Transcript of Cyberseminar
Mild TBI Diagnosis and Management Strategies
Photosensitivity after Traumatic Brain Injury (TBI): Mechanism, Diagnosis and Treatment
Presenter: Randy Kardon, MD, PhD
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Moderator: And we are now at the top of the hour. So I am just going to double check real quick. Dr. Depalma, do I have you on the call. Okay, I do not see him in the meeting. Generally, we have the series organizer present the speaker. But Dr. Depalma is not in the meeting currently. So I will take the pleasure of introducing Dr. Randy Kardon. He is a professor and director of neuro-ophthalmology, also director of Iowa City VA Center for Prevention and Treatment of Vision Loss and Pomerantz Family Chair of Ophthalmology in the Department of Ophthalmology and Visual Sciences. So at this time, I would like to turn it over to you Randy.

Dr. Randy Kardon: Thank you. Thank you all for joining in today. One of the reasons I wanted to give a webinar on this topic is that many of you out there are seeing patients that have photosensitivity of different causes and because this seems to be appearing more in patients after traumatic brain injury. We are seeing more of these patients especially in the VA system. And many people who try to treat these patients are frustrated. And the patients are frustrated. And many of these patients are sometimes referred for psychological or psychiatric evaluation because there does not seem to be anything wrong on their examination. Yet they are suffering from light sensitivity that is very debilitating. And many people want to run in the opposite direction when these see these patients because they are sitting in the waiting room with sunglasses on and it is very frustrating.

So I thought I would try to bring some of the science to there and this topic today and also our clinical experience and what we are doing to try to objectively determine whether patients have photosensitivity. And how we might use this to monitor new treatments, which I will share with you today.

Moderator: Randy, I apologize for interrupting. Can I ask you to please increase the volume on your telephone or speak a little louder? It is coming through quite softly. Thank you.

Dr. Randy Kardon: How is that?

Moderator: That is a little bit better thanks.

Dr. Randy Kardon: Okay. I did want to disclose any financial interests I have. These come in the form of funding from the National Eye Institute and also funding from the Department of Defense and funding from the VA Rehabilitation Research and Development. I also serve on steering committee for Novartis for monitoring MS using optical coherence tomography of the retina. And I serve on the steering committee for Acorda advising them about visual symptoms in MS. And I also give advice to Zeiss Meditec on better ways of doing perimetry and optical coherence tomography. None of these should have any impact on what I am going to tell you today.

I wanted to first start out with a poll question just to give us an idea of what your role is in the VA. So if you could please check whichever one applies to you. The last choice is other if we did not categorize every single person who is out there.

Moderator: Thank you very much. We do have the answers streaming in. So thank you to our attendees for responding to this poll question. It does help give us an idea of who is in our audience

and who best to direct this towards. So your options are ophthalmologist, optometrist, neurologist, primary care physician or physician's assistant, occupational/physical therapist, social worker, research scientist, or other. And it looks like the results have stopped streaming in. Do you want to review those real quick?

Dr. Randy Kardon: So it looks like about 28 percent are optometrists, about 2 of you out there are neurologists, 2 are primary care or physician's assistants, 5 are occupational therapists, 7 are in the field of social work, 4 are research scientists, and 31 are in the other category.

Moderator: Thank you.

Dr. Randy Kardon: Second poll question just out of interest is how many new patients with photosensitivity do each of you see in a year? And the choices are 1 -5 patients a year, 6 – 10 patients a year, 11 – 20 patients a year, or over 20 patients. And I guess if you do not see any, you could put in no vote.

So it looks like the great majority about over 70 percent sees more than 20 patients a year. About 11 percent see 11 – 20 patients. And 10 percent see about 6 – 10 patients. And about 8 percent see 1 – 5 patients. So most of the audience seems like you are seeing some of these patients in your different venues with the VA. Thank you.

Anyone who deals with the patients with photosensitivity recognizes that there is not just one cause. And I want to just briefly review the known causes of the patients that do come in with photosensitivity. There are patients who just come in with an eye problem with acute uveitis, which is commonly associated with photosensitivity. These patients usually do not have any other causes. Patients with retinal dystrophies, particularly cone dystrophies and there are some other rare dystrophies often have photosensitivity. And the reasons for this are not entirely known. Patients who have had a previous meningitis and after the meningitis clears, there is often an effect of photosensitivity that is long lasting that usually never goes away.

There are some brain tumors that present with photosensitivity. These are sometimes thalamic tumors such as thalamic gliomas. And there are a few patients reported with pituitary tumors, benign pituitary tumors that have photosensitivity.

The great majority of patients at this point in time are patients who have a history of migraines. And I do not mean just patients who have photosensitivity during their migraine, which is very common as well as sound sensitivity. But many migraine patients are left with photosensitivity even when they are not having a headache. It is a very common complaint. And the other common complaint is the recent self-reported survey shows that after traumatic brain injury in the military, about 59 percent report that as a common symptom. So that is one of the reasons, I think, many of you out there are seeing more of this in the last few years. Because it is the most common visual symptom reported in traumatic brain injury whether it is mild, moderate, or severe.

Some people have questioned whether there is a psychogenic component. I think that is still on the table. There might be psychological factors that may influence it. But I do not think there is much evidence that is purely just psychogenic in nature.

