International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 5(L); May 2018; Page No. 13031-13039
DOI: http://dx.doi.org/10.24327/ijcar.2018.13039.2312

Research Article

A SYSTEMATIC REVIEW OF OCULAR SIDE EFFECT OF SYSTEMIC MEDICATIONS AND ITS MANAGEMENT

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ARTICLE INFO

Article History:

Received 24th February, 2018
Received in revised form 19th March, 2018 Accepted 16th April, 2018
Published online 28th May, 2018

Key words:

Optic Neuritis, Papilledema, Glaucoma

ABSTRACT

Aim: Systemic medications that are widely used to treat different diseases have ocular adverse effects. The aim of this article is to generate evidence for physicians to monitor the outcome while using these medications.
Methods: 38 published articles from various journal were selected and complete literature review was done. Salient information pertaining to the drug, dosage and side effects was accumulated and compiled.
Results: 12 of the commonly used medications were identified and their side effects ranging from mild to vision threatening were noted. The adverse effects were highlighted and presented.
Conclusion: While prescribing these group of drugs physicians must be aware of their ocular side effects, and have a preset plan to monitor them, and to consult an ophthalmologist in order to manage them accordingly.

INTRODUCTION

There are widely-used medications to treat several diseases of different organs that have side effects on the eye, which are ranging from minor ocular complications to serious and vision threatening ones. It is important to know these drugs and their effect on the eyes especially for the physician who is prescribing these medications.

Aim

This review article aims to provide physicians with concise knowledge about these effects and to take proper action.

A total of 38 published articles from various internationally acclaimed journals were reviewed.

A thorough literature review was critically done for each of these articles. A total of 12 drugs were noted which produce minor to major effects on the oculi. These drugs are summarized based on their clinical relevance in this article.

Amiodarone

Amiodarone is the most effective anti-arrhythmic drug that is commonly prescribed worldwide.(1) The toxic side effects on the eye leading to formation of cataract, optic neuropathy, and corneal deposition (vortex keratopathy) (figure 1).

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The toxic side effect of amiodarone is due to the administered cumulative dose.

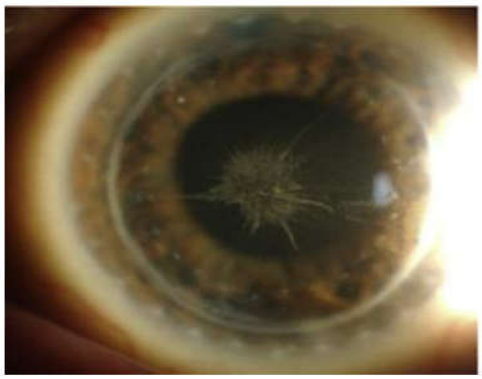

Fig 1 Amiodarone-induced vortex keratopathy.
(Image courtesy of Francis S. Mah, MD.) (3)

However, it might occur in short period after receiving amiodarone.(2) Amiodarone induced keratopathy (vortex keratopathy)(3): This dose related toxicity of the cornea is self-limiting and rarely effects visual acuity. Corneal deposits occur in around 98% of the patients who are receiving an approximate dose of 200-300 mg/dl and 99% of the patients who are receiving an approximate dose of 200-1200 mg 5 days per week. On slit-lamp examination they become apparent by 2 weeks after the initiation of amiodarone treatment, although the reported onset is between 1-4 months after starting the treatment, the pattern of corneal deposition increases with the

drug dose and duration, the condition is reversible in 3-20 months after drug cessation. [3]

Amiodarone associated optic neuropathy

There is no demonstrated direct causal-link, but 1-2% of optic-neuropathy/neuritis developed in amiodarone users. [3]Studies of amiodarone associated optic neuropathy showed that the mean duration of amiodarone use is 9 months with a range of 1-84 months, most of the cases were after 12 months of starting amiodarone, and the median dose of 200 mg with a range of 57-1200 mg/day. The range of visual acuity on the diagnosis of amiodarone associated optic neuropathy is 20/15 to light perception.[3]After discontinuation of amiodarone treatment, 58% of the patients visually improved, while 21% of them ended up with permanent blindness in one eyes at least. [1]Usually most of amiodarone-associated optic neuropathy cases occur within the first 12 months of amiodarone use.[1,2,3]

More than 10% of amiodarone associated optic neuropathy patients are asymptomatic, hence it is important to conduct a baseline examination, with a recommended regular follow up from the 4th month after starting amiodarone therapy.[3] Johnson and colleagues recommended an equal spaced-intervals examination within the 1st year, followed with annual-examination. Physicians must alert the patient on amiodarone medication of the importance of having a baseline ophthalmologicalexamination and regular follow up screening.[2] hui-chencheng thinks that it might be impractical to have an extensive screening for amiodarone associated optic neuropathy, as he conducted a population based cohort study using Taiwan's national health insurance research database, in 2015, aimed to determine whether amiodarone use was associated with increased risk of optic neuropathy, regarding the study result he found that the risk of optic neuropathy is higher in amiodarone treated patients, especially in males, and possibly in longer duration of amiodarone treatment. He recommends that physicians must be aware of the possibility of optic neuropathy secondary to amiodarone in male patients, with long duration of amiodarone therapy. Regular investigations of visual symptoms among these high-risk patients will help in early detecting the complications and manage them properly.[1]

