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Original Article

Effect of Psychotropic Medications on Ocular Parameters: A Naturalistic Study

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ABSTRACT

INTRODUCTION: The incidence of psychiatric diseases and consequently prescription of psychotropic medications is increasing day by day. Ocular problems rising in relation to use of these drugs have important effect on psychiatric patients' lifestyles. **AIM**: The need to undertake this study project is to fill the lacunae in the understanding of the effects of psychotropic medications on intraocular pressure and vision and to obtain concrete evidence. **MATERIAL AND METHODS**: 200 patients with various DSM-5 psychiatric diagnosis were assessed in a naturalistic longitudinal cohort study and ophthalmological examinations were carried out in Ophthalmology Department of a tertiary care centre. Patients were screened according to inclusion and exclusion criteria and patients fulfilling said criteria were recruited. Data was pooled, tabulated and subjected to appropriate statistical tests. **RESULTS**: Schizophrenia and related disorders were the most common diagnoses followed by substance use disorders, Major Depressive Disorder, Anxiety Disorders, Bipolar Mood Disorder, Obsessive Compulsive Disorder and others in that order. The range in duration of illness was 0.1 months in a patient of brief psychotic episode to 492 months in a case of alcohol use disorder. All 200 patients had their intraocular pressure within normal range. Majority of patients were started on and were receiving multiple psychotropic medications and in spite of receiving these medications, their intraocular pressure remained within normal range. After exposure to psychotropic medications, only 1 patient was found to have changes in the acuity of vision in the right eye and 2 patients had changes in the acuity of vision in the left eye, which may or may not have been effects of psychotropic medications. **CONCLUSIONS**: Psychotropic medications in persons who do not have a predisposition to ocular pathology, do not bring about any change in near vision, distant vision or color vision. Similarly, in patients who are not predisposed to glaucoma, starting such patients on psychotropic medications will not bring about a pathological rise in intraocular pressure (IOP). Even if does cause a change in intraocular pressure, it remains within the normal range and doesn't shift to pathological range.

Keywords*: intraocular pressure, vision, psychiatric disorders, psychotropic medications, visual acuity.*

INTRODUCTION

The incidence of psychiatric diseases and consequently prescription of psychotropic medications is increasing day by day. As with all medications, psychotropics too have their profile of side effects; of which the ocular side effects are not covered in depth [1]. Ocular problems rising in relation to use of these drugs have important effect on psychiatric

patients' lifestyle [2]. Psychotropic drugs can potentially lead to many ocular adverse effects depending upon the idiosyncrasies, dosages and the interactions with specific mechanisms of the body organs. After liver, the eye is supposed to be the second most frequent organ to manifest drug toxicity [3].

Intraocular pressure (IOP) is determined by a balance between aqueous humor production and its drainage, the regulation of which is done by neurotransmitters (norepinephrine, epinephrine, acetylcholine, dopamine, and serotonin) that activate receptors placed on the ciliary body and trabecular meshwork. Muscarinic cholinergic receptor blockade caused mainly by phenothiazines such as Chlorpromazine, Levomeprazine, Thioridazine and Fluphenazine, may lead to rise in intraocular pressure as a result of mydriasis and angle closure. The selective serotonin reuptake inhibitors (SSRI) class may be involved in raising IOP due to its serotonergic action. Tricyclic antidepressants (TCA) due to their anticholinergic proprieties can also lead to acute angle closure glaucoma or worsen primary open-angle glaucoma due to their potential of causing mydriasis [4].

Bupropion and Topiramate are both widely prescribed drugs that have been reported to cause angle-closure glaucoma via a choroidal effusion mechanism. Moreover, Topiramate also contributes to a rise in intraocular pressure by its anti-carbonic anhydrase activity [5]. Based on a study conducted by Deidre Smith, Christos Pantelis, John McGrath, Christine Tangas & David Copolov, (82.6%) revealed to have one or more ocular abnormalities, including lens opacities/cataracts and corneal pigmentation**.** The reasons for the relatively high ocular morbidity were considered to be both illness-related factors and the effects of antipsychotic medication. However, the presence of confounding factors such as the high prevalence of smoking, poor general health and the variety of antipsychotic medications used in the treatment of psychosis as well as substance abuse makes it difficult to pinpoint the cause of ocular complications [6]. Risk factors for acute angle closure glaucoma include race, increased age, narrow anterior chamber angle, shallow anterior chamber depth, hyperopia, nanophthalmos, previous angle closure of fellow eye, family history, female sex and use of any substance that causes pupillary dilation [7]. Certain ocular side effects produce symptoms like blurring of vision, difficulty in reading small letters, photophobia which affects the compliance of the patient to the psychotropic medications [3].

Understanding such side effects and tending to them lessens the chances of compliance being compromised by titrating the dose or changing the medication. Moreover, the ocular side effects such as an acute attack of angle closure glaucoma, if left untreated can result in irreversible blindness, which necessitates us to be observant [8].

