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Development and persistence of patient-reported visual problems associated with serotonin reuptake inhibiting antidepressants

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Abstract.
BACKGROUND: The majority of antidepressants inhibit serotonin reuptake and include the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and the serotonin reuptake inhibiting tricyclic antidepressants.
OBJECTIVE: The objective of this study was to investigate and describe the range and impact of reported adverse visual effects linked to serotonin reuptake inhibiting antidepressants.
METHODS: Using data from a global database of patient spontaneous reports of drug adverse events, we systematically identified eligible reports of visual problems linked to the use of serotonin reuptake inhibiting antidepressants. We analyzed these data using simple descriptive statistics to present the range and impact.
RESULTS: We identified 124 reports of visual problems. Reports originate from 18 countries and involve 11 different drugs. The most commonly reported symptoms were vision blurred/visual acuity reduced (n = 79, 63.7%), night blindness (n = 22, 17.7%), vitreous floaters (n = 21, 16.9%), photophobia (n = 19, 15.3%), diplopia (n = 15, 12.1%), palinopsia (n = 13, 10.5%), visual field defect (n = 12, 9.7%), photopsia (n = 11, 8.9%) and visual snow syndrome (n = 11, 8.9%). 74 patients indicated that the side effect was bad enough to affect everyday activities, 62 had sought health care, and 50 indicated that their work had been affected. 49 patients reported an enduring vision problem after discontinuation of treatment.
CONCLUSIONS: The data suggest that serotonin reuptake inhibiting antidepressants can produce a range of adverse effects on vision that in some cases can be long-lasting after discontinuation of the drug. Further efforts are needed to understand the mechanisms involved, the incidence among those prescribed these medications, and identify any risk or mitigation factors.

Keywords: Antidepressants, selective serotonin reuptake inhibitors (SSRIs), vision, night blindness, visual snow syndrome

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1. Introduction

Around 10–15% of the populations of most Western countries take antidepressants [1]. The majority inhibit serotonin reuptake and include the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and the serotonin reuptake inhibiting tricyclic antidepressants. Warnings about adverse effects on vision are listed in the product labels, although the specifics vary between individual drugs and between countries.

The SSRIs and SNRIs were launched in 1987 and 1993, respectively. There was early concern about whether acute closed-angle glaucoma (ACAG), described for tricyclics, was an issue for these classes also, and this is now mentioned in product labels for SSRIs. Studies of adverse effects on vision in the published literature have typically focused on specific symptoms or conditions. Several studies and a case report have suggested a possible increased risk of developing cataracts [2–5]. In 2015, Lochhead reported five cases of optic neuropathy linked to SSRIs, with only one of the patients achieving full recovery after discontinuation of the drug [6]. There have been four published cases of maculopathy linked to sertraline [7–10], and in 2019, the European Medicines Agency recommended a warning to be added to the product label [11]. Other reported issues have included diplopia linked to citalopram and sertraline [12–15].

Serotonin (5-HT) receptors have been identified in many different tissues in the eye. Currently there are seven different types of 5-HT receptor ($5\text{-HT}_{1A,\ 2A,\ 2C,\ 3,\ 4,\ 6,\ 7}$). Many have been found in different structures of the eye including some subgroups which are associated with a wide range of different physiological functions.

The aim of the current study is to undertake an analysis of adverse event reports to understand and describe the full range, clinical pattern and impact of complaints of visual disturbances linked to serotonin reuptake inhibiting antidepressants.

This article is supplemented by a brief analysis of ophthalmic adverse events from Study 329, a randomized controlled trial involving paroxetine and imipramine, both of which are potent serotonin reuptake inhibitors (Appendix).

2. Methods

Pharmacovigilance databases of drug adverse event reports are robust sources of data for generating signals and descriptions of previously undetected or suspected drug adverse effects. Patient self-report has been determined to be as reliable as physician report and offers the opportunity for direct reporting of the patient impact. RxISK.org is an independent drug safety website set up by an international group with the aim of facilitating data collection of patient adverse event reports for analysis to increase independent pharmacovigilance data [16,17], as well as making information on medication safety more accessible to consumers. The patient adverse event reporting facility began collecting data on all drugs and all adverse events in 2012.

The patient report collects data on four main dimensions: patient characteristics, drug characteristics, adverse drug reaction (ADR) probability and patient-reported impact.

