Psychopharmacology After Brain Injury

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• None
AREAS COVERED

- Principles
- Medication uses by diagnostic category
• Withdraw offending meds when possible before starting new ones
• Individual responses vary enormously
• Medications can be combined--with caution
  - Especially with different mechanisms of action
  - Check drug interactions
• “Start low, go slow”— when possible
• But don’t give up before going to high therapeutic doses…
  - If no side effects or contraindications
• 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
• Symptoms can fool you
  – e.g., “Hallucinations” may be visual-perceptual + executive function problem; or memory problem
  – e.g., Reduplicative phenomenon (Capgras syndrome)
  – 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, disinhibition
JUST POUR IT INTO MY FACE

I AM EXPERIENCING
PRE-COFFEE
AGITATION
PRINCIPLES OF DIFFERENTIAL DIAGNOSIS

• Ask staff
• Ask family
• Talk to the patient
NON-PHARMACOLOGIC TREATMENTS

- Optimize medical condition
- Treat sleep disorders
- Treat other disabilities
- Individual counseling
- Motivational interviewing
- Group treatment
- S.A.D. lights
- Acupuncture
- Meditation
- Exercise
- Behavioral interventions
- Transcranial magnetic stimulation

(Gertler et al, 2015)
ATTENTION, ALERTNESS, AND INITIATION: NON-PHARMACOLOGIC TREATMENTS

- Optimize medical condition
- Treat sleep disorders
- Cognitive rehabilitation
- S.A.D. lights
- Exercise
- Behavioral interventions
A 23 y.o. male with TBI is transferred to the rehabilitation unit 9 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 alerting drugs (e.g., amantadine to once daily)
• Melatonin
  – Low doses (0.5-3 mg) may work best
  – Very short half-life (20-50 minutes)
  – Consider time release melatonin
• Ramelteon (Rozerem): melatonin receptor agonist
• Trazodone

(Larson & Zollman, 2010)
• Other (not as good) alternatives
  – Other sedating antidepressants
    • Mirtazepine (Remeron): half-life 20-40 hrs; weight gain
    • Tricyclics (doxepin, amitriptyline, nortriptiline): 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);
  • Eszoplicone (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)
A 23 y.o. male with TBI is transferred to the rehabilitation unit 9 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.
• You see a 45 y.o. man in consultation on a rehabilitation unit. He is 47 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 is short. His working memory and memory are impaired. He is on quetiapine 50 mg at bedtime.
– Withdraw offending agents if appropriate

• Anticonvulsants
  – Worst offenders: phenytoin, phenobarbital, topiramate
  – Not as bad: carbamazepine, valproic acid
  – Sedating, but not otherwise cognitive-impairing: gabapentin
  – Levitiracetam: studies indicate less cognitive-impairing, but anecdotally, may be?, especially re: confusional state

• Neuroleptics/typical antipsychotics (e.g., chlorpromazine, haloperidol, etc.)

• Atypical antipsychotics (e.g., quetiapine, olanzepine)
– Withdraw offending agents if appropriate
  • Benzodiazepines (e.g., diazepam, lorazepam, clonazepam)
  • Other hypnotics: diphenhydramine (Benadryl), others
  • Anticholinergic drugs-chronic use associated with dementia
    – Sedating antihistamines: diphenhydramine, chlorpheniramine
    – Tricylic antidepressants: doxepin, amitriptyline
    – Overactive bladder inhibitors: oxybutynin (Ditropan), tolterodine (Detrol), trospium (Sanctura), others
  • Antispasticity agents (benzodiazepines, baclofen, tizanidine)
• CNS stimulants and dopaminergics
• Inverted U-shaped curve of effect
(Wood et al, 2014)
• Dopaminergic & Noradrenergic
  – Methylphenidate
    • Processing speed after TBI
    • Attention to task after TBI
      (Whyte et al, 2004; Wilmot & Ponsford, 2010)-Both RTC’s
  • Fatigue, attention, processing speed, WM, SF-36 vitality & social functioning scales dose dependent at 0, 5, & 20 mg 3x/day (Johannson et al, 2014; 2015)-RCTs
    – Effect still good after 6 months of treatment in responders (Johansson et al, 2017)
  • Working memory (Maktelov et al, 2017)-RCT
  • Side effects: jitters/irritability, anxiety, hypertension, tachycardia, depression, anorexia, psychosis
  • Does not provoke seizures at therapeutic doses (Wroblewski et al, 1992)
    – Dexmethylphenidate (Focalin)
ALERTNESS, INITIATION, ATTENTION, SPEED

