TBI-BH ECHO

Traumatic Brain Injury – Behavioral Health ECHO

UW Medicine | Psychiatry and Behavioral Sciences

Treatment of Anger, Irritability and Aggression following TBI

(Behavioral Intervention)

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Speaker disclosures

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Objectives

1. Describe negative attribution bias & give brief overview of its relationship to anger and aggression after TBI

2. To describe factors that increase risk for negative attribution bias after TBI

3. To describe a behavioral intervention that targets negative attributions as a mechanism for treating anger and aggression after TBI

What are negative attributions?

Appraisals of others' actions (trying to understand cause)

1. Intent: were actions intentional?
2. Hostility: were actions hostile/ mean?
3. Blame: were actions the cause for a negative outcome?

Attribution-Emotion Theory

Negative Attributions of behaviors → Emotional Response

Intent, hostility, blame → Anger

Negative Attribution Bias (NAB)

- Distorted/disproportionate to situation
- > Norm
- No benefit of the doubt
- Associated with cognitive and social inferencing deficits
- Associated with social misconduct, aggressive behaviors, domestic violence

Negative Attributions in TBI

1. Are they associated with anger and aggression?- yes
2. Are people with TBI prone to more negative attributions (negative attribution bias)? -yes
3. What are the risk factors? Poor SI, trait aggression, Hispanic ethnicity
4. Can we reduce negative attributions after TBI with treatment, if so, does that reduce anger and aggression (& emotion dysregulation)? yes

Case Presentations

NeuroRehabilitation 39 (2016) 153–162
DOI:10.3233/NRE-161347
IOS Press

Case Study

Perspective training to treat anger problems after brain injury: Two case studies

Jill Winegardner[a,*], Clare Keohane[a], Leyla Prince[a] and Dawn Neumann[b]
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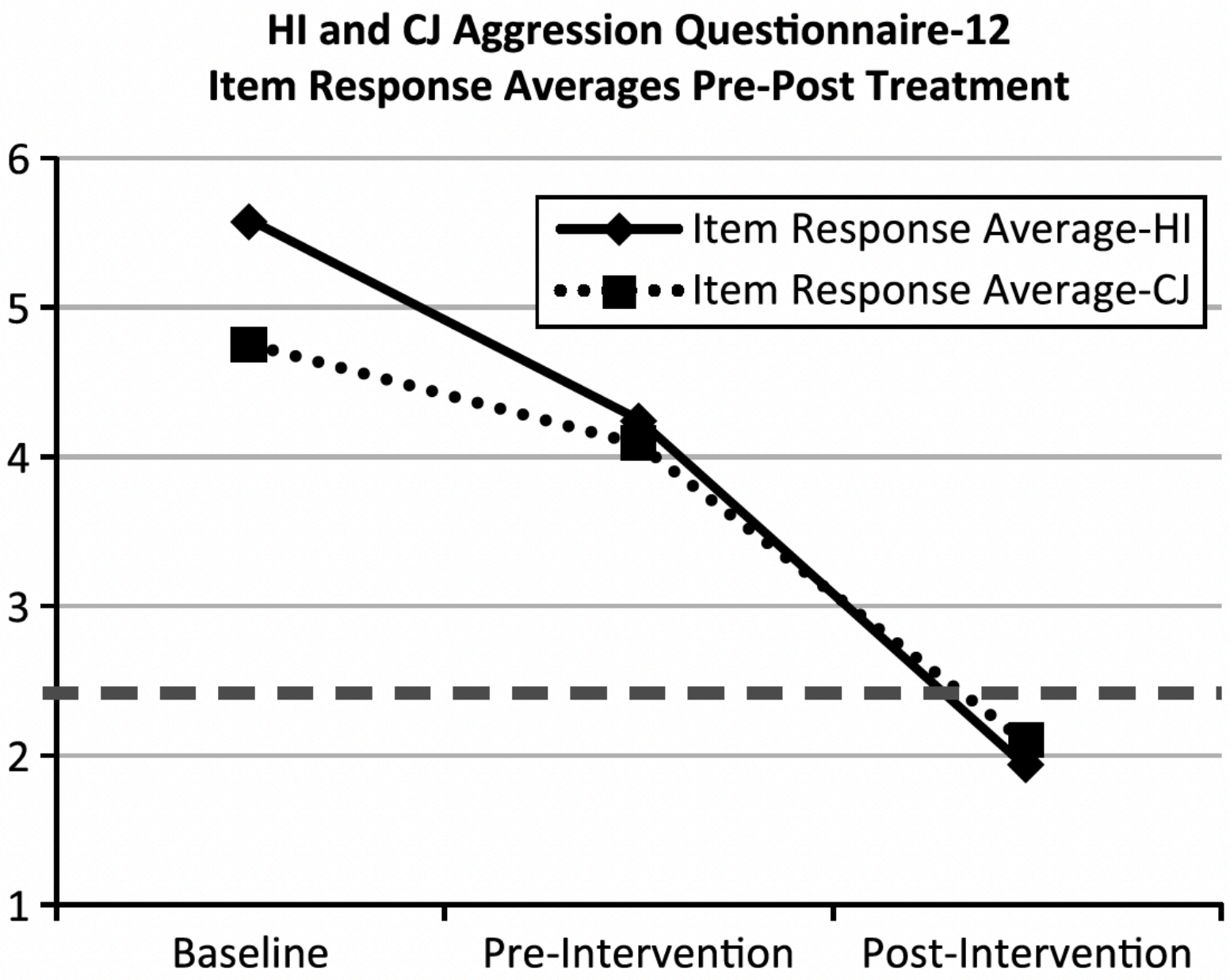
CJ

