Presenter Disclosure Information

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FLAME: a multicenter randomized double-blind placebo-controlled trial with Fluoxetine in Motor Recovery of Patients with Acute Ischaemic Stroke.

NOTHING TO DISCLOSE

FLAME: a multicenter randomized double-blind placebo-controlled trial with Fluoxetine in Motor Recovery of Patients with Acute Ischaemic Stroke.

Artery deocclusion with IV thrombolysis within 4.5 hours after ischaemic stroke onset is currently the only validated treatment.

Brain spontaneous plasticity has been demonstrated in humans with stroke. Neural basis for spontaneous recovery.

Modulation of brain plasticity with monoaminergic drugs has been proposed to improve recovery after acute brain monofocal lesion (noradrenergic, serotoninergic…)

FLAME: a multicenter randomized double-blind placebo-controlled trial with Fluoxetine in Motor Recovery of Patients with Acute Ischaemic Stroke.

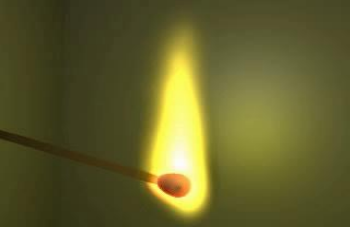
- Rationale for FLAME trial: Serotonin reuptake inhibitors modulate brain cortical activity:
  - Basic science (animal models):
    - Primary function of the brain serotoninergic system would be to facilitate motor output (**Jacobs 1997)**
    - neuroprotective effect in the post ischemic brain via its anti-inflammatory effects **(Lim et al 2009)**)
    - Improve ischaemia-induced spatial cognitive deficits by increasing hippocampal neurogenesis after stroke (**Li et al 2009**).
    - Serotonin enhances short-term facilitation, storage of long-term memory in sensorimotor synapses, long-term facilitation, growth factor gene expression. (**Loubinoux I, Chollet F 2010 Review**).
  - Few clinical trials with serotonin reuptake inhibitors. Small series.

FLAME: a multicenter randomized double-blind placebo-controlled trial with Fluoxetine in Motor Recovery of Patients with Acute Ischaemic Stroke.

- Inclusion criteria:
  - acute ischaemic stroke causing hemiparesia or hemiplegia**.**
  - No residual motor deficit from previous stroke
  - Fugl-Meyer Motor Scale (FMMS) score ≤ 55
  - randomized between day 5 and day 10 after stroke onset.
  - Informed consent
- Exclusion criteria
  - Significant premorbid disability or pre-existing deficit that could interfere with assessments: comprehension deficits, severe aphasia masking depression, severe neurological status (NIHSS >20).
  - Patients with a clinically diagnosed depression or MADRS score >19 ,
  - Patients on treatment with antidepressants, MAOI, neuroleptics or benzodiazepine during the month before inclusion
  - patients undergoing carotid endarterectomy
  - General exclusion criteria: renal, hepatic insufficiency, pregnancy…

FLAME: a multicenter randomized double-blind placebo-controlled trial with Fluoxetine in Motor Recovery of Patients with Acute Ischaemic Stroke.

- Patients from 9 stroke centers were randomly allocated to receive either fluoxetine 20mg o.d or placebo over 90 days.
- All patients, irrespective of the treatment arm, also received physiotherapy during the duration of treatment.
- All participants received standard care (organized in-patient stroke team care).
- Occuring depression:
  - Investigators instructed to continue treatment
  - 20 mg o.d open Fluoxetine given if necessary
  - If another antidepressant drug was given the study treatment was stopped.
  - The blinding code was not broken.
  - In all cases patients were followed until day 90.



Flow chart

N=118 patients with mild to severe motor deficit after ischemic stroke

INCLUSION

N=59 randomly allocated to Placebo

N=59 randomly allocated to Fluoxetine

N=1 deceased (Septic shock)
N=2 withdrew (Kidney tumour; Pulmonary embolism)

N=1 deceased (Respiratory distress after inhalation)
N=1 withdrew (Severe hypoxia)

DAY 90

N=56 analysed for primary endpoint in full data set analysis

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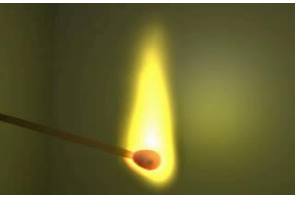
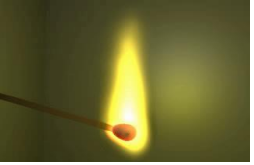


- **Outcome measures**
  - Primary outcome measure: mean progression of FMMS score (between inclusion and day 90).
    - All motor assessments were made at baseline (before inclusion) and then 30 and 90 days after inclusion.
  - Secondary endpoints
    - National Institutes of Health Stroke Scale [NIHSS] ,
    - Modified Rankin Scale
    - MADRS , all scores being measured at the same periods during the same visit.