Phototoxicity

There are three mechanisms for the occurrence of retinal photo toxicity which are: chemical, thermal, and, mechanical. There are lots of pharmacological drugs lead to phototoxicity particularly with photo-chemical damage as the drug deposit in the retina and gets activated when exposed to light, releasing oxygen species leading to oxidative damage to the cells and its components. There are some well-known medications of their photosensitizing property on the retina such as chloroquine and phenothiazine.[4] Amiodarone is one of the photosensitizing drugs that affect the skin in patient with prolonged treatment with amiodarone, leading to hyperpigmentation slate grey appearance of sun exposed skin, development of photosensitivity can occur following a minimum total dose of 40 g after 4 months of contentious treatment, this thought to be due to destruction of the cell membrane, DNA, and lipid oxygenation secondary to formation of reactive species.[4] In vivo studies failed to reveal any side effect of amiodarone on the retina, on the other hand, in vitro studies revealed that amiodarone Decreases the survival of retinal pigmented epithelial cells whenever exposed to ultra violet radiation, due to the deposition of amiodarone that have been found in the ganglion cells as well as the RPE cells, so that regarding in vitro studies there is a theoretical risk of retinal-phototoxicity, amiodarone has a photosensitizing effect on the skin as well as the RPE cells in vitro. [4]

Alpha receptor blockers, 5-alpha reductase inhibitors, and anti-psychotic

Selective alpha-1 adrenergic receptor blockers that is used to treat BPH is well known for its association to intra-operative floppy iris syndrome (figure 2,3).[5,6] regarding the literature it is not the only drug that lead to (IFIS), there are many cases reported in the literature that suggest other drugs association with (IFIS) other than alpha-1 adrenergic receptor blockers, such as 5-alpha reductase inhibitors, as well as the antipsychotic drugs. Intra-operative floppy iris syndrome is a condition that was first described in 2005, by Chang and Campbell. It occurs during cataract surgery (phacoemulsification), it has a characteristic triad of three features, flaccid iris stroma that leads to undulating and billowing of the iris, tendency of iris prolapsing toward the surgical-incision, and progressive constriction of the pupil intra-operatively.[5, 6, 7] Severe or complete IFIS is referred to the presence of all three features, whereas mild/moderate or incomplete IFIS is described when one of the three features missing.[5] IFIS makes the phacoemulsification more difficult and increases the risk of surgical complications.[5,6] In general population, the reported incidence of IFIS was between 0.6% and 2%, while male patients who were exposed to tamsulosin had developed the IFIS with a rate of 57% to 100%. The ability of alpha-1 receptor antagonists to cause intra-operative floppy iris syndrome might be influenced by several factors including the duration and dosing of the drug, intra-ocular drug level, affinity of the medication to the dilator muscle receptors of the iris, and the individual susceptibility for IFIS development. [6]

5-alpha reductase inhibitors (finastride)

Finastrid inhibits testosterone conversion to dihydrotestosterone by inhibiting the type II 5-alpha-reductase enzyme. This drug is used commonly in treating (propecia) male pattern alopecia with a dose of 1 mg once per day, and BPH with 5 mg once per day, and it is effective in treating both conditions. There are many side-effects of finasteride such as depression, loss of libido, ejaculation disorder, and erectile dysfunction, all these side effects are listed on the package information leaflet of the medication, and no mentioned ocular side-effects, despite there is an association between finasteride and development of cataract anterior sup-capsular in nature as it had been reported once in the literature.

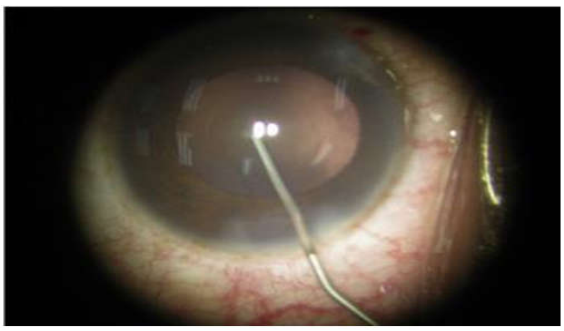

Figure 2 The pupil in the left eye failed to dilate fully despite application of preoperative mydriaticeyedrops. [7]

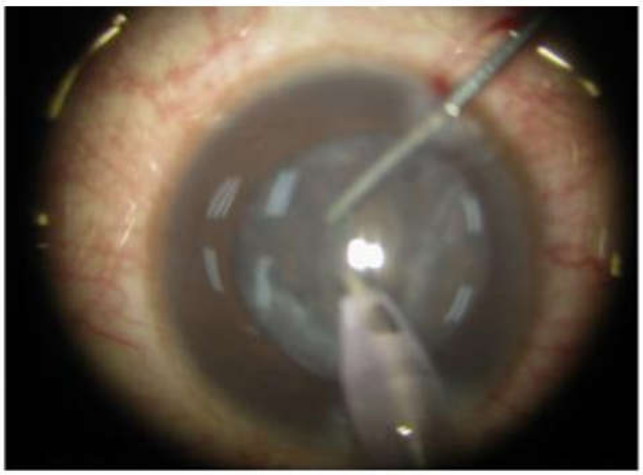

Figure 3 The iris of the left eye was floppy and undulated and billowed throughout the cataract surgery.[7]

Antipsychotic Drugs

The main effect of anti-psychotic is on the serotonin and\or dopamine receptors, any class of anti-psychotics has a side effects secondary of the antagonistic effect on histamine, acetylcholine, and alpha-adrenergic receptors. There are at least 5 reported cases in the literature of antipsychotic drug induced IFIS, in 2016 Masato Matsuo had reported a case series of IFIS associated with antipsychotic drug use the three cases had the same features of incomplete intra-operative floppy iris syndrome, with a history of chronic use of anti-psychotic drugs accompanied by glaucoma. Any class of anti-psychotic medication can result in IFIS due to its side effect of alpha adrenergic receptors antagonism, it has a lesser intensity than selective alpha-1 blockers, the nature of IFIS related antipsychotic drugs is relatively mild, surgeons must be aware of the possibility of antipsychotic induced IFIS when treating patient with a history of antipsychotic drug use to avoid surgical complications.[5]

