Neurostimulants in Stroke Recovery

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Objectives

• Review principles of stroke recovery
• Understand considerations for use of medications to enhance recovery after stroke
• Identify commonly used neurostimulant medications for post-stroke recovery
• Use clinical cases to highlight possible indications for neurostimulant medication use post-stroke
• Understand considerations for choice of medication based on clinical experiences and current literature
Cognitive Changes after Stroke

- Arousal
- Attention
- Concentration
- Memory
- Executive functions
Stroke Recovery/Neuroplasticity

• Early onset of rehabilitation program improves functional recovery
  – focus on facilitating, directing or promoting plasticity of nerve tissue

• Neurotransmitters such as glutamate, dopamine, acetylcholine, norepinephrine, serotonin thought to be involved in plasticity process

• Stimulation and modulation of these neurotransmitter systems may increase recovery after acquired brain injury
General Considerations for Neurostimulant Use

- Goals of therapy
- Location of infarct/lesion
- Medical comorbidities
- Sedating medications
- Sleep
- Measures of efficacy
Clinical Cases

1. 69 yo M, large R MCA/ACA infarcts, lethargy/poor arousal, L hemiplegia, L neglect
2. 25 yo F, pontine hemorrhage, poor arousal and command-following
3. 62 yo F, L MCA infarct, moderate Broca’s aphasia, R hemiparesis, impaired attention
4. 46 yo M, anoxic BI, poor arousal, bradykinesia
Neurostimulant Medications

- Fluoxetine/SSRIs
- Donepezil
- Methylphenidate
- Modafinil
- Bromocriptine
- Levodopa

- Amantadine
- Memantine
- Zolpidem
SSRI

• Fluoxetine
  – FLAME study
  – Immediate administration > delayed
  – Possible clopidogrel interaction
  – Dosing: 20mg daily

• Other SSRIs
  – Less evidence for motor recovery
  – Positive effects on mood, dependency, disability
Donepezil

- Acetylcholinesterase inhibitor
- Associated with improvements in:
  - Cognitive function
  - Aphasia
  - Motor function
- Relatively good tolerability/safety profile
- Dosing: 5-10mg daily
Amantadine

- NMDA receptor antagonist, dopaminergic
- Most data in TBI
- Associated with:
  - Faster recovery in disorders of consciousness
  - Improved irritability/agitation
  - Improved memory and reaction time in subjects with concussion
- Fair tolerability
- Dosing: 100-200mg bid
Memantine

- NMDA receptor antagonist
- Possible neuroprotective effects
- Improvements in aphasia
- Good safety/tolerability
- Dosing: 10-20mg daily
Levodopa

• Dopaminergic
• Associated with improvements in:
  – motor function/motor learning
  – ?aphasia
  – ?mood
  – ?neglect
• Relatively good tolerability
• Dosing: 100-200mg daily to TID
Bromocriptine

• Dopaminergic
• Associated with improvements in:
  – aphasia
  – Cognition/memory/executive functioning
  – Neglect/inattention
• Variable tolerability
• Dosing: 2.5-10mg daily
Methylphenidate

• Dopamine, norepinephrine, serotonin
• Associated with improvements in:
  – arousal
  – motor function
  – Mood (post-stroke depression)
  – Cognitive function
  – Aphasia
• Fair tolerability at low doses
• Dosing: 2.5-5mg daily-bid
Modafinil

• CNS stimulant; monoaminergic
• Improvements in:
  – Arousal
  – Fatigue
  – Quality of life
• Good tolerability
• Cost/coverage possibly prohibitive
• Dosing: 100-200mg daily-bid
Zolpidem

• Non-benzodiazepine hypnotic
• Emerging data for use in disorders of consciousness
• Associated with:
  – Improved arousal in vegetative and minimally conscious states
  – Improved cerebral perfusion, metabolic activity in studies using functional neuroimaging
  – Improved verbal communication
• Low percentage of responders
• Good tolerability
• Dosing: 10-15mg, daily+
Case 1

