

Chlorpromazine-Induced Skin Pigmentation With Corneal and Lens Opacities

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Practice Points

- Medications should be suspected in patients with blue-gray oculocutaneous dyspigmentation.
- Management with immediate cessation of suspected medications and strict sun avoidance is recommended.
- Improvement is possible but is gradual and unpredictable.

Chlorpromazine is known to cause abnormal oculocutaneous pigmentation in sun-exposed areas. We present the case of a psychiatric patient who developed blue-gray pigmentation of the skin as well as corneal and lens opacities following 7 years of chlorpromazine treatment. Ten months after discontinuation of chlorpromazine, the skin discoloration and anterior lens deposits showed partial improvement, but the corneal deposits remained unchanged. A review of the literature on the reversibility of chlorpromazine-induced abnormal oculocutaneous pigmentation also is provided.

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Chlorpromazine can cause abnormal blue-gray skin pigmentation in sun-exposed areas such as the face. Abnormal skin pigmentation is seen in 1% to 2.9% of psychiatric patients who are hospitalized long-term.¹ Additionally, corneal and lenticular pigmentary changes also have been

associated with chlorpromazine use at a prevalence of 15% to 74% in patients using chlorpromazine.²

There are several biochemical mechanisms by which chlorpromazine is theorized to cause abnormal pigmentation. It has been suggested that chlorpromazine forms photoadducts with DNA and photosensitizes DNA strand breaks, which could be responsible for associated cutaneous and ocular phototoxicity.³ Furthermore, liposomal lipids are peroxidized in the presence of chlorpromazine and UVA irradiation, and it is suggested that reactive oxygen species might play an important role in the development of abnormal pigmentation.⁴ A metabolite of chlorpromazine, 7-hydroxychlorpromazine, also may be responsible, as it becomes purple after exposure to sunlight and is oxidized by melanoproteins to produce a melaninlike substance.^{5,6} We present the case of a young woman with chlorpromazine-induced blue-gray oculocutaneous dyspigmentation along with a review of the literature summarizing management and prognosis.

Case Report

A 23-year-old white woman presented with blue-gray discoloration of the skin. Her medical history was remarkable for schizoaffective disorder and hypothyroidism. She had been hospitalized long-term for mental illness, treated with a variety of antipsychotics and maintained on oral chlorpromazine for the last 7 years. In addition to chlorpromazine, the patient's current medications at the time of presentation included benztropine, desmopressin,

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divalproex sodium, docusate sodium, famotidine, gabapentin, levothyroxine, omega-3 fatty acid, and polyethylene glycol 3350.

Initially, the dose of chlorpromazine was less than 300 mg daily. The dose was increased after 3 years, ranging from 600 to 800 mg daily. After 4.5 years of regular chlorpromazine therapy, the patient developed photosensitivity. At first her skin appeared flushed following sun exposure despite sunscreen use. Over time she appeared flushed more frequently and developed a marked orange hue in sun-exposed areas that gradually progressed into a sustained orange hue. Eventually, darker pigmentation was noted with colors described as brick red, bronze, gray, or bluish at times (Figure 1). Approximately 6.5 years after starting regular treatment with chlorpromazine, blue-gray discoloration of the face was noted, and she reported decreased visual acuity. Other skin sites, including the vaginal and oral mucous membranes, were unaffected. The patient had a visual acuity of 20/80 OU and an ophthalmic examination revealed moderate stromal opacities with mild anterior lens deposits. A complete panel of laboratory tests was normal and ruled out other systemic causes of skin pigmentation including Wilson disease, Addison disease, and hemochromatosis.

Chlorpromazine discontinuation and aggressive sun protection was recommended. Ten months after discontinuation of chlorpromazine and rigorous sun protection, near-complete resolution of the marked

orange hue was achieved, but only minimal improvement in the blue-gray pigmentation was observed (Figure 2). Mild improvement was noted in the anterior lens deposits, and visual acuity improved to 20/50 OU. Corneal deposits remained unchanged. The corneal and lens opacities are shown in Figures 3A and 3B, respectively. There were no retinal changes (Figure 4).



Figure 1. Hyperpigmentation and photosensitivity while on chlorpromazine therapy.



Figure 2. Persistent blue-gray hyperpigmentation 8 months (A) and 10 months (B) after discontinuation of chlorpromazine.

