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Mesopic pupillary reflex in patients treated with fluoxetine

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Introduction. currently the treatment of mental illness by antidepressants is very frequent. Selective serotonin reuptake inhibitors are the most prescribed antidepressants worldwide and have been associated with alterations in accommodation or pupil. The objective of this study is to evaluate the effects of fluoxetine on the pupillary reflex and the accommodation in young population.

Methodology. The study group included seven patients diagnosed with depression and treated with fluoxetine; 22 subjects were included as a control group. The pupillary reflexes and the accommodative state were evaluated using the Power Refractor II pupilometer. Five phases of 3 seconds each were measured. In phase 2 there was a glare with a white light.

Results. For the pupil diameter, maximum and minimum values were obtained in the group of patients treated with fluoxetine than in the control in all the measurement phases. For the control group, a maximum pupillary contraction is observed in the glare phase, however, in the study group it is observed in the phase after glare. As for the accommodation, there are no significant differences between the two groups.

Conclusions. In patients treated with fluoxetine there are pupillary alterations like a bigger pupillary diameters and slower pupillary contraction. The lack of conclusive results in terms of accommodation does not mean that there are no changes related to it, whose detection requires future studies with different methodologies and with a larger sample size.

Keywords: Mesopic Pupillary Reflex, Fluoxetine, Depression, Visual System, Predictive Indicator

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Actas Esp Psiquiatr 2020;48(2):47-53

Reflejo pupilar mesópico en pacientes tratados con fluoxetina

Introducción. Actualmente el tratamiento de enfermedades mentales mediante antidepresivos es muy frecuente. Los inhibidores selectivos de la recaptación de serotonina son los antidepresivos más prescritos a nivel mundial y han sido asociados con alteraciones en la acomodación o la pupila. El objetivo de este estudio es evaluar los efectos de la fluoxetina sobre el reflejo pupilar y la acomodación en población joven.

Metodología. El grupo de estudio contó con siete pacientes diagnosticados de depresión y tratados con fluoxetina; como grupo control se incluyeron 22 sujetos. Se evaluaron los reflejos pupilares y el estado acomodativo mediante el pupilómetro Power Refractor II. Se midieron 5 fases de 3 segundos cada una. En la fase 2 se produjo un deslumbramiento con una luz blanca.

Resultados. Para el diámetro pupilar se han obtenido valores máximos y mínimos mayores en el grupo de pacientes tratados con fluoxetina que en el control en todas las fases de medida. Para el grupo control se observa una contracción pupilar máxima en la fase de deslumbramiento, sin embargo, en el grupo de estudio se observa en la fase tras el deslumbramiento. En cuanto a la acomodación no se obtuvieron diferencias significativas entre ambos grupos.

Conclusiones. En pacientes tratados con fluoxetina existen alteraciones pupilares observándose diámetros pupilares mayores y menor velocidad de contracción pupilar. La falta de resultados concluyentes en cuanto a la acomodación no significa que no existan cambios relacionados con esta, cuya detección requerirá de futuros estudios utilizando diferentes metodologías y con un tamaño Samplel mayor.

Palabras clave: Reflejo Pupilar Mesópico, Fluoxetina, Depresión, Sistema Visual, Indicador Predictivo

INTRODUCTION

Currently, the treatment of mental illness by antidepressants is very frequent, affecting many millions of people. Mental illness affects people of any age range and sociocultural background.

The different forms of depression have been included in the DSM-5 in a group called mood disorders, which is characterized by presenting a depressed mood and a group of emotional, cognitive, behavioral and physiological disorders related to the main diagnostic condition. It also expresses a certain absence of positive affective condition in people, which is expressed in the loss of cognitive and behavioral interest in the daily life activities[1].

Depression can start at any age, although its highest prevalence occurs between 15 and 45 years, hence it has a great impact on education, productivity, functioning and personal relationships[2].

In order to treat depression, there are different types of drugs that are grouped into four families: tricyclic, tetracyclic, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors. Fluoxetine (Prozac) is currently one of the most prescribed drugs, among the selective serotonin reuptake inhibitors.

