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Original Article

Characterization of pentosan polysulfate patients for development of an alert and screening system for ophthalmic monitoring

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Objective: Pentosan polysulfate (PPS; ELMIRON, Janssen Pharmaceuticals, Titusville, NJ) is a U.S. Food and Drug Administration–approved oral medication for interstitial cystitis. Numerous reports have been published detailing retinal toxicity with the use of PPS. Studies characterizing this condition are primarily retrospective, and consequently, alert and screening systems need to be developed to actively screen for this disease. The goal of this study was to characterize ophthalmic monitoring trends of a PPS-using patient sample to construct an alert and screening system for monitoring this condition.

Methods: A single-institution retrospective chart review was conducted between January 2005 and November 2020 to characterize PPS use. An electronic medical record (EMR) alert was constructed to trigger based on new PPS prescriptions and renewals offering ophthalmology referral.

Results: A total of 1407 PPS users over 15 years was available for characterization, with 1220 (86.7%) being female, the average duration of exposure being 71.2 ± 62.6 months, and the average medication cumulative exposure being 669.7 ± 569.2 g. A total of 151 patients (10.7%) had a recorded visit with an ophthalmologist, with 71 patients (5.0%) having optical coherence tomography imaging. The EMR alert fired for 88 patients over 1 year, with 34 patients (38.6%) either already being screened by an ophthalmologist or having been referred for screening.

Conclusions: An EMR support tool can improve referral rates of PPS maculopathy screening with an ophthalmologist and may serve as an efficient method for longitudinal screening of this condition with the added benefit of informing pentosan polysulfate prescribers about this condition. Effective screening and detection may help determine which patients are at high risk for this condition.

Objectif: Le polysulfate de pentosan sodique (PPS; ELMIRON, Janssen Pharmaceuticals, Titusville, New Jersey) est un médicament oral approuvé par la Food and Drug Administration américaine dans le traitement de la cystite interstitielle. Or, de nombreux rapports publiés font état de la toxicité rétinienne du PPS. Les études à ce sujet étant surtout de nature rétrospective, des systèmes d'alerte et de dépistage doivent être mis en place pour surveiller activement l'apparition de cet effet secondaire. Notre étude avait pour objectif de dépeindre les tendances en matière de surveillance ophtalmologique au sein d'un échantillonnage de patients qui reçoivent le PPS afin de mettre sur pied un système d'alerte et de dépistage de cette affection.

Méthodes: Un examen rétrospectif des dossiers médicaux des patients d'un seul établissement a été réalisé entre janvier 2005 et novembre 2020 afin de recenser l'utilisation du PPS. On a ensuite mis au point un système commandant le déclenchement d'une alerte lors de l'ajout de nouvelles ordonnances et de renouvellements d'ordonnances de PPS dans les dossiers médicaux électroniques (DME), de façon à offrir au patient la possibilité de consulter un ophtalmologiste.

Résultats: Au total, 1407 patients qui ont pris le PPS pendant la période de 15 ans ont servi à décrire le patient type : 1220 sujets (86,7 %) étaient de sexe féminin; la durée moyenne de l'exposition au PPS était de 71,2 ± 62,6 mois; et l'exposition cumulée moyenne a atteint 669,7 ± 569,2 g. Une consultation en ophtalmologie figurait au dossier de 151 patients (10,7 %), et 71 patients (5,0 %) ont subi une tomographie par cohérence optique (OCT). L'alerte DME s'est déclenchée pour 88 patients sur une période de 1 an, dont 34 patients (38,6 %) qui avaient déjà été examinés par un ophtalmologiste ou avaient été dirigés vers un spécialiste en vue d'un dépistage.

Conclusions: Un outil annexé aux DME peut accroître le nombre de patients prenant le PPS qui sont orientés vers un ophtalmologiste en vue du dépistage d'une maculopathie. Cet outil pourrait également être efficace pour réaliser un dépistage longitudinal de cet effet toxique, sans compter qu'il permet d'aviser les prescripteurs de PPS d'un tel risque. Un dépistage efficace pourrait contribuer à identifier les patients qui courent un risque élevé de présenter cette affection.

Pentosan polysulfate sodium (PPS; ELMIRON, Janssen Pharmaceuticals, Titusville, NJ) is a low-molecular-weight heparin–like molecule that is clinically indicated for interstitial cystitis. Interstitial cystitis and bladder pain syndrome is a condition of bladder discomfort that can include features such as urinary frequency, urgency, and chronic pelvic pain without a clear etiology. The condition affects millions of Americans, including approximately 2%–6% of the

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American female population.[1] PPS is the only oral option for this condition approved by the U.S. Food and Drug Administration.

