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Stroke Recovery Drugs

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Stroke recovery Drugs

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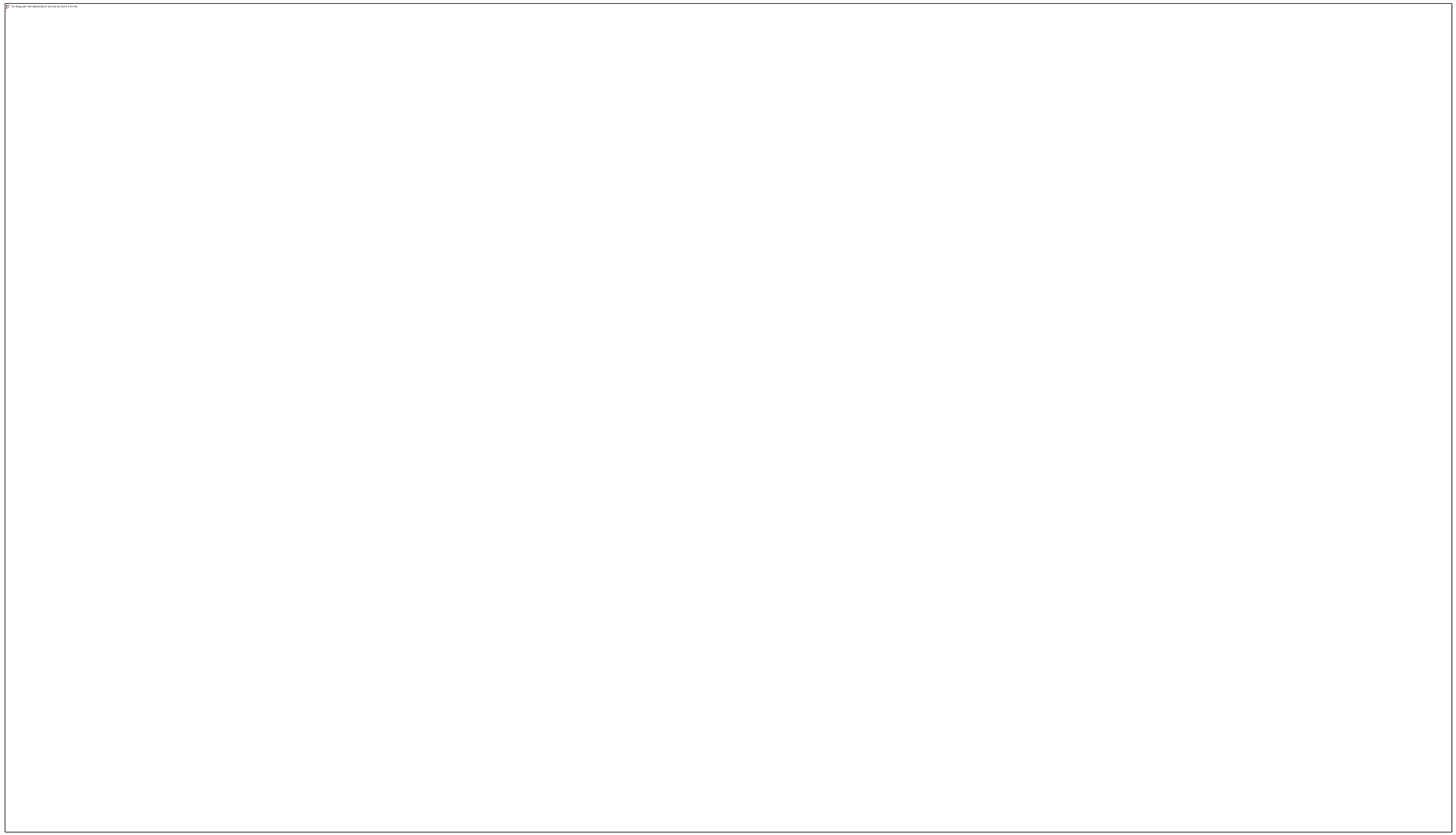
Disclosures

- 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)



https://www.researchgate.net/figure/Anatomical-and-functional-changes-in-brain-after-stroke-Representation-of-the_fig1_277087731

- 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

† Linear regression including treatment and centre as fixed effects, and confounding factors (age, history of

	Fluoxetine	Placebo	p value
NIHSS scores on day 90	n=57	n=55	..
Total score, mean (SD)	5·8 (3·7)	6·9 (4·4)	0·151 *
Patients with score 0–5, adjusted mean (95% CI)	55% (45 to 64)	43% (34 to 52)	0·193 †
Motor scores, mean (SD)	4·7 (3·2)	6·3 (3·2)	0·012 ‡
mRS scores on day 90	n=57	n=55	..
Patients with mRS score 0–2 §	15 (26%)	5 (9%)	0·015 ‡
Patients with mRS score 0–2 §, adjusted mean (95% CI)	34% (25 to 43)	11% (6 to 15)	0·021 ¶
MADRS scores	n=56	n=54	..
Day 90, mean (SD)	5·4 (4·9)	8·4 (7·9)	..
Day 90, median (IQR)	4·5 (1·5 to 8)	7·5 (0 to 14)	0·101 ‖
Change from day 0 to day 90, mean (SD)	0 (6·1)	3·1 (9·1)	..
Change from day 0 to day 90, adjusted mean (95% CI)	−0·1 (−2·1 to 1·9)	3·2 (1·1 to 5·3)	0·032 **

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

Lancet Neurology, The.

Chollet, François, Prof; Tardy, Jean, MD... Show all. Published February 1, 2011. Volume 10, Issue 2. Pages 123-130. © 2011.

- 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).

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- 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 andEuroQol-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)

FLAME

- Ischemic stroke
- 3 months
- +Physiotherapy
- 1º outcome: FMMS

FOCUS

- Ischemic + hemorrhagic stroke
- 6 month treatment
- “Routinely available stroke rehabilitation in the UK”
- 1º outcome: MRS

- 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!

https://www.mtzion.lib.il.us/kids-teens/question-mark.jpg/image_view_fullscreen

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