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3 **Disclosure**

- I have no disclosures concerning relationships with commercial entities that may have a direct/indirect interest in the subject matter of this presentation.
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4 **Objectives**

- Identify common neurostimulants used in ICU patients with traumatic brain injury
- Understand pharmacotherapeutic considerations for selecting a safe neurostimulant in the ICU based on available literature in the appropriate patient population
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5 **Traumatic Brain Injury (TBI)**

- Trauma to brain leading to structural injury
  - Loss or ↓ level of consciousness
  - Memory loss
  - Alteration in mental status
  - Neurological deficits
  - Intracranial lesions

7 **Trends in Age-adjusted Rates of TBI**

8 **Disabilities**

9 **Morbidity and Mortality**

10 **Mechanism of Injury**

11 **Mechanism of Injury**

12 **Acute Phase of Traumatic Brain Injury**

14 **Neurophysiology of Traumatic Brain Injury**

Neurotransmitter Storm

15 **Brain Neurotransmitter Pathways**

16 **Catecholaminergic Pathway - NE**

17 **Catecholaminergic Pathway - NE**

18 **Catecholaminergic Pathway - DA**

19 **Catecholaminergic Pathway - DA**

20 **Goals of Neurostimulant Use in TBI**

1. Restore Balance of neurotransmitters' production vs. reuptake
2. Accelerate Recovery

3. Improve cognitive and memory function
4.

21 **Catecholaminergic Pathway Dysfunction**

DA and NE modulate cognitive functions:

1. Information processing speed
2. Attention
3. Memory
4. Learning

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22 **Amantadine**

Randomized, multi-center, placebo-controlled trial

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24 **Primary Outcome**

- Both groups had significant improvement in DRS scores (P <0.05)
- Faster recovery rate (slope of line) in amantadine group, P=0.007

25 **Safety Outcome**

No statistical difference in rates of:

- Seizure
- Agitation
- Insomnia

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26 **Limitations**

- Selection bias
  - Patients being admitted to rehab: the decisions about admission to a rehabilitation center may be influenced by the probability of further improvement
- Brief treatment interval and a short-term assessment of the outcome
  - ? Treatment effect in long-term therapy
- No restriction in other rehab measures
  - ? Synergistic effect
- Confounding effect of other psychoactive medications enhancing or blocking the effect of amantadine

27 **Amantadine in ICU**

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- GCS ≤ 9
- Admitted to critical care unit

- The protocol included administration of the drug (placebo or AMH) for 6 weeks. We administered AMH as 100 mg twice a day (q 8 AM and 8 PM). After 6 weeks of drug therapy, the study AMH was stopped without tapering.

29 **Amantadine in ICU**

31 **Modafinil**

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33 **Modafinil**

34 **Modafinil – Combined Periods**

35 **Modafinil – Combined Periods**

36 **Modafinil – Safety Outcome**

37 **Conclusion**

- Improvement in verbal memory on week 4 but was not maintained at week 10
- This study does not support the use of modafinil in treating fatigue in individuals with TBI

38 **Modafinil**

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Changes from baseline in ESS and FSS values, and in mean sleep latencies on MWT (in minutes):

40 **Conclusion**

- After 6 treatment weeks and compared with the placebo group, the decrease in ESS scores was higher in the modafinil group
- 100 to 200 mg modafinil is effective and well tolerated in the treatment of posttraumatic EDS but not of fatigue

41 **Antipsychotic Interactions**

- Primary mechanism of action is due to D2 antagonism
- Dose dependent D2 receptor occupancy
- Variability in duration of D2 receptor occupancy
  - Haloperidol >>> Quetiapine
- Dopaminergic blocking competition in patient receiving concurrent stimulant and antipsychotic therapies
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42 **ICU Administration Recommendation**

To optimize sleep/wake cycle:

- AM: 6:00 – 9:00
- PM: 12:00 – 14:00
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In the setting of acute agitation or ICU-related delirium consider pharmacokinetic profile of each drug (half-life and receptor binding) to optimize administration times

43 **ETHOS Attendance Code**

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