I wanted to review some of the literature that brings to bare some of what is the current thinking about light sensitivity. And I wanted to preface this by saying that most of this falls into two categories in terms of clinical patients. Those that perceive the light as being brighter, but they do not really have a headache or pain component. And that would be usually in the minority. The great majority have more of a pain component that is exacerbated by light, pain either around their eyes or headache. And many patients, as I mentioned, are known migraineurs and it may induce a migraine headache when they see light. So you should keep this in mind when you are questioning a patient which of the two they fall in to.

The reason this is important is some current thinking is that patients with increased perception of brightness may be caused by a retinal or a visual cortical abnormality. But patients who have pain, actual discomfort and pain with photosensitivity are more likely to be having something that involves the thalamus and the trigeminal system of the brain.

This is one paper that was interesting because it brought together information from both patients and also from animal models. And this was out of Harvard. And Dr. Rami Burstein is a headache specialist at Harvard and also deals with a lot of photosensitivity. And I am going to show some summary diagrams. And in a nutshell, what this study found is first that there are patients that have loss of photoreceptors. They do not have any functioning rods and cones that also have photosensitivity. So this was a paper that highlighted the fact that you do not need rods and cones to be photosensitive. And the second important aspect in the animal model is they showed that the neurons conveying a light signal from the eye, the ganglion cells that contain the photopigment, melanopsin, a relatively new class of retinal ganglion cells that have been discovered in the last 10 – 12 years. These melanopsin containing retinal ganglion cells that can be directly activated by light, they feed into areas of the thalamus that modulate pain sensitivity that is converging onto the thalamus from the meninges and from other pain sensitive areas of the brain including the peripheral trigeminal nerve.

This is a diagrammatic view of this. And what you are seeing here is that in the eye diagram in the upper left hand corner of your screen, there are these intrinsically photosensitive retinal ganglion cells that are labeled red that convey their input from light directly into the optic nerve. And most of these either project to the areas of the brain in the hypothalamus that set the circadian rhythm. They also project to the pupil centers of the brain. So they are the main nerve that conveys our pupillary light reflex, the after arms of the brain. But they also project to the thalamus. And it was in this area of the thalamus where they actually did recording of nerves there. It showed when you record from nerves in the thalamus, the recording of the thalamic nerves that convey pain sensation, the firing increased dramatically when light was shined into the animal's eye. And they also seemed to be the weight station conveying pain input from the, as I mentioned, the meningeal nociceptors shown in the left hand portion in blue. And these are conveyed by trigeminal neurons to the thalamus.

So it is thought that the thalamus is acting somewhat as a weigh center for the pain. And input from the optic nerve via these melanopsin containing retinal ganglion cells in the animal model was recording seems to modulate this response dramatically. So here is a physiologic basis for how input from the eye can modulate pain and headache that is commonly seen in these patients.

Right now, there is not any anatomical evidence that the input from the melanopsin containing retinal ganglion cells projects directly to the spinal area of the sensory nucleus and the trigeminal nerve in the lower brain stem. But this is also a possibility. Right now, most of the evidence is this is conveyed directly to the thalamus, which is also connected by nerves to the sensory trigeminal nucleus in the lower brain stem.

Another important concept in the area of migraine photosensitivity is that one of the main neurotransmitters in both animals and in humans is the neuropeptide called calcitonin gene-related peptide, abbreviated CGRP. And this is a neurotransmitter that mainly modulates trigeminal activity in the eye and the brain. So this is a major neurotransmitter found in the trigeminal sensory system that senses pain. And it has been found in a number of papers that this neuropeptide level goes up during a migraine attack. And also, if you inject this substance under the skin, for example, in migraineurs, it will induce headache and photophobia. And there are receptors for this calcitonin gene-related peptide in different areas of the brain. But they are highly concentrated in the trigeminal sensory nucleus in the brainstem, which is one of the weigh stations for the brain.

So there is mounting evidence that this is a neurotransmitter who has a receptor. And both of these play a key role in not only headache and migraine, but probably also in photosensitivity. The reason this is important, which I will touch on at the end of the talk, is that some of the new drugs being developed to treat migraine that are not yet approved for use that are in clinical trials are antagonists to CGRP. And so while these drugs may relieve migraine or prevent migraine, they may also have a similar effect on light sensitivity. So I wanted just to give the audience the information that there are new drugs that are being developed that might have a large therapeutic impact on these patients that are debilitated by light sensitivity.

This is just a screenshot from another interesting paper on the mechanisms of photophobia. And what is interesting about this study, it does not look like it is coming through very well on the Power Point. Maybe you can see it better. Is that bright light increases a trigeminal mediated blink reflex. So whenever we blink, if someone touches our cornea or if you feel something in your cornea that is a brainstem reflex. But there is also a reflex to light that causes us to blink. And this can be measured in humans and in rodents. And light can modify this reflex through a system in the brain.

This is also an important paper in an animal study that showed that bright light activates the trigeminal system. And this was not previously understood how this might happen. I am going to show a diagram on the next slide that outlines what the studied showed. And in a nutshell, it showed that it appears as though light activates nerves in this trigeminal sensory nucleus in the brainstem. And what is interesting about it is that the paper addresses how does the light actually get to stimulate the trigeminal system. And what the paper showed is that there appear to be some

mechanisms by which light actually makes the blood vessels in the choroid, the vascular layer in the back of the eye that supplies much of the photoreceptors. It causes these vessels to dilate and stretches trigeminal nerves that supply the blood vessels that might stimulate the trigeminal nerves.

