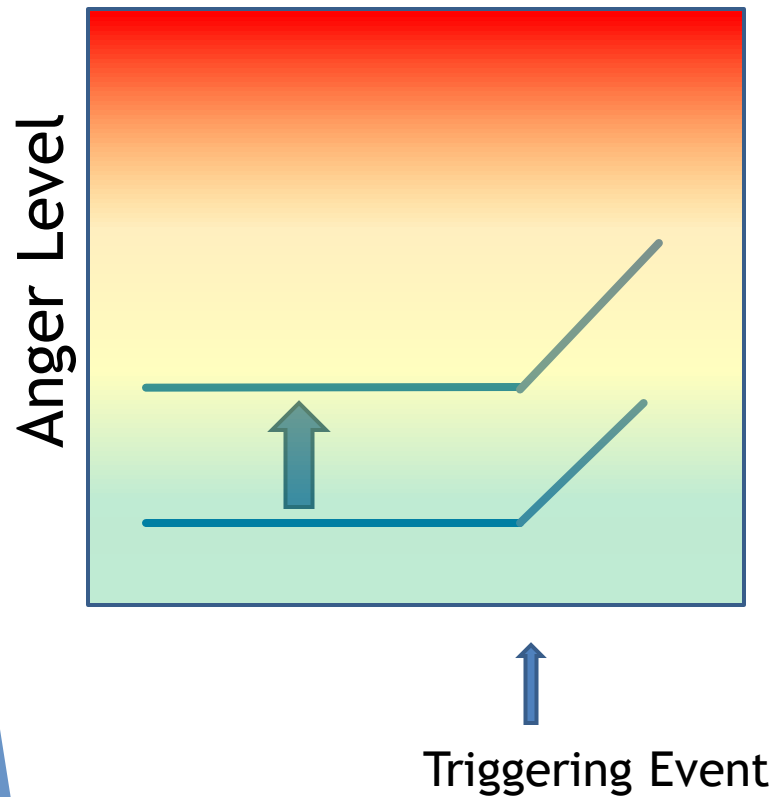


Anger after TBI--Generic Factors

- ▶ Difficulty noticing and labeling ones own emotions
- ▶ Under-developed listening skills
- ▶ Limited assertiveness skills (i.e., passive or aggressive)
- ▶ Normal difficulties thinking and communicating well when experiencing diffuse physiological arousal during conflict i.e., “flooding”



Anger after TBI--Contextual Factors



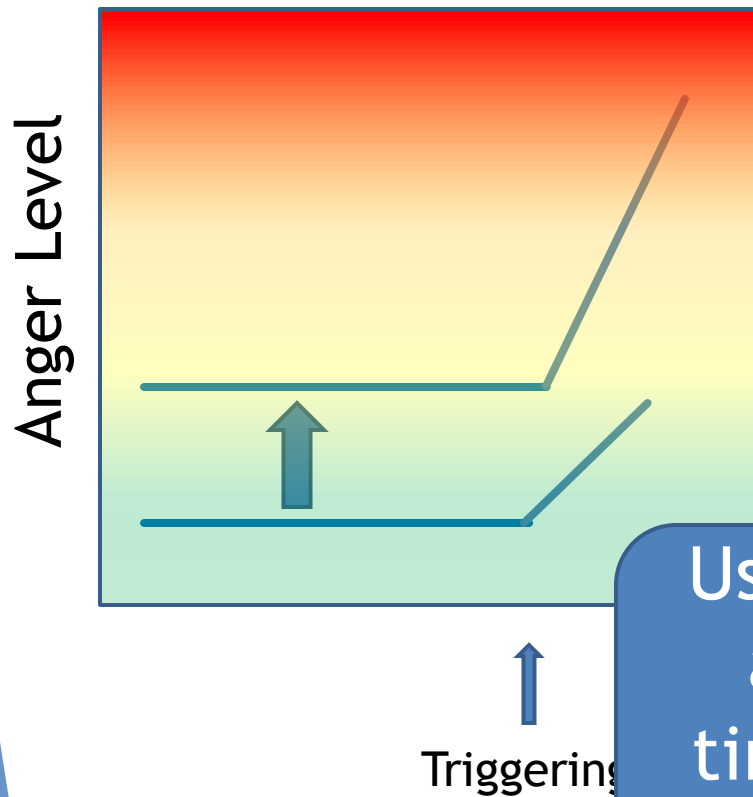
- ▶ Disruption in life
- ▶ Loss of/changes in important relationships, isolation
- ▶ Loss of freedom and independence
- ▶ Loss of work, money, enjoyable activities
- ▶ Worries, uncertainty
- ▶ Things are harder, more frustrating
- ▶ *Can create a baseline shift towards higher anger, less of a margin before losing control*

