

SPECTRUM HEALTH
The Medical Group

Agitation and Traumatic Brain Injury

Aashish Deshpande, MD, FAAPMR
ABPMR, Brain Injury Medicine
Division Chief, PM&R
Brain Injury Association of Michigan
Fall Conference 2017

SPECTRUM HEALTH
The Medical Group

Overview

- Definition/Incidence*
- Pathology*
- Evaluation and Monitoring*
- Environmental/Behavioral Modifications*
- Medications*

SPECTRUM HEALTH
The Medical Group

Definition of Agitation

A state of altered consciousness, posttraumatic amnesia, and aggression during recovery from TBI typically in the coma awakening period.

Typically short duration (10-14 days), but can come on later and last longer

Can include aggression, akathisia (restlessness), disinhibition, emotional lability, motor restlessness, impulsivity, disorganized thinking, perceptual disturbances, impaired capacity to sustain attention, reduced adaptation.

Hagen, C et al. Post Grad Course on Rehab of TBI (1979)
Bogner, J et al. Neurosurgery (1990)
Sandoz, NS et al. Arch PM&R (1995)
Lavin, HD et al. Arch Neurol (1978)
Rogers, RL et al. Arch PM&R (1987)
Fogarty, LP et al. Arch PM&R (1997)

SPECTRUM HEALTH
The Medical Group

Incidence of Agitation

Ranges from 11% to 70 %; mean incidence estimated 46%

Variability due to definitions of Agitation

Multifactorial

When is a patient "out" of agitation?

Brooke MM et al. Arch PM&R (1992)
Wolf AP et al. Brain Inj (1996)
Bogner JA et al. Am J PM&R (2001)
Noh MT et al. Brain Inj (2008)

SPECTRUM HEALTH
The Medical Group

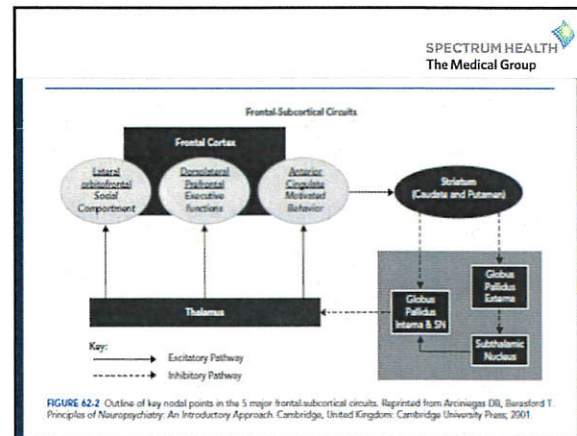
Pathophysiology Structural

3 subtypes of aggression: Social, Predatory, and Defensive

Defensive is most like TBI aggression

Temporal Lobes and amygdala appear in most studies (fMRI, PET, etc) to be predominantly involved in the disorder

No studies indicate a specific site or neurochemical in Agitation: Multifactorial



SPECTRUM HEALTH
The Medical Group

Environmental/Behavioral Modifications

General Behavior Modifications

- Rest breaks, assist with sleep/wake patterns, quiet time
- Meals/Therapies in isolated areas
- Restlessness can be eased with activity, such as walking, duties on the unit, scheduled distraction activity
- Minimize restraints with alternatives or non-contact devices (enclosure bed, supervision by staff)
- Eliminate lines, catheters, tubes, anything that can be a distraction and focus (or use covers/binders to hide them)

SPECTRUM HEALTH
The Medical Group

Environmental/Behavioral Modifications

- Scheduled toileting and meals can restore order and control for injured patients
- Carefully monitor sleep cycles and pain management

SPECTRUM HEALTH
The Medical Group

Environmental/Behavioral Modifications

- Many Behavioral Treatment models exist
- Information to patient and families
 - Interpersonal/adaptive approach
- Contingencies for behaviors
 - Token/Reward (if cognitively intact)
- Awareness of behavior and self-monitoring of performance
 - Cognitive Behavioral, Holistic
- Relationship with Psychologist and team
 - Systemic Family Therapy
- Other
 - Breathing, Tai Chi

Ward L. et al. Ann PMAR (2016)

SPECTRUM HEALTH
The Medical Group

Medications

- If possible, try not to use medications and wait out the 10-14 average days until patient past agitated phase
- Risk of harm to patient/staff/families often necessitates use of medications
- Need to shorten LOS in all treatment areas also adds to the need for medication use

SPECTRUM HEALTH
The Medical Group

Medications - Anticonvulsants

Valproic Acid (Depakote)

- Used in mania/bipolar disorder
- Studies support use in TBI population
- Can lead to cognitive dysfunction but studies in TBI patients with both neutral and negative effects
- May need high doses in TBI due to increased metabolism
- Hepatotoxicity, thrombocytopenia