Psychotropic medications have the potential to induce unwanted adverse eye effects. Selective serotonin reuptake inhibitors are the most commonly prescribed antidepressants worldwide and have been associated with alterations in accommodation, mydriasis and other possible pupillary factors.

The pupil is the dynamic hole that is located in the center of the iris. It has several functions: regulating the light entrance that reaches the retina in the eye, increasing the depth of focus, reducing chromatic and spherical aberrations.

Changes in pupillary diameter are regulated, automatically and symmetrically, by the balance between the sphincter muscle of the pupil and dilator muscle of the iris in response to the level of light and convergence, as well as emotions or pain. Pupillary contraction (myosis) is controlled by the sphincter muscle, whose innervation is parasympathetic (afferent pathway). The light that affects the retinal photoreceptors causes the excitation of the axons of the ganglion cells, travel through the visual route and synapse with the mesencephalic pretectal nucleus. This structure is connected bilaterally in the Edinger-Westphal nuclei, emit parasympathetic fibers and travel through the third cranial nerve until reaching the ciliary ganglion in the orbit. The short ciliary nerves innervate the sphincter muscle causing pupillary contraction.

The opposite mechanism (mydriasis) is regulated by the dilator muscle of the iris, whose innervation is sympathetic (efferent route). The fibers that come from the posterior hypothalamus descend through the brain stem, reach and synapses with the spinal cord neurons. These fibers continue, they synapse in the upper cervical ganglion and their postganglionic fibers go through the internal carotid until they reach the long ciliary nerves[3].

Pupillary contraction and dilation can occur abnormally due to the presence of various pupil alterations or the consumption of certain drugs. When one eye is illuminated, if both pathways work correctly, the myosis detected in that eye is called a direct reflex while myosis of the contralateral eye is called a consensual reflex. Similarly, when removing the illumination, the mydriasis will be because of the direct reflex and that of the contralateral eye because of the consensual[4].

As for the accommodation process, when an observer transfers the binocular fixation from an object located at a long fixation distance to another that is at a closer fixation distance, changes occur in the refractive state of the eye at the relative positions of the visual axes to maintain a clear image. Meaning, when a subject binocularly fixes an object located at a certain distance, as the object approaches, the eyes have to increase their refractive power more and more in order to maintain the image of this object sharp in the retina. At the same time, the angle formed by the visual axes increases so that the image of the object remains in both foveae. The process in which the refractive power of the eyes is altered to ensure a clear retinal image is called accommodation. The increase of the angle of the visual axes is known as convergence. In addition, the pupils contract due to fixation in near vision. The association between accommodation, convergence and pupillary constriction during fixation in near vision is called syncinesia.

The basic mechanism that induces accommodation is the blurred retinal image, which causes the lens to change its shape by increasing its central thickness and curvature as the object approaches the individual[5]. When fuzziness is detected, the information is sent through the optical fascicle to Brodmann area 19 and from there to the Edinger-Westphal nucleus. Then the information passes through the III cranial nerve to the ciliary body where the response occurs[6].

The study of the pupillary reflex in mesopic conditions in clinical practice is not only important to evaluate the condition of the patient's visual system and to be able to prevent the possible side effects of its treatment; but it can also provide clinical help in psychiatric consultations to be able to control and adjust the dose based on an objective measurement (predictive indicator).

Therefore, the objective of this study is to evaluate the effects of fluoxetine on the pupillary reflex in mesopic conditions and accommodation in young population.

METHODOLOGY

The sample was composed with patients from the Clínica López-Ibor diagnosed with mood disorders following the criteria of the DSM-5.

In the study group, there were seven patients (5 women and 2 men) between 18 and 37 years old with an average of 26 ± 4 years diagnosed with depression and treated only with an average dose of 20 mg of fluoxetine per day without the presence of concomitant medication. In the control group 22 subjects (4 men and 18 women) between 22 and 28 years old were included.

The inclusion criteria were: ages between 18 and 40 years and, for the study group, being treated with fluoxetine for at least six months.