Patient reports include a set of structured questions covering age, gender, country of origin, drug consumption, medical history and other relevant health information (e.g. smoking, pregnancy, alcohol use) along with clinical details. This is followed by a causality assessment based on the Naranjo algorithm to help determine whether the reported drug is responsible for the event [18]. A score of 0–4 means that more information is required, 5–8 indicates a likely link between medication and side effect, and 9 or

higher indicates a strong possibility of a link. The reporting process concludes with a set of questions designed to capture the impact of the problem on various aspects of the person's life including work and social activities.

A total of 5579 patient adverse event reports were submitted between 17 June 2012 and 11 October 2020. We searched the database for reports of effects on vision linked to serotonin reuptake inhibiting antidepressants using a set of vision related keywords. For inclusion, descriptions were mapped to the Medical Dictionary for Regulatory Activities (MedDRA) terminology for vision disorders [19].

Exclusion criteria were reports of other eye problems without associated description of changes in vision, and reports where visual problems were alluded to but were not the main reason for reporting. We searched for and excluded duplicate entries.

3. Results

The initial search produced a dataset of 395 potential reports. We excluded 15 duplicate entries and 33 reports of eye problems (e.g. dry eyes, pain) without any associated description of changes in vision. We excluded 172 reports in which vision problems were listed but either did not feature as a primary reason for reporting or were included alongside a large number of other side effects, often as part of a withdrawal syndrome.

51 other reports were excluded from the analysis for various reasons: possible involvement of confounding factors as a more likely cause of the reported problem ($n = 26$), incomplete or inadequate detail in the data in the report ($n = 25$).

A total of 124 cases were included in the final study dataset.

3.1. Patient characteristics

Reports originated from 18 countries across six continents: North America ($n = 73$), Europe ($n = 42$), Oceania ($n = 4$), Asia ($n = 3$), Africa ($n = 1$) and South America ($n = 1$). The age range was 17 to 68 years (mean 40 years) for female patients and 18 to 68 years (mean 36 years) for male patients. 119 (96.0%) reports were completed by the affected person, 3 (2.4%) were submitted by someone caring for the affected person, and 2 (1.6%) were submitted by a parent about their child. Duration of treatment was recorded by 122 (98.4%) patients which ranged from a single dose to over 18 years.

3.2. Drug characteristics

Medications linked to vision problems are presented in Table 1.

3.3. Characteristics of reported ADRs

The mean causality score for reported potential ADRs was 8.3. Table 2 provides an analysis of reported features by gender.

The most common complaint was vision blurred/visual acuity reduced with 79 (63.7%) reports.

Within the 21 (16.9%) reports of vitreous floaters, 18 patients specifically used the term "floaters" while the remainder provided descriptions of floater-like anomalies e.g. blobs, streaks, lines, shapes and black spots in the field of vision.

Table 1
Treatments linked to vision disorders

Drug	Female	Male	Total (%)
Sertraline	19	10	29 (23.4)
Venlafaxine	17	4	21 (16.9)
Fluoxetine	16	4	20 (16.1)
Escitalopram	13	5	18 (14.5)
Citalopram	12	2	14 (11.3)
Paroxetine	7	1	8 (6.5)
Duloxetine	4	2	6 (4.8)
Vortioxetine	2	2	4 (3.2)
Fluvoxamine	1	1	2 (1.6)
Desvenlafaxine	0	1	1 (0.8)
Imipramine	1	0	1 (0.8)
Total	92	32	124 (100)

Table 2
Vision disorder type and frequency

Symptom	Female (%)	Male (%)	Total (%)
Vision blurred/visual acuity reduced	60 (65.2)	19 (59.4)	79 (63.7)
Night blindness	19 (20.7)	3 (9.4)	22 (17.7)
Vitreous floaters	17 (18.5)	4 (12.5)	21 (16.9)
Photophobia (light sensitivity)	13 (14.1)	6 (18.8)	19 (15.3)
Diplopia (double vision)	11 (12.0)	4 (12.5)	15 (12.1)
Palinopsia (afterimages)	9 (9.8)	4 (12.5)	13 (10.5)
Visual field defect	11 (12.0)	1 (3.1)	12 (9.7)
Photopsia (flashes)	9 (9.8)	2 (6.3)	11 (8.9)
Visual snow syndrome	3 (3.3)	8 (25.0)	11 (8.9)
Halo vision	2 (2.2)	4 (12.5)	6 (4.8)
Oscillopsia	3 (3.3)	2 (6.3)	5 (4.0)
Cloudy vision	3 (3.3)	0	3 (2.4)
Metamorphopsia	1 (1.1)	0	1 (0.8)

Note these represent 124 individual patients but column numbers are greater than 124 as patients reported more than one symptom.

