OARJ OPEN ACCESS RESEARCH JOURNALS

(RESEARCH ARTICLE)

Check for updates

Fluoxetine for non-arteritic anterior ischemic optic neuropathy: A double-blind, randomized clinical trial

Mohammad Hossein Abbasi [1], Zahra Pourmousa [2], Farzan Vahedifard [1], Shahnaz Rimaz [3] and Mostafa Soltan Sanjari [2, *]

[1] Neurology department, Iran University of Medical Sciences (IUMS), Tehran, Iran
[2] Ophthalmology research center, Rasool Akram hospital, Nyayesh street, sattarkhan district, Tehran, Iran
[3] Radiation Biology Research Center, Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Iran.

Abstract

Introduction: Fluoxetine raises the levels of BDNF (brain-derived neurotrophic factor). BDNF is known to improve neurogenesis and plasticity, so it seems to improve Anterior Ischemic Optic Neuropathy (AION). The goal of this study was to find out how Fluoxetine affects the clinical outlook of people with AION.

Methods: In this double-blind, placebo-controlled, randomized clinical trial, patients with AION split into two groups: the fluoxetine group (n=50), which took 20 mg of Fluoxetine every day, and the control group (n=50), which took a placebo pill instead. Both groups were followed for six months. Before and after the trial, patients were given clinical and non-clinical evaluations.

Results: 100 people took part in this study and were evaluated. Subjects in the Fluoxetine group had better visual acuity than those in the placebo group. They had lower scores on the LogMAR scale (P: 0.008 and 0.002), better MD parameters of perimetry (P: 0.003 and 0.002), and shorter VEP latencies (P (in 1st minute): 0.001 and 0.001, P (in 15th minute): 0.038 and 0.011. After the trial of Fluoxetine therapy, there were no changes in color vision, Rnfl in all dimensions, PSD parameter of perimetry, or VEP amplitudes (Ps> 0.05.

Conclusion: Fluoxetine showed promise as a therapy for people with AION, and it was safe to use as a treatment option in addition to corticosteroids

Keywords: Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION); Fluoxetine; Selective Serotonin Reuptake Inhibitor (SSRI); Brain-Derived Neurotrophic Factor (BDNF); Neuro-regeneration

1. Introduction

Brain-derived neurotrophic factor (BDNF) is believed to play a prominent role in the augmentation of neuronal repair, synaptic plasticity, and re-establishment of axonal interactions in the central nervous tissues, including the retina; where its concentration increases in case of neurodegenerative disorders involving the optic nerve [1],[2][3][4]. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), can potentially increase plasma levels of BDNF [5]. Fluoxetine therapy improves functional outcomes, motor performance, Poststroke Anxiety, Depression, and Cognitive Impairment and decreases three-year recurrence in ischemic stroke by potentiating neuroplasticity and neurogenesis [6-11]. Fluoxetine has also shown the potential to improve the clinical outcome and prognosis in patients with multiple sclerosis (MS) [12]. It has also improved cognitive performance in patients with vascular dementia [13]. Some reports

* Corresponding author: Mostafa Soltan Sanjari; Email: msoltansanjari@yahoo.com
Ophthalmology research center, Rasool Akram hospital, Nyayesh street, Sattar khan district, Tehran, Iran.

indicate Fluoxetine can improve the vision in patients with Amblyopia, likely by improving neuroplasticity in the visual cortex [14].

However, the main mediator of neurogenesis by Fluoxetine is BDNF [5],[15-17]. Lauterio et.al. Reported an increase in IGF-2 by Fluoxetine as an alternate effect [18].

IGF-1 and IGF-2 are members of seven IGF receptor binding proteins family. They are somewhat identical in action with differences in the stages of growth they support. While IGF-2 is primarily responsible for fetal development and likely neuroregeneration [19], IGF-1 maintains accelerated growth. IGF-1 as a neuroprotectant, is involved in neurogenesis and neurotransmission. Lower concentrations of IGF-1 are associated with higher mortality and morbidity in stroke patients; IGF-1 is a prognostic factor and an indicator of stroke outcome. Exogenous administration of IGF-1 in stroke animal models resulted in improved functional outcomes [20].

