Agitation in Acute Traumatic Brain Injury

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Objectives

- Definition of agitation
- Pathophysiology of agitation
- Approach to management
- Pharmacologic options for treatment

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Case Example 1

- 24 yo male s/p MVC; initial GCS 3
- Imaging
  - CT head: bifrontal & temporal contusions, SDH, SAH
- Medications
  - Precedex, Oxycodone, Keppra, PRN Tylenol
- Sleep: unknown
- Hospital day #4: agitated, unable to wean Precedex

Case Example 2

- 20 yo male s/p motorcycle crash; GCS 3
- Imaging
  - CT head: SDH, frontal contusions
  - Right brachial plexus vs. root avulsion
- Meds
  - Phenytoin, Clonidine, Cefepime, PRN Ativan
- PE: pulse 140-150, temp 99.5
  - Pulling tubes, hitting when you touch his RUE
  - Continuous tube feeds via PEG

Definition of Agitation

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What is Agitation?

- Episodic motor or verbal behavior
  - Brooke 1992
- Subtype of delirium
  - Sandel & Mysiw 1996
- Period of aggression during post-traumatic amnesia
  - Lombard & Zafonte 2005
  - Manifested by intermittent or continuous verbal or physical behaviors
  - Identified by a score of > or = to 22 on the Agitated Behavior Scale
- Presents as a combination of behaviors
  - Stefan and Mathe 2016
  - Aggression, akathisia, disinhibition, emotional lability, motor restlessness, impulsivity, disorganized thinking, perceptual disturbances, impaired ability to sustain attention, and reduced adaptation

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Statistics

- Recent meta-analysis by Phyland et al 2001
  - 44% of patients in PTA experience agitation
- Self-limited
  - Generally resolves within 2 weeks, but can last longer
- Levin & Grossman (1978)
  - Young, aphasic
  - No difference in gender

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Why is it important?

- Increased ICP
- Removal of lines, catheters and feeding access
- Injury to self or others
- Inability to participate in therapies
- Longer length of stay in both acute care and rehabilitation

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Why does it happen?

- Multifactorial
  - Preinjury characteristics
  - Structural damage
  - Alterations in biochemistry
  - Concomitant neuro-medical and environmental conditions

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Pathophysiology of Agitation

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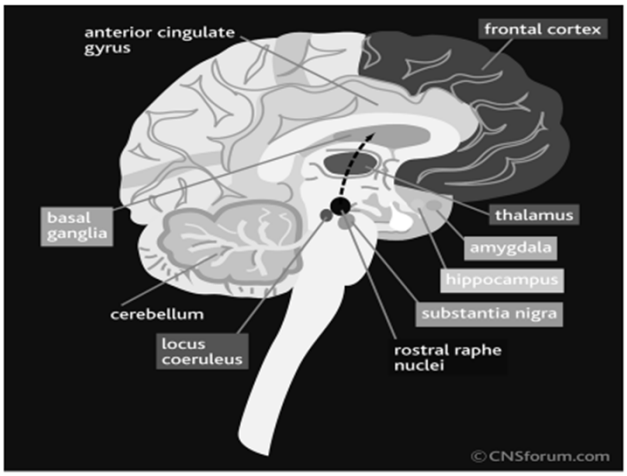

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Pathophysiology

- Damage to prefrontal cortex
  - Increased hostility, impulsivity, aggression
- Hypoperfusion in orbitofrontal and basotemporal regions
- Loss of balance between inhibitory pathways in the orbitofrontal cortex and limbic structures

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Pathophysiology

- Hypothalamus
  - Fight or Flight
- Limbic System
  - Amygdala
    - Activates or suppresses hypothalamus, input from neocortex, impulse mediation
  - Temporal cortex
    - Aggression in both ictal and interictal states
  - Frontal Neocortex
    - Modulates limbic and hypothalamic activity
      - Social judgement aspects of aggression
      - Disinhibited anger after minimal provocation

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Pathophysiology

- Neurochemical dysregulation
  - Dopaminergic
  - Noradrenergic
    - Arousal/attention
  - Cholinergic
    - Memory
  - Serotonergic

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Neurotransmitter & Aggression

- Norepinephrine
  - Elevated levels in TBI
  - Associated with aggression
- Serotonin
  - Low levels in TBI
  - Associated with fighting, impulsivity
- Dopamine
  - Prominent in mesolimbic and mesocortical regions
  - Low levels associated with decreased attention, processing speed, memory and executive function

