Review Article

Current Trends in Ophthalmology

Review of Subthreshold Diode Micropulse Laser Treatment for Retinal Diseases

Juhn AT, Shyu AP, Benjamin J and Zhang Y*

Department of Ophthalmology, Temple University Hospital, Philadelphia, Pennsylvania, USA

***Correspondence:** Zhang Yi, Department of Ophthalmology, Temple University Hospital, Philadelphia, Pennsylvania, USA, Tel: 215-707-3185; E-mail: Yi.Zhang2@tuhs.temple.edu

Received: June 02, 2018; Accepted: July 23, 2018; Published: July 27, 2018

Abstract

Subthreshold diode micropulse (SDM) laser is a relatively new treatment modality that confers very little to no anatomical risk to the retina. However, its efficacy is still being studied, and the scenario where SDM is most useful is still being elucidated. This paper reviews articles from 1997 to 2017 and reviews the settings, results, and outcomes of SDM in various clinical settings including diabetic macular edema, branch retinal vein occlusion, central serous chorioretinopathy, proliferative diabetic retinopathy, and age-related macular degeneration.

Keywords: Subthreshold diode micropulse laser, micropulse laser, diabetic macular edema

Abbreviations: SDM: Subthreshold Diode Micropulse; DME: Diabetic Macular Edema; PDR: Proliferative Diabetic Retinopathy; BRVO: Branch Retinal Vein Occlusion; HSP: Heat-shock Proteins; LIRD: Laser-induced Retinal Damage; CNV: Choroidal Neovascularization; TGLT: Threshold Grid Laser Treatment; hdPDT: Half-dose Verteporfin Photodynamic Therapy; FAF: Fundus Autofluorescence; CSCR: Central Serous Chorioretinopathy; AMD: Age-related Macular Degeneration.

Introduction

Conventional argon retinal photocoagulation has been universally accepted for over forty years [1-3]. It is primarily used for retinal diseases including proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), choroidal neovascularization, macular edema associated with retinal vein occlusion (RVO), and central serous chorioretinopathy (CSCR) [4-10]. However, the role of conventional laser therapy is limited due to complications such as scar enlargement, visual field scotoma, subretinal fibrosis, and subretinal neovascular membranes [4,8,11]. New laser modalities such as subthreshold diode micropulse (SDM) have been introduced in hopes to prevent permanent retinal scarring and ultimately improve visual acuity. In this article, we examine the role of SDM laser treatment in retinal diseases.

History

While conventional retinal photocoagulation is effective, various methods have been explored to attain a therapeutic effect while limiting or avoiding damage to the retinal tissue [8]. Titrating the laser power introduced the concept of subthreshold burns in DME, which reduced tissue damage but nevertheless still produced visible scars to the retina [1,4]. In 1990, Pankratov developed the micropulse diode laser, designed to fire a series of millisecond laser pulses in spaced-out intervals [1,4,12]. Initial micropulse diode lasers reduced thermal retinal damage and allowed selective treatment to the RPE. However, the parameters still generated thermal retinal injury which was deemed necessary to produce the therapeutic effect. It was not until a subset of micropulse laser that brought about a method that not only reported clinical efficacy but also preserved retina and reduced

inflammation [11].

Mechanism of action

Conventional retinal laser is absorbed mostly by the retinal pigment epithelium (RPE) with heat conducted to the neurosensory retina and choroid [5]. Although it still remains unclear, there have been numerous theories for the therapeutic effect of conventional retinal photocoagulation. It is postulated that laser-induced retinal destruction reduces the metabolic demand of a hypoxic retina by 1) targeting metabolically active photoreceptors, 2) increasing choroidal retinal oxygenation, 3) upregulating heat-shock proteins (HSPs), and/or 4) altering vasoactive cytokines including VEGF [4,11,13,14]. In particular, focal retinal laser is thought to photocoagulate microaneurysms and lessen macular edema [6,14]. However, the progression of SDM and their clinical benefits have refuted the need for thermal retinal burning and reinforced the necessity to target the RPE. With the micropulse laser firing a pulse every 100 to 300 μ s with a 1700-1900 μ s pause between each pulse, the "duty cycle" is decreased. This allows tissues to minimize heat buildup and transduction, and therefore avoid any thermal damage to the neurosensory retina [5,6,11,15]. Compared to conventional photocoagulation, the limited inflammation induced by SDM may preserve the RPE and neurosensory retina, which may be linked directly to improved visual function shortly after the procedure [11]. Additionally, unlike conventional laser in which the effect may come primarily from the adjacent RPE cells rather than the damaged RPE cells in the targeted area, SDM laser may stimulate more cytokines and heat shock proteins (HSPs) by preserving the RPE cells in the targeted area [5,16,17]. Numerous HSPs are responsible for modulating stress response to heat, chemotherapy, or radiation. Sramek et al. and Inagaki et al. showed an increased HSP70 expression with a sublethal threshold power, providing a method to facilitate the protective roles of HSP expression without retinal damage [16,18,19]. Along with the low-intensity/high-density SDM parameter, the effective surface area of the RPE is maximally modulated to alter cytokines important in mediating retinal diseases, such as matrix metalloproteinases [5,11,17,20].