- 37 year-old male
- severe TBI at age 13
- No rehab services prior to entering the programme
- Right frontal lesion
- Rehab referral prompted by GP due to expecting a child and concern that anger and hostility would be detrimental to the child.
- Remote hx of alcohol abuse.
- Good physical recovery post-TBI; lived independently
- Difficulty with attention and memory
- Problems in controlling his emotions (anger),
- Expelled from school for behaviour problems
- Unable to sustain employment for more than a few months at a time due to interpersonal conflict.
- During his initial assessment, he said “I think people are talking about me and this winds me up.”

HI

- 46-year-old male sustained a subarachnoid haemorrhage during neurosurgical intervention at age 35.
- Married and a father of two children w/ autism.
- Severe anxiety, depression, fatigue, unable to work competitively, and limited social participation.
- Severe marital discord with the possibility of dissolution
- Cognitive deficits: divided attention, organizing, planning and self-monitoring in unstructured situations. Impulsive and disinhibited.
- Earlier psychological assessment:
  - “trying to keep calm and away from stress and paranoia”,
  - “quick to anger,” “emotions build up too much” (verbal aggression),
  - says things that upset others; ‘blunt’,
  - rumination, especially with an angry or vengeful theme.


HI and CJ Aggression Questionnaire-12
Item Response Averages Pre-Post Treatment
6
5
4
3
2
1
Item Response Average-HI
Item Response Average-CJ
Baseline
Pre-Intervention
Post-Intervention

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Qualitative semi-structured interviews

CJ: "I've noticed a big difference definitely. Perspectives that was a good one, I didn't like to put myself into someone else's shoes."

HI's wife Dottie: "And yes now you've saved our marriage, number one, but you really did because it was getting to that point where, you know something was going to have to happen, it was getting unbearable, and now we have a father, a husband someone who listens, who doesn't just think of himself anymore he thinks of other people, how they might feel.. and yes, we're all so much more ~~relaxed and a proper family for the first time ever.~~"

HI: "I'm trying to get in touch with my dad again, because I can see his point of view on that…. I've put myself in his shoes to see how it is."

THE Oliver Zangwill CENTRE

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Can Negative Attributions be treated and reduce Anger, Aggression (& Emotion Dysregulation)?

Journal of Emotion and Psychopathology
2023, Vol 1, Issue 1, 72-89
https://doi.org/10.55913/joep.v1i1.5

Intervention to Change Attributions that are Negative (ICAN): A Feasibility Study on Reducing Anger After Brain Injury

Dawn Neumann[1,2], Samantha Backhaus[1,2], Jeong Hoon Jang[3], Sruthi Bhamadipalli[3], Jill Winegardner[4], Beth Helton[2], Flora M. Hammond[2]

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[2]Rehabilitation Hospital of Indiana, USA
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[4]University Hospitals Cleveland Medical Center, USA

ICAN Intervention

6 two-hour group sessions 1/week

- Brief psychoeducation anger and attributions (Session 1)

1. **Review ICAN core principles**
   - ICAN put myself in someone else's shoes
   - ICAN change my perspective
   - ICAN change how I think about others' actions
   - ICAN change how I feel about others' actions
   - ICAN change how angry I get about others' actions
   - ICAN change how I react to others' actions

2 co-facilitators:
1 Neuropsych
1 SLP

ICAN Intervention- Role Play (Video Scenarios)

- Watch video of scenario
- Brainstorm reasons for behavior
- Select most benign response
- Role play scenario assuming benign intent

Perspectives Positioning Exercise

Produce personal examples of situations in which the motives of others were unclear or unknown, such as someone pulling into a parking space ahead of you

- Participant asked to sit in the chair of each person in the scenario:
  - Chair 1=self;
  - Chair 2=other: take the perspective of that person.
- Express thoughts & feelings from both perspectives

Results (Pre/post outcomes (n=21)

Outcome Measure	Result
Intent attributions (scenarios)	☺
Hostility attributions (scenarios)	X
Blame attributions (scenarios)	☺

RHI Youtube Interview of ICAN participant

- Male in late 30's who had severe TBI 8 prior to participating in ICAN

https://www.youtube.com/watch?v=v-OcTZaA7pI&list=PLHJIOLj6cQ4m7jQomhtFY-nF23nONc6_w

2:30-3:00
3:25-4:19
7:10-7:49
10:40-11:01

Power of Pause

Managing Anger & Irritability After TBI

The power of the PAUSE

Anger and irritability are common side effects of a brain injury. They're heightened when we view other's actions through a negative lens: "That waiter spilled soup on me on purpose" or "That stranger intentionally stepped on my foot."