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Approach to Management

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Approach to Management

- Systematically monitor
- Assess environment
- Consider safety
  - Avoid restraints if possible
- Look for other causes
- Medication trials
- Family education and support

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Agitated Behavior Scale

- Serial assessment of agitation
- Allows for evaluation of interventions
- 14 item scale
- High inter-rater reliability

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Agitated Behavior Scale

- Subscale scores
  - Disinhibition
  - Aggression
  - Lability
- Rating
  - 1 not present
  - 2 slight
  - 3 moderate
  - 4 extreme

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14-items (scored 1-4), total score ranges from 14 - 56

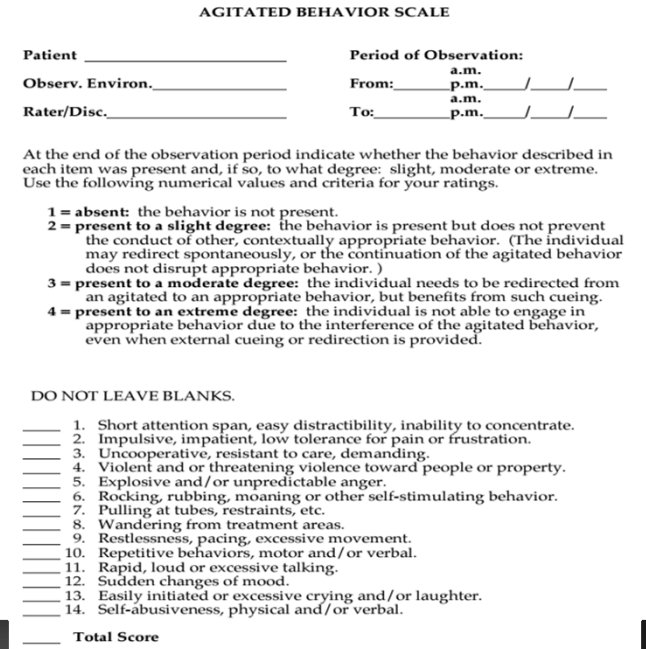
For total or converted subscale scores: (Bogner)

Scores of 21 or below: within normal limits

Scores of 22-28: mild agitation

Scores of 29-35: moderate agitation

Scores greater than 35: severe agitation



AGITATED BEHAVIOR SCALE

Patient _____ Period of Observation:

Observ. Environ._____ From:_____a.m./p.m._____/_____/_____

Rater/Disc._____ To:_____a.m./p.m._____/_____/_____

At the end of the observation period indicate whether the behavior described in each item was present and, if so, to what degree: slight, moderate or extreme. Use the following numerical values and criteria for your ratings.

1 = absent: the behavior is not present.
2 = present to a slight degree: the behavior is present but does not prevent the conduct of other, contextually appropriate behavior. (The individual may redirect spontaneously, or the continuation of the agitated behavior does not disrupt appropriate behavior.)
3 = present to a moderate degree: the individual needs to be redirected from an agitated to an appropriate behavior, but benefits from such cueing.
4 = present to an extreme degree: the individual is not able to engage in appropriate behavior due to the interference of the agitated behavior, even when external cueing or redirection is provided.

DO NOT LEAVE BLANKS.

_____ 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.

_____ **Total Score**

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Differential Diagnosis

- Infections
- Drug/Alcohol Withdrawal
- Seizures- consider temporal lobe
- Pain
- Occult fractures
- Neuroendocrine or metabolic dysfunction
  - Sodium, thyroid, adrenal, testosterone
- Hypoxemia/PE
- Medication side effects or toxicity

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Environmental Modification

- Dim lights
- Limit visitors
- Minimize nighttime awakenings
- Structure environment
- Discontinue unnecessary lines (Foley)
- Hide necessary lines (PEG)
- Avoid restraints

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Pharmacologic Options for Treatment

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Pharmacologic Management

- Depends on stage of recovery
  - ICU vs. floor
- Taper harmful medications
  - Ex: Reglan, Haldol, Dilantin
- Improve nighttime sleep
- Improve daytime arousal