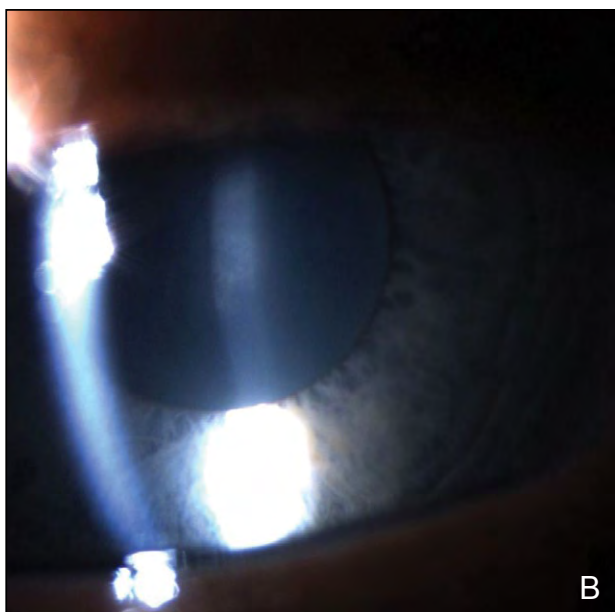
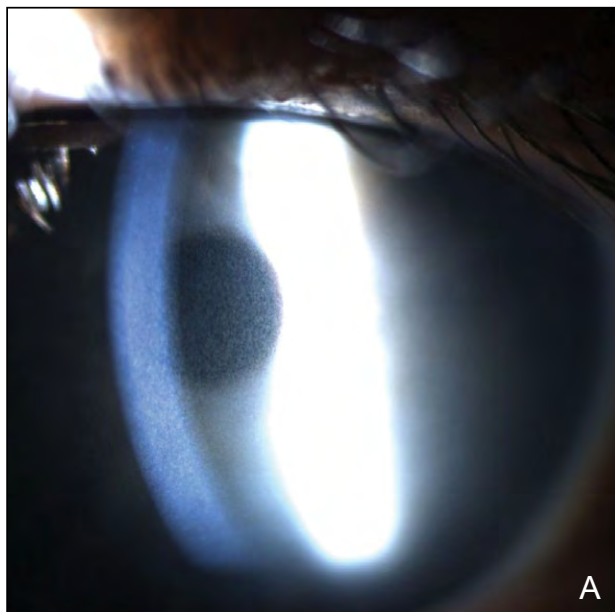


Figure 3. Cornea (A) and lens (B) of the right eye with opacities 10 months after discontinuation of chlorpromazine.

Comment

Chlorpromazine-induced skin pigmentation is well documented in the literature. Of the various antipsychotics, studies suggest that abnormal skin pigmentation is predominantly or exclusively a side effect of chlorpromazine.⁷⁻¹¹ Originally thought to be irreversible, newer data have demonstrated that skin pigmentation begins to resolve after chlorpromazine is discontinued, sometimes up to 5 years later. In one study, 93% (14/15) of patients with abnormal



Figure 4. Retina of the right eye with decreased clarity 10 months after discontinuation of chlorpromazine due to the corneal and lens opacities, corresponding to a decrease in visual acuity.

skin pigmentation, presumably from treatment with chlorpromazine, showed complete resolution of skin pigmentation within 6 months to 5 years after discontinuing chlorpromazine.⁷ In 3 other case reports, chlorpromazine-induced skin pigmentation resolved 17 months to 4 years after discontinuing chlorpromazine.¹²⁻¹⁴ In contrast to cutaneous pigmentation, ocular changes can be persistent. In a study by Lal et al,⁷ endothelial corneal deposits completely resolved in 2 of 8 (25%) patients and improved in an additional 2 (25%) patients after 7 to 13 years. However, lenticular pigmentary deposits remained in all 8 patients, with only 1 (12.5%) showing any improvement.⁷

The mechanism of action may be different for chlorpromazine-induced cutaneous pigmentation versus ocular pigmentation. Animal studies showed that rabbits developed only cutaneous changes and guinea pigs developed only ocular changes when treated with chlorpromazine. Neither animal developed both cutaneous and ocular changes, as seen in humans.⁵ Furthermore, other antipsychotics have been implicated in causing ocular pigmentation, including levomepromazine, fluphenazine, and trifluoperazine.^{5,15-18} These data, in addition to the fact that cutaneous pigmentation resolves and ocular changes appear more persistent, suggest 2 different mechanisms of tissue discoloration.¹⁹⁻²¹

There is no specific treatment of chlorpromazine-induced cutaneous pigmentation. Current recommendations include discontinuing the medication and rigorous sun protection.²² No chelating agent has been reported as effective.²³ Other antipsychotics such as haloperidol, loxapine, flupenthixol, or clozapine are thought to be safe alternatives and do not interfere with the resolution of the discoloration.^{7,12-14,23}

Chlorpromazine is an important cause of skin dyspigmentation and ocular deposits in psychiatric patients. It is important to discontinue treatment as soon as pigmentary changes are noted. Although there are no studies on the efficacy of sun protection in these cases, this practice currently is recommended. The existing literature suggests that lenticular deposits are less likely to resolve versus corneal deposits.⁷ Substitution of other antipsychotics, even other phenothiazines, should be safe without worsening or preventing resolution of abnormal pigmentation.^{7,12-14,23}

Conclusion

The blue-gray pigmentation of our patient's sun-exposed skin likely was from long-term chlorpromazine use. Discontinuation of the drug and aggressive sun protection resulted in partial improvement after 10 months. Long-term follow-up will be necessary for complete resolution of skin discoloration. In contrast to the literature, which suggests corneal deposits abate more readily than lens deposits,⁷ our patient showed mild improvement in the lens deposits but no change in the corneal deposits. She continues to be followed closely by dermatology, ophthalmology, and psychiatry. Her psychiatric condition is stable after chlorpromazine was substituted with clozapine, paliperidone, and aripiprazole.

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