In 2018, Pearce et al.[2] elucidated that some patients with chronic PPS exposure developed a unique maculopathy. There is growing literature supporting this finding, but most studies have been of a retrospective nature.[3–5] Retrospective studies are reliant on available imaging and clinical data, but key information may not be available because imaging and clinical examinations were not performed with enough frequency to document disease progression. Two prospective cohort studies found a prevalence of 16%–20% for PPS maculopathy among PPS users who agreed to participate.[6,7] However, this study depended on voluntary participation for screening specifically for PPS maculopathy, which may introduce self-selection bias. Another study with prospective recruitment using a letter and phone call found pentosan polysulfate toxicity in 41% of eyes with a 27% participation rate.[8] This elevated rate compared with the other 2 prospective cohort studies could be attributable to possible false-positive results in those without fundus autofluorescence (FAF) findings.

The clinical presentation is still being described and established, but some presenting symptoms include prolonged dark adaptation, nyctalopia, and blurred vision. Notwithstanding, the progressive nature of this condition may contribute to some patients presenting with imaging findings only without symptomology and preserved visual acuity. On dilated fundus examination, the condition presents with bilateral pathology of the fovea with hyperpigmented macular spots and yellow subretinal deposits in earlier disease onset and retinal pigment epithelium (RPE) atrophy in late disease progression. However, a normal dilated fundus examination does not exclude this condition because findings may not be present on physical examination. The onset of PPS maculopathy can lead to cystoid macular edema, vitelliform maculopathy, macular neovascularization, and RPE atrophy that can lead to vision loss.[3,6,9,10] Initial damage is suspected to be at the RPE–photoreceptor interface.[2,3,6] The pathophysiology of this condition has yet to be well elucidated but has been hypothesized to be secondary to fibroblast growth factor antagonism.[11]

Imaging can lead to additional findings. Imaging is typically symmetric between both eyes, and colour fundus photography may have hyperpigmented macular spots, deep yellowish subretinal deposits, or parafoveal RPE atrophy.[3,6,9,10] FAF can reveal hyper- and hypoautofluorescent spots.[2,3,6] Hyperautofluorescent spots have been demonstrated to be associated with the yellow subretinal deposits on fundus imaging.[2,3,6] Optical coherence tomography (OCT) can elicit hyper-reflective nodules at the level of the RPE that colocalize with FAF and colour fundus photography findings.[2,3,6,12] These lesions are unique from typical drusen or subretinal drusenoid deposits because they appear at the RPE and project a shadow onto the underlying choroid.[3,12] These lesions may disappear with progressive toxicity as greater retinal damage manifests as atrophy.[8,13] Patients with >1000 g pentosan polysulfate exposure have been shown to have ~4% larger choriocapillaris flow deficit on OCT angiography compared with control individuals (32.7% ± 3.6% in the PPS group compared with 28.6% ± 4.3% in the control group; $p = 0.023$) before the onset of macular toxicity signs in OCT, near-infrared imaging, and FAF.[14] This potentially indicates that the choroid may be initially insulted in PPS maculopathy.

Current knowledge on risk factors for this condition most notably relates to high cumulative PPS exposure.[4,15] One study reported that PPS maculopathy prevalence varied from 12.7% to 41.7% depending on whether cumulative exposure was 500–999 g or up to >1500 g, respectively.[15] Length of exposure is also a consideration because a few patients have been reported to have this maculopathy in >7 years of cumulative dosing.[3] Only 1 case has been reported in >5 years.[3] There are currently no known additional genetic or medical comorbidities associated with this condition.

Janssen Pharmaceuticals has recommended baseline retinal examination including OCT and autofluorescence imaging within 6 months of initiating treatment with periodic monitoring while continuing treatment.[16] While there are no formal guidelines for PPS maculopathy screening, providers have recommended annual ophthalmic imaging as cumulative doses approach or exceed 500 g.[6] Accordingly, the overarching goal of this paper is to establish the benefit of building a system for screening and referring PPS patients for retinal examinations with monitoring of PPS-induced maculopathy. Building such a system can potentially allow for more thorough monitoring that can yield more nuanced knowledge of the clinical presentation, imaging findings, and risk factors for this condition.