And this is a diagram from this paper. And without going into a lot of detail, what I would like to show you here is that the evidence in this paper showed that these melanopsin containing retinal ganglion cells labeled in blue, shown in this diagram, which input to the pupillomotor center. They also input from there to the superior salivary nucleus, which is one of the areas that gives rise to parasympathetic nerves, which supply the blood vessels and the choroid of the eye and can cause them to dilate. And those blood vessels are richly innervated by the trigeminal nerve. So this paper was showing evidence that just light via this pathway may dilate the blood vessels and cause stretch receptors and activation of trigeminal nerves. And they recorded increased activity in the area of the brainstem where these trigeminal nerves supply. And lesions that lock this pathway greatly reduced the trigeminal input to the brainstem. So here, you can see some evidence, experimental evidence, trying to outline how light can actually modulate pain areas in the brain, particularly here in the brainstem.

This is a human study. A patient who had a severe case of photophobia and they were able to do functional MRI scanning during an episode of light sensitivity. And the take home point, which I wanted to show in this series of MRI scans, is that what you will see is this is a functional MRI in different areas of the brainstem recorded during the episode of photosensitivity. And then they retested the patient after recovery. Well first, you can see that the visual cortical area of the brain is being activated. But that was also activated after recovery. But what is interesting is this lower area of the brainstem in the area of the trigeminal sensory nucleus is the area where there was intense activation during the light sensitivity in this patient, but not after recovery. Here it is shown in a coronal section, the same area, looking at it and on and not during the recovery.

And so here was some very nice functional MRI, physiologic and anatomical evidence showing that this area that I showed in the previous slide. Which was an important weigh station for conveying light signals to pain centers in the brainstem was activated in this one patient who they were lucky enough to be able to study during the episode of photosensitivity. So I am trying to give you some anatomic and physiologic basis for how these things happen in patients with photosensitivity.

This is one further paper that recorded electrically from these areas in the brainstem both on the side where light was given to the eye on that side and also from the other side of the brainstem, which was activating both sides when light was shined into the eye. So this is just, again, showing anatomic evidence for activation of that area in the brain.

This is a special label that allows you to visualize nerves that are being activated so it is an actual label that you can stain after the fact to show where the activated neurons were located. This is an induced messenger R&A in neurons that are being activated.

This is one last diagram I would like to show you that was taken from a review of photophobia by Kathleen Digre that appeared in the Journal of Neuro-ophthalmology. And the reference is down at

the bottom here in 2012. And this was a very nice review that I would recommend that goes over all of the experimental and clinical evidence for what are the current working theories about what causes light sensitivity. And what Dr. Digre, what she has tried to do here is show the different pathways. So here is light coming into the eye. And there are these melanopsin containing retinal ganglion cells that we talked about that have input into the thalamus that can modulate pain pathways that are converging on the thalamus.

These melanopsin ganglion cells that also project to the pupillary center may also modulate parasympathetic autonomic discharge to the vessels in the eye, which as I outlined a few slides ago, gives input to the trigeminal pain centers in the brainstem. And so you can see how there are a number of circuits that appear to be activated. And this last interesting circuit is that these melanopsin containing retinal ganglion cells also seem to go directly to the iris and the others in the front part of the eye and could potentially input directly into the trigeminal neuron. So here is a direct pathway that may be important in clinical situations such as uveitis inflammation of the anterior segment that could activate these neurons and the trigeminal neurons causing light sensitivity.

I wanted to show a video here. Before we show the video, this is a video taken from a normal subject. And we just flashed a light to the eye. And what you will see is there is an involuntary blink reflex just caused by light.

Moderator: Thank you. I am pulling up that video right now. And I want to thank our attendees for your patience. This is actually the first time we have shown a video. So I am going to start it back at the beginning. And here we go.

Dr. Randy Kardon: So this is that one per second. And you can see every time there is a flash there is a partial or a full blink. And we have actually done this. Even if you go as high as ten per second, you blink at that rate. It is almost like a machine. It is irresistible. And this is a primitive reflex that I alluded to previously that probably has something to do with trying to protect the eye from bright light. But it is an involuntary reflex. The afferent side or the input side has to do with obviously light being sensed by the retina. And the output side goes through a similar mechanism as the corneal blink reflex. The input goes through the trigeminal nerve and into the trigeminal sensory nucleus of the brain stem. That stimulates the facial nerve, which causes it to blink. And it is not just blinking. Many of you, if you have looked at people when you go out in bright light you not only tend to blink, but you tend to squint. And these are bringing in other facial muscles, the procerus and corrugator muscles that cause you to narrow your palpebral fissure. It is another mechanism of limiting the amount of light getting into the back of the eye besides the pupil. So as you are squinting, you are actually making a slit without realizing it. It helps to compensate for bright light that reduces the amount of light getting in the eye. It allows you to still see.

