Title:

Photophobia – What's new?

Learning Objectives:

1. To review the clinical characteristics and disorders associated with photophobia

2. To provide an update on the pathophysiology of photophobia

3. To provide an approach to diagnosis and treatment of photophobia

CME Questions:

1. Which of the following is true
   a) uveitis is the most common ocular cause of photophobia
   b) the use of sunglasses indoors should be strongly discouraged in patients with photophobia
   c) psychiatric disorder is the most common cause of photophobia in patients with a normal neuro-ophthalmic examination
   d) approximately 50% of patients with blepharospasm suffer from light sensitivity

2. The intrinsically photosensitive retinal ganglion cells are also known as:
   a) amacrine cells
   b) bipolar cells
   c) melanopsin cells
   d) horizontal cells

3. Migraineurs are particularly sensitive to which wavelength?
   a) 425 nm
   b) 480 nm
   c) 550 nm
   d) 630 nm

Keywords (Max 5):

1. Photophobia

2. Migraine

3. Blepharospasm

4. Melanopsin

5. FL-41 tint

Introduction/Abstract:

Photophobia, an abnormal intolerance to light, is associated with a number of ophthalmic and neurologic conditions. However, in the presence of a normal neuro-ophthalmic examination, the most common conditions associated with photophobia are migraine, blepharospasm, and traumatic brain injury. Recent evidence indicates that the intrinsically photosensitive retinal ganglion cells play a key role in the pathophysiology of photophobia. Although pharmacologic manipulation of intrinsically photosensitive retinal ganglion cells may be possible in the future, current therapies are directed at optical modulation of these cells.

Body:

WHY WE HATE PHOTOPHOBIA

In medicine we are taught that 80% of the time, one should be able to make a diagnosis based on the history alone. The practice of ophthalmology turns that dictum on its ear, as 80% of the time an ophthalmologist can make the correct diagnosis based on the examination alone, without any history. The ophthalmologist's microscopes and lenses enable him or her to rapidly diagnose corneal ulcers, cataracts, glaucoma and macular degeneration. For this reason, ophthalmologists are understandably uncomfortable when a patient's chief complaint is photophobia and the ophthalmic examination is entirely normal. However, armed with a bit of knowledge about the conditions that most commonly cause this symptom, neither the patient nor the neuro-ophthalmologist need despair.

CLINICAL PRESENTATION

The definition of photophobia is an abnormal intolerance to light, but no patient will ever walk into your clinic with a chief complaint of abnormal intolerance to light. What they will tell you is that they are light sensitive in situations where most other people are not. Some patients will recognize that they are especially sensitive to artificial indoor lighting. The perspicacious patient will recognize that they're specifically sensitive to *non-incandescent* artificial indoor light. Computer monitors are another common source of discomfort for the photophobic patient. These patients tend to have less trouble with natural light from the sun, unless they are faced with glare from snow or other highly reflective surfaces.

Most patients with photophobia will have a normal eye and neurologic exam, but there are still a few signs to observe: It's not uncommon for photophobic patients to be seen in the waiting room wearing sunglasses. If you walk into an exam lane and all the lights have been turned out, chances are your patient has photophobia. I can recall a patient seen in residency who sat with her long hair pulled over her eyes.

CONDITIONS ASSOCIATED WITH PHOTOPHOBIA

A number of ophthalmic and neurologic conditions are associated with photophobia (Table 1). However, most of these conditions are associated with additional signs and symptoms. Although not a neuro-ophthalmic condition, dry eye is one of the most commonly encountered conditions in an ophthalmic practice and is the most common ocular cause of photophobia. The majority of patients complain of itchy, dry, scratchy, burny eyes. Dry eye can sometimes be more challenging to diagnose when patients present with atypical symptoms. Useful examination tools include a careful evaluation of the tear film, tear film breakup time, corneal staining with fluorescein or rose bengal, and Schirmer test. In some neurologic conditions such as supranuclear palsy and Parkinson disease, severe dry eye syndrome is seen in nearly all affected patients. A subset of these patients may also complain of photophobia.

Chronic dry eyes can lead to corneal neuropathy, a condition also frequently associated with photophobia. Resolution of the pain after instillation of topical anesthetic drops in a patient with an otherwise unrevealing anterior segment evaluation should raise a suspicion for corneal neuropathy. Other causes of corneal neuropathy include zoster keratitis, diabetic neuropathy, and chemotherapy.

