Review

Acute Angle-Closure—A Rare but Vision-Threatening Ocular Adverse Effect of Selective Serotonin Reuptake Inhibitors

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Abstract: Acute angle closure (AAC) is a relatively rare but serious ophthalmological condition in which early diagnosis and intraocular pressure (IOP)-lowering treatment play a key role in prognosis. The aim of this review is to present current understanding of the pathophysiology, symptoms, diagnosis, potential mechanisms as well as management of AAC associated with the use of selective serotonin reuptake inhibitors (SSRIs). In most cases, AAC in individuals receiving SSRIs occurs in the pupillary block mechanism, secondary to SSRI-induced mydriasis. However, SSRIs may also cause uveal effusion and, consequently, iridocorneal angle closure. Other factors such as impaired metabolism and elimination of SSRIs, individual genetic conditions, as well as inhibition of SSRIs metabolism due to the effects of other drugs used may also promote AAC.

Keywords: selective serotonin reuptake inhibitors; acute angle closure; antidepressants; SSRIs; AAC

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1. Introduction

Depression is a disease with a complex etiology that affects millions of people of all ages throughout the world [1]. Currently, selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line therapy in the treatment of depressive disorders [2]. High safety profiles, good tolerance, low cost of therapy [3], and similar efficacy compared to tricyclic antidepressants (TCAs) influence the increased number of patients using SSRIs. In 2016, SSRI prescriptions in England increased by more than two million compared to 2015, reaching 36 million [4]. Depression is predicted to take second place after ischemic heart disease in the global disability adjusted life years (DALYs) ranking in 2020, which will further increase SSRIs prescriptions [5].

Fluoxetine—the first SSRI—was launched in 1988, seventeen years after it was synthesized for the first time [6]. The next authorized drugs from this group were sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram, respectively [5,7]. Currently, indications for the use of SSRIs beside of depression include panic disorder, social and generalized anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorders, eating disorders, chronic pain, and premenstrual stress disorders [5,8].

Acute angle closure is a serious ophthalmological condition that occurs mainly in people with risk factors, in which early diagnosis and treatment play a key role in prognosis because the lack of proper management may result in a loss of vision [9]. The most common risk factors for iridocorneal angle closure include: female gender, Asian, Indian and Inuit origin, age, positive family history of glaucoma, specific biometric structure of an eye, and so forth [10,11]. It has been proven that the use of antidepressants, including SSRIs, is associated with an increased risk of AAC [12,13]. This paper presents current

understanding of the pathophysiology, symptoms, diagnosis, potential mechanisms as well as management of AAC associated with SSRIs.

2. Pathophysiology of Acute-Angle Closure

Acute-angle closure is an emergency condition resulting from the iridocorneal angle closure, which disturbs the proper circulation of aqueous humor from the posterior to the anterior chamber of the eye [14]. The balance between production and outflow of aqueous humor is the main mechanism regulating intraocular pressure (IOP); thus, blocking the proper drainage of aqueous humor leads to a sudden increase in IOP [11,15]. Therefore, AAC requires immediate initiation of IOP-lowering treatment to prevent the development of glaucomatous optic neuropathy (GON) [14].

AAC can occur in two main mechanisms—pupillary block, as well as non-pupillary block [16]. Pupillary block is the most common mechanism that leads to AAC and is a common finding in individuals with anatomically predisposed eyes, e.g., with shallow anterior chamber or hypermetropia [14]. Pupil dilation called as mydriasis is a trigger factor that initiates the AAC in pupillary block mechanism by producing the iris-lens contact, resulting in disturbed outflow of aqueous humor from the posterior to the anterior chamber of the eye. Accumulation of aqueous humor generates increased pressure in the posterior chamber, which pushes the iris forward and subsequently leads to iridotrabecular contact (ITC); this displacement leads to acute angle closure. Non-pupillary mechanisms include plateau iris, ciliary block, and abnormalities in lens position [16].

3. Clinical Presentation, Assessment, and Diagnosis

In published case reports, AAC associated with SSRIs administration was characterized by variety clinical presentation. The most frequently presented symptoms include blurred vision, eye pain, redness or discomfort in the eye, headache, haloes around light sources, photophobia, nausea, and vomiting [17–22]. It is worth emphasizing that in two reported cases, three days before the onset of AAC, heralding symptoms such as ocular pain and blurred vision were observed [21,23].

