Stroke Recovery Drugs

Maria Humayun
Stroke recovery Drugs

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Disclosures

• None
Objectives

• Review different pharmacologic approaches that promote neural repair after stroke
• Spontaneous recovery
  • Acute phase
    • Neuronal excitotoxicity and cell death in infarcted core and peri infarct regions

• Subacute phase
  • Neuroplasticity
  • “Sensitive period” (Kumar, 2019)
• Medications that enhance recovery vs meds that promote neuroprotection

• Reperfusion therapies
  • Neuroprotection
  • Salvageable ischemic penumbra
  • Narrow therapeutic window

• Restorative therapies
  • plasticity and growth, improvements in behavioral outcome that are not accompanied by a reduction in infarct volume
  • Wider time window, days – months → stimulate plasticity
  • Target large percentage of stroke patients
• Restorative therapies
  • Medications
    • Small molecules, growth factors, monoclonal antibodies
  • Biological agents (stem cells)
  • Brain stimulation
  • Robotics
  • Activity based therapies
Why do we care?

• Leading cause of long term disability
• Motor deficits common after stroke (82% of stroke patients)
  • → reduced quality of life
  • @ 6 months, 65% still with deficits  (Cramer, 2015)
Selective Serotonin Reuptake Inhibitors

• Depression

• Influences learning, memory and neuroplasticity, modulating excitatory/inhibitory balance in brain

• Animal studies have shown that SSRIs may have other direct effects on the brain, such as encouraging the development of new brain cells
• Fluoxetine for Motor Recovery after Acute Ischemic Stoke (FLAME trial) (Chollet at al, 2011)
  • DB, placebo controlled phase II multicenter trial
  • 118 pts with ischemic stroke causing mod-severe hemi (median NIH SS13)
  • Randomized to fluoxetine 20mg daily or placebo x 90 days (started 5-10 days after CVA)
  • 90 days
  • All received rehabilitation
<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS scores on day 90</td>
<td>n=57</td>
<td>n=55</td>
<td>..</td>
</tr>
<tr>
<td>Total score, mean (SD)</td>
<td>5.8 (3.7)</td>
<td>6.9 (4.4)</td>
<td>0.151 †</td>
</tr>
<tr>
<td>Patients with score 0–5, adjusted mean (95% CI)</td>
<td>55% (45 to 64)</td>
<td>43% (34 to 52)</td>
<td>0.193 †</td>
</tr>
<tr>
<td>Motor scores, mean (SD)</td>
<td>4.7 (3.2)</td>
<td>6.3 (3.2)</td>
<td>0.012 ‡</td>
</tr>
<tr>
<td>mRS scores on day 90</td>
<td>n=57</td>
<td>n=55</td>
<td>..</td>
</tr>
<tr>
<td>Patients with mRS score 0–2 §</td>
<td>15 (26%)</td>
<td>5 (9%)</td>
<td>0.015 ‡</td>
</tr>
<tr>
<td>Patients with mRS score 0–2 §, adjusted mean (95% CI)</td>
<td>34% (25 to 43)</td>
<td>11% (6 to 15)</td>
<td>0.021 ‡</td>
</tr>
<tr>
<td>MADRS scores</td>
<td>n=56</td>
<td>n=54</td>
<td>..</td>
</tr>
<tr>
<td>Day 90, mean (SD)</td>
<td>5.4 (4.9)</td>
<td>8.4 (7.9)</td>
<td>..</td>
</tr>
<tr>
<td>Day 90, median (IQR)</td>
<td>4.5 (1.5 to 8)</td>
<td>7.5 (0 to 14)</td>
<td>0.101 †</td>
</tr>
<tr>
<td>Change from day 0 to day 90, mean (SD)</td>
<td>0 (6.1)</td>
<td>3.1 (9.1)</td>
<td>..</td>
</tr>
<tr>
<td>Change from day 0 to day 90, adjusted mean (95% CI)</td>
<td>-0.1 (-2.1 to 1.9)</td>
<td>3.2 (1.1 to 5.3)</td>
<td>0.032 ‡</td>
</tr>
</tbody>
</table>

