A 48-year-old diabetic woman with bipolar disorder presented with rapid onset of blurred vision after starting the antipsychotic drug ziprasidone. On examination, she was found to have advanced cataracts with a prominent posterior subcapsular component. Because her preoperative blood sugar levels had become elevated while on ziprasidone, the patient discontinued the medication before uneventful cataract surgery in the right eye. Postoperatively, the blood sugar level was improved; simultaneously, she noticed an improvement in vision in not only her operated eye but also her unoperated left eye. Examination showed near-complete resolution of the cataract in the left eye. We propose that initiation of therapy with ziprasidone in this patient promoted formation of bilateral cataracts, possibly through its hyperglycemic effect, while its cessation led to cataract regression in the unoperated eye.

CASE REPORT

Rapid formation of cataract after starting ziprasidone with spontaneous regression after therapy was discontinued

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The patient’s initial corrected distance visual acuity was 20/80 in the right eye and 20/60 in the left eye. The slitlamp examination was significant for bilateral 2+ to 3+ nuclear sclerosis combined with dense posterior subcapsular cataracts, which had an asymmetric petaloid pattern (Figures 1 and 2). The patient was scheduled to have cataract extraction, beginning with the right eye. Soon after her initial visit and 2 weeks before her cataract surgery, the patient’s antipsychotic medication was changed from ziprasidone to olanzapine 7.5 mg orally every day to see whether her blood sugar control might improve on a different agent. Thereafter, she took no more ziprasidone. She then had uneventful cataract surgery in the right eye.

At the first postoperative visit, the patient reported noticing improved vision, not only in her operative eye but also in the unoperated left eye. Lenticular nuclear sclerosis in the left eye was less dense than at the preoperative examination. Cataract surgery in the second eye was tentatively postponed because of the improvement in uncorrected distance visual acuity (to 20/40) in the left eye. At the 1-month postoperative visit, the patient’s right eye was healing uneventfully. The left eye now had only mild nuclear sclerosis, with an interval improvement of the posterior subcapsular cataract as well. Another month later, the left eye showed complete resolution of the posterior subcapsular component of the cataract, and only mild residual nuclear sclerosis remained (Figure 3). The patient’s blood sugar level was also improved, with the fasting blood sugar measured at 85 mg/dL shortly after cataract surgery and 81 mg/dL 4 months later. No HbA1c, or cholesterol values were available. The patient’s ocular examination remained stable at subsequent visits.

At the most recent examination 9 months postoperatively, corrected distance visual acuity was 20/25 in the right eye and 20/30−1 in the left eye. The lens in the left eye continued to have only mild...
nuclear sclerosis without evidence of recurrent posterior subcapsular cataract.

DISCUSSION
Commonly known risk factors for cataract development include age, diabetes mellitus, hypertension, ocular trauma, uveitis, smoking, sunlight exposure, corticosteroid use, and phenothiazine antipsychotic drugs.

Approximately a decade after the introduction of chlorpromazine, drug-related cataract development was noted in those receiving high doses of the medication. Later, it was shown that the use of other typical antipsychotics also increased risk for cataracts. Phenothiazines appear to photosensitize tissue proteins where the drug accumulates, such as in the crystalline lens. The proposed mechanism for cataract formation is an interaction between phenothiazines and ultraviolet B light that produces toxic free radicals that ultimately cause lens opacification.

The association, if any, between AAPs and cataracts is less clear; a strong correlation between AAPs and cataracts has not been shown thus far. The newer AAPs might have similar clinical uses; however, they differ chemically from the first-generation phenothiazines, which target dopamine receptors. Although their exact pharmacologic pathways have not been fully elucidated, AAPs appear to have affinity to a broader variety of neurotransmitter and other receptors. There have been infrequent reports of cataracts in AAP users, however, they occur at a significantly lower incidence than in typical antipsychotic users. A recent retrospective case-control study did not find a significant correlation between AAPs, including ziprasidone, and cataracts in schizophrenic patients. A second study focusing on patients with bipolar disorder found significantly reduced odds for AAP users to develop cataracts. Similarly, in a large nested case-control study from British Columbia, patients exposed to AAPs were less likely to progress to cataract surgery than controls. In the two cited papers, AAPs ostensibly exerted a protective effect from cataract progression, something that could be related to their capability to block receptors for serotonin, which has been linked to cataractogenesis. However, El Sanharawi et al. opined in a response to the Canadian study that merely finding a lower cataract surgery rate among AAP users, per se, was insufficient evidence to infer an actual protective mechanism. They also pointed out other potentially confounding factors.