We thought this was an important phenomenon since it is involuntary that perhaps could be made use of it if there was a way of recording it objectively. So part of the hypothesis was that not only does this photo blink reflex that has been characterized previously does it protect the eye after a bright flash. But also, these melanopsin containing retinal ganglion cells may mediate the input side

or the afferent arm of this reflex through projections to the thalamus and the trigeminal nucleus. It may also explain why patients have this paradoxical photosensitivity even if they have lost their rods and cones, they squint, and they blink. Because these neurons that are still left in those patients are in the inner retina and are directly activated by light and do not require rods and cones. So these are some clinical clues that these same neurons may also not only mediate the pupillary response, but also the blink and squinting response which is another accessory pupil, if you would, that helps to limit the amount of light getting into a person's eye.

I wanted to stop for a second and take another poll question. And the question has four possible answers. Of the patients that you do see with photosensitivity, which one of these four seems to characterize the majority that you see. Do you think that most of them seem to be caused by the history of traumatic brain injury? That is number one. Do you think that most of the ones that you see in your clinical experience are a part of migraine either during a migraine or are just known migraineurs that are bothered by migraine and they are just more sensitive to light whether they are having a migraine or not? Or do you think the majority that you see in your practice are related to an ocular cause such as uveitis or after direct ocular trauma? And the last choice, related to some other brain disorder such as a patient who has had meningitis, a tumor, or some central nervous system disturbance other than traumatic brain injury?

So it looks like the majority, about 70 percent feel that the patients that they are seeing mainly have a history of traumatic brain injury. About 20 percent are seeing patients that are mainly having a history of migraine type headaches and have a lot of light sensitivity either during or between the headaches. And about ten percent are seeing mainly causes related to the eye in terms of uveitis or some type of trauma directly to the eye. I think that is very helpful. It is interesting at least in the VA clinical setting based on who is attending this session. Most of it does seem to be related to traumatic brain injury.

And I wanted to give one more poll question right now before we delve into the rest of the webinar. Of the patients that you do see with photosensitivity, I alluded to this, which of these two choices best characterize their light sensitivity, everything seems too bright, but headache is not a major component of their symptoms. So they are not really bothered by headache. They are just bothered because they say that everything seems too bright. They are not really in much pain; they are just sensitive to light. Or two, light seems to cause headache or make their headaches worse, but visually the light does not really seem that bright or is fairly normal. It is just that they are having a lot of pain with the light. So that is interesting. It looks like about 25 percent chose that most of the symptoms seem to be bright light but not much headache. And about 75 percent is associated with a lot of pain, discomfort, and headache. Thank you.

So the leading hypothesis for photosensitivity is that there may be an abnormal sensitivity of the trigeminal nerve and its areas that receive its information either in the thalamus or in the sensory trigeminal area of the brain stem. So that any stimulus, mainly light, but other stimuli also are hypersensitive in that if this were the case then a reflex is mediated by this pathway like the photo blink reflex or the squinting reflex would be exaggerated in photosensitivity.

So I wanted to relay to you some of the studies that we recently completed a pilot study. And we are doing a much larger study now on veterans with traumatic brain injury and patients who have other causes of photosensitivity. So these were comparing normal subjects and patients with photosensitivity. And we tested them using a red light and a blue light that was projected into a bowl that is commonly used to test the electroretinogram. So it is a wide field called a Ganzfeld light, which stimulates all of the retina. And each light stimulus was only one second in duration. But we covered about six log units of intensity. So we started a low intensity and each light, red and blue, was gradually increased up to six-log units brightness. So we work up to a very bright one-second stimulus. And we recorded the pupillary response and also the electrical activity of the squinting muscles and the blinking muscles by just putting surface skin electrodes over those muscles similar to a heart-monitoring electrode like an EKG.

We also monitored skin conductance, which is a measure of sympathetic nerve activity. It is like a lie detector test and heart rate. But I am going to relate to you what the squinting muscles and the blinking muscles did during this type of a test.

Here is a subject. The subject just sits in front of this bowl. And they are wearing a pair of eye frames that have tiny video cameras so we can monitor their pupils. And they see a red light flash or a blue light flash. And we have these small surface electrodes that are painless that just rest on the skin with adhesive that monitor the muscles around the squinting muscles and the blinking muscles. We are also monitoring the skin conductance and the heart rate. I am not going to relate that evidence right now. And the light stimulus, as I mentioned, starts out low level, red and blue light, and gradually steps up to a bright light level.

What I am showing here is an example of what actually is recorded when you do that. So when the light flash comes on, there is an intense activation of the muscles that are used for squinting and the muscles that are used for blinking. And so this just shows that this is an objective measure that can be easily obtained. And I am going to show you the results as a function of intensity of light in the two different patient groups. The point that I want to make is that this is an involuntary reflex that probably is easily accessible and recorded so that we have some objective evidence of what is happening in response to light and in response to any treatments in the future not only for light sensitivity, but also for treatment of migraine.

This just shows an example. If you look at all the red light responses at lower intensities and brighter light, this is looking at a moving average of showing the peak electrical response of the muscles that have to do with squinting and blinking. And you can see that there is a very transient large activation that goes up with a brighter light, with red light and also with blue light. And I want to call your attention to the fact that with blue light the response is sustained more than the red light. The reason that this is important is that these melanopsin containing retinal ganglion cells that I mentioned were found in the retina and project to these different areas of the brain have been shown to have a characteristic greater activation with blue light. And when they are activated with blue light through their intrinsic activation, the response is much more sustained. And this might also be why these neurons are conveying more of a response to blue light than to red light.

