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FLUORESCE: A Pilot Randomized Clinical Trial of Fluoxetine for Vision Recovery After Acute Ischemic Stroke

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Background: Poststroke homonymous hemianopia is disabling, and complete spontaneous recovery is rare. In this randomized, placebo-controlled, double-blind, pilot clinical trial, we tested whether fluoxetine enhances vision recovery after stroke.
Methods: We randomized 17 consecutive adults 1:1 to 90 days of fluoxetine 20 mg daily vs placebo within 10 days of an ischemic stroke causing isolated homonymous hemianopia. The primary end point was percent improvement in 24-2 automated perimetry at 6 months. Twelve participants completed the study. Clinical trial registration NCT02737930.
Results: Intention-to-treat analysis of the primary end point, percent improvement in perimetric mean deviation, showed a nonsignificant benefit of fluoxetine (64.4%, n = 5) compared with placebo (26.0%, n = 7, one-tailed 95% confidence interval (CI) = (−2.13, ∞), $P = 0.06$). The original blind field completely recovered in 60% receiving fluoxetine and 14% receiving placebo (odds ratio = 7.22, one-tailed 95% CI = (0.50, ∞)).
Conclusion: These results suggest a trend in favor of fluoxetine for vision recovery after stroke and have the potential to inform the design of a larger multicenter trial.

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Strokes affecting the geniculostriate pathway lead to blindness in at least part of the visual hemifield contralateral to the lesion. This type of visual impairment occurs in an estimated 25% of all stroke patients (1). While about 50% of patients with a stroke affecting the geniculostriate pathway experience some degree of spontaneous improvement in their homonymous visual field deficits, only 12.5% completely recover vision (2). During spontaneous recovery, the blind field begins to contract within the first 10 days after stroke (3), with some patients continuing to improve out to 6 months (2,4). Beyond spontaneous recovery, current treatments for stroke patients with visual field deficits, including compensatory strategies, prism glasses, and computer-based visual retraining regimens, yield little to no additional benefit (5,6).

There has been a growing interest in the potential for plasticity-inducing pharmacological interventions, such as selective serotonin reuptake inhibitors (SSRIs), to enhance poststroke recovery. In animal models, SSRIs reopen the critical period for ocular dominance plasticity in adulthood (7) by altering the excitatory/inhibitory balance of the circuit (8,9). As reviewed by these authors elsewhere (9), numerous studies suggest that the SSRI-induced acute increase in local serotonin concentrations causes a decrease

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in long-range horizontal inhibition. This decrease in inhibition, paired with novel experiences, allows for the strengthening of unmasked preexisting connections and supports further synaptogenesis to generate new connections. Initial trials suggested that SSRIs in conjunction with rehabilitation therapy improve motor outcomes and decrease disability after stroke (10). More recent clinical trials did not confirm this effect; however, these trials did not ensure that SSRIs were paired with aggressive motor therapy (10–14; **Supplemental Digital Content 1**, http://links.lww.com/WNO/A614).

Because most basic science research investigating the neuroplastic effects of SSRIs has been conducted in the visual system, and reorganization of the visual circuit is possible (15–17), we hypothesized that fluoxetine initiated early after a stroke in patients with homonymous visual field deficits would improve vision recovery more than placebo. Here, we report pilot data from a randomized, placebo-controlled, double-blind, clinical trial of 90 days of fluoxetine 20 mg daily vs placebo in acute ischemic stroke patients with isolated homonymous visual field deficits. We are the first to study the potential for SSRIs to enhance poststroke vision recovery.

METHODS

Recruitment

Patients aged 18–85 years old with an MRI-confirmed ischemic stroke causing isolated homonymous hemianopia were prospectively enrolled at the University of Rochester Medical Center (Rochester, NY, FLUORESCE, NCT02737930). Table 1 lists inclusion and exclusion criteria. The University of Rochester Research Subjects Review Board approved the study (RSRB#00000781). Participants provided written informed consent.

Protocol

Participants were randomized 1:1 to 90 days of fluoxetine 20 mg vs placebo within 10 days of their strokes and received standard care. An Investigational New Drug (IND) application was submitted to the Food and Drug Administration (FDA) before study commencement. The FDA concluded that the study met all of the requirements for exemption from IND regulations. The investigational drug service at the University of Rochester manually created a randomization list using a block randomization scheme. The randomization list was stored in the study file that was located in a locked cabinet used solely by the investigational drug service to store study drugs. Access to the study file was only available to pharmacy staff. The pharmacist who enrolled the participant assigned them to a study arm by sequential numbering of the random allocation sequence. Researchers and participants were masked to assignments. Study visits occurred at enrollment and at 1, 3, and 6 months.

