

Management of Post Traumatic Brain Injury (TBI) Agitation

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I. Definition, Assessment, Diagnosis

A. Agitation Definitions: No consensus

1. Subtype of delirium unique to TBI which occurs during period of Post-traumatic amnesia (PTA – period of time in which new memory formation is impaired), characterized by excess of behavior that includes some combination of aggression, disinhibition, akathisia, disinhibition, and emotional lability.^{[2], [3], [5]}
2. State of aggression during the period of post-traumatic amnesia, in the absence of other physical, medical or psychiatric causes, with a score of ≥ 21 on the Agitated Behavior Scale (ABS)^[6]

B. Agitation Assessment:

1. Agitated Behavior Scale: reliable and validated measure that describes level of agitation.^[4]
 - a. Helpful for monitoring patient’s recovery progression and assessing effectiveness of interventions
 - b. High inter-rater reliability^[7]
 - c. Rating of 1 to 4 (based on severity) for 14 different behaviors
 - d. Can be completed quickly and via observation^[6]
2. Galveston Orientation and Amnesia Test (GOAT):^[8]
 - a. Reliable and valid indicator of PTA in TBI patients^[9]
 - b. Score of 78 or more on three consecutive occasions is considered to indicate that patient is out of PTA
 - c. Can be administered daily until patient is out of PTA
3. Rancho Los Amigos (RLA) Scale/ Levels of Cognitive Functioning Scale
 - a. Represents the typical sequential progression of recovery in TBI
 - b. Stage IV: Confused, Agitated Response
 - c. Barriers: These patients have deficits in attention, memory, initiation, problem solving, sequencing, information processing speed, and safety awareness. Anagnosia (lack of awareness of deficits) is also a challenge.
4. Other scales used: The Overt Agitation Severity Scale and the Neurobehavioral Rating Scale^{[5],[10]}

C. Agitation Diagnosis ^{[3], [4], [5]}

1. A diagnosis of exclusion after physical, medical, psychiatric, and neurological conditions have been ruled out
2. Score of 21 or greater on ABS
3. Can also result from physical, medical, psychiatric, and neurological conditions:
 - a. Physical:
 - i. Pain (fractures, post-operative, heterotopic ossification, spasticity, wounds, or other noxious stimuli)
 - ii. Environmental: Excessive stimulation, Temperature, Restraints
-“ICU Syndrome” : acute state of confusion seen even in patients without primary brain pathology, secondary to constant stimulation in ICU - vital signs, alarms, medication administration, constant lighting, and ambient hallway noise. ^{[11],[12]}
 - iii. Tubes/lines
 - b. Medical:
 - i. Metabolic disturbance (electrolytes, thyroid, hypoglycemia)
 - ii. Infection
 - iii. Hypoxemia, pulmonary embolism
 - iv. Urinary retention/incontinence
 - v. Nausea, Constipation
 - c. Neurological:
 - i. Hydrocephalus
 - ii. Seizures
 - iii. Intracranial mass lesion/rebleed
 - iv. Headache
 - d. Psychiatric:
 - i. Premorbid or exacerbation of premorbid Personality/Psychotic/Anxiety/Mood disorders
 - ii. Sundowning in patients with dementia
 - e. Substance/medication related:
 - i. Iatrogenic
 - ii. Acute intoxication
 - iii. Withdrawal ^[6]
 - Alcohol: Hypertension, tachycardia, hallucinations, disorientation, agitation
 - Opioid: Restlessness, abdominal pain, yawning, piloerection
 - Benzodiazepine: Hypertension, tachycardia, diaphoresis, tremors, hyperthermia, and seizures
4. Work up of Agitated patient: CMP, Thyroid function tests, CBC with differential, UA, B12/Folate, Urine toxicology screen, CT/MRI of Brain, EEG, XRay