Diabetic macular edema

The approach to DME with subthreshold diode micropulse (SDM) laser has changed over the past few decades, from an initially laser-induced retinal damage (LIRD) approach to a low-intensity/high-density approach with no visible retinal damage. In 1997, Friberg and Karatza first reported that 75% of their 40 patients with

clinically significant macular edema (CSME) improved when treated with a micropulse 810-nm diode laser. Notably, the authors employed a grid pattern over areas of retinal thickening (microaneurysms were not specifically targeted as recommended in mETDRS) with light visible laser burns as the endpoint of treatment [21]. In 2004, Larsen et al. performed the first prospective randomized trial comparing micropulse diode grid laser (810-nm) to conventional argon grid laser (510-nm) in 23 eyes. The authors divided edema into diffuse and focal categories (based on whether retinal thickening was 2 or more disc areas or less, respectively). Patients were then randomized into two groups receiving either argon laser photocoagulation or SDM laser. The settings in the diode group were variable, but had the goal of establishing a power level half of what was required to create a barely visible burn. While the micropulse laser was non-inferior to argon laser in terms of visual outcomes, the authors found it difficult to achieve an ideal power setting that avoided LIRD and still maximized effective laser treatment [22].

Figueira et al. demonstrated in a prospective randomized controlled study of 84 eyes that SDM laser had comparable visual outcomes, central retinal thickness, and contrast sensitivity outcomes to argon laser [23]. However, laser scars were still noted in 14% of the eyes treated with SDM vs. 59% treated with argon [23]. While the incidence of LIRD was significantly lower in the SDM group, it was still higher than expected in a typical SDM laser setting. However, the argon group had a 59% rate of LIRD rather than the expected 100%, suggesting some eyes in this group may have been undertreated.

Further studies looked to employ a high-density confluent laser technique that would have no LIRD and can be safely applied to the fovea [24]. Prior studies have utilized a minimal duty cycle of 5% in SDM laser application including Laursen and Stanga et al., but authors noted the difficulty of optimizing power settings as laser burns could not be titrated by appearance [23,25]. Luttrull et al. chose to base their SDM parameters on the American National Standards Institute Z136.1 standard of maximal permissible and threshold exposure. Their parameters were 125 μ m diameter spot size, 750 mW power, 0.3 second laser exposure, and 5% duty cycle (each exposure contains 150 micropulses, with each pulse delivered every 2 ms with 100 μ s ON, and 1900 μ s OFF). These parameters resulted in no residual retinal burns, and visual acuity remained stable or improved in 85% of 95 treated eyes with CSME, with 79% resolution of edema at

a mean follow-up of 12.2 months [24]. Additionally in this study, Luttrull showed that “painting” a treatment area with repeat, high-density coverage resulted in no residual retinal scars. Lavinsky et al. further demonstrated that utilizing a confluent application of SDM laser had superior visual outcomes than when a standard modified ETDRS technique or a normal-density (two burn-widths apart) technique was employed for early DME [26]. As other long-term studies supported the safety of SDM, the lack of LIRD with SDM laser prompted physicians to treat fovea-involving DME. Luttrull and Sinclair demonstrated in a retrospective study of 39 eyes that transfoveal SDM resulted in an improvement in Log MAR visual acuity and macular thickness with no adverse effects [27].

Patient selection is crucial for effective treatment of DME with SDM laser. Mansouri et al. showed that in a study of 63 eyes, those with a central macular thickness (CMT) $\leq 400 \mu\text{m}$ had an average reduction of $55 \mu\text{m}$ at 1-year follow-up with no persistent CSME or need for rescue anti-VEGF injections with SDM laser mono-therapy [28]. However, those with CMT $> 400 \mu\text{m}$ all required anti-VEGF injections to achieve resolution of the CSME. Additional studies have supported treating mainly early-onset DME with SDM laser for maximal effect. Lavinsky et al. found those without retinal degeneration or macular ischemia and foveal hard exudates had improved visual acuity with high-density SDM laser therapy [26].

SDM may be a useful alternative to traditional grid laser, but anti-VEGF treatments tend to be first-line therapy for DME. While unlikely to supplant anti-VEGF therapy, SDM may have a role in reducing the frequency of injections in early treatment of DME. Moisseiev et al. showed in a retrospective comparative study in 19 eyes that were treated with micropulse laser had a clinically significant decrease in injections both at 1 year and final follow-up (1.7 ± 2.3 vs 5.6 ± 2.1 injections and 2.6 ± 3.3 vs 9.3 ± 5.1 injections respectively, $P < 0.001$ for both) [29]. In summary, SDM has great potential and value in treating patients with early, central involving DME with relatively good vision, but there still remains a need for a formalized treatment plan and ideal patient selection criteria. Table 1 reviews the mentioned authors’ laser parameters and settings.

