



NEURO
INSTITUTE

Continuing Education for Rehabilitation Professionals



Psychopharmacologic Approaches to Attention, Alertness, and Initiation after Brain Injury

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DISCLOSURES

- Staff Psychiatrist, Spaulding Rehabilitation Hospital, Charlestown, MA
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- Advisor, Traumatic Brain Injury Model Systems grant, National Institute on Disability, Independent Living, and Rehabilitation Research, U.S. Dept. of Health and Human Services

AREAS COVERED



- Why attention, alertness, & initiation?
 - All foundations to cognition and behavior
 - Basic to everyday functioning
 - Tend to be affected by same medications

LOOK FOR SYMPTOM'S UNDERLYING CAUSE

- Pre-injury disorders
- Medical disorders
- Sleep disorders
- Sensory or motor disorders
- Medication-adverse effects
- Reactive: depression, anxiety
- ABI-provoked psychiatric disorders: depression, anxiety, psychosis
- Neuropsychological disorders

LOOK FOR SYMPTOM'S UNDERLYING CAUSE



- Symptoms can fool you
 - e.g., Abulia/apathy can be a symptom of depression or be neurologically-based
 - e.g., Aggression/agitation-can be provoked by under-arousal, poor initiation, depression, and/or disinhibition

ATTENTION, ALERTNESS, AND INITIATION: NON-PHARMACOLOGIC TREATMENTS

- Optimize medical condition
- Treat sleep disorders
- Cognitive rehabilitation
- Exercise
- Diet
- Meditation
- S.A.D. lights (Sinclair et al, 2014)
- Transcranial electrical or magnetic stimulation

CASE REPORT

- A 23 y.o. male with TBI is transferred to the rehabilitation unit 10 days after injury. He is restless and paces up and down the halls, but is not aggressive. He is up much of the night and sleeps on and off during the day. He is on quetiapine 50 mg 2x/day, levetiracetam 750 mg 2x/day and amantadine 200 mg 2x/day.

INSOMNIA & DISRUPTED SLEEP-WAKE CYCLE

- Change or discontinue long-acting alerting drugs, e.g.
 - Amantadine to once daily (or reduce dose if once daily)
 - Sustained-release methylphenidate & amphetamines
 - Make sure last doses are not being given late

INSOMNIA & DISRUPTED SLEEP-WAKE CYCLE

- Melatonin
 - Melatonin levels can be low after TBI (Shekleton et al, 2010)
 - Low doses (0.5-3 mg) may work best
 - Very short half-life (20-50 minutes)
 - **Time-release melatonin**-RCT of 2 mg ER in chronic TBI showed improved sleep quality & efficiency (Grima et al, 2018)

INSOMNIA & DISRUPTED SLEEP-WAKE CYCLE

- Ramelteon (Rozerem): melatonin receptor agonist (Atkin et al, 2018)
- Trazodone-better sleep quality, fewer awakenings (Yi et al, 2018)
- Magnesium: improved sleep time in elderly (Abbasi et al, 2012)
- Suvorexant (Belsomra)
 - Orexin antagonist (Atkin et al, 2018)
 - Prevents delirium in ICU/acute care/stroke? (Hatta et al, 2017; Azuma et al, 2018; Kawada et al, 2018)
 - Some abuse potential (schedule IV), probably less than zolpidem (Shoedel et al, 2016)

INSOMNIA & DISRUPTED SLEEP-WAKE CYCLE

- Other (not as good) alternatives
 - Other sedating antidepressants
 - Mirtazepine (Remeron): half-life 20-40 hrs; weight gain
 - Tricyclics (amitriptyline, nortriptyline) when pain is an issue
 - Long 1/2-lives
 - ACh effect

(Larson & Zollman, 2010)

INSOMNIA & DISRUPTED SLEEP-WAKE CYCLE

- Benzodiazepines
 - Lorazepam-cognitive side effects in AM (Dawson et al, 2008)
 - Oxazepam-no cognitive side effects in AM (Feldmeir et al, 1983)
- Other GABA agonists
 - Zolpidem (Ambien)-after 10 mg: cognition, driving impaired in AM (Leufkens et al, 2009)

