# Methoxsalen-induced macular toxicity

*Aditya Maitray, Pukhraj Rishi*

Psoralen compounds such as methoxsalen are photosensitizer agents used in conjunction with ultraviolet A (UVA) radiation exposure as photochemotherapy (Psoralens and ultraviolet-A therapy [PUVA therapy]) for certain epidermal skin disorders such as psoriasis and vitiligo. Methoxsalen has been shown to be associated with premature cataract formation by forming adducts with lens proteins following oral administration and subsequent UVA exposure. Hence, the use of UV-filtering glasses is recommended during PUVA therapy sessions. Ocular tissues can be exposed to its photosensitizing effect with subsequent UV radiation exposure through sunlight if the patient was to be without protective eye glasses, potentially causing macular toxicity. Till date, there have been no reports in the literature of any posterior segment ocular toxicity arising from methoxsalen use. Here, we describe a case of a bilateral macular toxicity in a middle-aged male treated with methoxsalen for vitiligo.

**Key words:** 8-methoxypsoralen, macular toxicity, methoxsalen, psoralens and ultraviolet-A exposure

Methoxsalen or 8-methoxypsoralen (8-MOP) is a photosensitizer agent which is used in photochemotherapy in conjunction with exposing the affected skin to ultraviolet A (UVA) (320–400 nm) radiation (PUVA therapy) through lamps or sunlight for the treatment of certain epidermal proliferative disorders such as psoriasis, eczema, and vitiligo.[1,2] It intercalates into the DNA double helix and upon excitation by UVA, forms adducts with the DNA, thereby inducing the therapeutic and also the potential side effects.[3] It helps in the treatment of psoriasis by reducing the proliferation of skin cells and in vitiligo by increasing the number of melanocytes.[3,4] Methoxsalen has been shown to be present in the crystalline lens after oral administration and may form adducts with lens proteins on subsequent UVA exposure, leading to premature cataract formation. Hence, the use of UV-filtering glasses is recommended during PUVA therapy sessions.[4] Methoxsalen is metabolized by the liver and can be detected in plasma for 12–24 h before excretion in urine.[5] Thus, ocular tissues can be exposed to its photosensitizing effect with subsequent UV radiation exposure through sunlight if the patient was to be without protective eye glasses, potentially causing macular toxicity.

Till date, there have been no reports of any ocular toxicity of the posterior segment arising from methoxsalen use (PubMed search). Here, we describe a case of a bilateral macular toxicity in a middle-aged male treated with methoxsalen for vitiligo.

## Case Report

A 49-year-old Asian male presented with painless, progressive decrease in vision, and metamorphopsia in both eyes for a 3-year duration. He had no associated history of steroid intake, nyctalopia, or trauma. He had no significant family history. However, he had been using oral methoxsalen (8-MOP) 10–30 mg/day for vitiligo for the past 15 years without dermatologist supervision and without concomitant use of UV protective spectacles while on treatment. He was not being treated for any other conditions. He had been diagnosed elsewhere with choroidal neovascular membrane associated with age-related macular degeneration in both eyes and advised anti-vascular endothelial growth factor injections.

On general examination, he had depigmented patches over his ankles and forearms suggestive of vitiligo [Fig. 1a]. On ocular examination, his best-corrected visual acuity (BCVA) was 6/6 in both eyes, and his color vision was normal. Anterior segment examination was essentially normal. Fundus examination revealed yellowish-white deposits at the macula with a dull foveal reflex in both eyes [Fig. 1b and c]. Spectral-domain optical coherence tomography (SD-OCT) showed sub-retinal pigment epithelium (RPE) deposits with RPE elevation and thickening at the macula in both eyes [Fig. 1d]. At this stage, a diagnosis of MOP toxicity was entertained, keeping adult-onset foveomacular vitelliform dystrophy (AOFVD) as a close possible differential diagnosis. A standard full-field electroretinogram (ff-ERG), performed as per the International Society for Clinical Electrophysiology of Vision protocol, showed normal photopic and scotopic responses [Fig. 1e]. Multifocal electroretinogram (mf-ERG) revealed normal foveal, parafoveal, and perifoveal ring responses for both eyes [Fig. 1f]. Electrooculogram (EOG) showed normal response [Fig. 1g] with Arden ratio of 4.7 and 3.4 in the right and left eye, respectively. The patient was counseled, reassured, and asked to review annually. One year later, he presented with slight decrease in vision with BCVA of 6/9, N8 in both eyes, and clinically unaltered fundus findings [Fig. 2a and b]. Repeat SD-OCT showed similar findings [Fig. 2c]. Repeat mf-ERG revealed mild blunting of foveal peak in the right eye [Fig. 2d]. Fundus autofluorescence revealed hyperautofluorescence corresponding to the lesions in both eyes [Fig. 2e]. EOG was normal for both eyes with Arden ratio of 3.4 [Fig. 2f].

