

## Cover Letter

To: editor of clinical trial

Topic: Cover letter for Submission of protocol for registration in clinical trial.

Dear Sir/Madam,

I wish to register an article entitled **“Possible Beneficial Effects Of Combined Fluoxetine And Occlusion Therapy In Improving And Maintaining Vision In Amblyopia Using Optical Coherence Tomography Angiography (OCTA) And Visual Evoked Potential (VEP)”**

**This article is co-authored by:**

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All authors have contributed significantly and all are in agreement with the content of the manuscript.

The authors declare that there is no conflict of interests regarding the publication of this article.

- 5- On behalf of all contributors, I'm Alyaa Abdelfattah Abdelmonaem Gad, will correspond with the journal from this point onward.

Thank you,

Yours' sincerely,

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## **Title**

**Possible Beneficial Effects Of Combined Fluoxetine And  
Occlusion Therapy In Improving And Maintaining Vision In  
Amblyopia Using Optical Coherence Tomography Angiography  
(OCTA) And Visual Evoked Potential (VEP)**

**Protocol of Thesis Submitted to  
the Faculty of Medicine  
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in Ophthalmology By:  
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## Introduction

Amblyopia is described as a limitation of the visual function of one or both eyes with no pathological cause, with a prevalence of about 1–5% of the total world population. This disorder is caused by early abnormal visual experience with a functional imbalance between the two eyes owing to anisometropia, strabismus, congenital cataract and ptosis, resulting in a dramatic loss of visual acuity (VA) in an apparently healthy eye (**Baroncelli, and Maffei, 2011**).

Clinically, amblyopia can be defined as the presence in one or both eyes of a VA of 6/12 or worse, with one or more lines of difference in VA between eyes in unilateral amblyopia which cannot be improved by refractive correction. This condition is an alteration of the visual cortex function which is due to suppression and deprivation of one eye leading to unilateral visual deterioration (**Milla, and Piñero, 2020**).

Optical coherence tomography (OCT) is a noninvasive technique that can reveal morphology of the retinal layers in vivo. OCT determines structural changes in the macula that may be correlated with measures of subjective visual function such as visual acuity and visual field (**Bachmann et al., 2006**). OCT angiography (OCTA) can provide vascular system visualization of the posterior segment in amblyopic eyes (**Lu et al., 2022**).

Visual evoked potentials (VEPs) are a non-invasive technique routinely used in clinical and preclinical practice. VEPs allow to quantify the functional integrity of the visual system from the retina via the optic nerves, optic tracts, to the thalamus, and form projections to the visual cortices (**Marenna et al., 2023**).

In strabismic and anisometropic amblyopia, VEP responses are reduced. VEP may be used as an alternative objective method for diagnosis and monitoring of amblyopia (**Moschos et al., 2010**) .

Passive treatments such as occlusion, optical and/or pharmacological penalization, and Bangerter foils have been demonstrated to be potentially useful treatments for amblyopia. Researches are being done on new pharmacological

options to improve and maintain VA after occlusion treatment in amblyopia (**Milla, and Piñero, 2020**).

Adults with amblyopia cannot be treated because their brains do not have enough plasticity. However, results obtained both in clinical trials and in animal models have challenged this traditional view, unmasking a previously unsuspected potential for promoting recovery after the end of the critical period for visual cortex plasticity. These studies point toward the intracortical inhibitory transmission as a crucial brake for therapeutic rehabilitation and recovery from amblyopia in the adult brain (**Baroncelli, and Maffei, 2011**).

Selective serotonin reuptake inhibitors (SSRIs) increase serotonin activity in the brain. While they are mostly known for their antidepressant properties, they have been shown to improve visual functions in amblyopia and impact cognitive functions ranging from attention to motivation and sensitivity to reward (**Gacoin, and Ben Hamed., 2023**).

### **Aim of Study**

To evaluate possible beneficial effects of fluoxetine on improving and maintaining visual function in amblyopia in different age groups using VA, OCTA and VEP.

## **Patients and Methods**

### **Study design:**

A prospective clinical non-randomized comparative controlled study.

