Objectives
- To understand the rationale for using SSRIs for post-stroke motor recovery
- To compare and contrast the FLAME and FOCUS trials
- To discuss the potential for SSRIs in post-stroke motor recovery

Patient Case
- A 50 year old man presented to the ER one week ago.
- He was diagnosed and treated for an ischemic stroke.
- The patient is started on aspirin 81 mg and atorvastatin 40 mg daily.
- Baseline NIHSS score 8, FMMS total score 52.

Should fluoxetine 20 mg be added to this patient's post-stroke management?
A. Yes, the data supports its use for both motor recovery and depression prevention
B. Yes, but only for depression prevention
C. Yes, but only for motor recovery
D. No, the data does not support use for either motor recovery, nor depression prevention

Abbreviations Used
- FMMS: Fugl-Meyer motor scale
- HSS: Hemispheric stroke scale
- MADRS: Montgomery-Asberg depression rating scale
- mRS: Modified Rankin Scale
- NIHSS: National Institute of Health Stroke Scale
- SIS: Stroke Impact Scale
- smRSq: Simplified Modified Rankin Scale Questionnaire
- TCA: Tricyclic antidepressant

Disclosures
No financial conflicts to disclose
Background Information

What is Stroke?

- Types:
  - Ischemic Stroke
  - Hemorrhagic stroke

- Signs and Symptoms:
  - Sudden onset of:
    - Numbness
    - Confusion
    - Vision changes
    - Motor ability
    - Severe headache

- Recognition: FAST

Sequelae of Stroke

- Stroke survivors are often affected by psychological distress and neuropsychological disturbances
  - ⅓ depression, anxiety, apathy

- Left Brain
  - Paralysis on right side
  - Speech/Language Problems
  - Slowed/Inattentive behavior
  - Memory Loss

- Right Brain
  - Paralysis on left side of body
  - Agitated/Impulsive behavior
  - Quick, inquisitive behavior
  - Memory Loss

Motor Recovery Post-Stroke

Stroke is the most frequent cause of adult-onset disability in the U.S. Hemiparesis/hemiplegia, paralysis on one side of the body:

- Affects 70-80% of stroke survivors and is often the deficit most in need of rehabilitation

- Sense of Permanence:
  - 20-25% are unable to walk without full physical assistance
  - 35% with initial paralysis of the leg do not regain useful function
  - 42% of patients cannot incorporate the affected limb into their usual activities
  - Only 25% return to comparable level of functioning when compared to non-stroke persons

- Functional scales tend to plateau of gains by 3 to 4 months after stroke

Measuring Stroke Impairment

General Stroke Impairment Scales:
- National Institute of Health Stroke Scale
- European Stroke Scale
- Modified Rankin Scale

Specific Neurologic Impairment Scales
- Motor Impairments: Fugl-Meyer Assessment, Motor Assessment Scale, Motricity Index
- Balance: Berg Balance Scale
- Mobility: Rivermead Mobility Index
- Aphasia: Frenchay Aphasia Screening Test
- Cognition: Montreal Cognitive Assessment

National Institute of Health Stroke Scales (NIHSS)

- A scale used to objectively quantify the degree of impairment caused by stroke
- The most commonly used scale in the United States

- 11 domains:
  - Level of consciousness, horizontal extraocular movements, visual fields, facial palsy, left/right arm motor drift, right/left leg motor drift, limb ataxia, sensation, Language/Aphasia, dysarthria, extinction/attention

- Score of <6 usually indicative of patient recovery, >16 predictive of death

- Increases of 1 point decreases chance of positive outcome by 17%

- High degree of reliability and validity

References:
Modified Rankin Scale (mRS)
- Measurement of neurologic disability
- 0: No symptoms at all
- 1: Able to carry out all usual duties and activities
- 2: Unable to carry out all previous activities, but able to look after own affairs without assistance
- 3: Requires some help, but able to walk without assistance
- 4: Bedridden, incontinent, and requiring constant nursing care
- 5: Dead

Validity and reliability:
- Strong test-retest validity, moderate inter-rater reliability

Simplified mRS Questionnaire
- Able to live alone without assistance?
- Able to do everything prior to stroke, even if slower?
- Return to baseline?
- Able to walk from one room to another without assistance?
- Able to sit up in bed without assistance?

