

A Discussion With
Gerard M. Nolan, M.D., F.A.C.S.
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Topic: ECHO Therapy

DAN: Dr. Nolan practices at the Nolan Eye & Laser Center in Farmington, Connecticut. He has been having success with an experimental therapy for macular degeneration, and he has agreed to answer questions from the subscribers to our email discussion group (MDList). To download Dr. Nolan's yet-unpublished paper on this research, select this link. To read personal experiences with this treatment, as submitted by our MD Community, see "ECHO Therapy" in the Treatment Archives on this site.

Dr. Nolan, thank you for your time. Please begin by giving us a little background information about ECHO therapy.

DR. NOLAN: In the course of my ophthalmic practice, I discovered that a topical drop of dilute echothiophate (ECHO) can restore lost visual acuity in some cases of chronic retinal disease. A formal clinical study has not yet been launched, but I have been treating my patients with an off label use of this diluted eye drug. Please note that the FDA has not evaluated these uses of this drug. Only after FDA review and approval can a drug be determined to be safe and effective of these off-label uses.

In response to several excellent questions from the MD Support group, I made an offer to Dan Roberts to reply to your unsolicited collective questions. Hopefully this will help to clarify.

PATTY: Can you treat wet AMD? If so, how long after PDT [photodynamic therapy] can a person be treated?

DR. NOLAN: One of the benefits that ECHO appears to offer is an increase in ocular blood flow.

In patients with active Wet AMD, this increased blood flow could also lead to increased retinal leakage. In some cases, where a patient has undergone successful photodynamic laser therapy to eliminate retinal leakage, pursuant ECHO

treatments have restored a small amount of their lost visual acuity. I have found that PDT patients treated 4-weeks after the last PDT treatment have better vision gains. Typically, however, I would not prescribe ECHO unless the Wet AMD was mild and episodic.

As we age, the ciliary muscle of the eye becomes less active. This intraocular muscle of the eye is responsible for aqueous outflow and for reshaping the lens for near and distant vision, much like a camera lens. Movement of the ciliary muscle likely creates the force behind choroidal) blood flow through the eye.

ECHO raises ocular neurotransmitter levels and thereby increases the activity and strength of ocular neurons and ciliary muscle.

ECHO increases the capability of surviving nerves, muscles and vessels. For this reason, early intervention is important. If ECHO is applied to an eye which was first diagnosed 3-months ago, the effect will be much greater than to an eye diagnosed 3-years ago. We have witnessed improvements to eyes which have been diseased for decades, but early intervention is always better.

As with most ocular drugs, ECHO administered to one eye will also have a small effect on the other (contralateral) eye. For this reason, I typically prescribe ECHO only in cases where the patient has no evidence of vascular leakage in either eye.

Vessel leakage resulting from diabetic retinopathy should be treated with the same caution as Wet AMD.

PATTY: Could the treatment help my left eye, which has no central vision, due to an old scar.

DR. NOLAN: Much like a digital camera, the human eye builds each image from millions of bits of information collected by as many retinal photoreceptors. Throughout Rod cells collect information on light/dark and cone cells collect information on color. Together, these photoreceptors pool their information in order to stimulate higher-level ganglion cells and communicate with the brain.

As AMD destroys more and more photoreceptors their population becomes too sparse to generate a ganglion response.

In the patients I treated, ECHO appeared to increase the capability of the few surviving neurons, endowing this reduced population with an enhanced stimulus potential. These effects need to be studied in multi-center controlled clinical trials.

Early intervention is important. If ECHO is applied to an eye which was first diagnosed six months ago, the potential improvement appears to be much greater than if diagnosed six years ago. We have witnessed measurable improvements within eyes that have been diseased for decades, but these gains are typically not dramatic.

FLORA: How about if the MD is caused by high myopia?

DR. NOLAN: In myopic degeneration, the changing shape of the eye can cause retinal stress and tearing; typically centered about the macula. Myopic degeneration results in stretched or malformed blood vessels similar in nature to the neovascularization of Wet AMD. The resulting vision loss may be severe and may progress rapidly.

ECHO has been useful in treating some of the individual symptoms of myopic degeneration, such as peripapillary atrophy and RPE thinning/clumping. But based upon the above approach to Wet AMD, ECHO would only be suggested in the case that there was no sign of vascular leakage. These uses have not been evaluated and approved by FDA. In order to obtain approval for these promising new indications, substantial evidence in the form of controlled clinical trials need to be conducted. My colleagues and I are currently trying to obtain sufficient interest from clinical investigators and funding sources to conduct this expensive evidentiary research.