Dikmen S. et al. Neurology (2000)
Massagi, T. Arch PMAR (1991)

SPECTRUM HEALTH
The Medical Group

Medications - Anticonvulsants

- Carbamazepine (Tegretol)**
 - Studies show decreased irritation, disinhibition, and combativeness in TBI population with limited cognitive effects
 - Hyponatremia, renal failure
 - Can monitor levels, but therapeutic is to behavioral effect
- Gabapentin (Neurontin)**
 - one study showed agitation after use in TBI
- Lamotrigine (Lamictal)**
 - one case study of effectiveness, four cases of emotional lability symptoms treated
- Oxcarbazepine (Trileptal)**
 - No studies after TBI, few studies in aggression
- Levetiracetam (Keppra)**
 - one study showed lack of efficacy

Azzouf et al. Brain Inj (1999)
Chatham-Shewether J Neuropsych Clin Neurosci (1996)
Plante D. et al. Ann PMAR (2016)

Medications - Antidepressants

Tricyclic Agents

Used commonly until SSRIs became available
Several studies show efficacy
Amitriptyline (Elavil); Imipramine (Tofranil)
drowsiness, maybe better at night
Noradrenergic agents = arousal effects, better in
hypo arousal states
Desipramine (Norpramin); Protryptline (Vivactil)
better tolerated with less side effects

Medications - Antidepressants

SSRIs

Less side effects vs TCAS (cardiac arrhythmia, decreased
seizure threshold)
Used frequently in depression and TBI
May take weeks for full effect, not helpful in acute agitation

Sertraline (Zoloft) in many case studies, mixed results in
aggression

Trazodone (Desyrel) is an SSRI with sleep cycle regulatory
effects

Kauf, R. et al. *Eram Int* (1996)

Medications - Antidepressants

Buspirone (Buspar) mixed SSRI and dopaminergic agent
Case studies show helpful
Watch seizures

Medications – Antipsychotic Agents

Haloperidol (Haldol)

Most popular Rx for immediate use in agitation
IM, IV or PO
Studies indicate poorer cognitive and motor performances
Unique and repeated low doses safer vs continuous
high doses
Greater than 19 days exposure prevented motor and
cognitive recovery

Longer Post traumatic amnesia with use
Neuropsych testing better after d/c of medication
Dyskinesia, parkinsonism, neuroleptic malignant
syndrome (not dose dependent) risks

Medications - Antipsychotics

Typical antipsychotics have a high affinity for D2 dopamine
receptor

Newer, Atypical antipsychotic agents have less affinity for
D2 and more affinity for 5HT-2A receptors, thereby
reducing side effect risks

olanzepine, clozapine, quetiapine, ziprasidone

No studies looking at these medications and long term
recovery, effects

Medications - Benzodiazepines

Main medication used for short term sedation/ agitation
management

Short acting and long acting medications in IM or PO formulations
Lorazepam (Ativan); Diazepam (Valium)

Short term use helpful, but some studies indicate slower recovery
paradoxical agitation seen especially in the elderly,
sometimes amnesic syndrome worsening agitation

TBI symptoms worsened in a small study of TBI pts given
midazolam

Lombard, L. et al. *Am J PMR* (2005)

SPECTRUM HEALTH
The Medical Group

Medications – Beta Blockers

Helpful in agitation, hyperadrenergic states, and in restlessness
Lipophilic agents more effective suggesting central action
Propranolol, Metoprolol
Off label use
Older studies indicate heterogenous results, some studies on Stroke not TBI
Hypotension, Bradycardia

Brooke, MM et al. Arch Fam&R (1992)
Greensky, RM et al. J Nerv Ment Dis (1986)

SPECTRUM HEALTH
The Medical Group

Medications

Lithium

Used in mania and bipolar disease
Mechanism of action not known
Dopamine blocking effects?
Therapeutic and toxic doses separated by small amounts
Many side effects (tremor, seizures, bradycardia)

SPECTRUM HEALTH
The Medical Group

Medications

Neurostimulants

Paradoxically increase concentration/attention thereby improving agitation
Amantadine, bromocriptine, Methylphenidate
One study with higher level evidence for Amantadine
Doses vary 50-400mg/day
Hypertension, tremor, sleep disturbances

Meythaler, JM et al. J Head Trauma Rehabil. (2002)

SPECTRUM HEALTH
The Medical Group

Medications

Hormonal Agents

One case study of Medroxyprogesterone in TBI related sexual behavior

Bitton, NR. Brain Inj (1996)

SPECTRUM HEALTH
The Medical Group

Conclusion: Approach to Agitation

Initial management

Non-medication environmental and patient/family education to remove obstacles and irritants
Look for causes not related to TBI
Low dose benzodiazepines with unstable medical problems, multiple lines/tubes (or if able consider Beta Blockers)