- Dopaminergic & noradrenergic: amphetamines
- No good studies on amphetamines in TBI (Forsyth R, Cochrane DTBS review, 2006) except lisdexamfetamine
  - Lisdexamfetamine (Vyvanse)
    - Prodrug-converted to dextroamphetamine
    - Bypasses 1st pass metabolism (mechanism unknown) & so slows conversion
    - 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
• Dopaminergic
  – Modafinil (Provigil): small RCT shows beneficial effect on daytime sleepiness after TBI (Kaiser, 2010)
    • Improved alertness, tracking, following commands in uncontrolled study of patients with DOC (Dhamapurkar et al, 2016)
    • Non-TBI studies show improved attention too
    • Less frequent, but can cause anxiety & psychotic behavior
  – 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 (see also “Executive Function”)
    • 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
• Dopaminergic
  – Up and coming?: (−)-OSU6162
  – monoaminergic stabilizer: can either up- or down-regulate dopamine receptors
  – RCT in stroke & TBI
    • Improved mental fatigue scale scores
    • trends for gains in attention & processing speed
      (Johannson et al, 2012)
  – RCT in TBI
    • No difference in fatigue between drug & placebo groups
      (Berginstrom et al, 2017)
• NMDA receptor antagonists
  – Amantadine (also dopaminergic &
    noradrenergic) (Sommerauer, 2011; Deep et al, 1999)
  • Pilot study: trend for improvement in inpatients (Meythaler, 2002)
  • RCT-speeds recovery in MCS patients (Giacino et al, 2012)
  • RCT-decreases fatigue in MS (Krupp et al, 1995)
  • Side effects: nausea, orthostatic dizziness, edema, livedo reticularis,
    depression, anxiety/jitters, psychosis, arrhythmias, constipation
• NMDA receptor antagonists
  – Memantine (Namenda)
    • Increased prefrontal glucose metabolism on PET scan correlated with improved MMSE in TBI
      – Also were areas of decreased glucose metabolism
        (Kim, 2010)
    • Side effects: dizziness, confusion, constipation, HTN, psychosis, somnolence, nausea
• Noradrenergic
  – Atomoxetine (norepinephrine transporter inhibitor )
    • RCT shows no effect on attention in TBI (Ripley et al, 2014)
    • Side effects: nausea, vomiting, hepatoxicity, hypertension
  – 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
• Acetylcholinesterase inhibitors
  (e.g., donepezil, rivastigmine, galantamine)
  – Studies show possible benefits on attention, working memory
    (immediate memory), speed of processing after TBI
  – One was largely negative

(Silver et al, 2006; Zhang et al, 2004)
Occasional dramatic recovery in DOC patients

• Zolpidem (Ambien) (Claus & Nel, 2006; Whyte et al, 2008)

• Benzodiazepines—effect usually not sustained with sustained treatment
  (Glenn: personal communication)
You see a 45 y.o. man in consultation on a rehabilitation unit. He is 45 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 is short. His working memory and memory are impaired. He is on quetiapine 50 mg at bedtime.
• A 20 year-old woman is seen as an outpatient 2 months after a TBI. She is on amantadine 100 mg 2x/day. She is making rapid gains in attention, memory, and executive skills. She is becoming aware of her cognitive impairment. She calls herself “stupid” and on several occasions states that she wishes that she had not lived. She is tearful at times. Counseling has had a limited effect.
DEPRESSION

- Withdraw offending agents (e.g., amantadine, baclofen)
Hello, birdie!

Edgar A. Poe

Huguette Mauzel
DEPRESSION

- SSRI’s (e.g., escitalopram, citalopram, sertraline, fluoxetine, fluvoxamine, paroxetine*)
  - 2 negative trials of sertraline in TBI (Ashman et al, 2009; Fann et al, 2017)
    - Fann et al: 32% severe; 68% anxiety; 69% history of alcohol or drug dependence
  - Meta-analysis showed positive effect of antidepressants (Salter et al, 2016)
  - Sertraline prevented depression in acute TBI in 2 trials (Novack et al, 2009; Jorge et al, 2016)
  - Low/non-sedating
  - Low/non-anticholinergic (*except paroxetine)
  - Side effects: nausea, diarrhea, decreased libido, erectile dysfunction, anorgasmia, HA, dry mouth, insomnia, sedation, anxiety, suicidal ideation, hemorrhage (see next slide), small increase all-cause mortality for >65 y.o.
• **SSRI’s**
  – Citalopram (& escitalopram, perhaps less so) associated with serious cardiac risk above 40 mg (QT prolongation)
  – Increased risk of GI & intracerebral hemorrhage-RR 1.26 in Khokar et al. (Haccam & Mrkobrada, 2012; Khokar et al, 2017)