Branch retinal vein occlusion

Macular edema is the main cause of vision loss after a branch retinal vein occlusion (BRVO). Grid argon laser has traditionally been employed to reduce visual acuity loss, but is associated with typical laser complications such as

scars and even choroidal neovascularization. SDM laser is able to forego these complications. In terms of efficacy, Parodi et al. demonstrated in a randomized clinical trial of 36 eyes that grid SDM laser was as effective as threshold grid argon laser treatment (TGLT) in reducing macular edema and vision loss [30]. Though patients who received TGLT had a more rapid resolution of edema by 6 months, visual outcomes and foveal thickness were similar between the two groups by year 1 [30]. By year 2, the average number of lines gained in the SDM laser group was 2.06 vs 1.37 in the TGLT group (no significant difference). However, those who received SDM laser had the benefit of not having any detectable biomicroscopic or angiographic signs of laser treatment.

Additionally, SDM laser may have some synergistic effects when combined with other treatment modalities for BRVO-induced macular edema. In a pilot study of 24 eyes, Parodi et al. compared monotherapy grid SDM laser therapy to grid SDM laser combined with intravitreal triamcinolone injection (Table 2). The results showed that more patients in the combined group gained at least 2 lines of visual acuity more than in the monotherapy SDM laser group (average line gained 3.4 vs 1.3, respectively) [31].

Inagaki et al. studied the role of SDM laser in those with persistent edema with vision better than 20/40 [32]. 32 eyes with persistent edema (6 to 156 months prior to treatment, foveal thickness $< 600 \mu\text{m}$) were studied, with 11 having received some form of therapy in the past. Edema and total macular volume was reduced by 6 months in these patients, though there was no significant change in visual acuity [32]. Interestingly enough, Parodi showed that SDM laser failed to have any beneficial effect in the treatment of recurrent macular edema in BRVO, and bevacizumab injection was found to be superior over SDM laser [33].

Central serous chorioretinopathy

The majority of central serous chorioretinopathy (CSCR) cases are self-limited, but treatment with photocoagulation or photodynamic therapy may be indicated for patients with recurrent or chronic disease. However, the former cannot be used in subfoveal or juxtafoveal edema due to the risk of retinal scarring, and the latter may lead to RPE atrophy, ischemia, CNV, and choroidal hypoperfusion [34,35]. As such, SDM may be useful to treat CSCR while minimizing the iatrogenic lesions that limited traditional therapy.

Table 1: SDM Laser Parameters for the Treatment of DME

Study Author and Year	Indication	Duty Cycle of Laser	Spot Size (µm)	Duration (sec)	Power (mW)
Friberg (1997)	DME	67%	75 within fovea 125-200 outside fovea	0.2 -0.4	150-1200
Laursen (2004)	DME	5%	125	0.1	Diffuse: 350-900 Focal: 190 -850
Luttrull (2005)	DME	5%	125	0.3	750
Figueira (2009)	DME	15%	125	0.2	Not specified

Table 2: SDM Laser Parameters for the Treatment of BRVO

Study Author and Year	Indication	Duty Cycle of Laser	Spot Size (µm)	Duration (sec)	Power (mW)
Parodi (2006)	BRVO	10%	125	0.2	Not specified
Parodi (2008)	BRVO	15%	125	0.3	Not specified
Inagaki (2014)	BRVO	15%	200	0.1	663 – 1094

Table 3: SDM Laser Parameters for the Treatment of CSCR

Study Author and Year	Indication	Duty Cycle of Laser	Spot Size (µm)	Duration (sec)	Power (mW)
Roisman (2013)	CSCR	15%	125	0.3	300 – 660
Malik (2015)	CSCR	5%	Not specified	0.2 - 0.3	750-1000
Kretz (2015)	CSCR	15%	75 – 125	0.3	1000
Breukink (2016)	CSCR	5%	125	0.2	≤1800
Luttrull (2016)	CSCR	5%	200	0.15	1400
Maruko (2017)	CSCR	15%	200	0.2	140-200

Table 4: SDM Laser Parameters for the Treatment of AMD

Study Author and Year	Indication	Duty Cycle of Laser	Spot Size (µm)	Duration (sec)	Power (mW)
Friberg (2006)	AMD	Not specified	125	0.1	Variable (200mW increasing by 50mW increments)
Luttrull (2015)	AMD	5%	300	0.2	2000
Johnson & Glaser (2005)	AMD	Not specified	100	0.01	Up to 600
Luttrull (2016)	AMD	5%	200	0.15	1400

In a prospective, double-blind, sham-controlled pilot trial, 15 patients with chronic CSCR for more than 6 months were randomized to SDM and sham laser [36]. BCVA (ETDRS letter) was significantly improved at 3 and 6 months (from 35.4 to 47.9 and 50.0, respectively) in the treatment group, while there was no significant change in the sham group at each point (from 26.6 to 25.6 and 31.0, respectively). At 6 months, the treatment group also achieved a significant improvement in central macular thickness (from 419.6 µm to 247.2 µm, $P = 0.008$), while no significant improvement was seen in the sham group

(from 349.6 µm to 283.6 µm, $P = 0.50$). All 5 patients in the sham group eventually received SDM treatment 3 months or 6 months after the sham laser, and gained better BCVA (27.4 to 39.6, $P < 0.05$) and CMT (340.2 to 233.6 µm, $P < 0.01$) [36].