Methods

Establishing baseline characteristics of PPS users

A retrospective study was performed for patients >18 years of age with a history of PPS use who received care at a single institution between January 2005 and November 2020. Institutional review board approval was obtained, and all study-related procedures were performed in accordance with the Declaration of Helsinki. A flow diagram summarizing the chart review is provided in Figure 1. A total of 1546 patients from a single institution were found to have taken PPS between January 2005 and November 2020. All patients had clinically diagnosed interstitial cystitis. Patients who discontinued PPS at the initial appointment or are deceased were excluded from this study because they were unable to undergo future monitoring. To establish baseline PPS use and baseline ophthalmic screening characteristics, electronic medical record (EMR) charts for the remaining patients were evaluated for PPS medication

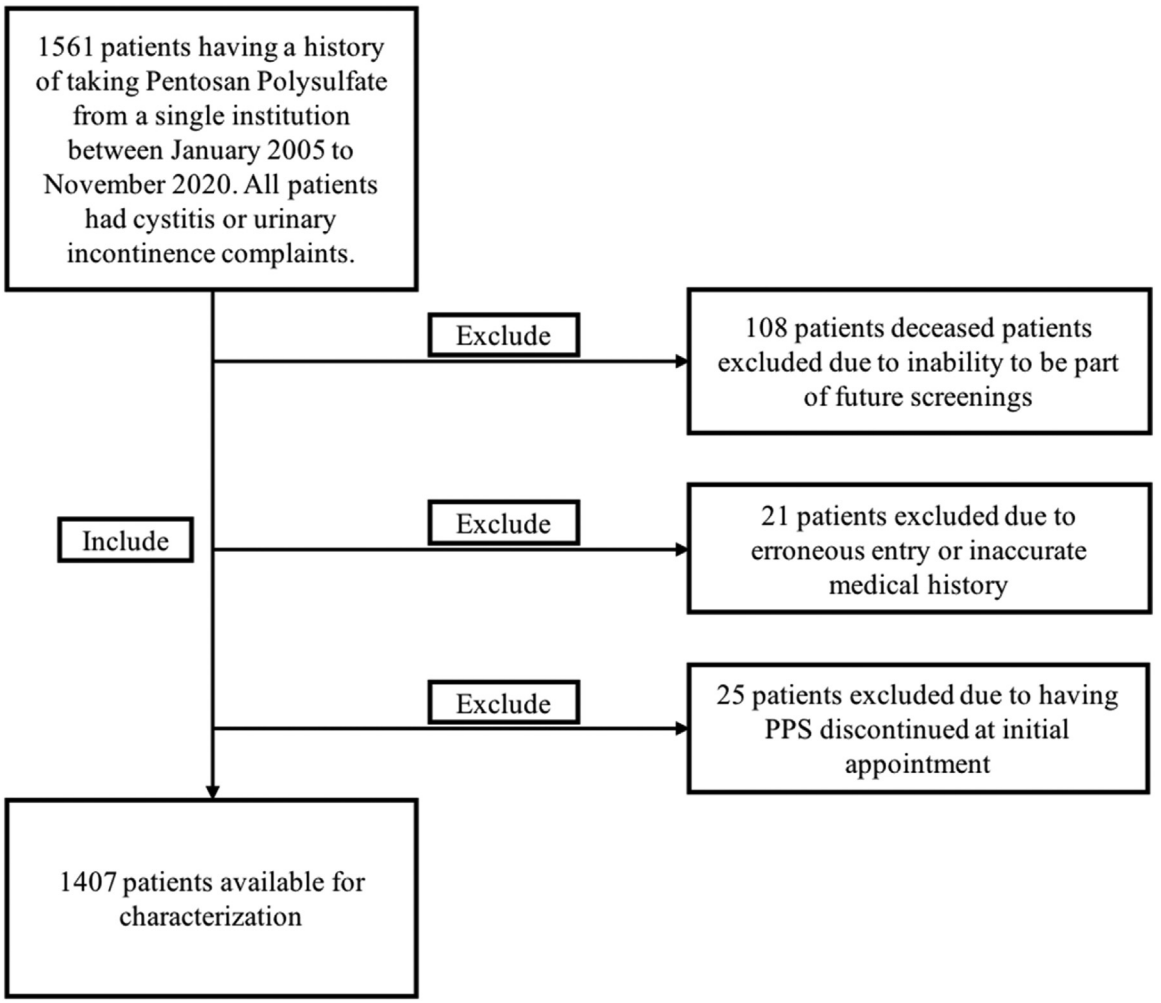

Fig. 1—Flow diagram of retrospective chart review methodology for characterizing patients taking pentosan polysulfate.

history, including duration and the cumulative amount of medication taken, presence of ophthalmic visit within the Cleveland Clinic health system, visual acuity, ocular history, relevant ocular imaging information (e.g., history of OCT tomography and FAF) if available, and the department that recorded and managed the PPS use.

