

CANADIAN EYE CARE TODAY

Staying ahead of dupilumab-associated ocular surface disease

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Mélanie Hébert, MD, MSc

Uveitis following COVID-19 vaccination: a literature review for Canadian ophthalmologists

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Drug induced (toxic) glaucoma

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Screening for depression and suicide: a vital part of glaucoma care

Paul Harasymowycz, MD
Oksana Kaminska, MD

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EDITORS WELCOME

Dear Canadian Eyecare Community,

As we move into the last few weeks of summer, we are thrilled to share the second issue of *Canadian Eye Care Today* with all of you. The inaugural issue reached over 2,500 eye care professionals across the country and we received tremendous feedback both at the 2022 COS Annual Meeting and afterwards via personal communications. If you haven't told a colleague about this new journal, please do!

We are tremendously proud of the content that has been curated in this current issue, which focuses on toxicities. We have a great article on dupilumab-associated ocular surface disease and an important article on drug-induced glaucoma. We also present valuable insights on pentosan polysulfate maculopathy and uveitis following COVID-19 vaccination. Finally, we have an important article on the association between glaucoma diagnosis and depression.

We are incredibly grateful to all the authors who have contributed to this second issue and to the ongoing support of our advertising partners. As the journal continues to grow, we welcome new ideas, new topics and new submissions which can be sent directly to info@catalytichealth.com.

We do sincerely hope you enjoy this issue, and we look forward to your readership and your ideas for future articles as we grow and expand the reach of this publication!

Best wishes,



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Staying ahead of dupilumab-associated ocular surface disease

Patricia-Ann Laughrea, MD, FRCSC and Mélanie Hébert, MD, MSc

INTRODUCTION

Dupilumab is an immunomodulatory medication blocking interleukins. This biologic drug is an injectable human monoclonal antibody targeting the α subunit of interleukin (IL)-4 which affects the IL-4 and IL-13 pathways. Since its approval by the United States Food and Drug Administration and Health Canada in 2017,¹ it has been used extensively for the treatment of multiple diseases, including chronic rhinosinusitis with nasal polyposis, asthma, and most notably atopic dermatitis. In patients with moderate-to-severe atopic dermatitis (AD), dupilumab has significantly improved patients' quality of life. In the pivotal SOLO 1 and SOLO 2 trials involving patients aged 18 years and older, dupilumab was compared with placebo and demonstrated a significant reduction in Investigator Global Assessment (IGA) atopic dermatitis score down to "clear" or "almost clear" (i.e., 0 or 1) and a ≥ 2 -point improvement from baseline in that same score at week 16. This primary endpoint was achieved in 36-38% of patients on dupilumab compared with 8-10% of patients on placebo.² However, these outcomes are not without drawbacks.

The emergence of dupilumab-associated ocular surface disease (DAOSD) or dupilumab-induced ocular surface disease (DIOSD) is now commonly reported by both dermatologists and ophthalmologists who treat AD patients using dupilumab.³⁻⁵ Interestingly, dupilumab has not been associated with increased conjunctivitis rates in studies in other diseases, including asthma and chronic rhinosinusitis with nasal polyposis, which suggests that the increased rates of conjunctivitis in AD studies may reflect a unique interaction between AD and dupilumab-related mechanisms.⁶ The SOLO 1 and SOLO 2 trials were the first to detect a higher rate of conjunctivitis in dupilumab-treated patients with 3-5% of the dupilumab-treated patients developing "conjunctivitis of an unspecified cause" compared to 1% in the placebo groups,² with 1 of 920 patients discontinuing dupilumab because of conjunctivitis in SOLO 1.⁶ The highest rate among dupilumab trials was in LIBERTY AD CAFÉ where conjunctivitis was reported in 16%, 28% and 11% of patients in the weekly dupilumab + topical corticosteroid (TCS), every two weeks + TCS and placebo + TCS groups, respectively; all but one event were mild or moderate.^{7,8} However, in those trials patients did not undergo complete ophthalmological examinations to characterize the type of ocular involvement that was

reported. Subsequent research and real-world experience has since detailed the variety of findings associated with DAOSD. With more studies now published, including those which involve subjects examined by ophthalmologists, we have a better idea of the incidence of DAOSD. A recent Canadian study reported a rate of DIOSD at 37% over a 52-week follow-up period, with 19% of these patients requiring a consultation in ophthalmology.⁹ Most of the time, only the most severe cases will be referred to ophthalmologists, while milder cases will be treated by dermatologists or primary care providers through the use of artificial tears.

The aim of this article is to provide a basic framework for clinicians to understand the pathophysiology of DAOSD, how to diagnose DAOSD, and the optimal treatment strategy for these patients.

PATHOPHYSIOLOGY AND RISK FACTORS

The exact pathophysiological mechanism leading to DAOSD has not yet been clearly elucidated. However, two hypotheses are worthy of mention. First, IL-13 inhibition may induce loss of conjunctival goblet cells, which are responsible for lubrication and production of mucin.^{10,11} These are essential components of the tear film and deficiency can lead to dry eye disease.^{5,10} Second, an increase in Th1-mediated inflammatory response, in relation with the chronicity of atopic disease, is another mechanism to be considered.^{12,13}

The time to onset of clinically apparent DAOSD seems to require a few months. This may be related to the achievement of a steady-state concentration of dupilumab in the blood by the four month timepoint. Alternatively, the onset of DAOSD could also be related to the time required for deterioration of the ocular surface, and for the patient to become symptomatic. In studies which examined symptomatic patients referred by dermatologists, the average time to diagnosis of DAOSD by an ophthalmologist varied between 1 and 10 months.^{14,15} This differs from studies with patients examined earlier and more systematically where signs of ocular surface disease could be detected within two weeks of dupilumab treatment being initiated.¹⁶

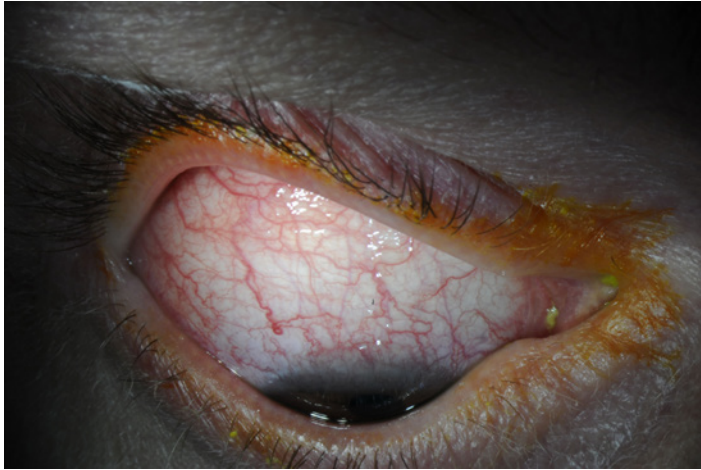
The relationship between the severity of atopic dermatitis and of previous atopic facial or palpebral involvement remains uncertain but these may be predisposing factors.^{8,15,16}

CLINICAL SIGNS AND SYMPTOMS

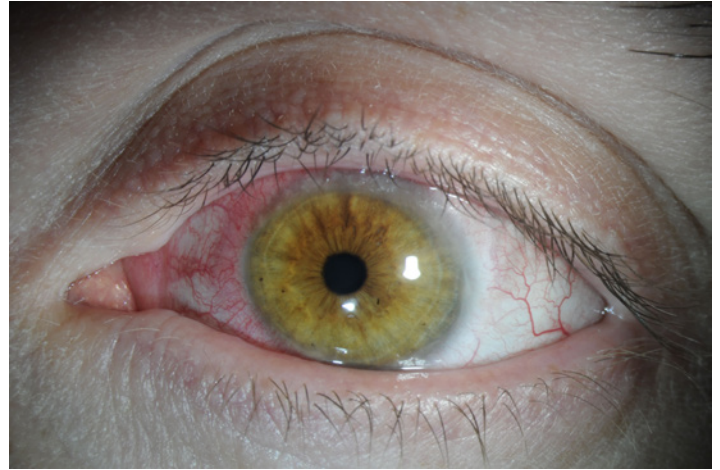
Patients who develop DAOSD often complain of redness, burning, tearing, and foreign body sensation. Patients may also complain of crusting and discharge with occasionally worsening of periocular atopic dermatitis-like findings.

On ophthalmological examination, visual acuity is usually preserved, though patients can complain of blurred vision. Ocular findings are most often bilateral but can be asymmetric and are usually limited to the anterior segment.

The associated redness is the most frequent sign and is often striking. This could be described as an episcleritis-like, inflammatory conjunctivitis (**Figure 1**). Diffuse or sectoral hyperemia of the limbus with nodular swelling and Horner-Trantas-like dots can also be found. Infrequently, the inflammation will lead to conjunctival scarring, cicatricial symblepharon, punctal stenosis, or ectropion.^{17–20}



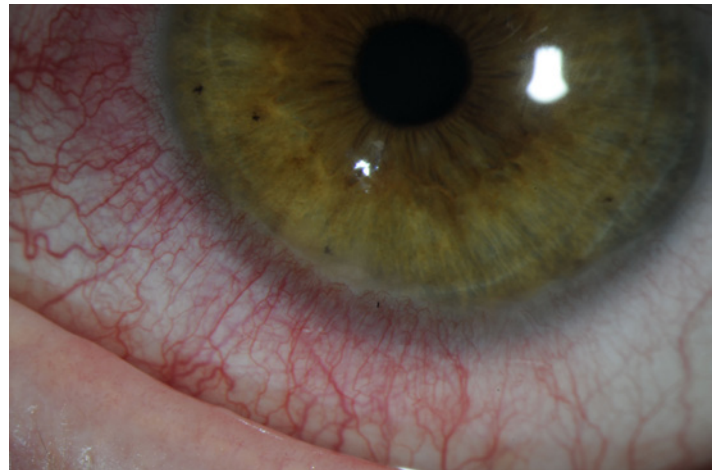
A



D



B



E



C

Figure 1: Photographic examples of dupilumab-associated ocular surface disease (DAOSD), including (A, B) diffuse, inflammatory conjunctival hyperemia, (C, D) limbitis with Horner-Trantas-like dots in the absence of significant eyelid disease, and (E) magnified view of concomitant peripheral sterile corneal infiltrates; photos courtesy of Patricia-Ann Laughrea, MD and Mélanie Hébert, MD