Chlorpromazine

Is an anti-psychotic drug which induces vortex like corneal epithelial deposition with the high doses administration and or low long term dose. Typically, the deposits are found in the stroma or endothelium. 43 patients were receiving chlorpromazine, 4.7% of them developed corneal epithelial findings of diffuse opacification. 44.2% developed corneal stromal pigment dusting, 67.4% developed anterior lens capsule dusting. These were the most commonly encountered optic manifestations. Corneal changes usually developed with a dose of >300 mg/d for a period of 2 years, but it can occur in patient with high doses as >2 g/d in a shorter period of months. Other associated ophthalmic toxicities are anterior sub capsular cataract, pigmentary retinopathy, and corneal edema. Corneal changes are slowly reversible after cessation of the drug, while the lenticular changes are less likely to be reversible.[3]

Nonsteroidal anti-inflammatory drugs (NSAID)

There are some non-steroidal anti-inflammatory medications that induce vortex keratopathy, such as naproxen, indomethacin, and ibuprofen, described as intra-cellular deposition of the epithelium, and opacification of bowman and Descemet membrane, these depositions can develop quickly within days after drug initiation of high dose 1200 mg/d of ibuprofen, and the vortex keratopathy rapidly resolves within several weeks after drug discontinuation, while in patients treated with naproxen for 2 months the superficial corneal deposits began as parallel lines, and developed into defined vortex pattern after 3 months, which resolved completely after discontinuation of treatment. Indomethacin induced keratopathy occurs more frequently than ibuprofen and naproxen related keratopathy, up to 18% of patients on indomethacin developed corneal deposits in a long-term study carried out by Bernstein. The prolong use of indomethacin is associated with corneal-deposits as well as retinopathy (bull's eye maculopathy).[3]

Dermatological drugs that has ocular side effects

Isoretinoin

Isoretinoin is the most commonly and widely prescribed oral retinoid indermatology.[8,9] It is a synthetic derivative of Vitamin A, and it is associated with many adverse effects, involve the skin, mucous membranes and multiple body systems such as, gastrointestinal, genitourinary, respiratory, and nervous systems. Moreover, it has an ocular side effects commonly the patients complain of photophobia, itchiness, burning, eye pain, visual disturbance occurring within days up to few months of drug initiation, ocular adverse effect can be classified to changes to the corneal surface (Figure 4), changes to the eyelid (Figure 5), lacrimal abnormalities, abnormal retinal function, refractive changes, and papilledema. Also, permanent loss of dark adaptation and decreased color vision were reported as isoretinoin side-effects.[8]

The most common side effects are dry eye syndrome and blepharoconjunctivitis that appear in 20-50% in patients on retinoids therapy, usually occur after 3–5 weeks of drug initiation.[9]

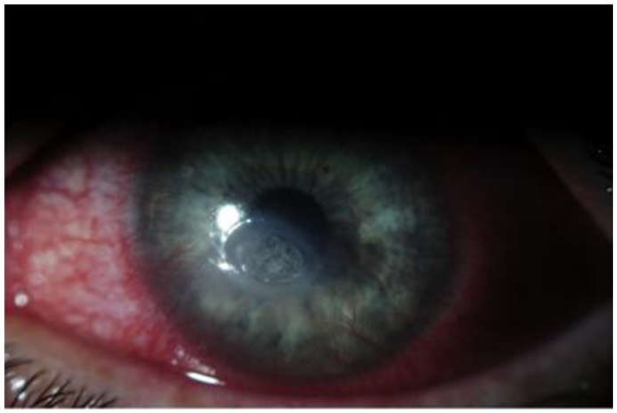

Figure 4 Corneal ulcer, a typical complication of dry eye syndrome.[8]

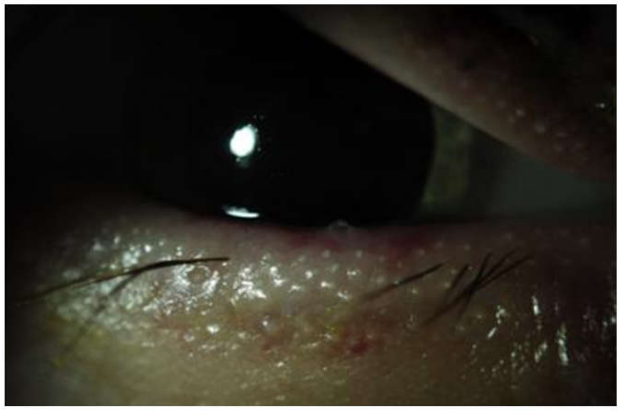

Figure 5 Chronic blepharoconjunctivitis with loss of eyelashes.[8]