Fugl-Meyer Motor Scale (FMMS)
- A method for assessment of motor recovery after stroke
- Five domains: Max score of 226
  - Motor function
  - Sensory function
  - Balance
  - Joint Range
  - Joint Pain
- Motor Function Component: Max score of 100/226 points
  - 66 points for upper limb, 34 for lower limb
  - Score of 0 = hemiplegia; 100 = normal motor function
- Validation: Reasonable to measure motor function for stroke patients

Motor Recovery: The Theory
- Neural plasticity: The ability of the brain to adapt to changes in the environment or lesions
  - Biological: Recovery of injured tissue, engagement of new uninjured areas, and training of other areas to perform new functions
  - Behavioral: Recovery of function and limitation of ability to pre-injury level

Motor Recovery: Non-Pharmacologic
- Non-pharmacological Interventions:
  - Activities of daily living (ADLs)
  - Strengthening
  - Weight-bearing
  - Joint mobilization
  - Manual therapy
  - Electric stimulation

Motor Recovery: Pharmacological Interventions
- Pharmacological Interventions:
  - Tissue Plasminogen Activator (tPA): given within 4.5 hours → improved recovery post-stroke
  - Dopamine: May promote neuroplasticity in the cerebral cortex
  - Amantadine: Increased recovery speed during active treatment phase and improved Disability Rating Score (DRS)
  - Carbidopa/Levodopa: Significant improvement in motor recovery and earlier ability to walk independently
  - +/- methylphenidate or amphetamine → no difference

References:
5. Sharma N. Handb Clin Neurol. 2013
What about Serotonin?

- Serotonin (5-HT) and Brain-Derived Neurotrophic Factor (BDNF)
  - Regulate synaptic plasticity, neurogenesis, and neuronal survival
  - Previous studies have looked into implication in promoting healthy brain aging
- Proposed mechanism in post-stroke:
  - Neuroprotective effect through anti-inflammatory effects
  - InCREASED hippocampal neurogenesis
  - Increase in serotonin levels = enhanced neural plasticity
- Implicated in modulating neuronal plasticity
  - Animal studies = neurogenesis and activation of cortical motor areas

- Previously studied serotonin modulators:
  - Citalopram
  - Fluoxetine

Previous Studies

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Time of Inclusion after stroke</th>
<th>Clinical outcomes</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel</td>
<td>1-6 months</td>
<td>Graded neurological scale (HSS)</td>
<td>10.7% improvement in HSS score</td>
</tr>
<tr>
<td>crossover</td>
<td>15-30 days</td>
<td>Finger tapping and dynamometer</td>
<td>20-30% finger tapping and dynamometer improvement</td>
</tr>
<tr>
<td>Parallel</td>
<td>Not reported</td>
<td>NIHSS score</td>
<td>38.8% improvement of NIHSS score</td>
</tr>
</tbody>
</table>

Rationale for Studies

- Debilitating after-effects of stroke + Decreased Quality of Life
  - Continued weakness, paralysis, balance and gait problems
  - Inattention to one side of the body
  - Tingling sensations
  - Currently low rates of recovery, full or partial
  - No definitive treatments
  - Promising results of previous trials

Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial


**FLAME Trial- Trial Design**

- Multicenter, double-blind, randomized, placebo-controlled
- Population: Acute ischemic stroke within past 1-10 days that caused hemiparesis or hemiplegia ≥ 40 y.o., with NIHSS > 20
  - Excluded: NIHSS < 20, current antidepressant use, residual motor deficit from previous stroke
- Intervention: Randomly allocated to placebo or fluoxetine 20mg daily. All patients get physiotherapy
- Outcomes: Primary: Mean change in NIHSS score between inclusion and day 90
  - Secondary: NIHSS, mRS, and FAMAS, all scores measured at baseline, day 30 and day 90

Literature Review: FLAME Vs. FOCUS
Statistics
- Designed for 90% power for a difference detection of 40% in FMMS score
  - E.g. 12 points = full recovery of six functions or incomplete recovery of 12 functions after 3 months
- Student’s T-test or Mann-Whitney for FMMS, NIHSS, and MADRS at day 90
- CHI-squared for mRS scored
  - Independent: scores 0-2
  - Non-independent: scores 3-5
- Analyses adjusted for center, age, history of stroke, and mRS or NIHSS score at baseline