SIGNS OF DAOSD	RELATIVE FREQUENCY
Conjunctival hyperemia	very frequent, typical sign
Inflammatory conjunctivitis	very frequent, typical sign
Dry eye disease	very frequent, typical sign
Limbal inflammation / limbitis (including nodules and Horner-Trantas-like dots)	frequent
Blepharitis (atopic dermatitis-like)	frequent
Peripheral or central corneal infiltrates	rare sign, association less clear
Episcleritis	rare sign, association less clear
Corneal ulceration (up to perforation)	very rare sign, few case reports
Cicatricial conjunctivitis (including punctal stenosis, fornix shortening, symblepharon, ectropion)	very rare sign, few case reports

Table 1: Clinical findings in dupilumab-associated ocular surface disease (DAOSD) by relative frequency; courtesy of Patricia-Ann Laughrea, MD and Mélanie Hébert, MD

On the cornea, inferior punctate epithelial erosions are common. Other signs of dry eye disease can be expected such as decreased tear breakup time (TBUT) and reduced tear meniscus. Inflammatory, marginal keratitis-like sterile infiltrates can be found in the periphery of the cornea, or centrally. These tend not to be very dense, contrary to infectious ulcers but can be confounding in establishing a differential diagnosis. A few isolated cases of corneal ulceration and thinning with possible perforation and cases of intraocular or posterior involvement have been reported (e.g., posterior scleritis, anterior uveitis, placoid chorioretinitis, macular edema).^{20–22} Further studies and cases are needed to confirm these findings. See **Table 1** for common signs of DAOSD and their relative frequency.

DIAGNOSIS

DAOSD remains a clinical diagnosis relying on a complete ophthalmological exam with slit-lamp biomicroscopy. Other tests such as Schirmer's test and TBUT can be useful but are less likely to differentiate DAOSD from other types of ocular surface diseases. To properly identify patients with possible DAOSD, probing for a history of dupilumab use is crucial as this could otherwise go unnoticed. At consultation, the clinician should determine the duration in months and dosing interval (e.g., every week or every two weeks) of dupilumab use. Additionally, some patients may report worsening of their symptoms shortly following dupilumab injection, which would be more specific for DAOSD.

Exacerbation of pre-existing atopic keratoconjunctivitis can be a significant confounder for the diagnosis of DAOSD; however, in patients who had little or no symptoms of atopic keratoconjunctivitis prior to starting dupilumab, DAOSD becomes more likely. Other diagnoses may help in the differential diagnosis, including atopic keratoconjunctivitis, allergic keratoconjunctivitis, vernal keratoconjunctivitis, dry eye syndrome, bacterial blepharoconjunctivitis, meibomian gland dysfunction, marginal keratitis / staphylococcal hypersensitivity, viral keratoconjunctivitis, episcleritis, phlyctenulosis, superior limbic keratitis, contact lens-associated giant papillary conjunctivitis or keratitis, and infectious infiltrates.^{23,24} Identifying possible factors leading to a deterioration of symptoms such as seasonal changes or contact lens wear may help differentiate from other etiologies.

Given that DAOSD is generally a bilateral disease, when unilateral symptoms are present, careful examination of the fellow eye should always be performed, as it may reveal subtle signs of DAOSD as well. In the absence of signs in the fellow eye, an alternative diagnosis to DAOSD should be considered.

MANAGEMENT

A management flowchart for DAOSD is suggested in **Figure 2**. For mild disease, artificial tears and antihistamine-mast cell stabilizer eyedrops (e.g., olopatadine 0.2%) will help to control signs and symptoms associated with dry eye and allergic keratoconjunctivitis, respectively.^{13,16} The initiation of prophylactic artificial tear treatment, before the onset of symptoms, has been documented in the literature and has resulted in a decreased incidence of DAOSD.^{4,13,25} Artificial tears should ideally be preservative-free with a frequency that can be titrated up to every hour. Some patients may prefer a more viscous formula like a gel or ointment, especially at night. Warm compresses with or without lid hygiene to address meibomian gland dysfunction can be a useful adjunct.

If clinical response is not achieved, especially in the setting of severe and diffuse conjunctivitis or limbal inflammation, mild (e.g., fluorometholone 0.1%, fluorometholone 0.25%, loteprednol 0.2%, loteprednol 0.5%, rimexolone 1%) or strong (e.g., prednisolone 0.12%, prednisolone 1%, dexamethasone 0.1%, difluprednate 0.05%) corticosteroid eye drops can be used. This can be titrated depending on the severity of the symptoms and the degree of inflammatory involvement. Corticosteroid eyedrops are typically started q.i.d. with a taper of one drop every 2 to 4 weeks depending on treatment response. In the absence of clinical response, the strength and frequency of corticosteroid eyedrops can be increased. The taper of corticosteroids can be lengthy and require multiple adjustments. Prolonged corticosteroid eyedrop use necessitates close ophthalmologic follow-up as serious adverse events such as increased intraocular pressure, glaucoma, infection, and cataracts may appear, sometimes in just a few weeks. It can then be necessary to reduce the potency and frequency to the minimum tolerated dose.

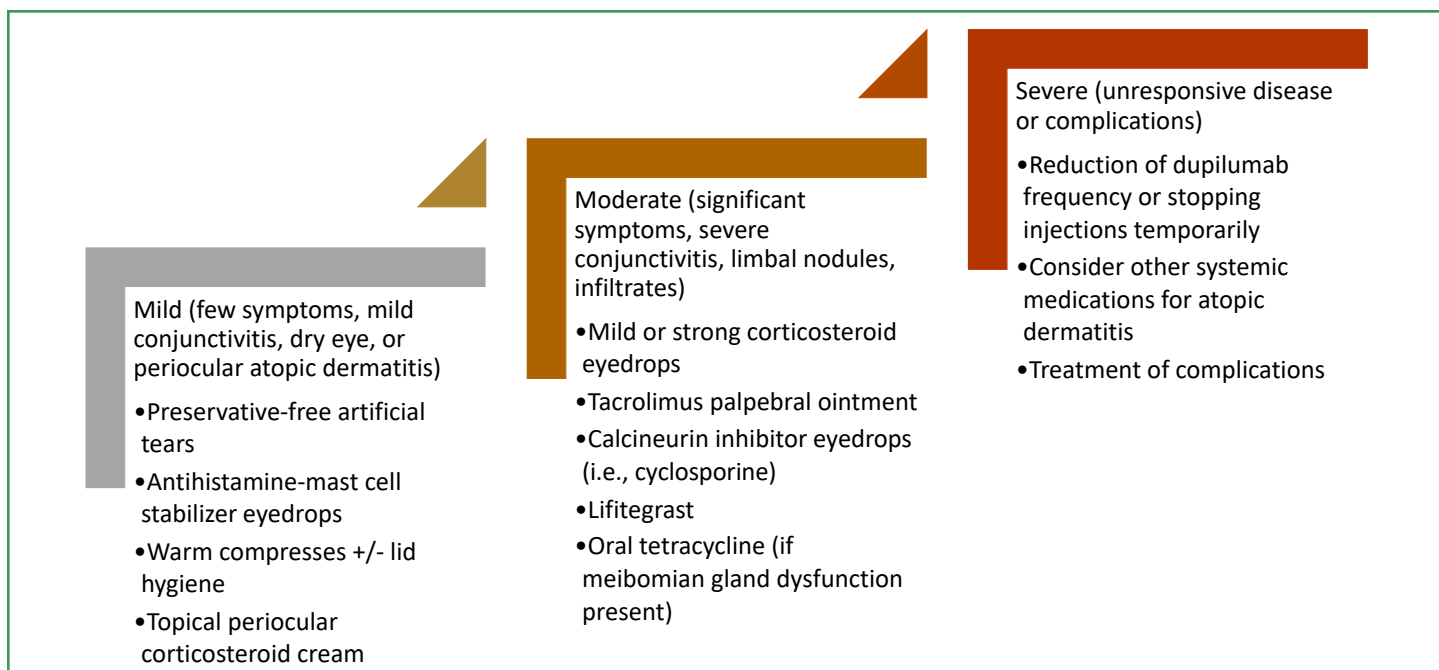


Figure 2: Suggested management flowchart for patients with mild, moderate, and severe dupilumab-associated ocular surface disease; courtesy of Patricia-Ann Laughrea, MD and Mélanie Hébert, MD

Calcineurin inhibitor eyedrops such as cyclosporin 0.05% to 1%^{13,26} or tacrolimus 0.03% eye ointment (off-label use)²⁷ and lifitegrast³ have been tried, with authors reporting good response in a few small series and case reports. Tacrolimus ointment 0.03% or 0.1% applied to the lid margins has demonstrated improvement in some cases,^{14,28} and has been proposed as a potential first-line therapy for moderate-to-severe dupilumab-induced blepharoconjunctivitis.¹⁶ The addition of oral tetracycline antibiotics (e.g., doxycycline or minocycline) may be considered when meibomian dysfunction seems prominent. A discussion with the patient's dermatologist may be necessary if sufficient DAOSD control cannot be achieved with corticosteroid eyedrops or if the patient exhibits serious side effects such as steroid-response glaucoma. This could require reducing dupilumab frequency or discontinuing dupilumab temporarily or considering alternate atopic dermatitis medications including drugs that are currently in research protocols.

In DAOSD cases with corneal infiltrates and ulceration, an infectious cause should be ruled out first and broad-spectrum antibiotics such as a fluoroquinolone should be used to treat a presumed infectious ulcer. If the infiltrates are bilateral and do not have an associated epithelial deficit in a non-contact lens wearer, an ophthalmologist can more comfortably assume a sterile, inflammatory cause such as DAOSD or marginal keratitis and start the necessary corticosteroid eyedrops.

In certain patients, the eyelids and periocular skin may have findings like atopic dermatitis even with quiescent cutaneous disease. The body's response to dupilumab may be heterogenous with some systems (i.e., the skin) having a different response compared to others (i.e., the eyes). For example, de novo blepharitis may occur or existing blepharitis may worsen despite the excellent cutaneous

response for the treatment and management of the underlying AD.⁶ In these cases, periocular corticosteroids (e.g., hydrocortisone 0.5%) or periocular calcineurin inhibitors (e.g., tacrolimus 0.03%-0.1%) will often help. Again, a discussion with the patient's treating dermatologist may be necessary to select a more potent cream if these do not provide appropriate clinical response.