Diseases of the ocular surface

Per a retrospective cohort-study the most common side effects of isoretinoin were hordeolum, conjunctivitis, blepharitis (Fig 6), chalazion, and dry eye, these side effects usually occur at the 3rd to 5th weeks of drug initiation.[8] The excretion of Meibomian gland protects the film osmolality and stability, and it prevents the excessive evaporation of aqueous layer, [9] so that dysfunction of Meibomian glands with atrophy and Inadequate lipid secretion into the tear film, will result in damage to the ocular-surface epithelium, the corneal surface directly gets irritated by the presence of isoretinoin and its metabolites in the tear that causes irritation and dryness of the cornea and conjunctiva,[8,9]leading to blepharitis, conjunctivitis, photophobia, and contact lens intolerance.[9] The reported incidence of meibomitis and blepharoconjunctivitis were 37% of patients on the therapy of isoretinoin. Chalazion and hordeolum are a common result of chronic blepharitis. The ocular surface and changes of the tear film in patients on isoretinoin should be routinely monitored by anesthetized Schirmer test, conjunctival impression cytology, tear breakup time monitoring, and rose bengal staining.[8] Dry eye (Keratoconjunctivitis sicca) also occur during isoretinoin treatment, characterized by reduction of goblet cells density in impression cytology test, as well as early sign of squamous-metaplasia of the epithelium and the reduction of the mucin layer in teat film. Ocular surface epithelia and preocular tear-film can get markedly-affected in patients on isoretinoin, leading to dry eye syndrome. Dryness of the eye is dose dependent and disappears after 1 month of drug discontinuation. It's better for the dermatologists to prescribe ocular lubricants with isoretinoin as well as artificial tears, and cooperate with the ophthalmologists whenever the eye symptoms persist or progress to prevent possible serious corneal problems of severe keratoconjunctivitis sicca such as herpes simplex virus activation, corneal opacification, corneal ulceration, and vascularization.[8]

Refractive changes

Isoretinoin are associated with visual disturbances that is related to steeping and peripheral edema of the cornea, that result in permanent or temporary myopic shift. The mechanism of the corneal edema is unknown, and it is maybe due to the isoretinoin presence in the tear-film.[8]

Abnormality of the retinal function

Fraunfelder and colleagues conducted a study of 1,741 patients and noted decreased dark adaptation in 8 % of them.Decresead color vision and Impaired night vision are among the most serious side effects of retinoids,[9]as it interferes with the metabolism of Vitamin A in the visual-cycle it inhibits the retinol dehydrogenases, and thus causes functional impairment of rod photoreceptors.[8,9]There are a risk factors of this ocular complication which are low retinol binding protein level and Vitamin A deficiency. Patients such as drivers and pilots should be examined during and before the therapy with electroretinography, retinol binding protein, and vitamin A blood levels. All patients on the therapy of isoretinoin should be instructed to report any changes in the night vision, although it is a rare side effect but it might persist even after discontinuation of the therapy. It is recommended to discontinue the medication with the 1st sign of night-blindness or decreased color-vision.[8]

Papilledema

Retenoin therapy might be associated with intracranial hypertension and papilledema as suggested by published data, with an average-time of symptoms onset of 2-3 months after drug initiation, it's recommended to discontinue the isoretinoin therapy in patients who develops un-explained blurry vision and headache.[8]

Etretinate and Acitretin

Etretinate is an oral retinoid used to treat psoriasis characterized by the safety profile but it might be potentially retinotoxic. Depending on many authors, there is no evidence of ophthalmological adverse effect associated with etretinate even with high dose and prolong treatment. However, in rare cases it may lead to intracranial hypertension. Etretinate had been replaced with other retinoid which is acitretin, in treatment of psoriasis. The side effects of acitretin includes dry eye and blepharoconjunctivitis, but these side effects are dose dependent, it is recommended to start the treatment with low dose of 10-25 mg/kg and gradually increase the dose if necessary. Acitretin rarely cause intracranial hypertension and papilledema [8]. It is important to inform the patients about the side effects of isotretinoin medication on the eye, and arrange a follow up visits with the ophthalmologist after 4 month of isotretinoin initiation.

Topiramate

Topiramate (TMP) is a sulfa-derivative monosaccharide, it is used as a treatment for some seizure disorder and as preventive medication against atypical migraine [10]. Several ophthalmic side effects were reported worldwide after administration of topiramate [10]. The exact mechanism for these ophthalmic manifestations is not completely understood [15].

Topiramate induce myopic shift

The patient usually presented with acute transit sudden blurred vision which is resolve after cessation of TMP [11]. One case reported by ArjunaMedagama in 2014 for 35 years old female diagnosed as case of migraine. She presented with acute blurring of vision 2 weeks after using TMP. Ocular examinations were normal except for a bilateral refractive error of (–0.5 diopters). The drug was discontinued and within 10 days the refractive error became(0diopters)[12].

Topiramate induce angle closure glaucoma

There are 115 case reports with ocular side effects, 86 cases of secondary angle-closure glaucoma, and 7 cases of permanent visual loss related to TPM therapy [13].The pathophysiology of secondary close-angle glaucoma induced by TMP is ciliochoroidal effusion, idiosyncratic response will happen due to anterior rotation of the ciliary body and forward displacement of the iris-lens diaphragm with closure of the anterior chamber angle [15]. It is usually occurred after a doubling of the dose of TMP or in the first two week after starting the medication.[11]Most of the patients presented with sudden bilateral blurred vision, in addition to other symptoms such as: headache, transit vision loss, bilateral ocular pain, nausea and vomiting, these symptoms could be misdiagnosed with migraine attack.[11]The imaging technique such as Ultrasound biomicroscopy is the best way to confirm the diagnosis though assessment of angle parameters and find out any ciliochoroidal effusion [11]. Other technique which may help is B-scan ultrasonography to detect posterior choroidal

Detachment and ocular coherence tomography for anteriorciliochoroidal effusion and anterior rotation of the ciliary body[11]. In most cases, themanagement is by discontinue of TMP followed by antiglaucoma medications [11]. Chanda Kulkarni recommended a routine ophthalmic examination like gonioscopicexamination with ultrasound biomicroscopy for patients who are on TMP and presented with high intraocular pressure [13].