Patients Characteristics at Inclusion (I)

	Placebo N=59	Fluoxetine N=59
Demographics		
Age (years), mean (SD)	62.9 (13.4)	66.4 (11.7)
Male sex, N (%)	35 (59.3)	37 (62.7)
BMI (kg/m²), mean (SD)	25.3 (4.2)	26.2 (4.4)
Vascular risk factors		
Diabetes, N (%)	11 (18.6)	14 (23.7)
Hypertension, N (%)	40 (67.8)	39 (66.1)
Dyslipidemia, N (%)	33 (55.9)	36 (61.0)
Smoking, N (%)	26 (44.1)	30 (51.7)
Previous cardiac disease, N (%)	28 (47.5)	34 (57.6)
Atrial fibrillation, N (%)	7 (12.1)	6 (10.2)
History of stroke, N (%)	4 (6.8)	10 (16.9)

Patients characteristics at inclusion (II)

	Placebo N=59	Fluoxetine N=59
Stroke lesion characteristics		
Location		
Carotid territory, N (%)	49 (83.1)	51 (86.4)
Vertebrobasilar territory, N (%)	4 (6.8)	6 (10.2)
Lacunar, N (%)	6 (10.2)	2 (3.4)
Baseline stroke severity		
FMMS, mean (SD)	13.4 (8.8)	17.1 (11.7)
Upper extremity FMMS, mean (SD)	4.7 (4.2)	5.5 (5.5)
Lower extremity FMMS, mean (SD)	8.7 (6)	11.6 (7.9)
NIHSS score, mean (SD)	13.1 (4.3)	12.8 (3.9)
NIHSS Motor component score, mean (SD)	10.3 (1.9)	9.9 (2.2)
Modified Rankin scale score		
3 Moderate disability, N (%)	0 (0)	2 (3.4)
4 Moderately severe disability, N (%)	22 (37.3)	25 (42.4)
5 Severe disability, N (%)	37 (62.7)	32 (54.2)
IV Trombolysis, N (%)	17(29.3)	21 (36.2)
MADRS score, mean (SD)	5.2 (5.5)	5.6 (5.9)