Clinicians should note that most DAOSD patients will improve while continuing dupilumab therapy. However, this may require ocular and palpebral topical treatment to be used for prolonged periods. Dupilumab will rarely need to be discontinued.

CONCLUSION

Dupilumab has solidified its place in the dermatology armamentarium and is likely to remain a staple in the treatment of moderate-to-severe atopic dermatitis. The conjunctivitis first reported in association with dupilumab treatment for atopic dermatitis is a complex entity. Early identification of DAOSD and prophylactic treatment with artificial tears appear to be beneficial. For moderate-to-severe cases, antihistamine/mast cell stabilizer eyedrops, topical ocular corticosteroids, and palpebral calcineurin inhibitors have demonstrated efficacy. Corticosteroid-sparing topical medication is a promising approach, but further studies are still needed. Most importantly, ophthalmologists, dermatologists, patients and caregivers should be alerted to the risk of DAOSD when using dupilumab. Prompt referral to ophthalmology should be considered for any suspicious ocular sign or symptom in a patient taking dupilumab. Collaboration between ophthalmologists, dermatologists, and primary care providers is crucial to maintaining ocular comfort and preventing ocular complications while still providing control of a patient's atopic dermatitis.

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Uveitis following COVID-19 vaccination: a literature review for Canadian ophthalmologists

Larissa Derzko-Dzulynsky, MD, FRCSC, Seema Emami, MD, Austin Pereira, MD, MEng

INTRODUCTION

The advent of SARS-CoV-2 (COVID-19) vaccines markedly reduced adverse outcomes associated with COVID-19 infection. With over 12 billion doses of COVID-19 vaccines administered globally as of June 2022, reports have emerged of ocular sequelae following immunization.¹ Vaccination remains the most effective way to reduce the risk of COVID-19-related morbidity and mortality. However, it is important for ophthalmologists to understand the potential adverse events related to SARS-CoV-2 vaccination to provide opportunity for appropriate patient counselling and diagnosis. This review outlines the reported associations between COVID-19 vaccination and uveitis, including proposed mechanisms and recommendations for treating ophthalmologists.

REVIEW OF VACCINE TECHNOLOGY

In Canada, the most widely available vaccines against SARS-CoV-2 infection include the Moderna Spikevax (mRNA-1272) and Pfizer-BioNTech Comirnaty (BNT162b2) mRNA vaccines, as well as the AstraZeneca Vaxzevria (formerly Covishield, ChAdOx1nCoV-19/AZD1222) and Janssen Jcovden (Ad26.COVS.2) viral vector vaccines. Inactivated viral vaccines are also widely used in other countries. mRNA vaccines deliver an antigen derived from the SARS-CoV-2 spike glycoprotein to the host deltoid muscle cell. Viral vector vaccines carry DNA that encodes for the SARS-CoV-2 spike glycoprotein within an adenovirus vector. Both vaccines trigger innate immune responses by toll-like receptors, inflammasomes, and other immune sensors, leading to the release of inflammatory cytokines.^{2,3} B-cell response includes formation of antibody-secreting plasma and memory B cells.^{2,3} T-cell response predominantly features production of T-helper 1 cytokines, including interferon gamma, interleukin-2, and tumour-necrosis factor. A second vaccine dose is required for both mRNA and viral vector vaccines to amplify the production of adaptive immune cells.

REPORTED UVEITIC COMPLICATIONS

Anterior Uveitis

Anterior uveitis (AU) is the most common site of ocular inflammation following inoculation with any COVID-19 vaccine. Over 200 cases of AU have been published to date.^{4,5,7} Most cases are idiopathic, unilateral, and occur within 14-21 days of vaccination.^{4,5} There does not appear to be a clear association with first or second dose of vaccine, or association with gender.^{4,5} Treatment with topical or periocular steroids over one month typically resolves inflammation with preservation of baseline visual acuity.^{5,7}

At our centre, we report a healthy 54-year-old man with new onset bilateral, chronic AU following vaccination with the BNT162b2 Pfizer-BioNTech booster dose. The patient's previous vaccine doses did not trigger any adverse events. Two days following his booster inoculation, the patient developed bilateral non-granulomatous AU (**Figure 1**).

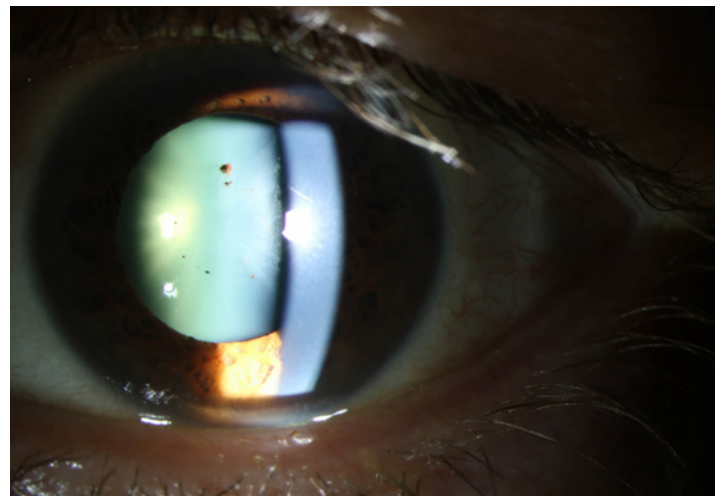


Figure 1: Slit lamp photograph of the left eye demonstrating residual fine keratic precipitates and anterior lens pigmentation following posterior synechiae, associated with non-granulomatous anterior uveitis 2 days after Pfizer booster inoculation; patient photos courtesy of Derzko-Dzulynsky, MD, Emami, MD and Pereira, MD

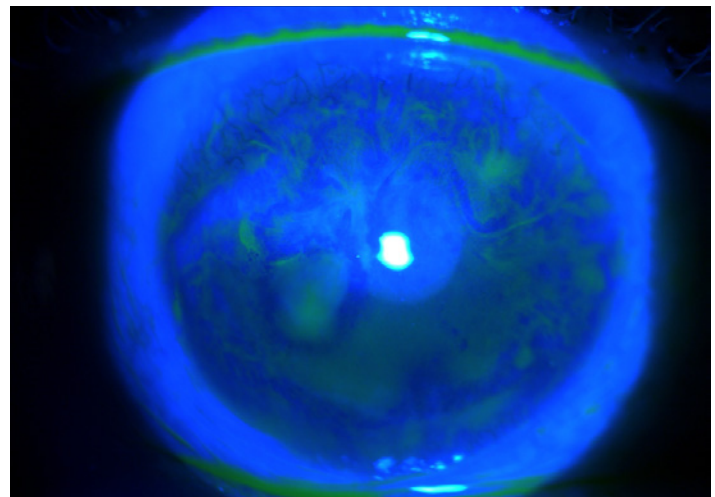
Topical steroid therapy was initiated and treatment was required for over six months. Investigations for infectious and inflammatory etiologies were negative and the patient's vision was preserved at 20/25 in both eyes. Among patients who experience a relapse of AU following COVID-19 vaccination, the vast majority of cases resolve with a short course of topical steroid drops; however, researchers have reported two patients who required escalation of baseline immunomodulatory therapy (IMT) to achieve AU remission, with good visual outcomes.⁶

Reactivation of HLA-B27 and herpetic AU have been reported by several groups.^{7,8} We report a 30-year-old female with recurrent HLA-B27-positive AU, previously controlled with one drop of topical prednisolone acetate 1% per week, who presented with eye pain two days following her COVID-19 mRNA booster vaccination. The patient's slit lamp examination revealed 0.5+ cells OS, consistent with AU. Topical steroids were increased to six times daily and tapered over 3 months, with complete resolution of AU and preserved visual acuity of 20/25. In addition, we evaluated an 81-year-old female with well-controlled herpes simplex virus (HSV) keratitis on prophylactic acyclovir 400 mg PO b.i.d.. She presented with decreased vision two weeks following her second dose of Pfizer-BioNTech. Her examination revealed moderate corneal edema, acute stromal haze and 1+ anterior chamber cell OS. She required one month of treatment with topical dexamethasone 0.1% and acyclovir 400 mg PO five times per day. Despite resolution of the keratouveitis, her limbal stem cell deficiency progressed as a result of this vaccine-associated flare (**Figure 2**).

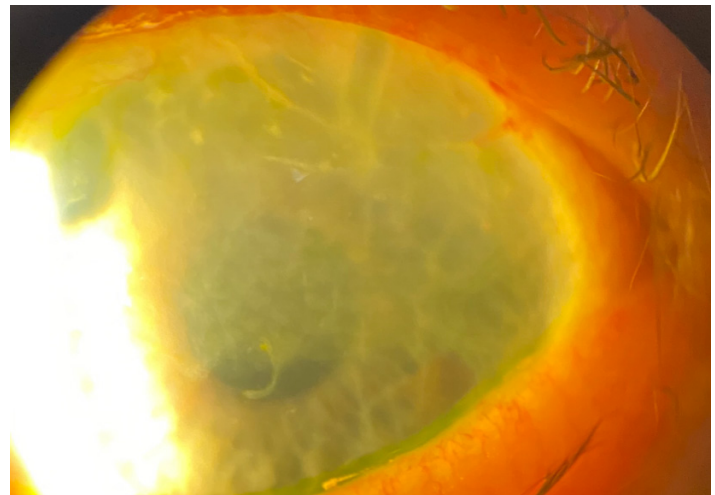
COVID-19 vaccine-associated AU typically presents with mild blurred vision, photophobia, and mild-to-moderate anterior chamber reaction; keratic precipitates and posterior synechiae may also be present. In 2022, researchers reported a case of hypopyon-associated unilateral idiopathic AU in a healthy 21-year-old female two days following her second dose of the BNT162b2 Pfizer-BioNTech vaccine.⁹ Despite its rapid onset, the patient regained 20/20 vision and achieved quiescence within one month of treatment with topical and oral steroids. These cases in the literature, and our single centre experience, demonstrate the heterogeneity of AU presentation following COVID-19 vaccine administration. Importantly, no cases of permanent vision loss have been reported secondary to vaccine-associated AU. Patients with AU following COVID-19 inoculation have uniformly responded rapidly to local and systemic therapy and demonstrated complete resolution of symptoms.^{6,7,9}