• **Vilazodone (Viibryd)**
  – Inhibits Serotonin (5-hydroxytryptamine [5-HT]) reuptake
  – Partial Agonist 5-HT1a receptor
• Vortioxetine (Trintellix)
  – Inhibits Serotonin (5-HT) reuptake
  – Agonist at 5-HT$_{1a}$ receptors; Partial Agonist at 5-HT$_{1b}$ receptors
  – Antagonist at 5-HT$_3$, 5-HT$_{1d}$, and 5-HT$_7$ receptors
  – Meta-analysis: Not as effective, but better tolerated than duloxetine for depression (Li et al, 2016)
  – Meta-analysis: Improved attention (DSST) even apart from depression scores (not seen with duloxetine) (McIntyre et al, 2016; 2017)
  – Improved performance on TMT-1 in MDD & healthy subjects (Smith et al, 2016)
  – Improved performance on DSST & RAVLT (memory) independent of effect on depression (Frampton, 2016)
DEPRESSION

• SNRI’s (e.g., venlafaxine, desvenlafaxine, duloxetine, mirtazepine, levomilnacipran)
  – Low/non-sedating*
  – Low/non-anticholinergic
  – Side effects: similar to SSRI’S
    • But can raise BP

* mirtazepine is generally sedating & often causes weight gain
• Bupropion-noradrenaline & dopamine reuptake blocker
  – Avoid or use cautiously (seizures at high doses?)
    • 1-yr seizure rate at max 300 mg/day in non ABI, non-epileptic, non-eating disorder population = 0.15% (Dunner et al, 1998)
    • Risk in smoking cessation some w h/o sz = 0.05% (n=168,000) (Bevins et al, 2008)
    • Increased risk with IR forms, but not extended release (Alper et al, 2007)
    • Less likely to cause sexual side effects
• Methylphenidate? (Lee et al, 2005)
• Methylphenidate plus L-dopa improve mood in stroke (Delbari et al, 2011)
• If insomnia, sedating drug may help [e.g., Mirtazepine, sedating tricyclics, trazodone-(not a great antidepressant)] (Larson & Zollman, 2010)

• In the Pipeline: SAGE-217-neuroactive steroid that is an agonist of GABA_\text{A} receptor subtypes
PATHOLOGICAL LAUGHING AND CRYING (PSEUDOBULBAR AFFECT)

• PLC: Paroxysmal stereotyped laughing & crying with little or no provocation
  – Antidepressants (SSRI’s preferred)
  – Methylphenidate
  – Lamotrigine, valproate, carbamazepine
  – Levodopa
  – Amantadine
  – Dextromethorphan/quinidine (Nuedexta)
    • Interacts with many other drugs to change levels
    • Can prolong QT interval

(Arciniegas & Wortzel, 2014)
EMOTIONAL OR AFFECTIVE LABILITY

• AL: Displaying intense emotions in response to meaningful stimuli that ordinarily would induce more modest emotional responses.
  – Antidepressants (SSRI’s preferred)
  – Methylphenidate
  – Lamotrigine, valproate, carbamazepine
  – Levodopa
  – Amantadine

  (Arciniegas & Wortzel, 2014)
ANXIETY

• Benzodiazepines
• Buspirone
• Antidepressants (Especially SSRI’S, SNRI’S)
• Treat insomnia
CASE REPORT

• A 20 year-old woman is seen as an outpatient 2 months after a TBI. She is on amantadine 100 mg 2x/day. She is making rapid gains in attention, memory, and executive skills. She is becoming aware of her cognitive impairment. She calls herself “stupid” and on several occasions states that she wishes that she had not lived. She is tearful at times. Counseling has had a limited effect.
CASE REPORT

- There is no improvement when she is tapered off of amantadine. There is no change in attention, processing speed, initiation, or alertness. Her depressive symptoms improve with the addition of sertraline. Six months after her injury she is still making cognitive gains, though has substantial cognitive impairment, particularly in the areas of working memory and executive skills. Her only medication is sertraline.
EXECUTIVE FUNCTION

• Methylphenidate
  – Participants with TBI improved performance on N-back test
  – Increased activation of left cerebellum on fMRI
    (Manktelow et al, 2017)

• Lisdexamfetamine (Vyvanse)
  – RCT in pts with TBI: shows benefit for working memory; subjective initiation & organization
    (Tramontana et al, 2014)
EXECUTIVE FUNCTION