And I am showing here on the same person what the pupillary responses look like to the same light. So this is just pupil contractions to brighter and brighter red light and to brighter and brighter blue light. And you can again see the differences that the pupil response once you get up to a bright blue light, even just to a one-second light is shown here. It just stays contracted. Whereas to red light, the pupil is being activated mainly through the photoreceptors to the melanopsin ganglion cells. And once you get up to the bright light, these special neurons are activated directly. And they are very long lasting in their response whether it is to the pupillary response or to the activation of the muscles in the face.

And this is just plotting the activation as a function of light intensity with a blue light, which responds greater for the same amount of matched light intensity compared to the red light. And our hypothesis was that in patients with photosensitivity, this response is shifted over so that with a smaller amount of light you still get a very large activation. So the hypothesis was there is an increased sensitivity to light in these brainstem areas. And we can use the EMG response of the squinting muscles as an objective way of studying that.

This is what I would call the money slide. It shows the ration of the EMG activity under baseline conditions compared in normal subjects, which is the squares that are open versus the red light; versus the subjects that were photosensitive which are the closed red circles. And this is increasing light intensity. So what you see is the patients who we studied in this pilot study who had light sensitivity had much greater activation of their orbicularis and procerus muscles, their squinting muscles. And the activation was even greater with blue light under matched lighting conditions.

So I think is the first subjective evidence that this is a natural reflex that makes sense that would be more activated because you are trying to limit the amount of light getting into your eye. And it is reflex that goes through the trigeminal areas of the brain. And this is the reflex that we are currently monitoring to see if different treatments have more of an effect to reduce this response.

We also have the patients subjectively say how bright they thought the light was. And also to the same light, how much discomfort it brought. So this is what is called magnitude of estimation. We normalize it to their own scale. And take home point is that in a normal person shown here, these are the control subjects. They can very well estimate how bright a light is as the light intensity goes up in logged steps. And their discomfort also goes up. But the amount of discomfort on the same scale lags behind how bright they think the light is. But the patients that had traumatic brain injury, they had an amount of discomfort that matched the amount of brightness they were observing which is shown in this graph.

So what I am graphing here are the control subjects. This is their brightness sense and this is their discomfort sense. And these are the patients with traumatic brain injury whose discomfort index was the same as the brightness whether it was to red or to blue light. So the take home message here is that even subjectively, patients feel that there is a lot more discomfort for the same amount of brightness, which makes sense. That is what they are trying to tell us. But the EMG response as I showed in the previous slide is an objective way of trying to monitor that and see how they respond to new treatments.

One last thing before I summarize and show you some of the new treatments, we also measured this calcitonin gene-related peptide in the saliva. So we just did a little swab in their mouth before they started getting the light stimuli, during the light stimulus, and after the light stimulus. And actually, even in the saliva, this calcitonin gene-related peptide goes up in concentration with bright light. And in the small group that we studied, it went up much higher in the patients with migraine compared to the normal subjects. So these were patients that were not having migraine at the time. So this neurotransmitter that I mentioned in the beginning of the talk may be a key modulator of photosensitivity.

One last thing is that we also have a mouse model of this. Just like the humans, we can actually implant electrodes chronically into the orbicularis muscle with an implanted telemeter. It conveys the electrical activity in conscious free roaming mice. And we have them in a cage where we can control the amount of light coming in. And also, we can give an air puff, which stimulates the corneal reflex, and also see how light influences that same blink reflex that we are studying in humans and see how calcitonin gene-related peptide injected under their skin or into their peritoneal area affect this reflex. So here is a mouse model that goes hand in hand with measuring the same output, the orbicularis response that we are measuring in humans. But we can test out some of these new drugs and new treatments. And just like in the humans, whenever you give light, you can see activation in these awake mice to light. And this is just magnifying this area. Whenever the light is on shown by the yellow bar, the muscles around the eyes are activated just like they were in the humans.

And if you take these mice, put them in darkness, and give an air puff, yes, they blink because they are getting their cornea stimulated. And to light, they blink just a little bit more with the air puff. But when you inject this calcitonin gene-related peptide and add light, the response is not only greater, but it is much more long lasting. So this is just showing us what we are finding in the humans in a testable animal model for treatments. And this graph just summarizes what I just showed is that with injection of calcitonin gene-related peptide bright light causes a much greater response of the orbicularis muscle similar to what is seen in the humans.

These last two slides are some new treatments that have been proposed. My colleagues at Syracuse at SUNY Upstate Medical Center presented this work at the Association for Research in Vision and Ophthalmology this last May. And in this particular graph, they used contact lenses that had a four-millimeter artificial pupil. So these are not just colored contact lenses. These actually block out light in all of the contact lens except the central four millimeters. And they had a scoring of light sensitivity that the patient scored their symptoms before they put in these contact lenses. So the higher the score, the worse symptoms they had of photosensitivity. And then the same patients, while they were wearing these contact lenses for the next two to five weeks filled out the questionnaire again. And so this is a non-medical, but if someone can tolerate contact lenses, it might be something that is worth trying. It needs to be validated. But this has some potential because it is actually limiting the amount of light getting into the eye without debilitating them in any way and causing them to have much less symptoms. So I thought that was a very interesting approach, non-medical approach that might have a lot of potential treatment.