Encourage social connectedness e.g., +

Link people to vocational rehab, volunteer work to bolster meaning and purpose



Anger after TBI--Brain Factors



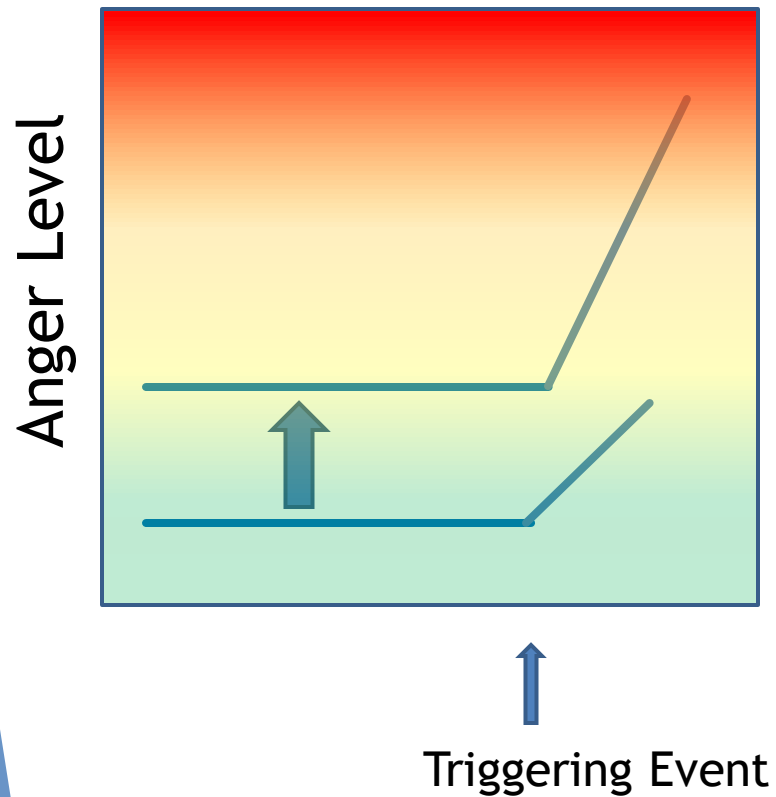
- ▶ Decreased concentration speed
- ▶ Physical and mental fatigue, low energy
- ▶ Overstimulation from lights, noise, people

Use active listening and distraction, time-out; problem-solve later

Assertiveness training to ask people to speak
Sleep hygiene, scheduled rest breaks or short naps

Reduce ambient noise, light, limit number of people, make quiet space available

Anger after TBI--Brain Factors



- ▶ Normalization, self-monitoring
- ▶ Limited ability for what you want not what you don't want
- ▶ Impaired mirror technique, ask
- ▶ Biased attention, Assess and treat intent, hostility
- ▶ Co-morbid PTSD and major depression

Antecedents “Triggers”

- ▶ What are the contextual factors that trigger anger for the person?
- ▶ Obtain this information through self-monitoring, perhaps with assistance of another person if needed
- ▶ Common triggers to look for are
 - ▶ later in the day when the person is tired
 - ▶ in situations where they are over-stimulated
 - ▶ when the person is reminded of loss or limitation
 - ▶ When they feel pressured, loss of control, afraid, disrespected