The need to undertake this study project is to fill the lacunae in the understanding of effects of psychotropic medications on intraocular pressure and vision and to obtain concrete evidence.

MATERIALS AND METHODS

This observational prospective study was conducted in patients attending Psychiatry OPD from 1st January 2018 to 1st August 2019 (20 months) at a tertiary care centre in Mumbai after approval from the institutional ethics committee. New patients who came to psychiatry OPD and were drug naïve, were explained the nature and purpose of the study.

Patients above 18 years of age of either gender who never received psychotropic medications but requiring the same were included in the study. Patients with any pre-existing ophthalmological conditions or who were on any other medications which have a propensity of causing ophthalmological side effects were excluded from the study.

After obtaining informed consent, patients and relatives were interviewed on a semi structured proforma and demographic, phenomenological and treatment related details were obtained. Those patients who did not wish to sign the consent received regular treatment without any hindrance.

1. Patients' eye examinations were done under the guidance of an experienced ophthalmologist who was blind to the treatment:

Distant Vision: **Snellen's chart [9]:**
Near Vision: **Jaeger chart [10]:**
Color Vision: **Ishihara's chart/ Isochromatic charts [11]**:
Intraocular Pressure: **Goldmann's applanation tonometry [12]:**
They were put on treatment as per the routine practice and followed up on Days 7 and 28. The eye examinations were repeated on each follow up. Data thus obtained was pooled and analysed using computerised statistical software.

RESULTS

In all, at baseline, 227 patients were recruited of which 27 patients dropped out by the 28th day of follow up, leaving 200 patients in the study.

The patients were in the age range of 18-75 years with the mean age being 36.5 years. There were more males than females in the study population. Mean years of education were from illiteracy to 15 years (highest), but on an average the education was up to secondary level only. 61% of the study population was employed and 16% was unemployed. There

were more married patients (63.5%) in the study population than single persons (30.5%) with a few being divorced, separated or widows.

Schizophrenia and related disorders were found to be the most common diagnosis assigned to the patients, followed by substance use disorders, Major depressive disorder, anxiety disorders, Bipolar mood Disorders, Obsessive compulsive disorder and others in that order. The range in duration of illness was 0.1 months in a patient of brief psychotic episode to 492 months in a case of alcohol use disorder [Table 1].

Treatment Profile:

Amongst the myriad of psychotropic medications being received by the patients attending psychiatry OPD, it was seen that antipsychotics, both first and second generation were widely prescribed, followed by antidepressants, anti-craving medications, anxiolytics and mood stabilizers in that order.

Change in IOP:

200 patients with their intraocular pressure within normal range. Majority of patients were started on and were receiving multiple psychotropic medications and in spite of receiving these medications, on day 7 and day 28, their intraocular pressure remained within normal range [Table 2].

Change in Visual Acuity:

Almost 50% of the patients had decreased acuity of vision and were using glasses. After exposure to psychotropic medications, only 1 patient had change in the acuity of vision in the right eye and 2 patients had changes in the acuity of vision in the left eye, which may or may not have been because of effect of psychotropic medications [Table 3]. The three patients demonstrating a change in their distant vision, were receiving at least one the following common medications - Escitalopram (20 mg) and Tablet Lorazepam (2-4 mg) [Table 4]. After exposure to psychotropic medications, only 2 patients had changes in near vision [Table 5]. The two patients who had a change in near vision had only Tablet Clozapine and Tablet Trihexyphenidyl as the overlapping psychotropic medications but these medications were being received in varied doses by both the patients [Table 6].

Color Vision

There was no change in color vision with patients on psychotropic medications in the present study.

Tables:

Table1: Phenomenological details of study population:

Diagnosis (N = 200)	No. of Patients	Mean Duration (months)	Standard Deviation (months)	Min-Max (months)
Schizophrenia and related Disorders	60	39.65	6.61	0.1-240
Substance use Disorder	50	153	17.78	6-492
Major Depressive Disorder	46	23.50	6.03	0.7-180
Anxiety and related Disorders	17	14.35	5.43	1-96
Bipolar Mood Disorder	14	62.29	28.44	1-396
Obsessive Compulsive Disorder	4	60.13	28.47	0.5-120
Others	9	5.39	1.74	0.5-18

Table 2: Change in IOP

Intra Ocular Pressure (mm of Hg)	Day 0 (Number of patients)	Day 7 (Number of Patients)	Day 28 (Number of Patients)
Normal Range (12-22)	200	200	200
Less than 12	0	0	0
More than 22	0	0	0

Table 3: Change in Visual Acuity (Distant Vision):