Non-Anterior Uveitis

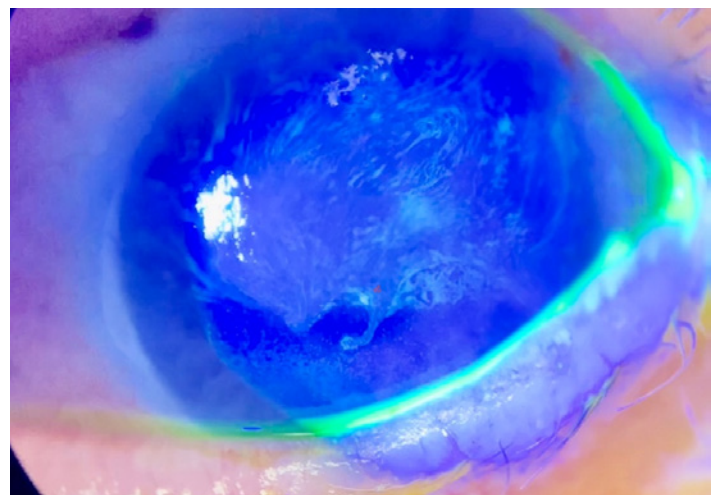
Non-AU (intermediate, posterior and panuveitis) occurs much less commonly than AU following COVID-19 vaccination and more often presents with severe vision loss requiring more intensive treatment. In 2021, a single case of idiopathic unilateral panuveitis, which occurred three days following the second dose of the Pfizer-BioNTech vaccine, and involved a 43-year-old female presenting with 20/500 vision, 2-3+ vitreous cells and peripheral retinal



A



B



C

Figure 2: Left eye slit lamp photos (A) Baseline with moderate limbal stem cell deficiency (note the whorl pattern of "late" fluorescein staining) with best corrected Snellen vision of 20/50. (B) 1 month following treatment of HSV immune stromal keratitis and uveitis which flared up 2 weeks after second dose of the Pfizer vaccine. (C) Slit lamp photograph with inactive herpetic disease but extensive advancement of the whorl pattern of "late" fluorescein staining indicating progression of limbal stem cell deficiency; patient photos courtesy of Clara C. Chan, MD

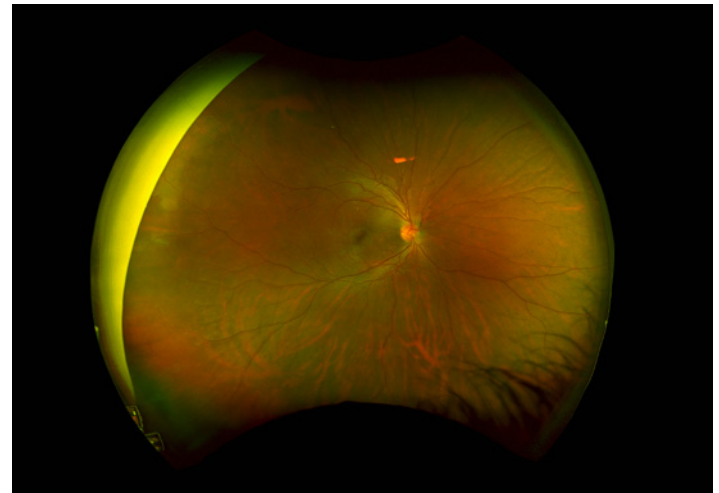
vascular leakage was reported.¹⁰ This case was treated with 50 mg oral prednisone daily with subsequent steroid taper, leading to an excellent visual outcome. Another group reported 6 cases of recurrent non-infectious panuveitis, intermediate or posterior uveitis following mRNA vaccination in patients with uveitis controlled with oral steroids or IMT.⁶ All cases were managed with local ophthalmic and/or systemic steroids, or escalation of baseline IMT, without lasting complications.⁶ In a review of almost 2.5 million Pfizer-BioNTech vaccinations in Israel, researchers identified 17 cases of intermediate, posterior, or panuveitis occurring within 3 weeks of inoculation.⁴ Although no treatment outcomes were reported, the study highlights the rare nature of vaccine-associated posterior uveitis.

There have been more than ten reported cases of Vogt-Koyanagi-Harada (VKH) onset or relapse following administration of all COVID-19 vaccine types, occurring within 1 day to six weeks after vaccination.^{7,11,12} This bilateral exudative panuveitis typically requires treatment with high-dose systemic steroids and/or IMT to achieve quiescence, though permanent vision loss can occur due to damage of the retinal pigment epithelium (RPE) and choroid.¹³ VKH is believed to be caused by T-cell mediated autoimmune reaction against melanocytes in the uvea and other target organs. Molecular mimicry, whereby vaccine epitopes resemble host epitopes and thereby trigger innate immune activation, is one of the hypothesized mechanisms of VKH activation following inoculation.¹² Despite a relatively prolonged treatment course requiring systemic corticosteroids and occasionally IMT, most patients with vaccine-related VKH achieve resolution of subretinal exudation and excellent visual acuity.^{12,13,14}

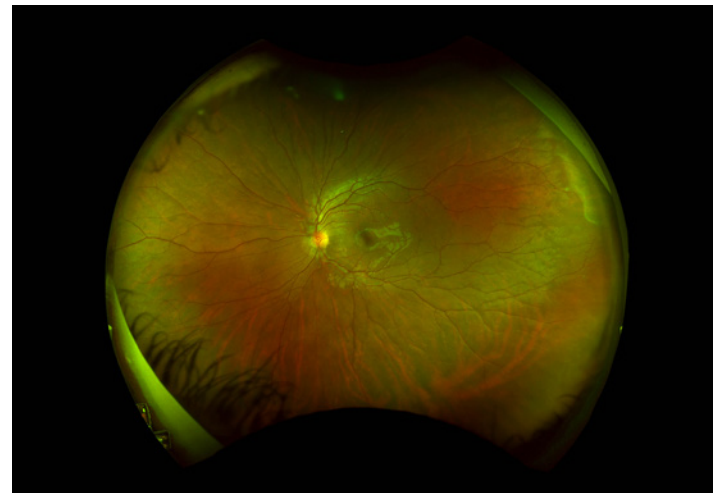
Similar to other reports of post-vaccination uveitis, white dot syndromes have been associated with COVID-19 vaccination. There was a reported case of unilateral acute posterior multifocal placoid pigment epitheliopathy 2 weeks following administration of the second dose of Pfizer-BioNTech vaccine in a healthy adolescent male.¹⁵ Oral steroids were initiated to treat mild vitreous cell, and the disease became inactive after several weeks. Visual acuity returned to baseline; however, RPE scarring remained. Multiple evanescent white dot syndrome (MEWDS) is a self-limited autoimmune chorioretinitis that typically affects young, myopic females and may be associated with a viral prodrome. Over ten cases of MEWDS have been reported following COVID-19 mRNA vaccination,^{7,16,17} inactivated,^{18,19} and protein subunit vaccines.²⁰ All cases resolved within several weeks.

We report one case of unilateral panuveitis with retinal vasculitis at our centre. A 29-year-old male, previously known for well-controlled idiopathic AU, presented with blurred vision 20 days after administration of his second mRNA vaccine dose. Moderate anterior chamber cell and flare, optic disc edema, and cystoid macular edema were noted OU (**Figures 3a-b**). Fluorescein angiography demonstrated cystoid macular edema and peripheral vascular leakage in both eyes (**Figures 3c-d**).

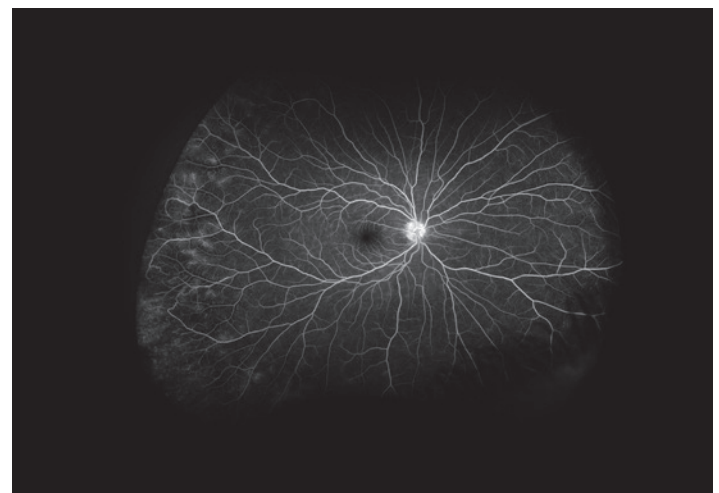
The intraocular inflammation and vasculitis initially resolved with the use of high dose oral prednisone (1mg/kg); however, retinal vasculitis recurred as steroids were tapered and methotrexate was initiated. Given the patient's history of uveitis prior to his vaccination, the relationship between COVID-19 vaccination and retinal vasculitis remains unclear.



A



B



C



D

Figure 3: Optos colour widefield photograph (Optos California) of the (A) right eye and (B) left eye demonstrating peripheral vascular sheathing and blunted foveal reflex (due to cystoid macular edema). Intravenous fluorescein angiography late phase images (Optos) of the (C) right eye and (D) left eye demonstrating leakage in macula and retinal periphery demonstrating cystoid macular edema and peripheral retinal vasculitis; patient photos courtesy of Derzko-Dzulynsky, MD, Emami, MD and Pereira, MD

Infectious posterior uveitis has also been reported following COVID-19 immunization. In 2021 researchers reported a single case of the development of unilateral varicella zoster virus acute necrotising retinitis (ARN) three days after receiving an adenovirus vector vaccine.²¹ The aqueous humour at presentation was positive for varicella zoster virus by qualitative polymerase chain reaction test. The patient had a history of diabetes mellitus. Despite appropriate systemic antiviral treatment and resolution of the active retinitis over several months, the patient's final visual acuity was impaired at 20/50 at final follow-up. Of note, the patient did not demonstrate antibodies to the SARS-CoV-2 spike glycoprotein on serologic testing despite previous vaccination, suggesting impaired immune function that may have contributed to development of ARN.²¹

PROPOSED MECHANISMS OF UVEITIS FOLLOWING SARS-COV-2 VACCINATION

Vaccine-associated uveitis is not a new phenomenon. In fact, uveitis flares have been reported following most widely-administered inoculations, most frequently for hepatitis B, human papilloma virus, Bacille Calmette-Guerin, influenza, and varicella zoster virus vaccines.^{22,23} Most cases of uveitis in this context are mild, short-lived, and resolve with observation or minimal intervention.²²

Multiple mechanisms may link COVID-19 vaccination and uveitis flares. Several explanations have been proposed, including: (1) molecular mimicry, whereby the vaccine antigen may resemble self-antigens (often uveal self-peptides) that activate adaptive immunity; (2) activation of sequestered self-antigens by innate and adaptive immune cells triggered by recent vaccination; and (3) over-secretion of inflammatory cytokines in the setting of vaccination that

cause additional recruitment of T-helper cells.²⁴ Molecular mimicry, in particular, has been implicated in HLA-B27-associated diseases. HLA-B27-expressing immune cells, including macrophages, have molecular similarity to certain bacterial and viral antigens. Peptides originating from viruses, bacteria, or other pathogens may therefore cross-react with HLA-B27 expressing immune cells due to antigen mimicry, initiating an inflammatory response.²⁵ This molecular pathway may explain relapses of HLA-B27 uveitis following COVID-19 vaccination. Some studies further suggest that the release of type 1 interferon induced by mRNA vaccines could initiate autoimmune activity resulting in uveitis.⁵ In addition, reports from the dermatology literature postulate that the large-scale shift of naïve CD8+ cells induced by vaccination may temporarily exacerbate T-cell mediated autoimmune conditions such as herpes zoster virus.^{26,27} It is possible that relapses of VKH and other cell-mediated uveitis conditions may be derived from a similar immunologic reaction post-vaccination.