Topiramate induce Massive Bilateral Choroidal Detachment

The first case of massive Bilateral Choroidal Detachment induce by topiramate was reported by AlirezaDehghani for 79 years old male admitted for evaluation of acute painless decrease of vision. He was on topiramate 50 mg/day and propranolol 40 mg/day started two weeks before the admission for essential tremor. Past ocular history was uncomplicated cataract surgery for both eyes. Ophthalmic examinations finding showed: best-corrected visual acuity was 20/800 OD and 20/600 OS, intraocular pressure was normal, Meibomian gland dysfunction and bilateral mild hyperemia. Anterior chamber, Ocular motility, pupil reaction was within normal. Retina examination showed drusen compatible with mild dry age-related macular degeneration and notable choroidal detachments in all quadrants of the periphery (figure 6). Ultrasonography was done to confirm the physical examination (figure 7). Topiramate was discontinued and by the end of the 7th day the visual acuity was 20/25 OD and 20/30 OS and recovery of choroidal detachment [14].

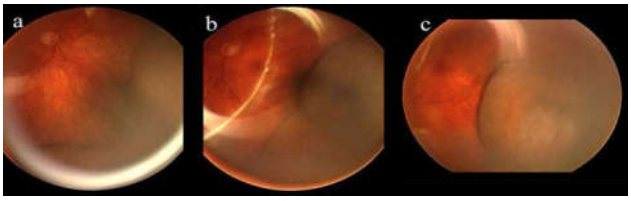

Fig 6 Fundus photographers of both eyes showing massive choroidal detachment. a Right eye.b, c Left eye [14]

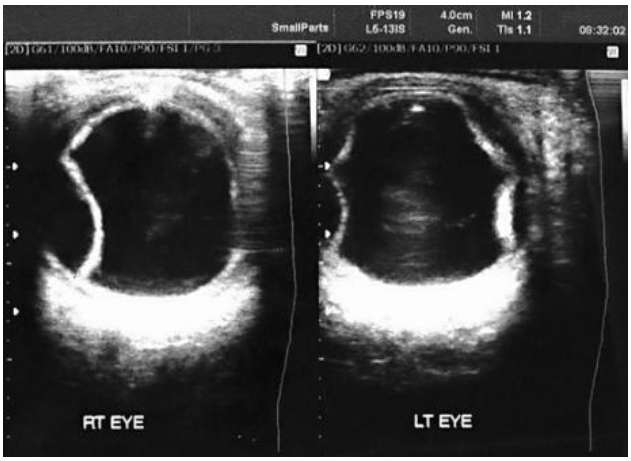

Fig 7 B scan ultrasonography confirming massive choroidal detachment in both eyes [14]

Topiramate induce uveitis

Uveitis is one of the rare side effects of TMP [15]. One rare case reported in Indian for 49 years old male on TMP presented with severe bilateral headache, redness, and watering for one day. He was diagnosed as a case of TMP induce acute angle glaucoma. TMP was discontinued and antiglaucoma treatment was given. One day later the patient presented with severe non-granulomatous anterior uveitis with grade 4 cells and flare in both eyes and Diffuse fine-to-medium keratic precipitates on the posterior surface of the cornea. Uveitis was controlled with topical and systemic steroid in addition to antiglaucoma medication [16].

Aminoquinolines

The antimalarial drugs are a common cause of drug induced corneal deposition, such as mepacrine (quinacrine), amodiaquine, chloroquine, and hydroxychloroquine (Plaquenil).[3] in addition to treatment of malaria chloroquine and hydroxychloroquine are also used to treat, lupus erythematosus, rheumatoid arthritis, and extraintestinal amoebiasis. [3,17, 18, 20] The toxic ocular adverse effects of hydroxychloroquine was described initially in 1960s.[21] These side effects ranges from non-significant revisable keratopathy up to retinopathy that is potentially blinding.[22]

Aminoquinolines induced keratopathy

The aminoquinoline are one of the common cause of drug induced corneal deposition,[3] a transient corneal deposition can occur when the patients receive a daily dose of >250 mg.[18] Tafenoquine is a long acting aminoquinoline, 93% of the treated subjects developed vortex keratopathy secondary to its use. These patients clinically present after 2-3 weeks to few month of receiving these drugs, with diffuse-punctate deposition that over time progress into vortex-pattern. Some patients are asymptomatic and other patients might present with halos and blurry vision, the drug induced corneal deposition is gradually reversible on drug cessation, like in amiodarone induced keratopathy.[3]

Aminoquinolines induced retinopathy

The estimated incidence of Hydroxychloroquine retinopathy is 1% with 5 years' consumption of the drug. There are some predisposing factors for the development of Hydroxychloroquine retinopathy such as elderly age, dysfunction of either the liver or kidney, the duration of more than 5 years of drug consumption, a dose of > 6.5 mg/kg/day, a cumulative dose of >100g, a previous evidence of retinal disease or maculopathy,[17, 20, 21, 22] and a concurrent use of tamoxifen drug, in 2014 there is a study that was carried out by Ronald, they discovered a strong relationship between tamoxifen use and retinal toxicity, the long term administration of low dose of tamoxifen has a synergistic adverse effect with hydroxychloroquine due to the cumulative dose effect,[20] however, the retinal toxicity can also occur in low risk individuals,[22] the optimal dose of chloroquine is 3.5-4 mg/kg/day and for hydroxychloroquine is 6.0-6.5 mg/kg/day. Chloroquine is more toxic than hydroxychloroquine,[18] the long-term use of these drugs can lead to irreversible retinopathy, with a possibility of progression even after drug cessation.[3] The prevalence of retinal toxicity induced by long term use of hydroxychloroquine is 7.5% which is 3 times higher than the previous reported prevalence.[20] The risk of irreversible retinal damage is dose dependent, with a total cumulative dose more than 300g. [18]Toxic macular-changes are well established, bull's eye maculopathy begins as a fine pigmentary-mottling of the macula, which result in a range of reduced vision up to blindness possibility. [18] Toxic-maculopathy is only reversible on the early phase of the pathological changes, here comes the importance of early detecting the toxic reaction. [17] Even after discontinuation of the drug the pigmented tissue of the eye and the neurosensory

