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

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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.

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CASE REPORT

A 48-year-old diabetic woman with bipolar disorder was evaluated in our university clinic with a chief complaint of “severely blurry vision for the past 3 days, like everything is in a cloud.” She was taking ziprasidone for treatment of bipolar disorder and had been on it for at least 6 months. Recently, her dose had been increased from 60 mg to 80 mg orally twice daily. Her other medical history consisted of diabetes for 9 years, hyperlipidemia, obesity, hypertension, Hashimoto thyroiditis, asthma, and smoking. Additional chronic medications at the time of her first visit included alprazolam, atenolol, gabapentin, canagliflozin, levothyroxine, lisinopril, oxycodone–acetaminophen, insulin, and liraglutide. The patient’s glucose was uncontrolled, with recent finger sticks over 500 mg/dL and hemoglobin A1c (HbA1c) of 15%. Her weight of 112 kg was high for her height of 165 cm (5’5”) but had not increased in the past several years.

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+–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....

Ziprasidone (Geodon) is an atypical antipsychotic (AAP) drug that can be administered orally as well as intramuscularly for the treatment of psychiatric conditions such as bipolar disorder.\(^\text{4}\) Cataract development is listed as an infrequent adverse reaction to ziprasidone.\(^\text{5}\) Further details about this particular side effect have not been specified.

In this report, we present the case of a patient who developed bilateral cataracts after being placed on oral ziprasidone. We describe, for the first time to our knowledge, the specific clinical appearance of the ziprasidone-related cataracts as well as the patient’s clinical course. We postulate the possible mechanism of pathogenesis.
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 nondiabetic 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{33} 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{22,23} 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{4,6}) 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