RECOMMENDATIONS FOR OPHTHALMOLOGISTS

This literature review highlights the ocular inflammatory events associated with SARS-CoV-2 vaccination. It is reassuring that the vast majority of vaccine-associated uveitis cases are mild, anterior, of short duration, treated adequately with topical steroid drops, and have not been associated with permanent vision loss. Non-anterior uveitis occurs less frequently following COVID-19 vaccination and may require treatment with oral steroids or systemic immunosuppression. Pre-existing uveitis can be reactivated by COVID-19 vaccination, if not previously well-controlled. The onset of uveitis following COVID-19 vaccination ranges between 2 days to 3 weeks following vaccination.

In a study of approximately 2.5 million doses of administered Pfizer-BioNTech vaccine, an attributable risk of only one case of non-infectious uveitis per 1,000 vaccinated people among patients with a pre-existing history of uveitis was demonstrated.⁴ In contrast, the lack of vaccination carries considerable risk of COVID-19-related morbidity and mortality. Unvaccinated patients with a pre-existing history of non-infectious uveitis have been shown to be at higher risk of COVID-19 infection if taking systemic corticosteroids or tumour necrosis factor-alpha agents, and may be at higher risk of COVID-19-related hospitalization and death if taking systemic corticosteroids.²⁸

There is currently insufficient evidence to recommend universal monitoring for uveitis flares in patients who receive COVID-19 vaccination. However, chronic uveitis should be well-controlled prior to COVID-19 vaccination. Ophthalmologists may wish to counsel patients with a history of uveitis about the small, increased risk of uveitis exacerbation following COVID-19 immunization and consider following patients more closely after COVID-19 vaccination.

Ophthalmologists may consider increasing topical steroid medications prior to COVID-19 vaccinations in patients with a history of AU. This approach should not reduce the

immunogenicity of vaccination and may blunt the severity of potential ocular inflammation. We recommend that ophthalmologists collaborate with cross-disciplinary specialists to optimize the timing of IMT relative to COVID-19 vaccination to maximize vaccine immunogenicity.²⁹

Finally, we encourage all healthcare providers who suspect ocular adverse events following COVID-19 immunization to report their findings to local and national vaccine surveillance bodies to facilitate early identification of potential safety concerns.^{30,31}

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Pentosan polysulfate maculopathy: keep an eye out for this masquerader

Nieraj Jain, MD and Emily H. Jung

Pentosan polysulfate sodium (PPS) (Elmiron; Janssen Pharmaceuticals), a drug used to treat bladder pain and discomfort associated with interstitial cystitis (IC), has been linked to a distinctive vision-threatening maculopathy.¹ As with the case of hydroxychloroquine maculopathy, it is worthwhile for the general ophthalmologist to be familiar with this potentially preventable condition. In this article, we briefly summarize the evidence supporting this association, review the clinical manifestations of PPS maculopathy, and provide some guidance regarding screening protocols.

Pentosan polysulfate sodium is a semi-synthetic heparin-like macromolecule that was approved by Health Canada in 1993 for treatment of interstitial cystitis. Interstitial cystitis, also known as bladder pain syndrome, is a regional pain syndrome characterized by chronic discomfort in the bladder and pelvis, in addition to urinary frequency and urgency. Studies estimate that IC may affect more than one million individuals in the United States alone.² IC is estimated to account for about 3% or more of all outpatient urology clinic visits in Canada.³

While the exact mechanism of action is unknown, the therapeutic effects of PPS for IC appear to stem from its resemblance to glycosaminoglycans and its ability to adhere to the bladder wall mucosal membrane and control cell permeability, thereby acting as a buffer between irritants in the urine and the bladder epithelium.⁴ PPS is approved for oral use only, but intravesical administration has been used as an alternative.⁵ The most common side effects observed with PPS include hair loss, diarrhea, nausea, stomach pain, headache, dizziness, rash, and liver function abnormality. Two serious side effects that have been reported are increased bleeding and a pigmentary maculopathy.

Our group first described a distinctive maculopathy among a series of six patients undergoing long-term treatment with PPS in 2018.¹ Since then, many additional studies across numerous centers have corroborated this finding.⁶

STRENGTH OF ASSOCIATION

Several studies have identified an association between long-term PPS use and a unique pigmentary maculopathy. In a 2019 retrospective study, 14 of 219 patients with IC at a tertiary referral eye center exhibited the characteristic maculopathy.⁷ These 14 cases were exclusively among the 80 patients who reported prior PPS use; there was not a single case of this distinctive maculopathy among the 139 IC patients with no history of PPS use. Furthermore, of all medication exposures and other covariates evaluated, the only risk factor significantly associated with the presence of

this pigmentary maculopathy was exposure to PPS (odds ratio 11.25, 95% CI 3.69-34.33).⁷ Subsequent studies independently conducted at numerous centers have reported a significant dose-response relationship between PPS exposure and presence of maculopathy.⁸⁻¹³ A study from 2020 demonstrated prevalence rates of 13%, 30%, and 42% among patients with 500-999 grams (g), 1000-1499 g, and >1500 g of cumulative PPS exposure, respectively.⁸ In another study from earlier this year, researchers found prevalence rates of 46% and 83% among patients with cumulative PPS exposures of 1500-2000 g and ≥2000 g.¹¹

Studies of large administrative claims databases have yielded mixed findings. In a 2019 study analyzing claims data, the authors reported that PPS exposure was significantly associated with a new diagnosis of macular disease seven years after the initiation of the drug.¹⁴ In contrast to this, another claims database study did not find a significant association between PPS exposure and a new maculopathy diagnosis.¹⁵ However, when assessing these studies, clinicians must be aware of the inherent limitations in these datasets, which included patient visits having taken place prior to the widespread recognition of this novel maculopathy. In the latter study, only 0.26% of the PPS users had at least five years of exposure to the drug, and only 29% of all patients had an eye examination performed.¹⁵ It is likely that patients with early or mild disease did not have any notable findings on exam. Furthermore, eye examinations in these studies could have been performed at any time and not necessarily at the end of the observation period when the maculopathy was most likely to manifest.¹⁶

CLINICAL MANIFESTATIONS

Long-term use of PPS appears to be the primary risk factor in developing the characteristic maculopathy. The initial series from 2018 reported a median treatment duration of 186 months (range, 144-240 months) and median cumulative exposure of 2263 g (range, 1314-2774 g).¹ Subsequent studies have corroborated this finding, although several cases have been identified after just three years of PPS use.¹⁷ The prevalence of this condition remains unclear, but we believe the closest estimates to date were reported from the aforementioned study from the Kaiser Permanente Northern California health system [13%, 30%, and 42% among patients with 500-999 g (4.6-9.1 years at the standard daily dose), 1000-1499 g (9.2-13.7 years), and >1500 g (longer than 13.8 years) of cumulative PPS exposure, respectively].⁸

Affected patients commonly report difficulty reading, blurry vision, and prolonged dark adaptation. While most patients have preserved visual acuity, there have been cases of loss

of visual acuity as well, typically in the setting of progressive retinal pigment epithelium (RPE) atrophy, cystoid macular edema (CME), and/or macular neovascularization. A prospective study of visual function in PPS maculopathy demonstrated that patients may suffer from prominent visual disability despite relatively preserved visual acuity, with pronounced impact on low luminance visual function.¹⁸

On examination, PPS maculopathy may share some resemblance to age-related macular degeneration (AMD) and macular dystrophies. A large study at our institution found that 43% and 29% of affected patients initially carried a diagnosis of macular dystrophy and AMD, respectively.¹⁹ On closer evaluation, however, these conditions can be differentiated from each other through the use of multimodal imaging techniques.^{20,21}

Dilated fundus examination (DFE) may demonstrate parafoveal pigmented spots amidst yellowish subretinal deposits in mild disease, and paracentral RPE atrophy in more advanced disease (**Figure 1**). These findings can be quite subtle in some patients, and modern fundus imaging is an essential part of the diagnostic assessment. Fundus autofluorescence (FAF) imaging demonstrates a striking pattern of densely packed hypo- and hyper-autofluorescent spots that is symmetric between eyes and typically involves the central macula. In some cases, these changes can expand well beyond the vascular arcades. Near-infrared reflectance (NIR) and optical coherence tomography (OCT) imaging can also aid in establishing a diagnosis of PPS maculopathy, particularly in milder disease. OCT imaging can help distinguish this condition from typical AMD. Eyes with PPS maculopathy often contain focal nodular thickening of the RPE that casts a shadow on the underlying choroid. These “bumps” on OCT imaging appear to be at the level of the RPE itself and differ from the typical drusen or subretinal drusenoid deposits of AMD, which appear to be below or above the RPE, respectively.²¹

To date, no other risk factors for development of PPS maculopathy have been identified. Small studies have evaluated potential risk factors, such as smoking history,

diseases involving the kidney, liver, and spleen, and body mass index; however, no significant associations have been demonstrated.^{7,19} Furthermore, no genetic variants associated with PPS maculopathy have been identified to date.

