Psychotropic Drugs and Ocular Side Effects
Psikotropik İlaçlar ve Oküler Yan Etkileri

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Summary
Nowadays, the number of patients using the types of drugs in question here has significantly increased. A study carried out in relation with the long-term use of psychotropic drugs shows that the consumption of this group of drugs has substantially increased in terms of variety and quantity. In this paper, we present our review of the literature pertaining to ocular complications of psychotropic drugs in long-term treatment profile of numerous patients. If the doctor and the patients are informed about the eye problems related to the use of psychotropic drugs, potential ocular complications can be easily prevented, supervised, and controlled and can even be reversed. 
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Introduction
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. The visual system consists of numerous tissues derived from different origins, and the eye has an extensive, rich blood supply although having a relatively small mass. Besides, neural tissues within the eye exhibit a very high metabolic rates. All these factors are important for the human eye becoming sensitive to psychotropic treatments. In this review, we report the ocular adverse effects of common psychotropic agents and conclude that the majority of the psychotropic drug-induced eye disorders can easily be prevented, supervised, and even be reversed, if both the clinicians and the patients become aware of ocular sign and symptoms.

Antipsychotics
In typical antipsychotics, phenothiazine family forms the most examined group in psychotropic agents. The group of phenothiazines has the potential of creating ocular and dermatological side effects. Chlorpromazine, especially when used in high doses, causes abnormal pigmentation in the eyelids, interpalpebral conjunctiva, cornea, and the lens. Moreover, epithelial keratopathy related to chlorpromazine is discussed by many authors in the literature. Abnormal pigment accumulations related to chlorpromazine, especially dose of drugs used more than 2 grams daily, develops secondarily.2-4
Typical antipsychotics also have effects on uveal tissues. Antipsychotics which have strong anticholinergic and/or antidiurenergic effects (such as chlorpromazine and fluphenazine) cause mydriasis and cycloplegia.4 Due to this effect profile, the feature of weakening accommodation by phenothiazines is identified.5
Theoretically, anticholinergics and antiadrenergics which have high-dose antipsychotics (such as phenothiazine) should be foreseen that they might form a risk factor in terms of angle-closure glaucoma (ACG). Actually, when antipsychotics are compared with the tricyclic antidepressants (TCAs), they relatively have less effects on ocular smooth muscles and risk of producing ACG is far less in proportion to TCA.\textsuperscript{6} No report on ACG induced by antipsychotics has been encountered in the literature.

Almost all drugs in the group of antipsychotics can form eye opacity. Chlorpromazine and thioridazine are the mostly examined two drugs in this group.\textsuperscript{1,5,7,8} This unwanted side effect is related to drug being used and the dose. Eye opacities emerge after using high dose. Of 61 patients who have used 800 mg of chlorpromazine for two years, 35 have faced the development of pigment accumulation.\textsuperscript{9} In another study, 35\% of 384 patients with long-term chlorpromazine use have shown deposits in the lens and cornea.\textsuperscript{10} However, there is not a finding of risk of high opacity creation subject to phenothiazines in relation with exact dose/period relation yet.\textsuperscript{11}

Butyrophenones such as haloperidol do not show cataractous effect in long-term use.

In treatments by typical antipsychotics, oculogyric crisis is not a side effect seen rarely. It can be quickly seen after the haloperidol injection form treatment in 12-24 hours.\textsuperscript{12}

Antipsychotic drugs also show effects on the retina which is ontogenetically a part of the brain. Most frequently, retinal lesion occurring as a result of using phenothiazine is retinitis pigmentosa. Phototoxic period plays an important role both in retinitis pigmentosa and retinal degeneration. Pigment accumulation progresses from the periphery of the retina through the central area. By this way, peripheral vision loss, night blindness, central scotoma, and as a result total loss of sight develop.\textsuperscript{13-15} Knowing this retinal diseases’ early symptoms is highly important in terms of controlling it before disease progression. Before the occurrence of retinitis pigmentosa, these patients state either that they have visual haze or loss in the scotopic vision sharpness. If these initial symptoms are early diagnosed and the use of drugs is stopped, disease progression can be prevented. In this case, even if the pigmentation is permanent, an increase in vision function can be provided.\textsuperscript{13} A study done on dogs has shown that histological lesions are clear and retinitis pigmentosa has an aptness to be irreversible.\textsuperscript{16}

In most cases where the retinal complications are stated, thioridazine is shown as the responsible drug. Less frequently, cases related to chlorpromazine and rarely to other phenothiazines are reported.\textsuperscript{4,13,15} Retinopathy can be seen in people who have used high dose of phenothiazine in long term. The dangerous quantities for thioridazine regarding the retina are 800 mg, and especially doses over 1000 mg daily.