Malik and Luttrull independently explored the “low-intensity and high-density” strategy for CSCR. They both used an 810-nm SDM laser with only 5% duty cycle without using a test burn. In Malik’s study, 11 eyes with symptomatic CSCR were enrolled. Of the 11 eyes, only 1

required re-treatment after 6 months for recurrent fluid, and mean ETDRS visual acuity improved from 39.2 letters to a final acuity of 45.5 letters (follow-up period ranged between 5 to 88 months, but 2 were excluded for lack of follow-up and 1 excluded for the use of systemic steroids) [37]. Maximal CMT decreased significantly in the final 8 eyes (average 97 μm decrease, $P = 0.0046$). In Luttrull's study, 11 eyes were enrolled. After one "low-intensity and high-density" SDM treatment (average shots 772/session), visual acuity and maximal retina thickness significantly improved [38]. Subretinal fluid was eliminated in all eyes by 3 months. Their studies suggested that low-intensity/high-density SDM laser using a 5% duty cycle is a safe and effective modality for treatment of chronic CSCR. However, both studies were limited by small sample size, and had no control group.

Chen et al. studied the effect of SDM laser on varying degrees of source leakage and present RPE damage. Eyes with longer than 4 months of CSCR were split between those that had 1) source leakage without RPE atrophy (6 eyes), 2) source leakage with RPE atrophy (9 eyes) and 3) unknown source leakage with diffuse RPE atrophy (11 eyes). After one session of SDM laser, all eyes in group 1 had total resorption of subretinal fluid with no recurrence within 8 months of follow-up. The majority of group 2 had resorption of subretinal fluid after 1 to 3 sessions, whereas 1 eye from group 2 and more than half of the eyes in group 3 needed photodynamic therapy for complete subretinal fluid resolution. Their results suggested that though SDM may be as effective in those with source leakage (groups 1 and 2), it was less efficacious when patients had diffuse RPE atrophy and leakage (group 3) [39].

In 2011, Koss et al. evaluated the efficacy between intravitreal bevacizumab versus SDM laser for CSCR. They included 52 eyes that had no more than two active leakage sites on fluorescein angiography and persistent RPE leakage for more than 3 months with or without RPE decomposition. 10 months after treatment, it was found that only 12.5% of eyes had persistent leakage in the SDM group, compared to 60% in the injection group, and 92% in the sham group. CMT decreased more in the SDM group than in the bevacizumab group (94 μm vs. 38 μm), and mean parametric deficit improved by 1.5 decibels in the SDM group versus 0.6 in the bevacizumab group. While this study showed better efficacy of SDM over bevacizumab, both groups required retreatment with SDM laser (44% and 50% in the SDM and bevacizumab group, respectively) [40].

Kretz et al. performed a comparative, prospective study of SDM versus half-dose verteporfin PDT (hdPDT) versus a control group; his group looked specifically at visual acuity and contrast sensitivity, subretinal fluid changes, and RPE health on fundus autofluorescence (FAF) at week 16. Both treatment groups showed a significantly decreased amount of leakage compared to the control group at week 16 (60% and 66.7% of patients in the SDM and hdPDT group respectively, versus 37.5% in the control group). Visual acuity and contrast sensitivity were improved in the treatment groups, but they were not significantly superior from the control group. There was reduced central macular thickness in all 3 groups, with no statistical difference between the groups. Comparison of FAF showed no significant changes in the size of hypo- or hyper-FAF areas suggesting the safety of both techniques [41].

Breukink et al. studied the role of SDM laser in eyes refractory to hdPDT. His group demonstrated in a prospective study of 59 eyes, that 37 eyes had resolution after a single hdPDT treatment (mean follow-up time 8.7 weeks), with an additional 7 out of 19 eyes retreated with hdPDT showed resolution after a second treatment at mean follow-up of 6.3 weeks. In this re-treatment group, 10 unresponsive eyes underwent further treatment with SDM, with only 1 eye having resolution of edema (mean follow-up time was 12 weeks) [42].

Maruko et al. demonstrated that SDM was non-inferior to conventional focal laser, with no statistically significant differences in retinal thickness and visual acuity between the two groups in a study of 29 eyes [43]. Overall, SDM seems to be a safe and relatively effective treatment modality for CSCR. Refer to table 3 for parameters.

Proliferative diabetic retinopathy

Conventional panretinal photocoagulation for proliferative diabetic retinopathy results in visible retinal burns, scars and unwanted side effects including constriction of visual field, nyctalopia, and even loss of vision. Pollack et al. proposed that the regeneration and proliferation of new RPE cells may restore the blood-retinal barrier, aiding in the regression of neovascularization [44]. Moorman investigated "minimal intensity" PRP with high duty cycle SDM laser. The goal was to treat PDR with minimal LIRD. In his cohort of 13 eyes, 10 patients showed at least some regression, though 3 did not show any improvement. All patients tolerated the procedure well [45].