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Medication Options

- Beta blockers
- Anticonvulsants/Mood stabilizers
- Benzodiazepines
- Neuroleptics/antipsychotics
- Atypical antipsychotics
- Antidepressants
- Neurostimulants

Beta-blockers

- Hyperadrenergic state
- Lipophilic vs. Hydrophilic
- Propranolol
  - Reduced intensity, but not frequency
  - Maximum dose of 420mg/day
  - Side effects
    - Sedation, hypotension, bradycardia, depression

Anticonvulsants/Mood Stabilizers

- Use especially if:
  - Complex-partial or temporal seizure control
  - Disinhibition
  - Impulsivity
- Avoid Phenytoin and Phenobarbital- more sedating
- Consider: Valproic acid (Depakote), carbamazepine (Tegretol), or gabapentin (Neurontin)

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Carbamazepine (Tegretol)

- Mechanism of Action
  - Voltage-dependent sodium channels and potassium channels
  - May suppress limbic kindling
  - Increased activity in glutamate receptors
  - Affects GABA-mediated inhibition
- Side effects
  - Aplastic anemia, agranulocytosis, hyponatremia, ataxia, nausea, sedation, skin reactions(Toxic epidermal necrolysis)
- Dosing
  - Initial dose 200mg TID
  - Therapeutic level 4-12
- Monitoring
  - Follow CBC, LFTs, vitamin D level

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Carbamazepine (Tegretol)

- Evidence for efficacy
  - Open-labeled trial with 10 participants with severe TBI- Azouvi, et al 1999
    - Lacked a control population
    - Demonstrated improvements
      - Agitated Behavior Scale, Katz Adjustment Scale and elements of the Neurobehavioral Rating Scale
    - No worsening of scores on the Mini-Mental Status Examination
  - Case series by Chatham-Showalter 1995
    - 7 patients with acute TBI(medication started between 5 and 21 days after injury)
    - Improvement within 4 days on doses of 400-900mg
    - No objective measures of agitation

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Valproic Acid (Depakote)

- Mechanism of Action
  - Delays repolarization of sodium channels
  - Increases GABA activity
  - Anti-kindling effect on limbic system
  - Animal Models
    - Reduces cortical glutamate release, enhances the activity of GABA, antagonizes N-methyl-D-aspartate receptor, and increases dopamine release in the prefrontal cortex
- Side effects
  - Hepatotoxicity, somnolence, thrombocytopenia, weight gain
- Dosing
  - Initial dose: 250mg TID
  - Therapeutic level 50-100
- Monitoring
  - Follow ammonia levels, CBC, hepatic function, vitamin D levels
- Benefits- Comes in different formulations-Tablet, liquid, sprinkles, IV

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Valproic Acid (Depakote)

- Evidence for efficacy
  - Numerous studies have shown efficacy and safety of VPA in ameliorating alcohol withdrawal syndrome
    - Common co-morbidity in patients with TBI
  - Dikmen et al 2000
    - Randomized, double-blinded trial of patients with TBI demonstrated no adverse effects on cognition
  - Most commonly prescribed medication for agitation among TBI specialists
  - Chatham-Showalter and Kimmel 2000
    - Retrospective chart review of 29 patients
      - Mean dose of 1257mg/d, 62% were judged to have improved
      - Mean dose of 714mg/d, 28% of the patient had rapid resolution of symptoms
  - Wroblewski et al 1997 – 5 patients
    - VPA had a beneficial effect on behavior
    - Improvement noted within 1-2 weeks
    - Doses ranged from 750-2250mg

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Gabapentin(Neurontin)

- Mechanism of Action
  - Blocks voltage-dependent calcium channels
  - Modulates excitatory neurotransmitter release
- Side Effects
  - SJS, renal failure, dizziness, sedation
- Dosing
  - Initial dose: 100mg q8h; can use qHS dosing for sleep
- Monitoring
  - Follow creatinine
- Especially useful if:
  - Neuropathic pain
  - H/O alcohol misuse

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Benzodiazepines

- Enhance central GABA activity
- Used for “acute” management
- May exacerbate confusion
  - Anterograde amnesia, paradoxical agitation
- Decrease REM sleep

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Neuroleptics/antipsychotics

- Block central dopamine type 2 (D2) receptor
- Side effects
  - Extrapyramidal and dyskinetic reactions
  - Prolongs PTA (Rao 1985)
  - Slowed motor recovery
- Psychotic features or h/o psychosis
- Typical vs. atypical

