Ocular adverse effects of Antidepressants – Need for an Ophthalmic screening and follow up protocol

Abstract

Depression is emerging to be one of the commonest mental health disorders worldwide affecting a wide age group. The prescription of antidepressants has risen considerably in last decade with a preference for using newer antidepressants like Selective Serotonin Reuptake Inhibitors (SSRIs). There have been many published reports of Ocular side effects with Antidepressants related to Dry eye, Visual disturbance, Angle closure glaucoma and Retinal effects. There has also been a significant rise in antidepressant usage by the elderly, which is a population at risk for ocular adverse effects. Therefore, it is pertinent to understand the antidepressants from the perspective of their mechanisms of action and all possible Ocular adverse effects, and develop an Ophthalmic screening protocol and follow up for patients being put on Antidepressants. Patients should also be counselled for reporting alert signs of ocular side effects immediately. These steps may help to avert and decrease visual complications with Antidepressants.

Key words: Selective Serotonin Reuptake Inhibitor (SSRI), Tricyclic Antidepressant (TCA), Angle closure glaucoma, Ocular adverse effect, Depression

Introduction

The world has more than 300 million sufferers of depression (almost 5% of the population). WHO ranks depression as the single largest contributor to global disability (7.5% of all years lived with disability).[1] Depression is also one of the foremost causes of suicide.
In India, the National Mental Health Survey 2015-16 revealed 1 in 20 Indians suffers from depression. In 2018, India was ranked as the 6th most depressed country. Therefore, timely diagnosis and treatment of depression is important to maintain productivity and prevent serious consequences like suicide.

A recent study in elderly population in Maharashtra India, showed a depression rate of 16.75% in the elderly.[2] This is also the population likely to be at risk of ocular conditions like glaucoma, dry eyes, and retinal degeneration.

The etiology of Depression has been studied to be due to a decrease in the availability of neurotransmitters Serotonin, and possibly Noradrenalin and Dopamine in the brain.[3] Therefore, Serotonin is one of the main neurotransmitters targeted by antidepressant drugs. The SERT (Serotonin Transporter) is responsible for reuptake of serotonin in the synaptic clefts, therefore SERT binding with/without NAT (Noradrenalin transporter) binding is the mechanism of certain classes of antidepressants. Monoamine oxidase causes breakdown of Serotonin, Noradrenalin and Dopamine, therefore, inhibition of this enzyme increases the availability of these neurotransmitters.

There has been a rapid increase in the use of antidepressant drugs in the last decade. Statistics show an increase of 64% in antidepressant usage between 1999 and 2014 in the USA with almost 20% population over 60 years using antidepressants.[4] Women were twice likely users of antidepressants than men.

A recent Indian survey showed that a total of 62.2% patients were using selective serotonin reuptake inhibitors (SSRIs)[5] with escitalopram being the most commonly prescribed and used antidepressant (36.5%), possibly due to a dual orthosteric and allosteric action on the SERT.[6] There was a clear preference to the newer antidepressants (87%) with up to 10% being prescribed more than one antidepressant.[5]

The classification of antidepressants, mechanism of action (MOA) and studied ocular adverse effects in literature is given in Table 1. Given the drastic increase in antidepressant usage in the last decade, it is imperative to revisit the ocular side effects of these drugs and consider having an ophthalmic pre-screening protocol in place along with regular eye examination follow ups for patients starting on antidepressants.

Classification of Antidepressants based on MOA and Ocular side effects[7-25]

	Class	Commonly prescribed	Mechanism of action (MOA)	Ocular adverse effects
1.	Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine, Paroxetine, Escitalopram, Sertraline Citalopram Fluvoxamine	Inhibit reuptake specifically of Serotonin by binding to SERT	Dry eye Decreased accommodation and visual blurring (mainly Paroxetine) Mydriasis, precipitation of AACG Ocular dystonia (rare) Optic neuropathy (rare) Maculopathy (Sertraline)
2.	Serotonin Noradrenalin Reuptake Inhibitors (SNRIs)	Duloxetine, Venlafexine, Desvenlafexine, Milnacipran, Levomilnacipran	Inhibit reuptake of both 5HT and NA by acting on SERT and NET	Mydriasis, Precipitation of AACG (lesser than SSRIs and TCAs)
3.	Tricyclic Antidepressants (TCA)	Amitriptyline Nortriptyline Imipramine, Desipramine Clomipramine Nortriptyline Doxepin	Inhibit reuptake of both 5HT and NA by acting on SERT and NET. Anti H1, H2; Anticholinergic	Dry eye Decreased accommodation and visual blurring (1/3rd patients) Mydriasis, precipitation of AACG
4.	Mono Amine Oxidase Inhibitors (MAOI)	Phenelzine Selegiline Moclobemide	Conventional (rarely used) New Reversible	Mydriasis and AACG precipitation
5.	Atypical Antidepressants	Bupropion Nefazodone Vortioxetine Trazodone Mirtazapine	Dopamine reuptake inhibitor Serotonin receptor modulators and reuptake inhibitors Above action with added anti Alpha 1 and anti H1 action	 Retinopathy (rare) Mydriasis and AACG precipitation (rare)

Ocular side effects of antidepressants

Serotonin in tears modulates sensitization of corneal nociceptor. Increase in serotonin levels can decrease corneal nerve sensitivity, lacrimal reflexes and the tear film.[11] Thus, SSRIs have much greater propensity for dry eye than SNRs.[10] In addition to Serotoninergic action, the Anticholinergic and Anti H1 effects of TCAs increase dry eye. Dry eye may also manifest as photophobia, and rarely keratoconjunctivitis.