In a retrospective study, Luttrull observed 99 eyes ranging from severe NPDR to PDR who received between 1 to 6 treatment sessions of SDM laser, but there was no conventional PRP group as a control. While no complications were observed nor were any laser lesions visible, very few patients (4 in total) had any form of regression from their initial diagnosis, with 12.5% of patients progressing to vitreous hemorrhage and 14.6% requiring vitrectomy [46]. While SDM may be a relatively safe procedure with minimal complications, its applications may be better served elsewhere outside of PRP for PDR.

Age-related macular degeneration

Given that a dysfunctional RPE/Bruch's membrane is a key feature of the pathogenesis of age-related macular degeneration (AMD), there is great interest in utilizing SDM technology for therapy.

Friberg and colleagues investigated the effect of SDM on the development of choroidal neovascularization (CNV) in patients with high risk drusen (> 5 large druse) in one eye and wet AMD in the contralateral eye. Unexpectedly, there was more CNV in the treatment group at one year, 15.8% versus 1.4% in the control group, ($P = 0.05$) [47]. They advised against prophylactic SDM laser treatment in these eyes. Three years later, they studied patients with high risk drusen in both eyes with no CNV. Small visual acuity benefit was noticed with treatment, but the effect was not seen 3 years out from therapy [47]. It is worth noting that the subthreshold laser used in both studies was not micropulsed.

It is thought that SDM may have a restorative effect in RPE function and therefore may resensitize RPE in wet AMD unresponsive to anti-VEGF therapy. In a small retrospective study, Luttrull et al. performed 810-nm SDM laser in 13 eyes of 12 patients that were deemed unresponsive to anti-VEGF injections. One month later, these eyes were re-treated with monthly aflibercept, and 92% (12/13) eyes showed improving foveal thickness with 69% (9/13) having complete resolution in macular exudates [48]. These effects may be mediated by upregulation in transcription of certain heat-shock proteins (specifically HSP70) within the RPE [49].

Johnson and Glaser examined the role of SDM in exudative AMD with concurrent retinal choroidal anastomoses (RCAs) identified by ICG angiography. After an average of 3.52 sessions (1-12) over a mean 11.7 month (2-23) period of treatment, 53% of eyes

had complete resolution of subretinal fluid; and 43% had complete closure of RCAs. However, there was no statistically significant change in mean visual acuity [50].

In 2016, Luttrull and his colleagues reported "functionally guided retina protective therapy" with panmacular SDM for high-risk dry AMD. With SDM treatment, 139/158 eyes were improved by pattern electroretinography measures (PERG) ($P < 0.0001$); Snellen VA remained unchanged, but macular sensitivity by automated microperimetry and Central Vision Analyzer testing were improved ($P = 0.0439$ and $P = 0.006$, respectively). The authors advocated SDM as a retinal protective therapy in early stages of chronic progressive retinal diseases, guided with PERG [51]. In a recent retrospective study, Luttrull et al. suggested that panmacular SDM may reduce the incidence of CNV in high risk dry AMD more than vitamin therapy alone [52]. Due to limited data, the exact role of SDM remains to be fully illustrated in the treatment algorithm for exudative AMD and high risk AMD, and larger randomized, controlled trials are required. Table 4 goes over the laser parameters utilized by the mentioned authors for AMD.

Summary

The practice of SDM laser treatment has been evolving since the 1990s. Numerous studies have proven that SDM laser is an effective and non-invasive treatment for various retinal diseases, especially for early DME with mild foveal involvement. Combined with anti-VEGF agents, SDM laser helps reduce the frequency of intravitreal injections and risks of severe complications. However, its development is accompanied by controversy over its efficacy. Presently, there are no well-established laser parameters for SDM. At a 2017 AAO annual meeting debate, the majority of retina specialist voted against SDM for DME treatment; this reflects the current reality of SDM laser treatment, that it is a promising but still controversial procedure. Widespread adoption of SDM will require large well-designed, prospective randomized multiple centers clinical studies. These trials should compare SDM to current standards of care, evaluate SDM laser's role in the treatment of early mild central DME in combination with anti-VEGF agents, and establish standardized laser parameters.

References

1. Kozak I, Luttrull JK. Modern retinal laser therapy. *Saudi Journal of Ophthalmology*. 2015;29(2):137-146. doi: <https://dx.doi.org/10.1016/j.sjopt.2014.09.001>