Retrospective imaging review of PPS users

Two masked retinal specialists (R.P.S. and S.S.) independently reviewed the available ophthalmic imaging of PPS users to detect PPS maculopathy. These experts reviewed available deidentified imaging to determine the most likely diagnosis. Classification of PPS maculopathy was based on the American Academy of Ophthalmology's characteristic features for PPS, which include (*i*) focal nodules of hyperreflectance at the level of the RPE, (*ii*) macular hyperpigmented spots, yellow-orange deposits, and (or) patchy RPE atrophy, (*iii*) irregular autofluorescence centred around the macula or disc, or (*iv*) an irregular reflectance pattern with prominent hyper-reflectance colocalizing with hyperpigmented spots.[4,17]

Alert implementation and condition surveillance

An EMR alert was developed and implemented in July 2021. The alert was designed to automatically trigger when providers order or renew a PPS prescription (Fig. 2). The alert has the option for providers to order a consult to ophthalmology with an additional option to include OCT imaging at the initial appointment with ophthalmology. The alert triggered only when a provider (e.g., urologist or obstetrics and gynecology specialist) prescribed PPS, and therefore, typically nonophthalmic clinicians saw the alert. Ophthalmologists were aware of PPS use and were prompted to screen for PPS maculopathy based on reviewing the note of the referring provider. Ophthalmologists in their own notes acknowledged PPS use and stated in their assessment and plans whether there were signs of PPS maculopathy and when the patient should follow-up. Data including the number of times the alert was fired, ophthalmology referrals placed, OCT imaging ordered, accepted alerts without referrals placed, alert cancellations, and alert declinations were collected. An alert declination involved choosing to ignore the alert after acknowledgement, whereas an alert cancellation

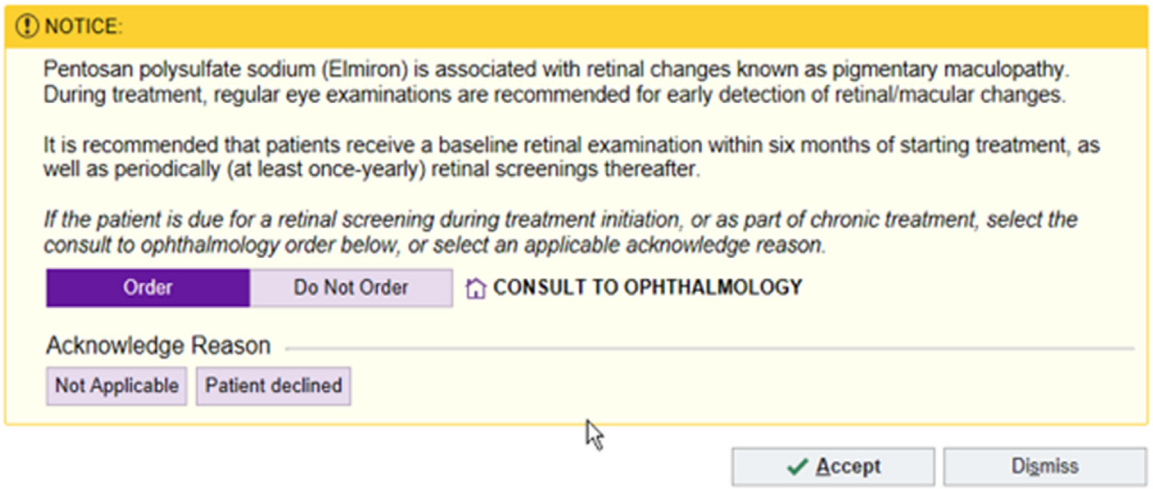

Fig. 2—Electronic medical record alert that triggers when providers prescribe or renew a pentosan polysulfate prescription. Providers have the option to order a consult to ophthalmology that includes an order for optical coherence tomography imaging or decline the alert. © 2022 Epic Systems Corporation.

refers to alert dismissal without acknowledgement. A specific comment box allowing providers to explain the rationale for declining or cancelling the alert request was included into the alert but is optional for providers to fill out.

Statistical analysis

The study cohort outlined in the methodology is characterized by descriptive statistics. Categorical variables are described using frequencies and percentages, whereas continuous variables are described using means and SDs, medians, quartiles, and (or) ranges. Analyses were performed using Microsoft Excel, version 16.49 (Microsoft Inc, Redmond, Wash.).

Results

PPS user characterization

A total of 1407 PPS users over 15 years were characterized, with 1220 (86.7%) being female, the average duration of exposure being 71.2 ± 62.6 months, and the average medication cumulative exposure being 669.7 ± 569.2 g (Table 1). The most common departments involved in PPS medication management included urology (539; 38.3%), internal medicine and other internal medicine subspecialties (313; 22.2%), and obstetrics and gynecology (143; 10.2%) (Table 2). A total of 151 patients (10.7%) had a recorded visit with an ophthalmologist, with 71 patients (5.0%) having OCT imaging (Table 3).

