

## Mirtazapine-induced acute angle closure

Nilay Kahraman, Onur Durmaz<sup>1</sup>,  
Mehmet Murat Durna<sup>2</sup>

Acute angle closure (AAC) is an ocular emergency with symptoms including blurred vision, eye pain, headache, nausea, vomiting and reddening of the eye those results from increased intraocular pressure. This clinical condition can lead to permanent damage in vision, thus causing blindness by generating progressive and irreversible optic neuropathy if left untreated. There are several reasons of AAC, including several types of local and systemic medications; mainly sympathomimetics, cholinergics, anti-cholinergics, mydriatics, anti-histamines, antiepileptics like topiramate, tricyclic and tetracyclic antidepressants, serotonin reuptake inhibitors, antipsychotics, sulfa-based drugs and anticoagulants. Mirtazapine, a noradrenergic and specific serotonergic antidepressant, is an atypical antidepressant with a complex pharmacological profile. This case report describes a patient with major depressive disorder, who experienced AAC after the first dosage of mirtazapine treatment, and highlights the importance of close monitoring of individuals under antidepressant treatment particularly immediately after initiation of the drug.

**Key words:** Glaucoma, mirtazapine, side-effects

Acute angle closure (AAC) is an ocular emergency with symptoms including blurred vision, eye pain, headache, nausea, vomiting and reddening of the eye that results from increased intraocular pressure (IOP). This clinical condition can lead to permanent damage in vision, thus causing blindness by generating progressive and irreversible optic neuropathy if left untreated. Glaucoma is reported to be responsible of estimated 12% of all global blindness while the incidence of drug-induced AAC glaucoma is unclear.<sup>[1]</sup> AAC usually presents unilaterally. Predisposing factors for the development of AAC are positive family history of angle closure, small eyes, old age, female sex, narrow irido-corneal angle, shallow anterior chamber depth, shorter axial length and increased lens thickness.<sup>[1,2]</sup> There are also several types

of local and systemic medications causing AAC, including mainly sympathomimetics, cholinergics, anti-cholinergics, mydriatics, anti-histamines, antiepileptics like topiramate, antidepressants, antipsychotics, sulfa-based drugs, and anticoagulants.<sup>[2,3]</sup> These agents have the potential to precipitate AAC by their mydriatic effects. As major depressive disorder (MDD) is one of the most common mental disorders, antidepressants are widely prescribed drugs. While psychopharmacological treatments have effects mainly on serotonergic, dopaminergic and noradrenergic systems, many of them have the capability to influence other neurochemical pathways, including cholinergic, adrenergic and histaminergic receptors, that can result in undesired side-effects. Mirtazapine, a noradrenergic and specific serotonergic antidepressant, is an atypical antidepressant with a complex pharmacological profile. It acts as an antagonist on serotonin (5-HT<sub>2a/c</sub>, 5-HT<sub>3</sub>) receptors, norepinephrine ( $\alpha$ <sub>2</sub>) autoreceptor and histamine (H<sub>1</sub>) receptor, as an indirect agonist on 5-HT<sub>1a</sub> receptor and  $\alpha$ <sub>1</sub> adrenoreceptor, and as an inverse agonist on 5-HT<sub>2c</sub> receptor while its weak anti-muscarinic effect also exists.<sup>[4,5]</sup> With this wide range of effect profile in neurotransmission pathways, mirtazapine has a variety of areas in clinical use, such as MDD, anxiety disorders, substance use disorders, sexual dysfunction, sleep disturbances, weight gain, pain symptoms and some gastrointestinal problems either alone or in combination with other drugs.<sup>[6]</sup> The most common adverse effects of this agent are sedation and weight gain by means of 5-HT<sub>3</sub> and H<sub>1</sub> receptor antagonism. Here, we describe a patient with MDD, who experienced AAC after the first dosage of mirtazapine treatment.

### Case Report

A 27-year-old woman referred to the outpatient clinic with depressive symptoms including unhappiness, unwillingness, and sleep problems. She had no history of psychiatric treatment. Montgomery-Asperg depression scale score was 36 in her first visit. She was diagnosed with MDD and escitalopram was started 10 mg/day. During the 3<sup>rd</sup> day of treatment, she reported serious sleep disturbance, and mirtazapine 15 mg/day was initiated as add-on treatment. About 1 h after the first dose of mirtazapine, she reported nausea and severe headache with pain, blurred vision and reddening on the right eye. Her neurological examination was intact, and vital signs were found to be normal while she did not have any chronic diseases or any other medications. The patient also reported no history of glaucoma as well as other ophthalmological diseases or refractive errors, and she had no predisposing factors for angle closure other than being female.