Managing Antecedents/Triggers

- ▶ Good night-time sleep, scheduled rest breaks/ brief naps to avoid over-fatigue
- ▶ Maintain low stimulation environments, provide options for person to retreat into low stimulation environment
- ▶ Schedule pleasant, enjoyable activities into daily life as well as activities where the person can experience a sense of success; provide challenges but at a difficulty level where the person can experience 90% success
- ▶ Use lots of affirmations of positive behaviors (“catch the person doing good”) to build greater confidence in order to tolerate limitations



Personal Definition of Anger

- ▶ Identification and self-monitoring of physical, behavioral, thinking, and affective aspects of anger
- ▶ Promote early identification and intervention (self-management and interventions by support persons)
- ▶ Thoughts: What is the story we are telling ourselves when we are angry? Use thought records. CBT Three column technique Activating Event → Beliefs/Thoughts → Consequences
- ▶ Affect recognition: Feelings list, 0-10 rating, Secondary Feelings



Personal Definition of Anger

Physical

- ▶ Turning red
- ▶ Heart racing,
- ▶ Fists clenched, tense, shaking
- ▶ Feeling hot, sweating
- ▶ Feeling cold or numb
- ▶ Upset stomach
- ▶ Staring, glaring

Behavioral

- Yelling
- Saying hurtful, insulting things
- Making threats
- Hitting kicking throwing things
- Hitting, kicking pushing others
- Hitting or harming oneself
- Shutting down, withdrawal, avoidance



Coping Strategies

- ▶ Begin by eliciting and reinforcing anything positive they already do
- ▶ Keep it simple
 - ▶ Notice anger building up early
 - ▶ Walk away, take time-out
 - ▶ Count to 10 slowly
 - ▶ Breathing/Relaxation/Meditation exercises
 - ▶ Light to moderate intensity exercise
 - ▶ Written, pre-planned coping statements in their own words they can keep with them
 - ▶ Access comforting objects, places, music



Managing Anger Escalation

- ▶ Sit if possible, get below eye level, soft voice, speak slowly, simple language, open stance, give them space, one person speaks
- ▶ Active listening to show you understand and care
 - ▶ Open questions-*What is going on for you right now?*
 - ▶ Reflections-*You felt ignored/criticized/talked down to/etc.*
 - ▶ Affirmations-*I appreciate you letting us know how you feel*
- ▶ Request a time-out to calm down before trying to explain or problem-solve; for recurrent events agree on a signal to take time out
- ▶ Sometimes, use distraction to change subject, engage in counter activity such as go for a walk, change topic
- ▶ Be sure to address their concern at another time



Pharmacological Management

Case 1 - Agitation

- 30 year-old patient who was found down after a presumed fall
- Head CT demonstrated subarachnoid hemorrhage in bilateral frontal region with skull fracture
- Admitted to the hospital. Initially in coma and unresponsive
- On day 5 of admission, emerged and noted to be agitated

- **Patient has pulled out trach, NG tube, and foley. Staying up all night**

Case 2 - Irritability and Aggression

- 30 year-old patient who was in a motor vehicle collision
- No loss of consciousness
- Noted headache, dizziness, light sensitivity, and fatigue. Discharged home from ED
- Family finds that the patient continues to be short tempered 6 months after the injury

- **Getting in fights with family and fired from the job due to conflicts with coworkers**



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- Getting in fights with family and fired from the job due to conflicts with coworkers. ABS 25.

What class of medication would you recommend at this time?