II. Management and Treatment Recommendations

A. FIRST LINE: Environmental Modification^[6]

1. Reduce stimuli:
 - a. Light, noise, distractions (especially at night) – place patient in bed, draw curtains, turn off television, etc.
 - b. Limit number of visitors at one time
 - c. Staff and family should speak in low volume, slowly, one at a time
 2. Avoid/minimize restraints: Use non-contact restraints if able (safety net beds), padded hand mittens, one-to-one staff supervision
 3. Minimize tubes and lines: May cover them (abdominal binder, etc)
 4. Frequent re-orientation by staff and family
 5. Obtain any hearing devices or vision aids from home to improve orientation
 6. Consistent schedule and staff
 7. Timed toileting
 8. Create a familiar environment: Allow family to bring in personal possessions^[15]
 9. Monitor sleep cycle and sleep quality
 - a. Consider use of Trazodone, Melatonin
- B. Behavioral Modification**
1. Allow patient to pace (if safe) or be walked /wheeled around by staff to address akathisia/restlessness.
 2. Mobile patients may benefit from a closed unit or sensors for safety
 3. De-escalation techniques (see prevention and education section below)^[14]
 4. Structured behavioral programs^{[6],[15]}
 - a. Limited application depending on patient's level of cognitive and communication impairment
- C. Pharmacologic Management**
1. Agents which slow cognition may prolong/exacerbate agitation.^[14]
Dopaminergic agents should be avoided if able as they can prolong PTA and slow cognitive recovery^[5]
 2. Antipsychotics:
 - a. Typical Antipsychotics: Not recommended as first line, rescue only
 - i. Haldol:
 - shown to slow cognitive recovery
 - shown to slow motor recovery in rat model^[16]
 - associated with longer time in PTA^[17]
 - Easily accessible in the hospital and can be given IM, IV: useful for patients who are imminently a danger to self or others.
 - ii. Droperidol:
 - Also available in IM
 - Found to be faster and superior to Haldol, Ativan, and Benadryl in controlling acute agitation^[18]
 - iii. Cognitive improvement seen after discontinuing typical antipsychotics^[19]
 - iv. Associated with extrapyramidal side effects, dystonic reactions, restlessness, Neuroleptic Malignant Syndrome, QTc prolongation
 - v. Not recommended as long term agents
 - b. Atypical antipsychotics

- i. Quetiapine:
 - Shown to be effective in treating agitation ^[20]
 - Better side effect profile compared to typical agents
 - ii. Olanzapine:
 - Shown to have effect in treating agitation
 - Favorable side effect profile when compared to other antipsychotics^[21]
 - Available orally or IM
 - iii. Others: Risperidone, Ziprasidone ^[52]
3. Anxiolytics
- a. Benzodiazepines
 - i. Impair cognition ^[22]
 - ii. May cause paradoxical agitation ^[22], anterograde amnesia ^[23], disinhibition, respiratory depression, impaired coordination
 - iii. Useful for rapid resolution of violent agitation (rapid onset of action)
 - iv. Lorazepam preferred
 - Less effect on cardiovascular and respiratory centers than other benzodiazepines ^[23]
 - Doses of 0.5-1mg q8h, titrating up to maximum of 8-12mg/day ^[22]
 - Start long-term agents concurrently ^[22]
 - Discontinue as soon as possible to minimize chances of delaying cognitive recovery ^[22]
 - b. Buspirone ^{[6],[14],[32]}
 - i. Preferred anxiolytic in TBI patients
 - ii. No significant adverse neurological or cognitive effects, non-sedating, non-addictive, does not interact with other CNS agents, not a respiratory depressant ^[14]
 - iii. Side effects: Lowers seizure threshold, light-headedness, headache
 - iv. Disadvantage: Delay in therapeutic action. Rapid neuropsychiatric effects, but 2-3 weeks for anxiolytic effects ^[45]
 - v. Dosing: 60mg/day is maximum, but as high as 180/day seen ^[14]. Usual dose of 5-20mg TID
4. Beta blockers
- a. Propranolol
 - i. Best evidence for efficacy in treating post-traumatic agitation with minimal side effects per Cochrane review ^[24]
 - ii. shown to reduce agitation intensity and need for physical restraints ^[25]
 - iii. Also improves restlessness and disinhibition ^[14]
 - iii. Also helpful for treating hyperadrenergic/dysautonomic state after TBI
 - iv. Also used to treat drug-induced akathisia, EtOH withdrawal, mania, generalized anxiety disorder, lithium induced tremor ^{[31],[27]}
 - iv. Side effects
 - Hypotension and bradycardia are limiting side effects
 - May also cause depression and lethargy ^{[31],[27]}
 - No adverse effect on motor recovery ^[14]
 - v. Dose:

- Starting dose: up to 40-60mg/day divided into BID –QID dosing ^[25]
- Maximum dose of 420 mg/day has been used
- vi. Lipophilic properties
 - More effective CNS penetration
 - Propranolol is the most lipophilic beta blocker
- b. Moderately lipophilic beta blockers
 - i. Metoprolol and pindolol
- 5. Anticonvulsants
 - a. Mood-stabilizing AEDs reduce agitation ^[29]
 - b. Valproic acid ^{[30],[32], [33]}
 - i. Initial dose of 250mg BID, may be titrated up 250mg every 2-3 days to maximum of 1000-2500mg/day ^[20]
 - ii. Serum levels of 40-100 ug/mL with positive effects ^[34]
 - iii. Limited, if any, adverse effects on cognition^[31]
 - iv. Side effect limitations: hepatotoxicity, thrombocytopenia.
-More common side effects of sedation, nausea, and vomiting, are limited by meal time administration and gradual titration
 - v. Less likely than carbamazepine to have negative impact on cognition and has safer side effect profile^{[35],[32]}
 - vi. Potential for rapid loading
 - c. Carbamazepine ^{[35],[36]}
 - i. Dose to therapeutic effect with titration up. Aggression-limiting doses seen starting at 300-400mg/day ^[14]. Other studies with effective doses 400-900 mg/day (BID-TID dosing).^{[36],[37]}
 - ii. Side effects: Hyponatremia, renal impairment, imbalance, sedation. Rarely, aplastic anemia, and Steven-Johnson syndrome^[20]
 - iii. Monitor serum levels for toxicity
 - iii. Rapid onset of action makes it useful in trauma critical care setting^[37]
 - d. Others
 - i. Gabapentin, Lamotrigine
 - Not as well studied
 - Reports of negative effects, such as anxiety and agitation ^{[38],[39],[40]}
 - ii. Phenytoin, Topiramate
 - Negative cognitive impact ^{[38],[41],[42]}
- 6. Neurostimulants
 - a. Amantadine
 - i. Can be effective for both acute ^[44] and chronic ^[43] TBI agitation
 - ii. Shown to improve cognition: Attention, concentration, processing time, initiation, orientation, sequencing, verbalization, and participation ^{[40], [41], [32]}

- iii. Dosing from 50-400 mg/day, in divided doses ^{[44],[46]}
- iv. Therapeutic effects typically seen within several days ^[14]
- v. Side effects:
 - Overstimulation, irritability, hypomania, agitation
 - Increased HR and BP, use with caution in patients with dysautonomia and cardiovascular complications
 - Lowers seizure threshold, so use with caution in seizure history patients and early stage TBI when increased intracranial pressure also lowers the threshold ^[45]
 - Some side effects potentiated when combined with anti-cholinergic agents: hallucinations, confusion, nightmares ^[47]
 - Side effects are generally mild, dose dependent, and reversible ^[32]

b. Methylphenidate

- i. Useful in both acute and chronic TBI agitation^{[31] [32], [34], [35]}
- ii. Improves cognition similarly to Amantadine
- iii. Quick onset of action ^[32]
- iv. Relatively benign side effect profile ^[32]
- v. Dosing: 10-60 mg/day in divided doses, usually at 8AM and noon ^[14]

c. Bromocriptine: Dopaminergic neurostimulator similar to Amantadine

d. Dextroamphetamine: Sympathomimetic neurostimulator similar to Methylphenidate

7. Antidepressants

a. Selective Serotonin Reuptake Inhibitors (SSRIs)