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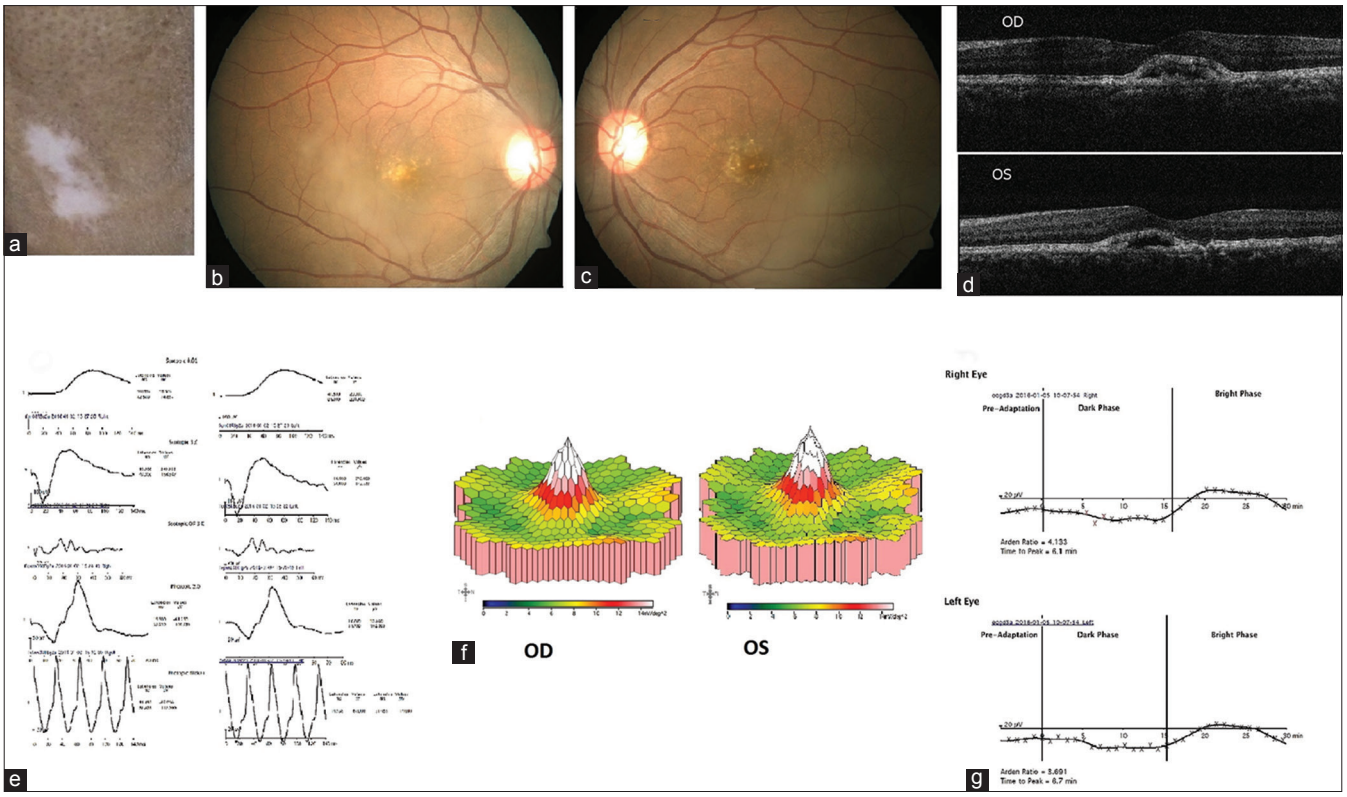