Primary Outcome Criteria

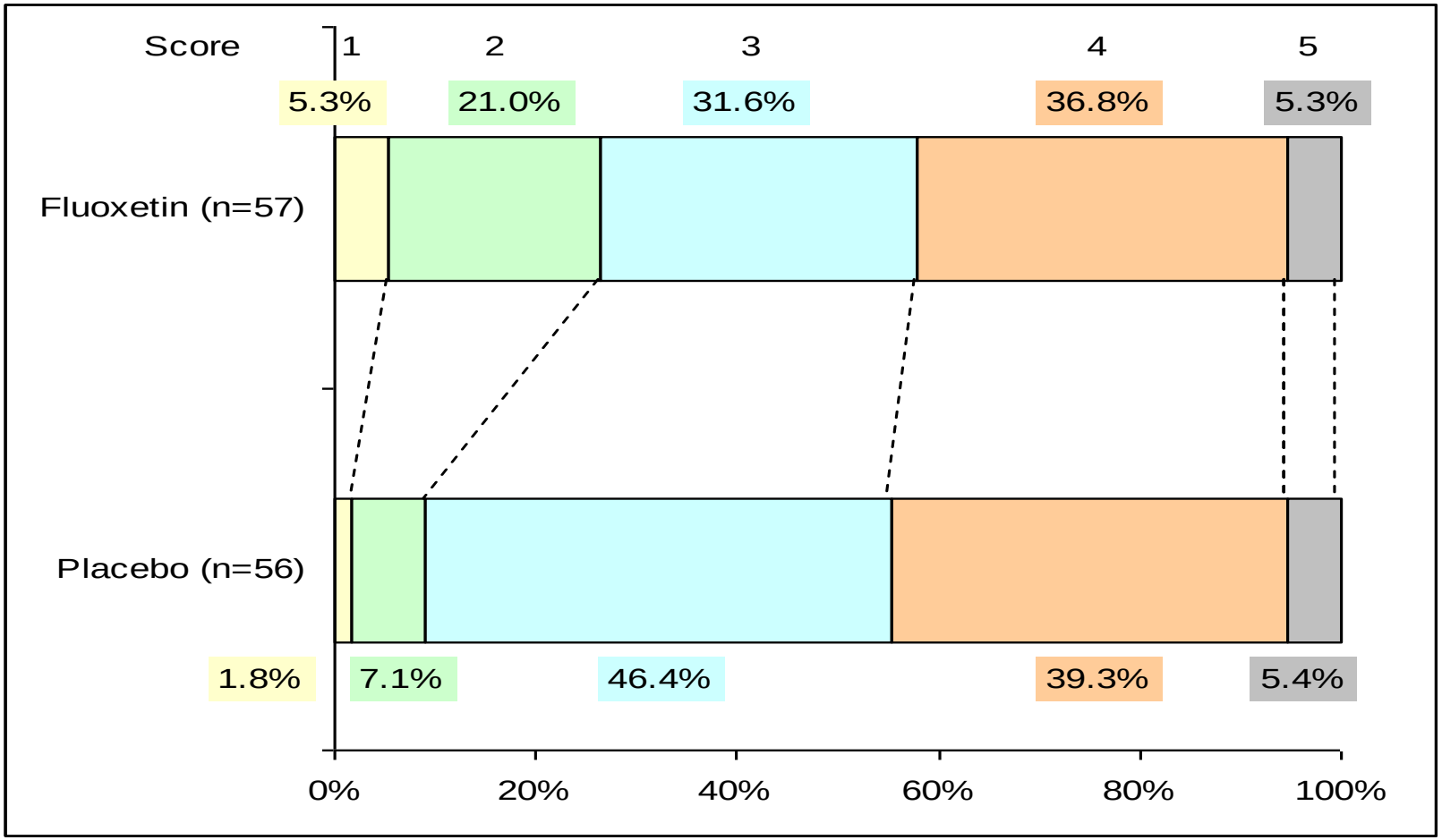
FMMS progression from D0 to D90

	Placebo	Fluoxetine	
FMMS, adjusted mean [95%CI]	+24.3 [19.9-28.7]	+34.0 [29.7-38.4]	0.003**
FMMS upper limb, adjusted mean [95%CI]	+13.1 [8.9-17.4]	+22.9 [18.6-27.1]	0.002**
FMMS lower limb adjusted mean [95%CI]	+9.5 [7.8-11.2]	+12.8 [11.1-14.5]	0.010**
	N=56	**N=57**	

FLAME: Secondary endpoints at D90

	Placebo	Fluoxetine	
	N=56	**N=57**	
NIHSS Total score on Day 90, mean (SD)	6.9 (4.4)	5.8 (3.7)	0 151
Patients with **NIHSS** score 0–5, adjusted mean (95% CI)	43% (34 to 52)	55% (45 to 64)	0 193
NIHSS Motor items on D 90, mean (SD)	6.3 (3.2)	4.7 (3.2)	0 · 012
	N=54	**N=56**	
MADRS score at day 90 [0-60], mean (SD)	8.4 (7.9)	5.4 (4.9)	0.101
0 to D90 **MADRS** score's variation, adjusted mean (SD)	3.2 (1.1 to 5.3)	–0.1 (–2.1 to 1.9)	0.032

FLAME: Distribution of Modified Rankin scale scores at day 90



	Placebo N=56	Fluoxetine N=57	
mRS at day 90, 0-2[$], N (%)	5 (8.9)	15 (26.3)	0.015

FLAME: adverse events

	Placebo	Fluoxetine
Depression	17 **	4
Hyponatremia	2	2
Transient digestive disorders	7	14
Hepatic Enzymes Disorders	10	6
Psychiatric Disorders	5	4
Insomnia	21	19
Partial Seizure	0	1

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- **Discussion (I)**
  - Other clinical trials in the field of brain-stimulating drugs
    - Amphetamine:
      - Several trials: Cristosomo 1988, Treig et al 2003, Platz et al 2005, Gladstone et al 2006, Walker-Batson 1995, Sonde et al 2007
      - Acute and more chronic strokes
      - Globally negative
      - But limited number of patients (from 8 to 71)
      - Dosage ? and regimen? Side effects?
    - Dopamine :
      - Conflicting results (Scheidtmann et al 2001, Sonde et al 2007)
    - Serotonin reuptake inhibitors
      - Limited number of trials: Dam et al 1996, Acker et al 2009, Zittel et al 2008, Pariente et al 2001, Gerdelat et al 2005
      - Small series (8 to 16 patients)
      - Acute and chronic strokes
      - Most of them positive suggesting a drug effect on motor recovery