Yamada et. al. reported that the survival-promoting effect of BDNF is much weaker than that of IGF in serum deprivation-induced death of cultured cortical neurons. On the other hand, they also stated that phosphorylation signals of mitogen-activated protein kinase (MAPK) and cAMP-responsive element-binding protein (CREB), which had also been reported to be involved in survival promotion, had been stimulated by BDNF much more potently than by IGF-1[21]. Lindholm et.al. Indicated the complementary action of IGF-1 and BDNF to each other; in their study, "BDNF and IGF-1 both had increased the survival of the hippocampal neurons lacking BDNF, showing complementary action for these factors in supporting survival" [22].

NAION is a hypoxic event in the optic nerve head that its final consequence is the loss of retinal ganglion cells (RGC) and so the vision. A pathophysiologic cascade from hypoxia to inflammation, apoptosis and RGC loss has been peoposed for AION; each part of it has been the target for NAION treatment in various studies. Unfortunately, most of these studies had unsatisfactory outcomes. Knowing that Fluoxetine has proper pharmacologic distribution into the retina [23], and considering the promising neurodegenerative effect of this drug, this study was designed to evaluate the effect of treatment with Fluoxetine in long-term prognosis of patients with NAION.

2. Material and methods

This double-blinded randomized clinical trial was aimed to assess the effects of Fluoxetine on the clinical prognosis of patients with non-arteritic Anterior Ischemic Optic Neuropathy (NAION).The study population consisted of non-arteritic AION patients referred to Rasool Akram Hospital, Ophthalmology Clinic. Eligible participants were asked to sign the consent form to participate in the study. Inclusion criteria were patients diagnosed with NAION with an age of 18 years old and above while the exclusion criteria were over 3 weeks of latency from the beginning of symptoms, visual impairment correlated to other diseases but not due to AION, any contraindication or drug interaction for Fluoxetine such as pregnancy, history of using psychiatric drugs with the inclusion of Fluoxetine, and any history of eye trauma or any surgical interventions other than uncomplicated cataract extraction more than 6 months before the attack. Patients were also excluded if features of arteritic AION were present.

All the subjects underwent complete history taking and ocular examination including visual acuity (Snellen chart), slit lamp examination and funduscopy, and IOP measurement (Goldmann applanation tonometer). Pattern Visual evoked potential (VEP, EvokeDx NextGen icVEP) was assessed in every patient based on the ISCEV 2016 protocol [24]. Humphrey Field Analyzer II performed a central 24-2 Visual field assessment with the Swedish Interactive Threshold Algorithm (SITA; Carl Zeiss Meditec, Inc., Dublin, CA) as well as Peripapillary retinal nerve fiber layer (RNFL) thickness measurement which was measured using a spectral-domain optical coherence tomography (Spectralis HRA+OCT, Heidelberg Engineering, Germany). Subjects that met the inclusion criteria were randomly assigned into two groups; the Fluoxetine group were given Fluoxetine capsule 20mg daily for six months and the control group who received placebo. All the clinical and para-clinical evaluations were reperformed after 6 months of fluoxetine therapy.

Both patients and investigators were unaware of the type of medication received by patients to provide double-blinding of the trial. Block randomization using 25 quaternary blocks was used. Concealment was preserved by placing patients in the study groups according to the order of the randomization list.

2.1. Analysis

Statistics of quantitative data are presented by means and standard deviations or medium and interquartile ranges and qualitative data are presented by frequencies. For comparison of quantitative variables between study groups, student independent samples T-test or its non-parametric equivalent, Mann-Whitney U test was used while compared T-test or

its non-parametric equivalent, Wilcoxon test was used in order to compare the results before and after treatment in each group. For comparison of parameters between study groups, possible confounding biases by baseline characteristics were addressed by covariance analysis (Bootstrapping for non-parametric data). The sample size was determined in 45 cases in each group using G power by considering the effect size d : 0.6, alpha error equal to 5 %, and power equal to 80%. 10 percent lost to follow-up was predicted and 50 patients in each of the two study groups was considered. A P-value equal to or less than 0.05 was considered statistically significant. IBM statistics SPSS version 22 was used for obtaining statistical analysis.

