

## Are Medications Triggering Acute Angle Closure?

**H**ow big a role do systemic medications play in tipping a patient's anatomically narrow angles into acute angle-closure (AAC) glaucoma? Various medications are associated with the onset of an AAC crisis. But quantifying the risk of individual drugs remains challenging, even with recent retrospective studies on large, at-risk populations.

### Risks of Systemic Drugs

**Recent study flags problems.** In a study published last year, Na and Park aimed to quantify the risk of various medications by analyzing insurance claims of more than 13,500 Koreans over several years.<sup>1</sup> They identified 61 drugs statistically associated with AAC—out of a total of 949 drugs prescribed—and calculated the odds of developing AAC associated with each medication, expressed as an odds ratio (OR).

The three drugs with the highest ORs were the antimigraine medication sumatriptan, the antiseizure medication topiramate, and the antidepressant duloxetine (ORs, 12.6, 5.1, and 4.04, respectively). The study also identified two drugs not previously on the “risky” list for AAC: lactulose, which is used for constipation (OR, 2.81), and metoclopramide, which is used to treat slow emptying of the stomach (OR, 2.52). For comparison, ORs for other common drugs that can trigger AAC were as follows: naproxen (3.49); the

urinary drug propiverine (3.22); the respiratory drugs aminophylline (2.23) and mequitazine (2.02); alprazolam (1.59); and ibuprofen (1.57).

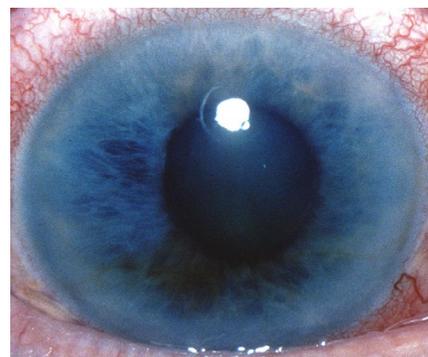
**Nondrug risk factors.** Aside from the question of medications, other risk factors for AAC are generally agreed upon. “For demographic risk factors we have advanced age, female sex, and Asian descent,” said Thasarat S. Vajaranant, MD, MHA, at the University of Illinois, Chicago. “For ocular risk factors, we have narrow angles, shallow anterior chamber, short axial length, hyperopia, and a history of glaucoma, especially prior ACC.”

### Two Proposed Mechanisms

How, then, are demographic and ocular risk factors amplified by certain drugs?

Medications associated with AAC work via two proposed mechanisms. “Either they have pupil dilation effects that trigger pupillary block, or they shift the lens-iris diaphragm forward in the so-called posterior-push mechanism,” said Ken Y. Lin, MD, PhD, at the University of California, Irvine.

**Pupillary dilation and block.** Some drugs dilate the pupil through their anticholinergic effects, and that puts the pupil in a position where it maximally touches the lens, said Anthony Khawaja, MD, at Moorfields Eye Hospital in London. “This results in a buildup of aqueous fluid behind the iris, pushing it forward into acute angle closure.”



**ACUTE CLOSED ANGLE.** Acute angle-closure glaucoma carries a high risk of vision loss, given how quickly and how high IOP can rise.

Examples in this group of medications include tricyclic antidepressants, antispasmodic drugs, and treatments for asthma (ipratropium bromide) and urinary incontinence (oxybutynin), Dr. Khawaja said. He added, “anything that dilates the pupil can tip people into acute angle closure.”

**Idiosyncratic effects.** In addition, some medications have idiosyncratic effects that close the drainage angle in a variety of ways: they push the iris forward into the trabecular meshwork that normally drains the eye,<sup>1</sup> possibly via edema, supraciliary effusions, or rotation of the ciliary body.<sup>2</sup> “These idiosyncratic effects are not yet fully understood,” said Dr. Khawaja. “It’s probably a rare pharmacogenomic effect, where people are genetically predisposed to respond in this way.”

### Association Versus Causation

Long lists of medications have been associated with angle closure, said Dr.

BY REBECCA TAYLOR, CONTRIBUTING WRITER, INTERVIEWING ANTHONY KHAWAJA, MD, KEN Y. LIN, MD, PHD, AND THASARAT S. VAJARANANT, MD, MHA.

Khawaja. The difficulty lies in differentiating “the list of drugs we think definitely do precipitate acute angle closure from those with less convincing evidence, which perhaps we don’t need to worry so much about,” he said.