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- **Discussion (II)**
  - Limitations:
    - number of patients,
    - selected patients,
    - long-term remaining effect (?)….
  - Mechanisms of action:
    - Antidepressive drug
      - serotonin reuptake inhibitors proved efficacy in post stroke depression (Freehwald et al 2003, Robinson et al 2008, Anderson et al 2008)
      - Prevent occurence of depression in FLAME trial
      - Mood effect in FLAME Trial

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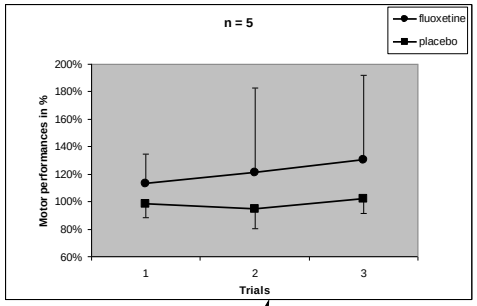
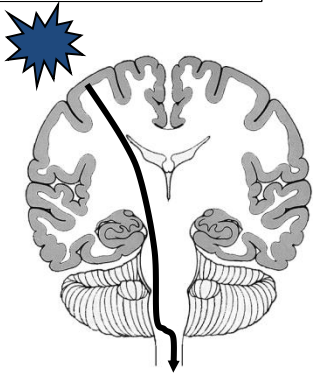
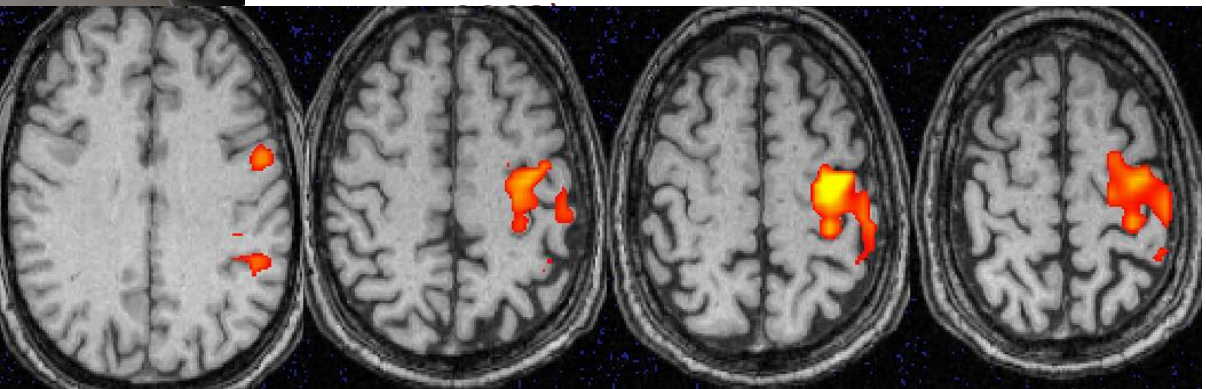
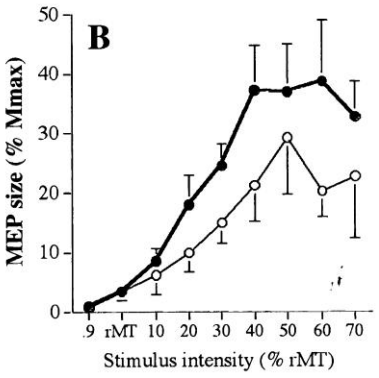


- **Discussion (III)**
  - Mechanisms of action:
    - Evidence for other mechanisms
      - Improvement of motor function and over activation of primary motor cortices after a single dose (Pariente et al 2001)
      - Hyper excitability of motor cortices with rTMS in normals after a single dose (Gerdelat et al 2005)
      - Hyopexcitability of motor cortices after chronic doses in normals (Gerdelat et al 2005) and in patients (Acler et al







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- **Conclusion:**
  - Fluoxetine improves motor function of patients with severe motor deficit when given early after ischemic stroke
  - Fluoxetine increases the number of independant patients at D90
  - Post stroke brain reorganization target either directly on motor function or indirectly through other networks or both
  - World public health interest
    - Fluoxetine in the public domain
    - Well-tolerated drug
    - No need for major technical facilities
    - Could be given to large cohorts of patients with ischaemic stroke

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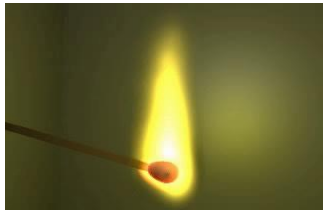

J Tardy, JF Albucher, C Arnaud, C Thalamas,
E Berard , Y Bejot M, C Lamy, S Deltour, A Jaillard,
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I Loubinoux