3. Results

Table 1 Descriptive statistics of baseline parameters and their comparison between study groups

Parameter (#\%)		All cases	Study Group		P-value [a]
			Drug	**Placebo**	
Age (Mean ± SD)		58.62 ± 12.13	56.68 ± 11.24	60.56 ± 12.79	0.110 [b]
Sex	Male	64 (64%)	36 (72%)	28 (56%)	0.096 [c]
	Female	36 (36%)	14 (28%)	22 (44%)	
Profession	Labor	56 (56%)	30 (60%)	26 (52%)	0.420 [c]
	clerical	44 (44%)	20 (40%)	24 (48%)	
Smoking	Smoker	33 (33%)	21 (42%)	12 (24%)	0.056 [c]
	Non-smoker	67 (67%)	29 (58%)	38 (76%)	
Alcohol	Drinker	13 (13%)	7 (14%)	6 (12%)	0.766 [c]
	Non-drinker	87 (87%)	43 (86%)	44 (88%)	
Opium	Abuser	11 (11%)	7 (14%)	4 (8%)	0.338 [c]
	Non-abuser	89 (89%)	43 (86%)	46 (92%)	
First presentation	Pain	11 (11%)	5 (10%)	6 (12%)	0.749 [c]
	Vision loss	89 (89%)	45 (90%)	44 (88%)	
Family Hx of AION	Positive	20 (20%)	12 (24%)	8 (16%)	0.317 [c]
	Negative	80 (80%)	38 (76%)	42 (84%)	
HTN Hx	Positive	34 (34%)	16 (32%)	18 (36%)	0.673 [c]
	Negative	66 (66%)	34 (68%)	32 (64%)	
DM Hx	Positive	42 (42%)	25 (50%)	17 (34%)	0.105 [c]
	Negative	58 (58%)	25 (50%)	33 (66%)	
IHD Hx	Positive	29 (29%)	17 (34%)	12 (24%)	0.271 [c]
	Negative	71 (71%)	33 (66%)	38 (76%)	
CVA Hx	Positive	2 (2%)	0 (0%)	2 (4%)	0.495 [d]
	Negative	98 (98%)	50 (100%)	48 (96%)	
HLP Hx	Positive	23 (23%)	11 (22%)	12 (24%)	0.812 [c]
	Negative	77 (77%)	39 (78%)	38 (76%)	

Hx: History, AION: Anterior Ischemic Optic Neuropathy, HTN: Hypertension, DM: Diabetes Mellitus, IHD: Ischemic Heart Diseases, TIA: Transient Ischemic Attack, CVA: Cerebrovascular accidents, HLP: Hyperlipidemia; a: comparison between study groups; b: Independent samples T-test; c: Chi-square test d: Fischer exact test

Table 2 Descriptive statistics of clinical parameters and comparison between study groups