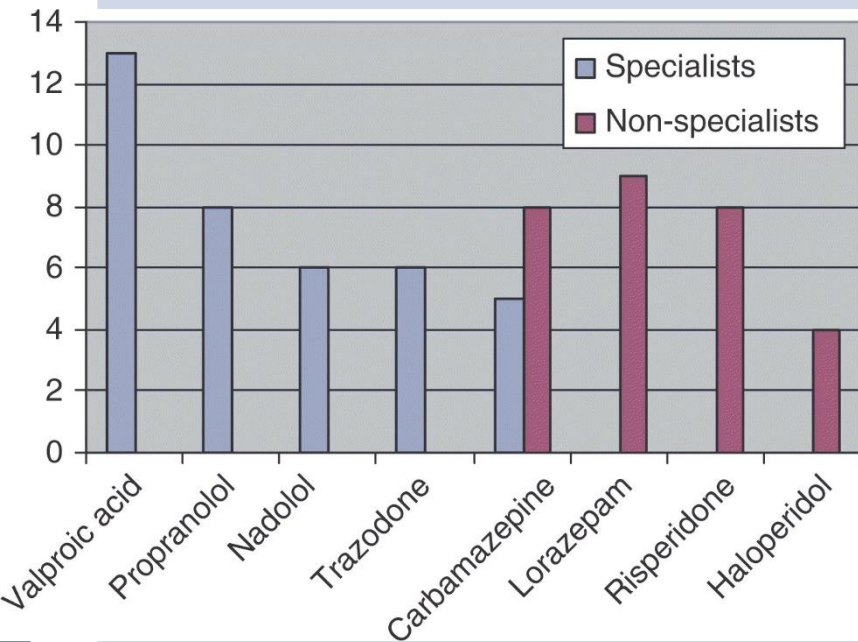
Pharmacological Management

- What class of medication would you recommend at this time?
 - Beta blockers
 - Antipsychotics (neuroleptics)
 - Antiepileptics
 - SSRI
 - Stimulants/dopaminergic



Most Common Drug Choices

| Neurobehavioral symptom | Top drug choice of specialist | Top drug choice of non-specialist |
|-------------------------|--|-----------------------------------|
| Agitation | Valproic acid (VPA) and its derivatives (13) | Lorazepam (9) |
| | Propranolol (8) | Carbamazepine (8) |
| | Nadolol (6) | Risperidone (8) |
| | Trazodone (6) | |
| | Carbamazepine (5) | |
| | VPA (6) | VPA (11) |
| | SSRI (5) | Carbamazepine (7) |
| | | |



Beta Blockers

- Most amount of evidence (Cochrane and ABIKUS) for Agitation
 - Propranolol
 - Start 10 mg tid; up to 300 mg/day
 - Pindolol
 - Start 5 mg bid; up to 30 mg/day
 - Nadolol
- May help to treat hyperadrenergic state in Agitation
- Weak evidence for reduction in anger/aggression



Antiepileptics

- Valproic acid (VPA)
 - 250mg daily; then increase to bid
 - Adverse effects: hepatotoxic, thrombocytopenia, teratogenic, rash, GI upset, fatigue, weight gain
 - RCT: reduction in irritability without serious adverse events¹
- Carbamazepine (CBZ)
 - Start 100-150mg BID
 - Adverse effects: aplastic anemia, hyponatremia (SIADH), hepatic impairment, teratogenic, renal failure, fatigue, dizziness
 - RCT for chronic irritability/aggression: improved but no statistical difference between placebo and CBZ groups²

1. Beresford, 2022
2. Hammond, 2021



Stimulants

- Improvement in speed of processing, attentiveness that helps with agitation
- Also shown to improve anger particularly in setting of concentration deficits

- Amantadine 100 mg twice daily (morning and noon)
 - Mixed but overall positive for reducing both irritability and aggression

- Methylphenidate

Hicks, 2021



TBI-BH ECHO

SSRI

- May be more helpful in those with aggression or violent behavior
- Sertraline 100 - 200 mg/day for both Agitation and Irritability/Aggression
- Fluoxetine has shown to improve agitation compared to placebo in Stroke
- Amitriptyline is not commonly used and not efficacious



Antipsychotics

- Risperidone
 - Ziprasidone
 - Quetiapine
 - Olanzapine
 - Clozapine
 - Aripiprazole
- ▶ To protect the patient from harming self or others
 - ▶ Need for quick sedation
 - ▶ + delirious symptoms