(Larson & Zollman, 2010)

INSOMNIA & DISRUPTED SLEEP-WAKE CYCLE

- Eszopiclone (Lunesta)
 - Conflicting evidence on cognitive, driving impairment in AM (Boyle et al, 2008; FDA, 2014)
 - FDA changed starting dose to 1 mg due to impairment (FDA, 2014)
- Zaleplon (Sonata): no AM cognitive effects when given in evening, but yes if given in the middle of the night (Larson & Zollman, 2010)

(Larson & Zollman, 2010)

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CASE REPORT

- You see a 45 y.o. man in consultation on a rehabilitation unit. He is 40 days since a TBI. He is combative when asked to cooperate with nursing treatments or is challenged in therapies, but otherwise is quiet and initiates very little. He is sleeping through most of the night, but is still sleepy on and off during the day. He is largely coherent, but mildly confused. His ability to sustain attention and stay on task are short. His working memory and memory are impaired. He is on mirtazapine 15 mg at bedtime.

AROUSAL, INITIATION, PROCESSING SPEED, & ATTENTIONAL DISORDERS

- Withdraw offending agents if appropriate
 - Anticonvulsants
 - Worst offenders: phenytoin, phenobarbital, topiramate (Javed et al, 2015)
 - Not as bad: carbamazepine (Javed et al, 2015), valproic acid
 - Sedating, but not otherwise cognitive-impairing?: gabapentin (Javed et al, 2015; Kay et al, 2016)
 - Levitiracetam: studies indicate less cognitive-impairing
 - » can be sedating
 - » can cause irritability
 - (Koo et al, 2013; Javed et al, 2015; Schoenberg et al, 2017)
 - Neuroleptics/typical antipsychotics (e.g., chlorpromazine, haloperidol, etc.)
 - Atypical antipsychotics (e.g., quetiapine, olanzepine)

AROUSAL, INITIATION, PROCESSING SPEED, & ATTENTIONAL DISORDERS

- Withdraw offending agents if appropriate
 - Benzodiazepines: diazepam, lorazepam, clonazepam
 - Other hypnotics: diphenhydramine (Benadryl)
 - Anticholinergic drugs-chronic use associated with dementia in general population (Collamati et al, 2016; Richardson et al, 2018)
 - Sedating antihistamines: diphenhydramine, chlorpheniramine
 - Tricyclic antidepressants: doxepin, amitriptyline
 - Overactive bladder inhibitors: oxybutynin (Ditropan), tolterodine (Detrol), trospium (Sanctura), others
 - Antispasticity agents: benzodiazepines, baclofen, tizanidine (Shah et al, 2006)
 - Muscle relaxants: cyclobenzaprine (Flexeril)

ALERTNESS, INITIATION, ATTENTION, SPEED



- Dopaminergic & Noradrenergic
 - Methylphenidate->13 RCT's
 - Processing speed, attention to task/sustained attention, RT after TBI (Whyte et al, 2004; Wilmott & Ponsford, 2010; Kim et al, 2012; Wilmott et al, 2013; Johansson et al, 2014; 2015; Zhang & Wang, 2017; Dorer et al, 2018)-All RCT's
 - Fatigue, SF-36 vitality & social functioning scales after TBI (Johansson et al, 2014; 2015; Zhang & Wang, 2017)-RCT's

– Methylphenidate (continued)

- Working memory after TBI (Maktelov et al, 2017;

Johansson et al, 2014; McDonald et al, 2017)-All RCT's

- Effects dose dependent at 0, 5, & 20 mg 3x/day (Johansson et al, 2014; 2015)
- Effect still good after 6 months of treatment in responders (Johansson et al, 2017)
- Word-list learning and nonverbal learning (Brown Location Test)- (McDonald et al, 2017)-RCT

ALERTNESS, INITIATION, ATTENTION, SPEED



- Dopaminergic & Noradrenergic
 - Methylphenidate
 - Cognitive, post-concussive, & PTSD complaints in **mild TBI &/or PTSD** (McAllister et al, 2016)-RCT
 - Apathy after TBI (Kant, 2002)
 - Side effects: jitters/irritability, anxiety, hypertension, tachycardia, anorexia, psychosis
 - Does not provoke seizures at therapeutic doses (Wroblewski et al, 1992)