Continued Management

Provide treatment to enhance patient/staff/family and caregiver safety
Begin at earliest interval environmental modifications, sleep cycles and pain management

SPECTRUM HEALTH
The Medical Group

Approach to Agitation

Medications can now be used when other modifications done and alt diagnoses ruled out
Look at major symptoms to point to best medication(s) to use

Hyperadrenergia = beta blockers
Attention/Concentration deficits = neurostimulants
Severe agitation = Anticonvulsants
Pre-morbid psychiatric history = antipsychotics

Use scales/measures to monitor progress

1. Hagen, C et al. Levels of Cognitive Functioning. Post Grad Course on Rehab of TBI 1979. P. 14-6
2. Bogner, J. et al. Epidemiology of Agitation following Brain Injury. *Neurorehab* 1995;5:293-7
3. Sandel, ME et al. The Agitated Brain Injured Patient. Part 1: definitions, differential Diagnosis, and assessment. *Arch PM&R* 1996 77:617-23
4. Levin, HS et al. Behavioral Sequelae of Closed Head Injury. *Arch Neurol* 1978 35:720-7
5. Reyes RL et al. Traumatic Head Injury. Restlessness and Agitations as Prognosticators of Physical and Psychological improvements in Patients. *Arch PM&R* 1981 62:20-3
6. Fugate LP et al. Measurement and Treatment following Traumatic Brain Injury. II. A Survey of the Special Interest Group of the AAPMR. *Arch PM&R* 1997 78:924-8
7. Brooke MM et al. Agitation and Restlessness after closed Head Injury. A prospective study of 100 consecutive admissions. *Arch PM&R*. 1992;73:320-3
8. Wolf AP et al. The prevalence of Agitation and Brain Injury at Skilled Nursing facilities: a survey. *Brain Inj*. 1996;10:241-5

9. Bogner JA et al. Role of Agitation in Prediction of Outcomes after Traumatic Brain Injury. *Am J PM&R* 2001;80:636-44
10. Nott MT et al. Agitation following Traumatic Brain Injury: an Australian Sample. *Brain Inj* 2006;20:1175-82
11. Arciniegas, DB et al. (2001) Principles of Neuropsychiatry: An Introductory Approach.
12. Bogner, J. (2000). The Agitated Behavior Scale. *The Center for Outcome Measurement in Brain Injury*. <http://www.tbims.org/combivabs>
13. Corrigan, J.D. (1989). Development of a scale for assessment of agitation following traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*, 11, 261-277.
14. Rancho Los Amigos National Rehabilitation Center (11 March 2011). The Rancho Levels of Cognitive Functioning
15. Haddad and Arabi Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 2012, 20:12

16. Wiait, L. et al. Non-Pharmacological treatments for psychological and behavioural disorders following TBI: A Systematic literature review and expert opinion leading to recommendations. *Annals of Physical and Rehabilitation Medicine* 59 (2016), 31-41
17. Dikmen, S et al. Neuropsychological Effects of Valproate in Traumatic Brain Injury: a randomized trial. *Neurology* 2000. 22: 895-902
18. Massagli, TL. Neurobehavioral Effects of Phenytoin, Carbamazepine, and Valproic acid: Implications for Use in Traumatic Brain Injury. *Arch. Physical Medicine and Rehabilitation* 1991;72:219-25
19. Azouvi, P. et al. Carbamazepine in agitation and aggressive Behavior following closed head injury: results of an open trial. *Brain Inj* 1999;13:797-804
20. Chatham-Showalter, J. et al. Carbamazepine for combativeness in acute traumatic brain injury. *J. Neuropsych Clin Neurosci* 1996;8:96-9
21. Plantier, D. et al. 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*. (2016) 59:42-57

22. Kant, R. et al. Treatment of Aggression and Intability after Brain Injury. *Brain Inj*. 1998;12:661-6
23. Lombard, L. et al. Agitation after Traumatic Brain Injury: considerations and treatment options. *Am J Physical Medicine and Rehab*. 2005;84:797-812
24. Brooke, MM et al. The treatment of agitation during initial hospitalization after Traumatic Brain Injury. *Arch Physical Medicine and Rehabilitation* 1992;73:917-21
25. Greendyke, RM et al. Propranolol Treatment of assaultive patients with Organic Brain Disease. *J Nerv Mvmt Dis* 1986 174:290-4
26. Meythaler, JM et al. Amantadine to improve Neurorecovery in Traumatic Brain Injury-Associated Diffuse Axonal Injury. *J Head Trauma Rehabil*. 2002;17:300-13
27. Britton, KR. Medroxyprogesterone in the Treatment of Aggressive Hypersexual Behavior in Traumatic Brain Injury. *Brain Inj* 1998. 12:703-7