- 69 yo M, no PMH
- R MCA, ACA infarcts, hemorrhagic conversion
- R hemicraniectomy
- Medical complications
- L hemiplegia, neglect
- Decreased arousal
- 50% command-following
Case 1

• Primary issues:
  – Arousal
  – Cognition
  – Hemiplegia

• Fluoxetine 20mg daily

• Modafinil
  – 100mg daily, initiated day 2 of IPR
  – Increased to 200mg daily week 2
Case 2

• 25 year-old female
• No PMH
• Pontine hemorrhage
• Poor arousal
• <30% command-following
Case 2

- Primary issue: arousal
- Methylphenidate: 5mg bid
- Markedly improved arousal
- >75% command-following
- Improved therapy participation
Case 3

- 62 year-old female
- Left frontal and basal ganglia infarcts
- Mild R hemiparesis
- History depression
- Expressive, Broca’s type aphasia
- Oral motor apraxia
- Decreased initiation
- Impaired attention
Case 3

• Primary issues:
  – Aphasia
  – Initiation
  – attention

• Donepezil 5mg daily

• Escitalopram 20mg daily
Case 4

• 46 year-old male
• Hypoxic ischemic brain injury
• CKD, HTN, DM1
• Bradykinesia on exam, R side > L side
• Shuffling gait
• Slowed processing
Case 4

• Primary Issues:
  – Arousal/attention
  – Bradykinesia

• Carbidopa/Levodopa
  – Initiated 25/100mg TID
  – Titrated up to 50/200mg TID
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Targeted neurotransmitter</th>
<th>Indications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>20mg daily (x3 months)</td>
<td>Serotonin</td>
<td>Motor recovery</td>
<td>Plavix interaction, QTc prolong, Serotonin syndrome</td>
</tr>
<tr>
<td>Donepezil</td>
<td>5-10mg daily</td>
<td>Acetylcholine</td>
<td>Cognition, Arousal, Aphasia, Motor function</td>
<td>Nausea, Irritability, Muscle cramps, seizure</td>
</tr>
<tr>
<td>Memantine</td>
<td>10-20mg daily</td>
<td>NMDA antagonist/glutamate</td>
<td>Cognition, Aphasia, Arousal</td>
<td>Dizziness, nausea, Headache, SJS</td>
</tr>
<tr>
<td>Levodopa</td>
<td>100-200mg daily - TID</td>
<td>Dopamine</td>
<td>Motor function, Aphasia, Neglect, mood</td>
<td>Anxiety, Hallucinations, Nausea, emesis, Orthostasis</td>
</tr>
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<tr>
<td>Bromocriptine</td>
<td>2.5-10mg daily</td>
<td>Dopamine</td>
<td>Aphasia, Cognition, Neglect</td>
<td>Hypotension, Lightheadedness, Nausea/emesis, Agitation</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>2.5 – 5mg bid (inc. as tol)</td>
<td>Dopamine, norepinephrine</td>
<td>Cognition, Arousal, Mood</td>
<td>Tachycardia, Paranoia/Irritability, Decreased appetite</td>
</tr>
<tr>
<td>Amantadine</td>
<td>100mg-200mg bid</td>
<td>NMDA antag./glutamate</td>
<td>Arousal, Agitation</td>
<td>Orthostasis, Seizure, Livedo reticularis</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5-10mg daily</td>
<td>GABA A agonist</td>
<td>Arousal</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Modafinil</td>
<td>200mg daily (100-400)</td>
<td>DA, NE, GABA Glutamate serotonin</td>
<td>Fatigue</td>
<td>Headache, nausea, Insomnia, anorexia, SJS</td>
</tr>
</tbody>
</table>
References

References

References

• Mead GE, Heish CF, Lee R et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database Syst Rev 2012; 11: CD009286