And they went one-step further in other patients that had light sensitivity. They put one drop of one percent pilocarpine, a miotic, into each eye. And so the pupil went from a large size to a small size. And they did the same questionnaire one week prior to the drop given to their eye. And this is the most interesting part of this study. This was a single administration of a drop. And the patient was given the questionnaire one week later. Now the drop wears off after four or five hours as most of you know. But at least from the patients' symptom scoring, they think it broke some cycle so that even after a week when the drop was long worn off in terms of the miotic effect, they were having some benefit. And I think this also needs to be explored to see if there is some kind of cycle that is being broken that just giving them one drop may last a whole week and help relieve their symptoms.

So I wanted to give one more poll question before I summarize. In your hands, in their clinical setting, which of these different potential therapies have you tried that you think are helpful. One is just dark sunglasses just the darker the better, not any particular color. Two is orange colored sunglasses. And the reason why some people have used orange colored sunglasses is it blocks out the blue component of light. And some people feel much more comfort especially when they are sensitized to fluorescent lights or colder lights. The orange colored glasses seem to relieve their symptoms. Some people out there have found that lightly tinted blue colored sunglasses seem to help just the opposite. Has anyone used contacted lenses in guard official pupils or miotic eye drops as a next choice or medications used to treat migraines? Or the last one is really nothing seems to help significantly. None of these choices seems to help.

So it looks like the great majority in patients that seem to come in with this seem to feel that just very dark sunglasses are one of the only things that help. And obviously, the down side of that is these patients' visual experiences of their visual environment is greatly diminished because with dark sunglasses they have very little contrast discrimination. And obviously, the eye is dark-adapting. So as soon as they take them off, it is even worse. So it looks like 80 percent are feeling their patients feel that just dark sunglasses are mainly the only thing that helps. And a smaller percentage, about eight and a half percent, likes the orange tinted glasses. And about the same percent, around seven percent like the blue colored tint glasses. A very small percent, about three percent, felt that treating their migraine or migraine like medications seemed to help.

So the conclusion so far based on evidence in the literature with humans and animals is that this photic EMG response is a brainstem reflex that seems to be exaggerated in photosensitive patients and may be a biomarker that can be used clinically to help characterize the patients and their response to treatment. This photo blink reflex may be mediated by these melanopsin containing retinal ganglion cells have been shown in physiologic studies to input to the areas of the pain sensitive areas of the brain and modulate them such as the thalamus.

That these melanopsin containing retinal ganglion cells likely provide input to the trigeminal sensory nucleus in the brain stem which stimulates the facial nucleus, which causes you to blink and to squint, is evidenced by the EMG responses. The calcitonin gene-related peptide might mediate excessive trigeminal sensory activation. And that is why drugs that are being developed that

antagonize the CGRP may be a viable treatment option in the near future. So that summarizes the treatment options are potentially medications to treat migraine which might include CGRP, blue blocking lenses, inclusive contact lenses, potentially a drop of pilocarpine that might last for a long time.

Thank you for your attention. I think we have a few minutes to take any questions that you can type in the upper right part of the box on your screen.

Moderator: Wonderful! Thank you very much. Yes, we do have several questions that have come in. And as Randy just said, if you do have any questions or comments, please type them into the Q&A box located in the upper right hand corner of your screen. And the first question that came in, I see combat vets primarily with service in Iraq without a clear head injury event who still complain of photosensitivity yet have a normal optometry eye exam. What might this be due to? And this is independent of headaches.

Dr. Randy Kardon: That is a very good question. I want to give you some insight as to the patients that I see in my clinic at the VA that are like this. You might go in the room and ask them if they have had any history of traumatic brain injury and they say no. And then I go on to ask them well have you not ever been exposed to blast weights. They say well yes. And I say well how many times. And they say oh, perhaps 20 to 30 times. And what that has been telling me is that they do not consider themselves having had traumatic brain injury because they were not knocked unconscious. No one told them they had traumatic brain injury. But many of the veterans are getting exposed to blast injury not only from improvised explosive devices, but also during training. Some of them are around of a lot of explosives during training and are right in the line of blast. So that is an important, I think, question to ask.

Another important question is, as you know, traumatic brain injury is being very much of a concern in sports related injuries. And I have been asking the veterans that I see how active they were in concussive sports like football. And of course, many of the people that enlist in the military, the males, have a strong history of having concussive injury during high school or college football. And so I think it is also important to ask outside of the military what types of exposure they have had particularly in sports that have had impact not only football, but also boxing, soccer, and other sports that may have a history of that.

And then if they have no history of any of that, then I start asking about what might be migraine headache that has never been diagnosed as migraine. They may have been told they have "sinus" headaches, which might really be a form of migraine. Some of these patients do have migraine, but never have been diagnosed as having such. And they have photosensitivity as part of that constellation.

Moderator: Thank you very much for that response, we have peaked the interest. And we do have several more pending questions. So I will get right to the next one. I am sorry. I am going to butcher this. If the trigeminal nerve is activated, why do patients complain of headache pain but not facial pain?

Dr. Randy Kardon: So that is a good question. The trigeminal nerve, it does not actually – the sensory part does not innervate the brain itself. It innervates the meninges or the part of the face for pain. And it may be that most of the headache is coming from the meninges or lining of the brain that is rich in trigeminal innervation. And so the idea is that when the trigeminal nerve is activated, if it is activated at a central level, the referred pain that they experience may be mainly the nerve endings that are in the meninges. And that is what gives a headache and not necessarily facial pain. So it may be the part of the central nervous system that is mediated by trigeminal. If it is becoming sensitive and most of the trigeminal input to it arises from the meninges that might be one potential explanation why we do not see a lot of facial pain with photophobia. We mainly see headache.