Sample Size Determination

Sample size was based on an estimated improvement in the visual field deficit of 50% of participants in the placebo group. A sample size of 20 per group afforded 80% power to detect 35% greater improvement in the fluoxetine group compared with placebo. We planned for an enrollment of 40 participants over 24 months. The trial was prematurely terminated due to failure to recruit the full sample size.

Data Collection and End points

Each participant completed a neuro-ophthalmology examination at the time of enrollment. At each visit, participants completed 24-2 automated perimetry for each eye. The modified Rankin Scale (mRS), a measure of global disability, was administered by a certified clinician at baseline and at 3 months and the 25-Item Visual Functioning Questionnaire (VFQ-25) at baseline (answered based on premorbid vision) and 6 months (18).

The primary end point was percent improvement in perimetric mean deviation (PMD) (mean vision sensitivity across all tested visual field locations) averaged between 2 eyes. Secondary end points included percent visual field recovered and incidence of complete recovery (defined as >95% recovery). To rule out the role of 1 treatment group having a greater practice effect than another on automated visual field testing, the difference (final visit minus initial visit) in the percent of fixation losses (losses per study-visit, summed over both eyes, and divided by the total number of trials in both eyes), false-positives (averaged over both eyes), and false-negatives (averaged over both eyes) were compared between the fluoxetine and placebo groups. Additional secondary end points were percent change in VFQ-25 and mRS score at 3 months. Data are available through FigShare, DOI:10.1184/R1/14489103.

Calculating Lesion Volume

The clinical diffusion-weighted image (DWI) scan, collected when the patient presented acutely to the hospital, was used to draw a lesion mask for each patient, using Clusterize, a semiautomatic lesion segmentation toolbox for SPM (19). This lesion mask was then isovoxeled, coregistered to the T1 anatomy collected at the first study visit for each patient, and converted to Talaraich space.

Definition of the Blind Visual Field

At each visit, 24-2 automated perimetry was completed for each eye (Zeiss HFAIIi, Swedish Interactive Threshold Algorithm (SITA) Standard, size III white target, fixation enforced, corrected for near vision). The cutoff of a sensitivity of 10 dB to define sighted vs blind test locations was chosen for 2 reasons: (1) this is the cutoff prescribed by the Guide for the Evaluation of Visual Impairment (20) and (2) a cutoff of 10 dB is equivalent to the stimulus strength

TABLE 1. Inclusion and exclusion criteria

Inclusion criteria	MRI-confirmed acute ischemic stroke Clinically verified homonymous visual field deficit without neglect
Exclusion criteria	History of stroke
	Premorbid diseases of the visual pathway • Monocular or binocular visual field deficits • Retinopathy • Optic neuropathy • Angle-closure glaucoma • Elevated intraocular pressure
	Premorbid neurologic disease • Cognitive impairment • Dementia • Neurodegenerative disorder • Seizure disorder • Mania or hypomania • Premorbid mRS score >2
	Index stroke severity • NIH stroke scale score >5 • Hemorrhagic transformation
	Contraindications for being randomized to SSRI or placebo • Current use of an antidepressant medication • Premorbid or newly diagnosed depression • Current use of a medication likely to have an adverse interaction with fluoxetine • Known hypersensitivity to fluoxetine or other SSRIs • History of hyponatremia • Current alcohol abuse • Current impaired liver function
	Current use of a medication likely to impair poststroke recovery
	Pregnancy or lactation
	Enrollment in another clinical trial at the time of the index stroke

used in kinetic perimetry in a large natural history study of spontaneous vision recovery in stroke patients (2). Tiel and Kolmel used 4e (1,000 asb) isopters of varying sizes for kinetic perimetry. This translates to a size III target of 10 dB in automated perimetry testing, according to the automated Visual Field Analyzer manual (21).

Safety Monitoring

Hematologic and metabolic abnormalities and QTc prolongation were assessed at baseline and 1 month. Adverse event questionnaires were administered at 7 days and at 1, 3, and 6 months. The 9-item Patient Health Questionnaire (PHQ-9) was administered at each time point to evaluate for depression. A data safety monitoring board reviewed adverse events on a monthly basis and could terminate the study at any time for safety reasons.