2. Sherif Eissa, Kotb M, Sadik S, Othman I. Subthreshold diode-laser micropulse photocoagulation as a primary and secondary line of treatment in management of diabetic macular edema. *Clinical Ophthalmology*. March 2014;653. doi: <https://dx.doi.org/10.2147/OPTH.S59669>
3. Preliminary Report on Effects of Photocoagulation Therapy. *American Journal of Ophthalmology*. 1976;81(4):383-396. doi: [https://dx.doi.org/10.1016/0002-9394\(76\)90292-0](https://dx.doi.org/10.1016/0002-9394(76)90292-0)
4. Chhablani J, Roh YJ, Jobling AI, et al. Restorative retinal laser therapy: Present state and future directions. *Surv Ophthalmol*. 2018;63(3):307-328. doi: <https://dx.doi.org/10.1016/j.survophthal.2017.09.008>
5. Sivaprasad S, Elagouz M, McHugh D, Shona O, Dorin G. Micropulsed Diode Laser Therapy: Evolution and Clinical Applications. *Survey of Ophthalmology*. 2010;55(6):516-530. doi: <https://dx.doi.org/10.1016/j.survophthal.2010.02.005>
6. Su D, Hubschman J-P. A Review of Subthreshold Micropulse Laser and Recent Advances in Retinal Laser Technology. *Ophthalmology and Therapy*. 2017;6(1):1-6. doi: <https://dx.doi.org/10.1007/s40123-017-0077-7>
7. Shilling JS, Jones CA. Retinal branch vein occlusion: a study of argon laser photocoagulation in the treatment of macular oedema. *British Journal of Ophthalmology*. 1984;68(3):196-198. doi: <https://dx.doi.org/10.1136/bjo.68.3.196>
8. Photocoagulation for Diabetic Macular Edema: Early Treatment Diabetic Retinopathy Study Report Number 1 Early Treatment Diabetic Retinopathy Study Research Group. *Archives of Ophthalmology*. 1985;103(12):1796. doi: <https://dx.doi.org/10.1001/archophth.1985.01050120030015>
9. Leaver P, Williams C. Argon laser photocoagulation in the treatment of central serous retinopathy. *British Journal of Ophthalmology*. 1979;63(10):674-677. doi: <https://dx.doi.org/10.1136/bjo.63.10.674>
10. Malik KJ, Sampat KM, Mansouri A, Steiner JN, Glaser BM. Low-intensity/high-density subthreshold micropulse diode laser for chronic central serous chorioretinopathy. *Retina*. 2015;35(3):532-536. doi: <https://dx.doi.org/10.1097/IAE.0000000000000285>
11. K. Luttrull J, Dorin G. Subthreshold Diode Micropulse Laser Photocoagulation (SDM) as Invisible Retinal Phototherapy for Diabetic Macular Edema: A Review. *Current Diabetes Reviews*. 2012;8(4):274-284. doi: <https://dx.doi.org/10.2174/157339912800840523>
12. Rebeiz EE, Aretz HT, Shapshay SM, Pankratov MM. *Cur Tre Ophthal*, 1(1): 62-70 (2018)
- Application of pulsed and continuous wave 1.32 and 1.06 μm wavelengths of the Nd:YAG laser in the canine tracheobronchial tree: A comparative study. *Lasers in Surgery and Medicine*. 1990;10(6):501-509. doi: <https://dx.doi.org/10.1002/lsm.1900100602>
13. Brader HS, Young LHY. Subthreshold Diode Micropulse Laser: A Review. *Seminars in Ophthalmology*. 2016;31(1-2):30-39. doi: <https://dx.doi.org/10.3109/08820538.2015.1114837>
14. Stefansson E. The therapeutic effects of retinal laser treatment and vitrectomy. A theory based on oxygen and vascular physiology. *Acta Ophthalmologica Scandinavica*. 2001;79(5):435-440. doi: <https://dx.doi.org/10.1034/j.1600-0420.2001.790502.x>
15. Dorin G. Subthreshold and micropulse diode laser photocoagulation. *Seminars in Ophthalmology*. 2003;18(3):147-153. doi: <https://dx.doi.org/10.1076/soph.18.3.147.29812>
16. Inagaki K, Shuo T, Katakura K, Ebihara N, Murakami A, Ohkoshi K. Sublethal Photothermal Stimulation with a Micropulse Laser Induces Heat Shock Protein Expression in ARPE-19 Cells. *Journal of Ophthalmology*. 2015;2015:1-9. doi: <https://dx.doi.org/10.1155/2015/729792>
17. Beckham JT, Wilmink GJ, Mackanos MA, et al. Role of HSP70 in cellular thermotolerance. *Lasers in Surgery and Medicine*. 2008;40(10):704-715. doi: <https://dx.doi.org/10.1002/lsm.20713>
18. Sramek C, Mackanos M, Spitler R, et al. Non-damaging Retinal Phototherapy: Dynamic Range of Heat Shock Protein Expression. *Investigative Ophthalmology & Visual Science*. 2011;52(3):1780. doi: <https://dx.doi.org/10.1167/iovs.10-5917>
19. Rylander MN. Thermally Induced Injury and Heat-Shock Protein Expression in Cells and Tissues. *Annals of the New York Academy of Sciences*. 2005;1066(1):222-242. doi: <https://dx.doi.org/10.1196/annals.1363.009>
20. Flaxel C, Bradle J, Acott T, Samples JR. Retinal pigment epithelium produces matrix metalloproteinases after laser treatment. *Retina*. 2007;27(5):629-634. doi: <https://dx.doi.org/10.1097/01.iae.0000249561.02567.fd>
21. Friberg TR, Karatza EC. The Treatment of Macular Disease Using a Micropulsed and Continuous Wave 810-nm Diode Laser. *Ophthalmology*. 1997;104(12):2030-2038. doi: [https://dx.doi.org/10.1016/S0161-6420\(97\)30061-X](https://dx.doi.org/10.1016/S0161-6420(97)30061-X)
22. Laursen ML. Subthreshold micropulse diode laser treatment in diabetic macular oedema. *British Journal*