Parameter (Mean ± SD)		Study Group		P-value a	P-value b	P-value c
		Drug	Placebo			
VA	1st visit	0.95 ± 0.29	1.03 ± 0.27	0.312 d	0.008 e	0.132 e
	End of 6th month	0.78 ± 0.33	0.97 ± 0.21	0.002 d		
VA improvement	< 0.2	43	40	0.424 h		
	= or > 0.2	7	10			
VA improvement	< 0.1	39	32	0.123 h		
	= or > 0.1	11	18			
Perimetry MD	1st visit	- 23.55 ± 4.86	- 22.07 ± 5.33	0.171 f	0.003 g	0.801 g
	End of 6th month	- 20.07 ± 3.53	- 22.87 ± 4.75	0.002 f		
Perimetry PSD	1st visit	8.25 ± 2.81	8.69 ± 3.52	0.669 d	0.217 g	0.076 g
	End of 6th month	6.74 ± 3.08	8.04 ± 2.69	0.093 f		
Rnfl	Nasal — 1st visit	106.76 ± 38.11	105.61 ± 42.09	0.896 f	0.732 g	0.759 e
	Nasal — End of 6th month	108.63 ± 33.14	104.71 ± 34.82	0.604 f		
	Superonasal — 1st visit	95.05 ± 35.06	91.80 ± 31.84	0.661 f	0.139 g	0.112 e
	Superonasal — End of 6th month	105.65 ± 29.67	103.48 ± 41.26	0.383 d		
	Superotemporal — 1st visit	111.79 ± 36.23	114.88 ± 32.89	0.685 f	0.678 g	0.403 e
	Superotemporal — End of 6th month	107.80 ± 30.27	108.88 ± 43.32	0.666 d		
	Temporal — 1st visit	117.12 ± 36.23	116.68 ± 36.64	0.957 f	0.662 e	0.301 e
	Temporal — End of 6th month	111.63 ± 31.56	105.95 ± 39.46	0.186 d		
	Inferotemporal — 1st visit	106.40 ± 36.12	117.63 ± 41.31	0.191 f	0.940 g	0.566 e
	Inferotemporal — End of 6th month	106.08 ± 32.56	113.21 ± 42.64	0.714 d		
	Inferonasal — 1st visit	116.38 ± 39.93	127.41 ± 46.84	0.251 f	0.534 e	0.124 e
	Inferonasal — End of 6th month	107.00 ± 32.93	112.83 ± 46.75	0.864 d		
VEP latency 1 minute	1st visit	108.28 ± 14.67	109.51 ± 9.39	0.205 d	< 0.001 e	0.121 e
	End of 6th month	97.72 ± 18.05	112.68 ± 16.88	<0.001 f		
VEP amplitude 1 minute	1st visit	7.02 ± 1.99	7.17 ± 2.16	0.799 d	0.409 e	0.079 e
	End of 6th month	6.82 ± 3.32	6.16 ± 2.89	0.292 f		
VEP latency 15 minutes	1st visit	120.90 ± 12.42	119.83 ± 19.26	0.912 d	0.038 e	0.160 e
	End of 6th month	101.95 ± 23.10	114.94 ± 26.59	0.011 f		
VEP amplitude 15 minutes	1st visit	5.49 ± 3.56	5.75 ± 2.57	0.138 d	0.907 e	0.189 e
	End of 6th month	6.56 ± 3.07	6.41 ± 2.91	0.749 f		
IOP	1st visit	14.74 ± 1.74	14.56 ± 1.75	0.660 d	0.967 e	0.353 e
	End of 6th month	13.92 ± 1.45	13.86 ± 1.62	0.855 d		

a: Compare between Drug and Placebo study groups; b: Compare between before and after of parameters between Drug group subjects; c: Compare between before and after of parameters between Placebo group subjects; d: Mann-Whitney U test ; e: Wilcoxon test; f: independent samples T-test; g: Paired samples T-test; h: Chi-square

One hundred patients with Anterior Ischemic Optic Neuropathy (AION) were enrolled 50 in each of the two study groups from August 2019 to December 2020 (64 males and 36 females) with a mean age of 58.62 ± 12.13 years old. Demographic data are represented in table 1.

Patients in both groups were equal in baseline characteristics such as age, sex, occupation (laborer or clerical jobs), history of smoking, alcohol abuse, opium abuse, hypertension (HTN), Diabetes Mellitus (DM), ischemic heart diseases (IHD), Cerebrovascular Accidents (CVA) and hyperlipidemia (P-values > 0.05) [Table 1].

Vision loss was the initial presentation of AION in 89% of patients while 11% of patients expressed globe pain as the first presentation. Family history of AION was positive in 20% of cases [Table 1].

Visual acuity score, color vision score, perimetry parameters (MD and PSD), Rnfls in all six dimensions (Nasal, superonasal, superotemporal, temporal, inferotemporal, and inferonasal), VEP amplitudes and latencies on 1st and 15th minutes, and intraocular pressure (IOP) were equal in the baseline measurements between study groups (P-value > 0.05).