Atypical antipsychotic drugs have been found to alter glucose metabolism, lowering insulin levels while increasing insulin resistance, elevating blood sugar, exacerbating preexisting diabetes, and escalating the risk for type 2 diabetes. Hyperglycemia results in accumulation of cytotoxic advanced glycation end products (AGEs) in the crystalline lens. Tissue proteins such as crystallins undergo nonenzymatic glycosylation in the setting of hyperglycemia. Glycated crystallins become covalently crosslinked, stiffening lens fibers. The chaperone activity of crystallins also diminishes, interfering with their function of preventing cell apoptosis, and allowing high-molecular-weight proteins to aggregate in the lens. AGEs are similarly active in the posterior capsule, leading to apoptosis and fibrosis of lens epithelial cells. The above and other biochemical and cellular developments ultimately result in lens opacification. The rate of crystallin glycation as well as AGE levels are higher in the lenses of diabetics than nondiabetics. One could therefore imagine that diabetic patients on chronic AAP therapy might experience accelerated cataract formation and progression, as persistent hyperglycemia is a
known risk factor for cataract development.\textsuperscript{2,26,28} Although we are not aware of a study specifically comparing the cataract rates of diabetic patients and non-diabetic patients on AAPs, no such difference has been observed thus far. We speculate this reflects general compliance with the requirement for AAP prescribers to monitor for and maintain stable glycemic levels in patients.\textsuperscript{A,B}

In short-term placebo-controlled trials,\textsuperscript{A} Geodon administration was found to be associated with abnormal vision in 6.0\% of bipolar mania patients and in 3.0\% of schizophrenic patients. It was not specified whether the visual alterations in this group might have been due to cataracts in some instances. During clinical trials for ziprasidone, cataract occurrence was observed as an infrequent finding.\textsuperscript{A} The pathophysiologic mechanism behind the cataract formation has not been elucidated, up to now.\textsuperscript{7} Other infrequent adverse side effects were conjunctivitis, dry eye, blepharitis, and photophobia.\textsuperscript{A} Diplopia was a frequent development, while eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis, and nystagmus rarely occurred.\textsuperscript{A}

Ziprasidone was not implicated in epidemiologic studies assessing the association between antipsychotic drugs and glucose metabolism or diabetes\textsuperscript{16}; the exact relationship between hyperglycemic events and ziprasidone is still considered unknown at this time.\textsuperscript{A} Nevertheless, we believe it to be likely that in our patient, chronic ziprasidone therapy had adverse effects on her glucose metabolism, leading to hyperglycemia and cataract development. Discontinuation of ziprasidone coincided with normalization of the patient’s blood sugar levels; regression of cataract in the unoperated eye ensued. The distinctive petaloid morphology of our patient’s posterior subcapsular cataracts is not infrequent among diabetic patients.\textsuperscript{31} Although uncommon, reversal of diabetic cataract, especially of the posterior subcapsular variety, has been described in several case reports in the literature, usually after improved glycemic control.\textsuperscript{2,23} It is not completely clear how regularly the patient’s blood sugar levels were being checked and monitored, as recommended in the drug prescribing information monograph.\textsuperscript{A} Fortunately, our patient was checked shortly after her ziprasidone dosage was increased, leading to the discovery of the severe hyperglycemia.

We cannot rule out additional effects of ziprasidone from mechanisms apart from diabetes that might have contributed to cataract development. Posterior subcapsular cataracts have been observed in patients taking other AAPs, such as clozapine.\textsuperscript{11} There have also been reports linking olanzapine therapy to cataract formation,\textsuperscript{7,18} although cataract is not specifically identified as an adverse side effect in the olanzapine drug monograph.\textsuperscript{A} Regardless, we do not believe that olanzapine was a factor for our patient because her cataracts were already quite advanced before she switched from Geodon. Along the same lines of other medications that could factor into promoting cataract growth, the patient was regularly taking alprazolam, a benzodiazepine. Tranquilizer use was found to be a risk factor for cataracts in a North Carolina study,\textsuperscript{7} with a $\times 2.2$ odds ratio. (Incidentally, it should be kept in mind that the concurrent administration of ziprasidone with benzodiazepines as well as with oxycodone, all of which the patient was concurrently taking, is cautioned against in the ziprasidone drug monograph because of concern about excessive central nervous system depression.\textsuperscript{43}) A patient’s cumulative dose of AAP ingested over a period of time has been postulated to possibly relate to cataract development through unexplained mechanisms.\textsuperscript{11} Over the course of 6 months, our patient would have taken a cumulative dose of over 20 g of ziprasidone. Although not completely comparable, this would be more than the 9.1 g cumulative dose reported to have been taken by a young woman who developed cataracts while on chronic clozapine therapy.\textsuperscript{11}

In conclusion, we suspect that the effects of ziprasidone on the patient’s blood sugar levels played a primary role in the behavior of her cataracts. The patient’s exposures to olanzapine and especially alprazolam might have added to her risk for cataract development. Other factors, such as direct drug toxicity to the lens, cannot be ruled out however and might be uncovered on further investigation.

REFERENCES


OTHER CITED MATERIAL


Disclosures: None of the authors has a financial or proprietary interest in any material or method mentioned.