Graylands Hospital
Drug Bulletin

Ocular Effects of Serotonin Antidepressants

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Although there is a vast body of literature published about side effects of psychotropic medications and serotonergic medications in particular, when it comes to visual disturbance, the studies seldom describe the visual effects in detail; they only mention vague terms such as 'visual disturbances' or 'visual symptoms'. [1] There is also a tendency for only the more serious effects to be reported rather than all levels of visual disturbance.[2] A 2007 paper looking at specific side effects causing discontinuation of Selective Serotonin Reuptake Inhibitors (SSRIs) listed 'visual change' as the 10th most likely cause of discontinuation ahead of headaches.[2]

Table 1 (at the end of the article) shows the information presented in the Australian Medicines Handbook (AMH) and MIMS regarding ocular side effects to be relatively vague and not particularly useful when faced with a clinical situation where your patient is complaining of a specific side effect like 'blurred vision' and an alternative antidepressant is desired.

To decide which antidepressant is most forgiving regarding visual disturbance, the underlying cause of the visual disturbance should first be considered. Mechanisms of medication induced 'blurred vision' could be varied including:

- Eyelid and keratoconjunctival disorders
- Uveal tract disorders
- Accommodation interference
- Glaucoma (specifically angle-closure glaucoma) .
- Cataract and pigmentary deposits in the lens and cornea
- Retinal abnormalities/retinopathy
- Dystonia of ocular musculature/oculogyric crisis

Summary

SSRIs have been shown to have a higher prevalence for dry eye than SNRIs.

TCAs, SSRIs and SNRIs have all been reported to precipitate acute angle-closure glaucoma

SSRIs and SNRIs may cause mydriasis by noradrenergic effects or anticholinergic effects or by 5-HT_7 effects which can cause relaxation of the sphincter muscle of the pupil

Mirtazapine, moclobemide and trazodone have been reported to cause mydriasis

TCAs and Antipsychotics have been reported to cause accommodation interference by anticholinergic effects

Reports of SSRI induced EPSEs can, rarely, affect ocular muscles and lead to visual symptoms.

SSRIs have been linked to optic neuropathy, possibly via multiple transient vasospasms in the optic nerve which could progressively induce ischaemic optic neuropathy.

Dry Eye

An association between antidepressant use, particularly tricyclic antidepressants and SSRIs, and dry eye, with decreased lacrimal secretion being the likely mechanism, has been reported in several studies.[3] Animal studies have suggested several mechanisms:

- Parasympathetic denervation of the human lacrimal gland may cause reduced tear flow
- Neuronal release of serotonin (5-HT) may be involved in regulation of lacrimal secretions
- Chronic exposure to histamine and 5-HT altered the secretory process

SSRIs have been shown to have a higher prevalence for dry eye than Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) despite the SNRIs having more anticholinergic effects.[3]

It has been proposed that altered levels of serotonin due to SSRI treatment can affect the sensitivity thresholds of corneal nerves, resulting in disruption to tear film which covers the ocular surface.[4] Serotonin has been detected in human tears, and may affect corneal nociceptor sensitisation. Changes in serotonin levels in tears could be associated with specific dry eye subtypes.[5]

Glaucoma

Tricyclic antidepressants (TCAs) and SSRIs e.g., citalopram, escitalopram, fluoxetine and paroxetine and the SNRI venlafaxine, have been reported to precipitate acute angle-closure glaucoma. There have also been case reports of other antidepressants precipitating acute angle-closure e.g. mirtazapine.[6]

The underlying mechanism is pupillary block caused by pupil dilatation, which is attributed to the significant anticholinergic and serotonergic side effects of these antidepressants.[6-8] The role of serotonin in human ocular physiology has yet to be fully determined, however, serotonin is known to be an effector on various smooth muscle including the ciliary muscle and sphincter of the eye. [9] Dysfunction of the serotonin system has been implicated in intra ocular pressure (IOP) modifications. It is believed that serotonin 5-HT_{1A}, 5-$HT_{2A/2C}$ and 5-HT_7 receptors are located at the level of the iris-ciliary body (ICB) complex but only 5-HT_7 receptors have been identified at the level of iris musculature. These receptors are responsible for relaxation of the sphincter muscle of the eye and subsequent mydriasis.[9] In patients with a biometric predisposition to an occludable angle, the further reduction in the width of the iridocorneal angle induced by mydriasis may block circulation of the aqueous humour with the possible development of glaucoma.[9]

Stimulation of 5-HT_{1A} receptors reduces IOP and reduces the rate of production of aqueous humour. This counterbalances the effect of stimulation of 5-HT_7 which increases aqueous humour production.[9] Theoretically then, vortioxetine, which is a 5-HT_{1A} agonist and a 5-HT_7 antagonist, should prove beneficial to raised IOP.