IOP measurement using a tonometer is the first choice diagnostic method; however, usually a definitive diagnosis is made by an ophthalmologist after assessing the drainage angle during gonioscopy. An anterior segment examination using a slit lamp, or with the use of ultrasound biomicroscopy (UBM), assessment of pupil reactivity to light, visual acuity test as well as fundus examination with the evaluation of optic discs are also performed [14,24]. Frequent findings in the ophthalmological examination included decreased visual acuity, corneal oedema, fixed and mid-dilated pupils, shallow anterior chamber, increased IOP (usually up to 60–80 mmHg), closure of the iridocorneal angle, iris plateau configuration, and cataractous changes in the lens [17,19–21,25]. In some cases, the optic disc may be swollen [14]. Moreover, in a report of AAC associated with citalopram overdose, retinal, subhyaloid, and vitreous hemorrhages were noted [26], whereas choroidal effusions and detachments were present in cases of AAC associated with uveal effusion (UE) after intake of escitalopram [18,27].

4. Pharmacology of Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs exhibit a diverse ability to block serotonin reuptake, which is their main mechanism of action, as well as norepinephrine and dopamine reuptake by the drug molecule binding to the serotonin transporter (SERT), norepinephrine transporter (NET), and dopamine transporter (DAT) proteins, respectively [15,28]. In addition, SSRIs have an anticholinergic effect, which is most widely presented by paroxetine and is similar to, but weaker than, the anticholinergic effect of TCAs [29]. SSRIs are excreted mainly via the kidneys, but in the case of fluoxetine, sertraline, and paroxetine, some of the metabolites are also excreted in the feces [30]. The pharmacokinetic and pharmacodynamic properties of SSRIs are shown in Table 1.

Table 1. Pharmacokinetic and pharmacodynamic properties of the SSRIs.

Drug Name	CYP 450 Isoenzymes In-Volved in Metabolism	Inhibited CYP 450 Iso-Enzymes	Peak Plasma Concentration ^b (Hours)	Bioavailability ^b (%)	Protein Binding (%)
Fluoxetine	<u>2D6</u> , 3A4/5, 2C9, 2C19	<u>2D6</u> , 2C19, 2C9, 3A4/5, 1A2	4–8	90	94
Sertraline	<u>2D6</u> , <u>2C19</u> , 3A4/5, 2C9, 2B6	2C19, 2D6 ^a	5–9	28 ^c	99
Paroxetine	<u>2D6</u> , 3A4, 1A2	2D6	6–10	50	95
Fluvoxamine	<u>2D6</u> , <u>1A2</u>	<u>2C19</u> , <u>1A2</u> , <u>2C9</u> , 3A4/5, 2D6	4–8	53	77
Citalopram	<u>2C19</u> , 3A4/5, 2D6	2D6, 2C19	2–4	80	80
Escitalopram	<u>2C19</u> , <u>3A4/5</u> , 2D6	-	3–5	80	56
References	[8,31–34]	[8]	[7,31,32]	[31,35–37]	[5,7,31]

SSRIs-selective serotonin reuptake inhibitors; highlighted-potent inhibitor or isoenzyme strongly involved in metabolism of the drug;

^a dose-dependent inhibitor of 2D6 subunit (>100 mg high inhibitor; <50 mg mild inhibitor); ^b after oral administration; ^c after oral administration with a meal.

5. SSRIs and AAC: Potential Mechanisms

Previous studies have shown a higher incidence of acute angle closure in patients initiating SSRIs treatment [12,13]. Chen et al. showed a 5.8-fold greater risk of AAC in patients starting therapy with SSRIs [12]; while results obtained by Seitz et al. revealed that among the study population, 5.6% of participants of which 1.3% were SSRIs users have received antidepressants in the year preceding the onset of AAC [13]. Drugs that cause mydriasis may induce AAC in the pupillary block mechanism, especially in anatomically predisposed eyes with occludable angles [10,15]. A positive correlation between the long-term use of SSRIs and the incidence of mydriasis has been observed [38,39]. To date, both animal and human studies have demonstrated that SSRIs can cause an increase in IOP. A single intravenous administration of fluoxetine increased IOP in rabbits [40]; while Farnia et al. revealed that the three-month use of sertraline at a dose of 25–100 mg by patients without eye disease is associated with a statistically significant increase in IOP and cup-to-disc ratio [41]. Furthermore, an increase in IOP 2 h after a single oral dose of 20 mg of fluoxetine in 20 healthy volunteers aged 33–47 years [42], as well as in 11 individuals aged 32–70 years using SSRIs from one week to five years was shown [43]. Additionally, fluoxetine and its active metabolite, norfluoxetine, exhibit antagonistic properties at the 5-HT_{2C} receptor, which may lead to co-stimulation of the dopaminergic and adrenergic pathways, and predispose to both an increase in IOP and mydriasis [44]. Table 2 explains the potential mechanisms linking the use of SSRIs and the occurrence of AAC in the pupillary block mechanisms.

