Pharmacological Therapies for Motor Recovery After Stroke

Jessica Colyer, MD
University of Kentucky
Department of Physical Medicine and Rehabilitation
13 April 2017

Presenter Disclosure Information

Jessica Colyer
Pharmacological Therapies for Motor Recovery After Stroke

FINANCIAL DISCLOSURE:
No relevant financial relationships exist

UNLABELED/UNAPPROVED USES DISCLOSURE:
Use of carbidopa/levodopa and SSRIs in patients with motor deficits from stroke is off-label/investigational only
Objectives

• Discuss medications utilized in the post-stroke recovery process
• Explore the evidence showing improvement of motor function with use of dopaminergic or serotonergic medications
• Address the stigma associated with antidepressant use

Stroke Stats

• Worldwide prevalence of stroke was 33 million in 2010
• Stroke was the second-leading global cause of death behind heart disease
• In the US, about 800,000 people have a stroke every year
• Stroke is the No. 5 cause of death in the United States, killing over 130,000 per year
High Cost and Disability

• Stroke costs the United States an estimated **$33 billion** each year
  – includes cost of health care services, medicines to treat stroke, and missed days of work.
• Stroke is a leading cause of serious long-term disability.
  – **reduces mobility** in >50% of survivors over age 65
Stroke Recovery

• Most stroke survivors recover over time, albeit to differing degrees
• Tissue plasminogen activator (tPA) thrombolysis within the first 4.5 h after the stroke is currently the only validated and registered treatment able to improve the spontaneous—and most of the time incomplete—recovery of neurological functions after stroke

Stroke Recovery

• Neurons, when destroyed after ischemia, are not restored despite localized neurogenesis
• Physiological basis of recovery is due to
  – Recruitment of remote functional areas
  – Over-activation of primary cortices
  – Changes in cortical maps
Can other meds help in recovery?

- Small animal model studies have shown that monoamine drugs can modify functional recovery
- Complex signaling cascades may mediate therapeutic effects exerted by antidepressants
  - Increased expression of neurotrophic factors
  - Neural and glial cell precursor proliferation
  - Axonal sprouting
  - Synapse formation
Dopamine

• Dopamine or 3,4-dihydroxyphenethylamine (DA) is an organic molecule that acts as a local chemical messenger throughout the human body and acts as a neurotransmitter within the central nervous system (CNS)
• Dopamine may promote neuroplasticity in the cerebral cortex
• Animal studies suggest that dopamine is an important neurotransmitter for learning and working memory

Serotonin

• Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter primarily found in the GI tract, platelets, and the CNS
• Popularly thought to be contributor to feelings of well-being and happiness
• Serotonin affects neuroplasticity related to brain development
• Selective serotonin reuptake inhibitors (SSRIs) have been shown to influence neurogenesis in the cerebral cortex and the hippocampal area
http://drjockers.com/boost-up-dopamine-for-motivation-and-focus/

REPLACING DOPAMINE
Carbidopa/Levodopa

• In 2001, Scheidtmann et al. randomized 53 patients between 3 weeks and 6 months post-CVA to either 100 mg of carbidopa/levodopa or placebo
• Treated with daily dose, 5 days per week, before PT session over a 3 week trial
• Levodopa arm showed significant improvement in motor recovery
  – in particular, earlier ability to walk independently

Adding Neurostimulant Not Helpful

• Subsequent small studies using levodopa with or without methylphenidate or levodopa with or without amphetamine could not show a difference in motor recovery or improvement in functional outcomes with treatment
• More study needed!
DARS Trial

• Dopamine Augmented Rehabilitation in Stroke trial started up in UK in 2010
• Plan to enroll 572 patients with a new stroke who cannot walk 10 m
• Will receive 100 mg of levodopa and 25 mg of carbidopa, or placebo, 1 h before PT
• Treated for a maximum of 6 weeks.
• Primary outcome will assess the number of patients walking independently at 8 weeks after randomization

REPLACING SEROTONIN
FLAME Trial

- FLAME: multicentered randomized double blind placebo controlled trial with FLuoxetine in Motor recovery of patients with Acute ischemic stroke
- Excluded if dx with depression, aphasia, etc
- 9 stroke centers – patients randomly allocated to fluoxetine 20mg daily vs placebo
- All with PT during duration/standard care
**FLAME Trial Results**

- **Fugl-Meyer Motor Score (FMMS)**
  - UE maximum score = 66; LE maximum score = 34
- Baseline, 30, and 90 days measurements

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fluoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMMS total</td>
<td>+24.3</td>
<td>+34</td>
</tr>
<tr>
<td>Upper limb</td>
<td>+13.1</td>
<td>+22.9</td>
</tr>
<tr>
<td>Lower limb</td>
<td>+9.5</td>
<td>+12.8</td>
</tr>
</tbody>
</table>

---

**Fugl-Meyer Assessment**

**Upper Extremity (FMA-UE)**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ID:</td>
<td>Date:</td>
</tr>
<tr>
<td>Examiner:</td>
<td></td>
</tr>
</tbody>
</table>


A. Upper Extremity, sitting position

<table>
<thead>
<tr>
<th>Reflex activity</th>
<th>can be elicited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexors: biceps and finger flexors (at least one)</td>
<td>0 2</td>
</tr>
<tr>
<td>Extensors: triceps</td>
<td>0 2</td>
</tr>
</tbody>
</table>

Subtotal I (max 4)