The exclusion criteria were: pathologies and/or eye surgeries, systemic pathologies, pregnant women and, for the study group, being treated with drugs other than fluoxetine.

The tests were carried out at the Clínica López-Ibor in Madrid after having the approval of the Ethics Committee of the San Carlos Clinical Hospital. All tests were carried out following the Declaration of Helsinki and after signing an informed consent by each of the participants.

Material

The instrument used to evaluate the pupillary reflexes was the binocular dynamic pupilometer Power Refractor II (Plusoptix, Germany). This instrument is valid for pupillary diameters between 4-8 mm with an accuracy of 0.1 mm and with an error ± 0.3 mm. It also determines the interpupillary distance with an accuracy of 1 mm and provides data on the monocular refraction that allows evaluation of the accommodative state. It measures spherical ametropias in a range between +5.00 D and -7.00 D in steps of 0.25 D, with an error of ±0.25 D. In addition, it measures every 0.04 seconds, which means a total of 25 images per second[7].

This instrument consists of three components: an infrared camera that allows dynamic recording of the pupil; a signal adapter that transforms the binary signals sent by the camera into digital image and the Plusoptix software, which is incorporated in the pupilometer itself and allows the recording and extraction of the data obtained by the infrared camera. The Plusoptix software records and processes changes in pupil diameter over time, compiling the required values in CSV files.

The digital image, together with all the numerical records associated with the variables related to refraction and pupillary diameter, are presented on the screen of the computer connected to the adapter. The measured frequency of the Power Refractor II device is 25 Hz[7].

The main advantage of this pupilometer compared to more traditional methods is that it allows the measurement of pupillary reflexes in mesopic conditions. In this way it is possible to evaluate the response of the pupillary contraction against a light stimulus based on its state of maximum dilation.

Method

The pupilometry was performed with the subject sitting a meter away from the pupilometer, after having adapted to the darkness, in mesopic conditions (<10 cd/m^2). Once the patient was placed comfortably and binocularly fixating the stimulus of the infrared camera it began to measure changes in the pupillary reflex and refraction; during the first 3 seconds without glare (Phase 1), then with glare for another 3 seconds (Phase 2) and finally the rest of the test also without glare (Phase 3, 4 and 5). Glare was produced from the position of the pupilometer with a white flashlight, providing illumination of 0.3 cd/m2. The completion of the entire test was 15 seconds for each individual.

Statistical analysis

The statistical software SAS 9.4 was used to analyze the data obtained in the study. First, the descriptive statistics of the numerical variables were gathered, obtaining the useful sample, mean, standard deviation, minimum value, median and maximum value. Regarding the normality of the numerical variables, in the groups to be compared, it was evaluated with the Shapiro-Wilks test. For the variables that presented significant deviations from normality, the Wilcoxon ranks sum test was used and for the rest the t-Student test was applied.

RESULTS

Pupillary reflex

In Figure 1, the maximum and minimum values of the pupillary diameter for the five middle phases are shown. In the case of the maximum pupillary diameter, it can be observed that for both eyes and in all phases of measurement,