MANAGEMENT

Currently there is no known treatment for PPS maculopathy. Thus, following a diagnosis of PPS maculopathy, patients and clinicians should have a discussion regarding drug discontinuation. If the decision is made to continue the use of PPS, patients with confirmed PPS maculopathy should continue to undergo regular comprehensive retina evaluations. It is important to note that there have been multiple reports of treatable vision-threatening sequelae, including CME and macular neovascularization.^{9,19,22}

Patients with CME have responded well to a wide range of therapies, including carbonic anhydrase inhibitors and anti-vascular endothelial growth factor (VEGF), and there have been reports of successful management of macular neovascularization with anti-VEGF treatment.^{19,22-24}

Studies evaluating the long-term prognosis after PPS cessation have suggested that there is no disease regression. A 2020 retrospective study analyzed 11 affected patients who were followed for a median of 11.5 months after PPS cessation.²⁵ Eyes with atrophy at baseline demonstrated growth of atrophy at a median linearized growth rate of 0.32 mm/year (IQR, 0.13-0.38 mm/year), and some eyes without atrophy at baseline were found to have new onset incomplete RPE and outer retinal atrophy on OCT imaging.²⁵ For comparison, growth of atrophy in geographic atrophy, an advanced form of non-neovascular age-related macular degeneration, has been estimated at 0.33 mm/year (IQR, 0.31-0.35 mm/year).²⁶ Multiple case reports have found that some patients developed initial symptoms of PPS maculopathy several years (up to six years) after discontinuing PPS.^{19,25,27,28}

SCREENING

In October 2019, Health Canada approved changes to the Elmiron label, noting the potential risk of pigmentary maculopathy. In June 2020, the United States Food and Drug Administration approved changes for its Elmiron label. In October 2020, Health Canada listed a personal history of any macular disease as a contraindication to PPS use and recommended that for patients with pre-existing ophthalmologic conditions, a comprehensive baseline retinal exam including color fundoscopic photography, OCT, and FAF imaging be performed prior to initiating PPS therapy.

At our institution, it is recommended that patients starting treatment with PPS undergo baseline screening and annual screening thereafter and that DFE, OCT imaging, FAF imaging, and NIR imaging be performed. Given the use of multimodal fundus imaging, retina specialists may be most comfortable performing these assessments. Clinicians should consider using the lowest dose and duration of therapy needed for disease control, and explore alternative IC therapies wherever possible.

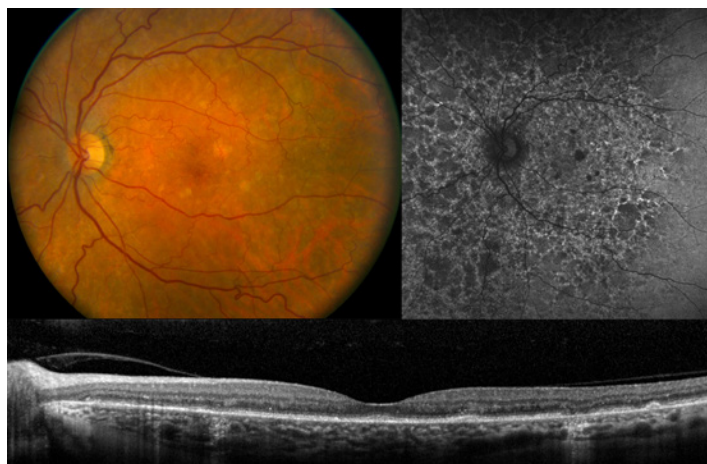


Figure 1: Multimodal fundus imaging of the left eye of a patient with pentosan polysulfate maculopathy. (Top Left) Color fundus photo; (Top Right) fundus autofluorescence image; (Bottom) optical coherence tomography image; images courtesy of Nieraj Jain, MD

In summary, ophthalmologists should take note of this newly recognized, preventable, vision-threatening maculopathy associated with long-term PPS use. Given that PPS has been used for decades, many under- and undiagnosed patients may already be in our clinics. Moving forward, ophthalmologists and PPS prescribers should consider implementing screening programs with multimodal fundus imaging and limiting the dose and duration of therapy wherever possible. Ongoing studies will likely refine our understanding of the prevalence and clinical manifestations of this distinctive maculopathy.

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Drug induced (toxic) glaucoma

Dima Kalache, MD

Glaucoma is the leading cause of irreversible blindness in the world and the second most common cause of blindness overall. The prevalence of glaucoma is approximately 3% of the population worldwide¹. Due to the fact that increasing age is a risk factor for the development of glaucoma, an increase in life expectancy worldwide will be associated with a predicted increase in the prevalence of glaucoma. Similarly, advancements in medicine and an aging population have led to an increase in polypharmacy. Nearly two-thirds of all US adults aged 40–64 and 90% of individuals ≥ 65 years of age have been prescribed 5 or more medications at a time². Unfortunately, when assessing glaucoma patients, physicians may overlook systemic medications and focus solely on the topical medications. However, many systemic drugs have been shown to cause or worsen glaucoma³. Therefore, the rise in polypharmacy and its effect on glaucoma must be better understood in order to decrease the worldwide glaucoma burden.

Drug-induced glaucoma, or toxic glaucoma, is a form of secondary glaucoma that can be distinguished by the mechanism causing the glaucoma: open angle or closed angle glaucoma. The overall incidence of drug-induced glaucoma is unknown.

OPEN ANGLE DRUG-INDUCED GLAUCOMA: **Corticosteroids**

The most common drug that induces open angle glaucoma is corticosteroids. Corticosteroids are used both systemically and locally for their anti-inflammatory properties.

Corticosteroid-induced glaucoma is seen most commonly

after topical drops, periocular, or intraocular injections. However, it can also occur after intranasal, inhalational, systemic use, and dermatological applications⁴.

Systemic treatment usually results in a bilateral increase in intraocular pressure (IOP), while topical treatment usually results in elevated intraocular pressure in the treated eye (although it can be bilateral). Common indications for the use of corticosteroid eye drops include anterior uveitis and post-operative inflammation. Additional uses of cortisone include peri-bulbar and intravitreal injections to treat inflammation and macular edema, respectively. Not surprisingly, intravitreal injections of steroids lead to the highest acute increase in intraocular pressure. This is followed by peri-bulbar injections, and finally topical eye drops. Systemic corticosteroids are also prescribed for many auto-immune diseases and local injections of steroids are often used to manage pain in rheumatological or orthopedic diseases. Although systemic use of steroids is less likely to cause glaucoma, if it does occur, it is not dose or duration dependent⁵.

Pathophysiology of corticosteroid-induced glaucoma

Corticosteroids increase IOP by causing structural and functional effects on the trabecular meshwork outflow system. This occurs through increased production as well as a decreased destruction of the extracellular matrix of the trabecular meshwork. The resulting increase in the deposition of glycosaminoglycans in the trabecular meshwork as well as the reduced activity of matrix metalloproteinases to remove the debris, increases the aqueous outflow resistance, leading to increased IOP⁴.

Epidemiology of corticosteroid-induced glaucoma

The onset and severity of IOP increase depends on the type of corticosteroid use, its frequency, duration, location, as well as patient risk factors. Increased IOP usually manifests 2 to 6 weeks following topical steroid use; however, it may occur earlier, namely among patients with a known history or predisposition for glaucoma prior to corticosteroid application.

Patients in whom an increase in intra-ocular pressure is seen post corticosteroid application, are known as “steroid-responders.” Patients with underlying primary open angle glaucoma (POAG) are at a much higher risk of significant steroid response. Additionally, studies have shown that a family history of glaucoma, diabetes mellitus, and connective tissue diseases such as rheumatoid arthritis can increase the risk of steroid response (**Table 1**). Furthermore, the elderly and children under the age of 6 are more prone to having a steroid response⁴.

Research has demonstrated three levels of response to steroids in the patient population^{6,7}.

- 1) High responders (4-6% of the population)
 - a. IOP above 31 mmHg or an increase of more than 15 mmHg from baseline pressure
- 2) Medium responders (~30-33% of the population)
 - a. IOP between 25-31 mmHg or an increase of 6-15 mmHg from baseline
- 3) Non-responders (~60-66% of the population)
 - a. IOP less than 20 mmHg or a rise of less than 6 mmHg from baseline

Diagnosis and Treatment

Similar to open angle glaucoma, patients with steroid-induced glaucoma are often asymptomatic. Thus, diagnosing steroid-induced glaucoma is the first step in initiating its treatment. The clinician’s awareness of the risks of corticosteroid-induced glaucoma as well as close follow up is important in preventing irreversible glaucoma damage. The suggested follow up should include baseline IOP measurements, followed by subsequent IOP measurements after two weeks, then every 4 to 6 weeks for about three months, and then semi-annually if the initial steroid response has been ruled out⁸.

Discontinuation of the offending agent, in this case the corticosteroid, is the first step. Stopping the medication usually results in a decrease in IOP within 2-4 weeks but can take up to 2 months. The duration of the corticosteroid use may also dictate the time required for the IOP to return to baseline as well as its potential reversibility⁸. If the corticosteroid cannot be completely discontinued, then

titrating to a lower potency corticosteroid or decreasing the frequency may help decrease the IOP. Glaucoma treatment, medical and/or surgical, may also be required if the pressure does not reverse to baseline or glaucoma progression occurs.

Anti-VEGF intravitreal injections

Repetitive intravitreal anti-VEGF injections are frequently used to treat many retinal diseases including, but not limited to, diabetic macular edema, wet age-related macular degeneration, as well as retinal neovascularization due to any ischemic retinal cause.

It is well known that there is an immediate increase in intra-ocular pressure immediately post intra-vitreous injection due to a volume effect⁹. The average IOP within 1 minute of injection has been reported to be >40 mmHg; however, this increase is often times transient and well tolerated by most patients⁹. Nonetheless, serial injections of anti-VEGF can lead to a sustained increase in intra-ocular pressure¹⁰. Recent meta-analysis data showed that the prevalence of sustained IOP increase (> 25 mmHG) post anti-VEGF injection is approximately 5%¹¹. Furthermore, this sustained increase in IOP may be dose related. Several studies have shown that patients receiving 7 or more injections per year have a higher prevalence of sustained IOP rise than those receiving 3 or less¹².