Here are some strategies to help reduce anger, irritation, and aggression. Sometimes it helps to **PAUSE** before you react:

Put yourself in the other person's shoes.

Ask yourself calmly why the other person did what they did. Were they really trying to harm you?

Understand that there may be a cause for the other person's behavior that isn't related to you.

See alternative and innocent reasons that might account for the other person's behavior.

Expect that most people are doing their best and try to give others the benefit of the doubt.

This information is made possible by a partnership between Indiana University and WETA/BrainLine.
For more information, please visit **Brainline.org/brain-injury-and-anger**

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brainline.org

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Evidence for Pharmacologic Treatment of Irritability and Aggression following TBI

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- There are no medications FDA approved for brain injury or irritability/aggression; thus, all agents discussed will be “off-label” uses.
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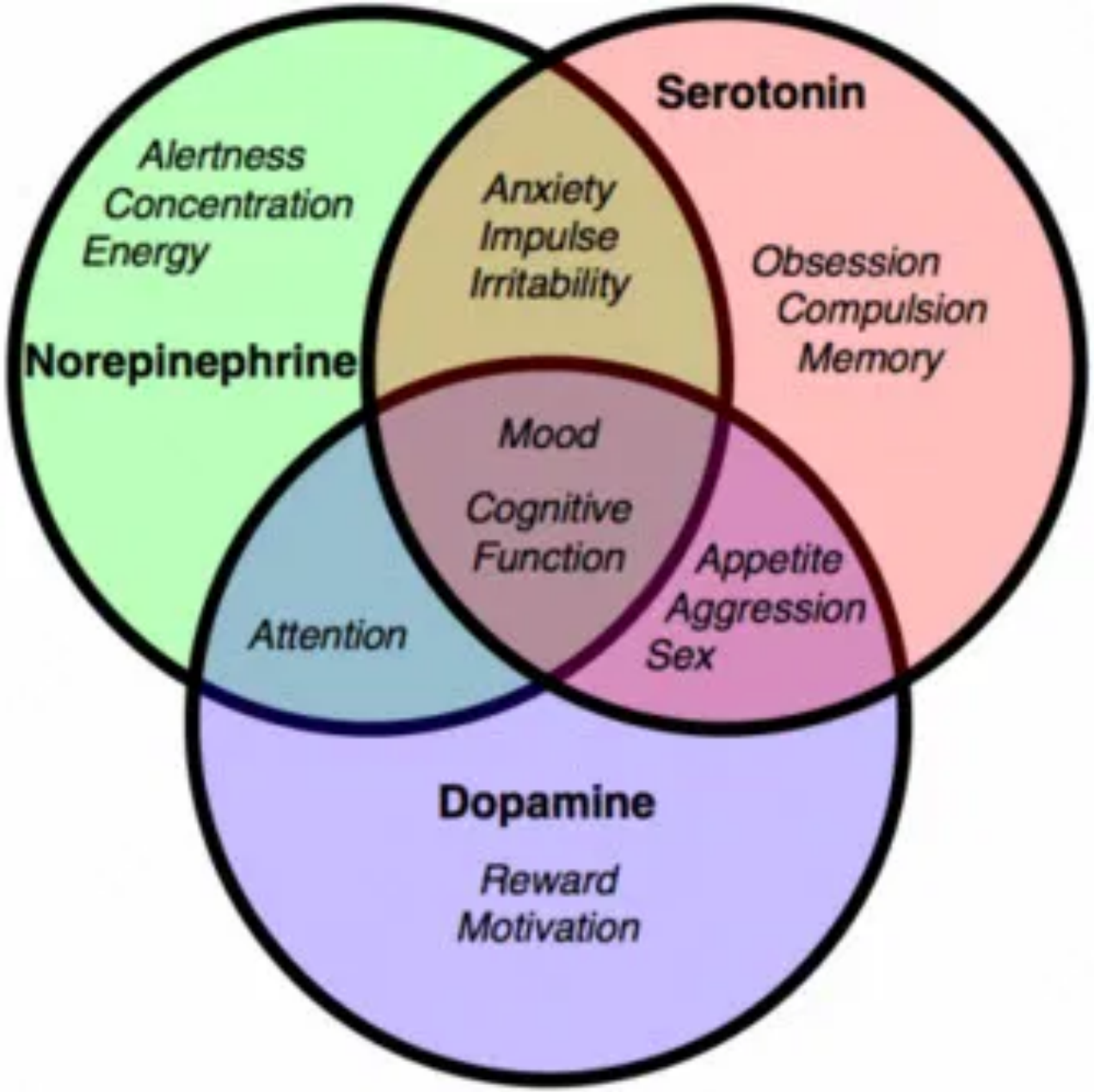
Neuromodulation of Aggression Framework in Psychiatric Disorders