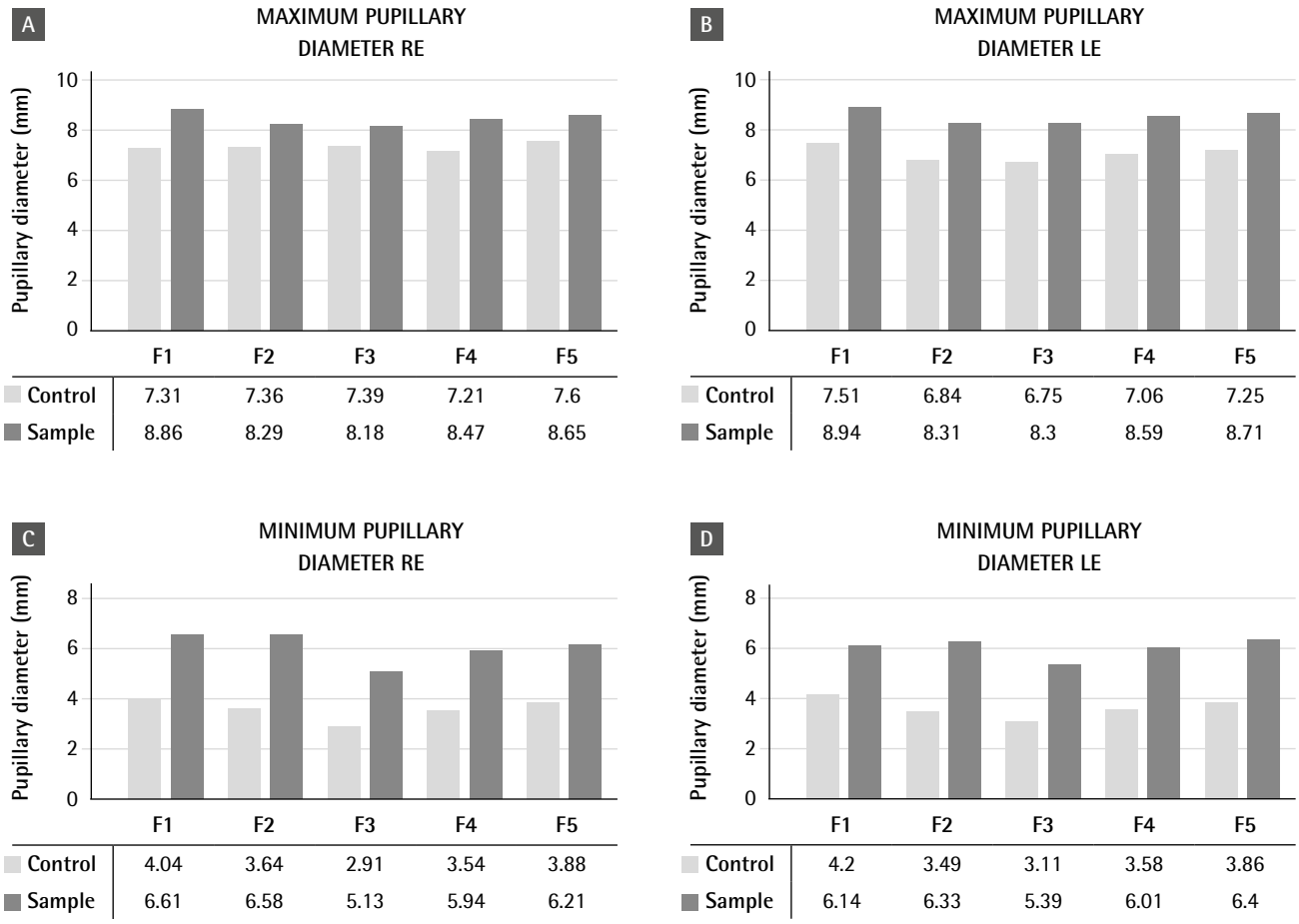


Figure 1 — *Maximum and minimum pupillary diameters for each of the five measurement phases. (a) and (b): Maximum pupillary diameters of the control group and the sample for the right and left eye respectively. (c) and (d): Minimum pupillary diameters of the control group and the sample for the right and left eye respectively*

the values obtained for the group treated with fluoxetine are around 1 mm higher than those obtained for the control group. As for the minimum diameters, these differences showed again higher values for the treated group, in this case greater than 2 mm.

