# Subthreshold Diode Microsecond Pulse Laser:

*A Critical Evaluation of the Evidence for Managing Age-Related Macular Degeneration*

**Retinal Protection Sciences**

# Table of Contents

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# Introduction

## AMD: A Global Health Problem with Substantial Patient Impact

Age-related macular degeneration is a progressive degenerative disease affecting the central retina with profound consequences for patient quality of life and functional independence. AMD remains the principal cause of irreversible visual loss in persons over 50 years of age worldwide, with a particularly high burden in developed countries. The estimated global prevalence of AMD in 2020 was projected to be 196 million, growing to 288 million by 2040.[1] In the United States alone, approximately 7.3 million people have high-risk AMD, with about 1.75 million suffering severe visual loss due to advanced AMD.[2]

At the patient level, AMD leads to difficulties with reading, facial recognition, driving, and other activities of daily living. A systematic review of AMD impact studies found significant decreases in quality-of-life measures comparable to those seen with severe stroke or advanced cancer.[3] The economic burden is similarly substantial, with direct medical costs in the United States estimated at $49.4 billion annually and indirect costs due to depression, injuries, and loss of independence reaching into the tens of billions.[33]

Advanced AMD manifests in two forms: dry (non-neovascular) AMD characterized by geographic atrophy (GA) of the retinal pigment epithelium (RPE) and choroidal neovascularization (CNV), also known as wet AMD. While dry AMD accounts for approximately 90% of all AMD cases, conversion to wet AMD represents about 90% of all cases of severe vision loss from AMD.[2]

## Limitations of Current Standard of Care in Clinical Practice

The current standard of care for dry AMD consists primarily of lifestyle modification, AREDS nutritional supplements, and monitoring. The Age-Related Eye Disease Study (AREDS) demonstrated that antioxidant vitamins combined with zinc reduced the risk of progression to advanced AMD by approximately 25% over six years.[13] However, this leaves a substantial 75% of expected progression unaddressed, highlighting the need for more effective interventions.

**Figure 1:** Global Prevalence of AMD[1]



Global Prevalence of AMD
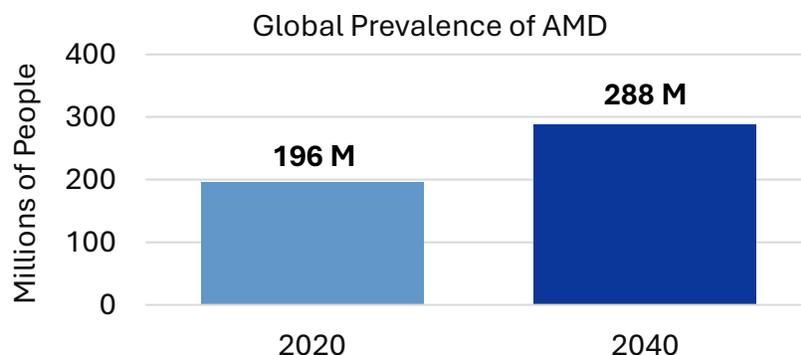
For wet AMD, the introduction of anti-VEGF agents has significantly improved visual outcomes compared to previous therapies. Nevertheless, these treatments have important limitations in real-world settings. The SEVEN-UP study, which followed patients from the original MARINA and ANCHOR trials of ranibizumab, found that after 7 years of treatment, 37% of patients had visual acuity of 20/200 or worse, and only 23% maintained 20/40 or better.[4] Additionally, the treatment burden of frequent intravitreal injections, substantial costs (exceeding $20,000 annually per patient), and the development of drug tolerance represent significant barriers to optimal outcomes in clinical practice. [34]

## A Physiologic Approach to AMD: Subthreshold Diode Microsecond Pulse Laser

Subthreshold diode microsecond pulse laser (SDM) represents a physiologic approach to addressing the underlying pathophysiology of both forms of AMD. Unlike conventional retinal laser photocoagulation that purposely damages retinal tissue, SDM delivers laser energy in microsecond pulses that are designed to be sublethal to retinal cells while producing therapeutic cellular responses.

By improving retinal function rather than causing structural changes, SDM aims to address AMD at an earlier stage in the disease process, potentially before irreversible damage occurs. This paper critically examines the current evidence suggesting that SDM may offer meaningful benefits in AMD management through regular periodic applications of panmacular treatment.