B. Volitional movement within synergies, without gravitational help

<table>
<thead>
<tr>
<th>None</th>
<th>Partial</th>
<th>Full</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexor synergy: Hand from contralateral knee to ipsilateral ear. From extensor synergy (shoulder adduction/ internal rotation, elbow extension, forearm pronation) to flexor synergy (shoulder abduction/ external rotation, elbow flexion, forearm supination). Extensor synergy: Hand from ipsilateral ear to the contralateral knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder retraction elevation abduction (90°) external rotation</td>
<td>0 1 2</td>
<td></td>
</tr>
<tr>
<td>Elbow flexion</td>
<td>0 1 2</td>
<td></td>
</tr>
<tr>
<td>Forearm supination</td>
<td>0 1 2</td>
<td></td>
</tr>
<tr>
<td>Shoulder adduction/internal rotation Elbow extension Forearm pronation</td>
<td>0 1 2</td>
<td></td>
</tr>
</tbody>
</table>

Subtotal II (max 18)
FLAME Trial Results

• Fugl-Meyer Motor Score (FMMS)
  – UE maximum score = 66; LE maximum score = 34
• Baseline, 30, and 90 days measurements

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fluoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMMS total</td>
<td>+24.3</td>
<td>+34</td>
</tr>
<tr>
<td>Upper limb</td>
<td>+13.1</td>
<td>+22.9</td>
</tr>
<tr>
<td>Lower limb</td>
<td>+ 9.5</td>
<td>+12.8</td>
</tr>
</tbody>
</table>

SSRI use = less disability

• Patients treated with fluoxetine were more likely to reach functional independence as measured by the modified Rankin Scale (score varies from 0 to 6, 0 = normal, 6 = death)
FLAME Adverse Events

• Transient digestive disorders
• Insomnia

• Depression was high in placebo treated group

Trial for hemorrhagic CVA

• Fluoxetine for motor recovery after acute intracerebral hemorrhage (FMCH): study protocol for a randomized, double-blind, placebo-controlled, multicenter trial
  – Recruitment halted due to lack of funding
  – Final data collection August 2014
Earlier the better

- Narushima et al. compared 34 patients treated with antidepressants within 1 month of index stroke (mean time post stroke, 19 days) to patients with later treatment initiation (mean time post stroke, 140 days).
- Daily general function as measured by the FIM was superior in the early initiation of treatment group, suggesting a time-related therapeutic window for quality of life and perhaps antidepressant therapy post stroke.
Even short course helps

- Jorge et al demonstrated improvement in clinical outcome and decreased mortality with antidepressant use within 6 months of index stroke independent of baseline depressive status.
- RCT indicated that even a short, 12-week course of antidepressant use after the index episode of stroke has a protective effect in long-term outcome.

But there’s this...

Rick Warren @RickWarren 6d
Why is it...if any other organ in your body breaks you get sympathy, but if your brain breaks, you get secrecy and shame?
Stigma of Mental Illness

• Stigma is a social construct that defines a person based on a specific or distinctive characteristic or mark that has as its primary consequence the devaluation of the individual.

Stigma of Mental Illness

• Stigma against mental illness is influenced by a number of factors:
  – Nature and gravity of the disease
  – Personal relationship to the disease
  – Degree of willingness to reveal its existence to others
Stigma with Treatment

• Stigma of depression is associated with a difficulty in dealing with problems, indicating emotional weakness
• Stigma relating to the use of antidepressants appears to be similar to the stigma of depression weakness and an inability to deal with emotional problems
  – Whites, African-Americans, and Latinos seem to hold very different attitudes regarding acceptance of the therapy prescribed for depression

How to Stop the Stigma

• Media campaign in the UK reduced stigma and improved reaching out for treatment
• Theatre was used as a successful way of changing attitudes toward the mentally ill in a community in Australia
• Blogs/Personal Experiences increase awareness
• Key is to individualize – unique to culture
Even if you’re not depressed

- Robinson et al. = 176 nondepressed patients were randomized to 3 treatment arms within 3 months of acute stroke, either ischemic or hemorrhagic. One year trial time frame
- First arm, 10 mg escitalopram daily if <age 65 and 5 mg daily if > 65
- Second arm received only placebo
- Third arm received “problem-solving” psychological therapy program
- Both escitalopram and problem-solving therapy were significantly better than placebo in lowering the incidence of depression
- Only treatment with the SSRI remained statistically significant in an intention-to-treat (ITT) analysis.
- Patients who received placebo were 4.5 times more likely to suffer clinically defined major or minor depression when compared to patients receiving escitalopram

Conclusions

- Carbidopa/levodopa may have significant role in post-stroke motor recovery
- FLAME trial revealed significant evidence improvement of motor function with use of fluoxetine following CVA
- Antidepressant use has associated stigma for myriad of factors which have to be ameliorated prior to patient acceptance
References

- Poststroke Depression: A Review Emphasizing the Role of Prophylactic Treatment and Synergy with Treatment for Motor Recovery. Murray Flaster, MD, PhD, Aparna Sharma, MD, and Murali Rao, MD. Top Stroke Rehabil 2013;20(2):139–150
- Selective Serotonin Reuptake Inhibitors for Stroke Recovery. Gillian Elizabeth Mead, FRCP; Cheng-Fang Hsieh, MD; Maree Hackett, PhD. JAMA September 11, 2013 Volume 310, Number 10
- Perceptions of and Attitudes Toward Antidepressants Stigma Attached to Their Use- A Review. Joao Mauricio Castaldelli-Maia, MD,Luciana Bunn Scomparini, MD, Arthur Guerra de Andrade, MD, PhD, Dinesh Bhugra, MA, MSc, MBBS, FRCP, FRCPsych, MPhil, PhD, Tania Correa de Toledo Ferraz Alves, MD, PhD, and Gilberto D’Elia, MD, PhD. The Journal of Nervous and Mental Disease Volume 199, Number 11, November 2011