There were 13 (10.5%) reports of palinopsia (afterimages), 7 patients describing these as persistence of bright images such as lights that remained as afterimages for longer than normal or a persistent brightness when moving from a light to a dark environment.

There were 11 (8.9%) reports of visual snow syndrome: a disturbance consisting of flickering dots in the field of vision, similar to static seen on an old analogue television. The syndrome is often associated with palinopsia, night blindness and photophobia. Altogether there were 65 instances of these symptoms reported by 43 patients.

A false perception of movement (oscillopsia) was described by 5 (4.0%) patients who reported that stationary patterns or objects appeared to move. There was a single report of straight lines appearing curved (metamorphopsia) which began a few days after starting to taper venlafaxine and continued to worsen as the dose was decreased.

Table 3
Treatments linked to persisting vision disorders

Drug	Female	Male	Total (%)
Sertraline	6	5	11 (22.4)
Escitalopram	6	3	9 (18.4)
Venlafaxine	6	2	8 (16.3)
Fluoxetine	6	1	7 (14.3)
Citalopram	3	1	4 (8.2)
Duloxetine	1	2	3 (6.1)
Paroxetine	2	1	3 (6.1)
Desvenlafaxine	0	1	1 (2.0)
Fluvoxamine	1	0	1 (2.0)
Imipramine	1	0	1 (2.0)
Vortioxetine	1	0	1 (2.0)
Total	33	16	49 (100)

Patients also reported a number of secondary symptoms along with their primary vision issue: eye pain ($n = 12$), dry eyes ($n = 4$), eyelid twitching ($n = 2$), eye bleeding ($n = 1$), eye swelling ($n = 1$), nystagmus ($n = 1$) and ptosis ($n = 1$).

In some cases, it was noted that diagnostic testing had revealed issues such as reduced visual acuity or astigmatism. Some patients listed specific eye conditions: cataracts ($n = 2$), glaucoma ($n = 2$), retinopathy ($n = 2$), bull's eye maculopathy ($n = 1$), keratitis ($n = 1$), optic neuritis ($n = 1$) and papilledema ($n = 1$). However, in other cases, investigation did not reveal any obvious explanation for the perceived difficulties.

There were three cases involving the onset or worsening of astigmatism. In the first, a subject with a mild pre-existing nearsightedness (myopia) described a sudden onset of pain and blurred vision in one eye after starting escitalopram. Investigation found a unilateral decrease in visual acuity and an astigmatism which the subject reportedly had never had before. The second case involved a progressive worsening of vision after starting sertraline. Visual acuity had declined twice on testing within only a few months, with new astigmatism which subsequently went away while tapering off the drug. In the third case which involved venlafaxine, a subject reported severe light sensitivity, night blindness and an increase in a pre-existing astigmatism.

In 49 (39.5%) cases, patients reported an enduring vision problem after discontinuation of treatment. 34 involved problems that began on the drug and remained after stopping, while 15 emerged or worsened on stopping the drug. Tables 3 and 4 provide detail of the treatments and features linked to these enduring problems.

Although many patients did not report an enduring post-treatment problem, the majority of these were still on an antidepressant at the time of reporting. Only 10 patients described a resolution of symptoms upon discontinuing the antidepressant.

3.4. Patient-reported impact

74 (59.7%) patients indicated that the side effect was bad enough to affect everyday activities, 62 (50.0%) indicated that it was bad enough to seek health care from a doctor, and 50 (40.3%) indicated that their work had been affected. 22 (17.7%) patients reported having an enduring vision problem for at least a year since stopping the antidepressant, with the longest case being over eight years. The shortest

Table 4
Persisting vision disorder: type and frequency

Symptom	Female (%)	Male (%)	Total (%)
Vision blurred/visual acuity reduced	19 (57.6)	10 (62.5)	29 (59.2)
Night blindness	11 (33.3)	2 (12.5)	13 (26.5)
Vitreous floaters	9 (27.3)	4 (25.0)	13 (26.5)
Palinopsia (afterimages)	8 (24.2)	3 (18.8)	11 (22.4)
Photophobia (light sensitivity)	5 (15.2)	5 (31.3)	10 (20.4)
Visual snow syndrome	3 (9.1)	7 (43.8)	10 (20.4)
Diplopia (double vision)	6 (18.2)	3 (18.8)	9 (18.4)
Visual field defect	6 (18.2)	1 (6.3)	7 (14.3)
Halo vision	1 (3.0)	4 (25.0)	5 (10.2)
Photopsia (flashes)	5 (15.2)	0	5 (10.2)
Oscillopsia	1 (3.0)	1 (6.3)	2 (4.1)
Cloudy vision	1 (3.0)	0	1 (2.0)