Visual acuity score in the LogMAR scale was significantly lower among the Fluoxetine group in the final evaluation compared to the baseline result (P-value: 0.008) and the final evaluation result of the placebo group (p-value: 0.002). No significant difference was noted in the visual acuity score of the placebo group before and after the trial (P-value: 0.132) [Table 2]. Also, no significant difference was noted on the color vision on the two groups before and after the trial (P-values > 0.05)[Table 2]. MD parameter in perimetry was statistically significant, near zero among the Fluoxetine group on the final evaluation compared to the preliminary assessment (P-value: 0.003) and in comparison to the final result of the placebo group (P-value: 0.002). No significant improvement was observed on MD parameter on the placebo group (P-value: 0.801. Also, no significant difference was noted on the PSD parameter in perimetry on the Fluoxetine group in the final assessment compared to the baseline assessment (P-value: 0.217) and in comparison to the final result of the placebo group (P-value: 0.093). The PSD parameter also showed no significant improvement in the placebo group (P-value: 0.076)[Table 2].

Latencies in 1st and 15th minutes in the assessment of VEP were both statistically significantly lower among the Fluoxetine group in the final assessment compared to their preliminary results (P-values: <0.001 and 0.038, respectively) and in comparison to the placebo group's final result (P-values: < 0.001 and 0.011, respectively). Results indicated no significant difference in optic nerve latencies on the placebo group before and after the trial (P-values: 0.121 and 0.160, respectively). Also, no significant difference was noted of the Amplitudes in 1st and 15th minutes of visual disability assessment by VEP in the Fluoxetin group before and after the clinical trial (P-values: 0.409 and 0.907, respectively) nor to the placebo group's final result (P-values: 0.292 and 0.749, respectively) [Table 2].

Results of Rnfl assessment in all six dimensions using OCT (optic coherence tomography) indicated no significant difference between the preliminary and final evaluation results on both groups (P-values > 0.05)[Table 2].No significant changes were noted in the IOP on both Fluoxetine and placebo groups in the baseline and final assessments (P-value > 0.05)[Table 2].

Any Flouxetine group did not report adverse effects such as glaucoma or cataracts, but some participants reported mild drowsiness or insomnia and no follow-up loss.

4. Discussions

This study has found Fluoxetine as a safe complement therapeutic option in Anterior Ischemic Optic Neuropathy (AION) with promising improvements in their clinical prognosis.

Since there were no severe noted side effects of Fluoxetine, it seems to be a safe treatment strategy to complement corticosteroids. However, Fluoxetine has shown improvements in visual acuity, perimetry, and VEP latencies; there were no statistically significant changes in VEP amplitudes, color vision, or Rnfls. Overall, the improvements observed, especially in visual acuity, are enough evidence to support the desirable effect of Fluoxetine in the prognosis of patients with AION.

The equality of the baseline characteristics such as demographic parameters were ensured and confounding biases were addressed by covariance analysis.

Serum levels of BDNF as a neuroprotective factor increase in the case of pathologies involving the optic nerve [1]. Fluoxetine is a BDNF inducer involved in neuronal plasticity and neuroregeneration besides its high penetration into the retina [2][5][25]. Previous studies have shown improvements in visual cortex plasticity and re-establishment of axonal interactions by Fluoxetine, leading to desired clinical efficacy in Amblyopia and improvement in vision [3][4][14]. However, many interventional techniques are also there to improve neuroplasticity [26-29], pharmacologic interventions harbor lower possibility of side effects, while antidepressants are potential candidates [30]. This is not the first time medication with an alternative medical application exerts neuroprotective effects [31].

Since AION is an ischemic disease that involves neural tissue of the retina, therefore, AION is comparable to ischemic stroke in its pathophysiology. Fluoxetine has been reported as an effective treatment option for improving the post-stroke motor function by the acceleration of the neurogenesis and neuroplasticity [32][9-11][33]. Cognitive performance has improved, and three-year recurrence in stroke patients has decreased by Fluoxetine [34][7]. However, some studies have disagreed to the efficacy of Fluoxetine in stroke patients [31][35][36]. It should be considered that the therapeutic effectiveness of Fluoxetine widely depends on the early initiation of treatment upon the manifestation of symptoms [11]. Fluoxetine has also improved the clinical prognosis in patients with vascular dementia and multiple sclerosis as examples of other neurodegenerative disorders [12][13]. Further studies should be considered regarding the effectiveness of Fluoxetine in AION on the early initiation of treatment upon the initial manifestation of symptoms.