Besides pupillary block, AAC in individuals using SSRIs may be associated with the occurrence of UE, which leads to AAC by the anterior chamber becoming more shallow as a result of ciliary body edema and secondary forward displacement of the iris-lens diaphragm [11]. This phenomenon causes iridocorneal angle closure in the non-pupillary block mechanism. So far, two cases of bilateral AAC associated with the use of SSRIs have been described, both in patients receiving citalopram [18,27].

Table 2. Potential mechanisms linking SSRIs with the occurrence of AAC.

Mechanism	Receptor	Stimulation/Inhibition	Localization	Effect in the Eye Tissue
Serotonergic	5-HT ₇	Stimulation	Iris Ciliary body Iris sphincter muscle	Increase IOP Mydriasis-relaxation of the iris sphincter muscle
	5-HT _{2C}	Inhibition	Iris Ciliary body	Possible co-stimulation of adrenergic and dopaminergic transmission in the CNS
Adrenergic	α_1	Stimulation	Iris dilator muscle	Mydriasis-contraction of the iris dilator muscle
	α_2	Stimulation	E-W nucleus	Mydriasis-inhibition of the parasympathetic innervation of the iris muscles by stimulation of the α_2 -adrenergic receptors located in the E-W nucleus
	β_2	Stimulation	Ciliary body	Increase IOP-increased aqueous humor production
Dopaminergic	D1-like (D1 and D5)	Stimulation	Ciliary body	Increase IOP-increased aqueous humor production
Anticholinergic	M1; M3; M5	Inhibition	Ciliary body Iris sphincter muscle	Increase IOP Mydriasis-relaxation m. sphincter of the pupil

References: [10,15,38,45]. Abbreviations: IOP, intraocular pressure; CNS, central nervous system; E-W nucleus, Edinger-Westphal nucleus.

CYP2D6, CYP2C19, and CYP3A4 polymorphisms may condition poor metabolism of SSRIs and their higher serum concentrations [46]. Concomitant use of CYP2D6 (e.g., chinidin, lewomepromazine, methadone), as well as CYP2C19 (e.g., isoniazid, proton pump inhibitors) and CYP3A4 (e.g., clarithromycin, isoniazid, verapamil) inhibitors may increase the plasma concentration of SSRIs [7,32,33,47,48]. Moreover, a high degree of binding of sertraline, paroxetine, and fluoxetine to plasma proteins can cause interactions with other highly protein-bound drugs [7,31,35,36,49] (Table 1) and can contribute to the higher risk of side-effects through increased serum concentration of SSRIs. On the other hand, due to the extensive metabolism of SSRIs in the liver, as well as their elimination via the kidneys, impaired function of these organs may reduce the elimination of SSRIs and their metabolites from the organism, which may increase the serum concentration of the drug [30].

Interestingly, nearly half of the reported cases were associated with the use of paroxetine. This observation is supported by the results of a retrospective population-based study conducted by Seitz et al. where paroxetine along with citalopram was the most frequently used SSRI in patients diagnosed with AAC [13]. Several hypotheses may explain the more frequent occurrence of AAC associated with paroxetine administration compared to other SSRIs. Paroxetine is characterized by the greatest affinity for SERT and is the most potent 5-HT reuptake inhibitor among SSRIs [50,51]. These pharmacological properties suggest that the serotonergic mechanism may be a crucial factor connecting paroxetine with a higher incidence of AAC. A similar hypothesis was formulated in relation to the occurrence of AAC associated with the use of SNRIs, a similar group of antidepressants, as all described cases are associated with the intake of venlafaxine and duloxetine, which are characterized by the highest ratio of 5-HT:NE reuptake among SNRIs [10]. Paroxetine also has a stronger effect on norepinephrine reuptake than the other SSRIs, which shows both the low value of the inhibitor constant (K_i) for NET and low half maximal inhibitory concentration (IC_{50}) for NE reuptake [15,50]. Stimulation of the α_1 -adrenergic receptors located in the pupil dilator muscle may act synergistically with the serotonergic stimulation, which