Note these represent 49 individual patients but column numbers are greater than 49 as patients reported more than one symptom.

duration of treatment with a reported enduring effect was a single dose in two separate cases. The first described blurred vision which was still present 26 days after a single dose of vortioxetine. In the second, there was a reported persistence of blurred vision, light sensitivity, floaters and visual snow after a single dose of venlafaxine, which at the time of reporting had persisted for over two years.

From a choice of five options, reporters were asked to rate their experience on the suspect drug, taking into consideration the treatment of their condition and the side effects they experienced. The results were: very unsatisfied ($n = 42$), unsatisfied ($n = 33$), neutral ($n = 23$), satisfied ($n = 13$) and very satisfied ($n = 4$). Nine reports did not have a rating.

4. Discussion

There were almost three times more reports from females than males. Most pharmacovigilance datasets such as the FDA Adverse Event Reporting System (FAERS) contain more reports on women than men (6.5 million female, 4.1 million male) [20]. While the main source database across all drugs and all adverse events also has a higher number of reports from females (3239 female, 2278 male, 62 not specified), the proportion is greater in this study. However, it is generally accepted that around twice as many women take antidepressants compared to men which may help to explain the disparity.

The prevalence of reports for particular drugs is likely influenced by prescribing habits and the popularity or otherwise of certain antidepressants. A class effect is more likely rather than specific medications having a greater propensity to cause vision problems, although this cannot be ruled out.

4.1. Anterior segment

Dry eyes and ocular discomfort have been reported in several studies in association with reduced lacrimal secretion [21]. It has also been proposed that SSRI treatment can alter sensitivity thresholds for corneal nerves. Serotonin receptor subtypes are also thought to play a role in corneal homeostasis and regulation of fluid transport.

Blurred vision is the most commonly reported problem. It is difficult to attribute this to a single mechanism, however it seems likely that many cases are subclinical since ophthalmology clinics are not overwhelmed with SSRI related referrals. Traditionally, these effects have been put down to anticholinergic actions, but SSRIs are largely devoid of these actions. Subtle changes in corneal thickness could also be implicated. Corneal thickness can also be influenced by rapid fluctuations in intraocular pressure (IOP).

IOP changes have been postulated via a number of serotonin pathways, however the most serious clinical mechanism is that of partial mydriasis leading to ACAG via relaxation of pupillary sphincter smooth muscle. This may result from direct 5-HT_7 stimulation [22]. Halos around lights are often described as the corneal epithelium becomes oedematous secondary to elevated IOP. Pain is also a feature when IOP becomes significantly raised. It has been estimated that the risk of ACAG is increased 5.8 fold with SSRI treatment [23]. It is likely that patients with pre-existing glaucoma should be more closely monitored after starting SSRI drugs, particularly if there is a narrow angle component. Elderly hypermetropes who are at a higher risk of angle closure may benefit from gonioscopy.

Cloudy vision can be attributed to the cornea but is more typical of cataracts formation. Although serotonin is thought to have a role in lens metabolism, lenticular changes have not been widely reported and this could be due to the avascularity of this structure.

Altered astigmatism would implicate corneal or lenticular changes, however this could also be confounding given that refraction has a strong subjective component. Astigmatism normally results from anatomical variations in corneal and lens curvature. Changes can occur with age, keratoconus, trauma and surgery. The reported findings of astigmatism during diagnostic testing may have been incidental as there is no previous known link between serotonin reuptake inhibitors and changes in astigmatism.

It is difficult to attribute reports of light sensitivity to a single structure since a wide range of eye conditions can result in photophobia. It is however tempting, in the absence of frequent specialist referrals, to speculate that much of this could result from partial pupil mydriasis which could be easily managed by the subject by remaining indoors or using dark glasses in bright conditions.