Ophthalmological consultation was planned due to her ophthalmic complaints. In her ophthalmic examination, the best corrected visual acuities were 8/10 and 10/10 while IOP was found to be 26 mmHg and 12 mmHg in the right and left eyes respectively. A slit-lamp examination revealed mild corneal edema and conjunctival injection of the right eye, a shallow anterior chamber while her left eye examination was normal. Her right pupil was mid-dilated and unreactive to light stimulus. Gonioscopy revealed 360° of angle closure on her right eye, consistent with grade 0 in Shaffer classification while it was wide open on the left side. No lens thickening was

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Department of Psychiatry, Cerkezkooy State Hospital, Çerkezköy Devlet Hastanesi, 34000 Istanbul, Departments of <sup>1</sup>Psychiatry and <sup>2</sup>Ophthalmology, Balikesir Military Hospital, Balikesir Asker Hastanesi, 10000 Balikesir, Turkey

**Correspondence to:** Dr. Onur Durmaz, Department of Psychiatry, Balikesir Military Hospital, Balikesir Asker Hastanesi, 10000 Balikesir, Turkey. E-mail: drodurmaz@gmail.com

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observed, and her fundus examination was unremarkable for both eyes. Central corneal thickness (pachymetry) was 474  $\mu$  for the right eye and 470  $\mu$  for the left eye. No lens thickening was observed, and fundus examination was unremarkable for both eyes. Axial length was 23.12 mm for the right eye and 23.14 mm for the left eye. A diagnosis of right AAC was made and 450 ml of intravenous mannitol 20% was administered as indicated by the ophthalmologist in order to reduce IOP. Mirtazapine treatment was stopped, and she was kept in the short stay unit. Her ophthalmic symptoms resolved dramatically after mannitol administration and in her ophthalmic examination including IOP measurement 12 mmHg shown in both eyes and kept normal IOP even 1-day after cessation of mirtazapine. Her fundus examination was normal and corrected visual acuity was 10/10 in both eyes. She was discharged with escitalopram monotherapy. Her ophthalmological examination remained unremarkable at 1-week and 1-month follow-up visits.

## Discussion

AAC is a rare side-effect induced by antidepressants. Antidepressants like tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) can trigger AAC by their anticholinergic potency. Except for their anticholinergic effect, the underlying pathophysiological mechanism of antidepressant-induced AAC remains unclear, it may be due to the direct effect of serotonin on iris or ciliary body. Moreover, the histaminergic mechanism can play a role in developing AAC. Mirtazapine has several different mechanisms from SSRIs and SNRIs including 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptor antagonism, 5-HT<sub>1a</sub> agonism, and  $\alpha$ <sub>2</sub> adrenoceptor blockage effect, whereas it also has an affinity for muscarinic cholinergic receptors. Mirtazapine has no effect on monoamine reuptake and has no significant dopaminergic receptor affinity.<sup>[6]</sup>

But above all, especially multi-serotonergic receptor affinity of mirtazapine seems to play a role in developing AAC. Although the anti-cholinergic effect of drugs contributes to the development of AAC, it was reported that serotonergic activation is associated with mydriasis and thus raising IOP. And it was also documented that serotonergic receptors exist in the human eye.<sup>[7]</sup>

There are some reports of antidepressant-induced AAC cases in the literature. Main antidepressant agents associated with AAC are TCAs including imipramine, amitriptyline, SSRIs including paroxetine, fluoxetine, citalopram, escitalopram and SNRIs including venlafaxine.<sup>[2,3,7,8]</sup> Distinct from these antidepressants, mirtazapine also has significant histaminergic receptor antagonism with mild anticholinergic effects, and it enhances noradrenergic system via autoreceptor blockage.

This may be associated with a sympathomimetic effect on the eye and result in mydriasis. In this case, during treatment of escitalopram, patient had no complaint associated with her eye or vision prior to mirtazapine addition. After the initiation of mirtazapine, she reported sudden ophthalmic symptoms while they ceased spontaneously after cessation of mirtazapine and did not recur. In this case, although escitalopram is an SSRI with potency of inducing angle closure, AAC emerged right after the first dose of mirtazapine add-on treatment, suggesting either this side effect is associated with pathways other than serotonin or mirtazapine potentiated the serotonergic effect of escitalopram.

## Conclusion

To our knowledge, this is the first report of unilateral AAC case following administration of mirtazapine add-on treatment. Although novel antidepressants are considered to have mild anticholinergic effects with safer side-effect profiles, underlying mechanisms of vision and ocular pathology associated with drugs are obscure and clinicians should give careful consideration to initiation of an antidepressant, and follow the particularly predisposed individuals closely in terms of ophthalmic symptoms and complaints.

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