- i. Useful for behavioral syndromes in TBI
- ii. Trazodone
 - Helpful for sleep-wake cycle regulation
 - Starting dose: 50-100 mg.
 - Side effects: Anticholinergic, Rare priapism
- iii. Others: Sertraline ^[48], Fluoxetine, Paroxetine, Citalopram
- iv. Side effects: Serotonin syndrome, QTc prolongation, anxiety, sexual dysfunction, excessive weight loss

b. Tricyclic Antidepressants (TCAs)

- i. Amitriptyline ^{[14], [54]}
 - Dosing: 10-75 mg/day
- ii. Side effects: Anticholinergic, QTc prolongation, potential seizure threshold lowering ^[55]

c. Bupropion

- i. Useful for restlessness at 150mg daily ^[51]

8. Lithium

- i. Has been suggested to reserve its use in patients with mania and cyclic mood disorders ^[57]
- ii. Dosing: Start at 300mg BID and titrate by serum levels (0.6-1.2 mEq/L is therapeutic and >1.4 mEq/L is toxic level) and side effects ^[6]

iii. Side effects: sedation, movement disorders, hypothyroid, seizures, bradycardia, vomiting, QTc prolongation, renal impairment. [6], [58]

9. Summary:

- a. Choose agent based on clinical presentation. Every TBI is different.
 - i. Restlessness/Akathisia: Frequent ambulation, Beta-blocker
 - ii. Hyperadrenergic state: Beta-blocker
 - iii. Episodic Behavior Dyscontrol / Mood Labiality: Anticonvulsants/Mood stabilizers; possibly Atypical antipsychotics, SSRI, Neurostimulator
 - iv. Anxious/fearful: Buspar, SSRI/TCA, Trazodone
 - v. Paranoid: Atypical antipsychotic
- b. Start low, go slow
- c. Ideal agent is non-sedating, not affecting cognitive recovery, low side effect profile
- d. May need to discontinue drugs which may amplify agitation:
 - i. Narcotics
 - ii. Benzodiazepines
 - iii. Dopamine agonists (e.g. metoclopramide)
 - iv. H2-receptor antagonists (e.g. famotidine)
 - v. Anticholinergic medications (e.g. oxybutynin)

III. Prevention and Education [50]

- A. Educate staff and family on how to approach TBI pt
 - Use social greetings: these are cues to relax
 - Speak calmly, slowly, briefly, clearly, and directly
 - Do not need to correct confused statements. Instead of disagreeing, make a neutral statement or re-direct attention to another topic
 - Explain what you are going to do before you do it (e.g. vitals, procedures, physical exam, etc)
 - Avoid sudden grabbing or touching of the patient. Approach from the front.
 - Do not crowd patient
 - Formally end the interaction as patient may not be aware of normal social cues
 - Provide patient with choice instead of command.
 - Therapies in quiet area, at bedside
 - Positive reinforcement
 - Give patient ample time to process information and formulate responses
 - Break down difficult tasks into small steps
- B. Patient Resources
 - PM&R inpatient consult services and outpatient TBI clinic
 - Brain Injury support groups (e.g. Baptist Rehabilitation Institute)
 - Online Resources, such as Brainline.org
 - Arkansas Trauma Rehabilitation Program: <https://atrp.ar.gov/>[59]

This guideline was developed to improve health care access in Arkansas and to aid health care providers in making decisions about appropriate patient care. The needs of the individual patient, resources available, and limitations unique to the institution or type of practice may warrant variations.

Guideline Developers

Guideline updated by Rani Lindberg, MD, in collaboration with the TRIUMPH team led by Rani H Lindberg, MD, and Thomas S. Kiser, MD.

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