4.2. Posterior segment

Night blindness (nyctalopia) is frequently the result of rod photoreceptor dysfunction. 5-HT receptors have been confirmed within mammalian retina, but their effects on visual processing are currently unknown. Night blindness is listed in US product labels for paroxetine and clomipramine, however the present study included reports of impaired night vision linked to seven different drugs which suggests it may be a more widespread effect within this group of medications than is currently indicated. FAERS shows that reports of night blindness involving serotonin reuptake inhibitors go back to 1989 with a report linked to fluoxetine.

It is difficult to know whether the reports of vitreous floaters are entoptic phenomena (i.e. emanating from within the eye) or whether they involve elements of higher cortical altered perception. Although some patients used the term “floaters” (i.e. opacities in the vitreous), this may simply have been the word that they reached for or were told was the right one to describe what they were experiencing. Vitreous floaters have not been previously linked to serotonin reuptake inhibitors and are relatively common within the general population. Nevertheless, the reports of floaters in this study typically had a strong temporal link to treatment and were often accompanied by other visual symptoms or other side effects. European patient information leaflets for sertraline list “spots in front of the eyes” as a possible side effect, though it is unclear what this refers to. There is potentially some crossover here with the terminology used in visual snow syndrome.

4.3. Neurological

Visual snow syndrome is thought to be a result of changes in cerebral cortical visual processing. The syndrome is often associated with palinopsia, nyctalopia and photophobia. Blobs and floaters have also been described as part of this syndrome, but it is more likely that these are entoptic in origin rather than cortical [24]. There is a previous case report of visual snow syndrome linked to the use of citalopram [25]. Interestingly, FAERS shows that as of 31 December 2020, almost half of all reports for visual snow syndrome were linked to serotonin reuptake inhibiting antidepressants (n = 12, 48.0%), with citalopram having the highest number of reports across all drugs (n = 11, 44.0%). These reports only go back to 2017, so this reaction may only have been added in recent years.

The origin of diplopia in many cases is unclear without formal orthoptic assessment. Cranial nerve palsy is the most serious clinical presentation because this can often be the result of microvascular ischemia. Decompensated phoria is more likely in concomitant diplopia particularly in the presence of previous squint or amblyopia. Ocular dystonia has been reported with SSRI drugs as an extrapyramidal side effect presenting as acute gaze palsy. This is however very rare [26].

The optic nerve is thought to be vulnerable to the effects of serotonin principally through transient vasospasm and also possible increased tendency for platelet aggregation in vessels with pre-existing atheroma. The presentation tends to be as an acute posterior ischaemic optic neuropathy with asymmetric reduced acuity and corresponding altitudinal visual field defect. It is also possible that an optic nerve vascular insufficiency could present with a more chronic picture of progressive visual field defects and decreased peripheral vision or blind spots. This could simulate a normal tension glaucoma which is thought to be related to optic nerve vascular insufficiency. It is also important not to lose sight of the theoretical effects of serotonin on IOP homeostasis, particularly in patients with pre-existing glaucoma. The current literature suggests a mixture of physiological effects on IOP from different populations of 5-HT receptors involved in aqueous production and outflow [27]. In some cases the effects may be beneficial. As previously mentioned, the best described adverse clinical event is related to partial mydriasis leading to reduced aqueous outflow at the iridocorneal angle.

4.4. Red flag symptoms

Red flag symptoms are acute asymmetric loss of vision and diplopia. Visual loss requires initial exclusion of ACAG followed by optic nerve assessment with visual fields to detect optic neuropathy. Subsequent neuroimaging and visual evoked potentials may be indicated. Diplopia requires initial orthoptic assessment with Hess test and then neuroimaging if indicated.

15 patients described diplopia and 9 cases exhibited symptoms of profound loss of vision, frequently asymmetric and consistent with ACAG or the SSRI associated optic neuropathy previously described in the literature.

4.5. Withdrawal

Vision problems arising upon withdrawal of an antidepressant have previously been reported in the literature. There is a case report in which palinopsia occurred during three attempts at withdrawal of venlafaxine, each time resolving upon reinstatement of the drug [28]. In a separate case, Terao noted that paroxetine had recently been withdrawn in a published report of palinopsia linked to mirtazapine, and raised the possibility that the problem may have been linked to paroxetine withdrawal rather than the

introduction of mirtazapine [29]. A case of blurred vision developing upon withdrawal of paroxetine has also been published [30].

The enduring post-treatment vision problems reported in our study have similarities to post-SSRI sexual dysfunction (PSSD) [31] and antipsychotic-induced tardive dyskinesia in that some emerged on treatment and remained afterwards, while others appeared or worsened upon stopping the drug.