**Figure 1:** (At first presentation): External photograph shows vitiligo patch (a) over the right ankle. Color fundus photograph of the right (b) and left (c) eye, respectively, showing yellowish deposits at the macula with dull foveal reflex. Spectral-domain optical coherence tomography shows sub-retinal pigment epithelium deposits with retinal pigment epithelium elevation and thickening (d) at the macula in both eyes. Full-field electroretinogram of both eyes showing normal photopic and scotopic responses (e). Multifocal-electroretinogram shows normal foveal, parafoveal, and perifoveal responses in both eyes (f). Normal electrooculogram of both eyes (g)

A diagnosis of methoxsalen-associated macular toxicity was arrived at, and the patient was advised to discontinue the drug and continue regular follow-up.

## Discussion

A variety of systemic medications are known to cause retinal toxicity. In most instances, the resulting visual dysfunction is reversible on discontinuation of the drug, especially if recognized at an early stage. However, in some cases, delayed recognition can lead to progressive and/or irreversible retinal dysfunction causing advanced visual impairment.[6] Medications commonly known to produce retinal toxicity include chloroquine and hydroxychloroquine, vigabatrin, deferoxamine, ethambutol, interferon-α, tamoxifen, digoxin, sildenafil, canthaxanthin, aminoglycosides, and amiodarone.[6,7]

PUVA therapy involves administering of oral 8-MOP in dose of 0.3–0.6 mg/kg followed 1–2 h later by UVA exposure (starting at 0.5 J/cm$^2$) when the drug generally attains peak plasma levels.[2] Patients generally require several weekly sessions for a long time for improvement of their cutaneous disease.[5] Significant levels of methoxsalen have been demonstrated in aqueous humor, crystalline lens, vitreous, and retinal tissue in guinea pigs 3 h following oral administration.[8] Hence, ocular protection from UVA in using protective eye glasses is recommended during and up to 18 h following PUVA therapy sessions.

Literature is scarce about adverse effects of oral 8-MOP and UVA exposure (PUVA) on macular function. In 1986, Cox *et al*. reported a series of 46 patients on PUVA therapy with normal ophthalmologic assessment.[4] More recently, Shoeibi *et al*. studied the effect of PUVA on the retina in 40 eyes with ERG at baseline and at 6-month follow-up. They found no significant difference in photopic or scotopic responses.[9] In their study, the patients were instructed to wear UV protective eyeglasses for up to 18 h after each PUVA session.

However, our patient was using oral methoxsalen 10–30 mg daily for 15 years in an unsupervised manner, without using protective eyewear. Although he did not have UVA sessions, he did have a history of abundant sunlight exposure. Hence, even though his ff-ERG was apparently normal, the reduced foveal response on mf-ERG and a documented reduction in visual acuity pointed toward macular toxicity. Since 8-MOP acts by stimulating melanocyte proliferation (basis of its therapeutic use in vitiligo), it is possible that it may induce changes in the metabolically active RPE at the macula, subsequently leading to the clinical picture as seen in our case. AOFVD is a close differential diagnosis in this case. AOFVD typically has late onset (4–6$^{th}$ decade), typically showing bilateral but asymmetric yellowish elevated subretinal lesions in the foveal or perifoveal region, often with central pigmentation. Patients with AOFVD are usually asymptomatic or have mild blurring of vision, mild metamorphopsia, and/or small central or paracentral scotomas. Genetic testing to rule out BEST1 or PRPH 2/RDS gene mutation could further help in identifying the condition.[10]