For chlorpromazine, this side effect is related to the dose and period. Unwanted effects related to thioridazine rises earlier when compared to the other phenothiazines. In high-dose treatments, toxic cases can be seen in weeks. After retinopathy being induced with phenothiazine, retina undergoes pigment epithelium alteration and there develops a heavy vision loss.\textsuperscript{1,4,13-15}

Discussion on potential of atypical antipsychotics forming cataract is still present. Especially the studies in relation to quetiapine and the relation of this drug to cataract are worth referring.\textsuperscript{17} When the recommended dose of quetiapine for people is given four times to the dogs, cataract is seen but although this drug is used on monkeys 5 times the dose given to people, it has not increased the risk of cataract formation.\textsuperscript{17}

In the survey of PubMed, the case of cataract induced with quetiapine on humans is not described. However, the producing company mentions about cases which may cause changes in the lens and the relation of these changes with quetiapine is not defined literally.\textsuperscript{17} Cataract can be formed due to numerous different reasons as well as the age and even it is related to a drug, causal relation cannot be explained literally. Nevertheless, the producing company offers routine eye examination to the users of this drug.\textsuperscript{11,18}

The effects of clozapine and risperidone, which especially provide an effective treatment for resistant schizophrenia, on formation of cataract is not known. Developing lens changes are rarely mentioned in the prospectus of ziprasidone and olanzapine.\textsuperscript{11} Despite this, in study done on all users of atypical antipsychotic agents, potential of forming of cataract is found less than in it is in the population.\textsuperscript{11} In a 55-year-old patient being treated with long-term clozapine, the development of pigmented changes affecting the cornea and the retina as well as stellate cataract have been reported. This is the only case notifying the pigmentation development in association with the use of clozapine.\textsuperscript{19}

Diabetogenic effect, formed by certain antipsychotics such as olanzapine and clozapine, might cause an increase in the risk of cataractous change in the lens. There is not any known relation between aripiprazole and secondary cataract. It is indicated that amisulpride might cause secondary pseudomyopia and supplementation of anticholinergic agent might contribute to this side effect.\textsuperscript{20} In a study done with schizophrenic patients using antipsychotics, abnormalities in the intraocular pressure and optical disc cavitation ratios have been determined in users of ziprasidone.\textsuperscript{21} In the literature, there is a case of transient myopia induced by aripiprazole.\textsuperscript{22}

When the atypical antipsychotics are compared to typical ones, dystonic reactions and therefore cause of oculogyric crisis are not expected. In the literature, oculogyric crisis cases related to clozapine, aripiprazole, amisulpride, ziprasidone, and sertindole have been reported. Here, the responsible mechanism can be striatum sensitization due to the use of typical antipsychotics and underlying genetic predisposition in some patients.\textsuperscript{23-27}

An eye examination is recommended not only when unaccepted new antipsychotics are applied in the treatment process, but also in the early periods of the treatment and at semiannual follow-ups in the long-term periods.
Antidepressants

Tricyclic Antidepressant Agents (TCAs)

TCAs can cause serious ocular side effects in the early periods of the treatment. The two most common side effects are mydriasis and cycloplegia. When mydriasis occurs in a person who are not tolerant to the effect of TCAs upon the ocular smooth muscles, thus visual haze and/or myopia develop. Cycloplegia is related to the paretic effect on ciliary muscle. Mydriasis and cycloplegia rise in result of TCAs’ anticholinergic effect. Moreover, noradrenaline uptake blockage and adrenergic receptor blockages should also be considered in effective mechanisms. Visual haze in patients having TCA treatment is seen in the early periods of the disease and in one third of the patients roughly. Patients generally develop tolerance to this side effect and vision function returns to normal in the forthcoming days of the treatment instinctively. If the visual haze and wish for remaining the TCA treatment continue, topical Cholinergic agonist (pilocarpine) can be used additionally. If the visual haze is responsible for most of the glaucoma cases. In three of the six cases, paroxetine was identified in geriatric patients (aged between 70-91 years), 2 of the cases were young patients who were hypermetropic, and plateau iris configuration was identified in one patient. Development of bilateral ACG was stated in a 71-year-old patient using maprotiline and alprazolam. Planopsia was seen in three patients using trazodone. Its mechanism is not known and the effect has a relation with the dose. Decreasing the dose or stopping the use of antidepressants has removed the planopsia.