**Figure 2:** Diagram of Subthreshold Diode Microsecond Pulse Laser
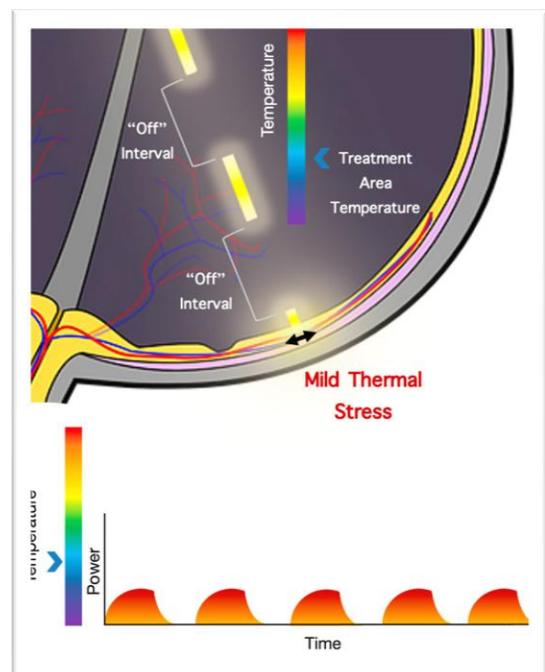
# The Evolution of Retinal Laser Therapy

## From Photocoagulation to Subthreshold Treatment

Historically, all attempts at laser treatment for dry AMD failed because they relied on laser-induced retinal damage (LIRD), which paradoxically increased disease progression and neovascular conversion risk. Conventional photocoagulation produces visible burns, causing thermal damage to the retina. Early "laser for drusen" studies showed that while drusen elimination could be achieved through LIRD-induced inflammation, this same inflammatory response compromised the critical RPE-Bruch's membrane barrier to choroidal neovascularization, ultimately increasing the risk of vision loss from wet AMD conversion.

Even "selective" short-pulse lasers (2RT nanosecond, SRT microsecond, and PASCAL) that were designed to reduce but not eliminate retinal damage have been associated with acceleration of AMD progression in high-risk eyes, particularly those with reticular pseudodrusen (RPD). A 2010 randomized clinical trial using SRT laser to slow geographic atrophy progression was discontinued prior to completion due to rapid doubling of the GA progression rate[33]. More recently, a randomized trial of nanosecond 2RT laser demonstrated reduced drusen density but failed to improve early AMD while accelerating disease progression and vision loss in higher-risk eyes.[32]

The risk-benefit ratio of conventional laser treatment has been improved through the development of more selective laser technologies. However, even "selective" short-pulse continuous wave lasers that limit retinal damage to the RPE have been associated with acceleration of AMD progression in high-risk eyes, particularly those with reticular pseudodrusen (RPD).[31,32]

**Figure 3:** Timeline of Retinal Laser Therapy Evolution



| 1940s | 1960s-1990s | Today |
|---|---|---|
| **Conventional Photocoagulation** | **Selective Laser Technologies** | **Subthreshold Diode Microsecond Pulse (SDM) Laser** |
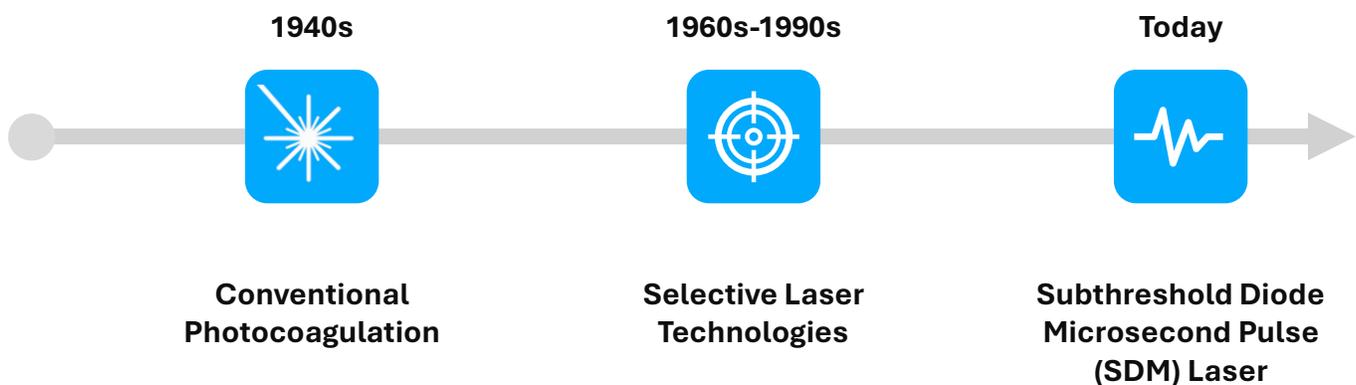
# Subthreshold Diode Microsecond Pulse (SDM) Laser: A Paradigm Shift