5. Conclusion

Fluoxetine is a safe complement therapeutic option in Anterior Ischemic Optic Neuropathy (AION) with promising effects on clinical prognosis.

Compliance with ethical standards

Authors' contributions

- Mohammad Hossein Abbasi: Conceptualization, Investigation, Formal analysis, Writing - Original Draft, Writing - Review & Editing.
- Zahra Pourmousa: Investigation, Writing - Original Draft, Writing - Review & Editing.
- Farzan Vahedifard: Writing - Original Draft, Writing - Review & Editing.
- Shahnaz Rimaz: Conceptualization, Project administration, Methodology, Investigation, Writing - Review & Editing.
- Mostafa Soltan Sanjari: Conceptualization, Project administration, Methodology, Investigation, Writing - Review & Editing.

Disclosure of conflict of interest

The authors of this study mentioned no conflicting or competing interests in the subject matters of this article.

Availability of data and materials

The datasets generated during and analyzed during the current study are not available publicly because it is collected on the data repository of the eye research center of Rasool Akram hospital, which are intended to be reused in another study too but are available from the corresponding author on reasonable request.

Statement of ethical approval

Ethics Committee approves this study of Vice Chancellor for Research & Technology, IUMS (code: IR.IUMS.FMD.REC.1397.093). This study was a registered Trial on 07/01/2019 with IRCT code

IRCT20181109041596N1. All patients and control subjects signed the informed consent. This study was performed under the ethical standards of the Declaration of Helsinki (2013) and its subsequent amendments.

Statement of informed consent

Informed consent was obtained from all patients with clinical data reported in this article to participate in the study and assessments.

References

[1] Tsakiri A, Ravanidis S, Lagoudaki R, Poulatsidou KN, Svane IM, Frederiksen JL, Grigoriadis N. Neuroprotective and anti-inflammatory mechanisms are activated early in O ptic N euritis. Acta Neurologica Scandinavica. 2015 May;131(5):305-12.

[2] Cohen-Cory S. BDNF modulates, but does not mediate, activity-dependent branching and remodeling of optic axon arbors in vivo. Journal of Neuroscience. 1999 Nov 15;19(22):9996-10003.

[3] Gore C, Wu C. Medical therapies of amblyopia: translational research to expand our treatment armamentarium. InSeminars in ophthalmology 2016 Mar 3 (Vol. 31, No. 1-2, pp. 155-158). Taylor & Francis.

[4] Avgan N, Sutherland HG, Spriggens LK, Yu C, Ibrahim O, Bellis C, Haupt LM, Shum DH, Griffiths LR. BDNF variants may modulate long-term visual memory performance in a healthy cohort. International journal of molecular sciences. 2017 Mar 17;18(3):655.

[5] Ghosh R, Gupta R, Bhatia MS, Tripathi AK, Gupta LK. Comparison of efficacy, safety and brain derived neurotrophic factor (BDNF) levels in patients of major depressive disorder, treated with Fluoxetine and desvenlafaxine. Asian journal of psychiatry. 2015 Dec 1;18:37-41.

[6] M Corbett A, Sieber S, Wyatt N, Lizzi J, Flannery T, Sibbit B, Sanghvi S. Increasing neurogenesis with Fluoxetine, simvastatin and ascorbic acid leads to functional recovery in ischemic stroke. Recent patents on drug delivery & formulation. 2015 Aug 1;9(2):158-66.

[7] He Y, Cai Z, Zeng S, Chen S, Tang B, Liang Y, Chang X, Guo Y. Effect of Fluoxetine on three-year recurrence in acute ischemic stroke: a randomized controlled clinical study. Clinical Neurology and Neurosurgery. 2018 May 1;168:1-6.

[8] Vahid-Ansari F, Albert PR. Chronic Fluoxetine induces activity changes in recovery from poststroke anxiety, depression, and cognitive impairment. Neurotherapeutics. 2018 Jan 1;15(1):200-15.