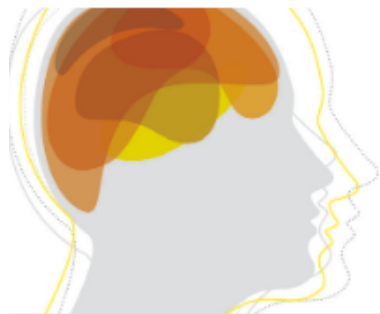
Choosing Antipsychotics

- Olanzapine, Clozapine, Quetiapine, Ziprasidone¹
 - Expert opinion:
 - Shortest possible course
 - Consider in case of associated delirious symptoms but otherwise avoid
 - Preferable to use atypical antipsychotics
- No clear evidence of benefit with antipsychotics^{1, 2}
- Choose based on side effect profile

1. Plantier, 2016
2. Elovic, 2008

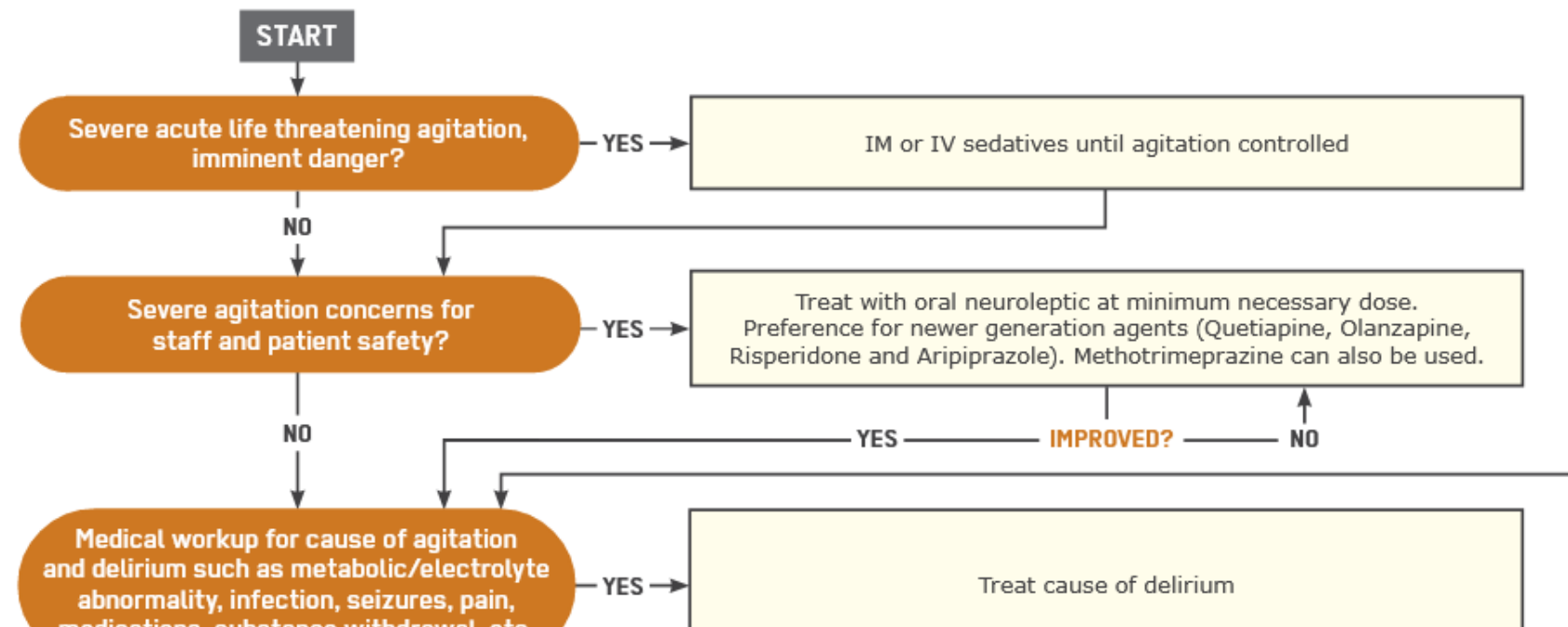


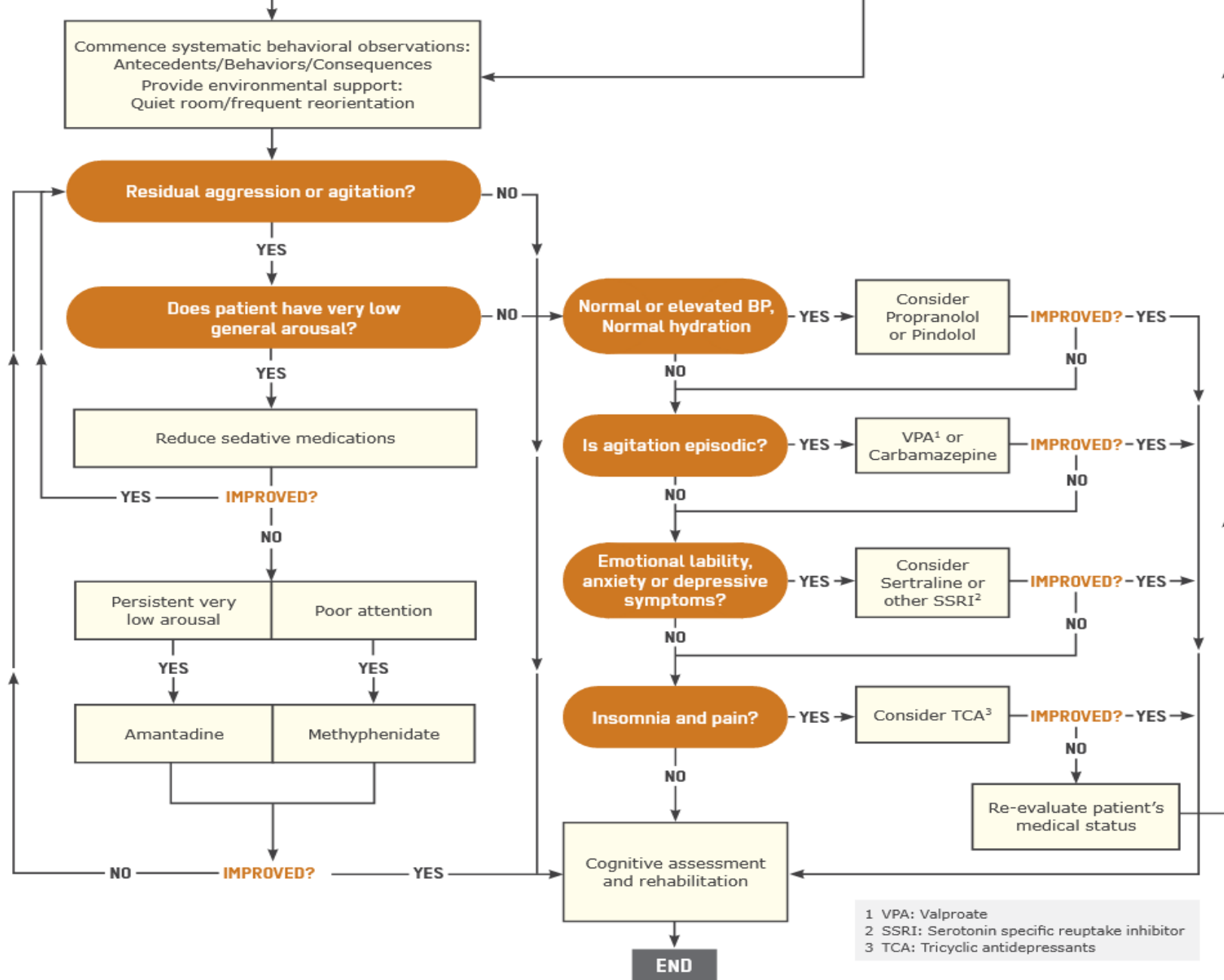
Clinical Practice Guideline - Moderate to Severe TBI