cause mydriasis, as a result of relaxation of the pupil-sphincter muscle due to stimulation of the 5-HT₇ receptors [15]. Moreover, paroxetine is characterized by the highest affinity for the muscarinic receptors among SSRIs [51], due to which anticholinergic mechanism may also act synergistically with serotonergic and noradrenergic mechanisms and cause mydriasis, resulting in AAC in the pupillary block mechanism in suspected patients [26,45]. Furthermore, paroxetine is metabolized by the CYP2D6 subunit and is a potent inhibitor of this isoenzyme [37,52]; thus, paroxetine can inhibit its own metabolism [34].

6. Case Reports of AAC Associated with SSRIs Administration

Fifteen cases of AAC associated with SSRIs have been reported to date (Table 3) [17–22,25–27,53–58]. Interestingly, they include all SSRIs drugs. The case reports vary substantially in the time from the start of SSRIs intake to the occurrence of AAC, from 3 h [53] to 3 months [54], and in one case of AAC was associated with discontinuation syndrome [55]. Patient's age ranged from 35 to 91 years, with an average of 60 years. Only two cases of AAC associated with SSRIs intake have been reported in men [19,22]. In addition to age and gender, the predominant risk factor was hypermetropia in six cases [18,20,21,53,54,56].

Table 3. Summary of case reports of AAC associated with SSRIs.

Drug and Daily Dose	Gender and Age (Years)	Laterality	IOP (mmHg) ^b	Risk Factors for AAC ^c	Time to Onset of Symptoms of AAC	BVA	FVA	Reference
Paroxetine -	Female, 91	Bilateral	OD: 70 OS: 70	Nuclear sclerosis (3+)	1 day	OD: CF OS: CF	OD: 6/9 OS: 6/6	[17]
Paroxetine 20 mg	Female, 70	Unilateral	OD: 15 OS: 85	-	4 days	OD: 20/100 OS: 20/400	OD: - OS: -	[57]
Paroxetine 20 mg	Female, 84	Unilateral	OD: 40 OS: -	Hypermetropia; Narrow angle (OS)	13 days	OD: - OS: -	OD: - OS: -	[20]
Paroxetine 20 mg	Female, 53	Unilateral	OD: - OS: 61	Hypermetropia	3 days	OD: - OS: -	OD: - OS: -	[56]
Paroxetine 20 mg	Male, 40	Unilateral	OD: 57 OS: 16	Plateau iris configuration	2 weeks	OD: 6/6 OS: 6/6	OD: 6/6 OS: 6/6	[19]
Paroxetine 20 mg	Female, 54	Bilateral	OD: 57 OS: 52	Plateau iris configuration	2 months	OD: 6/60 OS: 6/60	OD: 6/9 OS: 6/9	[25]
Paroxetine -	Female, 73	Bilateral	OD: 72 OS: 72	Hypermetropia Nuclear sclerosis	3 h	OD: HM OS: HM	OD: 6/60 OS: 6/24	[53]
Escitalopram 20 mg	Female, 41	Bilateral	OD: 47 OS: 45	-	4 weeks	OD: 20/40 OS: 20/40	OD: 20/20 OS: 20/20	[27]
Escitalopram 20 mg	Female, 73	Bilateral	OD: 30 OS: 29	Hypermetropia Bilateral pseudophakia	3 days	OD: 3/10 OS: 16/100	OD: 10/10 OS: 100/100	[18]
Escitalopram dis-continuation	Female, 45	Bilateral	OD: 60 OS: 60	-	1 month ^d	OD: 3/10 OS: 4/10	OD: - OS: -	[55]
Citalopram ^a	Female, 54	Unilateral	OD: 23 OS: 60	-	Soon after overdose ^a	OD: 6/9 OS: HM	OD: 6/6 OS: 6/24	[26]
Citalopram 20 mg	Female, 55	Bilateral	OD: 56 OS: 34	Hypermetropia	3 months	OD: 6/6 OS: 6/6	OD: 6/6 OS: 6/6	[54]
Fluoxetine 20 mg	Male, 35	-	OD:- OS: -	Positive family history of glaucoma	5 weeks	OD: - OS: -	OD: - OS: -	[22]

Table 3. Cont.