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


• Results

  • Fugl-Meyer motor score was significantly greater in the fluoxetine group than in the placebo group
  • Proportion of patients who were independent in daily living (MRS score of 0–2) was significantly higher in the fluoxetine group than in the placebo group (26% vs 9%, p=0·015)
  • More participants were free from depression at 3 months in the fluoxetine group than in the placebo group (93% vs 71%; p=0·002).
• Cochrane Review
  • Results of 52 trials (4060 participants) of SSRIs in people who had had a stroke in the previous year
  • To find out whether SSRIs might reduce dependency and disability
  • Other trials did not test effect of fluoxetine on functional outcomes (mRS)
  • The review found promising evidence that SSRIs might improve recovery after stroke, even in patients who were not depressed

Mead et al, 2012
Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial (Focus trial collaboration, 2019)

- Phase III randomized placebo controlled trial
- N=3127
- Over 4.5 years
- Randomly allocated to fluoxetine 20 mg once daily or matching placebo, initiated between 2 days and 15 days after stroke onset x 6 months
- Primary outcome: modified Rankin Scale
- Secondary: survival; quality of life (stroke impact scale and EuroQol-5); mood (mental health inventory); fatigue (SF36); adverse events (events of specific interest: depression, fracture, cv events, seizures, metabolic abnormalities, bleeding, self-harm)
• No benefit on functional outcome of fluoxetine compared with placebo at 6 months (adjusted common odds ratio 0·951 [95% CI 0·839–1·079]; p=0·439)

• Fluoxetine reduced the occurrence of depression in the first 6 months after stroke (210 [13·43%] patients vs 269 [17·21%]; difference 3·78% [95% CI 1·26–6·30]; (p=0·0033)

• Increased the frequency of bone fractures (45 [2·88%] patients vs 23 [1·47%]; difference 1·41% [95% CI 0·38–2·43]; p=0·0070)

• Therefore, data does not support the use of fluoxetine with the aim of promoting functional recovery after stroke

(Focus trial collaboration, 2019)
<table>
<thead>
<tr>
<th>FLAME</th>
<th>FOCUS</th>
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</thead>
<tbody>
<tr>
<td>• Ischemic stroke</td>
<td>• Ischemic + hemorrhagic stroke</td>
</tr>
<tr>
<td>• 3 months</td>
<td>• 6 month treatment</td>
</tr>
<tr>
<td>• +Physiotherapy</td>
<td>• “Routinely available stroke rehabilitation in the UK”</td>
</tr>
<tr>
<td>• 1º outcome: FMMS</td>
<td>• 1º outcome: MRS</td>
</tr>
</tbody>
</table>
• FOCUS is not the final chapter in the SSRI-stroke story
  • AFFINITY
  • EFFECTS
Dopaminergic Drugs

• Linked with synaptic transmission, reward processing and regulation of movement
• Widely used for tx of PD
• Dopaminergic input into motor cortex contributes to neuroplasticity
• Early RCT (n=53), 100mg L-Dopa prior to PT x 3 weeks → ↑ motor improvement (Rivermead Motor assessment) compared to placebo
  (Scheidtmann, 2001)
• Subsequent trials negative
• Dopamine Augmented Rehabilitation in Stroke (DARS), June 2019
  • DB, RCT, N= 593
  • Randomized to co-careldopa or placebo x 6 weeks + PT/OT
  • Ischemic or hemorrhagic CVA, unable to walk > 10 m, scored <7 Rivermead
  • Primary Outcome: ability to walk independently (Rivermead score > 7) @8 weeks

Ford et al, 2019
• Results:
  • No evidence that the ability to walk independent improved with co-careldopa (125 (41%) of 208) compared with placebo (127 (45%) of 285 patients)
  • No difference in mortality
  • Similar adverse events

Ford et al, 2019
GABAergic or Glutamatergic Drugs

• Peri infarct region becomes hypo excitable due to increases in GABA
• Enhancing glutamatergic signaling is another way to upregulate excitability

Kumar et al, 2019
• Other drugs
  • Noradrenergic drugs
    • Amplifies neuronal activity, increases general level of excitability and selectively amplifies activities evoked
    • Atipamezole
    • Reboxetines
  • Cholinergic drugs
    • Attention, cognitive flexibility
    • Donepezil
  • Amphetamines
    • RCT 71 pts with subacute stroke did not show drug related benefit

Kumar et al, 2019
Summary

• More studies are still needed!
References


• Ford, G et al. Safety and efficacy of co-careldopa as a add-on-therapy to occupational and physical therapy in patients after stroke (DARS): a randomised, double blind, placebo controlled trial. Lancet. 2019 June; Volume 18: 530-538