5-$HT_{2A/2C}$ receptors are also expressed in the ICB but the effect on IOP has not been fully elucidated. The known effects of 5-HT_{2C} stimulation on fluid balance could be a plausible mechanism for SSRI effects on IOP. The increase in IOP caused by fluoxetine in rabbits has been inhibited by the selective 5-HT_{2A} antagonist ketanserin. [9]

Other proposed mechanisms for increase pressure include ciliochoroidal effusion or an immune reaction in choroidal tissue.[10] However, Murphy et al makes the point that many drugs with probable Naranjo scores are involved in serotonin and dopamine metabolism.[10] Interestingly, although there are case reports of glaucoma associated with bupropion use, Kimat et al report a significant inverse association with bupropion use and glaucoma.[11] Their explanation is that bupropion may be protective against the development of glaucoma through inhibition of TNF-alpha.[11]

Clinicians should consider referring patients at increased risk of acute angle-closure glaucoma for an ophthalmic assessment prior to prescribing SSRIs. [8]

Table 2 Bazire's Recommendations for Antidepressants in Patients with Glaucoma[12]

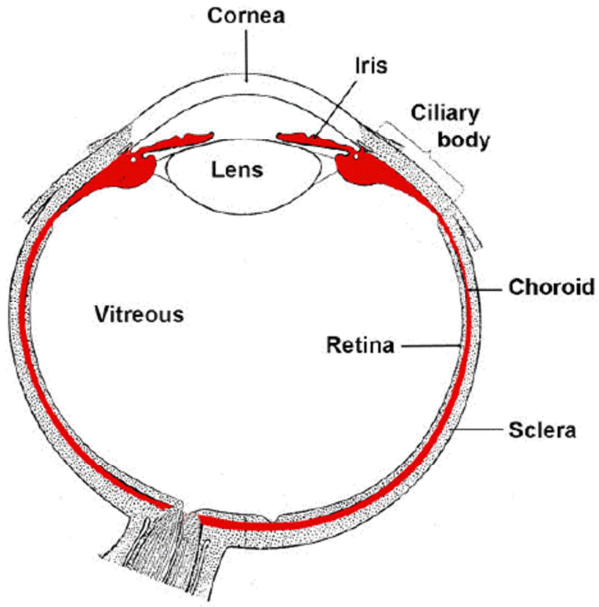
Lower Risk	Moderate Risk	Higher Risk
Agomelatine	Duloxetine	Tricyclics
Bupropion	Mirtazapine	
MAOIs	SSRIs	
Moclobemide	Venlafaxine	
Trazodone		
Vortioxetine		

Patients with narrow angle glaucoma can be prescribed anticholinergic medication provided intraocular pressure is monitored. The main symptoms of narrow angle glaucoma are blurred vision, coloured halos around bright lights, intense pain, lacrimation, lid oedema, red eye, nausea and vomiting.[12]

Uveal Tract Effects

The uveal tract is a layer of tissue located between the outer layer (cornea and sclera) and the inner layer (the retina) of the eye. The front portion (anterior) of the uveal tract contains the iris, and the back portion (posterior) of the uveal tract contains the choroid and the stroma of the ciliary body.

Figure 1. Structure of the eye with the uveal tract labelled red. The uvea can be divided into three parts: the iris, the ciliary body, and the choroids. [13]



Although SSRIs primarily act as antidepressants by inhibition of reuptake of serotonin in the central nervous system (CNS), they also lead to increases in available serotonin in other areas of the body such as blood and eye. Some SSRIs also have effects on dopamine, cholinergic and adrenergic receptors. The serotonin receptors thought to be involved in the dynamics of intraocular pressure in the eye are 5-HT_{1A}, 5-HT_{2A}, $5HT_{2C}$ and 5-HT_7.[1]

SSRIs may cause mydriasis by noradrenergic effects or anticholinergic effects or by 5-HT_7 effects which can cause relaxation of the sphincter muscle of the pupil.[1]

Mydriasis

Dilation of the pupil of the eye, especially when excessive or prolonged, is usually as a result of trauma, a medical disorder or a drug.

Antidepressants that can cause dilation of the pupil include SSRIs, mirtazapine, moclobemide and trazodone.[12] Mydriasis has been reported with duloxetine.[12]

This effect does not seem to cause major visual discomfort or problems, unless it becomes associated with a dramatic increase in IOP and with eventual glaucoma attacks. The mydriatic effects of SSRIs are likely to be reversible after cessation of therapy, especially if they do not become complicated by angle-closure glaucoma.[1]

Accommodation Interference

TCAs and antipsychotics have been reported to cause visual accommodation interference via their anticholinergic effects.[1] No reports of SSRIs or SNRIs having this effect were found. Since some of the SSRIs do have significant anticholinergic effects e.g. fluoxetine, it should be expected that accommodation difficulties could be caused by fluoxetine.

Cataract and Pigmentary Deposits in the Lens and Cornea

Reviews considering causes of ocular adverse effects are concerned firstly with photosensitivity e.g. chlorpromazine and then

the effects of atypical antipsychotics. Antidepressants generally were not mentioned.