PATTY: Could the treatment help my left eye, which has no central vision, due to an old scar.

DR. NOLAN: Dry AMD and geographic atrophy of many types have responded particularly well to ECHO therapy in patients initially treated. Historic scarring from inactive macular disease will often respond to ECHO therapy. I have witnessed cases of patients who were able to see using little more than a thread of viable retina. Their status following continuing long-term use of the drug for this purpose has not been established.

MAXINE: Is this improvement supposed to stay that way forever, or is there a slow decline?...

DR. NOLAN: I have treated retinal patients with ECHO for nearly three years. During that time, I have witnessed that the progress of many retinal diseases appeared to slow or stop altogether. Repeated retinal angiograms have not appeared to change, despite patient histories of consistent decline, but more research is required.

This drug is believed to improve blood supply and neural conductance. ECHO does not act to stop or reverse retinal disease. It is merely a tool to increase local acetylcholine levels and, thereby, strengthen the viability of surviving retinal cells. It is my observational belief, which must be confirmed by FDA based on controlled clinical trials enrolling a significant number of research subjects, that this apparent strengthening of the ocular system and improvement of retinal blood flow appear to slow the progress of many degenerative diseases.

FLORA: How about old scars in the eye which still have Wet MD going on?

DR. NOLAN: Although many eyes appear to be ideally suited for ECHO therapy, the risk presented by active leakage could far outweigh the benefit gained. I recommend against using ECHO in any case of vascular leakage, no matter how severe.

DR. HENSIL: This sounds more like a pinhole effect than anything, since echothiophate decreases pupil size. From a retinal standpoint, I doubt it will make any difference in retinal health.

DR. NOLAN: For purposes of clarification, the pinhole effect occurs when the pupil is overly constricted by a drug. The visual impact is as if you were looking through a straw. A pinholed pupil blocks out peripheral rays of light, letting in only those rays that pass directly through the center of the pupil. Any refractive error in the lens or cornea becomes less noticeable and only the central portion of the retina is being stimulated. The improvement in visual acuity can be striking.

The dosage of ECHO in use here does cause a mild pupillary constriction on the morning following administration. This constriction typically wears off by lunchtime or mid-afternoon at the latest. I have observed that visual acuity gains,

persist for 4-7 days with a fully dilated pupil. Obviously this effect requires more study in a larger patient population. I would welcome Dr. Hensil's review of the drug in her own patients, or her participation in a trial once funded and initiated.

Furthermore, I am treating one AMD patient who is a surgical aniridic. This means that she has had her iris surgically removed altogether. This patient's visual acuity gains cannot be related to pinholing.

KEITH: I am the father of two girls with Stargardts age 23 & 18 diagnosed about 3 yrs ago; visual acuity of 20/100 & 20/70. Can you explain what in your treatment causes this improvement? Is your treatment an ongoing process with these drops? Do you feel you could help my girls improve their vision?

DR. NOLAN: Keith, I would encourage you to review my Stargardt's article which I have recently submitted for publication. I have recently treated several younger patients with fewer years of disease with promising results in restoration of vision. Please give me a call to set up an appointment if you wish to have your daughters properly examined and evaluated.

PAM: Is your treatment or anything similar available here in the United Kingdom?

DR. NOLAN: I do not believe this treatment is available in Britain although the parent drug is manufactured there by Wyeth. I do have a few patients who visit me from other countries for evaluation and treatment. I make it available to appropriate patients after the initial consultation. Obviously I cannot treat patients without first examining them.

ANONYMOUS: I heard that the echo treatment has been used for treating glaucoma for about 40 years and that the dose for treating glaucoma is 300 times the amount being used for MD and other eye disorders. What are the side effects experienced with this dose.

DR. NOLAN: I have experienced no evidence of significant local or systemic side effects, however independent long-term controlled clinical studies of this use have not been conducted. Many patients have continued treatment for more than 36 months without apparent contraindications. The only discernable side effect I have discovered through this proof of concept use to date has been a mild, transient

dimming of vision within low-illumination on the morning that follows ECHO administration, due to mild pupillary constriction. Many patients consider this to be a positive effect, as they experience less glare and benefit from the pinhole effect.

There have been infrequent reports of redness, burning and blurring, but these symptoms always passed within the first two weeks.