[9] Pariente J, Loubinoux I, Carel C, Albucher JF, Leger A, Manelfe C, Rascol O, Chollet F. Fluoxetine modulates motor performance and cerebral activation of patients recovering from stroke. Annals of neurology. 2001 Dec;50(6):718-29.

[10] Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, Bejot Y, Deltour S, Jaillard A, Niclot P, Guillon B. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. The Lancet Neurology. 2011 Feb 1;10(2):123-30.

[11] Guo Y, He Y, Tang B, Ma K, Cai Z, Zeng S, Zhang Y, Jiang X. Effect of using Fluoxetine at different time windows on neurological functional prognosis after ischemic stroke. Restorative Neurology and Neuroscience. 2016 Jan 1;34(2):177-87.

[12] Cambron M, Mostert J, Haentjens P, D'Hooghe M, Nagels G, Willekens B, Heersema D, Debruyne J, Van Hecke W, Algoed L, De Klippel N. Fluoxetine in Progressive Multiple Sclerosis (FLUOX-PMS): study protocol for a randomized controlled trial. Trials. 2014 Dec;15(1):37.

[13] Liu X, Zhang J, Sun D, Fan Y, Zhou H, Fu B. Effects of Fluoxetine on brain-derived neurotrophic factor serum concentration and cognition in patients with vascular dementia. Clinical interventions in aging. 2014;9:411.

[14] Sharif MH, Talebnejad MR, Rastegar K, Khalili MR, Nowroozzadeh MH. Oral Fluoxetine in the management of amblyopic patients aged between 10 and 40 years old: a randomized clinical trial. Eye. 2019 Jul;33(7):1060-7.

[15] Jin HJ, Pei L, Li YN, Zheng H, Yang S, Wan Y, Mao L, Xia YP, He QW, Li M, Yue ZY. Alleviative effects of Fluoxetine on depressive-like behaviors by epigenetic regulation of BDNF gene transcription in mouse model of post-stroke depression. Scientific reports. 2017 Nov 2;7(1):1-5.

[16] Yan L, Xu X, He Z, Wang S, Zhao L, Qiu J, Wang D, Gong Z, Qiu X, Huang H. Antidepressant-like effects and cognitive enhancement of coadministration of chaihu shugan san and Fluoxetine: Dependent on the BDNF-ERK-CREB signaling pathway in the hippocampus and frontal cortex. BioMed research international. 2020 Feb 22;2020.

[17]   Li G, Jing P, Liu Z, Li Z, Ma H, Tu W, Zhang W, Zhuo C. Beneficial effect of fluoxetine treatment aganist psychological stress is mediated by increasing BDNF expression in selected brain areas. Oncotarget. 2017 Sep 19;8(41):69527.

[18]   Lauterio TJ, Rieg TS, Ahmed I, Aravich PF. Fluoxetine induced insulin-like growth factor II (IGF-II) changes in hypothalami of normal, exercised and food restricted rats. Regulatory peptides. 1993 Oct 20;48(1-2):21-8.

[19]   Younis S, Schönke M, Massart J, Hjortebjerg R, Sundström E, Gustafson U, Björnholm M, Krook A, Frystyk J, Zierath JR, Andersson L. The ZBED6–IGF2 axis has a major effect on growth of skeletal muscle and internal organs in placental mammals. Proceedings of the National Academy of Sciences. 2018 Feb 27;115(9):E2048-57.

[20]   Hayes CA, Valcarcel-Ares MN, Ashpole NM. Preclinical and clinical evidence of IGF-1 as a prognostic marker and acute intervention with ischemic stroke. Journal of Cerebral Blood Flow & Metabolism. 2021 Mar 24:0271678X211000894.

[21]   Yamada M, Tanabe K, Wada K, Shimoke K, Ishikawa Y, Ikeuchi T, Koizumi S, Hatanaka H. Differences in survival-promoting effects and intracellular signaling properties of BDNF and IGF-1 in cultured cerebral cortical neurons. Journal of neurochemistry. 2001 Sep 1;78(5):940-51.