Vision	No. of Patients Day 0		No. of Patients Day 7		No. of Patients Day 28	
	Right Eye	Left Eye	Right Eye	Left Eye	Right Eye	Left Eye
6/6	104	100	102	100	102	99
6/9	53	58	54	57	53	58
6/12	17	18	16	17	17	17
6/18	4	5	6	6	6	7

6/24	12	14	12	14	12	14
6/36	10	5	10	6	10	5
6/60	0	0	0	0	0	0
Finger counting	0	0	0	0	0	0

Table 4: Medications received by 3 patients who had changes in distant vision:

Patients	Change in vision	Name and Maximum Dosage of Drug Received				
Patient 1	6/9 to 6/12	Amitriptyline 25mg	Escitalopram 20mg	Flunarizine 5mg	Lorazepam 2mg	Olanzapine 5mg
Patient 2	6/6 to 6/9	Baclofen 30mg	Lorazepam 4mg	Quetiapine 50mg	-	-
Patient 3	6/9 to 6/18	Escitalopram 20mg	Mirtazapine 30mg	Etizolam 1.5mg	-	-

Table 5: Change in Visual Acuity (Near Vision):

Vision	No. of Patients Day 0	No. of Patients Day 7	No. of Patients 28
N-6	116	114	114
N-8	10	12	12
N-10	32	32	32
N-12	7	7	7
N-18	5	5	5
N-24	15	15	15
N-36	15	15	15

Table 6: Medications received by 2 patients who had changes in near vision:

Patients	Patient 1	Patient 2
Change In Vision	N-6 to N-8	N-6 to N-8
Name and Maximum Dosage of Drug Received	Clozapine 300mg	Clozapine 150mg
	Donepezil 5mg	Haloperidol 15mg
	Escitalopram 20mg	Olanzapine 25mg
	Lamotrigine 100mg	Trihexyphenidyl 10mg
	Propranolol 20mg	
	Tiapride 50mg	
	Trihexyphenidyl 6mg	

DISCUSSION

We know that Major Depressive Disorder (MDD) is rising all over the world at an alarming rate, both in developed and developing nations [13]. On the other hand, glaucoma, refractive errors and color vision problems are commonly seen by doctors all over the world.

A recent survey of psychiatrists and ophthalmologists suggested that about 6.5 % of physicians responding had seen one or occasionally two cases of glaucoma which they felt might be an instance of adverse reaction to psychotropic medication. The most frequently implicated drug was amitriptyline, although problems were rare, and the age group predisposed to treatment with amitriptyline is also the age group most susceptible to coincidental glaucoma as per the study conducted by William H. Reid et al. [14].

The pathophysiology of raised intraocular pressure caused by psychotropic drugs is complex. About 2.5 microliters of aqueous humor is produced per minute by the ciliary body of the eye [15]. The three processes involved in its production are ultrafiltration, active secretion and passive diffusion. Aqueous humor provides oxygen and nutrients to the structures in the anterior segment and removes waste products [16]. It is drained into the venous blood circulation via the trabecular meshwork and the canal of Schlemm. Approximately 5–10% of aqueous humor is drained following the uveo-scleral pathway [17].

There are broadly two types of glaucoma. In open angle glaucoma, the iris is in the correct position, and the uveoscleral drainage system is working properly. However, there is a blockage at the level of the trabecular meshwork. In closed angle glaucoma, the iris is in contact with the cornea, so the aqueous humor cannot even reach the trabecular meshwork [18]. Drugs like SSRIs work by blocking the reabsorption of serotonin in the synaptic gap between neurons. 5HT1A, 5HT2A/2C and 5HT7 are located in the iris-ciliary body complex. Stimulation of 5HT1A receptor reduces the IOP through the reduction of aqueous humor, but the 5HT2A/2C receptors increase IOP by stimulation of the ciliary body

blood flow, therefore they enhance the production of aqueous humor. 5HT7 receptors are responsible for mydriasis through the relaxation of the sphincter muscle and for rising IOP by increasing the production of aqueous humor. Hence if the 5HT1A receptors are blocked by the drugs like SSRIs or SNRIs, it can lead to glaucoma [17].

Epinephrine has many receptor types of which α2 inhibitory receptors from the ciliary epithelium can cause an increase in outflow facility of the aqueous humor while the blockage of these receptors by SNRI could reverse these effects leading to increased IOP. The noradrenergic effect of SNRI is more dominant than the one of SSRI, hence the former have a greater propensity to cause glaucoma [16].

Bupropion is a novel drug that has a variety of indications in Medicine, and Psychiatry in particular. It demonstrates anti-tumour necrosis factor (TNF) effects and a decreased activity on acetylcholine receptors that result in less anticholinergic side effects. Studies show that IOP might be raised by TNF through increased caspase activity or mitochondrial dysfunction in the aqueous humor outflow channels. TNF synthesis is decreased by noradrenaline (β2 receptor) and dopamine (D1 receptor) activation. Hence, we can say that that bupropion could have some protective proprieties regarding IOP and glaucoma.