ALERTNESS, INITIATION, ATTENTION, SPEED

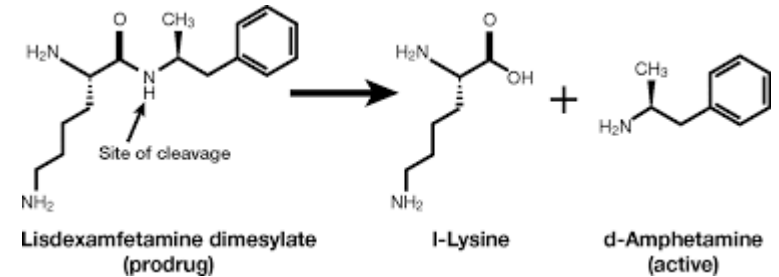
- Dopaminergic & noradrenergic
 - Dextroamphetamine
 - RCT: non-significant differences from placebo & **small effect sizes** for attention, speed, & function in pts 2 months p-TBI (N=32)
 - Side effects: similar to methylphenidate

(Hart et al, 2018)

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ALERTNESS, INITIATION, ATTENTION, SPEED

- Dopaminergic & noradrenergic
 - Lisdexamfetamine (Vyvanse)



- **Prodrug**-slowly converted to dextroamphetamine
- Decreases “liking” effect (Domnitei & Madaan, 2010)
- RCT in pts with TBI: shows benefit for sustained attention, response speed consistency & endurance, WM, subjective initiation, and other executive skills (Tramontana et al, 2014)
- Side effects: same

ALERTNESS, INITIATION, ATTENTION, SPEED



- Dopaminergic & noradrenergic
 - Modafinil (Provigil)
 - small RCT shows beneficial effect on daytime sleepiness after TBI (Kaiser, 2010)
 - RCT shows no effect on daytime sleepiness or fatigue (Jha et al, 2008)
 - Non-TBI studies show improved attention too
 - Side effects: Headache, nausea; less frequent, but can cause anxiety & psychotic behavior

ALERTNESS, INITIATION, ATTENTION, SPEED



- Dopaminergic & noradrenergic
 - Armodafinil (Nuvigil)
 - R-enantiomer of modafinil
 - RCT of mild-mod **TBI with EDS**: improved Clinical Global Impression-Severity of Illness scale & **increased sleep latency**, but not Epworth Sleepiness Scale (Menn et al, 2014)

ALERTNESS, INITIATION, ATTENTION, SPEED



- Dopaminergic
 - Bromocriptine
 - agonist at dopamine D2 receptors, some serotonin & alpha-adrenergic receptors
 - inhibits the release of glutamate
 - No improvement or worse attention in TBI (Whyte et al, 2008)
 - Alertness/activation-many case reports, uncontrolled studies in VS/MCS

ALERTNESS, INITIATION, ATTENTION, SPEED

- Catechol-O-methyltransferase (COMT) gene
 - COMT degrades catecholamines (dopamine, norepinephrine)
 - Common polymorphism causes amino acid valine to be replaced by methionine (Val158Met* genotype)
 - COMT **Met** results in **lower** COMT activity, so **higher** dopamine levels

(Bennett et al, 2016; Schact, 2016)

*valine changed to methionine at amino acid 158 in COMT gene

ALERTNESS, INITIATION, ATTENTION, SPEED

- Catechol-O-methyltransferase (COMT) gene (continued)
 - In **TBI**, COMT **Val** associated with
 - worse executive function (Flashman et al, 2004; Lipsky et al, 2005)
 - increased response latency (McAllister et al, 2005)
 - greater distractibility (Flashman et al, 2004)
 - worse behavior (FrSBe) in patients with TBI only in presence of depression (Myrgas et al, 2016)
 - In TBI, COMT Val not associated with performance on other cognitive tests in TBI in early rehabilitation (Willmott et al, 2014)

