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Psychopharmacologic Approaches to Affective Disorders and Executive Dysfunction after Brain Injury

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NeuroRestorative's COVID-19 Response

We are committed to protecting the health and safety of the individuals we serve, our staff, and the community. Our services are considered essential, and we are taking precautions to minimize disruption to services and keep those in our care and our team members safe. In some programs, that has meant innovating our service delivery model through Interactive Telehealth Services. We provide Interactive Telehealth Services throughout the country as an alternative to in-person services. Through Interactive Telehealth Services, we deliver the same high-quality supports as we would in-person, but in an interactive, virtual format that is HIPAA compliant and recognized by most healthcare plans and carriers.

You can learn more about our COVID-19 prevention and response plan at our Update Center by visiting **neurorestorative.com**.

Disclosures

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

Look For Symptom's Underlying Causes

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- 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

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- Symptoms Can Fool You
  - e.g., Abulia/apathy can be a symptom of depression or be neurologically-based
  - e.g., "Hallucinations" may be visual-perceptual + executive function problem; or memory problem
  - e.g., Reduplicative phenomenon (Capgras syndrome): "imposters"
  - e.g., Aggression/agitation-can be provoked by under-arousal, poor initiation, depression, and/or disinhibition

Non-pharmacologic Treatments

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

(Gertler et al, 2015)

Case Report

- A 20 year-old woman is seen as an outpatient 2 months after a TBI. She is on amantadine 200 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, varenicline, corticosteroids, gabapentin, cyclobenzaprine)

Depression

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- Is it okay to give an antidepressant to someone with a "real" reason to be depressed?
  - Should they work it out without drugs?
  - What if they are too cognitively impaired?
  - Will the antidepressant work?
  - Will it diminish their ability to benefit from psychotherapy?
  - Will it take away their creativity?

Depression

- SSRI's (e.g., escitalopram, citalopram, sertraline, fluoxetine, fluvoxamine, paroxetine, vilazodone-also 5-HT1a receptor agonist)
  - Mixed results of studies, but meta-analysis showed positive effect of antidepressants for people with TBI (Salter et al, 2016)
  - RCT negative for sertraline in depression after TBI (Fann et al, 2017), but
    - 68% had anxiety
    - 69% had a H/O alcohol or drug dependence
  - Sertraline prevented depression in acute TBI in 2 trials (Novack et al, 2009; Jorge et al, 2016)

Depression

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- SSRI's:
  - Side effects: nausea, diarrhea, decreased libido, erectile dysfunction, anorgasmia, HA, dry mouth, insomnia, sedation, anxiety, suicidal ideation, hemorrhage, hemorrhagic stroke (Haccam & Mrkobrada, 2012; Khokhar et al, 2017- TBI ≥65 study), small increase in all-cause mortality for ≥ 65 y.o.
  - Citalopram & escitalopram associated with QT prolongation above 40 & 20 mg, respectively
    - Ray et al (2017) found no increased risk of sudden cardiac death or all-cause mortality in a large TN Medicaid population on these drugs compared with other SSRI's`

Depression

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Serotonin receptor agonist/antagonist

- 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
  - More improvement in cognition in MDD than duloxetine (McIntyre et al, 2016)

Depression

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- Agomelatine
  - melatonin receptor agonist and 5-HT_{2C} receptor antagonist resulting in frontal norepinephrine and dopamine disinhibition
  - Not FDA approved in U.S.—never submitted
  - Approved in Europe by EMA

Depression

SNRI's (e.g.,venlafaxine, desvenlafaxine, duloxetine, levomilnacipran)

Withdrawal syndrome = use extended-release forms SNRI's

Side effects: similar to SSRI'S but

- Most can raise blood pressure
- Duloxetine can cause elevated LFT's
- Increased risk of ischemic stroke with SNRI's
- & PPA's* in ≥ 65 y.o. after TBI (Khokhar et al, 2017)

*Phenylpiperizone antidepressants: trazodone & nefazodone

Depression

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- Tetracyclics
  - Mirtazapine (Remeron™)-sedating, causes weight gain
  - Mianserin (not available in U.S.)
  - Maprotiline (not available in U.S.)