Pathophysiology

Several factors may contribute to the formation of glaucoma post intra-vitreous injections. Chronic elevation in IOP might be related to repeated and ongoing injury to the trabecular meshwork from the high volume, alterations in levels of trabecular meshwork vasodilating modulators such as nitric oxide, toxic effects of drugs or drug delivery, and/or inflammatory damage¹².

Treatment

Careful monitoring for sustained IOP rise after repeated intra-vitreous injections is important to prevent further glaucoma damage. This includes regular IOP monitoring as well as RNFL imaging. Pre-treatment with anti-glaucoma drops may be used to lower intra-ocular pressure immediately post injection as well as 20 minutes after and can be considered as standard procedure in patients with repeated injections. Furthermore, anterior chamber paracentesis can also be performed to lower intra-ocular pressure post-injection¹². Further studies are needed to evaluate whether a lower number of injections using a treat-and-extend protocol and/or a lower sized molecule of anti-VEGF medications can help reduce IOP spikes and sustained IOP elevation post injection¹².

INCIDENCE OF STEROID RESPONSE (%)			
	NON RESPONDERS	MODERATE RESPONDERS	HIGH RESPONDERS
Normal population	60	35	5
Primary open angle glaucoma (POAG)	0	10	90
Family history of POAG	20	50	30

Table 1: Steroid responsiveness in nonglaucomatous, glaucomatous, and glaucoma suspect eyes; adapted from Phulke S et al, 2017

CLOSED ANGLE DRUG-INDUCED GLAUCOMA:

Closed angle glaucoma occurs when there is a physical obstruction of the drainage angle. This can occur through two mechanisms: anterior pulling or posterior pushing of the iris towards the angle.

Anterior pulling angle closure glaucoma occurs when the iris is pulled forward to block the angle through membranous formation and/or synechiae, leading to a reduction in aqueous outflow facility. This is seen in cases of neovascular glaucoma, uveitis, as well as fibrous ingrowth/epithelial downgrowth.

Posterior pushing mechanism occurs when the iris/lens diaphragm is pushed forward with anteriorly-directed force to cause blockage of the angle (**Figure 1**). Risk factors for angle closure include a shallow anterior chamber, short eyes, plateau iris, lens rise or large lens, tumors, and choroidal detachment/effusions. Drug-induced glaucoma is thought to be caused by an anterior rotation of the iris/lens diaphragm and/or pupillary dilation that leads to closure of the drainage angle. Therefore, any systemic medication that dilates the pupils has an increased risk of inducing angle closure in patients with already narrow angles and shallow anterior chambers. Additionally, because these medications are taken orally, they may potentiate bilateral angle closure glaucoma. Patients may be symptomatic and can often complain of eye pain, blurry vision, headache, as well as nausea and vomiting due to the acute rise in IOP.

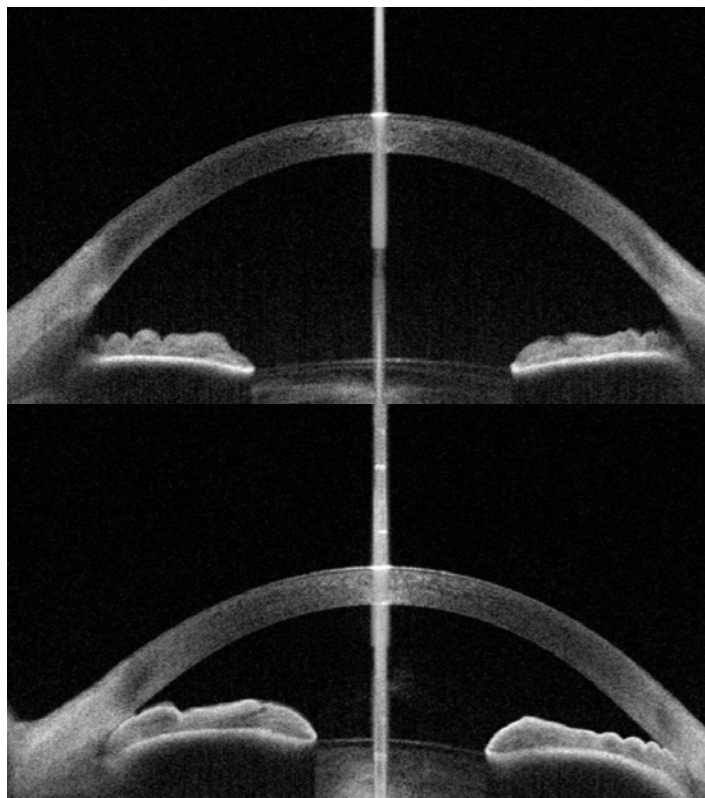


Figure 1: A) Anterior segment OCT of an open angle B) Anterior segment OCT of a closed angle and narrow anterior chamber. Patients with closed angles have a higher risk of acute angle closure in the context of drug-induced glaucoma; photo courtesy of Hady Saheb, MD, MPH.

1) Sulfa-based medications

Sulfa based drugs that have been associated with angle closure glaucoma include acetazolamide, a carbonic anhydrase inhibitor that is used as a diuretic and ironically used in ophthalmology to lower intraocular pressure; hydrochlorothiazide, an anti-hypertensive medication, and cotrimoxazole, an antibiotic often prescribed to treat urinary tract infections. Topiramate, a carbonic anhydrase inhibitor that is a sulfamate-substituted monosaccharide, that is frequently used as an anti-epileptic medication, is most commonly associated with inducing angle closure glaucoma.

Sulfa-based medications are thought to cause angle closure glaucoma through ciliary body edema and expansion that results in zonule laxity. This causes anterior rotation of the iris/lens diaphragm forward with resulting angle closure¹³. This can occur as early as two weeks after initiating the medication¹⁴. Due to its mechanism of action, there is no associated pupillary block and an iridotomy is not effective in treating the angle closure in these cases. Therefore, to treat sulfa-induced angle closure, the medication should be discontinued and the pressure should be treated using medical and or surgical therapy. Studies involving case reports have shown that if identified and treated early, discontinuation of the medication may lead to an improvement of intraocular pressure within hours or days, thereby preventing further glaucoma damage¹⁴.

2) Antidepressants

Fluoxetine, paroxetine, fluvoxamine (all selective serotonin reuptake inhibitors) and venlafaxine (a serotonin and noradrenaline reuptake inhibitor) have been associated with angle-closure glaucoma. The exact mechanism of angle closure with these medications is not known, however, it is thought to be due to the anticholinergic effects of these medications and/or pupil dilation from the increased level of serotonin. The acute angle closure can occur soon after starting these medications as well as after several days¹⁵. Treatment of acute angle closure in these cases requires discontinuation of the antidepressant and the performing of laser peripheral iridotomy to remove any component of pupillary block.

3) Antihistamines

Antihistamine medications such as ranitidine are H1 or H2 receptor antagonists that are used to treat allergies including allergic conjunctivitis. They have a weak anticholinergic effect that induces pupillary dilation and may induce angle closure glaucoma in susceptible patients¹⁵. Treatment of the glaucoma requires discontinuation of the medication and the lowering of the intraocular pressure through laser peripheral iridotomy and/or topical glaucoma medications.

4) Anticholinergic agents

Anticholinergic agents such as atropine and disopyramide are used to treat cardiac arrhythmias. The anticholinergic effect of these medications induces pupillary mydriasis and subsequent pupillary block and angle closure glaucoma in

at-risk patients¹⁵. Treatment of the glaucoma requires discontinuation of the medication and the lowering of the intraocular pressure through laser peripheral iridotomy and/or topical glaucoma medications.

5) Anticoagulants

Warfarin and other anticoagulants can increase the risk of hemorrhagic choroidal detachments (spontaneous or post-traumatic) that can lead to posterior pushing of the lens/iris diaphragm forward, leading to angle closure glaucoma¹⁵. Treatment requires discontinuation of the anti-coagulant, if possible, in addition to medical glaucoma therapy. Drainage of the choroidal hemorrhage may be indicated in certain cases. Since there is no associated

pupillary block, peripheral iridotomy is ineffective in the management of the acute attack.

CONCLUSION

Characteristic optic nerve damage due to glaucoma, with or without elevated intra-ocular pressure, cannot be differentiated by its mechanism. Therefore, secondary drug-induced glaucoma can mimic primary glaucoma (angle closure or open angle). Additionally, as noted previously, patients with drug-induced glaucoma can be symptomatic or asymptomatic. Therefore, when assessing a patient for potential glaucoma, it is imperative that the physician review the complete list of the patient's medications paying careful attention to those that may induce glaucoma in order to properly manage the disease.

DRUG CLASS	EXAMPLE OF DRUG	MECHANISM OF GLAUCOMA	TREATMENT
Corticosteroids	Dexamethasone Prednisone	Open angle glaucoma - Increasing resistance of outflow pathway	Withdrawing agent +/- medical/and or surgical therapy
Anti-VEGF	Bevacizumab Ranibizumab Aflibercept	Open angle glaucoma -Damage to the trabecular meshwork over repeated injections	Pre injection lowering of IOP with topical glaucoma medications and/or anterior chamber paracentesis
Sulfa based drugs	Acetazolamide Topiramate	Angle closure glaucoma- Ciliary body and choroidal effusions leading to anterior rotation of the lens/iris diaphragm	Withdrawing agent +/- medical/and or surgical therapy
Antidepressants	Fluoxetine Paroxetine Fluvoxamine Venlafaxine	Angle closure glaucoma- Pupillary block	Withdrawing agent and laser peripheral iridotomy +/- medical glaucoma therapy
Antihistamines	Cimetidine Ranitidine	Angle closure glaucoma- Pupillary block	Withdrawing agent and laser peripheral iridotomy +/- medical glaucoma therapy
Anticoagulant	Warfarin	Angle closure glaucoma- Anterior rotation of lens/iris diaphragm	Withdrawing agent + medical +/-surgical therapy

Table 2: Drug classes and their impact on glaucoma; courtesy of Dima Kalache, MD

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Screening for depression and suicide: a vital part of glaucoma care

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Case Presentation

In late 2014 a young male patient, M.Y., presented with previously diagnosed juvenile glaucoma, treated with drops. M.Y. was not compliant with treatment and had stopped his medication 3 years prior to this visit. Upon examination, his visual acuity was 20/25 and 20/50 +2 in the right and left eyes, respectively. His intraocular pressure (IOP) was 49 mmHg (OD) and 52 mmHg (OS). The visual field showed eccentric 5 degrees of vision of the right eye and 5-10 degrees of the left eye. The patient was initiated on the maximum tolerable medical treatment, including oral medication for glaucoma. A month later he had the first of two non-penetrating glaucoma surgeries, followed by monthly follow-ups. Several months later he had the same surgery for the second eye and resumed monthly follow-ups with bleb needling and anti-VEGF injections. At his last appointment, M.Y. refused visual acuity testing, and his IOP was 17 mmHg (OD) and 18 mmHg (OS) on maximal tolerated medical treatment. The decision was made to place a filtering implant device in the left eye, followed by surgery for the right eye at a later date. All risks and benefits of the procedure were carefully explained, including the possibility of loss of vision.