OCULAR
Anterior segment
Dry eyes: the most common ocular cause
Ocular inflammation (iritis, uveitis)

Conjunctivitis
Corneal diseases (corneal neuropathy, interstitial keratitis)
Blepharitis
Bilateral acute iris transillumination defects
Pterygium
Posterior segment
Vitritis, uveitis
Photoreceptor dysfunction/retinal dsytrophy (albinism, achromatopsia, cone dystrophy, retinitis pigmentosa)
Alström syndrome
Sjogren-Larsson syndrome
OPTIC NERVE
Optic neuritis
Papilledema
CHIASM
Pituitary tumor (including apoplexy)
Hypophysitis
THALAMIC PATHOLOGY (tumor, ischemia, hemorrhage)
OCCIPITAL LOBE
Alteration in excitability (migraine)
NEUROLOGIC
Migraine: the most common neurologic cause
Blepharospasm
Progressive supranuclear palsy
Traumatic brain injury
Meningeal irritation (meningitis, subarachnoid hemorrhage)
PSYCHIATRIC
Agoraphobia
Anxiety disorder (panic disorder)
Depression
MEDICATIONS
Barbiturates
Benzodiazepam
Chloroquine
Methylphenidate
Haloperidol
Zoledronate
OTHER
Hangover headache
Neurasthenia (chronic fatigue)
Fibromyalgia
Measles
Rabies
Inflammatory bowel disease
IFAP syndrome (ichthyosis follicularis,alopecia and photophobia)

PPK (psoriasiform lesions and palmoplantar keratoderma)
Trisomy 18
Zinc deficiency with exocrine insufficiency

TABLE 1: Conditions associated with photophobia

(Digre KB, Brennan KC. Journal of Neuro-Ophthalmology: March 2012 - Volume 32 - Issue 1 - p 68–81)

If your patient has a normal neuro-ophthalmic examination, they are most likely to have one of three conditions: migraine, blepharospasm, or traumatic brain injury.

Migraine affects approximately 9% of men and 18% of women, making it the most common neurologic condition. Nearly all migraineurs report light sensitivity during a headache, but many will also tell you that certain kinds of light can trigger a migraine. A subset of these patients will report chronic light sensitivity, even when they don't have a headache. Many patients with migraine are undiagnosed or misdiagnosed, so careful questioning may be required in order to identify migraines.

Similarly, nearly all patients with benign essential blepharospasm (BEB) have light sensitivity. Light makes their spasms worse and spasms make their light sensitivity worse. Many of these patients have chronic light sensitivity and addressing light sensitivity is a cornerstone of BEB treatment. Dry eye syndrome is almost universally seen in blepharospasm patients and aggressive dry eye therapy should be pursued.

The association between traumatic brain injury (TBI) and photophobia has gained more attention in recent years, not in small part due to the number of veterans returning from Iraq and Afghanistan with TBI. Patients with TBI can have several different visual complaints, but photophobia is one of the most common. These patients may also have migraine and/or chronic daily headache, so it's not entirely clear if the photophobia is a primary or secondary symptom of their brain injury.

Photophobia has been reported in cohorts with panic-agoraphobia and depression. However, I have personally never encountered a patient who presented with photophobia due primarily to a psychiatric condition. Anxiety and depression are frequent comorbidities of migraine and some of these patients will of course also have photophobia.