retina proceed to hold the drug for a long time leading to degenerative-changes of the RPE.[18]Early detection of retinopathy can be done by testing the central visual field, and the use of spectral domain optical coherence topography (SD-OCT).[20]Structural-retinal changes are common after hydroxychloroquine discontinuation, these changes are correlated with the progression of toxicity, and might continue up to one year or more, commonly as parafoveal retinal pigmented epithelium thinning. There is a retrospective study carried out by David in 2016 aimed to early diagnose and detect the structural changes of hydroxychloroquine retinopathy with the use of SD-OCT after drug-cessation. Parafoveal ellipsoid zone disruption is well reported in hydroxychloroquine toxicity, that's commonly in clinical practice clinicians look for this finding, in Davis's study they described three more early SD-OCT signs of hydroxychloroquine retinal toxicity that precede the disruption of parafoveal ellipsoid zone, these findings can aid in the early detection of hydroxychloroquine retinopathy. Reduced reflectivity of the parafoveal ellipsoid zone is detectable SD-OCT finding of early hydroxychloroquine toxicity. This finding is not diagnostic but it raises the suspicion of toxicity and indicates that further investigation is needed. Parafoveal interdigitation zone disruption is another early common and important finding preceding the disruption of the parafoveal ellipsoid zone, as this finding had been reported two times in hydroxychloroquine retinopathy. Changes in the macular thickness is minimal but early and severe finding at 1 year of the drug cessation, this changes is secondary to RPE and glial remodeling, as these eyes had developed severe foveal and parafoveal outer retinal atrophy at the drug cessation time, greater thinning was found in the inner nasal ring, in comparison to the inner temporal ring, as toxicity progresses it accelerates the thinning in the inferior outer ring, in the other hands other two studies noted the involvement of the inferior macula might be the earliest affected quadrant of hydroxychloroquine toxicity, but still further more studies are needed. SD-OCT can show the early signs of hydroxychloroquine retinopathy before the development of parafoveal EZ disruption, these signs might aid in the earlies detection of hydroxychloroquine toxicity, its critical to early detect these signs because both functional and critical progression might occur after drug discontinuation. The author recommended to carefully check for the visual field looking for paracentral defects, because paracentral visual field defect occurred as an early sign in many patients at the time of drug cessation, as this fact had been previously reported by Marmor and Melles, who described eyes with hydroxychloroquine retinopathy with normal SD-OCT images but had a paracentral visual field defect correlated with hydroxychloroquine toxicity.[21]

There is a published recommendation of screening by the American Academy of Ophthalmology for chloroquine and hydrochloroquine retinal toxicity. [17]Before the patient starts the treatment, a baseline examination should be done to including visual acuity, color vision, ophthalmoscopy, chronological fundus photography, electroretinography, visual field testing and Amsler grid for the detection of the bilateral maculopathy, the bull's eye maculopathy is typically advanced retinopathy secondary to aminoquinolines-induced ocular toxicity.[17, 18] The recommendation of follow up examinations is advised to be every 6-12 months for any patient receiving these drugs.[17]The drugs should be discontinued when toxicity is recognized or strongly suspected but this is a decision to be made in conjunction with the patient the rheumatologist, responsible with hydroxychloroquine administration and -the ophthalmologist, responsible with visual screening. [23]

Ethambutol

Ethambutol is used for the treatment of tuberculosis since 1960 [24]. Optic neuropathy iswell-known complication induces by ethambutol [25]. The patient may develop ocular symptoms few days after initiation of the drug or two years later[26]. Approximately 1% of patients who using the therapeutic dose of Ethambutol which is 15 to 25mg/kg/dayhas been presented with visual loss. A retrospective review was done from January 2002 to July 2011 for 4803 cases of tuberculosis. Sixty-two cases (1.29%) was diagnosed as case of ethambutol induce optic neuropathy [25]. The patients usually presented with painless progressive bilateral, symmetrical decrease in vision, Dyschromatopsia which means change in color vision, pallor of optic nerve head, and Central or cecocentral scotoma which is a characteristic feature of patient with optic neuropathy in the visual field test [27]. So, color vision and visual field test must be including to evaluate the patients who suspected of having optic neuropathy [27]. Optical coherence tomography (OCT) also can be useful to detect the loss of retina nerve fiber which consider as the first sign of ethambutol toxicity [28]. A retrospective observational case serious was done to evaluate changes in retinal nerve fiber layer thickness using Optical coherence tomography (OCT). OCT was performed for 8 patients with a history of ethambutol-induced optic neuropathy who stopped the ethambutol 3 months ago. The results of OCT showed decrease in retinal nerve fiber layer thickness especially in the temporal quadrant of the optic disc [28].The toxicity is reversible most of the time, but there is some previous reported study showed the permanent damage to the visual function after using the ethambutol [26]. There are some relative contraindications of ethambutol include patients who cannot report the visual symptoms like: dementia, mental retardation patients or children. Also, patients with poor vision is not recommended to be treat it with ethambutol [24]. Wei Song reported A 75 years old male presented with blurred vision for one month ago. Medication history showed: 1500 mg\day of ethambutol for 7 months before one year. His best correct visual acuity was 0.12 in left eye and 0.15 in the right eye, Intraocular pressure was normal. Anterior and posterior segments of both eyes were normal. Automated perimetry detect typical cecocentral visual field defects (figure 8). The patient was diagnosed as case of optic neuropathy induce by ethambutol. The patient stopped taking ethambutol and neurotrophic agents was given. One month later the patient is full recovery of cecocentral scotoma [26].

