

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.

38 A recent Indian survey showed that a total of 62.2% patients were using selective serotonin reuptake
 39 inhibitors (SSRIs) [5], with escitalopram being the most commonly prescribed and used antidepressant
 40 (36.5%), possibly due to a dual orthosteric and allosteric action on the SERT [6]. There was a clear
 41 preference to the newer antidepressants (87%) with up to 10% being prescribed more than one
 42 antidepressant [5].

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

48 **Table 1:**

49 **Classification of Antidepressants based on MOA and Ocular side effects⁷⁻²⁵**

	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, Venlafaxine, Desvenlafaxine, 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 (1/3 rd 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	Retinopathy (rare) Mydriasis and AACG precipitation (rare)

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51 **Ocular side effects of antidepressants**

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

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

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

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

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

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

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

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

90 *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

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92 **Ophthalmic screening and follow up examination**

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

105 **Conclusion**

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

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Conflicts of Interest: None

References

1. WHO India and Global Depression statistics updated 2019.
http://www.searo.who.int/india/topics/depression/about_depression/en/
2. Rathod MS, Dixit JV, Goel AD, Yadav V. Prevalence of depression in an urban geriatric population in Marathwada region of Western India. *Indian J Psychol Med* 2019; 41:32-7
3. Hasler G. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? *World Psychiatry* 2010; 9:155-161
4. Winerman L. By the numbers: Antidepressant use on the rise. American Psychological Association. November 2017, Vol 48, No. 10. Print version: page 120.
<https://www.apa.org/monitor/2017/11/numbers>
5. Tripathi A, Avasthi A, Desousa A, Bhagabati D, Shah N, Kallivayalil RA et al. Prescription pattern of antidepressants in five tertiary care psychiatric centers of India. *Indian J Med Res.* 2016 Apr; 143(4): 507–513.
6. Zhong H, Haddjeri N, Sánchez C. Escitalopram, an antidepressant with an allosteric effect at the serotonin transporter--a review of current understanding of its mechanism of action. *Psychopharmacology (Berl).* 2012 Jan;219(1):1-13
7. Taylor C, Fricker AD, Devi LA, Gomes I. Mechanisms of action of antidepressants: from neurotransmitter systems to signaling pathways. *Cell Signal.* 2005 May; 17(5): 549–557.
8. Richa S, Yazbek JC. Ocular adverse effects of common psychotropic agents: a review. *CNS Drugs.* 2010 Jun;24(6):501-26
9. Kirkham J, Seitz D. Evidence of ocular side effects of SSRIs and new warnings. *Evid Based Ment Health.* 2017 Feb;20(1):27.
10. Graylands Hospital Drug Bulletin. Ocular Effects of Serotonin Antidepressants. North Metropolitan Health Service - Mental Health October 2016 Vol 23 No.2 ISSN 1323-1251.
11. Acan D, Kurtgoz P. Influence of selective serotonin reuptake inhibitors on ocular surface. *Clin Exp Optom.* 2017 Jan;100(1):83-86
12. Fujishiro J, Imanishi T, Onozawa K, Tsushima M. Comparison of the anticholinergic effects of the serotonergic antidepressants, paroxetine, fluvoxamine and clomipramine. *Eur J Pharmacol.* 2002 Nov 15;454(2-3):183-8
13. Sanchez C, EH, Montgomery SA. A comparative review of escitalopram, paroxetine, and sertraline: are they all alike? *Int Clin Psychopharmacol.* 2014 Jul; 29(4): 185–196.
14. Hyttel J. Comparative pharmacology of Selective Serotonin Reuptake Inhibitors (SSRIs). *Nord J Psychiatry.* 1993; 47 (suppl 30): 5-12

- 154 15. Bazire S. Psychotropic Drug Directory - The Professionals' Pocket Handbook and Aide Memoire.
155 Malta: Gutenberg Press Ltd; 2012.
- 156 16. Ah-Kee EY, Egong E, Shafi A, Lim LT, Yim JL. A review of drug-induced acute angle closure
157 glaucoma for non-ophthalmologists. *Qatar medical journal* 2015;2015(1):6
- 158 17. Erie JC, Brue SM, Chamberlain AM, Hodge DO. Selective serotonin reuptake inhibitor use and
159 increased risk of cataract surgery: a population-based, case-control study. *Am J*
160 *Ophthalmol.* 2014 Jul;158(1):192-197
- 161 18. Lochhead J. SSRI-associated optic neuropathy. *Eye* 2015 Sep;29(9):1233-1235.
- 162 19. Samant H, Samant P. Fluvoxamine-induced intracranial hypertension in a 10-year-old boy. *Indian*
163 *J Ophthalmol.* 2018 May; 66(5): 712–714
- 164 20. Hutcheon ML. An unexpected case of swollen optic nerves. *Am J Ther.* 2011 Jul;18(4):e126-9
- 165 21. Ceylan ME, Evrensel A, Cömert G. Papilledema Due to Mirtazapine. *Balkan Med J.* 2016 May;
166 33(3): 363–365
- 167 22. Luu C, Kiely P, Crewther D, Kowal L, Crewther S. Central and peripheral vision loss associated
168 with nefazodone usage. *Doc Ophthalmol.* 2003 May;106(3):319-25
- 169 23. Mason JO, Patel SA. Bull's eye maculopathy in a patient taking sertraline. *Retin Cases Brief*
170 *Rep.* 2015 Spring;9(2):131-3
- 171 24. Sener EC, Kiratli H. Presumed sertraline maculopathy. *Acta Ophthalmol Scand.* 2001
172 Aug;79(4):428-30.
- 173 25. Agarwal A, Aggarwal K, Kumar A, Gupta V. Bilateral cystoid macular edema misdiagnosed as pars
174 planitis in a patient on sertraline therapy. *American Journal of Ophthalmology Case Reports*
175 *Volume 11, September 2018, Pages 135-138*
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