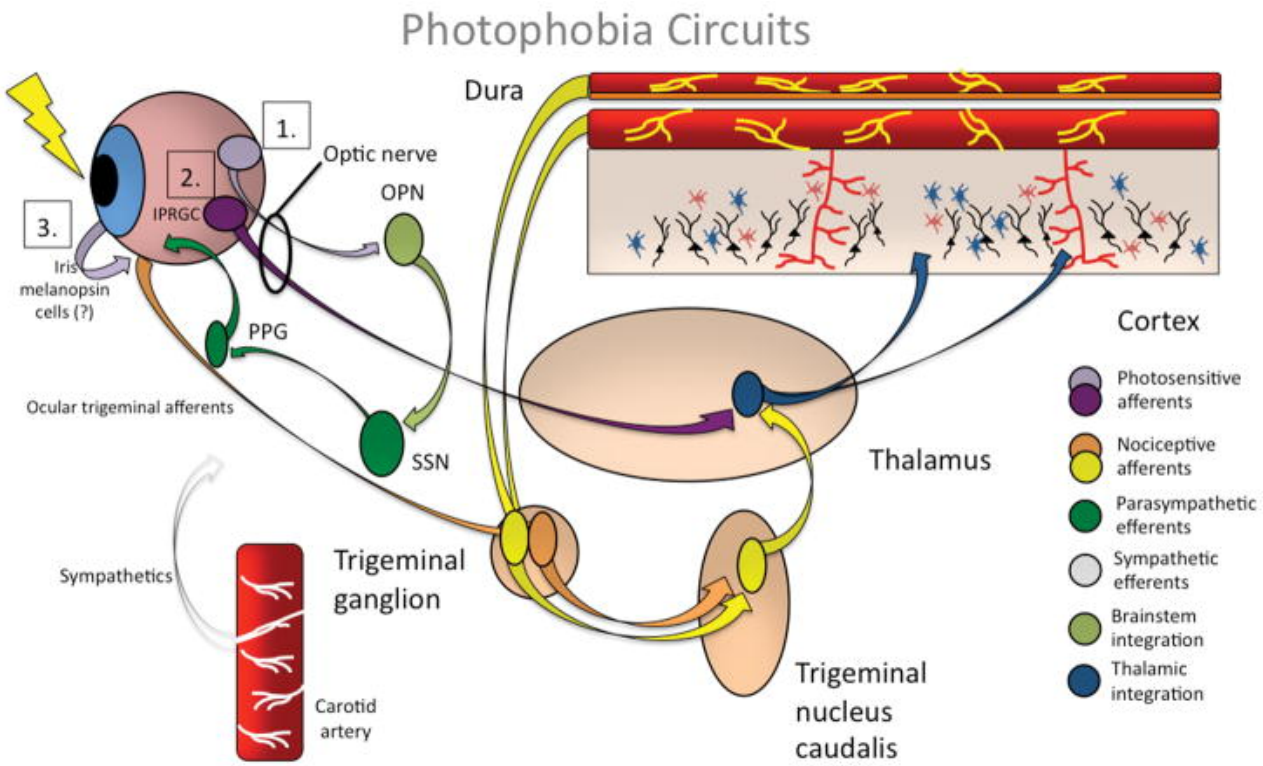
PATHOPHYSIOLOGY

For years clinical researchers have hypothesized about the existence of a photophobia "transducer" in the eye. A bright light, such as directly viewing the sun, will elicit the sensation of pain in nearly everyone. This painful sensation is almost certainly a protective response and is probably shared by all vertebrates. Light induced pain discourages us from viewing intensely bright objects that could harm our retina. But how does light get transduced into a painful stimulus?

The answer appears to reside with the intrinsically photosensitive retinal ganglion cell (IPRGC), also known as a melanopsin cell. I consider the discovery of these cells to be one of the most important discoveries about retinal physiology in the last 50 years. About 10% of all retinal ganglion cells are IPRGCs. Unlike their cousins who send their axons to the lateral geniculate, these cells send their axons to the suprachiasmatic nucleus and the Edinger-Westphal nucleus. In the suprachiasmatic nucleus these cells entrain circadian rhythms. In the Edinger-Westphal nucleus they control the pupillary light response. More recently, these cells have also been shown to project to pain centers in the thalamus. This connection may be an integral part of the "photophobia pathway" (Figure 1). Perhaps this connection or this pathway has a pathologic gain in patients with certain neurologic conditions?

IPRGCs contain the photopigment melanopsin, a chromophore that is related to and probably an evolutionary forerunner of rhodopsin. Because they contain a photopigment, these cells are "intrinsically photosensitive", meaning they can be stimulated by light in the absence of input from the traditional photoreceptors, rods and cones. The ability of these cells to become activated in the absence of input from photoreceptors likely explains the observation that some patients with photoreceptor degenerations (e.g. retinitis pigmentosa) can be exquisitely light sensitive. The action spectrum of IPRGCs peaks at 480 nm, midway between the action spectrum of green and blue cones. Although they are intrinsically photosensitive, IPRGCs are also stimulated by input from rods and cones, meaning that they can be activated by wavelengths other than 480nm.