Pharmacologic Class	Bottom-up Limbic Drive signal/trigger amygdala; insula	Brake suppression/ regulation orbital frontal cortex; anterior cingulate gyrus
Serotonergic (SSRIs & buspirone)		↑ Frontal inhibition
Stimulants		↑ Frontal inhibition
Atypical neuroleptics	↓ subcortical dopaminergic stimulation	↑ Frontal inhibition
Beta-blockers	↓ limbic noradrenergic blockade	
Anticonvulsants	↓ limbic irritability	
Opiate antagonists	↓ opiates	

Siever LJ: Neurobiology of Aggression. Am J Psychiatry 2008;165:429-442.

Role of Neurotransmitters in Behavior



Complex interactions simplified

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Evidence-based Reviews of BI Aggression Treatment

Medication	Fleminger 2003 ABI	Warden 2006 TBI (LOE)	ABIKUS 2007 ABI (consensus)	ERABI 2012 ABI (LOE)
Beta-Blockers	4 RCT	**Guideline**	Recommended **A**	**Level 1**
Methylphenidate	1 RCT	Option	Recommended **B**	**Level 2**
SSRIs		Option	Recommended **B**	No evidence
TCA		Option (amitriptyline & desipramine)	Recommended **B**	Level 4 (Trazadone)
Valproic Acid & Divalproex		Option	Recommended **B**	Level 4 (Divalproex)
Carbamazepine *	(1 RCT)	Option		Level 4 evidence
Amantadine *	1 RCT (now 3 RCTs)	Option		Not helpful?/uncertain; LOE 2 children
Buspirone *	(1 RCT pending)	Option		Level 5
Neuroleptic			Avoid (C)	Haldol not negative (LOE 4)?; Methotrimeprazine safe & effective (4)
Lithium carbonate		Option		Level 4 evidence

- Trial and error
- Clinician experience
- Literature in other diagnostic populations
- Little research to support or refute
- Several case studies, open-label case series; few RCTs
- Likely publication bias of + results or observations

Beta Blockers

- **GUIDELINE/ LEVEL 1 EVIDENCE: 4 RCTs in BI (lipophilic BB)**
  - Hydrophilic (tx into CSF) not studied in BI (nadolol non-TBI aggression)
- Limitations: small N, mixed BI diagnoses, short f/u
- **Propranolol: 420-520 mg/day**
  - Greendyke 1986a: Propranolol up to 520 mg/day; crossover design; n = 9; mixed violent BI pop; significantly **fewer assaults**
  - Brooke 1992: Propranolol 420 mg/day; severe TBI; n = 21; significant **reduction in intensity, but not frequency**
- **Pindolol: 60 – 100 mg / day**
  - Greendyke 1986b: Pindolol **60-100 mg/day;** crossover design; n = 11; mixed violent BI pop; significantly **fewer assaults & other aggression ratings**
  - Greendyke 1989: Pindolol **20 mg/day**; crossover design; n = 13; mixed violent BI pop; Trend but **NOT** statistically significant (**lower dose)**

May lower BP, pulse, peak aerobic performance, cause fatigue & depression

Methylphenidate

- Inhibits postsynaptic reuptake of dopamine
- Activates brainstem reticular activating system & cortex
- **Reduces aggression (10mg-60mg/day) in ADHD**
- **TBI population (1 RCT):**

  Mooney 1993: 30 mg/day

  - N = 38 men with moderate-severe TBI
  - **Reduces aggression:** improvement in KAS belligerence, State Trait Anger Scale & POMS anger/hostility factor
  - **Lacks details** re confounders, randomization, a priori responder definition, study entry not based on anger symptoms

Amantadine

- Dopamine agonist & NMDA receptor antagonist
- **3 RCTs:**
  - **1 acute agitation (Schneider 1999)**
  - **2 chronic irritability & aggression (Hammond 2013 & 2015)**

Amantadine cannot be dialyzed. Adequate renal clearance needed for amantadine!!