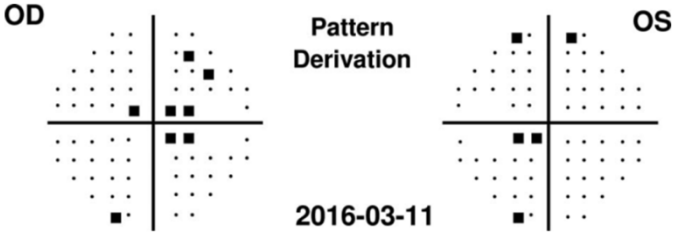

Figure 8 The bilateral automated perimetry indicated typical cecocentral visual field defects.[26]

There is no specific treatment of optic neuropathy induce by ethambutol other than discontinued the medication. So, some patients will recover, and others will still have decrease in vision if the damage is severe [27]. In conclusion, physicians should be aware of these complications because the real risk ethambutol in causing permanent visual loss by affecting initially on optic nerve then the optic chiasm which can result in a bitemporal hemianopia [24]. Ophthalmic evaluation is recommended every one to three months to detect any changes in best corrected visual acuity, colour vision, and visual field [24].

Tamoxifen

Is a selective estrogen receptor modulator with a hydrophobic ring and a hydrophilic ring with charges cationic amine group [3] It considered as one of antineoplastic agents that can be used for treatment and prophylaxis against breast cancer [3]. It is associated with a common side effects such as: nausea, vomiting, mood changes, hot flashes and rash [29]. Approximately 11% of patients will develop some ocular manifestations even with a low prophylactic dose (20mg\d). Ocular manifestations could be changes in the cornea or in the retina [3]. The cornea changes include whorl-like white to brown sub epithelial deposits located in the inferior of the central cornea, keratopathy which is usually in vortex pattern due to accumulation of phospholipids, and sub epithelial oblique lines in the center of the cornea or below the visual axis [3]. The retina changes, usually occurs at higher doses of tamoxifen (180-320 mg\d), include visual acuity reduction, optic neuritis and macular edema with refractile retinal Opacities surrounding the macula (figure 9)[3].The duration between using tamoxifen and the appearance of clear visual symptoms varies from 2 to 5 years with a prevalence varying from 0.6% to 3.1% [30]. Ocular cornea changes can be resolve if the drug is discontinued. But if these changes affect the retina it will be irreversible even after cessation of the drug [3]. A case repot was done in India 2017 for a 28 years old male patient presented with a history of blurring of vision in both eye in the last 5 months. His active medications were tamoxifen 80mg\day and celecoxib 200mg\day for right axilla desmoid fibromatosis. On eye examinations: the visual acuity was 20\20 on both eyes, intraocular pressure was normal, anterior chamber was normal. Fundus examination showed bilateral crystalline refractile deposits in the macula, optic disc and rest of retina was within normal. Optical coherence tomography of retina showed pigment epithelium and deposits in the inner retinal layers with normal outer layer. The case was diagnosed as tamoxifen induce retinopathy and the oncologist was stopped the tamoxifen. After 3 months, there was a gradual improvement in subjective vision of the patient [30]. There is a recommendation which advisespatients who are on tamoxifen and complain of floaters, scotoma and decrease vision to follow up with an Ophthalmologist in coordination with oncologist [29]

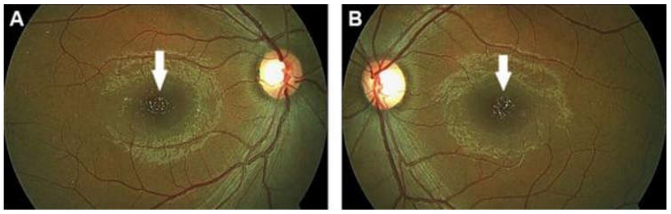

Figure 9 (A and B) Right and left eye fundus picture showing refractile white to yellow deposits at the macula[30].

Steroid

Steroid is an anti-inflammatory drug which is widespread used as a treatment of many ocular and systemic diseases. It can induce many ocular side effects that may lead to visual impairment [31].

Steroid induce Cataract

The relationship between using steroid and posterior subcapsular cataract (PSC) first noted by Black and colleagues in 1960. Patients with Long use of high dose of steroid for rheumatoid arthritis, asthma, and kidney transplant recipients will have developed PSC with incidence 22-58 %[32,8]. Aberrant migration of lens epithelial cells, proliferation, and suppression of differences in the lens are specific for PSC induce by steroid [32]. The possible pathophysiology of PSC induce by steroid is due to osmotic imbalance, oxidative damage, ocular growth factors imbalance, and changing in the cellular enzymes level. A recent study showed that matrix metalloproteinases (MMPs) has a strong relation with PSC induce by steroid. MMPs belong to endopeptidases family which maintain morphogenesis process and other normal physiological processes [32]. A perspective observation study consisted of 156 patients with uncomplicated cataract, 50 of them are PSC due to steroid and 106 are PSC not related to steroid use. Lens epithelial cells were collected during phacoemulsification and blood sample was collected also. By using succinylated gelatin assay, lens epithelial cells and blood sample analyzed to detect the activities of MMP-2 and MMP-9. The level of MMP-2 and MMP-9 were higher in those patients with PSC induce by steroid [32].