FIGURE 1



Photophobia circuits
1. Ganglion cells project light-related signaling to the olivary pretectal nucleus (OPN; light green). OPN projections activate superior salivatory nucleus (SSN; dark green), which via pterygopalatine ganglion, causes ocular vasodilation and activation of ocular trigeminal afferents (orange) which are heavily expressed on blood vessels. These afferents, with cell bodies in the trigeminal ganglion, project to trigeminal nucleus caudalis, thalamus and cortex. **2.** Intrinsically photosensitive retinal ganglion cells (IPRGCs) project directly to thalamic neurons (blue) that also receive intracranial nociceptive afferent signal (yellow neurons in trigeminal ganglion and trigeminal nucleus caudalis. Thalamic neurons fire in response to light and pain stimuli. Their output projects diffusely to sensory and association cortex. **3.** Melanopsin-containing, intrinsically photosensitive ganglion-like cells have been identified in rodent iris. These afferents may explain the fact that light can activate trigeminal blink reflex even after the optic nerve (through which circuits 1. and 2. pass) has been sectioned. Note that all three circuits may interact at different locations. (Digre KB, Brennan KC. Journal of Neuro-Ophthalmology: March 2012 - Volume 32 - Issue 1 - p 68–81).

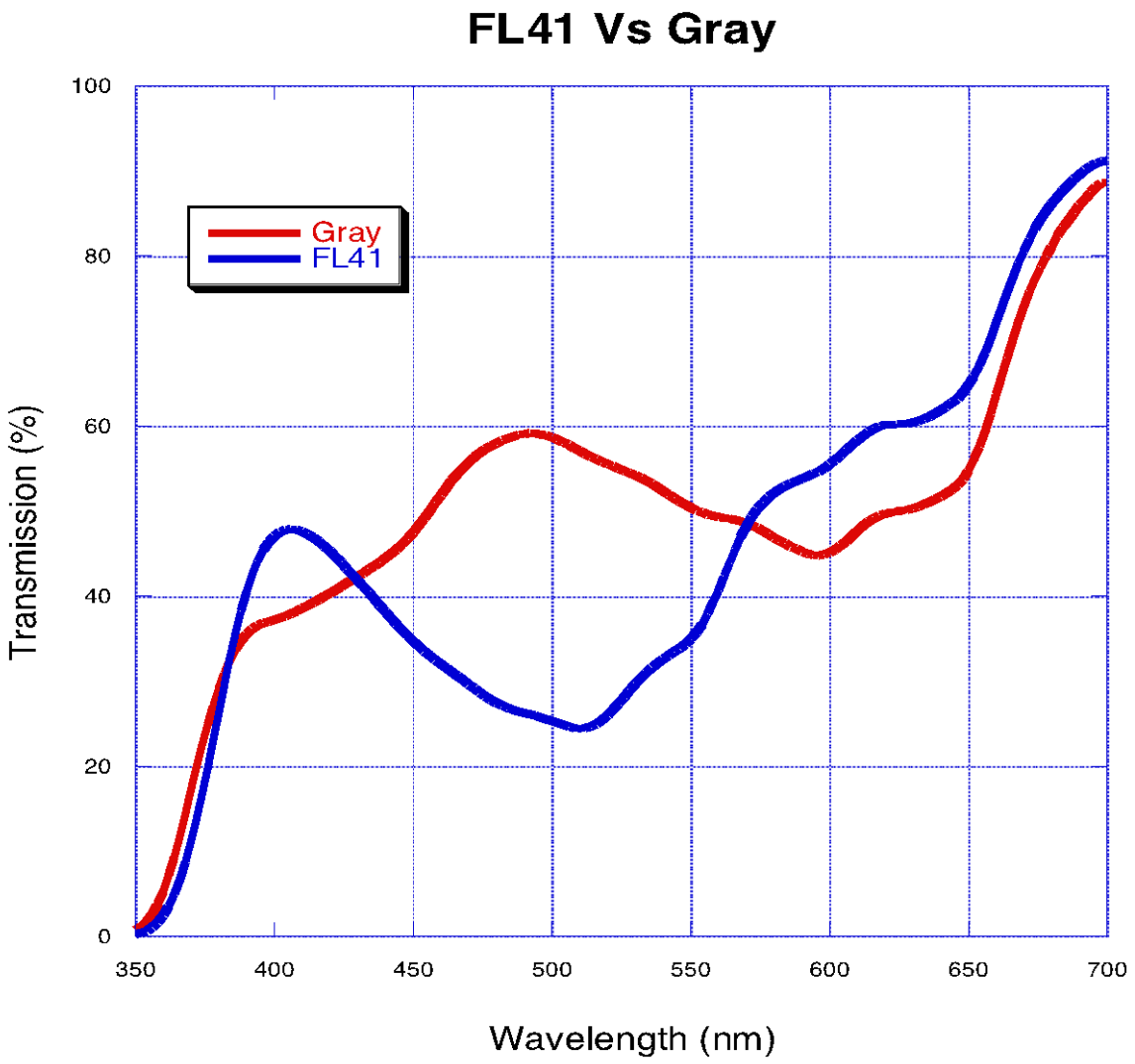
TREATMENT

Our understanding of the photophobia “pathway” is in its infancy and much of its neurochemistry remains unknown. As this knowledge matures, pharmacologic modulation of photophobia may become possible. In the meantime, treatment of photophobia relies primarily on optical means of modulating the pathway.