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Antidepressants

- SSRI's
  - Levels of 5-HT are decreased after TBI
  - Ex: Citalopram, Prozac, Zoloft

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Sertraline

- Mechanism of Action
  - Selectively inhibits serotonin reuptake
- Side Effects
  - Nausea, diarrhea, insomnia, fatigue
- Dosing
  - Start at 25mg/day, increase by 25mg per week to max of 200mg
- Monitoring
  - Mood/behavior

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Sertraline

- Evidence of Efficacy
  - Kant et al 1998- Prospective open label trial
    - 13 persons with TBI and post-traumatic aggression and irritability
    - 8 week trial of sertraline
    - Reduced aggression and irritability, no effect on depression
  - Fann et al 2000
    - Single-blind placebo controlled trial
    - 15 outpatients after TBI with severe depression
    - Noted decreased depression and aggression
  - Meythaler et al 2001
    - Randomized, placebo-controlled trial
    - 11 patients with DAI in acute inpatient rehabilitation
    - Treatment with sertraline
    - No difference in cognition, alertness or agitation

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Promoting Nighttime Sleep

- Why does sleep matter?
  - Impacts on rehabilitation and daily activities
  - Unable to stay awake/participate in therapies
  - Impacts on psychopathology and pain
  - Depression/irritability more prevalent when sleep is poor
  - Potential impacts on cognition
  - Poorer sustained attention
  - Slower average reaction times

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Pharmacologic Treatment Options

- Benzodiazepines
  - Animal studies-impaired neurological recovery
  - Side effects- dizziness, impaired memory, altered psychomotor skills
- Nonbenzodiazepines
  - Zolpidem, zaleplon, zopiclone
  - Fewer adverse effects
- Trazodone
- Melatonin
- Others

Optimizing Daytime Arousal

- Aminergic/dopaminergic agonists
  - Amantadine, bromocriptine, methylphenidate, modafinil
- Acetycholine esterase inhibitors
  - Aricept

Amantadine

- Dopamine agonist & NMDA receptor antagonist
- Use especially if:
  - Disinhibition, lability, impulsivity
- Side Effects- Dose related!
  - Hypotension, confusion, hallucination, seizure
  - Creatinine clearance is critical
    - 30-50: 100mg/day
    - 15-29: 100mg every 48 hours
    - <15: 200mg every 7days

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Ritalin/Methylphenidate

- Dopamine agonist (prevents reuptake)
- Use especially if:
  - Poor arousal, attention, distractibility, or processing speed
- Reduces aggression in ADHD & TBI populations with doses of 10-60mg/day
- Side effects
  - Tachycardia, interaction with Zyvox

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Case Example 1

- 24 yo male s/p MVC; initial GCS 3
- Imaging
  - CT head: bifrontal & temporal contusions, SDH, SAH
- Medications
  - Precedex, Oxycodone, Keppra, PRN Tylenol
- Sleep: unknown
- Hospital day #4: agitated, unable to wean Precedex

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Case Example 1

- Review medications, labs and co-morbidities
- Consider transition from Keppra to Depakote
  - Especially if seizure meds are needed
- Start gabapentin 100mg VT q8h(if renal function ok)
- Consider initiation of propranolol 10mg VT q6h for tachycardia and agitation
- Continue scheduled pain medications
- Consider initiation of trazodone for sleep

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Case Example 2

- 20 yo male s/p motorcycle crash; GCS 3
- Imaging
  - CT head: SDH, frontal contusions
  - Right brachial plexus vs. root avulsion
- Meds
  - Phenytoin, Clonidine, Cefepime, PRN Ativan
- PE: pulse 140-150, temp 99.5
  - Pulling tubes, hitting if you touch RUE
  - Continuous tube feeds via PEG

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Case Example 2

- Review medications, labs and co-morbidities
- Fever work-up: labs, cultures, dopplers
- Taper or transition Dilantin to Depakote
- Transition clonidine to propranolol 10mg q6h to address both agitation and tachycardia
- Treat pain (?RSD/neuropathic)-gabapentin
- Change to bolus tube feeds
  - use abd binder to prevent removal of tube

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Summary

- Transient
  - Often need to treat in order to decrease length of stay and prevent injury
- Sleep is key!
- Aim for daytime arousal!

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