- Bromocriptine
  - Stroop, dual-task, FAS, trailmaking, WCST (McDowell et al, 1998)
  - Working memory-no (Mcdowell et al, 1998)
  - Working memory-yes (Luciana et al, 1992)
  - Working memory 1 month p-mTBI-no for TBI; yes for healthy controls (McAllister et al, 2011)

(continued)
EXECUTIVE FUNCTION

• Bromocriptine (continued)
  – Placebo-controlled RCT of pergolide (D1D2 agonist) & bromocriptine (D2 agonist) in healthy subjects
  – Bromocriptine group improved on Stroop test

(Roesch-Ely et al, 2005)
EXECUTIVE FUNCTION

• Vitamin D
  – placebo controlled RCT of Norwegian adolescents
  – Vitamin D group demonstrated improvement in Tower of Hanoi performance & increase in vitamin D levels (44 nmol/L to 62 nmol/L)
    (Grung et al, 2017)
• There is no improvement when she is tapered off of amantadine. There is no change in attention, processing speed, initiation, or alertness. Her depressive symptoms improve with the addition of sertraline. Six months after her injury she is still making cognitive gains, though has substantial cognitive impairment, particularly in the areas of working memory and executive skills. Her only medication is sertraline.
• 25 y.o. man with TBI. Bifrontal contusions are seen on CT scan. He is started on levetiracetam for prevention of seizures. He is started on amantadine to facilitate recovery. He remains unconscious for 3 weeks, then gradually emerges and is transferred to the rehabilitation unit. He is restless and aggressive, trying to get out of bed, pulling on his g-tube, hitting staff who try to stop him.
POST-TRAUMATIC CONFUSION ON THE REHABILITATION UNIT

• Priorities:
  – Patient & staff safety
  – Rehabilitation progress
• Treat sleep, pain, somnolence
• Taper & stop levetiracetam if possible
• Consider not treating with drugs—use 1:1, net bed, wait
• Get off medications as soon as possible
MEDICATIONS FOR ACUTE AGGRESSION & IRRITIBILITY

• Atypical antipsychotics (e.g., quetiapine-sedating; aripiprazole-activating) (off-label): no well-done studies
  – See next slide
• Typical antipsychotics (e.g., haloperidol) (off-label)
  – no well-done studies
  – May cause global decrease in function
• Benzodiazepines (e.g., lorazepam, clonazepam) (off-label): can cause disinhibition
• Above can usually be given p.o.
  – Aggressive pts often agree to take
  – IM may exacerbate situation
  – IM still takes time to work-need to deal with situation
ATYPICAL ANTIPSYCHOTICS

• Less EPS
• Less tardive dyskinesia
• Can cause
  – Diabetes mellitus
  – Weight gain
  – Hyperlipidemia
• Small risk of cardiac arrest-get EKG, look for QT prolongation
• Stroke risk increased, especially in elderly
• Sedation varies
• 25 y.o. man with TBI. Bifrontal contusions are seen on CT scan. He is started on levetiracetam for prevention of seizures. He is started on amantadine to facilitate recovery. He remains unconscious for 3 weeks, then gradually emerges and is transferred to the rehabilitation unit. He is restless and aggressive, trying to get out of bed, pulling on his g-tube, hitting staff who try to stop him.
• 10 days later, he has made gains and is no longer restless, but becomes verbally and occasionally physically aggressive when he does not get what he wants. He says that staff are trying to poison him. He is sleeping well. He is on amantadine 200 mg 2x/day.
MEDICATIONS FOR AGGRESSION & IRRITIBILITY

- **Amantadine**: RCT (Hammond et al, 2014)
  - No difference in rating by observers/informants, but 68.3% placebo response
  - Significant difference in ratings by physicians & participants before correction for multiple analyses
  - Less aggression according to self-ratings, but not observer ratings (Hammond et al, 2017)

- **Stimulants, etc** (When due to sleepiness, poor initiation)

- **Anticonvulsants** (e.g., valproate, carbamazepine, oxcarbazepine) (Huband, Cochrane Review, 2010)

- **Antidepressants** (e.g., SSRI’s, tricyclics, trazodone)

- **Beta-blockers** (e.g., propranolol, pindolol) (Greendyke & Kanter, 1986)

- **Buspirone**

- **Lithium**

- **Atypical antipsychotics**
• Withdraw offending agents (e.g., tricyclic antidepressants)

• Anticonvulsants
• 10 days later, he has made gains and is no longer restless, but becomes verbally and occasionally physically aggressive when he does not get what he wants. He says that staff are trying to poison him. He is sleeping well. He is on amantadine 200 mg 2x/day.
SUMMARY

• Know what you are treating
• All else being equal, use medications with fewest side effects, particularly cognitive
THANK YOU!