Tricyclic Antidepressants (TCAs) were commonly used in the past but their use has declined in recent years because of many systemic side effects. They cause ACG which can be severe and lead to vision loss. The pupillary block via pupil dilatation that occurs during treatment with TCAs is attributed to the significant anticholinergic and serotonergic effects of these antidepressants [19].

Antipsychotic drugs also have been associated with glaucoma via the production of reactive oxygen species (ROS), especially the AAPs, that is Atypical Antipsychotics. Risperidone was demonstrated to have the ability to decrease oxidative stress (OS) in schizophrenic patients by controlling the inflammatory response. Other drugs that have been shown to decrease OS are clozapine and olanzapine. However, the relationship between AAP, OS and glaucoma has not been completely investigated. So we can say that future studies are necessary to elucidate this possible mechanism [3].
AAPs can enhance glaucoma through anti-muscarinic action. It is well known that Clozapine and Olanzapine have high affinity for muscarinic receptors (inhibition) and anticholinergic activity, which could possibly exacerbate glaucoma. Thus, the actions of AAP by downregulating OS and neurotrophins may be unbalanced because of their anti- muscarinic receptor action [5].

Variety of patients were recruited having different diagnosis in our population and duration of illness being as less as 2-3 days in cases of acute psychotic episode and as high as 40 years in patients taking alcohol for 40 years. The following findings were noted:

1. **IOP:**

In our study we could understand based on our data that psychotropic medications produce no significant change in patients' intraocular pressure and could be used safely. Interestingly in our study population of 200 patients, none of them had pathologically high intraocular pressure or evidence of glaucoma. The patients had normal intraocular pressure or else they wouldn't have been taken up for the study and all were proven safe against a diagnosis of glaucoma. If the preexisting intraocular pressure was normal, then there very minimal chances of aggravation of intraocular pressure but in patients with preexisting high intraocular pressure, aggravation was seen in a few but it still remained within the normal range of intraocular pressure in all 200 completed patients. Even on follow up of, it was seen that psychotropic medications do not cause a rise in intraocular pressure if the baseline intraocular pressure is normal. But it seems that if preexisting glaucoma is there, then it may get aggravated, but since in our population, none of the patients had preexisting glaucoma, our findings are in agreement with the literature. Two types of studies which have been conducted, overall studies where they have not found any change in intraocular pressure and case reports where they have found change in intraocular pressure after taking psychotropic medications. These results are along the same lines as the large multicentre study done by the researchers Vincent Chen et al in Taiwan [20]. Hence even though our study population was smaller, we can see that the results are in line with those of the larger trials.

2. **ACUITY OF VISION**

In our study too, we could find no evidence of change in visual acuity in patients receiving psychotropic medications except 3 patients who experienced a change in near and/ or distant vision. Medications being received by these 3 patients were studied but we couldn't isolate one particular medication responsible for the change in visual acuity. We could have stopped their psychotropic medications and rechecked their vision, but this was not implemented as it was not part of our thesis study. We compared the results of our study to the larger study done by Wang and Tseng and our findings are very similar to theirs [21].

3. COLOR VISION

Being a genetic disorder, the incidence, of color blindness, varies from race to race and different in the different geographical regions of the world inhabited by people of different ethnicity. Asian males have a prevalence of color vision defects of 4.9% compared to 0.6% in females that is quiet low [22]. Similarly, in our study population, none of the

patients had problem with color vision at the beginning and on follow ups also after exposure to a variety of psychotropic medications, none of them had change in color vision indicating psychotropic medications do not interfere with color vision. We couldn't find any studies case reports showing change in color vision through psychotropic medications. Also seen with non- psychotropic medications such as sildenafil citrate. The drug has a mild inhibitory effect on PDE6, which controls the level of cyclic guanosine monophosphate in the retina, and it may cause a perception of bluish haze or increased light sensitivity in some patients. Long-term retinal damage has not been reported according to a study conducted by Michael F.Marmor, RobertKessler et al but since none of our patients were on these medications, so we couldn't assess this aspect of sildenafil. If there are case reports of drugs causing a change in color vision, it is with other drugs and not with psychotropic medications [23].

CONCLUSION

1. 1.Psychotropic medications in persons who do not have a predisposition to ocular pathology, do not bring about any change in near vision, distant vision, color vision.
2. A change in visual acuity was seen only in a couple of patients which may or may not be because of psychotropic medications and any findings may be incidental.
3. Similarly, in patients who are not predisposed to glaucoma, starting such patients on psychotropic medications will not bring about a pathological rise in intraocular pressure.
4. Even if does cause a change in intraocular pressure, it remains within the normal range and doesn't shift to pathological range.

Thus, psychotropic medications are safe to use and do not cause any ocular pathology.

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