Amantadine for Acute Agitation

- **Schneider 1999:**
  - RCT, double-blind, placebo-controlled trial
  - **n = 10**
  - 6 week crossover ABA with 2 week blocks
  - 18-55 years old; TBI
  - Initial dose: 100 mg/day; final dose: **300 mg/day**
  - **No significant difference** between amantadine & placebo on neurobehavioral rating scale & neuropsych tests (orientation, attention, executive function; memory)
  - **No data for means & SD provided**

Amantadine for Chronic Irritability & Aggression

Hammond, et al. (2013):

- Single site
- RCT placebo-controlled ITT
- **N = 76 (38 each group)**
- 100 mg every AM & 12 Noon
- > 6 months post closed TBI
- Neuropsychiatric Inventory – Irritability (NPI-I) Domain > 2
- Creatinine clearance ≥ 60
- Assessments at **Days 28**
  - NPI observer > 2 point change
  - Did not collect participant ratings

Treatment Group	Change in NPI Irritability (Primary)	NPI Irritability > 2-point change	Change in NPI-Aggression
Amantadine n=38	-4.3	81%	-4.65
Placebo n=38	-2.6	44%	-2.46
p-value	p=0.0085	p=0.0016	p=0.046

- Change was among those with mod-severe irritability NPI ≥ 6
- No difference in AE's

Hammond (2015 & 2017): Multi-site Amantadine (n=168)

	Irritability				Aggression		Global
	Observer	Observer	Participant	Participant	Observer	Participant	Clinician
	NPI-I Mean Change	NPI-I >3 point change	NPI-I Mean Change	NPI-I >3 point change	NPI-A Mean Change	NPI-A Mean Change	Mean CGI
Day 28:							
Amant	-3.69	66.3%	-2.56	51.3%	-238	-2.26	3.17
Placebo	-3.58	66.7%	1.87	40.5%	-1.28	-1.57	2.94
P-value	0.961 Primary	0.955	0.349	0.166	0.047	0.223	0.2410
Day 60:							
Amant	-4.68	74.7%	-3.47	60.5%	-3.01	-2.63	3.01
Placebo	-3.80	68.3%	-2.29	48.8%	-1.61	-1.61	2.65
p-value	0.210	0.378	0.035*	0.137	0.025	0.025	0.0354

Clinician Ratings:

- More in placebo group worsened, though not statistically signifant
- NNTB and NNTH calculations demonstrated modest odds of benefit compared to low risk of harm.

* Participant irritability Holm-Bonferroni correction: not significant

- Not a "negative study": both groups improved (67% placebo)
- Null hypothesis cannot be rejected
- Cognition did not improve
- No statistically significant differences in AEs