Selective Serotonin Reuptake Inhibitors (SSRI’s)

The drugs in this group are the drugs mostly used as antidepressants and anxiolytic. Since their use in 1980, they have been used by millions of people in the world. Fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine, and sertraline are all SSRIs. They all increase serotoninergic conduction in SSRI; this effect develops secondarily on the reuptake inhibition of serotonin synapse level. These drugs generally have the perfect profiles of security and tolerance. Possible ocular side effects related to SSRI are mydriasis, increase in intraocular pressure (IOP), glaucoma, and oculogyric crisis. In the studies done with patients being treated with SSRI, the most common reason of patients leaving the study was the rise of visual impairment.

It is propounded that mydriasis related to SSRI, increased IOP, and development of glaucoma have a relation between themselves. There are seven different serotonin receptor families (5HT1-5HT7). Serotonin receptors functioning in eye are: 5-HT1A, 5-HT2A, 5-HT2C, and 5-HT7. All these receptors have a role in the IOP dynamics and the effect can be seen in IOP increase and development of glaucoma. The effect of serotonin on pupil sphincter-localized 5-HT7 receptor results in activation of adenylate cyclase, it causes an increase in c-AMP and muscle relaxation and may lead to passive mydriasis.

It is shown that SSRIs such as sertraline, paroxetine, fluoxetine, and citalopram specifically cause pupil dilation. As long as the mydriatic effect of SSRIs does not cause a dramatic increase in IOP and the development of glaucoma, it does not cause a major visual impairment or problem. If the mydriatic effect related to SSRI is complicated with ACG, the side effect disappears by stopping the use of the drug. Patients who will start using SSRI are recommended to have ophthalmologic examination and investigation of the risk of angle closure.

Paroxetine, which has the strongest potential in terms of NA reuptake inhibition, is the most blamed agent in SSRI in terms of ACG. Like in paroxetine, SSRI’s and SNRI’s like venlafaxine, noradrenergic effects with sympathomimetic effects might cause active mydriasis. With passive mydriasis related to serotonergic activity, conglomeration and crowding occur in active mydriasis at an important ratio. Therefore, aqueous outflow is prevented and glaucoma attack develops with IOP increase. Indeed, more and more evidence has risen for the fact that IOP is increased by SSRIs day by day. With this, most of these cases are not reported, stay asymptomatic, or turn into an ACG. In the PubMed survey, 11 articles have reported glaucoma in relation with SSRI. While 6 of these are related with paroxetine, 2 with citalopram, one with escitalopram, one with fluoxetine, and one with fluvoxamine, there is not case notified on sertraline. For this reason, paroxetine is responsible for most of the glaucoma cases. In three of the six cases, paroxetine was identified in geriatric patients (aged between 70-91 years), 2 of the cases were young patients who were hypermetropic, and plateau iris configuration was identified in one patient.

Two glaucoma attacks related with the use of citalopram were described. One of the cases was an alcoholic woman who used overdose of citalopram and the other one was a patient using citalopram regularly.
In the literature, ACG related with escitalopram was described in one case. The use of escitalopram by a 41-year-old woman caused rotation in the anterior chamber angle as a result of uveal effusion and development of acute bilateral ACG. The use of escitalopram was stopped, steroid treatment was started, and the patient showed complete recovery.60

Fluoxetine is the first SSRI correlated with ACG. ACG has developed in a young man patient after using oral fluoxetine for 5 weeks.44 The patient’s tendency to angle closure anatomically was not known. Apart from this, the symptomatic glaucoma case related with his drug was not reported but the experimental studies have shown that fluoxetine might cause a significant IOP increase both in animals and human beings.51,62

In conclusion, a 66-year-old male patient started using fluoxamine for headache and ACG has developed. When the use of drug was stopped, the symptoms of high IOP disappeared.50

In addition to these articles, in the report of “Australian Adverse Drug Reaction Bulletin of February 2001”, 11 glaucoma attacks related to SSRI are stated. Three of the cases were associated with fluoxetine and paroxetine, 4 with sertraline, and 1 with citalopram. The age of the patients varied between 32-70, most of them were asymptomatic, and the IOP increase was determined at the routine examination.63