Moderator: Thank you for that reply. The next question we have, is there a need for treatment for sensitivity to light if there is no pain involved?

Dr. Randy Kardon: I think that depends on how disabled the person feels as they are – in other words, I have had some patients who do not have a lot of headache who mainly have increased brightness. And they cannot really do anything that is enjoyable because they have to wear such dark sunglasses. At first, it socially ostracizes them, points a big finger at them in social situations, and is unpleasant. But also, even with sunglasses, many of them do not feel as completely adequate. So my answer to that is that I talk to the patient and ask specifically what are the things that they are not able to enjoy because of their light sensitivity. And if you do not get a huge answer then I agree that not every light sensitivity needs to have some treatment or attempted treatment. But if it is playing a significant impact on a person's functioning in their life and it is on an individual basis, I think then a decision has to be made. What are the different modalities? What is the patient willing to try? And how much of an affect is going to have on their quality of life.

Moderator: Thank you very much. I know that I am going to mispronounce this medication and I apologize in advance. Have you found brimonidine useful?

Dr. Randy Kardon: So brimonidine, most of the people out there know what it is. But it has been used to treat glaucoma. It is an alpha 2 agonist. And alpha 2 agonists decrease sympathetic discharge. So if you put a drop of brimonidine in the eye, it makes the pupil smaller. It does not make it as small as with pilocarpine. But it does reduce the size of the pupil mainly in dim light compared to not using it. We have not tried brimonidine yet. And I think it might be worth trying since it does not really affect accommodation or focusing. And so I do not have any experience. But it might be worth trying to see if it helps.

I did have two patients whose manifestation of their traumatic brain injury was not photosensitivity. But their near point of focus was fluctuating from moment to moment. So their focus kept going in and out. And I did give them brimonidine to try to give them more of a pinhole effect. And they both said their symptoms became less. So I have used it for that type of a problem. But I have not yet tried it for photosensitivity.

Moderator: Thank you. The next question, any research on the FL 41 40 percent topaz tint for improving reading ability and limited blinking response.

Dr. Randy Kardon: Yes so that FL 41 is a blue blocking filter. And the group from Utah, Kathleen Digre and Brad Katz who are neuro-ophthalmologists there, have found that in patients with blepharospasm who are also sensitive to light that it seems to help. And also some patients that have other forms of photophobia. So this is again a blue blocking filter. And it may have some scientific roots in trying to reduce the intrinsic activation of the melanopsin ganglion cells because they have peak activation in the blue wavelength of light. So and many optometrists have sets of these in their office of different filters at different wavelengths that come in a set that have been used to try to treat patients that have photoreceptor dystrophy such as achromatopsia. And I think it is worth trying especially if you have a set that you are using for something else, just trying it in the clinic or have them go outside with them and see if they can self-select which one of the filters seems to be the most subjectively comfortable.

Part of the funded study we are doing is we are going to be using that comparing that to just a darkened lens versus the orange or the blue blocking filter in measuring the EMG response to see if there is any objective evidence that it really reduces the activation. So I think that is a very good question.

Moderator: Thank you for that reply. The next question we have, we are trialing 40 percent plum and 40 – 54 percent yellow tints for night glare remediation. Any tests show other tints useful for night glare from oncoming headlights.

Dr. Randy Kardon: Any tests or any other treatments?

Moderator: Do any tests show other tints useful for night glare?

Dr. Randy Kardon: I am sorry that I do not have as much experience with glare. And I know that is hard to sometimes differentiate between glare and light sensitivity. But I have used the brimonidine drops for patients who are bothered with glare at night because it will reduce their pupil size in dim light conditions compared to not using the drop. And sometimes that is enough to reduce their glare and the halos and streaks around lights that are bothering them so much. So that is another thing to try besides different filters is brimonidine to reduce glare for nighttime driving.

Moderator: Thank you. We do have about a half a dozen pending questions left. Given the sensitivity to blue light, this would indicate that vets with photophobia effects are not good candidates for light therapy for season effective disorder whether to "old" NIMH used 10,000 locks of fluorescent boxes as well as the newer blue light smaller models, just checking. And thank you for the helpful presentation.

Dr. Randy Kardon: That is a very good question. There are different theories about seasonal effective disorder, which is a type of seasonal related depression. And currently, one theory is that patients who have this do not have enough input from the melanopsin ganglion cells. Patients that

have traumatic brain injury and photosensitivity also have a sleep disorder. But it may be because they are getting too much light or too much sensitivity to the hypothalamus instead of the opposite, which is the SAD patients, the seasonal affective disorder patients. So I would not try to treat someone who has photosensitivity who appears to be a seasonal related depression with – I do not think they would even tolerate the treatment with a blue light. I think those patients might be best treated medically under the care of a psychiatrist.

Moderator: Thank you. You may have touched on this already. Do you feel there is evidence supporting use of blue tinted lenses for TBI patients?