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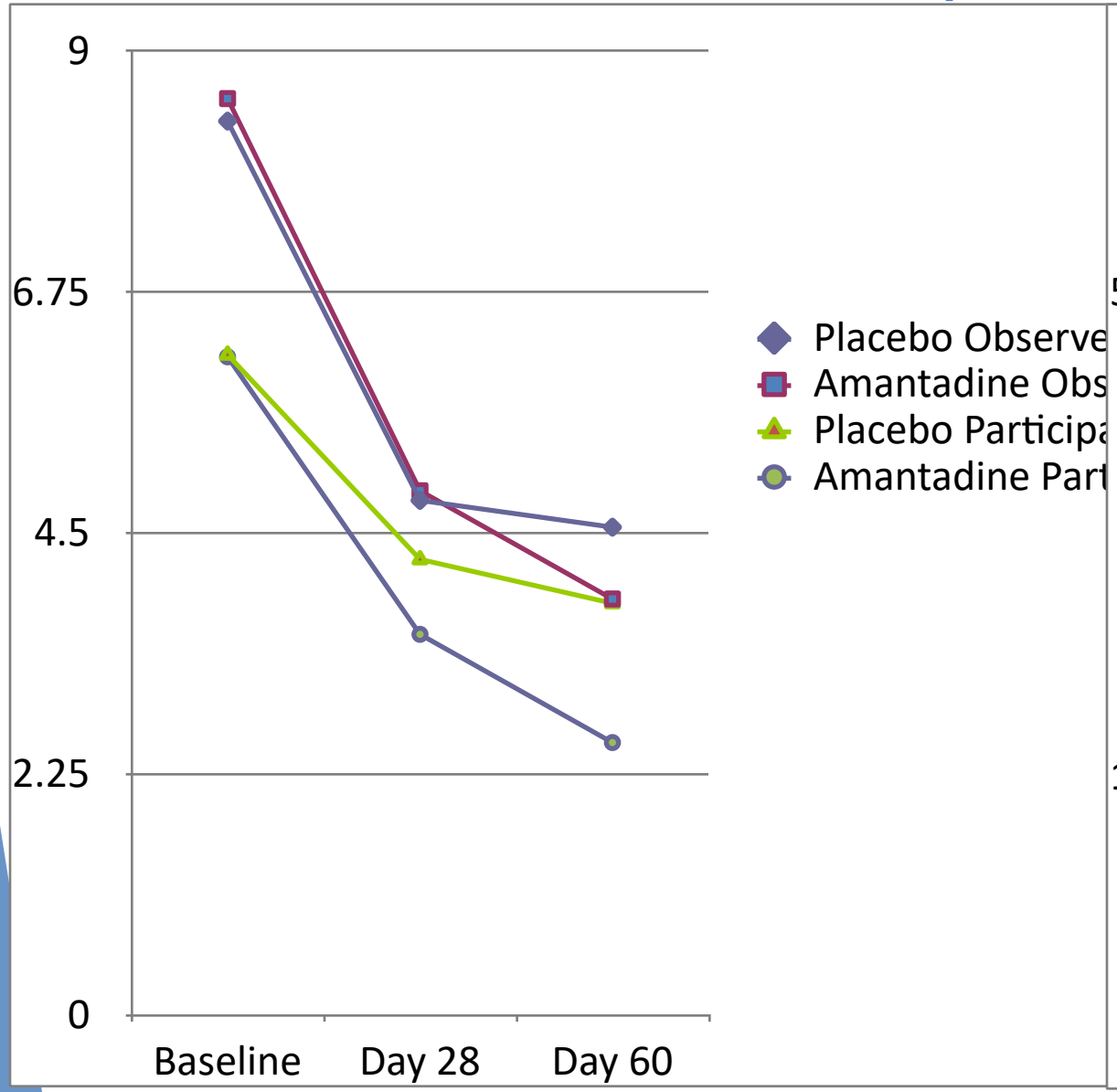
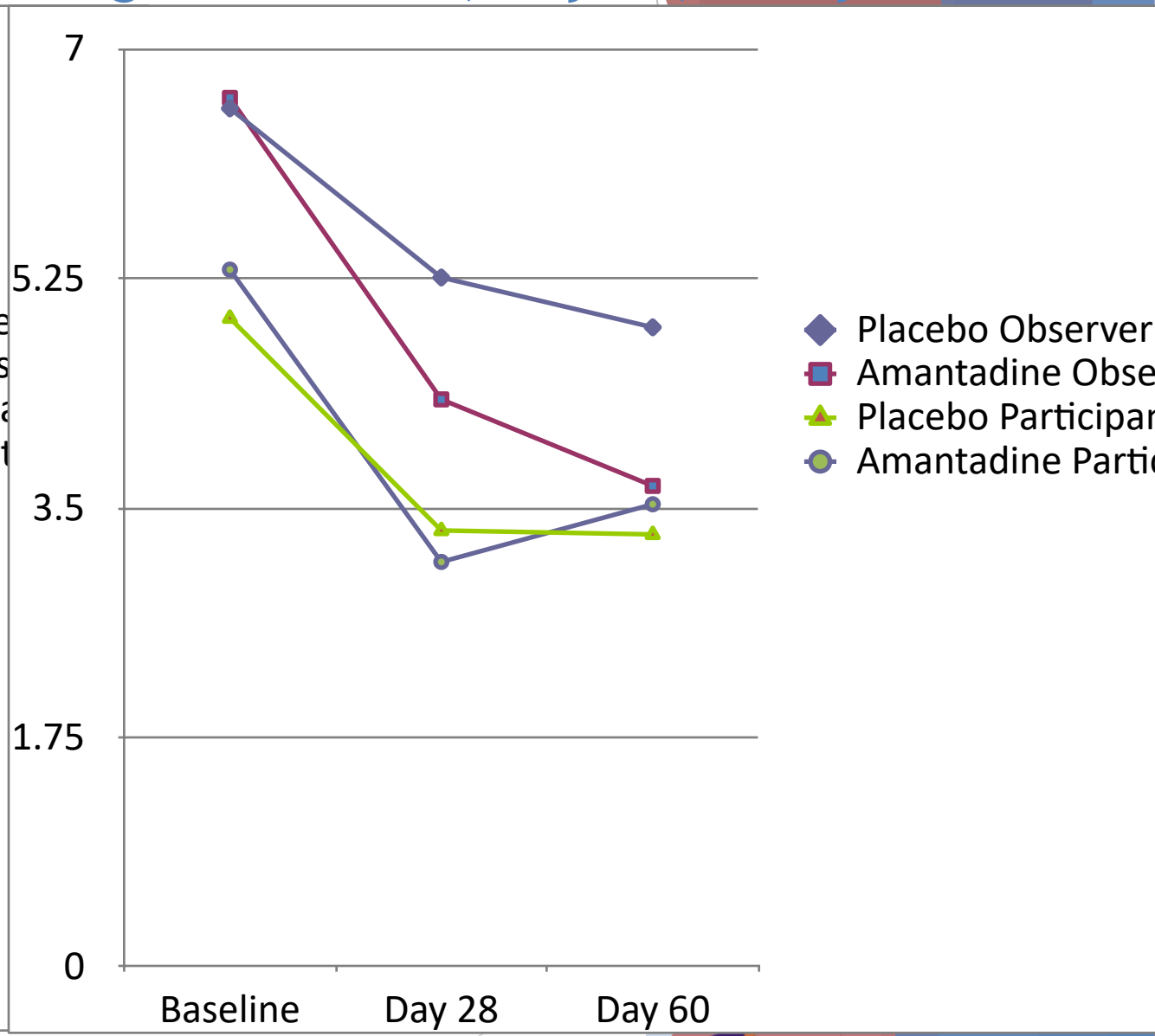
Mean Observer & Participant ratings at Baseline, Day 28, & Day 60