Steroid induce glaucoma

The first one who noted the elevation of intraocular pressure (IOP) induce by adrenocorticotrophic hormone is McLean in 1950, and the first case of increased IOP due to steroid was reported by Francois in 1954. [37] Systemic route of steroid is the least form that cause reversible IOP, irreversible glaucomatous cupping and visual field defects. [31,33] The onset of elevated IOP usually happen a few weeks after initiation of steroid treatment and the patient may not have any symptoms until irreversible glaucomatous optic nerve damage occurs. [8] Steroid responders mean increase in the IOP more than 6 mm Hg from baseline or two measurements 21 mm Hg after the initiation of steroid therapy in addition to decrease of IOP after discontinued the medication [36] Approximately 18-36% of the population are Steroid responders and 92% in patients with primary open-angle glaucoma.[8] The exact mechanism of steroid induce glaucoma is not well understood. But there are many proposed theories such as:

1. Stabilization of lysosomal membranes and accumulation of polymerized glycosamino-glycans (GAGs) in the trabecular meshwork, Biologic edema is result and cause increase in the aqueous outflow resistance.
2. Changing in the trabecular meshwork cell morphology by increase in nuclear size and DNA content.
3. Obstruction of the trabecular outflow due to crystalline steroid particles.
4. Decrease prostaglandin synthesis which is responsible of aqueous outflow regulation
5. Increase the expression of myocilin gene [31].

There are many risk factors that increase the risk of developing steroid-induced glaucoma as: patients with primary open angle glaucoma, high myopia, very young or very older adults, and traumatic angle recession or pigment dispersion eye, and endogenous hypercortisolism [(31)]. A prospective study analyzed 200 patients who were on systemic and topical corticosteroid for dermatological diseases. Eight weeks later, all of them developed raising in IOP and three of them developed posterior subcapsular cataract. Steroid was discontinued and the IOP became normal after 2-4 weeks [(33)]. Another cohort study was done for 27 very low birth weight infants with bronchopulmonary dysplasia, Past medical history was 3-week dose-tapering course of systemic dexamethasone. IOP transit increased only with maximum dose of systemic dexamethasone.[(38)]

Central Serous Chorioretinopathy

It is an idiopathic disorder which can be induce by long term use of corticosteroid. Serous detachment of the macula, retinal pigment epithelial (RPE) detachment and atrophy are characteristic features of Central serous chorioretinopathy (CSCR). CSCR can be occur with any route of corticosteroid administration like: oral, intravenous, inhaled, intranasal, epidural and intra-articular forms [(34)]. There are two main types of CSCR: acute and chronic type [(35)]. The patient with acute type presented with sudden vision loss and focal leakage spot on fluorescein angiography, and usually resolves spontaneously within 3 months. While, the patient with chronic type presented with less sudden of vision and multifocal leakage pattern on fluorescein angiography. It has more irregular retinal pigment epithelia changes compared to acute type. Most of the time the chronic type needs to be treat it with photodynamic laser therapy (PDT) [(35)]. One case was reported in Indian for 50 years old on hormonal replacement therapy with cortisol and thyroxine after trans sphenoidal resection of a pituitary adenoma. The patient presented 10 years later with 3 months history of dark ring in the central vision of the left eye. Ophthalmic examinations showed: visual acuity was 20\30 in the right eye and 20\80 in the left eye, serous neurosensory detachment was detecting with retinal pigment epithelial atrophy in the left eye. On fundus fluorescein angiography there was a leakage of fluorescein with ink blot appearance. Focal argon photocoagulation was done to the leakage site with resorption of the sub retinal fluid and improvement of visual acuity to 20\50[(34)]. There are previous studies suggested the mechanism of CSCR related to steroid. One of them reported the effects of glucocorticoids on the blood retinal barrier, choriocapillaris and the retinal pigment epithelium which increased hyperpermeability with modification of ion and water transport and sub retinal fluid accumulation. Another study done by Gass who clarify the accumulation of fibrin and formation of subretinal fibrosis is due to entrance of large proteins like fibrinogen into RPE and subretinal spaces through choriocapillaris which become more permeability after steroid used [(34)]. It is important for physician to be aware of these ocular side effects, and we recommend following up any patient on topical or oral steroid.[(8)]

CONCLUSION

Hence, it is evident from the information generated above that systemic drugs play an important role in producing deleterious eye conditions. It is necessary for every physician prescribing these medications to be aware of these issues. Particular care and awareness is needed when prescribing drugs like Tamsulosin, Amiodaraone, Ethambutol, Aminoquinolines, Finastride, steroids and many antipsychotic medications. Frequent ophthalmic examinations with dilated fundoscopy and visual fields are required to identify the ocular side effects and to manage these conditions accordingly. This article provides essential information to the physicians to inform the patients about the effects of these drugs on the eye and provide preventive measures. It includes base line eye examination and regular screening, and to instruct the patient to consult an ophthalmologist if they notice any changes in their vision. There by saving the eye from deleterious and blinding end results.

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How to cite this article:

EnasAlkhoutani *et al* (2018) 'A Systematic Review of Ocular Side Effect of Systemic Medications and its Management ', *International Journal of Current Advanced Research,* 07(5), pp. 13031-13039.
DOI: http://dx.doi.org/10.24327/ijcar.2018.13039.2312

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