Accommodation difficulty and near vision blurring is typically an anticholinergic effect seen most with TCAs and lesser with SSRIs (maximum for Paroxetine among SSRIs). The ratio of antidepressant to anticholinergic activity was >3.2 for fluvoxamine, 2.1-2.6 for paroxetine, and <0.8 for TCAs like clomipramine.[12] Sertraline, Fluoxetine and Escitalopram have approximately only 16%, 10% and 5% the anticholinergic activity of Paroxetine.[13,14]

TCAs, SSRIs and SNRIs cause mydriasis by relaxing sphincter pupillae, by 5HT7, noradrenergic or anticholinergic effects, which can cause a pupillary block and acute angle closure glaucoma precipitation in susceptible individuals. The risk is highest for TCAs, followed by SSRIs, and then some SNRIs (like Duloxetine and Venlafexine), and Mirtazapine, with lower risk with MAOI and Atypical antidepressants.[15] Asian population has a higher risk of Angle closure glaucoma with an earlier age of manifestation, and a higher incidence in women. Patients over 40 years, with hypermetropia, or family history of glaucoma should be screened with an ophthalmic examination before starting antidepressants.[16] The patients should also be counseled to promptly report any symptoms of blurred vision, colored halos around lights, redness, pain, tearing, lid swelling or nausea- vomiting, to the Eye specialist.

No association of antidepressants has been found with risk of development of cataract, though one study showed that SSRI use of 1 or more years in people aged 50+ years was associated with an increased risk of cataract surgery.[17]

SSRIs have a complex interaction of Serotonin uptake by platelets with an initial increase in platelet serotonin leading to increased platelet aggregation followed by longer term platelet serotonin depletion and increased bleeding time. The increased platelet aggregation can have implications in atherosclerotic vessels however the clinical relevance is not well established. Serotonin has also been studied to have vasospastic properties. There are so far five reported cases of optic neuropathy possible ischemic, and one of central retinal venous occlusion with SSRIs. have been linked to optic neuropathy, possibly via multiple transient vasospasms in the optic nerve which could progressively induce ischemic optic neuropathy.[18] Smoking and Diabetes can be potentiating factors in such cases.

There are isolated reports of papilledema due to raised intracranial pressure with SSRI use in children (Fluvoxamine, Sertraline) and an adult with Mirtazapine.[19-21]

A case report of possible retinopathy causing photopsia, decreased visual acuity and color vision with visual field defects with the atypical antidepressant Nefazodone was reported.[22] Very rarely there may be visual gaze impairment due to involvement of ocular muscles due to extra pyramidal effects of SSRIs.

In the last few years, cases have reported with maculopathy related to Sertraline, including bilateral bull's eye maculopathy and bilateral cystoid edema. [23-25] In spite of improvement and eventual resolution in the maculopathy on cessation of sertraline, visual recovery may not be complete.

Table 2: Ophthalmic screening Examination for patients to be started on Antidepressants

	Eye examination	***Purpose***
1	**Best corrected visual acuity**	Record for presence of hypermetropia, presbyopia
2	**Slit lamp examination** Tear film Cornea Pupillary reaction and examination Anterior chamber depth Intraocular pressure -Applanation tonometry	 Record if dry eye present (especially elderly) Record any corneal opacities Rule out synechiae Consider Gonioscopy if AC appears shallow
3	**Dilated Fundus Examination**	Record Cup: Disc ratio; Neuro-retinal rim appearance Foveal reflex Any evidence of ARMD, Retinopathy, or hemorrhages

Ophthalmic screening and follow up examination

Given the increasing prescription of Anti-depressants in today's world and more cases being reported of ocular side effects, it maybe a worthwhile protocol for an Eye specialist to screen patients before being put on antidepressants (Table 2). Pre-treatment Eye examination should include Vision testing and refraction for Best corrected Visual Acuity, Slit Lamp Examination for Tear film assessment, Corneal opacities, Pupillary reaction, Anterior Chamber (AC) depth (with Gonioscopy in cases of Shallow AC), and Intra Ocular Pressure measured with Applanation tonometry. Dilated fundus examination to record status of disc, macula and retina should also be preferably conducted. Systemic risk factors like Diabetes, Hypertension and family history of Glaucoma should be recorded. Patient should be advised a routine 6-12 monthly follow up depending on age, and risk factors. Patient should also be given an alert list of symptoms for immediate reporting and ophthalmic examination like blurring of vision, eye pain, redness, watering, haloes around lights, photophobia, headache, nausea/vomiting or eyelid/facial swelling.

Conclusion

There is well documented and published evidence of the ocular side effects of Antidepressants. In recent years, SSRIs have emerged as the most commonly prescribed Antidepressants, and several studies and case reports of different ophthalmic adverse effects of these drugs have been reported. The elderly population maybe at particular risk of some of these ocular effects. Some of these can be site threatening like AACG, and some like maculopathy or optic neuropathy/papilledema may lead to long standing loss in visual acuity even after stoppage of the drug. Therefore, it is important to screen patients being put on antidepressants and counsel them on the possible ocular effects and their symptomatic presentation, in order to avert and manage these effects in a timely manner.

Conflicts of Interest: None

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