A group in Birmingham, England formulated the optical tint FL-41 in 1989. The tint was formulated empirically for patients suffering from fluorescent light sensitivity. Different combinations of different color were tried until a specific combination seemed to be effective. Since then, FL-41 was shown to be helpful in alleviating migraine in a cohort of school children. Our group at Utah has also shown FL-41 to be effective in the treatment of benign essential blepharospasm.

The transmission spectrum of FL-41, shown in Figure 2, has its minimum right around 480 nm, the very same wavelength at which IPRGCs are maximally stimulated. Yet FL-41 was formulated more than 20 years before the discovery of IPRGCs and their action spectrum.

Spectral Characteristics of FL-41



I don't think the correlation between the action spectrum of IPRGCs and the transmission minimum of FL-41 is a coincidence. I think people with light sensitivity find 480 nm particularly annoying and they find a tint that blocks this wavelength especially comfortable. A study presented at the 2013 International Headache Congress concluded that migraineurs are particularly sensitive to 480 nm light compared to other wavelengths. Although FL-41 is not proprietary, it is difficult to find optical shops that carry it and know how to use it appropriately. The Moran Optical Shop (http://healthcare.utah.edu/moran/patient_care/optometry/optical_shops.php) is one of the few retail outlets that is a reliable source. The tint can also be purchased from Brain Power Incorporated (www.callbpi.com) and Phantom Laboratories (www.phantomresearch.com).

Theoretically, one should be able to create an optical filter that specifically blocks 480 nm light. Such a filter, termed a "notch filter" because of the shape of the transmission spectrum, cannot be easily produced using tints. Tints are organic dyes. Plastic spectacle lenses are dipped into a warm bath of the dye and the plastic absorbs the dye, giving the lens a particular shape and transmission spectrum. This process is used to tint spectacle lenses with FL-41. By contrast, one can design a notch filter using thin film technology. This technology involves the sequential deposition of ultra-thin layers of metal oxides onto substrate lenses. The composition, thickness, and order of the layers imbue the lens with particular optical properties. This technique is used to make modern day anti-reflective coatings that have become ubiquitous in spectacle lens manufacture. This technique is also used to produce mirror coatings on sunglasses that have enjoyed a recent resurgence in popularity. In collaboration with a University of Utah engineer who is familiar with this technology and a Florida company that specializes in the design and manufacture of these coatings, I have developed a thin film coating that specifically blocks 480 nm light. I am currently testing this coating in migraine patients to determine if it

reduces migraine frequency and severity.

Don't forget to diagnose and treat dry eye syndrome aggressively in photophobic patients. A discussion of dry eye syndrome and its treatment is beyond the scope of this manuscript. The mainstays of treatment are over-the-counter artificial tears, punctual occlusion, topical cyclosporine (Restasis), and oral omega-3 supplements. A significant subset of dry eye patients also has blepharitis and meibomian gland dysfunction that must also be treated appropriately.

Finally, the use of sunglasses indoors must be strongly discouraged. By wearing dark glasses indoors, patients are dark-adapting their retinas, aggravating their sensitivity to light. Encourage these patients to transition to the use of FL-41 for indoor light sensitivity. There is no need to restrict the use of sunglasses *outdoors* in these patients.

CONCLUSIONS

Patients with photophobia need not be a source of frustration. The majority of these patients have migraine or a migraine predisposition and recognition and treatment of the underlying illness is critical. Concrete measures can be taken to aid in their treatment: Ban the use of sunglasses indoors, use FL-41 tinted spectacles, and address their dry eye syndrome. Don't forget the treatment that is administered by ear: Words of comfort. Most of these patients have been to multiple physicians and have not been given a diagnosis or any hope of getting better. Just telling them that they have a recognized condition and that treatments are available can be incredibly therapeutic.

CME Answers:

1. b) the use of sunglasses indoors should be strongly discouraged in patients with photophobia

2. c) melanopsin cells

3. b) 480 nm

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