Drug and Daily Dose	Gender and Age (Years)	Laterality	IOP (mmHg) ^b	Risk Factors for AAC ^c	Time to Onset of Symptoms of AAC	BVA	FVA	Reference
Fluvoxamine 50 mg	Female, 66	Bilateral	OD: 52 OS: 52	Narrow angle	2 months	OD: - OS: -	OD: - OS: -	[23]
Sertraline 50 mg	Female, 64	Unilateral	OD: 56 OS: -	Hypermetropia Asian origin Nuclear sclerosis	3 days	OD: 1/80 OS: 20/30	OD: 20/30 OS: 20/30	[21]

AAC—acute angle closure; AC—anterior chamber; BVA, baseline visual acuity (visual acuity during the presentation); FVA, final visual acuity; SSRIs—selective-serotonin reuptake inhibitors; OS—left eye; OD—right eye; OU—both eyes; IOP—intraocular pressure; HM—hand movements; CF—counting fingers; ^a overdose—patient may have taken 280–600 mg of citalopram with alcohol; ^b maximum measured IOP value; ^c other than age and gender; ^d symptoms occurred 1 month after discontinuation of escitalopram, which was taken for a year.

7. Management

As AAC is a medical emergency, its treatment should be a priority and precede other additional examinations and ancillary medical procedures. The most important approach in the eyes with acute iridocorneal angle closure is the immediate implementation of IOP-lowering treatment and then reversing the mechanism of angle closure. Pharmacological therapy is based on drugs that reduce the volume of aqueous humor (e.g., intravenous mannitol), inhibit its production (intravenous acetazolamide, topically administered β -blocker-timolol or α_2 -agonist-apraclonidine), as well as agents that increase the outflow of aqueous humor (topical pilocarpine) [14,24]. According to the EGS guidelines, the initiation of IOP-lowering treatment with monotherapy is preferred; however, if the first drug is well tolerated but it is not possible to reduce the IOP to the patient's pre-AAC values, a second drug from a different class should be added [59]. Further, Nd:YAG laser peripheral iridotomy or rarely more invasive surgical iridectomy is performed to resolve pupillary block [14,24]. Nd:YAG laser peripheral iridotomy is the preferred method due to the lower risk of infection and better patient tolerance compared to iridectomy [60]. On the other hand, in patients with coexisting cataract and high IOP values, lens replacement surgery may be the most advantageous solution [24]. Other less frequently performed procedures include iridoplasty and trabeculectomy [60]. However, each case requires an individual assessment in order to choose the best therapeutic option [59].

Usually offending medication was discontinued when symptoms occur [19,20,26]. however, in one of the reported cases, the drug was maintained after psychiatric consultation and after IOP-lowering treatment supported by YAG laser iridotomies successfully continued [25]. In patients after an AAC episode, re-use of an antidepressant may be challenging. In the case of AAC secondary to the use of citalopram, switching to imipramine—a TCA—resulted in a sudden increase in IOP requiring IOP-lowering treatment; however, no disturbing symptoms were seen with mirtazapine, a tetracyclic antidepressant (TeCA) [54]. On the other hand, in the case described by Lewis et al., successful follow-up after switching to sertraline in a patient with AAC associated with paroxetine has been reported [57]. Thus, each case requires individual assessment and interdisciplinary management during the re-application of antidepressant treatment.

8. Conclusions

Although SSRIs are a well-tolerated group of drugs with a small percentage of adverse ocular effects, numerous reports of AAC occurrence have been published. AAC is a serious complication that should not be neglected, especially in patients with risk factors, and in the event of AAC symptoms, the patient should undergo a thorough diagnosis. The occurrence of AAC associated with the use of SSRIs may be the result of the coexistence of several mechanisms, and it is possible that the effects may be mutually reinforcing. Although performing a gonioscopic examination in all patients initiating SSRIs may be unacceptable from an economic point of view, ophthalmological consultation should be considered in

patients with risk factors, especially hyperopic patients starting paroxetine. This procedure can reduce the number of AACs associated with the use of this class of drugs.

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