Table 1—Demographic information of pentosan polysulfate users

Category (n = 1407)	Value
PPS starting age	48.0 ± 15.7 years
Female	1220 (86.7%)
Male	187 (13.3%)
Body weight	75.3 ± 20.0 kg
PPS dosage by body weight	75.3 ± 20.0 mg/kg
Percent of patients active on PPS per EMR	57.2%
Percent of patients visiting this single institution >4 months	70.5%
Percent of patients obtaining initial PPS prescription from an external institution (as indicated by "Historical medication" in EMR)	56.4%
Average duration of PPS exposure	71.2 ± 62.6 months
Average cumulative dose	669.7 ± 569.2 g

PPS, pentosan polysulfate; EMR, electronic medical record

Retrospective imaging review of PPS users

Expert graders disagreed only on 1 case of dry age-related macular degeneration (AMD) versus PPS maculopathy.

Table 2—Most common departments responsible for prescribing or managing (e.g., renewing) pentosan polysulfate

Most Common Prescribing Departments (N = 1253)	Number (%)
Urology	539 (38.3%)
Internal Medicine, Hospitalist, Family Medicine, and related specialties (e.g., Hematology, Endocrinology, Cardiology)	313 (22.2%)
OB-GYN	143 (10.2%)
Gastroenterology and Colorectal Surgery	131 (9.3%)
Neurology and Neurosurgery	127 (9.0%)

OB-GYN = Obstetrics and Gynecology
Note: The sample size is less than the total number of patients studied because departments with smaller numbers were not counted.

Table 3—Ophthalmic monitoring data of pentosan polysulfate users before implementation of electronic medical record alert tool

Category	Value (n = 1407)
PPS patients visiting an ophthalmologist at Cole Eye	151 (10.7%)
Visual acuity OD	79.4 ± 13.4 ETDRS letters
Visual acuity OS	79.6 ± 13.3 ETDRS letters
Patients having an OCT	71 (5.0%)
Patients having fundus photographs	6 (0.4%)
Patients having fundus autofluorescence	3 (0.2%)
Patients having fluorescein angiography	3 (0.2%)

PPS, pentosan polysulfate; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography

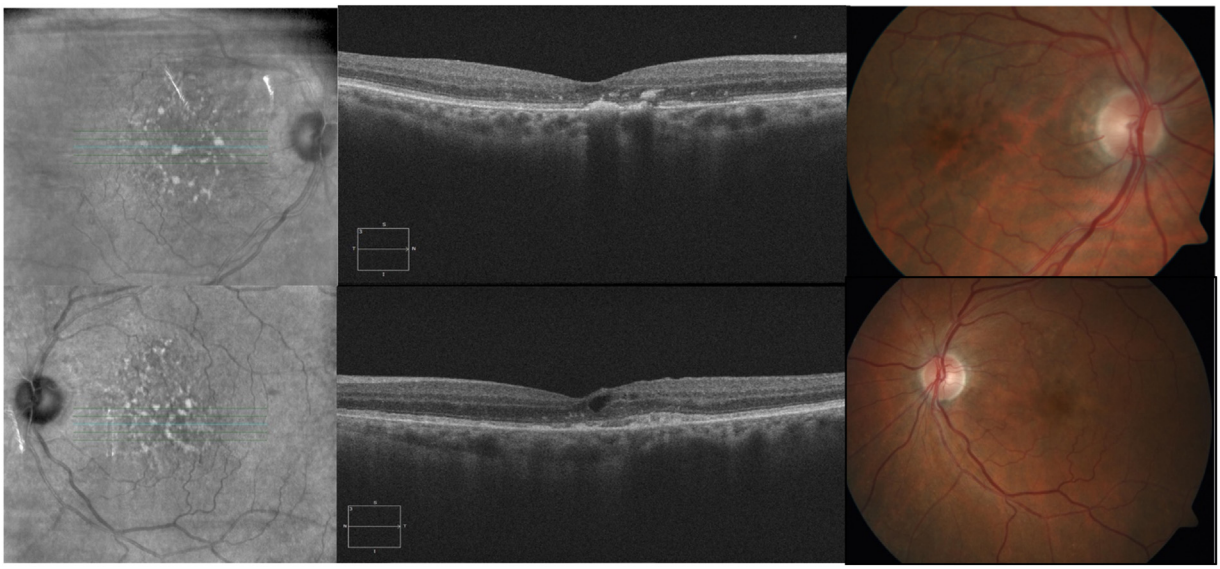

Fig. 3—Patient is an 89-year-old female originally diagnosed with intermediate age-related macular degeneration. On near-infrared imaging, irregular reflectance patterns can be seen. Focal nodules of hyper-reflectance at the level of the retinal pigment epithelium and elevation of retinal pigment epithelium on optical coherence tomography can be seen. Macular hyperpigmented spot deposits can be seen on fundus photography.