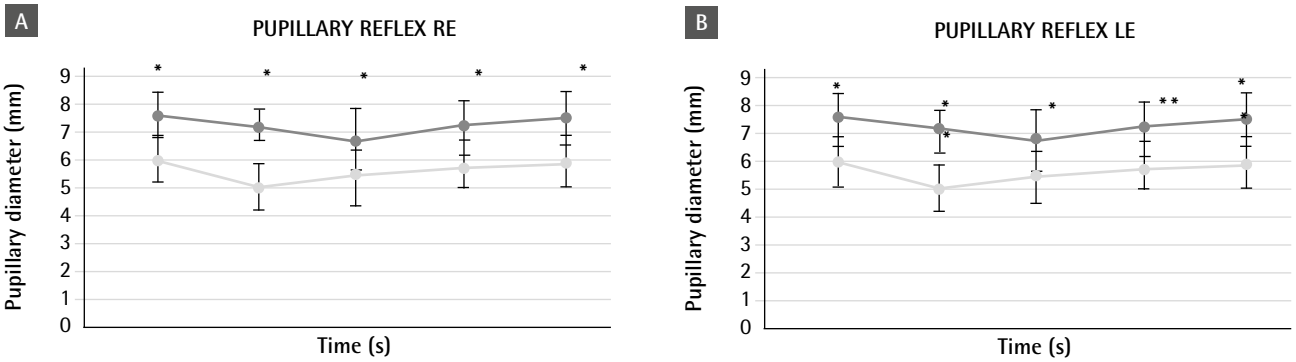
The mean values of the pupillary diameter are observed in Figure 2. Statistically significant differences ($p<0.01$) have been obtained between the group treated with fluoxetine and the control group for all measurement phases. In the second phase (seconds between 3"and 6"), at which time glare occurs, the control group shows a maximum pupillary contraction. However, the maximum myosis for the study group is given in the third measurement (F3).

Accommodation

Figure 3 shows the Diopter results of the accommodation put into play by the participants during the taking of measurements taken at a distance of 1 meter from the pupilometer. No statistically significant differences were observed when comparing the accommodative values between the control group and the study sample.

CONCLUSIONS

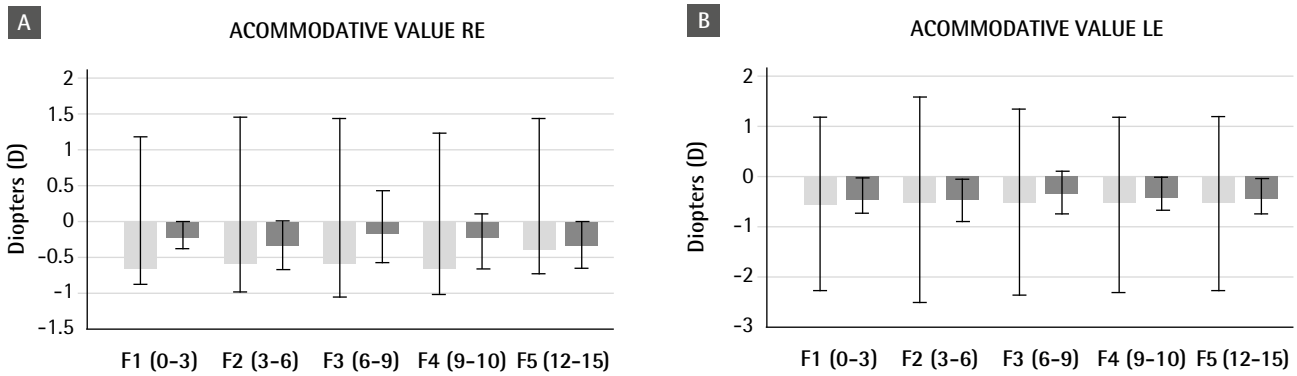
In this study, the results obtained regarding pupillary reflex and accommodation in young patients medicated with fluoxetine and healthy subjects are presented. Some studies have been found in research that relate the changes



	F1 (0-3)	F2 (3-6)	F3 (6-9)	F4 (9-10)	F5 (12-15)
Control	5.96	5.04	5.41	5.82	5.92
Sample	7.63	7.19	6.78	7.21	7.43

	F1 (0-3)	F2 (3-6)	F3 (6-9)	F4 (9-10)	F5 (12-15)
Control	5.98	5.13	5.51	5.84	5.91
Sample	7.42	7.07	6.73	7.11	7.31

Figure 2 — *Mean values of the pupillary diameter in each measurement phase (F1, F2, F3, F4 and F5) and their standard deviation. Values for the right eye (graph a). Values for the left eye (graph b)*



	F1 (0-3)	F2 (3-6)	F3 (6-9)	F4 (9-10)	F5 (12-15)
Control	-0.64	-0.61	-0.62	-0.63	-0.38
Sample	-0.21	-0.35	-0.16	-0.22	-0.33