Statistical Analysis

All statistical testing was predefined before unmasking and performed in R. All outcomes were assessed by intention-to-treat analysis. Pairwise deletion addressed missing data. T-tests were used for continuous, normally distributed variables, Mann–Whitney *U* tests for discrete variables, and Fisher exact tests for dichotomous variables. Binomial tests were used to compare the incidence of complete vision recovery between the groups. Effect sizes used Cohen *d* for t-tests, odds ratio for Fisher exact tests, and the glass rank biserial correlation coefficient for Mann–Whitney *U* tests. Tests were two-tailed for baseline characteristics and one-tailed for primary and secondary end points.

RESULTS

Participant Characteristics

Between 2016 and 2019, 17 stroke patients with isolated homonymous hemianopia were consented: 8 received fluoxetine and 9 placebo. One fluoxetine participant was excluded for optic neuropathy discovered after enrollment during the neuro-ophthalmology screening examination (screen failure). Two fluoxetine and 2 placebo participants withdrew before completing the first study visit. One placebo participant withdrew before completing the three-month visit and was included in final analyses (Fig. 1A). One participant was enrolled despite contraindications for MRI. Baseline characteristics were similar for both groups (Table 2).

Vision Recovery

Figure 1B shows perimetry at baseline and 6 months, constructed as described previously (22). Outcomes are summarized in Table 3. The primary end point, percent improvement in PMD, was 64.4% for fluoxetine and 26.0% for placebo (one-tailed 95% confidence interval (CI) = (−2.13, ∞), $P = 0.06$; Figure 1C, 1D). Percent area recovered, predefined as the change in the area of the blind field in the affected hemifield, was 72.4% for fluoxetine and 32.1% for placebo (one-tailed 95%CI = (−2.00, ∞); $P = 0.06$). Complete recovery of the original blind field was observed in 60% of participants on fluoxetine and 14% on placebo (one-tailed 95% CI = (0.50, ∞), $P = 0.15$). This incidence of complete recovery with fluoxetine (60%) was significantly greater than the expected 12.5% based on a natural history study ($P = 0.01$) (2).

One concern that may be raised is that the 2 groups differed in how their performance on automated visual field testing improved with each study visit, particularly in areas of the visual field with diminished visual sensitivity. This concern can be empirically ruled out because there was no significant difference between the 2 groups for changes in fixation loss, false-positives, or false-negatives on automated