NPI-Irritability



NPI-Aggression

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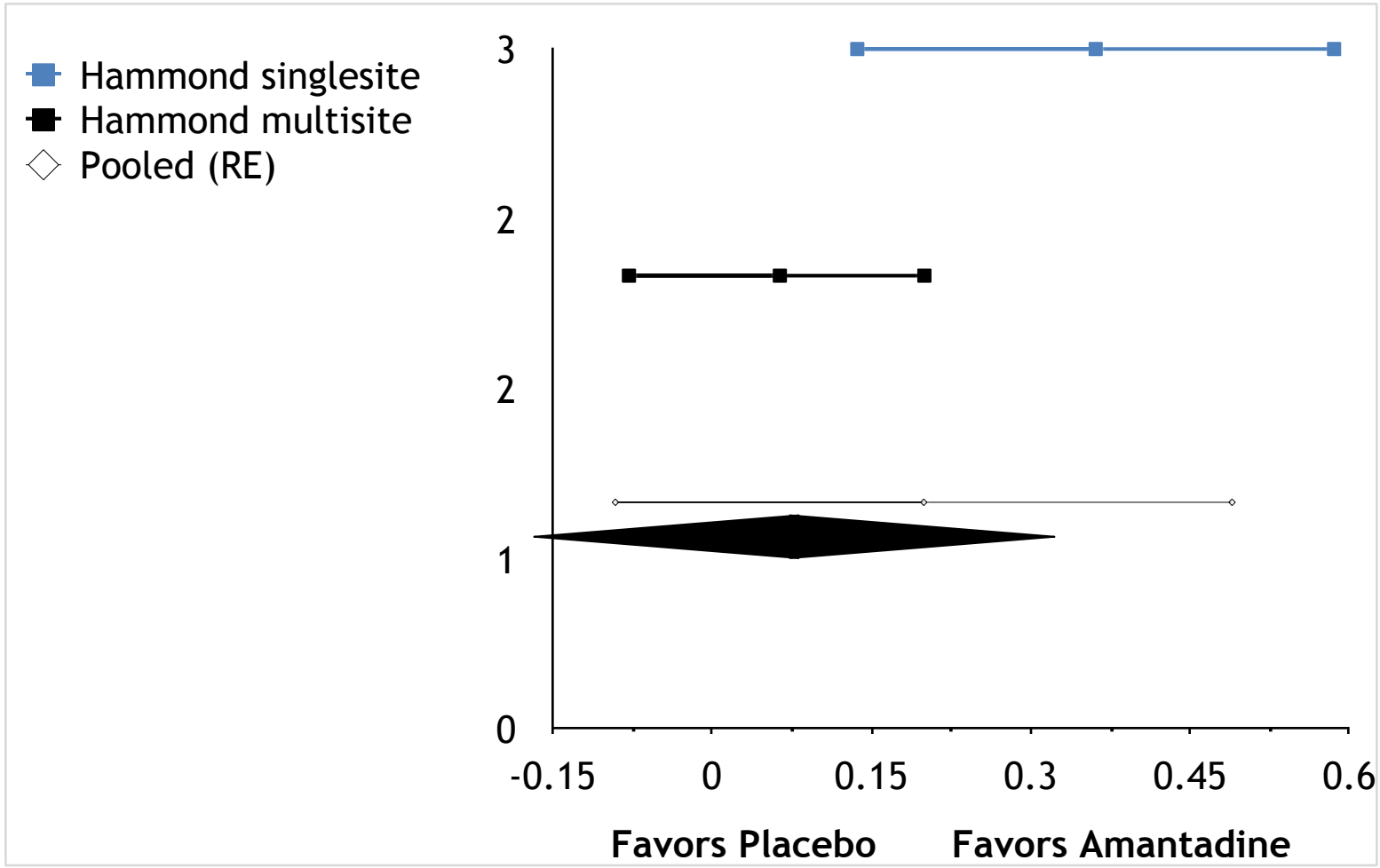
Meta-analysis Favors Amantadine



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Antidepressant agents

- SSRI
  - **Case series (Kant, Kim, Fann)**
    - **Sertraline 25-200 mg/day**
    - **Paroxetine 25 mg/day**
- Tricyclic antidepressants
  - Poorly understood mechanism
  - inhibits re-uptake NE & SE
  - Affinity for muscarinic & histamine H1 receptors to varying degrees
  - **2 *open* RCTs *acute* agitation: (Jackson 1989 AB only; Mysiw 1988)**
    - **Amitriptyline or Desipramine (<150 mg) & Amitriptyline**
  - **No studies for chronic irritability or aggression**