Depression

- Bupropion-noradrenaline & dopamine reuptake blocker
  - Not associated with sexual side effects
  - 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 with h/o seizures = 0.05% (n=168,000) (Bevins et al, 2008)
    - Increased risk with IR forms, but not extended release (Alper et al, 2007)

Depression

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- Esketamine (Spravato™) Nasal Spray
  - NMDA receptor antagonist
  - Adjunctive for treatment-resistant depression
  - Administered under supervision
  - Side effects: sedation, syncope, dizziness, vertigo, anxiety, dissociation

Depression

- Methylphenidate (Lee et al, 2005; Zhang & Wang, 2017-RCT)
- Methylphenidate plus L-dopa improve mood in stroke (Delbari et al, 2011)

Depression

- Antidepressant Augmenters
  - Atypical antipsychotics (e.g., aripiprazole, olanzepine)
  - Some anticonvulsants (lamotrigine, valproate, carbamazepine)
  - Methylphenidate (off-label)

Pathological Laughing And Crying (Pseudobulbar Affect)

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- PBA: Paroxysmal stereotyped laughing & crying with little or no provocation

Pathological Laughing And Crying (Pseudobulbar Affect)

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Center for Neurologic Study-Lability Scale (CNS-LS) for Pseudobulbar Affect (PBA)

Using the scale below, write the number that describes the degree to which each item on the next slide applies to you **DURING THE PAST WEEK**. Write only 1 number for each item, then add the numbers and enter the total at the bottom.

Never	Rarely	Occasionally	Frequently	Most of the Time
1	2	3	4	5

Pathological Laughing And Crying (Pseudobulbar Affect)

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Questions

- I find that even when I try to control my laughter I am often unable to do so
- I find that I am easily overcome by laughter
- There are times when I won't be thinking of anything happy or funny at all, but then I'll suddenly be overcome by funny or happy thoughts
- Others have told me that I seem to become amused very easily or that I seem to become amused about things that aren't really funny
- I find myself crying very easily
- There are times when I feel fine one minute, and then I'll become tearful the next over something small or for no reason at all
- I find that even when I try to control my crying I am often unable to do so

It is said that a score of ***13 or more*** may suggest **PBA**. It provided the best sensitivity (0.84) and specificity (0.81). (Moore et al, 1997)

NOTE: You get 1 point for "Never." If the 4 laughing items are "NEVER" and the 3 crying items are "Occasionally," you get 13.

Pathological Laughing And Crying (Pseudobulbar Affect)

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- Mean prevalence of PBA across 6 neurologic conditions including TBI:
  - 10.1% with Pathological Laughing and Crying Scale (PLACS) ≥ 13
  - 9.4% with CNS-LS ≥ 21
  - 37.5% CNS-LS ≥ 13

(Work et al, 2011)

- Mean prevalence of PBA in military with TBI:
  - 22% with CNS-LS ≥ 21
  - 70% CNS-LS ≥ 13
  - PTSD present in 46%
  - Major depression present in 26%

(Fonda et al, 2015)

Pathological Laughing And Crying (Pseudobulbar Affect)

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- Treatments
  - Antidepressants (SSRI's preferred)
  - Methylphenidate
  - Lamotrigine, valproate, carbamazepine
  - Levodopa
  - Amantadine
  - Dextromethorphan/quinidine (Nuedexta-FDA approved for PBA)
  - Open label study showed significant improvement and good tolerance (Hammond et al, 2018)
  - Did not distinguish affective lability from PBA (Engelman et al, 2014)
  - Mean PHQ-9 score was 13.9 (upper border moderate depression), improved with DM-Q

(continued)

Pathological Laughing And Crying (Pseudobulbar Affect)

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– Dextromethorphan/quinidine (Nuedexta™)

- Inhibitor of CYP2DS metabolism
- Interacts with many other drugs to change levels (desipramine, citalopram, amiodarone, amphetamine, fluoxetine, ciprofloxacin, levofloxacin, quetiapine, trazodone, tramadol, etc., etc.)
- Can prolong QT interval
- Other side effects: diarrhea, nausea, dizziness, headache, somnolence, fatigue, dry mouth

(Arciniegas & Wortzel, 2014; Pattee et al, 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)

  - Detromethorphan/quinidine? (Neudexta™)