[22]   Lindholm D, Carroll P, Tzimagiorgis G, Thoenen H. Autocrine—paracrine Regulation of Hippocampal Neuron Survival by IGF-1 and the Neurotrophins BDNF, NT-3 and NT-4. European Journal of Neuroscience. 1996 Jul;8(7):1452-60.

[23]   Lee Cantrell F, Vance C, Schaber B, McIntyre I. Fatal fluoxetine intoxication with markedly elevated central blood, vitreous, and liver concentrations. Journal of analytical toxicology. 2009 Jan 1;33

[24]   Odom JV, Bach M, Brigell M, Holder GE, McCulloch DL, Mizota A, Tormene AP. ISCEV standard for clinical visual evoked potentials:(2016 update). Documenta Ophthalmologica. 2016 Aug;133(1):1-9.

[25]   Costagliola C, Parmeggiani F, Sebastiani A. SSRIs and intraocular pressure modifications. CNS drugs. 2004 Jul 1;18(8):475-84.

[26]   Vahedifard F, Haghighi AS. The role of Neuroradiology in Neuroplasticity: New advancements. World Journal of Advanced Research and Reviews. 2022;14(2):156-60.

[27]   Chakravarthy K, Golovac S, Vahedifard F. Future Indications. InEssentials of Radiofrequency Ablation of the Spine and Joints 2021 (pp. 241-281). Springer, Cham.

[28]   Salehpour F, Khademi M, Vahedifard F, Cassano P. Transcranial Photobiomodulation Therapy for Sexual Dysfunction Associated with Depression or Induced by Antidepressant Medications. InPhotonics 2022 May 11 (Vol. 9, No. 5, p. 330). MDPI.

[29]   Esmaeili S, Abbasi MH, Malekdar E, Joghataei MT, Mehrpour M. A Pilot Clinical Trial of Repetitive Transcranial Magnetic Stimulation in Mild Cognitive Impairment. Journal of Neurology Research. 2020 Aug 15;10(5):188-92.

[30]   Vahedifard F. Personalized Treatment for Depression, Multimodality Approach For Disease Variations. Journal homepage: www ijrpr com ISSN. 2022;3(4):1848-52.

[31]   Esmaeili S, Abbasi F, Hossein Abbasi M, Eshraghi A, Mirzaasgari Z. Impact of pre-stroke metformin use on prognosis of Ischemic stroke; A pilot study. Journal of Bioengineering Research. 2019 Dec 1;1(4):45-9.

[32]   Dennis M, Forbes JF, Graham C, Hackett M, Hankey GJ, House A, Lewis S, Lundström E, Sandercock P. Fluoxetine to improve functional outcomes in patients after acute stroke: the FOCUS RCT.

[33]   He YT, Tang BS, Cai ZL, Zeng SL, Jiang X, Guo Y. Effects of Fluoxetine on neural functional prognosis after ischemic stroke: a randomized controlled study in China. Journal of stroke and cerebrovascular diseases. 2016 Apr 1;25(4):761-70.

[34]   Sun Y, Sun X, Qu H, Zhao S, Xiao T, Zhao C. Neuroplasticity and behavioral effects of Fluoxetine after experimental stroke. Restorative neurology and neuroscience. 2017 Jan 1;35(5):457-68.

[35]   Bonin Pinto C, Morales-Quezada L, de Toledo Piza PV, Zeng D, Saleh Vélez FG, Ferreira IS, Lucena PH, Duarte D, Lopes F, El-Hagrassy MM, Rizzo LV. Combining Fluoxetine and rTMS in Poststroke Motor Recovery: A Placebo-Controlled Double-Blind Randomized Phase 2 Clinical Trial. Neurorehabilitation and neural repair. 2019 Aug;33(8):643-55.

[36]   Lundström E, Isaksson E, Näsman P, Wester P, Mårtensson B, Norrving B, Wallén H, Borg J, Dennis M, Mead G, Hankey GJ. Safety and efficacy of Fluoxetine on functional recovery after acute stroke (EFFECTS): a randomised, double-blind, placebo-controlled trial. The Lancet Neurology. 2020 Aug 1;19(8):661-9.