In this case, the need of taking precaution before prescribing SSRI for patients who have the potential of IOP increase arises. Ophthalmologic consultation should be done periodically before starting antidepressant treatment and during the usage period especially on people with glaucoma predisposition. If there is a case of glaucoma, the use of drug should be stopped immediately, and treatment should be started by the ophthalmologists.64

One case of decreased visual acuity as a result of maculopathy related with sertraline is described.65 In this patient, maculopathy was solved after stopping the use of antidepressant drug but in the following 20 months, the visual acuity remained the same on suboptimal level. In this study, there was not any explanation on causality. Retinal vein occlusion was stated in relation to citalopram and fluoxetine.66,67

The use of SSRI may cause extrapyramidal symptoms. In the literature, akathisia is reported as the most common extrapyramidal side effect in relation with SSRI followed by dystonia.68,69 Gerber et al.69 have identified 127 extrapyramidal symptoms induced by SSRI. 19 of these symptoms are described as dystonia. Dystonia generally affects the muscles which are not related with the eye, but it rarely involves the eye muscles and visual symptoms arise.

In a case where escitalopram was being used, dose-related ocular dystonia and anaphylactic symptoms were stated.39 While “ocular dystonia and SSRI” is the only reported case in PubMed, this patient was thought to have developed panic attack, but the dystonic symptoms disappeared after IM adrenalin injection.

**Benzodiazepines**

These are the drugs mostly used in anxiety, insomnia, agitation, and many other psychiatric situations. Development of allergic conjunctivitis related to the use of diazepam has been previously reported.80 This situation is only notified for diazepam and no relation is identified on ocular allergy development in relation to other benzodiazepins (e.g.: clonazepam, lorazepam).52 In this case, if ocular allergy develops as a result of the use of diazepam, use of another benzodiazepine is recommended.

Only one case and diazepam is presented as it might cause ACG.71 For this reason, it can be said that benzodiazepines out of diazepam are secure in terms of glaucoma.

Clonazepam is stated to cure acquired nystagmus.72-74 In the year of 2001, Young et. al75 have shown that clonazepam is 100% effective in treatment of 5 patients with idiopathic downbeat nystagmus.

In another article published in 2006, Giersch et al.76 have made literature review on visual acuity of benzodiazepines on acute or chronic basis and the effect on contrast sensitivity. In addition, 15 patients who had a long-term treatment with lorazepam were compared to healthy control group. As a result, the use of benzodiazepine was determined to cause a global loss of contrast sensitivity.76,77 Furthermore, the development of contrast sensitivity and exophoria in patients using long-term lorazepam was found to be free of sedative efficiency of benzodiazepines. Visual acuity has remained normal in these patients. Due to this reason, it is propounded that testing visual acuity singly will not be determinant in terms of all visual dysfunctions

**Antiepileptics**

Carbamazepine is not only in the group of antiepileptic drugs but also is used in the treatment of some psychiatric illnesses such as affective disorders.78

In a 22-year-old asymptomatic case in 2007, the use of carbamazepine was blamed for the development of conjunctival squamous metaplasia.79 In this case, cause and effect relation was not proven, and carbamazepine is still thought to be a secure drug for conjunctiva.

In a prospective study on 45 patients with epilepsy who were long-term treated with carbamazepine and valproic acid, a change related to retinal nerve fiber layer and macula thickness was not determined.80 Nowadays, valproic acid, which is used as a mood stabilizer and an antiepileptic drug, is not determined as a cause of important or irreversible visual impairment.80,81

In relation with the use of carbamazepine, it is stated that two epileptic middle-aged female patients using this drug for more than 7 years have developed retinopathy.82 However, the causal relation between carbamazepine and retinopathy could not be established in these cases. Despite this, when the use of carbamazepine was stopped, both the symptoms and the objective retinal findings receded.82

Ocular dystonia related to carbamazepine has been reported several times.83,84 When the other antiepileptics are used as polytherapy, carbamazepine might cause various eye movement disorders including muscle palsy. This antiepileptic drug may cause dystonia both on ordinary and toxic dose.84,86 At the same time, it may rarely cause a idiosyncratic type of dystonia.83
Carbamazepine may induce a slight but specific color vision disability. In patients with one-year carbamazepine treatment, central and paracentral color vision functions decrease transparently.87 However, as this case was not identified in some human studies, this effect is not accepted by everyone.72 In a cross-sectional study done on 18 patients being treated with valproate monotherapy for twenty-two years, color vision defect was only seen in 2 patients at minor level.88 Cones sensitive to short wavelength are thought to be affected by antiepileptic drugs. This rarely seen side effect mostly stays at subclinical level and does not require monitoring. Visual acuity is protected permanently.88