M.Y. did not show up on his surgery date and we later found out that he had committed suicide. His death left many questions about the potential association between his advanced glaucoma diagnosis and suicide, including if there was anything that could have been done to prevent such a tragic outcome.

More and more patients are consulting the internet for medical information following a diagnosis or before consenting to medical or surgical treatment. A quick Google search for “*What happens if I get diagnosed with glaucoma*”, reveals some very discouraging information, including “*glaucoma can lead to blindness*”. Many people will not read further to better understand that, with appropriate treatment and follow-up, they can preserve good functional vision for life. Instead, they focus on the potential negative outcomes such as job loss, loss of independence and a vastly reduced quality of life. It is important to remember that “a patient’s assessment of his or her objective situation can differ significantly from a physician’s assessment and prognosis.”¹ At the time of diagnosis, patients need to know and hear the “good news”, such as the treatments that are available and the backup options in case of treatment failure. Explaining the treatment strategy can help prevent or ease anxiety. Managing expectations can help build trust between the patient and the doctor and provides the patient confidence in the treatment plan.

BREAKING BAD NEWS

Unfortunately, there will be occasions when physicians are required to share a difficult diagnosis and/or long-term prognosis. One protocol for “breaking bad news”, involves the utilization of the six-step SPIKES protocol (**Figure 1**).^{2,3} The first step is setting up the interview. Invite the patient to a quiet room and close the door to protect their privacy. Ask the patient if they would like a family member or friend with them for support. Establish a rapport with the patient and ensure that your time with them is uninterrupted and

sufficient to answer any questions they may have. The second step includes assessing the patient’s perception of the problem. Ask the patient what they already know about glaucoma to give you an idea of their level of understanding of the condition, as well as to reveal any fears they may have based on their knowledge that will help guide the discussion.

Step 3 involves gaining the permission of the patient to share the details of his/her illness. This step is often overlooked, but clinicians are reminded that some patients wish to delay or avoid discussing their illness. Step 4 centers on providing knowledge and information to the patient. The physician and/or the clinic staff must teach the patient about the disease and the available treatment options. This information that is shared should be concise and adapted to the patient’s knowledge and baseline health literacy. During this step, it is crucial to share positive aspects such as the availability of treatment(s) and its success rates in treating the disease. The fifth step involves the addressing of emotions. Identify the emotions expressed by the patient and try to isolate the cause. Ensure that the patient is given the opportunity to express his/her emotions so that an appropriate response, demonstrating an understanding of the emotions and what caused them, is shared. Remember that the patient who appears calm may still have concerns and fears that are not being expressed outwardly. The sixth step involves summarizing. Ask the patient if he/she has any other questions, particularly if they have not been very vocal, then explain important next steps.^{2,3}

STEP 1: S—SETTING UP THE INTERVIEW

- Arrange for privacy
- Involve significant others
- Sit down
- Make connection and establish rapport with the patient
- Manage time constraints and interruptions.

STEP 2: P—ASSESSING THE PATIENT'S PERCEPTION

- Determine what the patient knows about the medical condition or what they suspect
- Listen for and assess the patient's level of comprehension
- Accept denial but do not confront at this stage.

STEP 3: I—OBTAINING THE PATIENT'S INVITATION

- Ask the patient if they wish to know the details of the medical condition and/or treatment
- Accept patient's right not to know
- Offer to answer questions later if they wish

STEP 4: K—GIVING KNOWLEDGE AND INFORMATION TO THE PATIENT

- Use language the patient understands
- Consider educational level, socio-cultural background, current emotional state
- Give information in small chunks
- Check whether the patient understood the information
- Respond to the patient's reactions as they occur
- Give any positive aspects first e.g.: Cancer has not spread to lymph nodes, highly responsive to therapy, treatment available locally etc.
- Give facts accurately about treatment options, prognosis, costs etc.

STEP 5: E—ADDRESSING THE PATIENT'S EMOTIONS WITH EMPATHIC RESPONSES

1. Identify emotion expressed by the patient (sadness, silence, shock etc.)
2. Identify cause/ source of emotion
3. Give the patient time express his or her feelings, and then respond in a way that demonstrates you have recognized connection between 1 and 2.

STEP 6: S—STRATEGY

- Close the interview
- Ask whether they want to clarify something else
- Offer agenda for the next meeting eg: I will speak to you again when we have the opinion of cancer specialist

Figure 1: SPIKES: A Six-Step Strategy for Breaking Bad News; adapted from Singh et al, 2017

DEPRESSION IN GLAUCOMA PATIENTS

Depression in glaucoma patients has been described and studied. In a population-based retrospective cohort study using the Taiwan National Health Insurance Research Database from January 1, 2001, through December 31, 2011, glaucoma patients (n=8777) and age- and gender-matched control subjects without glaucoma (n=35,108) were compared for depression. The results of this study demonstrated that glaucoma patients had a significantly higher cumulative hazard of depression compared to the control group (p < 0.0001). The Cox regression model indicated that the glaucoma group had a significantly higher risk of depression (adjusted HR=1.71). Researchers also looked at predictors of depression within the glaucoma group and concluded that older age, female gender, low income, substance abuse, and living alone were significant risk factors for depression. However, the use of β -blocker eye drops and the number of glaucoma medications were not significant risk factors for depression.⁴

In another study researchers looked at depression in newly diagnosed open-angle glaucoma patients and found that 12.5% of subjects reported symptoms associated with mild or worse depression, and 55.3% reported at least one depressive symptom. By one-year post-treatment, symptoms associated with mild or worse depression had decreased to 6.7% and 38.4% of patients had reported at least one depressive symptom. These measures continued to decline over the next 9 years.⁵ The study reported several factors predictive for the risk of depression. The strongest association was with self-reported visual function. In contrast, clinical measurements such as MD (mean deviation) and IOP showed no correlation with depression.⁵ While the MD and IOP are variables that play an important role in treatment decision-making for the clinician, the results of this study suggest that the subjective feelings of the patient may be as important as the clinical factors in managing glaucoma.

According to a systematic review and meta-analysis performed, glaucoma is the ophthalmologic disease with the second-highest prevalence of depression or depressive symptoms at 25%.⁶

SCREENING FOR DEPRESSION

In a study from 2014, researchers found that a simple 2-question questionnaire (PHQ-2: Patient Health Questionnaire-2) was an acceptable method to use in ophthalmology clinics to screen for signs of depressive symptoms.⁷ This questionnaire asks if the patient has felt down, depressed, or hopeless and if they have had little interest or pleasure in doing things in the past 2 weeks. The answers are graded on a scale from 0 (not at all) to 3 (very often). A score equal to or greater than 3 has high sensitivity (83%) and specificity (92%) for depression.⁸

THE RELATIONSHIP BETWEEN DEPRESSION AND SUICIDE

It has been observed that depressed patients have a higher rate of mortality from suicide, highlighting the need for screening for depression and suicide.⁹ Suicide screening can be done quickly by asking 5 simple questions (**Figure 2**).¹⁰

According to The Canada Public Health report from 2022, 11.8% of people report having had suicidal thoughts during their life.¹¹ Despite this ominous statistic that demonstrates about 1 in 9 of our patients have had suicidal thoughts in the past, screening is rarely done.

MANAGEMENT OF A SUICIDAL PATIENT IN THE CLINIC

A patient that has been identified as having or being at risk for suicidal ideation should be transferred to the emergency department for psychiatric evaluation and possible inpatient hospitalization or referred for psychiatric evaluation on an outpatient basis. Clinicians should keep in mind that while awaiting transfer, the ophthalmology clinic is responsible for the patient’s safety.¹² Unfortunately, some patients may succumb to suicide which may be difficult for the treating physician to psychologically process and accept, leading to stress and anxiety. Talking to colleagues, particularly those who may have had similar experiences, may be helpful. Clinicians may also wish to review the patient’s chart to gain a greater understanding of the situation.^{13,14}

WHAT CAN WE DO DIFFERENTLY?

Preventing suicide and reducing the rate of depression in glaucoma patients is a team effort. Training clinic staff (i.e. assistants and nurses) to work with low-vision patients by educating them on how to question patients about depression and suicide can be extremely helpful in mitigating the risk. Clinic staff can provide basic information about glaucoma, treatment, and follow-up visits as well as emotional support. For some patients with anxiety or depression, care coordination involving follow-up visits with an optometrist can be reassuring. In addition, family members can be helpful, especially for older patients or those with comorbidities, with the administration of topical medications and with travel that is related to follow-up medical appointments.

Referring patients to a vision rehabilitation center may also be useful once the patient’s vision loss interferes with their activities of daily living. The resources provided by the vision rehabilitation center as well as the support that comes from interacting with other similar patients with vision loss can help patients accept and thrive while living with their glaucoma.

CONCLUSION

By remaining alert to the potential for negative emotions surrounding a glaucoma diagnosis and treatment, clinicians can intervene earlier by referring them for a consultation with a psychologist thereby preventing the onset of depression. Ultimately, listening to patients and understanding their perceptions and fears serves as an important reminder that we treat not only the disease, but the patient with the disease.

ASK THE PATIENT
1. In the past few weeks, have you wished you were dead?
2. In the past few weeks, have you felt that you or your family would be better off if you were dead?
3. In the past week, have you been having thoughts about killing yourself?
4. Have you ever tried to kill yourself?
IF THE PATIENT ANSWERS YES TO ANY OF THE ABOVE, ASK THE FOLLOWING ACUITY QUESTION:
5. Are you having thoughts of killing yourself right now? ¹⁰

Figure 2: ASQ Questionnaire; NIMH, accessed June 2022

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