FLAME: Study population

<table>
<thead>
<tr>
<th>Baseline Patient Characteristics</th>
<th>Fluoxetine (n=68)</th>
<th>Placebo (n=68)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS (0-20)</td>
<td>13.8 (3.4)</td>
<td>13.1 (3.8)</td>
<td>0.50</td>
</tr>
<tr>
<td>Total FLAME Score (0-100)</td>
<td>71.9 (17)</td>
<td>71.4 (21)</td>
<td>0.60</td>
</tr>
<tr>
<td>Upper Limb FMMS (0-10)</td>
<td>5.8 (3.1)</td>
<td>7.1 (5.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Lower Limb FMMS (0-10)</td>
<td>11.6 (7.9)</td>
<td>8.7 (6.0)</td>
<td>0.00</td>
</tr>
<tr>
<td>Modified Rankin Score (0-5)</td>
<td>2.5 (1.5)</td>
<td>2.7 (1.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>NIHSS &lt;20%</td>
<td>35 (51)</td>
<td>36 (53)</td>
<td>0.70</td>
</tr>
<tr>
<td>Total FLAME score ≤ 100%</td>
<td>68 (76)</td>
<td>68 (76)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

FLAME: Primary Outcome

<table>
<thead>
<tr>
<th>Change from Day 0 to 90</th>
<th>Fluoxetine (n=68)</th>
<th>Placebo (n=68)</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>36.6 (21.3)</td>
<td>39.5 (21.7)</td>
<td>-2.9 (10.4)</td>
<td>0.035</td>
</tr>
<tr>
<td>Adj. Mean (95%CI)</td>
<td>34.1 (29.7 to 38.5)</td>
<td>34.1 (29.7 to 38.5)</td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td>Upper Limb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>26.1 (23.4)</td>
<td>26.1 (23.4)</td>
<td>0.0 (10.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Adj. Mean (95%CI)</td>
<td>24.5 (20.0 to 29.0)</td>
<td>24.5 (20.0 to 29.0)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Lower Limb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>15.5 (8.4)</td>
<td>15.5 (8.4)</td>
<td>0.0 (10.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Adj. Mean (95%CI)</td>
<td>13.9 (8.0 to 16.3)</td>
<td>13.9 (8.0 to 16.3)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Non-independence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS score 0-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>33.0 (14.2)</td>
<td>33.0 (14.2)</td>
<td>0.0 (10.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Adj. Mean (95%CI)</td>
<td>31.4 (12.9 to 16.9)</td>
<td>31.4 (12.9 to 16.9)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>mRS score 3</td>
<td>6 (9)</td>
<td>10 (15)</td>
<td>4 (7)</td>
<td>0.05</td>
</tr>
<tr>
<td>mRS score 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS score 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from day 0 to 90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-0.1 (-2.1 to 1.9)</td>
<td>3.2 (1.1 to 5.3)</td>
<td>3.3 (1.1 to 5.3)</td>
<td>0.032</td>
</tr>
<tr>
<td>Adj. Mean (95%CI)</td>
<td>-0.1 (-2.1 to 1.9)</td>
<td>3.2 (1.1 to 5.3)</td>
<td>3.3 (1.1 to 5.3)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

FLAME: Secondary Endpoints

<table>
<thead>
<tr>
<th>NIHSS score at 90 days</th>
<th>Fluoxetine n=68 (%)</th>
<th>Placebo n=68 (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Score</td>
<td>5.1 (3.4)</td>
<td>6.0 (4.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>Modified Rankin Score</td>
<td>2.5 (1.5)</td>
<td>2.7 (1.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>NIHSS ≤ 20%</td>
<td>35 (51)</td>
<td>36 (52)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

FLAME: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Fluoxetine n=68 (%)</th>
<th>Placebo n=68 (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>3 (5)</td>
<td>4 (7)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7 (10)</td>
<td>4 (7)</td>
<td></td>
</tr>
<tr>
<td>Hepatic enzyme disorders</td>
<td>5 (9)</td>
<td>10 (18)</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>19 (25)</td>
<td>20 (36)</td>
<td></td>
</tr>
<tr>
<td>Partial seizures</td>
<td>1 (2%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

FLAME: Results

- Mean FMMS upper and lower limb score from baseline to day 90 was significantly higher in the fluoxetine group
- No statistically significant difference in NIHSS, after 3 months
- Adjusted NIHSS score of 0-2 was not significantly different between the groups
- Significant difference between groups for mRS independence, as measured by mRS score 0-2
- At 90 days, gain was significant for both upper and lower limb scores
- Adjusted mean FMMS score was significantly higher in the fluoxetine group
FLAME: Discussion Points

Study Limitations:
- Small patient population
- Selected for motor deficit, and not representative of general stroke population
- Trial duration of 90 days

Gaps:
- Number of patients on depression dosing?

Suggestions for the future:
- More inclusive population
- Use of mRS scale vs. FMMS

Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial


FOCUS: Study Design

Trial Design
- Multicenter, parallel group, double-blind, randomized, placebo-controlled

Population
- 1977 adults with clinical diagnosis of acute stroke with brain imaging compatible with ischaemic or haemorrhagic stroke, persisting focal neurological deficit (NIHSS) requiring 6 months of treatment.