Lamotrigine

This drug is used in the treatment of bipolar disorders. In some neuropathic pains, it has a therapeutic efficiency.89 Lamotrigine rarely causes nystagmus.90,91 In 2005, Alkawi et al.91 have presented two down-beat nystagmus cases related to lamotrigine toxicity. These kind of cases are seen in low-ordinary doses. Authors warn that lamotrigine might form this kind of unwanted ocular effects in high doses. When used with valproate, lamotrigine’s half life is prolonged and risk increases. Disorders in diplopia and eye movements are especially stated in low-high dose lamotrigine monotherapy.72,91 When lamotrigine is used in high dose or combined with carbamazepine, eye movement anomalies should be expected.92,93

Lithium

It is the oldest and very important mood stabilizer and can be effective apart from bipolar disorders. Mechanism of action is not entirely known and it changes sodium transport during nerve and muscle cell membranes, shows effect on intracellular signals, and causes nerve cell membrane stabilization.89 A side effect in relation with lithium is irritation in the eye which is generally observed in the first week of the treatment.94 The reason of this side effect is explained by the increase in lacrimal fluid sodium content. Lauf et al.95 have shown the presence of sodium-chlorine co-transport in lens epithelium cells. Irritation is thought to be developed due this effect. The complaint of the patients is for a short time. It is possible to keep it under control with the use of artificial tears.

Lithium can form various ocular side effects even in therapeutic doses. The adversity in all these is down-beat nystagmus.96-99 Reducing the dose of lithium or stopping the use of drug makes the side effect disappear. Nystagmus may rarely remain despite stopping the use of the drug.98 In these cases, disorders in slow-observer eye movement at subclinical level may arise.96

Until today, only 5 cases have developed optical disc edema in the ones using lithium at therapeutic dose. Blurred vision and papilledema end by stopping the use of the drug. Papilledema and related symptoms appear in patients who continue using the drug.100

Conclusion

Long-term use of psychotropic drugs is gradually becoming widespread and occurrence incidence of ocular side effects belonging to these drugs is increasing concordantly. Knowing the side effects of psychotropic agents potentially is extremely important. Rare ocular problems rising in relation to use of these drugs have important effect on psychiatric patients’ physical and psychical situations who have a tendency to be crumpled. When an anxious, psychotic, depressed or agitated patient meets an ocular disorder which will cause trouble in his/her daily life, he/she will feel himself/herself worse.

Typical antipsychotics, TCAs, lithium, benzodiazepines, carbamazepin, and topiramate are drugs known for causing ocular problems.

Thoridazine, which is a phenothiazine, may cause retinitis pigmentosa in high doses and visual impairment related to this. Chlorpromazine, which is another phenothiazine antipsychotic, not only causes rare pigmentary or granular retinosis but also mostly causes benign natured pigmentary segregation of these tissues on the lens or cornea with photosensitization mechanism. Corneal edema is the rarely occurring most serious visual disorder related to chlorpromazine.

Butyrophenones create serious risk of oculogyric crisis and although these dystonic reactions are reversible, they irritate the patient substantially.

TCAs mostly cause accommodation disorder. When compared with the side effect of serious ACG which mostly develops in narrow-angled eyes, accommodation disorder can be qualified as a slight and temporal side effect.

SSRIs form mydriatic effect. They may cause glaucoma attacks in patients at the risk of angle closure.

Benzodiazepines have the potential to form various eye movements related to dose. For this reason, it should not be used while consuming alcohol and driving.

Antiepileptic type of mood stabilizers also cause eye movement disorder. Carbamazepine provokes nystagmus and sometimes causes oculogyric crisis.

Lamotrigine, especially when combined with valproate, causes clear eye movement disorders. Valproate rarely causes subclinical color perception disorders.

Topiramate causes myopic situation as well as nystagmus and other eye movement disorders. In sensitive individuals as a result of idiosyncratic reaction induced by topiramate, all lens and ciliary body complex faces transformation (if the use of drug is stopped, it is reversible). This situation causes refraction defects, obstruction in angle and decrease in vision.

Lithium, especially at high doses, causes down-beat nystagmus.

If psychiatrists, ophthalmologists and patients are informed on side effects of the drugs and precautions are taken in the early period, most of serious and potentially irreversible ocular damage can be prevented.
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