Not everyone agrees with case-cross-over study designs that mine large datasets. The Na and Park study, for instance, cast a particularly wide net, including a range of diagnostic codes without clear distinctions.<sup>2</sup> High rates of polypharmacy—a patient taking five or more drugs simultaneously—further confounds assigning an objective risk for any one drug.<sup>3</sup>

“I don’t think we can draw firm conclusions from observational association studies; they’re so susceptible to confounding and other biases,” said Dr. Khawaja.

### Medications of Concern

Nonetheless, the experts agreed, there are medications of concern—and they noted that the decision of whether to advise patients against taking a given drug will depend on a risk/benefit analysis for each patient.

**Anticholinergics.** “The drugs we’re primarily concerned about are anticholinergics like tricyclic antidepressants,” said Dr. Khawaja.

“Anticholinergics are classic mydriatics, which can cause pupillary block and result in acute angle closure,” said Dr. Lin. Common examples include drugs for chronic obstructive pulmonary disease, bladder conditions, and Parkinson disease.

**Cholinergics.** Many cholinergics cause miosis and a forward shift of the lens; some also increase aqueous production and increase the blood flow to the ciliary body, said Dr. Lin. Common examples include drugs for dementia, post-op urinary retention, and open-angle glaucoma. Paradoxically, some drugs that decrease the risk of open angle-closure glaucoma appear to increase the risk of AAC.<sup>3</sup>

**Sulfa drugs.** “Sulfa drugs can cause angle closure by causing the ciliary body to rotate forward, so it pushes the lens-iris diaphragm forward,” said Dr. Lin. Common sulfa drugs, such as topiramate, are used for weight loss,

migraine, headache, and seizures, he said.

**Antidepressants.** While the tricyclic antidepressants have long been associated with angle closure, said Dr. Khawaja, “I’m not convinced that SSRIs [selective serotonin reuptake inhibitors] precipitate acute angle closure.” As he pointed out, “Clinicians don’t all agree, but there isn’t a strong body of evidence that these drugs have a profound effect on the pupils. Otherwise, you’d have a lot more people complaining of blurred vision,” given the ubiquitous use of these drugs.

**Anticoagulants.** While anticoagulants have been linked with AAC,<sup>3</sup> it is unclear whether this is a direct or indirect result of their use, said Dr. Lin. “Anticoagulants can cause choroidal hemorrhages, and any significant hemorrhage can lead to forward shifting of several anterior segment structures, which can trigger AAC.”

**OTC cold medications.** “Over-the-counter flu and cold remedies or nasal decongestants contain the alpha-1 agonist, which has mild mydriatic effects,” said Dr. Lin. “In patients with an occludable angle who haven’t had laser peripheral iridotomy, I remind them to stay away from these drugs, along with antihistamines.”

### Is There a Role for LPI?

Dr. Lin recommends laser peripheral iridotomy (LPI) for patients with occludable angles, but he noted that the conversation can be difficult, especially when IOP is still within normal range and vision is good. “For the few patients who refuse LPI, I make sure to advise them to refrain from taking medications known to precipitate AAC,” he said.

Others see the use of LPI changing. “The biggest thing we’ve learned is that the rate of developing acute angle closure after being diagnosed with these narrow drainage angles is smaller than we previously thought,” said Dr. Khawaja. “Most ophthalmologists have offered patients with narrow angles a laser iridotomy even if they didn’t have high intraocular pressure or signs of glaucoma, but the ZAP trial changed our thinking.”

**Impact of findings from ZAP.** The ZAP trial in China focused on patients with anatomically narrow drainage angles but without high IOP or signs of glaucoma.<sup>4</sup> Patients had one eye treated with peripheral laser iridotomy; the other eye was untreated. Patients were evaluated for 72 months for AAC, elevated IOP, or the synechiae that can precede angle closure. Of the 889 treated and 889 untreated eyes, only 19 treated eyes and 36 untreated eyes experienced one of these problems. The researchers concluded that the incidence of developing AAC was actually quite low—too low to warrant prophylactic laser iridotomy.

That study was critical, said Dr. Khawaja, because it confirmed that “the rate of having acute angle closure after being diagnosed with these narrow angles is very low,” with or without laser treatment, he said. “Colleagues around the world are interpreting this study in different ways, but the big thing that’s changed is that a lot more patients aren’t getting laser,” he said.

1 Na KI, Park SP. *JAMA Ophthalmology*. 2022; 140(11):1055-1063.

2 Foster PJ et al. *JAMA Ophthalmology*. 2022; 140(11):1064-1065.

3 Wu A et al. *Eye*. 2020;34(1):12-28.

4 He M et al. *Lancet*. 2019;393(10191):1609-1618.

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*Relevant financial disclosures: None.*

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