Because of a lack of consensus, this 1 case was not considered to be PPS maculopathy. Expert graders agreed that 2 patients likely had PPS maculopathy that was not previously detected. One patient's imaging demonstrated focal nodules of hyper-reflectance at the level of the RPE and RPE elevation on OCT, irregular reflectance patterns on near-infrared imaging, and macular hyperpigmented deposits on fundus photography (Fig. 3). The other patient had focal nodules of hyper-reflectance at the level of the RPE and RPE elevation on OCT and irregular reflectance patterns on near-infrared imaging (Fig. 4). Because of the retrospective nature of the imaging review, FAF imaging for the patient in Figure 4 was not performed because neither PPS maculopathy nor the utility of FAF had been established at the time of imaging. Both were originally characterized as intermediate age-related macular degeneration by their treating ophthalmologists, likely because the patients were seen prior to PPS maculopathy being a recognized entity.

One-year post-alert implementation and condition surveillance

One year after the EMR alert had been implemented (July 2022), the alert had fired a total of 88 times. For 34 of the 88 patients, either ophthalmology was consulted or the patient already noted seeing an external ophthalmologist (38.6%; $p < 0.001$). Seventeen of these 34 patients were new referrals, whereas the other 17 already saw an external ophthalmologist. OCT macula was ordered for all 17 patients who were referred to an ophthalmologist, but 2 of these were ordered separately by the ophthalmologist. Of the remaining alerts, 20 providers (22.8%) cancelled the EMR alert, and 23 (26.1%) accepted the alert but did not follow up with any action. Twenty-eight alerts (31.8%) were overridden (declined), and with 17 alerts (19.3%) the providers indicated that the patients had already had annual eye examinations. Based on percentages, the rate of PPS patients confirmed being seen by an ophthalmologist increased by approximately 3.5-fold (38.6% vs 10.7%), and the OCT imaging rate increased by 3.8-fold (19.3% vs 5.0%) because all 17 patients referred to ophthalmology at our institution had OCT imaging. At the 1-year mark, no patients who had been newly screened for PPS maculopathy with OCT imaging had been identified as having the condition.

Discussion

This study establishes that at a large tertiary academic centre, a small percentage of individuals who have taken PPS have obtained ophthalmic imaging and highlights the need for the development of a screening and alert system for ophthalmic monitoring. The sample population at our institution may be prime for PPS maculopathy screening because the average duration of PPS use was 71.2 ± 62.6 months, and some providers advise their patients to undergo annual repeat imaging beginning at 5 years (60 months) after PPS initiation.[18] Other providers recommend screening as cumulative doses approach or exceed 500 g, and our sample's average cumulative dose was 669.7 ± 569.2 g.[6] Nevertheless, our institution had fewer PPS users seen by ophthalmologists at baseline compared with other single-institution studies.[19,20] A plethora of reasons can be attributable to this, including the random chance of patients having other ocular comorbidities and longer study periods at other institutions, such as 17 years by Kalbag et al.[19] However, other institutions have retrospectively found more