The known side effects from the standard high-dose Glaucoma regimen are listed in Wyeth's product insert:

<http://www.wyeth.com/content/ShowLabeling.asp?id=410>. Keep in mind that the Glaucoma dosage is nearly 300-times the current regimen.

MAXINE: As I have active wet MD it sounds like there is no point in me pursuing this.

DR. NOLAN: I would not suggest ECHO therapy to anyone with active retinal blood vessel leakage. The risk of increased leakage presents too great a risk. However, once the leakage is stopped or controlled by laser therapy, ECHO may speed the recovery of vision. I hope clinical testing and FDA review can substantiate this use.

ANNA: Is the drug used in the treatment the same as iodine? I am extremely allergic to iodine and may be excluded from treatment with this drug for that reason.

DR. NOLAN: Unfortunately, an allergy to iodine would restrict your use of this therapy. It's not for certain, but the iodide component could pose an allergic danger.

DR. HAMMER: Do you think ERG would give a clue to the mechanism for action?

DR. NOLAN: I hope that in the case of Retinitis Pigmentosa, follow-up ERGs will shed a great deal of light on the neural action of ECHO.

DR. HAMMER: I note that the improvement in near vision is larger than in distance vision. Was near vision tested at a fixed distance, or was the patient free

to choose his reading distance? I think that the pinhole effect, coupled with the fact that (in younger patients) a given amount of innervation to accommodation yields more actual accommodation with the drug than without, would enable patients to bring the text closer to their eyes before it becomes blurred.

DR. NOLAN: If tested at the same working distance, there has been an observable and consistent improvement of reading vision in the patients I have treated.

J.D.: Is your Echo treatment approved by FDA?

DR. NOLAN: My use of diluted echothiophate is considered an off label usage of a legally marketed medication. Echothiophate is permitted for topical use in the eyes, however it has not yet been reviewed or approved by the FDA for the specific indication of retinal disease. Adequate and well-controlled clinical testing is still required. The clinical research studies required to support a New Drug Application can cost in excess of \$1 million.

J.D.: Will Medicare or Blue Cross reimburse it?

DR. NOLAN: Unfortunately, until ECHO receives formal FDA-approval, the drug itself likely cannot be covered by any type of insurance. The initial examination and follow-ups, however, are typically covered.

J.D.: Are you also testing ARMD patients?

DR. NOLAN: Due to limited supplies of this drug, I have focused on treating those in the greatest need. This has resulted in a number of RP, Stargardts and patients - many of whom are under 25-years-old.

ANN: My husband has Stargardts. Once you start the drops do you have to take them forever?

DR. NOLAN: ECHO therapy appears to relieve the symptoms of many retinal diseases. It appears to slow their progress as well in preliminary treatment of a limited number of patients. But the underlying diseases, whether genetic or acquired, seem to continue. My belief is that ECHO likely presents a long-term option to manage retinal disease, not to cure it. Long-term use of this diluted

dosage in a sufficient number of patients has not been tested yet to my knowledge.

ANN: What is the cost beyond the initial \$500?

DR. NOLAN: The drug itself costs approximately \$6-10/week, depending upon frequency of administration.

ANN: Does the treatment stop the degradation?

DR. NOLAN: Follow-up fluorescein angiograms appear to show little or no change during treatment, even across 36-months in the limited number of patients I have treated. In the absence of a formal clinical study, I can only offer my own observational opinion that the progress of these diseases appears to have slowed or even halted by dilute ECHO therapy in some but not all of the limited number of patients treated.

DR. WATT: I have several questions. First, is this a placebo-controlled, double-blind study?

DR. NOLAN: A placebo-controlled study has been written up, but I have not yet found a research university to partner with, or adequate funding to support this research protocol. I am approaching several and hope to have a formal clinical trial and approval to do human clinical research for submission to FDA in place by Winter.

DR. WATT: What are the inclusion and exclusion criteria?

DR. NOLAN: The following has been proposed in my draft clinical protocol, but will be subject to researcher, IRB and FDA approval:

Eligibility Criteria:

1. Each study participant must have the ability to understand and sign an informed consent form. The consent form must be obtained prior to enrollment.
2. Patients with significant vision loss due to dry, age-related macular degeneration.

3. Recruitment preference will be given to those subjects with the most recent onset of vision loss. Ideal candidates will have experienced most of their vision loss within the past twelve months.

4. Visual acuity of equal to or greater than 20/400 as measured on an ETDRS chart in the worse eye. If both eyes are eligible then the eye with the worst visual acuity will be considered as the study eye.