SDM represented a paradigm shift in the conception and performance of laser treatment for chronic progressive retinopathies when it was introduced in the early 2000s. First reported in 2005 for the treatment of diabetic macular edema, SDM was the first retinal laser strategy specifically designed to preclude laser-induced retinal damage (LIRD).[18]

## **Defining Characteristics of SDM:**

### Wavelength
Typically 810nm, which penetrates well to the RPE layer

### Microsecond Pulse Technology
Delivers laser energy in brief "on" cycles (typically 100-300 microseconds) separated by "off" periods

### Low Duty Cycle
Usually 5%, meaning the laser is "on" only 5% of the treatment time

### Sublethal Energy Levels
Power settings are chosen to remain below the threshold of retinal damage

### High-Density Application
Treatment spots are applied confluently over the target area

### Panmacular Treatment
For AMD, the entire macula within the vascular arcades is typically treated

Unlike conventional laser or even "clinically invisible" threshold treatments, SDM has no known adverse effects and produces no detectable morphologic changes to the retina by any imaging modality. LIRD at a 5% duty cycle has never been reported, illustrating the important influence of pulse frequency. The therapeutic effects of SDM are entirely physiological rather than anatomical.[19,20]

# Mechanism of Action: The "Reset" Phenomenon

## Heat Shock Protein Activation

The therapeutic mechanism of SDM appears to involve activation of cellular protective pathways, particularly heat shock proteins (HSPs), through sublethal thermal stress. HSPs are a family of proteins involved in protein folding, transport, and cellular repair. They are upregulated in response to various stressors, including thermal stress, and function to protect cells and restore normal function.[21,22]

In vitro and in vivo studies have confirmed that SDM activates HSP expression in RPE cells without causing cell death.[23,24] The rate of temperature change appears to be a critical factor in HSP activation. SDM's microsecond pulse format produces very steep thermal gradients—temperature elevations of approximately 7°C with each 100-microsecond pulse, or 70,000°C/second—making it particularly effective at stimulating HSP production compared to continuous wave lasers.[25]

## The "Reset to Default" Theory

The concept of "Reset to Default" has been proposed to explain the therapeutic mechanism of SDM.[16] This theory suggests that SDM triggers HSP-mediated RPE repair, which normalizes RPE function and consequently RPE cytokine expression and retinal autoregulation through low-dose adaptive thermal hormesis.

Protein misfolding is the common currency of cellular dysfunction in aging and chronic disease. Because HSP-mediated correction of protein misfolding is agnostic to the cause, SDM acts as a non-specific trigger of disease-specific repair, much like the "reset" function common to electronic devices.[17]

The therapeutic effects of SDM observed in clinical studies and documented in laboratory investigations include:

1. **Proteome normalization:** Correction of age-related and disease-related protein abnormalities

2. **Cytokine modulation:** Down-regulation of VEGF and up-regulation of pigment epithelial-derived factor (PEDF)

3. **Anti-inflammatory effects:** Reduction in markers of chronic inflammation

4. **Anti-oxidant effects:** Decreased reactive oxygen species and increased nitrous oxide and superoxide dismutase levels

5. **Improved mitochondrial function:** Enhanced cellular energy production
6. **Anti-apoptotic effects:** Inhibition of programmed cell death pathways
7. **Immunomodulation:** Beneficial local and systemic immune responses
8. **Stem cell recruitment:** Activation of bone marrow-derived cells that may contribute to retinal repair

When applied in a program of regular periodic treatments (typically every 3-4 months), these effects can be maintained over the life-time of the patient, potentially slowing disease progression and reducing the risk of vision loss.[18,19]