Dr. Randy Kardon: I think that is being tried. And our group is trying it too. I do not think there is any published evidence yet showing that it works. But I certainly think it is worth trying. And it does not really cost the patient very much. If you do not want to prescribe by prescription the blue blocking lenses, sporting goods stores have them. And the ones that are online are called Cocoons. They make other types of sunglasses too. But they make a very good blue blocking lens for recreation purposes that some of the patients find very helpful. Because through the – they look orange. But what the patient sees is a reduced sensitivity to light. But also, they still have good contrast and things are still easy to see as opposed to when they put on neutral density, very dark lenses. They have a hard time seeing things in their environment.

Moderator: Thank you for that reply. Do these phenomenons seem different in blast related events as opposed to other mechanisms of TBI?

Dr. Randy Kardon: So the question is do patients who have had traumatic brain injury from blasts versus concussion, are those two separate groups that maybe have different characteristics. To tell you the truth, that has not been effectively studied yet. And so I do not think I have any information to say. But I think it is worth looking at because the mechanism – the underlying mechanism of what has caused it may not be exactly the same in those two types of TBIs. So I am sorry I do not have a good response for that right now.

Moderator: Not a problem. Thank you. We will go to the next question. Almost all of my TBI patients are pain medications and/or sleep medication and extremely dry eyes. What role could this play in the photophobic complaints?

Dr. Randy Kardon: That is a very good question. Because of this relationship between photosensitivity and trigeminal input, it is possible that dry eye may exacerbate trigeminal sensitivity. And so I think that you have brought up a very important point that has not really been published in the literature. But I think treating dry eye in a case like that may help the photophobia. We are trying to see whether just a drop of proparacaine in a clinical experimental setting of numbing the cornea reduces light sensitivity to try to understand the role of the peripheral trigeminal input. But something like using either artificial tears or punctal plugs in those patients might bring them a lot of relief. But not only from the dry eye, but also as you implied, from some of the trigeminal modulation of photosensitivity. I think it is definitely worth trying.

Moderator: Thank you. I just wanted to make a quick note. The person that wrote in speaking about doing the trialing for 40 percent plum and 40 to 54 percent yellow tints for night glare remediation. I just wanted to make note that that person works at the TBI veteran – works with TBI veterans at Richmond, VA Medical Center in Virginia. I just wanted to make note of where that trial was taking place.

Dr. Randy Kardon: Thank you.

Moderator: Let me see. The next question is – sorry. I have got a lot there. How is it that trauma changes the trigeminal reactivity?

Dr. Randy Kardon: Oh, that is a very good question. So we know from some experimental evidence now that blast injury and concussion seems to cause an inflammatory response in the brain. And other inflammations I mentioned, meningitis, also may do the same. So it could be that inflammatory mediators in the brain sensitize these areas, these trigeminal areas. We do not know exactly how that happens. But that is one of the hypothesis of how blast injury or concussion would all the sudden make these areas more sensitive.

Moderator: Thank you for that reply. Just a few left. Any thoughts on the – I am going to – Irlen lenses and Irlen testing methods, I-R-L-E-N.

Dr. Randy Kardon: I personally have not had any experience with that. So I really cannot – and I do not know of any publications using those lenses. So I am sorry I do not have any input on that particular question.

Moderator: No problem. I am going to be closing the meeting in just a minute. And I would like everybody to stick around for a few seconds because once I close the meeting you will be directed to a survey. And we do very much appreciate your feedback, as it is what guides the program and what we have presentations on. But before I end the meeting, I just want to give you an opportunity to give any concluding comments.

Dr. Randy Kardon: I think that this is a bigger problem than most people who are not directly taking care of these patients realize. And I wanted to thank the people out there who are trying to be compassionate and do everything they can to help these patients because it is the most common symptom after traumatic brain injury. And also these patients can still see, so they are not blind, their quality of life is greatly diminished. And I know they are very grateful for all of the compassion and all of trying different things that may be different for each patient. So I just wanted to encourage everybody to keep in contact with these patients. And try some of these things because some may work in some patients and not in others. It was alluded to that these may be a heterogenous group of patients. Not all are alike. And I know that they are very appreciative. And I certainly appreciative of everybody out there that is trying to help these patients. So I wanted to thank everybody for that.

Moderator: Thank you very much. And I do just have one quick last question I overlooked. Can the medication I mentioned for photosensitivity be prescribed by an M.D. or the eye care provider?

Dr. Randy Kardon: Which medication?

Moderator: Brimonidine, I am trying not to pronounce it again.

Dr. Randy Kardon: Oh, it depends on the state. But brimonidine can be prescribed by any M.D. and in most states; they can be prescribed by optometrists as well.

Moderator: Thank you. I would very much like to thank you for lending your expertise to the field. And I also want to thank our attendees for joining us today. And I know that we have gotten a lot of people writing in saying thank you for this excellent presentation. Some people want to know where they can get a copy of the slide deck. And I just want to let you know that it is in the reminder email you received this morning, the one you used to enter the meeting. And also, I will pull up the first slide where you can click on that handout or I mean that link right there and get the handouts. And you will receive a followup email in the next day or two with a link to the recording. So please feel free to check that out and also pass it along to any colleagues who could not make it to the live presentation.

So once again, I want to thank all of you for joining us and for the wonder presentation. And please join us on the 31st for our next TBI presentation. And you can look up that and register for it in our cyber seminar catalog. So have a wonderful day everyone. And this does include today's HSR&D cyber seminar. Enjoy the long weekend.