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 200 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 (working memory, attention)-RCT (Manktelow et al, 2017)
  - Other RCT's showing gains in working memory (Johannson et al, 2014; McDonald et al, 2017)

- Lisdexamfetamine (Vyvanse™)
  - RCT in pts with TBI: shows benefit for working memory; subjective initiation and organization

(Tramontana et al, 2014)

Executive Function

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- Bromocriptine (1.25-2.5 mg)
  - Improved on Stroop (Roesch-Ely et al, 2005-RCT, non-BI), dual-task, FAS, trailmaking, WCST (McDowell et al, 1998-randomized, placebo crossover; TBI)
  - Working memory (verbal span, 8-second delayed spatial localization)-No (Mcdowell et al, 1998)
  - Working memory-No for 4-sec delayed spatial localization, Yes for 8-sec (Luciana et al, 1992-RCT, non-BI)
  - Working memory-No for N-back test at 1 month p-mTBI; Yes for healthy controls (McAllister et al, 2011)
  - Some rare but dangerous side effects, including pulmonary fibrosis

Executive Function

- Vitamin D
  - Placebo controlled RCT of Norwegian adolescents
  - Vitamin D group demonstrated improvement in Tower of Hanoi performance with increase in vitamin D levels (44 nmol/L to 62 nmol/L)

(Grung et al, 2017)

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.

Case Report

- 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 in the ICU & Rehabilitation Unit

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- Priorities
  - Patient and staff safety
  - Rehabilitation progress
- Treat insomnia (trazodone), pain
- Taper and stop levetiracetam if possible
  - After 7 days
- Consider not treating with drug
  - use 1:1, net bed, wait

Post-traumatic Confusion in the ICU & Rehabilitation Unit

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- Atypical antipsychotics (e.g., quetiapine, olanzapine, aripiprazole) (off-label)
  - RCT of quetiapine vs. placebo for delirium in critically ill non-TBI patients
    - Shorter duration of delirium
    - Less agitation
    - Fewer days of PRN haloperidol
    - More likely to be discharged to home or rehab
    - More sedation

(Devlin et al, 2010)

Post-traumatic Confusion in the ICU & Rehabilitation Unit

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- Benzodiazepines (e.g., lorazepam, clonazepam) (off-label):
  - Can cause disinhibition, sedation, impaired memory and attention
  - Generally not recommended
  - Get off medications as soon as possible

Case Report

- 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.

Case Report

- 14 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 & Irritability

- Classification of Aggressive Behavior: Pharmacology
  - Psychotic: antipsychotics
  - Impulsive: see forthcoming slides
  - Predatory (organized or instrumental): none

(Nolan et al, 2003; Meyer et al, 2016)

- Other Contributors/Classes: Pharmacology
  - Dysphoric (Depressive): antidepressants
  - Paradoxical (impaired initiation or alertness): stimulants or amantadine

Medications For Aggression & Irritability

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- Impulsive aggression, disinhibition
  - Amantadine: RCT (Hammond et al, 2014, 2015, 2017)
    - No difference in rating by observers, but 68.3% placebo response
    - Significant difference in ratings by physicians & participants before correction for multiple analyses
    - In subjects with mod-severe aggression
      - participant ratings significantly different between groups on some measures
      - but not observer ratings (56% placebo response rate)

Medications For Aggression and Irritability

- Impulsive aggression
  - Anticonvulsants (e.g., valproate, carbamazepine, oxcarbazepine) (Huband, Cochrane Review, 2010)
  - Beta-blockers (e.g., propranolol, pindolol) (Greendyke & Kanter, 1986; Plantier et al, 2016)
  - Lithium (Glenn & Joseph, 1987; Glenn et al, 1989)
  - Atypical antipsychotics
    - Atypical antipsychotics (e.g., quetiapine-sedating; aripiprazole-activating; clozapine-most effective?) (off-label): no well-done studies

(Meyer et al, 2016)

Medications For Aggression & Irritability

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- 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

Case Report

- 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

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- Determine underlying cause of symptoms
- Withdraw potentially offending medications
- Treat non-pharmacologically when feasible
- Use medications with the fewest possible side effects and the best evidence for efficacy

Questions?

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