- of *Ophthalmology*. 2004;88(9):1173-1179. doi: <https://dx.doi.org/10.1136/bjo.2003.040949>
23. Figueira J, Khan J, Nunes S, et al. Prospective randomised controlled trial comparing sub-threshold micropulse diode laser photocoagulation and conventional green laser for clinically significant diabetic macular oedema. *Br J Ophthalmol*. 2009;93(10):1341-1344. doi: <https://dx.doi.org/10.1136/bjo.2008.146712>
 24. Luttrull JK. Subthreshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular oedema. *British Journal of Ophthalmology*. 2005;89(1):74-80. doi: <https://dx.doi.org/10.1136/bjo.2004.051540>
 25. Stanga PE, Reck AC, Hamilton AMP. Micropulse Laser in the Treatment of Diabetic Macular Edema. *Seminars in Ophthalmology*. 1999;14(4):210-213. doi: <https://dx.doi.org/10.3109/08820539909069539>
 26. Lavinsky D, Cardillo JA, Melo LAS, Dare A, Farah ME, Belfort R. Randomized Clinical Trial Evaluating metdrs versus Normal or High-Density Micropulse Photocoagulation for Diabetic Macular Edema. *Investigative Ophthalmology & Visual Science*. 2011;52(7):4314. doi: <https://dx.doi.org/10.1167/iovs.10-6828>
 27. Luttrull JK, Sinclair SH. Safety of transfoveal subthreshold diode micropulse laser for fovea-involving diabetic macular edema in eyes with good visual acuity: *Retina*. 2014;34(10):2010-2020. doi: <https://dx.doi.org/10.1097/IAE.0000000000000177>
 28. Mansouri A, Sampat KM, Malik KJ, Steiner JN, Glaser BM. Efficacy of subthreshold micropulse laser in the treatment of diabetic macular edema is influenced by pre-treatment central foveal thickness. *Eye*. 2014;28(12):1418-1424. doi: <https://dx.doi.org/10.1038/eye.2014.264>
 29. Moisseiev E, Abbassi S, Thinda S, Yoon J, Yiu G, Morse LS. Subthreshold micropulse laser reduces anti-VEGF injection burden in patients with diabetic macular edema. *Eur J Ophthalmol*. 2018;28(1):68-73. doi: <https://dx.doi.org/10.5301/ejo.5001000>
 30. Parodi MB, Spasse S, Iacono P, Di Stefano G, Canziani T, Ravalico G. Subthreshold Grid Laser Treatment of Macular Edema Secondary to Branch Retinal Vein Occlusion with Micropulse Infrared (810 Nanometer) Diode Laser. *Ophthalmology*. 2006;113(12):2237-2242. doi: <https://dx.doi.org/10.1016/j.ophtha.2006.05.056>
 31. Parodi MB, Iacono P, Ravalico G. Intravitreal triamcinolone acetonide combined with subthreshold grid laser treatment for macular oedema in branch retinal vein occlusion: a pilot study. *British Journal of Ophthalmology*. 2008;92(8):1046-1050. doi: <https://dx.doi.org/10.1136/bjo.2007.128025>
 32. Inagaki K, Ohkoshi K, Ohde S, Deshpande GA, Ebihara N, Murakami A. Subthreshold Micropulse Photocoagulation for Persistent Macular Edema Secondary to Branch Retinal Vein Occlusion including Best-Corrected Visual Acuity Greater Than 20/40. *Journal of Ophthalmology*. 2014;2014:1-10. doi: <https://dx.doi.org/10.1155/2014/251257>
 33. Parodi MB, Iacono P, Bandello F. Subthreshold grid laser versus intravitreal bevacizumab as second-line therapy for macular edema in branch retinal vein occlusion recurring after conventional grid laser treatment. *Graefes Arch Clin Exp Ophthalmol*. 2015;253(10):1647-1651. doi: <https://dx.doi.org/10.1007/s00417-014-2845-6>
 34. Desmettre TJ. Micropulse and continuous wave diode retinal photocoagulation: visible and subvisible lesion parameters. *British Journal of Ophthalmology*. 2006;90(6):709-712. doi: <https://dx.doi.org/10.1136/bjo.2005.086942>
 35. Piccolino FC, Eandi CM, Ventre L, Rigault De La Longrais RC, Grignolo FM. Photodynamic Therapy for Chronic Central Serous Chorioretinopathy: *RETINA*. 2003;23(6):752-763. doi: <https://dx.doi.org/10.1097/00006982-200312000-00002>
 36. Roisman L, Magalhães FP, Lavinsky D, et al. Micropulse Diode Laser Treatment for Chronic Central Serous Chorioretinopathy: A Randomized Pilot Trial. *Ophthalmic Surgery, Lasers and Imaging Retina*. 2013;44(5):465-470. doi: <https://dx.doi.org/10.3928/23258160-20130909-08>
 37. Malik KJ, Sampat KM, Mansouri A, Steiner JN, Glaser BM. Low-intensity/high-density subthreshold micropulse diode laser for chronic central serous chorioretinopathy: *Retina*. 2015;35(3):532-536. doi: <https://dx.doi.org/10.1097/IAE.0000000000000285>
 38. Luttrull JK. Low-intensity/high-density subthreshold diode micropulse laser for central serous chorioretinopathy: *retina*. 2016;36(9):1658-1663. doi: <https://dx.doi.org/10.1097/IAE.0000000000001005>
 39. Chen S-N, Hwang J-F, Tseng L-F, Lin C-J. Subthreshold Diode Micropulse Photocoagulation for the Treatment of Chronic Central Serous Chorioretinopathy with Juxtafoveal Leakage. *Ophthalmology*. 2008;115(12):2229-2234. doi: <https://dx.doi.org/10.1016/j.ophtha.2008.08.026>
 40. Koss MJ, Beger I, Koch FH. Subthreshold diode laser