**Figure 4:** Reset to Default Theory System Diagram



**Progressive Decay** → **Treatment** → **Normalized Function**

*Aging causes disease & protein misfolding*

Cell Death

**RPE Cell Health**

*RPE: Retinal pigment epithelium cells*

**Spike in Misfolded Protein** ②

**Sublethal Laser Induced Heat Shock** *(VPT™)* ①

**Heat Shock Protein Activation** ③

④ **Restored Proteostasis**

*"Reset to Default"*

*Therapy triggers a thermal adaptive hormesis*

*Therapy inhibits cellular dysfunction & death*

Cell Death

**RPE Cell Health**

# Clinical Evidence for SDM in Dry AMD: Critical Analysis of Patient Outcomes

## Reduced Risk of Neovascular Conversion: Retrospective and Real-World Evidence

A series of retrospective and real-world studies suggests Subthreshold Diode Microsecond Pulse (SDM) laser may provide protection against conversion from dry to wet AMD. The most comprehensive analysis comes from a 2018 study by Luttrull and colleagues examining 547 eyes with dry AMD treated with SDM. Despite high-risk characteristics (median age 84 years, 39% with reticular pseudodrusen, 78% AREDS category 3 or 4, and 23% with CNV in the fellow eye), only 9 eyes (1.6%, annualized rate 0.87%) developed new CNV during an average follow-up of 22 months.[2]

The authors compared these results to historical controls from the AREDS study (approximately 4% annual conversion rate for antioxidant-treated eyes) and estimated an 80-98% reduction in neovascular conversion risk. However, it is important to note the limitations of historical comparisons across different patient populations and time periods.[2]

Subsequent studies have attempted to address these limitations through more robust methodologies. Large-scale real-world data studies using propensity score matching to balance known risk factors between eyes treated with SDM and those receiving standard care alone have provided validation of SDM's efficacy.

Two major propensity-scored real-world data studies examined data from the Vestrum Health database, which aggregates unidentified patient data from over 300 retina subspecialty practices in the United States:

**1** *RWD Comparison of SoC vs SDM for Prevention of Neovascular Age-Related Macular Degeneration (Clin Ophthalmol. 2022)*

A 2022 study employing propensity score matching found that SDM was associated with a hazard ratio of 13.04 for neovascular conversion compared to standard care alone, suggesting SDM-treated eyes were 13x less likely to develop neovascular conversion[3].

The study showed for eyes treated with SDM, the cumulative probability of conversion from dry AMD to wet AMD after four years was only 3.9%, compared for the 30.3% conversion rate observed in eyes treated with SoC.
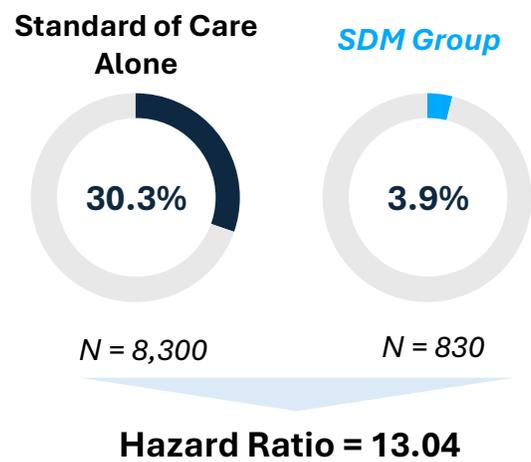


**Standard of Care Alone**

**30.3%**

*N = 8,300*

**SDM Group**

**3.9%**

*N = 830*

**Hazard Ratio = 13.04**

**Figure 5:** Cumulative probability of conversion from dry AMD to wet AMD *(Clin Ophthalmol. 2022)* [3]

**2** **Subthreshold Diode Microsecond Pulse Laser for Prevention of Neovascular Age-Related Macular Degeneration (***Nature Portfolio, 2023***)**

A 2023 study examining data from over 320 US retina specialists found a hazard ratio of 5.73 (p<0.0001) favoring the SDM group after propensity score matching for age, AMD severity, presence of reticular pseudodrusen, and fellow eye status.[4]

Both studies included quality checks with computational modeling showing high levels of matching concordance and successful tests of statistical validity. Quintile analysis of the propensity score analyses, able to detect 99% of unrecognized biases, revealed no evidence of undetected bias in any of the 6 different propensity score analyses between the two RWD studies.

**Standard of Care Alone**

**SDM Group**

**42.7%**

**11.3%**

*N = 7,370*

*N = 737*

**Hazard Ratio = 5.73**

**Figure 5:** Cumulative probability of conversion from dry AMD to wet AMD (Nature 2023) [4]

At the patient level, this reduction in neovascular conversion risk potentially translates to preserved central vision and avoidance of anti-VEGF injection burden.