Exclusion Criteria:

1. Patients will be excluded from this study if they are unable or unwilling to give informed consent.

2. AMD with associated Choroidal neovascularization or previous Visudyne treatment for choroidal neovascularization in the subject eye or disciform scar in the study eye.

3. Decreased vision, in the study eye, due to retinal vascular disease, for example diabetic retinopathy, papillophlebitis, branch retinal vein/artery occlusion, central retinal vein occlusion, arterial occlusion, retinal macroaneurysm or cystoid macular edema.

4. Retinal impairment not attributable to CNV, such as nonexudative forms of ARM, macular hole, retinitis pigmentosa, geographic atrophy, inherited retinal dystrophy, uveitis, acquired retinoschisis or epiretinal membrane. Decreased vision, in the study eye, due to retinal tumors, retinal inflammation, toxoplasmosis, pathologic myopia, ocular histoplasmosis, posterior uveitis, vitreal detachment, lattice degeneration, and idiopathic central serous chorioretinopathy.

5. Significant media opacity such as corneal disease or cataract, or opacity precluding photography of the retina.

6. History of other antiangiogenic treatment or concomitant administration of other experimental therapies for AMD other than nonfoveal confluent laser photocoagulation.

7. Any contraindications to performing the necessary diagnostic studies, especially the use of fluorescein angiography.

8. Allergy to iodine or previous iodine containing dyes.
9. Positive urine pregnancy test or currently lactating for women of childbearing potential.
10. Intraocular surgery within the last 2 months or capsulotomy within the last month in the study eye.
11. Use of any investigational drug within 90 days of enrollment.
12. Use of topical or intraocular medications including IsoptoRCarpine, OcuserTR, PilocarR, and PilopineR, EpifrinR and PropineR, BetaganR, BetimolR, BetopticR, OcupressR, OptipranalolR, TimopticR, AlphaganR, IopidineR, TrusoptR, LumiganR, ResculaR, TravatanR, XalatanR, DaranideR, DiamoxR, NeptazaneR.

DR. WATT: How do you determine the target eye?

DR. NOLAN: The initial target eye is typically the worse eye, provided that the vision in that eye is greater than CF 5/400.

DR. WATT: Is punctal occlusion used after instilling the drops?

DR. NOLAN: As this is a long-term regimen, punctal occlusion would be problematic over time. As long as the drop is applied immediately before bedtime, I have found that a sufficient amount of drug is absorbed.

DR. WATT: Is the IOP checked at the baseline and follow-ups?

DR. NOLAN: IOP is checked during each exam, at least as frequently as each three months.

DR. WATT: Will your study be affected by the shortage of Echothiophate?

DR. NOLAN: I am extremely concerned about the ongoing availability of echothiophate. I consider myself in a race against the clock to see this therapy developed.

DR. WATT: Have you had any cases of cystoid macular edema develop?

DR. NOLAN: I have observed no significant side effects and no long-term repercussions, but controlled research in a larger clinical population, and FDA review, is required.

PAM: My 17 yr old son has just been diagnosed with Stargardts in the past 5 weeks. His vision is at 20/200 in both eyes. Would he be a candidate? What about patients who are under 18 yrs of age. Can parents sign a consent form for them?

DR. NOLAN: I have treated several patients under 18-years of age. It is important that both the child and parents understand the therapy and properly manage their expectations. At that point, parents may certainly provide legal consent for the treatment of their children.

My belief is that ECHO therapy slows the continuing loss of retina characteristic of Stargardt's Disease. For this reason, the importance of early intervention is important. Your son sounds like an excellent candidate for ECHO therapy. I would welcome your call and look forward to discussing his condition in greater detail.

FRED & ROSIE: Is there any way we or I could help Dr. Nolan to get this valuable study started?

DR. NOLAN: This discovery has made for a challenging personal journey. I am an independent clinician, not a researcher, so I lack the big team and big budget behind most drug projects. I am working hard to establish a "proof of concept" and convince a research institution to adopt this as a controlled clinical study.

Your kind thoughts and prayers are most appreciated. Our important next-step is to gain the interest and confidence of the research community. Foundations, support groups and individuals such as yourselves play key roles in creating this researcher dialogue. I encourage you each to ask lots of questions and keep the discussion moving forward.

ANNE: I have had Stargardt's for 25 years. I have 20/400 acuity or worst in both

eyes. Could this be a help to me and would I be accepted for this? I live in N.H. and I am 51 years old.