	F1 (0-3)	F2 (3-6)	F3 (6-9)	F4 (9-10)	F5 (12-15)
Control	-0.53	-0.49	-0.51	-0.52	-0.5
Sample	-0.4	-0.45	-0.3	-0.36	-0.4

Figure 3 — *Evolution of the value of the average refraction in the five phases (F1, F2, F3, F4, F5) of the pupilometry for the right eye (graph a) and left eye (graph b)*

produced by selective serotonin reuptake inhibitors in pupillary diameter. In the classic study conducted by Ramaekers et al. a mydriatic effect was concluded with a 50% increase in the total range of pupil diameters, the measurements were performed in patients treated with paroxetine (SSRI)[8]. Schmitt et al. in 2002 also found a significant increase in pupillary diameter of subjects treated with sertraline and citalopram (SSRI)[9]. In a more recent study, pupillary diameter was significantly higher in patients treated with SSRIs than in the control group[10]. In this study, an increase in basal pupillary diameter was found, matching with the studies mentioned before. These results may be due to the anticholinergic and adrenergic effect of selective serotonin reuptake inhibitors that, although relatively weak, may influence the iris or ciliary muscle[11].

Pupil function abnormalities have been reported in a wide range of disorders, including alcoholism, mental health disorders such as seasonal affective disorders, schizophrenia and anxiety, among others. Pupil response latency describes the delay in pupil contraction after the onset of a light stimulus. This period is due to a delay in the contraction of the smooth muscle of the iris and, to a lesser extent, to the tem-

poral dynamics of the exit and innervation pathways of the retina[12].

Several recent studies have found a decrease in pupillary response in depressive people[13-15]. Mestanikova et al. found a decrease in pupillary light reflex in one eye in adolescents with major depression. These were examined before pharmacotherapy. In this study, patients treated with 20 mg of fluoxetine per day, have shown a significant decrease ($p < 0.01$) in the time of pupil reaction to light, with a maximum contraction in Phase 3, at the end of light stimulation[16]. On the other hand, in the study conducted by Mestanikova, the initial pupillary diameters were similar for the control group and the group with major depression, while in this study there are significant differences in the basal diameter that could be due to treatment with fluoxetine, absent in said study.

There is another research that also tests the relationship between depression and pupillary reflex through the use of light stimuli with different intensities and wavelengths (red and blue)[17,18]. In contrary to this study, the differences found between depressive subjects and controls are focused on the reduction in pupil constriction and not the delay in the reflex or the difference in basal diameter. This could be because in this study all subjects are treated with the same drug, while in those studies the treatments are different among subjects, which could alter the pupillary response.

Pupillary contraction is a necessary mechanism for a correct accommodative response. In this study, none statistically significant differences were found between accommodation values for the control group and the study group. These results do not agree with the hypothesis of a possible condition of the accommodative system given the anticholinergic and adrenergic effect of antidepressants that can affect the ciliary muscle[11,19]. Although these results are based on an objective measure of accommodation, there are other parameters subjectively evaluated regarding this, such as accommodative flexibility or amplitude of accommodation, which should be measured before ruling out a possible alteration caused by this type of drugs.

The most important limitation of this study is the small sample size, because the high restriction of the inclusion criteria limits the possible candidates to participate in the study, considering this research as a preliminary study. On the other hand, the confidentiality of patient data does not allow us to know beyond the diagnosis of depression of the participants at a psychiatric and symptomatology level.

In conclusion, it has been found that, in young patients treated with fluoxetine, the basal pupillary diameter of both eyes is greater. The pupillary reflex to the light in mesopic conditions, for both eyes, presents significant differences delaying in the Phase 3 the maximum myosis. This fact indicates a lower pupil contraction rate compared to a light stimulus. Regarding accommodation, the measures taken are not sufficient to determine that there is any alteration derived from the use of fluoxetine.

These results allow us to think about the design of an instrument that, by assessing the mesopic pupil reflex, helps clinical practice by controlling the suitability of the prescribed dose for each patient, as well as its visual side effects on the patient.

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