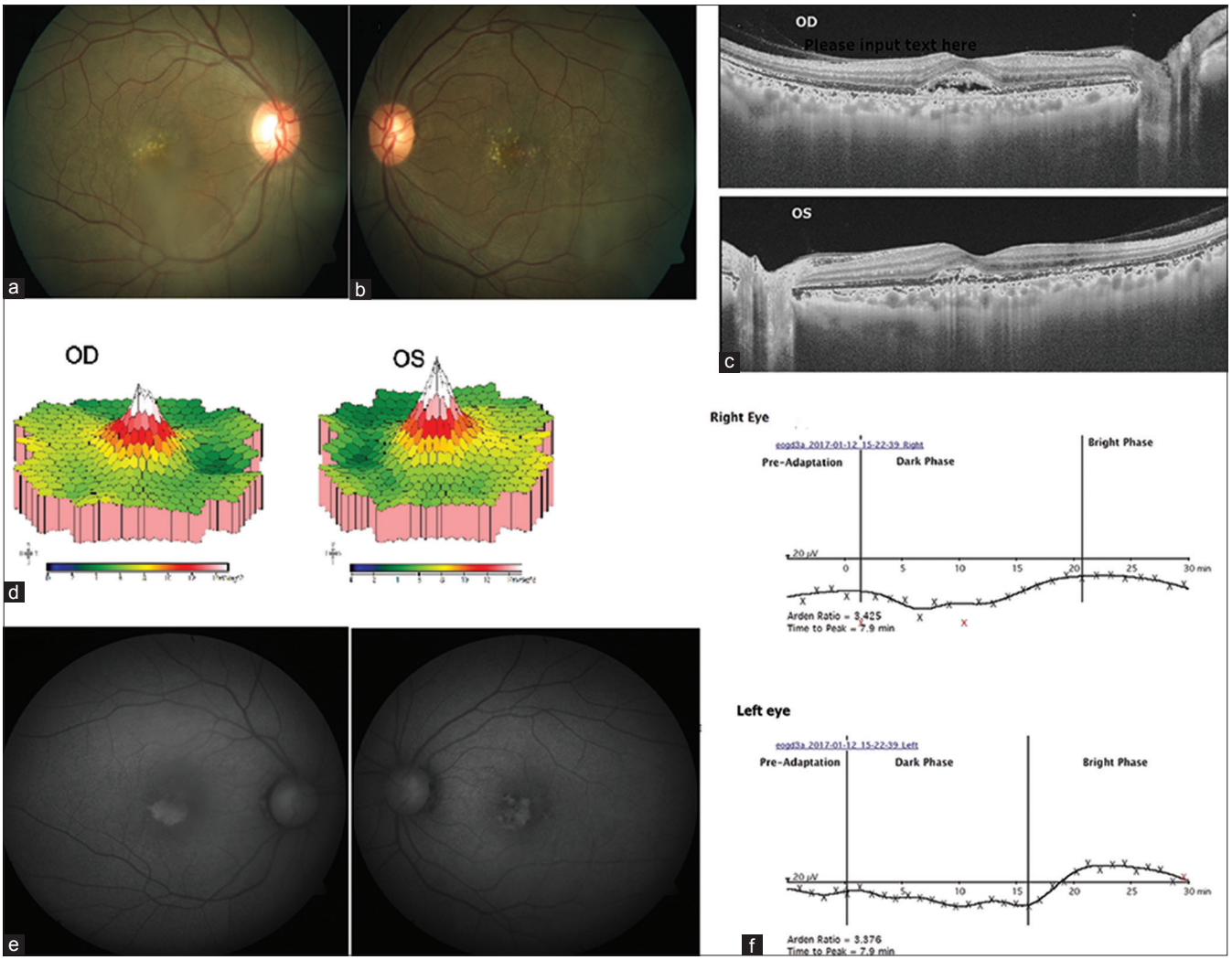


**Figure 2:** (At 1-year follow-up): Color fundus photograph of the right (a) and left (b) eye, respectively, appears unaltered compared to previous visit. Spectral-domain optical coherence tomography shows sub-retinal pigment epithelium deposits (c) and retinal pigment epithelium elevation and thickening at the macula (OD > OS). Multifocal-electroretinogram shows blunted foveal peak in the right eye (d). Fundus autofluorescence image (e) shows hyperautofluorescence at the macula in both eyes corresponding to the clinically visible lesions. Electrooculogram is normal in both eyes (f)

## Conclusion

Methoxsalen can cause bilateral macular toxicity. Further studies on potential long-term effects of psoralen therapy on macular function are required to understand this better.

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### Conflicts of interest

There are no conflicts of interest.

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