Excluded
- Subarachnoid, unless secondary to intracerebral hemorrhage, history of seizures, attempted suicide, or have taken medications within the past 5 weeks that have serious interactions with fluoxetine.

Intervention
- Fluoxetine (20mg daily) versus placebo

Outcomes
- Primary: functional status, measured with the mRS at 6-month follow-up (pointing towards independence). Functional status at 6 and 12 months (mRS), and health status using the Stroke Impact Scale (SIS). Likert scale for arm, hand, leg strength etc.

FOCUS: Statistics

- Goal to recruit 3000 patients; n=3127
- 90% power to detect increase in the proportion of patients with good outcomes (mRS 0-2) from 39.6% to 44.7%; 5.1% absolute difference

Primary analyses: patients were retained in groups they were assigned, regardless of treatment received.
- Secondary safety analysis: based on what patients actually received

FOCUS: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fluoxetine (n=1564)</th>
<th>Placebo (n=1563)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Stroke (%)</td>
<td>1410 (90)</td>
<td>1406 (90)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke (%)</td>
<td>154 (10)</td>
<td>157 (10)</td>
</tr>
<tr>
<td>NIHSS (median)</td>
<td>6 (3-11)</td>
<td>6 (3-11)</td>
</tr>
<tr>
<td>Presence of Motor Deficit (%)</td>
<td>1361 (87)</td>
<td>1361 (87)</td>
</tr>
<tr>
<td>Current Diagnosis of Depression (%)</td>
<td>9 (0.6)</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>Other complications (%)</td>
<td>66 (4.2)</td>
<td>77 (4.9)</td>
</tr>
<tr>
<td>Mean delay in treatment start (days)</td>
<td>9.8 (3.3)</td>
<td>9.3 (3.1)</td>
</tr>
<tr>
<td>Tablet return at end of study (%)</td>
<td>95 (6)</td>
<td>96 (6)</td>
</tr>
<tr>
<td>Adherence (% mean)</td>
<td>185</td>
<td>183</td>
</tr>
</tbody>
</table>

FOCUS: Primary Outcome

- No difference in mRS scores at 6-months

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fluoxetine (n=1553)</th>
<th>Placebo (n=1553)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0 (%)</td>
<td>114 (7)</td>
<td>124 (8)</td>
</tr>
<tr>
<td>mRS 1 (%)</td>
<td>302 (19)</td>
<td>309 (20)</td>
</tr>
<tr>
<td>mRS 2 (%)</td>
<td>156 (10)</td>
<td>155 (10)</td>
</tr>
<tr>
<td>mRS 3 (%)</td>
<td>518 (33)</td>
<td>510 (33)</td>
</tr>
<tr>
<td>mRS 4 (%)</td>
<td>121 (8)</td>
<td>122 (8)</td>
</tr>
<tr>
<td>mRS 5 (%)</td>
<td>213 (14)</td>
<td>203 (13)</td>
</tr>
<tr>
<td>mRS 6 (%)</td>
<td>129 (8)</td>
<td>130 (8)</td>
</tr>
</tbody>
</table>

FOCUS: Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fluoxetine</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Impact Scale (SIS)</td>
<td>Fluoxetine: 37 (35.69)</td>
<td>Placebo: 37 (34.89)</td>
<td>0.0835</td>
</tr>
<tr>
<td>Mobility</td>
<td>Fluoxetine: 63.89 (36.11-86.11)</td>
<td>Placebo: 63.89 (33.33-88.89)</td>
<td>0.5486</td>
</tr>
<tr>
<td>Motor</td>
<td>Fluoxetine: 54.86 (27.31-83.33)</td>
<td>Placebo: 56.78 (28.75-82.64)</td>
<td>0.5125</td>
</tr>
</tbody>
</table>

Survival

- 6 months: Fluoxetine: --, Placebo: --
- 12 months: Fluoxetine: --, Placebo: --

FOCUS: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Fluoxetine</th>
<th>Placebo</th>
<th>Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stroke</td>
<td>56 (3.58%)</td>
<td>64 (4.09%)</td>
<td>-0.51% (-1.90 to 0.80)</td>
<td>0.4543</td>
</tr>
<tr>
<td>Epileptic seizures</td>
<td>58 (3.71%)</td>
<td>40 (2.56%)</td>
<td>1.15% (-0.07 to 2.37)</td>
<td>0.0651</td>
</tr>
<tr>
<td>Fractured bone</td>
<td>45 (2.88%)</td>
<td>23 (1.47%)</td>
<td>1.41% (0.38 to 2.43)</td>
<td>0.0070</td>
</tr>
<tr>
<td>New depression</td>
<td>210 (13.43%)</td>
<td>269 (17.21%)</td>
<td>-3.78% (-6.30 to -1.26)</td>
<td>0.0033</td>
</tr>
<tr>
<td>New antidepressant</td>
<td>280 (17.90%)</td>
<td>357 (22.84%)</td>
<td>-4.94% (-7.76 to -2.12)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