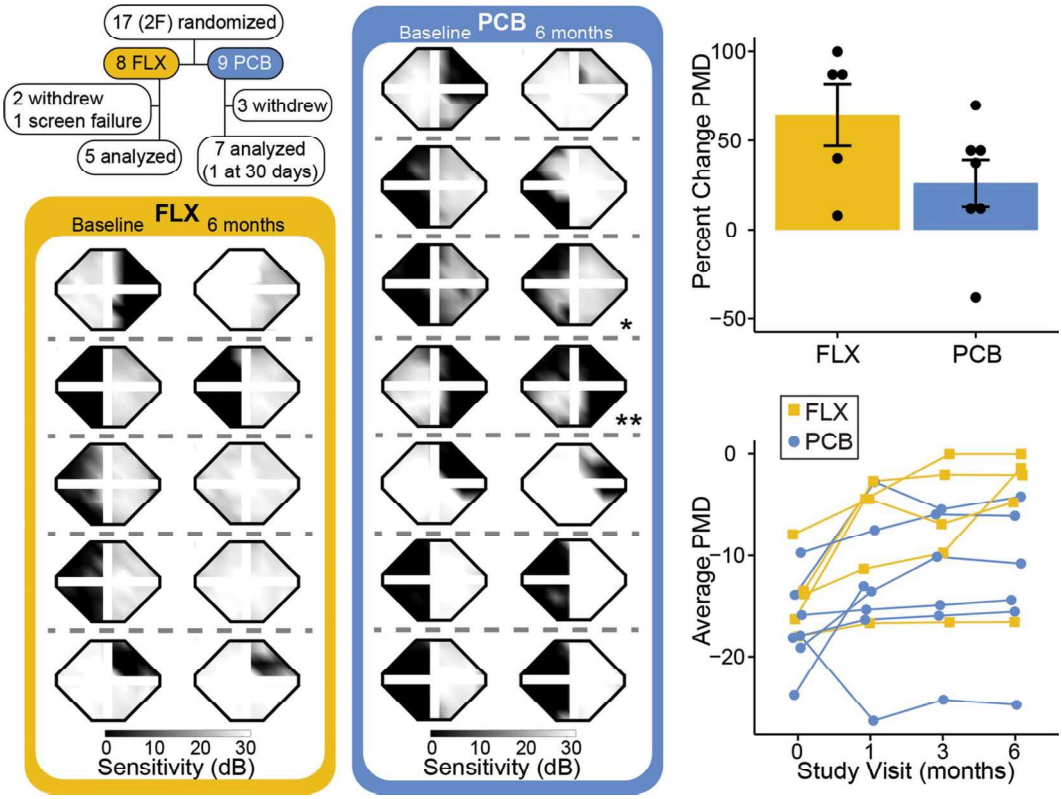

FIG. 1. Outcomes. **A**. Trial profile. **B**. 24-2 automated perimetry (combined into a binocular winner map) at baseline and 6 months (* participant withdrew after 1-month visit; ** participant had second stroke contralesionally after enrollment, therefore vision worsened). **C**. Percent improvement in binocularly averaged PMD with standard error of the mean and D) Trajectory of vision recovery by treatment group. FLX – fluoxetine; PCB – placebo.

visual field testing between the initial and final study visits (change in fixation loss: fluoxetine median = 3.7, interquartile interval (IQI) = (2.7, 6.3); placebo median = 0.1, IQI = (−11.5, 3.2), P = 0.15. Change in false-positive percent: fluoxetine median = 0.5, IQI = (0.0, 7.0), placebo median = 0, IQI = (−0.8, 0.8), P = 0.46. Change in false-negative

TABLE 2. Demographics and baseline characteristics

	Fluoxetine n = 5	Placebo n = 7	95% CI	P
Age	71 (70, 79)	61 (46, 70)	(-3, 31)	0.17
Male	4 (80%)	6 (86%)	(0.01, 65.25)	1.00
Caucasian	5 (100%)	7 (100%)	(0, ∞)	1.00
Received tPA	0 (0%)	1 (14%)	(0, 54.55)	1.00
Hypertension	5 (100%)	5 (71%)	(0.13, ∞)	0.47
Diabetes	3 (60%)	2 (29%)	(0.20, 75.60)	0.56
Lesion volume (cm^3)	26.6 (18.1, 35.1)	26.8 (12.4, 41.3)	(−19.66, 19.18)	0.98
V1 involvement	4 (80%)	6 (86%)	(0.01, 65.25)	1.00
Baseline PMD	−13.9 (−17.3, −10.6)	−16.9 (−20.2, −13.7)	(−2.33, 8.36)	0.24
Baseline area blind (deg^2)	742 (534, 949)	838 (680, 997)	(−403,209)	0.49
Premorbid mRS	0 (0, 0)	0 (0, 1)	(−2, 0)	0.21
Baseline NIHSS	2 (2, 2)	2 (2, 3)	(−2, 1)	0.54
Premorbid VFQ-25	96.1 (95.8,100)	98.9 (92, 100)	(-4.17, 12.73)	0.93
Premorbid PHQ-9	3 (1, 3)	1 (0.5, 2.5)	(-2, 3)	0.61

Means reported for normally distributed, medians for discrete or not normally distributed, counts for dichotomous variables. 95% confidence interval, interquartile range, or percentages in parentheses. All tests two tailed. Lesion volume excludes 1 fluoxetine participant who was not MRI-safe.

CI, confidence interval; tPA, t-PA; PMD, perimetric mean deviation; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Score; VFQ-25, 25-item Visual Functioning Questionnaire; PHQ-9, 9-item Patient Health Questionnaire for depression.

TABLE 3. Outcomes

	Fluoxetine n = 5	Placebo n = 7	95% CI	*P*	Effect Size
Percent improvement in PMD (average of both eyes)	64.4 (30.2, 98.6)	26.0 (0.2, 51.7)	(−2.13, ∞)	0.06	1.04[a]
Percent area recovered	72.4 (36.1,108.7)	32.1 (6.8, 57.4)	(−2.00, ∞)	0.06	1.06[a]
Full recovery incidence	3 (60%)	1 (14%)	(0.50, ∞)	0.15	7.22[b]
Percent change VFQ-25 from premorbid baseline	−11.2 (−23.2, 0.8)	−14.9 (−27.3, −2.5)	(−12.41, ∞)	0.34	0.25[a]
Three-month mRS	1 (1, 2)	2 (0.5, 2)	(−∞, 1.00)	0.33	0.14[c]
Change in PHQ-9	−1 (−1, −0.8)	0 (−1.5, 1.5)	(−∞, 1.00)	0.31	0.17[c]

One-tailed.