DR. NOLAN: ECHO therapy enhances the capability of surviving retinal photoreceptors. Your current visual acuity indicates that your retinas are heavily damaged, but functional. This is good news. The fact that you have been suffering from Stargardts for so many years stands as a challenge. In all likelihood, you would experience a noticeable benefit from ECHO, but I would be surprised to see a dramatic improvement. If you lived in California, I would not encourage your visit, but since you live within a few hours of Hartford, I would leave the decision in your hands. I would be happy to welcome you to our clinic.

DR. LAWS [Comments posted on the Stargardt's message board]: There are several levels of evidence available when assessing new treatments. The highest level that something works is a Prospective Randomised Controlled Trial published in a reputable ("peer reviewed") journal. At the other end of the scale is an unsubstantiated case report such as this.

If something is true, other investigators can repeat the work and confirm the result. A quick search of the literature has failed to find any other reference to this treatment.

So what if it doesn't do any harm, why not have a go? Ecothiopate is from a group of drugs that used to be used to treat glaucoma. While the dose used is very low there are other side effects not mentioned by Dr Nolan such as potentially fatal anaesthetic complications (my pharmacology book has four pages of side effects for this drug).

This will amaze you. Ecothiopate is an organophosphate, admittedly not thought to be neurotoxic, but related chemically to nerve agents and sheep dip.

In summary, this paper does not provide any significant evidence for a treatment using a drug abandoned for other eye uses largely because of side effects.

DR. NOLAN: Based upon the tone of David's criticisms, I don't see much value in responding directly to his questions. His main claim that this discovery cannot be true, just because it hasn't been published, makes little sense. David's criticisms are sincere, but they also strike me as a bit reactionary.

David Law is a Pediatric Ophthalmologist in Britain. He is on the board of the "British Ophthalmic Anesthesia Commission," and is, therefore, familiar with several studies from the 70's noting an interaction between high doses of echothiophate and a chemically related surgical anesthetic named succinylcholine. Patients on high-dose ECHO are recommended to pause treatment for a few days before surgery.

In 1936 Germany, Bayer AG invented an organophosphate compound called Tabun, intended for use as an insecticide. The German war machine soon realized its potential military applications. From Tabun evolved the discovery of toxic nerve agents, including Sarin gas. Bayer and other companies began introducing a large number of organophosphorus compounds, with a variety of medical effects and purposes. Organophosphates are highly neuroactive, via their effect on acetylcholinesterase. This 1936 discovery has led to both medical miracles and military nightmares.

There are certainly side effects related to high-dose ECHO. Potential cataract formation and systemic build-up of the drug are the two main concerns. But there is much research showing that these side effects are relatively non-existent below a 0.060% strength, used twice daily. I feel extremely confident that [a dosage of] about 5% of this is safe to use. Further, I intend to keep a close watch on the health of every patient involved.

MINDY: Will this therapy put me in a bad position to be an unlikely candidate for a future treatment or cure?

DR. NOLAN: In my experience with dilute ECHO, I have observed no drug effects which last longer than seven days. The therapeutic action of ECHO may slow the progress of certain diseases, but I believe this to be ECHO's only long-term effect. Patients receiving an active regimen of ECHO may indeed be ineligible for some clinical trials. This appears to be the case with microcurrent stimulation. Each therapy appears helpful when used individually, but when used in combination, the two contradict each other. 30-days after stopping ECHO treatments, any patient should be clear to try an alternative therapy.

GEOFF: As the effects of the medication on vision seems to be almost

immediate, I imagine that the trials will be very brief in determining whether vision is improved or not? Is there an intention to conduct a longer term study to determine whether Echo can actually slow down or even halt the progression of MD?

DR. NOLAN: You are right that the initial trial will be to determine the efficacy and the safety of the use of ECHO over the short term in patients with Stargardt's disease. Long-term follow-up of these patients after completion of the study would be very helpful in determining whether ECHO can slow down the progression of Stargardt's disease or other forms of macular degeneration.

ECHO has been used by patients with glaucoma for many years, so that I am certain of the long term safety of its use in patients. I have already treated several patients with Stargardt's disease for more than two years and found the benefit to continue in these patients. However, the questions of just how ECHO works and whether it may slow or arrest the disease in a large group of patients can only be answered by follow-up studies spanning a number of years.

DAN: Dr. Nolan, we greatly appreciate your taking the time to answer our questions about ECHO therapy. Thank you for the promising work that you are doing. Any readers who wish to contact Dr. Nolan may email him at gnolan@nolaneye.com.