**Figure 6:** Cumulative probability of conversion from dry AMD to wet AMD  *(Clin Ophthalmol. 2022)* [3]

## Age-Related Macular Degeneration (AMD) Conversion Rates



**Note:** Shaded area indicates the 95% confidence interval

Standard of Care (N = 8,300 eyes)
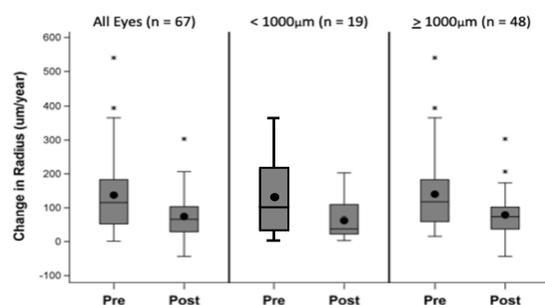
**SDM Group** (N = 830 eyes)
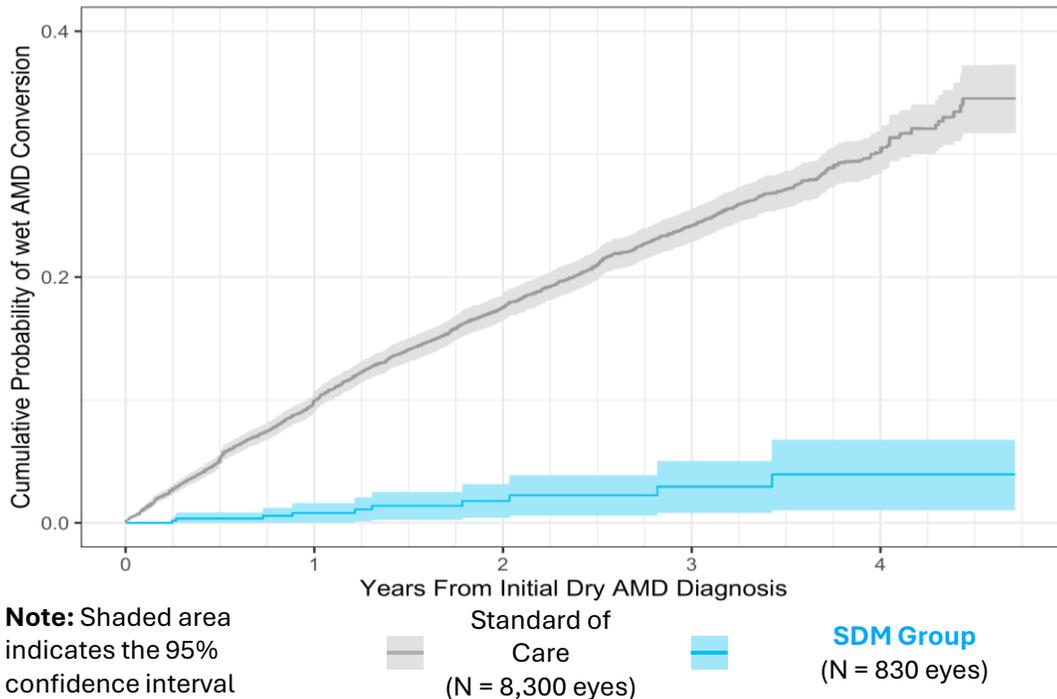
## Patient-Relevant Outcomes: Geographic Atrophy Progression

Geographic atrophy (GA) progression directly correlates with visual function loss and represents an important patient-centered outcome. A 2020 study by Luttrull et al. examined 67 eyes with established GA that served as their own controls, comparing GA progression rates before and after initiation of SDM. The velocity of radial linear GA progression decreased from a mean of 137μm/year before treatment to 73μm/year after treatment, representing a 47% reduction (p<0.0001).[5]

For individual patients, this translated to better preservation of retinal tissue and potentially slower visual function decline. Interestingly, even eyes with extensive preexisting GA showed significant slowing of further atrophy progression. The study also reported no adverse effects on visual acuity, which remained stable throughout the follow-up period. The authors noted that many patients with central scotomas reported

**Figure 7:** Distribution of change in GA radius, pre and post treatment. *(Clin Ophthal. 2020)* [5]

subjective lightening or disappearance of their scotomas following treatment.[5] This SDM approach was notably both safer and more effective than either retinal-damaging laser modes or currently available targeted drug therapies such as complement fixation inhibitor intravitreal injections, which achieve less slowing of GA progression while substantially increasing the risk of neovascular conversion.