NNH: 26

Fluoxetine 143 (9%) and placebo 122 (8%) stopped due to perceived adverse effects.


FOCUS: Results

- Fluoxetine does not significantly improve patients’ functional outcome or survival at 6 and 12 months.
- Incidence of new-onset depression was decreased at the cost of increased bone fractures at the 6-months.


FOCUS: Discussion Points

- Inclusion of hemorrhagic stroke
- 10% in both groups.
- Strengths:
  - Larger trial
  - Longer follow-up
  - Inclusive population.
- Weaknesses:
  - Adherence
  - Severity of patient population.


Trial Comparison

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FLAME Trial (n=118)</th>
<th>FOCUS Trial (n=3127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Severity (NIHSS)</td>
<td>~13 in both groups</td>
<td>~6 (3-11) in both groups</td>
</tr>
<tr>
<td>Interventions vs. Placebo</td>
<td>Fluoxetine 20mg daily for 60 days</td>
<td>Fluoxetine 20mg daily for 6 months</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Statistically significant change in FMMS (primary), total and lower limb score at 31 days</td>
<td>No difference in mRS scores 0-2 at 6 months vs. placebo.</td>
</tr>
<tr>
<td>Depression Development</td>
<td>Improvement defined as improvement in depression scales by at least one category across 90 days</td>
<td>Improvement defined as improvement in depression scales by at least one category across 90 days.</td>
</tr>
<tr>
<td>Improvement Scales</td>
<td>Hamilton Depression Inventory</td>
<td>Montgomery-Asberg Depression Rating Scale</td>
</tr>
<tr>
<td>Key Study Limitations</td>
<td>Size of population</td>
<td>Patient adherence</td>
</tr>
</tbody>
</table>


Patient Case

- A 50-year-old man presented to the ER one week ago.
- He was diagnosed and treated for an ischemic stroke.
- The patient is started on aspirin 81 mg and atorvastatin 40 mg daily.
- Baseline NIHSS score 8, FMMS total score 52.

Should fluoxetine 20 mg be added to this patient’s post-stroke management?

A. Yes, the data supports its use for both motor recovery and depression prevention
B. Yes, but only for depression prevention
C. Yes, but only for motor recovery
D. No, the data does not support use for neither motor recovery, nor depression prevention

Take-home Points

- Stroke survival is associated with debilitating motor dysfunction
- NIHSS vs mRS vs FMMS
- The FOCUS Trial does not support the findings of the FLAME trial
  - Different scales used to measure primary outcome of improvement
  - Elicited vs. mRS
  - Differences in patient population
  - FMMS inclusion of hemorrhagic stroke
- Controversy in fluoxetine use - Not currently recommended

Future Studies

- **EFFECTS:** Efficacy of Fluoxetine - a randomized controlled trial in stroke
  - Randomized, placebo-controlled trial
  - Intervention: Fluoxetine 20g daily x 6 months
  - Primary outcome: Functional outcome measured by mRS
  - Estimated completion date: July 2020

- **FLOW:** Fluoxetine opens windows to improve motor recovery after stroke
  - Randomized, placebo-controlled trial
  - Intervention: Exercise rehabilitation and standard care rehabilitation +/- Fluoxetine
  - Primary outcome: FMMS Lower extremity score
  - Estimated completion date: September 30, 2020

- **AFFINITY:** The Assessment of Fluoxetine IN Stroke recovery
  - Multicenter, prospective, randomized double-blind placebo controlled trial
  - Intervention: Fluoxetine 20mg daily
  - Primary outcome: Functional outcome measured by mRS at 180 days

Acknowledgements

- Dr. Eimera Padilla-Tolentino, PharmD, PhD
- Dr. Y-Nha Nguyen, PharmD, BCPS, BCCP
- Dr. Mario Varela, PharmD, BCPS, BCIDP
- Dr. Alejandra Suarez, PharmD, BCPS, BCCP
- Dr. Justin Gonzalez, PharmD, BCPS