1. Mitchell P, Hayes P, Wang J. Visual impairment in nursing home residents: the Blue Mountains Eye Study. Med J Aust 1997; 166:73–76
2. Rowe NG, Mitchell PG, Cumming RG, Wans JJ. Diabetes, fasting blood glucose and age-related cataract: the Blue Mountains Eye Study, Ophthalmic Epidemiol 2000; 7:103–1144
3. Richter GM, Torres M, Choudhury F, Azen SP, Varma R, for the Los Angeles Latino Eye Study Group. Risk factors for cortical, nuclear, posterior subcapsular, and mixed lens opacities: the Los Angeles Latino Eye Study. Ophthalmology 2012; 119:547–554
4. Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P, Murray P. Degree, duration, and causes of visual loss in uveitis. Br J Ophthalmol 2004; 88:1159–1162
5. Christen WG, Manson JE, Seddon JM, Glynn RJ, Buring JE, Rosner B, Hennekens CH. A prospective study of cigarette smoking and risk of cataract in men. JAMA 1992; 268:989–993
6. Zigman S, Datiles M, Toczyckski E. Sunlight and human cataracts. Invest Ophthalmol Vis Sci 1979; 18:462–467
7. Novais e Souza VB, Rodrigues de Moura Filho FJ, Gomes de Matos e Souza F, Rocha CF, Mendes Lopes Furtado FA, Gonçalves TBA, Vasconcelos KFX. Cataract occurrence in patients treated with antipsychotic drugs. Braz J Psychiatry 2008; 30:222–226
8. Collman GW, Shore DL, Shy CM, Checkoway H, Luria AS. Sunlight and other risk factors for cataracts: an epidemiologic study. Am J Public Health 1988; 78:1459–1462
9. Ernst P, Baltzan M, Deschênes J, Suissa S. Low-dose inhaled and nasal corticosteroid use and the risk of cataracts. Eur Respir J 2006; 27:1168–1174
10. Garner LL, Wang RI, Hieb E. Eye changes following phosphoinositide administration, Wos Med J 1974; 73:5119–5121
11. Alam MS, Praveen Kumar KV. Clozapine-induced cataract in a young female. J Pharmacol Pharmacother 2016; 7:184–186
12. Siddall JR. The ocular toxic findings with prolonged and high dosage chlorpromazine intake. Arch Ophthalmol 1965; 74:460–464
13. Satanove A. Pigmentation due to phenothiazines in high and prolonged dosages. JAMA 1965; 191:263–268
14. Delouise VP, Flynn JT. Asymmetric anterior segment changes induced by chlorpromazine. Ann Ophthalmol 1981; 13:953–955
15. Forrest IS, Forrest FM, Berger M. Free radicals as metabolites of drugs derived from phenothiazine. Biochem Biophys Acts 1968; 29:441–442
16. Kowalchuk C, Castellani LN, Chintoh A, Remington G, Giacca A, Hahn MK. Antipsychotics and glucose metabolism: how brain and body collide. Am J Physiol Endocrinol Metab 2019; 316:E1–E15
17. Horacek J, Bubenikova-Valesova V, Kopecek M, Palenicek T, Dockery C, Zigman S, Datiles M, Torczynski E. Sunlight and human cataracts. Invest Ophthalmol Vis Sci 1979; 18:462–467
18. Lim CZ, Sonny Teo KS, Tai E. Olanzapine-induced cataract in a teenage girl. Cureus 2018; 10:e2553
19. Chou P-H, Chu C-S, Lin C-H, Cheng C, Chen Y-H, Lan T-H, Huang M-W. Use of atypical antipsychotics and risks of cataract development in patients with schizophrenia: a population-based, nested case-control study. Schizophr Res 2016; 174:137–143
20. Chu C-S, Chou P-H, Chen Y-H, Huang, Hsu M-Y, Lan T-H, Lin C-H. Association between antipsychotic drug use and cataracts in patients with bipolar disorder: A population-based, nested case-control study. J Affect Disord 2017; 209:86–92
21. Pakzad-Vaezi KL, Etminan M, Mikelberg FS. The association between cataract surgery and atypical antipsychotic use: a nested case-control study. Am J Ophthalmol 2013; 156:1141–1146
22. El Sanharawi M, Basli E, Sandali O, Larocbe L. The association between cataract surgery and atypical antipsychotic use: a nested case-control study (letter). Am J Ophthalmol 2014; 157:746; reply by KL Pakzad-Vaezi, M Etminan, FS Mikelberg, 747
23. Bejarano E, Taylor A. Too sweet: problems of protein glycation in the eye. Exp Eye Res 2019; 178:255–262
24. Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998; 44:778–783
25. Lindenmayer J-P, Nathan A-M, Smith RC. Hyperglycemia associated with the use of atypical antipsychotics. J Clin Psychiatry 2001; 62 (suppl 23):30–38
26. Hashim Z, Zarina S. Advanced glycation end products in diabetic and non-diabetic human subjects suffering from cataract. Age 2011; 33:377–384
27. Kim J, Kim OS, Kim C-S, Sohn E, Jo K, Kim JS. Accumulation of argpyrimidine, a methylglyoxal-derived advanced glycation end product, increases apoptosis of lens epithelial cells both in vitro and in vivo. Exp Mol Med 2012; 44:167–175
28. Perry RE, Swamy MS, Abraham EC. Progressive changes in lens crystallin glycation and high-molecular-weight aggregate formation leading to cataract development in streptozotocin-diabetic rats. Exp Eye Res 1987; 44:269–282
29. Reddy VS, Reddy GB. Role of crystallins in diabetic complications. Biochim Biophys Acta 2016; 1860:269–277
30. Raghavan CT, Smuda M, Smith AJ, Howell S, Smith DG, Singh A, Gupta P, Giomb MA, Wormstone IM, Nagaraj RH. AGEs in human lens capsule promote the TGF-β-mediated EMT of lens epithelial cells: implications for age-associated fibrosis. Aging Cell 2016; 15:465–476
31. Vasavada AR, Mamidipudi PR, Sharma PS. Morphology of and visual performance with posterior subcapsular cataract. J Cataract Refract Surg 2004; 30:2097–2104
32. Sharma P, Vasavada AR. Acute transient bilateral diabetic posterior subcapsular cataracts. J Cataract Refract Surg 2001; 27:789–794
33. Epstein DL. Reversible unilateral lens opacities in a diabetic patient. Arch Ophthalmol 1976; 94:461–463

OTHER CITED MATERIAL
A. Geodon (ziprasidone hydrochloride) capsules. Full Prescribing Information. New York, NY, Pfizer, Inc, 2015; Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=Z584. Accessed May 10, 2019
B. Zyprexa/C210 (olanzapine) tablets [product monograph]. Toronto, Ontario, Canada, Eli Lilly Canada, Inc, 2018; Available at: http://pi.lilly.com/ca/zyprexa-ca-prm.pdf. Accessed May 10, 2019

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