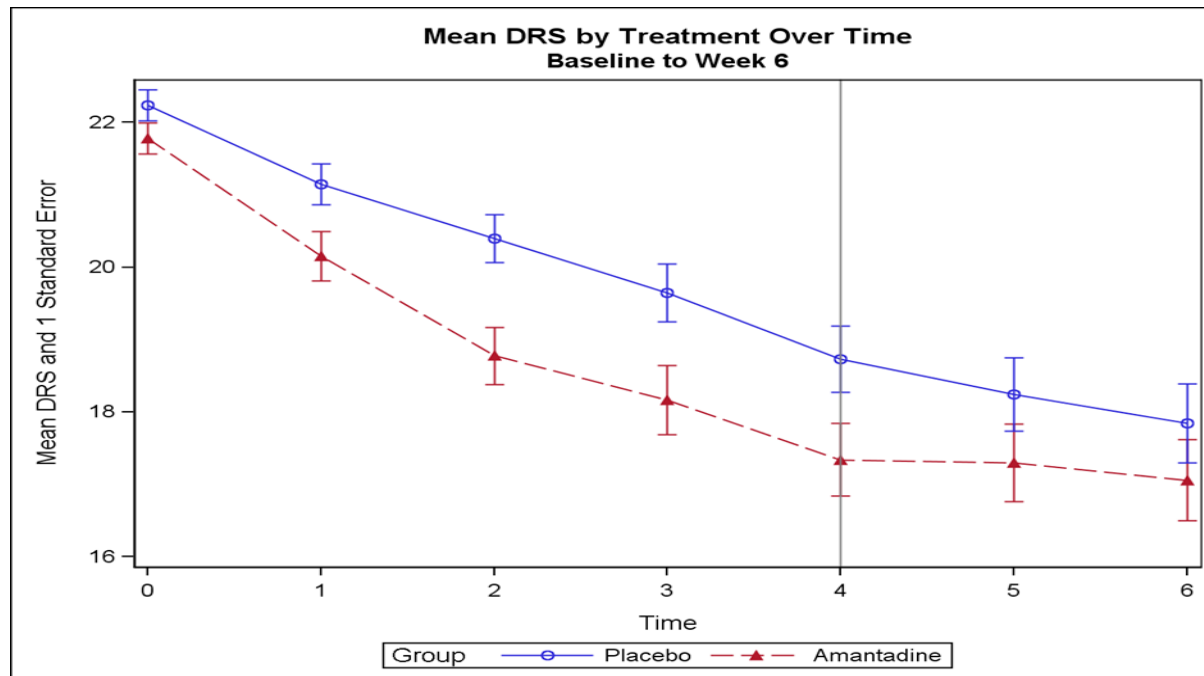
(Bennett et al, 2016)

ALERTNESS, INITIATION, ATTENTION, SPEED

- Catechol-O-methyltransferase (COMT) gene (continued)
 - Drug effects
 - Methylphenidate (reuptake inhibitor) in ADHD with COMT Val: Mixed results
 - Amphetamines (reuptake inhibitor) in ADHD with COMT Val: Mixed results
 - Tolcapone (**COMT inhibitor**)-Healthy controls with COMT Val improve in selective attention, working memory, executive function, verbal memory
- (Schact, 2016)
- Treatment implications:
 - Possible use of COMT inhibitors (e.g., tolcapone, entacapone) for cognitive deficits in patients with TBI who have COMT Val
 - Possible use also for behavior problems in depressed patients with TBI who have COMT Val

ALERTNESS, INITIATION, ATTENTION, SPEED

- NMDA receptor antagonists
 - Amantadine (also dopaminergic & noradrenergic) (Deep et al, 1999; Sommerauer, 2011)
 - **RCT-speeds recovery in patients in MCS** (Giacino et al, 2012)



ALERTNESS, INITIATION, ATTENTION, SPEED

- NMDA receptor antagonists
 - Amantadine
 - RCT-speeds recovery in MCS patients
 - Enrolled 4-16 weeks p-injury
 - Benefit (effect size) greater for those enrolled later than those enrolled early
 - Benefit (effect size) same for those in vegetative state vs. MCS

(Giacino et al, 2012)