Retinal Abnormalities/Retinopathy

There has been concern that a number of psychotropic medications can cause retinal changes. There is a report of sertraline causing maculopathy which does not clearly link sertraline to the side effect.[1, 14]

Dystonia of Ocular Musculature/Oculogyric Crisis

Oculogyric crisis is one of the possible presentations of dystonic reactions and any variant of gaze paralysis can appear. The dystonic effects of certain psychotropic medications (antipsychotics, carbamazepine, topiramate and possibly SSRIs) are of common concern in psychiatry. More often than not, they are of acute onset, but cases of tardive dystonia are also well documented in the literature. Acute dystonias have a complex aetiology; they can be secondary to dopamine receptor blockade, but other mechanisms are likely to play a role as well.[1]

Reports of SSRI induced extra pyramidal side effects (EPSE) are quite well known. Dystonia usually affects muscles unrelated to the eye but can also affect ocular muscles and lead to visual symptoms, but this phenomenon is relatively rare.[1, 15]

Other Reported Ocular Side Effects

SSRIs have been linked to optic neuropathy.[16] The proposed mechanism suggested is multiple transient vasospasms in the optic nerve could progressively induce a manifest ischaemic optic neuropathy.[9, 16, 17]

Central retinal vein occlusion is the second most common retinal vascular disorder after diabetic retinopathy. SSRIs are known to modulate peripheral serotonin, including that in platelets. Serotonin has been implicated as a powerful activator in platelet aggregation. [18] SSRIs inhibit serotonin uptake into platelets, block intracellular calcium mobilization and are associated with an increase in bleeding time.[19] Longer term use of SSRIs have been found to deplete platelet serotonin stores and have therefore been proposed to reduce the risk of hypercoagulability However, the initial effect of SSRI treatment is to increase serotonin levels within platelets although the duration of this effect is not known. [20] This is the proposed mechanism for a case report of central retinal vein occlusion.[18] This case report and explanation must be balanced against the more commonly reported side effect of prolongation of bleeding time attributed to SSRIs.[21]

This Drug Bulletin was written by Darren Schwartz and was reviewed by the Graylands Pharmacy Department

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Table 1. AMH and MIMS list of ocular side effects of antidepressants		
Drug	**AMH**	**MIMS**
Amitriptyline	Common: blurred vision, mydriasis, decreased lacrimation Rare: raised intraocular pressure	Blurred vision, increased intraocular pressure, mydriasis
Clomipramine		Very common: accommodation disorder, vision blurred. Common: mydriasis Very rare: glaucoma
Dosulepin (Dothiepin)		More common: disturbance of accommodation. Less common: mydriasis, Increased intraocular pressure.
Doxepin		Blurred vision, isolated cases of elevated intraocular pressure, mydriasis, angle-closure glaucoma.
Imipramine		Common: blurred vision, disorders of visual accommodation, lacrimation decreased. Very rare: mydriasis, glaucoma
Nortriptyline		Blurred vision, disturbance of accommodation, mydriasis
Citalopram	Infrequent: mydriasis Rare: acute angle-closure crisis (especially paroxetine)	Common: abnormal accommodation. Uncommon: conjunctivitis, eye pain. Rare: mydriasis, photophobia, abnormal lacrimation, cataract, diplopia. Unknown frequency: visual disturbance.
Escitalopram		Uncommon: accommodation abnormal, blepharospasm, eye infection, eye pain, mydriasis, vision abnormal, vision blurred, visual disturbance.
Fluoxetine		Common: abnormal vision. Uncommon: mydriasis.
Fluvoxamine		Frequency not known: glaucoma, mydriasis.
Paroxetine		Common: blurred vision, abnormal vision. Infrequent: abnormality of accommodation, conjunctivitis, eye pain, mydriasis, keratoconjuctivitis. Rare: ambylyopia, specified cataract, conjunctival oedema, corneal lesion, corneal ulcer, exophthalmos, eye haemorrhage, glaucoma, photophobia, retinal haemorrhage, anisocoria.
Sertraline		Common: abnormal vision. Uncommon: eye pain, visual field defect.
Desvenlafaxine	Common: blurred vision, mydriasis (infrequent with duloxetine)	Common: vision blurred, mydriasis.
Duloxetine		Uncommon: mydriasis, visual impairment, dry eye. Very rare: glaucoma
Venlafaxine		Common: abnormality of accommodation, mydriasis, visual disturbance. Very rare: angle-closure glaucoma

Phenelzine	Infrequent: blurred vision	Less common: blurred vision, glaucoma.
Tranylcypromine		Unknownfrequency: blurred vision.
Agomelatine	Infrequent: blurred vision	Uncommon: blurred vision.
Mianserin	-	Rare/very rare: vision abnormality, diplopia.
Mirtazapine	-	Very rare cases of glaucoma.
Moclobemide	Infrequent: visual disturbances	Uncommon: visual impairment. Unknown frequecy: photopsia, visual disturbances.
Reboxetine	Infrequent: mydriasis	>1%: Accommodation disorder. 0.1%-1%: mydriasis, visual impairment. <0.1%: conjunctivitis, diplopia, glaucoma.
Vortioxetine	-	Uncommon: dry eye.
Bupropion	-	Common: visual disturbance.

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