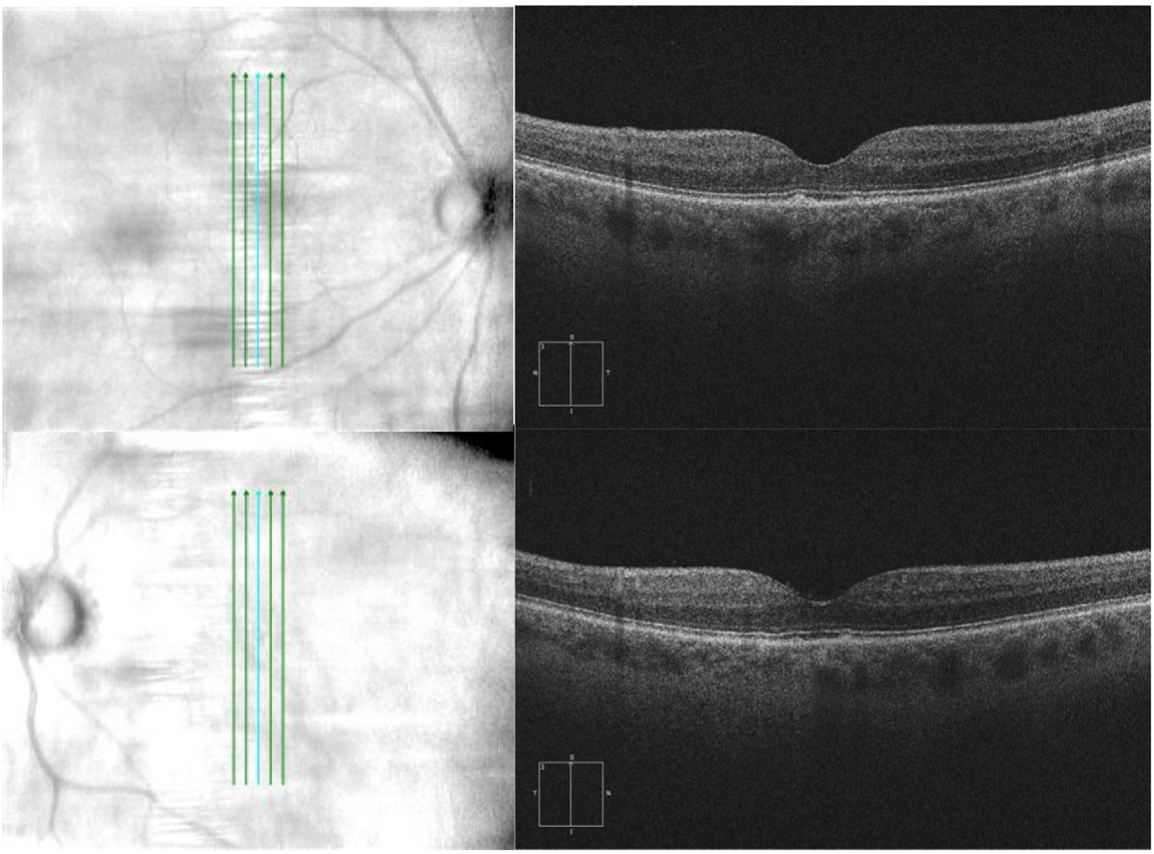

Fig. 4—The second patient is a 73-year-old female originally diagnosed with intermediate age-related macular degeneration. On near-infrared imaging, irregular reflectance patterns can be seen. Focal nodules of hyper-reflectance at the level of the retinal pigment epithelium and elevation of the retinal pigment epithelium on optical coherence tomography can be seen.

patients with PPS maculopathy in a shorter study time frame.[2,13,20] The condition's novelty, rarity, and subtlety of visual symptoms such as nyctalopia and blurry vision versus decreased visual acuity also may contribute to providers being less aware of this condition and thus less frequent referrals for ophthalmic screening.

An important finding of this study is the diversity of institutional departments involved in the management of patients taking PPS. While most PPS patients were being managed by departments such as urology and obstetrics and gynecology, a notable number of patients were managed by departments such as internal medicine, gastroenterology, cardiology, rheumatology, and neurology. While most screening and education efforts should focus on urology and obstetrics and gynecology providers because of their greater clinical familiarity with interstitial cystitis or bladder pain syndrome and PPS, education of other clinicians who may encounter PPS in any situation merits consideration because patient encounters with these providers may be the only opportunity to educate the patients on chronic PPS use and the risk of PPS maculopathy. Excluding ophthalmology, PPS maculopathy educational literature exists only in obstetrics and gynecology and urology presently.[21–23]

Another key consideration for the development of an effective screening and alert system for tertiary academic centres is that many of the patients in this study initially obtained PPS management from an external care provider, considering that 56% had a medication history of PPS before a documented encounter at this institution. Furthermore, our 1-year post-alert data suggest that nearly half the people who are confirmed to be followed by ophthalmology see an external ophthalmologist. Consequently, in addition to an EMR alert implemented at a single academic institution, more extensive education efforts are merited between tertiary academic institutions and providers in other health care settings. Notwithstanding, these findings may be unique to this institution considering the high-volume referral nature that is present.