ALERTNESS, INITIATION, ATTENTION, SPEED

- NMDA receptor antagonists
 - Amantadine 100 mg at 8 AM & 8 PM x 6 weeks
 - RCT in acute TBI of GCS 3-9 pts-only increases speed of recovery (GCS) in 1st 7 days (N = 40 – 8 [2/6] excluded for LFT's or Cr increase)
 - » At 6 months, GCS, GOS, DRS, and Karnofsky Performance Scale did not differ from placebo group

(Ghalaenovi et al., 2018)

- Retrospective study of amantadine started in ICU after TBI
 - » Decision to use amantadine at discretion of attending
 - » Those on amantadine more likely to be agitated

(Gramish et al, 2017)

ALERTNESS, INITIATION, ATTENTION, SPEED

- NMDA receptor antagonists
 - Amantadine for cognitive impairment
 - RCT in irritable participants with TBI
 - no difference in improvement in attention/speed
 - placebo better for learning/memory & general cognition at 28 days, not 60 days
- Pilot study: trend for improvement in inpatients (Meythaler, 2002)
- Side effects: nausea, orthostatic dizziness, edema, livedo reticularis, depression, anxiety/jitters, psychosis, arrhythmias, constipation

(Hammond et al, 2018)

ALERTNESS, INITIATION, ATTENTION



- NMDA antagonists
 - Memantine (Namenda)-also dopaminergic & upregulates BDNF gene
 - Increased prefrontal glucose metabolism on PET scan correlated with improved MMSE in TBI (Kim, 2010)

ALERTNESS, INITIATION, ATTENTION



- Noradrenergic
 - Atomoxetine (norepinephrine transporter inhibitor)
 - RCT shows no effect on attention in TBI (Ripley et al, 2014)
 - Protriptyline (norepinephrine reuptake inhibitor tricyclic antidepressant)
 - Case series shows positive effects in ABI (Wroblewski et al, 1993)
 - Anticholinergic, lowers sz threshold, 60-200 hr half-life

ALERTNESS, INITIATION, ATTENTION, SPEED

- Acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine)
 - **Studies are mixed** on attention, WM (immediate memory), speed of processing after TBI (Zhang et al, 2004; Silver et al, 2006; McAllister et al, 2016)
 - **Retrospective** study of acute-subacute (3-54 days p-injury) TBI showed patients on donepezil 10 mg did no better than non-donepezil patients on DRS, FIM, NP testing (Campbell et al, 2018)
- Alpha-2 adrenergic agonist: guanfacine
 - **Improved WM** in participants with mTBI 1 month p-injury compared to placebo (**N = 13/14**)
 - healthy controls not improved

(McAllister et al, 2011)

ALERTNESS, INITIATION, ATTENTION

Occasional Effect in Patients with DOC

- Zolpidem (Ambien)
 - 4/84 improved transiently on CRS (4.8%), most already in MCS (Whyte et al, 2014; Bomalaski et al, 2017)
 - 12/60 improved on CRS, but **only 1 from VS to MCS** & was not reproducible (Thonnard et al, 2013; Bomalaski et al, 2017)
 - Some cases of sustained effect with continued treatment (Clauss et al, 2000; Clauss & Nel, 2006; Whyte et al, 2014)
 - Doses
 - Usually 10 mg, some 20 mg (Whyte et al, 2014; Bomalaski et al, 2017)
 - 1 case up to 30 mg without adverse effects (Clauss et al, 2000)
- Benzodiazepines-effect usually not sustained with continued treatment (Glenn: personal communication)

ALERTNESS, INITIATION, ATTENTION

- You see a 45 y.o. man in consultation on a rehabilitation unit. He is 40 days since a TBI. He is combative when asked to cooperate with nursing treatments or is challenged in therapies, but otherwise is quiet and initiates very little. He is sleeping through most of the night, but is still sleepy on and off during the day. His speech is largely coherent, but mildly confused. His ability to sustain attention and stay on task are short. His working memory and memory are impaired. He is on mirtazapine 15 mg at bedtime.

ALERTNESS, INITIATION, ATTENTION

- Summary
 - Determine underlying cause of symptoms
 - Withdraw potentially offending medications
 - Treat non-pharmacologically when feasible
 - Add stimulants or dopaminergics
 - Try others as needed