CLINICAL PRACTICE GUIDELINE FOR THE REHABILITATION OF ADULTS WITH MODERATE TO SEVERE TBI

Pharmacological Management of Agitation and Aggression Following TBI





Pharmacological Management

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- Family finds that the patient continues to be short tempered 6 months after the injury
- Getting in fights with family and fired from the job due to conflicts with coworkers. ABS 25.

What class of medication would you recommend at this time?



Summary

- Agitation, irritability, and anger are common after TBI
- Objective measurement is necessary:
 - Agitated Behavior Scale
- Start with environmental and behavioral management once other possible causes have been ruled out
- Agitation: beta blocker has most evidence. AEDs & anti-depressants are useful. Consider stimulant
 - Avoid antipsychotics unless risk for harm
- Irritability/Aggression: amantadine, methylphenidate, VPA, CBZ are potential options



Reference

- Alderman, Nick. "Contemporary approaches to the management of irritability and aggression following traumatic brain injury." *Neuropsychological Rehabilitation* 13.1-2 (2003): 211-240.
- Beresford, Thomas, et al. "A Double-Blind Placebo-Controlled, Randomized Trial of Divalproex Sodium for Posttraumatic Irritability Greater Than 1 Year After Mild to Moderate Traumatic Brain Injury." *The Journal of Neuropsychiatry and Clinical Neurosciences* (2022): appi-neuropsych.
- Elovic, Elie Paul, Neil N. Jasey Jr, and Michal E. Eisenberg. "The use of atypical antipsychotics after traumatic brain injury." *The Journal of Head Trauma Rehabilitation* 23.2 (2008): 132-135.
- Francisco, Gerard E., et al. "Pharmacological management of neurobehavioural sequelae of traumatic brain injury: a survey of current psychiatric practice." *Brain injury* 21.10 (2007): 1007-1014.
- Hammond, Flora M., et al. "Carbamazepine for irritability and aggression after traumatic brain injury: a randomized, placebo-controlled study." *Journal of neurotrauma* 38.16 (2021): 2238-2246.
- Hammond, Flora M., et al. "Effectiveness of amantadine hydrochloride in the reduction of chronic traumatic brain injury irritability and aggression." *The Journal of head trauma rehabilitation* 29.5 (2014): 391-399.
- Hammond, Flora M., et al. "Amantadine effect on perceptions of irritability after traumatic brain injury: results of the amantadine irritability multisite study." *Journal of neurotrauma* 32.16 (2015): 1230-1238.
- Hicks, Amelia J., et al. "The efficacy and harms of pharmacological interventions for aggression after traumatic brain injury—systematic review." *Frontiers in neurology* 10 (2019): 1169.
- Kalapatapu, Raj K., and Gordon M. Giles. "The relational neurobehavioral approach: can a non-aversive program manage adults with brain injury-related aggression without seclusion/restraint?." *Disability and rehabilitation* 39.22 (2017): 2261-2268.
- Malec, James F., et al. "Rasch analysis, dimensionality, and scoring of the neuropsychiatric inventory irritability and aggression subscales in individuals with traumatic brain injury." *Archives of physical medicine and rehabilitation* 99.2 (2018): 281-288.
- Plantier, D., and J. Luauté. "Drugs for behavior disorders after traumatic brain injury: systematic review and expert consensus leading to French recommendations for good practice." *Annals of physical and rehabilitation medicine* 59.1 (2016): 42-57.
- Prigatano, George P. "Personality disturbances associated with traumatic brain injury." *Journal of consulting and clinical psychology* 60.3 (1992): 360.



Neuropsychiatric Inventory (NPI)

- Irritability and Aggression subscale
- NPI: divided into number of subscales
 - **Irritability/Lability**
 - **Agitation/Aggression**