Anticonvulsants

- High side effect profiles
- Thought to decrease limbic irritability
- Carbamazepine:
  - Tricyclic properties
  - Dose-related increases in extracellular serotonin concentration
  - **3 case studies/series**
  - **RCT (Hammond, et al.): up to 800 mg/day**
- Valproic acid:
  - **Case reports**
  - **750-2250 mg/day**
- Lamotrigine
  - **2 case studies/series**
- Other agents: No literature in brain injury

Carbamazepine for Chronic Irritability/Aggression

Hammond (2021):

- N = 70
- **Substantial improvement** observed for the majority of participants in both the placebo and CBZ (800 mg daily) groups with no statistically significant group differences based on observer and participant ratings. Clinician ratings in therapeutic analyses suggest benefit.
  - Large placebo effects may have masked detection of differences
- **Greater AEs observed** (**hypersomnia and dizziness**) with CBZ than placebo
- **Take home: Clinician ratings favored CBZ over placebo** with supportive NNT and NNH data. CBZ should remain a treatment option for experienced brain injury clinician.

Mood Stabilizers

- Lithium
  - Severe aggression associated w/ major depression & bipolar
  - 0.4-1.4 mEq/L
  - Potential neurotoxicity: Monitor levels every 2 months
  - **Case reports & 1 case series (Glenn 1989)**

Anxiolytics

- Buspirone
  - Affinity for D(2)-dopamine receptors (both an antagonist & agonist) & 5-HT(1A) receptors (agonist)
  - Does not block the neuronal reuptake of monoamines
  - Does not lead to changes in receptor density in models tested
  - **Open case series & case reports (10 – 60 mg/day)**
  - **RCT Hammond, et al. up to 60 mg/day: in progress**
- Benzodiazepams
  - Enhance GABA receptor function
  - Concerns over chronic use, yet frequently used clinically
  - **No studies**

Antipsychotics

- Particularly, atypical neuroleptics with prominent 5-HT2A antagonism
- May need acutely if **risks > benefits**
- Start low; titrate; promptly taper when able
- Concerns of side effects with chronic use
- **Quetiapine (Seroquel) open case series (Kim, et al 2006)**

Pharmacologic Evidence Summary

Evidence

- Strongest evidence:
  - B-blockers (high dose)
  - Amantadine
  - Methylphenidate
- Weaker evidence:

  (lack of studies)
  - Valproic acid
  - CBZ
  - SSRI
  - Buspirone
  - TCA
  - Lithium
  - Nuedexta? (results pending)

Target-based approach

- Deficit in attention / processing speed: catecholaminergic/methylphenidate
- Memory impairment: cholinergic
- Psychosis: Atypical antipsychotic (quetiapine, olanzapine, aripirazole)
- Tachycardia/htn/migraine: B-blocker
- Seizures: CBZ, oxy CBZ, VA, lamictal
- Pain: CBZ, gaba?, TCA
- Mania: CBZ, VA, lithium
- Anxiety: buspirone, SSRI
- Lability/PBA: SSRI, CBZ, VA, TCA, Nuedexta
- Depression: SSRI, TCA
- Insomnia: trazodone

Summary

- Look for treatable **causes/contributors**
  - Medical, psychiatric, **medications**, social, environmental, cognitive & sensory processing issues
- Consider treatments
  - Non-pharm treatment: perspective taking; CBT; multicomponent
  - Combine pharmacologic & non-pharm approaches
  - Medication selection
    - Consider target, side effects, drug interactions & dosing
    - Trials of neurotransmitter imbalance restoration
    - Aim to decrease limbic drive &/or increase cortical control
  - Trial & error
  - May require a combination of agents
  - Start low, go slow
- Research directions: understand mechanisms, develop tx, better measures, & strategies for non-specific effects
  - Sequential Parallel Comparison, Placebo run-in, simplified assessments, fewer sites, prospective baseline, longer study duration, dose titration

Case Presentation

- 29 yo male s/p severe TBI several years prior with spastic hemiplegia, dysarthria, cognitive impairment, fatigue, & irritability
- Experiencing confusion and irritability: PCP stopped his methylphenidate.
- Past 4 – 6 months: Family reported difficulty with emotional control and behavior, crying, inconsolable, suspicious of girlfriend (first girlfriend). Described as worst behavior since injury
- No evidence of sadness or depression
- No other new medication changes. No EtOH or drug use.
- PMHx: DVT, depression
- Discussed medication may not be the solution
- Was not sure if caused by stopping the methylphenidate
- Considered: restarting methylphenidate, trial: amantadine, carbamazepine, Nuedexta, buspirone
- Nuedexta too expensive even with patient assistance
- Amantadine 100 mg bid
- Carbamazepine 200 mg bid – too sedated; Carbamazepine 100 mg bid –excellent control; now 200 bid
- Amantadine since discontinued without worsening

Thanks

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Go one, go low, go slow

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