- micropulse photocoagulation versus intravitreal injections of bevacizumab in the treatment of central serous chorioretinopathy. *Eye (Lond)*. 2012;26(2):307-314. doi: <https://dx.doi.org/10.1038/eye.2011.282>
41. Kretz FTA, Beger I, Koch F, Nowomiejska K, Auffarth GU, Koss MJ. Randomized Clinical Trial to Compare Micropulse Photocoagulation Versus Half-dose Verteporfin Photodynamic Therapy in the Treatment of Central Serous Chorioretinopathy. *Ophthalmic Surgery, Lasers and Imaging Retina*. 2015;46(8):837-843. doi: <https://dx.doi.org/10.3928/23258160-20150909-08>
 42. Breukink MB, Mohr JK, Ossewaarde-van Norel A, et al. Half-dose photodynamic therapy followed by diode micropulse laser therapy as treatment for chronic central serous chorioretinopathy: evaluation of a prospective treatment protocol. *Acta Ophthalmol*. 2016;94(2):187-197. doi: <https://dx.doi.org/10.1111/aos.12938>
 43. Maruko I, Koizumi H, Hasegawa T, Arakawa H, Iida T. Subthreshold 577 nm micropulse laser treatment for central serous chorioretinopathy. Vavvas DG, ed. *PLOS ONE*. 2017;12(8):e0184112. doi: <https://dx.doi.org/10.1371/journal.pone.0184112>
 44. Pollack JS. Tissue Effects of Subclinical Diode Laser Treatment of the Retina. *Archives of Ophthalmology*. 1998;116(12):1633. doi: <https://dx.doi.org/10.1001/archophth.116.12.1633>
 45. Moorman CM, Hamilton AMP. Clinical applications of the micropulse diode laser. *Eye*. 1999;13(2):145-150. doi: <https://dx.doi.org/10.1038/eye.1999.41>
 46. Luttrull JK, Musch DC, Spink CA. Subthreshold diode micropulse panretinal photocoagulation for proliferative diabetic retinopathy. *Eye (Lond)*. 2008;22(5):607-612. doi: <https://dx.doi.org/10.1038/sj.eye.6702725>
 47. Friberg TR, Brennen PM, Freeman WR, Musch DC, the PTAMD Study Group. Prophylactic Treatment of Age-Related Macular Degeneration Report Number 2: 810-Nanometer Laser to Eyes with Drusen: Bilaterally Eligible Patients. *Ophthalmic Surgery, Lasers, and Imaging*. 2009;40(6):530-538. doi: <https://dx.doi.org/10.3928/15428877-20091030-01>
 48. Luttrull JK, Chang DB, Margolis BWL, Dorin G, Luttrull DK. Laser resensitization of medically unresponsive neovascular age-related macular degeneration: Efficacy and Implications. *Retina*. 2015;35(6):1184-1194. doi: <https://dx.doi.org/10.1097/IAE.0000000000000458>
 49. Sramek C, Mackanos M, Spitler R, et al. Non-damaging Retinal Phototherapy: Dynamic Range of Heat Shock Protein Expression. *Investigative Ophthalmology & Visual Science*. 2011;52(3):1780. doi: <https://dx.doi.org/10.1167/iovs.10-5917>
 50. Johnson TM, Glaser BM. Micropulse laser treatment of retinal-choroidal anastomoses in age-related macular degeneration. *Graefes Archive for Clinical and Experimental Ophthalmology*. 2005;243(6):570-575. doi: <https://dx.doi.org/10.1007/s00417-004-1082-9>
 51. Luttrull JK, Margolis BWL. Functionally Guided Retinal Protective Therapy for Dry Age-Related Macular and Inherited Retinal Degenerations: A Pilot Study: A Pilot Study. *Investigative Ophthalmology & Visual Science*. 2016;57(1):265. doi: <https://dx.doi.org/10.1167/iovs.15-18163>
 52. Jeffrey Luttrull: subthreshold diode micropulse laser. Md Magazine. <https://www.mdmag.com/conference-coverage/asrs-2017/jeffrey-luttrull-subthreshold-diode-micropulse-laser>.

Copyright: © **Juhn et al.** This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.