### **Ethical considerations:**

All subjects included in this study will be counseled about the details and the nature of the study and will be required to sign a written consent. Ethical approval will be obtained from the local Ethics Committee of Minia University Faculty of Medicine before commencement of the study. The study will be conducted in Ophthalmology Department, Minia university Hospital, Egypt .

### **Study population:**

Study participants will be recruited from the ophthalmology outpatient clinics of Minia University Hospitals. Imaging will be performed in the Department of Ophthalmology, Minia University Hospital.

Study will include 75 eyes that will be divided into 3 groups:

**Group A:** normal eyes of age-matched controls.

**Group B:** amblyopic eyes treated with patching.

**Group C:** amblyopic treated with patching and flouxetine.

### **Inclusion Criteria:**

Patients with unilateral amblyopia > 10 years old.

### **Exclusion criteria:**

- Ocular pathology: media opacity, uveitis, glaucoma, retinal or optic nerve diseases, and history of ocular trauma.
- Poor fixation.
- Lack of cooperation.
- Any psychological disorder.

### **Ophthalmologic Evaluation:**

All patients will undergo a thorough ocular and systemic history taking, as well as a comprehensive ophthalmic examination before, 3 months after patching and fluoxetine therapy and 3 months after therapy withdrawal, including:

- Measurement of uncorrected and best-corrected Snellen visual acuity .

- Assessment of pupillary reflex.
- Anterior segment slit-lamp examination.
- Intraocular pressure (IOP) measurement using Goldmann applanation tonometry (GAT).
- Fundus examination using both binocular indirect ophthalmoscopy (BIO) and slit-lamp biomicroscopy with a +78 D noncontact lens.

### **Ophthalmic Imaging**

Ophthalmic imaging will be performed for all patients before, 3 months after patching and fluoxetine therapy and 3 months after therapy withdrawal. Spectral-domain OCTA imaging will be done using the Avanti RTVue-XR system (Optovue, Fremont, CA, USA) which utilizes a split-spectrum amplitude-decorrelation angiography (SSADA) algorithm to extract OCTA information.

The machine has a light source centered on 840 nm with a bandwidth of 50 nm. It is capable of an A-scan acquisition rate of 70,000 scans/second allowing for an axial resolution of 5  $\mu$ m and a horizontal resolution of 20  $\mu$ m. Each OCTA volume contains 304 x 304 A-scans. Two consecutive B-scans are obtained at each fixed location before proceeding to the next position .

In order to minimize motion artifacts, 2 orthogonal OCTA volumes are acquired to perform motion correction. The Angio Retina protocol will be used for OCTA image acquisition. Evaluated parameters will include measurement of the foveal avascular zone (FAZ) and vessel density (VD) at the levels of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) of the macula, as well VD of the choriocapillaris.

### **Flash VEP (FVEP) and pattern VEP (PVEP)**

Ophthalmic functional assessment by FVEP and PVEP will be performed for all patients before, 3 months after patching and fluoxetine therapy and 3 months after therapy withdrawal. FVEP and PVEP will be done using the (Roland Consult supercolor Ganzfeld Q450 SC).



## **FVEP Ganzfeld**

Requirement:

- Light-adapted patient (photopic conditions)
- Pupils non dilated
- 3 x EEG-Electrodes at channel 1
- One eye covered with Impedance < 10 kOhm

## **PVEP**

Requirement:

- Distance patient → monitor: 100 cm
- Light-adapted Patient (photopic conditions)
- Patient refraction / correction for 100 cm viewing distance
- 3x EEG-Electrodes at channel 1 One eye covered
- Impedance < 10 kOhm

## **Outcome Measures**

1. Comparison of VA between 3 groups.
2. Comparison of vessel density (VD) of FAZ, superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillaris (CC) between 3 groups in OCTA.
3. Comparison of FVEP and PVEP between 3 groups:
  - FVEP: latency and amplitude of P2.
  - PVEP: latency and amplitude of P100.

## **Statistical Analysis:**

- Results will be analyzed using IBM SPSS.
- P value < 0.05 will be considered significant.

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