95% confidence interval, percentage, or interquartile range in parentheses. All tests were one-tailed. CI – confidence interval. Effect size is a) Cohen d, b) odds ratio, and c) glass rank biserial correlation coefficient. PMD – perimetric mean deviation, VFQ-25 – 25-item Visual Functioning Questionnaire, mRS – modified Rankin scale, PHQ-9 – Patient Health Questionnaire for depression.

percent: fluoxetine median = −4, IQI = (−8.5, 0); placebo median = −3, IQI = (−5.8, 4.5), $P = 0.63$).

In addition, we assessed the functional significance of vision improvement. The median three-month mRS score was 1 for fluoxetine and 2 for placebo (one-tailed 95%CI = (−∞, 1.00), $P = 0.33$). The worsening in VFQ-25 scores at 6 months from a premorbid baseline was numerically less for fluoxetine (−11.2%) than placebo (−14.9%, one-tailed 95%CI = (−12.41, ∞), $P = 0.34$). Finally, adverse events were not different between the groups (Table 4).

CONCLUSIONS

This pilot study demonstrated a trend in favor of fluoxetine on poststroke vision recovery, with a large effect size compared with placebo (Cohen d = 1.04). In addition, we observed a much higher incidence of complete vision recovery in the fluoxetine-treated group (60%) than the placebo group (14%). It is important to note that the incidence of complete vision recovery in the placebo group was similar to that observed in a large natural history study (12.5%) (2). Interestingly, the incidence of vision recovery in the fluoxetine-treated group was also greater than that in a study of stroke patients who received intravenous thrombolysis (26%) (23).

Prior clinical trials investigating a role for SSRIs in poststroke recovery have yielded mixed results (10–14). There have been 2 main criticisms of the FOCUS, AFFINITY, and EFFECTS trials (24), which failed to reproduce the positive results of the FLAME trial (10). First, the primary outcome measure in the FLAME trial was motor recovery (Fugl-Meyer Motor Scale), whereas the 3 larger negative trials (FOCUS (12), AFFINITY (13), EFFECTS (14)) used a disability measure (mRS) as their primary outcome. The mRS is a crude measure of recovery that may miss clinically significant improvements in function that enhance the quality of life but do not change a patient's level of overall disability. Like FLAME, the primary end point in our study was a physiologic measure of impairment, not disability. Second, repetitive training is required for new neural connections to form and existing neural circuitry to adapt (9). However, the 3 negative trials made no effort to enforce or quantify the amount of rehabilitation their subjects received. Our pilot study did not include a repetitive training component, but visual stimulation occurs during all waking hours regardless of effort, presenting less of a need for formal practice.

This is the first randomized, placebo-controlled, double-blind, clinical trial to test whether a pharmacological intervention improves vision recovery after stroke. Given the trends observed in favor of fluoxetine in this small pilot study, a larger multicenter clinical trial may be warranted to decisively test our hypothesis. Particular exclusion criteria limited the number of patients eligible for our study, including premorbid depression, prior or current SSRI use, delayed stroke recognition, contraindications for MRI, and preexisting eye disorders. Future studies may need to relax some of these exclusion criteria in order to recruit enough participants. In addition, our small sample size may have led to a study population that was primarily male and Caucasian, further underlining the importance of a larger follow-up study. Our retention rate of 70% demonstrates

TABLE 4. Adverse events

	Fluoxetine n=5	Placebo n=7	*P*
Hemorrhagic transformation	0 (0%)	1 (14%)	1.00
Recurrent stroke	0 (0%)	1 (14%)	1.00
TIA	1 (20%)	0 (0%)	0.42
Seizure	2 (40%)	0 (0%)	0.15

Counts with percentages in parentheses. All tests two tailed.

TIA, transient ischemic attack.

the feasibility of conducting a larger study if there is a greater pool of patients to recruit from. Fluoxetine could offer a glimmer of hope for a population of stroke patients who do not currently have access to any evidence-based interventions that promote poststroke vision recovery.

STATEMENT OF AUTHORSHIP

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