One challenge of relying on an EMR-based alert is alert fatigue. EMR alert fatigue has been well established as a challenge in using EMR support tools in a variety of other settings.[24,25] This study had only 38% of providers appropriately refer patients to ophthalmology or decline an alert if the patient was already being followed by an ophthalmologist despite having an EMR alert and order system that requires few clicks. However, a confirmed ophthalmology monitoring rate of 38.6% is approximately 3.5 times higher than the original percentage of PPS patients known to be monitored by an ophthalmologist, and thus the use of an EMR alert and screening approach demonstrates improvement in terms of confirmed eye evaluations for this

condition. Furthermore, this confirmed ophthalmology screening rate is higher than the study participation rates seen with other methods of prospective study such as letters and phone calls, with the added benefit of ease of repeatability over a long time as the alert automatically triggers based on PPS prescriptions.[8] While the EMR alert usage rate may seem low, this percentage is similar to those seen in other settings after prolonged exposure to an EMR alert.[26] Possible remedies for alert fatigue that have been previously implemented include implanting an alert "chart closure" hard stop, sharing alerts with patients instead of providers to educate patients and promote shared decision making, and further customization of alert settings such as incorporation of cumulative dosing considerations and previous alert triggers to reduce alert reappearances and improve clinical relevance.[27–30] Designating protective time for alert management was a preferred solution by primary care providers.[31] Changes within the EMR are hardly ever seamless, but the appreciable increase in ophthalmology referrals and OCT imaging of patients may increase the rate of detection and early intervention for PPS maculopathy.

A consensus retrospective review of available ophthalmic imaging of PPS users revealed that 2 patients likely had PPS toxicity when they were characterized as having other conditions. The mischaracterization of these patients is attributable to the fact that PPS maculopathy was established after both patients' initial presentation to a retina specialist, like other studies that retrospectively reviewed cases for PPS maculopathy. The number of patients who may be mischaracterized as having PPS maculopathy may be low, but caution should be taken if patients have a long-standing retinal diagnosis with chronic PPS use; imaging and symptomology should be carefully reviewed to delineate the timeline between PPS use and diagnosed retinal pathology. The rate of PPS maculopathy may be much higher than what was discovered based on the limited number of patients with imaging available to review. Furthermore, the type and frequency of imaging available also may hinder retrospective detection of this condition. Studies and institutions have varied greatly in terms of average PPS exposure among their user populations, which also can contribute to PPS maculopathy development.[4,9,13,19,32]

Previous studies characterizing PPS maculopathy outline extensive imaging features of this condition, including features on OCT, fundus photography, FAF, and near-infrared imaging. Few patients in the sample had FAF or fundus imaging, like the imaging availability seen at other institutions.[19] Practical constraints to providing patient care (e.g., patient time availability, patient imaging fatigue, imaging technician, and equipment availability) can limit the ability to extensively image patients with potential PPS maculopathy. The initial screening study by Wang et al.[6] of 50 patients required telephone contacting of 440 patients (11.4%). The group's second study had a 13.4% voluntary participation rate and cited lack of interest and logistic limitations such as distance and time constraints as reasons for not participating.[7] Another study using letters and phone calls had a 27% participation rate.[8] A notable limitation of our study is the use of OCT primarily to screen patients for PPS maculopathy rather than the use of FAF because other studies have sought to use both modalities.[6–8] Using OCT primarily can create screening challenges because FAF is more specific at distinguishing age-related RPE changes versus PPS toxicity–related RPE findings. Even though this may increase the false-positive rate, as possibly seen in the study be Dieu et al.,[8] no patients in active screening at 1 year in our study have been positively identified to have PPS maculopathy. Additionally, OCT use was chosen because PPS maculopathy screening was performed by eye care providers at both main campus and satellite clinics throughout our institution. Consequently, some regional clinics within our institution do not have FAF imaging capacity, but all clinics and eye care providers have access to OCT imaging. As a result, this study may simulate PPS maculopathy screening at eye care providers who practice in locations without FAF imaging. If patients had suspicious findings that merited FAF imaging, they would have been sent to a location where FAF imaging was available.

Overall, the ophthalmic literature on the topic of PPS has been related primarily to the characterization of PPS maculopathy. However, this paper examines the baseline rate of PPS users receiving ophthalmic screening at a single institution and demonstrates the potential benefit of implementing an EMR alert system to help nonophthalmic providers appropriately refer PPS users for ophthalmic monitoring. The alert is also useful because it provides patients with the opportunity to tell their provider that they are already receiving eye examinations with an external provider. This study highlights the need for educational and alert protocols for PPS maculopathy across several health care settings.

Additional study limitations should be noted. The percentage of PPS individuals receiving eye examinations may be underestimated secondary to incomplete documentation. Furthermore, this study was performed at a tertiary academic institution where many patients taking PPS may receive eye care from an external provider. Ophthalmic information such as imaging and examination findings are inaccessible for these patients. Future studies will aim to improve the ophthalmic referral rate by exploring nonophthalmic provider reasoning for declining ophthalmic referrals for patients taking PPS and exploring EMR alert tool modifications. This system will help improve recognition of the ophthalmic characteristics of patients chronically taking PPS for better characterization of PPS maculopathy.

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