

# *Re: Review - Proctor JG. Pentosan polysulfate and a pigmentary maculopathy: causation versus correlation?*

Jenelle Foote, MD,<sup>1</sup> Sakshi Shiromani, MD,<sup>2</sup> Nieraj Jain, MD<sup>2</sup>

<sup>1</sup>Midtown Urology, Atlanta, Georgia, USA

<sup>2</sup>Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia, USA

Referring to article published in *Can J Urol* 2023;30(6):11732-11739.

---

FOOTE J, SHIROMANI S, JAIN N. Re: Review - Proctor JG. Pentosan polysulfate and a pigmentary maculopathy: causation versus correlation? *Can J Urol* 2024;31(3):11867-11868.

Dear Editor,

We read with interest the paper by Dr. Proctor in the December issue regarding pentosan polysulfate maculopathy.<sup>1</sup> Dr. Proctor poses a fair question: Does pentosan polysulfate cause this distinctive vision-threatening macular disease, or is this a non-causal association? This is an important question we have considered since we described the condition in 2018.<sup>2</sup> Although for years we have refrained from describing this as a toxicity, we now believe that the totality of the evidence does support a causal link. Since the author has used the Bradford Hill criteria to frame his discussion, we will do so as well to briefly outline our rationale.

Many studies (> 40) by many authors across varied populations have demonstrated an association between PPS use and a distinctive macular disease.<sup>3-6</sup> Numerous studies have demonstrated temporality as well as a dose-response relationship; the maculopathy is noted after starting PPS, and the risk of maculopathy increases with cumulative exposure to PPS. Further, the retinal findings are highly specific.<sup>7,8</sup> The differential diagnosis for this unique phenotype typically includes inherited macular diseases, which

have a prevalence of less than 1 in 1000. We were therefore startled to observe 6 cases of this unique condition among 38 PPS users in our initial study.<sup>2</sup> Finally, new experimental data corroborates a causal relationship - we have recently reported our findings in an animal model demonstrating that PPS exposure leads to deleterious impacts on visual function and retinal structure in mice.<sup>9</sup>

Dr. Proctor theorizes that there may be an indication bias, and that the underlying disease of interstitial cystitis (IC) may be related to the maculopathy through shared pathologic mechanisms. However, there is no empiric evidence to support this. To the contrary, our retrospective study demonstrated that among 219 patients with IC, there were 0 cases of this maculopathy among 139 PPS non-users, and 14 cases among the 80 PPS users.<sup>10</sup> If we broaden our perspective, we can use Dr. Proctor's estimate of there being as many as 10 million individuals in the U.S. living with IC.<sup>1</sup> Administrative claims data suggests a much smaller number of PPS users (in the hundreds of thousands).<sup>3</sup> If the maculopathy were due to IC itself, we would expect to see many cases among PPS non-users; we have yet to see one. Finally, an anecdote: there are several urogynecology specialists in our region who are known for their expertise in IC. One of us (J.E.F.) is an FPMRS-certified urologist who has treated hundreds of IC patients over 30+ years but rarely uses PPS. Although we have seen many cases of PPS maculopathy in recent years, we have yet to see one from this practice.

PPS maculopathy is a visually disabling condition for many affected patients. We believe it is preventable. Prescribers of PPS should be aware of this important safety concern when treating patients with IC. We

---

Address correspondence to Dr. Nieraj Jain, Department of Ophthalmology, Emory University School of Medicine, 100 Woodruff Circle, Atlanta, GA 30322 USA

generally agree with the guidance in the commentary by Drs. Evans and Xu,<sup>11</sup> and prescribers can refer to our prior work for guidelines regarding vision screening.<sup>12</sup> In brief, we favor annual retinal screening among PPS users, ideally with a retina specialist who would have access to the recommended diagnostic testing.

Lastly, we want to alert the readers to new data from our group linking PPS use to a new-onset colopathy, diagnosed as inflammatory bowel disease in many of our patients.<sup>13</sup> In some cases, affected patients underwent colectomy to address severe disease with colonic dysplasia. Patients typically described an improvement in lower GI symptoms after stopping PPS. Further work is required to explore a potential causal relationship between PPS use and this colonic disease.

## Disclosures

Funding/Support: Foundation Fighting Blindness Career Development Award CD-C-0918-0748-EEC (NJ); Research to Prevent Blindness Challenge Grant; National Eye Institute P30EY00630; Sitaraman Family. □

10. Hanif AM, Shah R, Yan J et al. Strength of association between pentosan polysulfate and a novel maculopathy. *Ophthalmology* 2019;126(10):1464-1466.
11. Evans RJ, Xu R. Re: Pentosan polysulfate and a pigmentary maculopathy: causation versus correlation? *Can J Urol* 2023; 30(6):11740.
12. Jain N, Liao A, Garg SJ et al. Expanded clinical spectrum of pentosan polysulfate maculopathy: a Macula Society collaborative study. *Ophthalmol Retina* 2022;6(3):219-227.
13. Jung EH, Zheng W, Weiss RJ et al. Colopathy associated with pentosan polysulfate use [Internet]. Available from: <https://www.medrxiv.org/content/10.1101/2023.04.03.23288071v1>

---

## References

1. Proctor JG. Pentosan polysulfate and a pigmentary maculopathy: causation versus correlation? *Can J Urol* 2023;30(6):11732-11739.
2. Pearce WA, Chen R, Jain N. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. *Ophthalmology* 2018;125(11):1793-1802.
3. Jain N, Li AL, Yu Y, VanderBeek BL. Association of macular disease with long-term use of pentosan polysulfate sodium: findings from a US cohort. *Br J Ophthalmol* 2020;104(8):1093-1097.
4. Wang D, Au A, Gunnemann F et al. Pentosan-associated maculopathy: prevalence, screening guidelines, and spectrum of findings based on prospective multimodal analysis. *Can J Ophthalmol* 2020;55(2):116-125.
5. Vora RA, Patel AP, Melles R. Prevalence of maculopathy associated with long-term pentosan polysulfate therapy. *Ophthalmology* 2020;127(6):835-836.
6. Bae SS, Sodhi M, Maberley D, Kezouh A, Etminan M. Risk of maculopathy with pentosan polysulfate sodium use. *Br J Clin Pharmacol* 2022;88(7):3428-3433.
7. Barnes AC, Hanif AM, Jain N. Pentosan polysulfate maculopathy versus inherited macular dystrophies: comparative assessment with multimodal imaging. *Ophthalmol Retina* 2020;4(12):1196-1201.
8. Christiansen JS, Barnes AC, Berry DE, Jain N. Pentosan polysulfate maculopathy versus age-related macular degeneration: comparative assessment with multimodal imaging. *Can J Ophthalmol* 2022;57(1):16-22.
9. Girardot PE, Zhang X, Zhang N et al. Pentosan polysulfate sodium causes diminished function and subtle morphological changes in retina and RPE of mice. *Invest Ophthalmol Vis Sci* 2024;65(2):28.