The long term effects on the eye from long term SSRI use are unknown. While conditions such as optic neuropathy can result in permanent sequelae, there were many cases in the study without an obvious mechanism to explain the enduring nature of the disturbance. For example, it is difficult to know why a sudden onset of blurred vision upon starting a serotonin reuptake inhibitor can remain indefinitely, even after a short exposure.

Guclu et al. reported a link between SSRIs and decreased ganglion cell complex (GCC) thickness and retinal nerve fiber layer (NFL) thickness [32]. However, there is currently no information on how these small differences could impact on sight. The paper noted that a clinical ophthalmic assessment was made, but no functional information was provided. Reduced GCC and NFL are often found in glaucoma but can be affected in other global retinal diseases such as diabetes.

5. Conclusion

Visual disturbances induced by antidepressants may be under-reported and under-recognised. The tricyclic antidepressants may have set a template for linking these effects to anticholinergic actions, often regarded as minor problems that invariably resolve on stopping treatment. As most tricyclic antidepressants are also serotonin reuptake inhibitors, while few of the SSRIs have significant anticholinergic effects, it may be time to revisit these effects, encourage reporting and explore mechanisms.

In mild cases, decreased acuity is likely to be dealt with by way of glasses or contact lenses via an optometrist without anyone assessing the involvement of antidepressants. It also appears that some visual disturbances may not fit neatly into clearly defined eye conditions or follow expected pathophysiology. This may present a challenge for patients in terms of having their concerns taken seriously if routine testing does not reveal an obvious abnormality.

The data presented here on effects linked to withdrawal may be an under-representation as 67 reports that described the emergence of vision problems as part of a withdrawal syndrome were excluded from the study due to the large number of symptoms.

In summary, the data from this study suggest that serotonin reuptake inhibiting antidepressants can produce a range of visual disturbances which do not always resolve upon discontinuation of treatment, and in some cases can emerge or worsen upon stopping the drug. Many of these issues are likely dismissed, but they are poorly understood and the fact that the problems appear to endure after withdrawal calls for further investigation and a wider assessment of risk-benefit ratios. Patients who are started on serotonin reuptake inhibiting antidepressants should probably be alerted to the possibility of visual changes, with consideration given to changing treatment if these appear significant.

Clinicians must be aware of the common visual complaints associated with these medications and particularly the red flag symptoms requiring rapid assessment and intervention.

Conflict of interest

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Appendix: Brief analysis of ophthalmic adverse events from Study 329

Study 329 was a randomized controlled trial of 275 adolescents aged 12–18 with depressive disorders.[1] Of these, 93 were randomized to paroxetine in doses of 20–40 mg, 95 to imipramine in doses of 200–300 mg and 87 to placebo. The data cited here are drawn from Appendix B for concomitant drugs and Appendix D for adverse events. These appendices are in the public domain (Study329.org).

In the paroxetine group, two had changes coded as blurred vision and designated as related or possibly related. Three people had problems coded as conjunctivitis, itchy eyes and dry itchy eyes, of which one was designated as unrelated, one as probably unrelated and one as possibly related.

In the imipramine group, five were coded as blurred vision of which two were designated as related and three as possibly related. Three more were coded as visual bright spots, eye dilation and light sensitivity, all designated as related. A patient coded as irritation in eyes (dry eyes) was designated as possibly related.

The anticholinergic effects of imipramine are minor compared to its potent serotonin reuptake inhibiting effects. Just as imipramine's actions on the norepinephrine system are now viewed as causing urinary retention rather than its anticholinergic action, so also its serotonergic action may be more likely to cause visual effects previously viewed as arising from an anticholinergic action.

Combining these two active drugs, there were 14 effects from 188 patients of which 12 were regarded as related versus 3 that weren't.

In the placebo group, two were coded as blurring vision and blurry vision, designated as possibly related. Both of these patients were on concomitant serotonin reuptake inhibiting antihistamines. A case coded as eye infection was designated as unrelated.

In this trial, a number of common SSRI effects were coded as infections. Pain and dystonic reactions in the oropharyngeal area were designated as pharyngitis without any further evidence that this was in fact the case. Reports of itchy eyes and conjunctivitis may similarly have been coded as infectious or allergic when this was not the case.

We have not applied statistical tests to this data as the trial was not set up to capture visual effects, but the results are consistent with an acute effect of serotonin reuptake inhibitors on visual functioning in young people, and the likely frequency of these effects was almost certainly greater than the 7.4% reported here.

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