## Functional Vision Improvements: Beyond Standard Visual Acuity

Standard visual acuity measurements often fail to capture the full impact of AMD on patients' visual function. A 2016 pilot study by Luttrull and Margolis employed more sensitive and functionally relevant measures including pattern electroretinography (PERG), automated microperimetry (AMP), and contrast visual acuity (CVA) to assess treatment effects in 158 eyes with dry AMD.[6]

While Snellen visual acuity remained unchanged after SDM, 88% of eyes showed improvement in PERG parameters, indicating enhanced retinal function. More importantly from a patient perspective, significant improvements were observed in:

1. Macular sensitivity measured by AMP (p=0.0439), reflecting better detection of light stimuli across the macula

2. Contrast visual acuity measured by CVA under mesopic (low light) conditions (p=0.006), potentially translating to better performance in everyday low-light environments such as restaurants or evening activities

These functional improvements were most pronounced in areas of the retina most compromised before treatment. The study found through linear regression analysis that the worse the preoperative measure, the greater the improvement after treatment (p<0.05 for all testing measures).[6] This pattern suggests that SDM may preferentially benefit patients with more advanced disease who typically have fewer treatment options.

# Clinical Evidence for SDM in Wet AMD: Patient-Centered Benefits

## Addressing Anti-VEGF Drug Tolerance: A Critical Clinical Challenge

Drug tolerance represents a significant and previously intractable problem for patients with neovascular AMD receiving long-term anti-VEGF therapy. Unlike tachyphylaxis (which may resolve with drug interruption), true drug tolerance is generally considered permanent and affects patients who initially responded well to treatment[14]. When tolerance develops to one anti-VEGF agent, cross-tolerance to other agents in the same class often follows, leaving patients with limited options and progressive visual deterioration.

A pilot study by Luttrull and colleagues (2015) addressed this challenging clinical scenario in 13 eyes with established anti-VEGF drug tolerance. All eyes had previously responded to anti-VEGF therapy but had become unresponsive to all available agents, including at least three consecutive ineffective aflibercept injections. Each eye received a single session of panmacular SDM, followed by resumption of aflibercept one-month later.[14]

## Key Patient Outcomes:

- 92% of eyes showed renewed drug response

- 69% achieved complete resolution of macular exudation

- Both central and maximum macular thicknesses significantly improved

- Visual acuity remained stable despite previous declining trends

**Patient Outcomes in Treated Eyes**
*(n=13)*
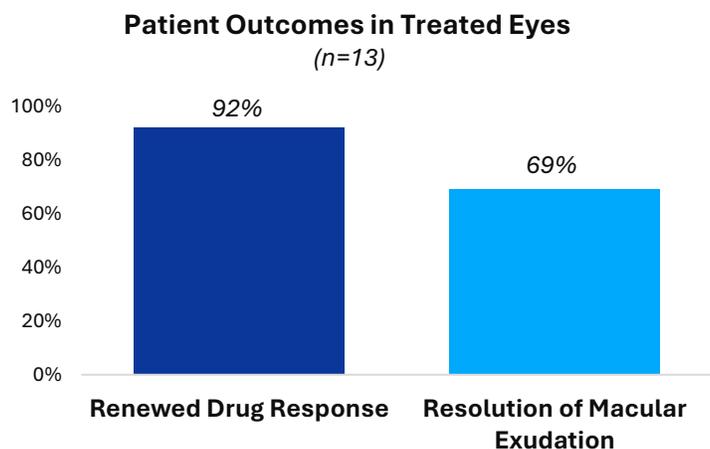


**Figure 9:** Rates of renewed drug response and complete resolution of macular exudation

*Laser re-sensitization of medically unresponsive neovascular age-related macular degeneration: efficacy and implications. (Retina 2015)*

While this was a small, uncontrolled study, the consistent response pattern across patients with long-standing drug tolerance (averaging 34 prior anti-VEGF injections) suggests a potential biological effect. For these patients, SDM potentially transformed a condition with poor prognosis into one that could again be effectively managed with standard therapy.[14]

# Patient Treatment Burden: Reduced Need for Anti-VEGF Injections

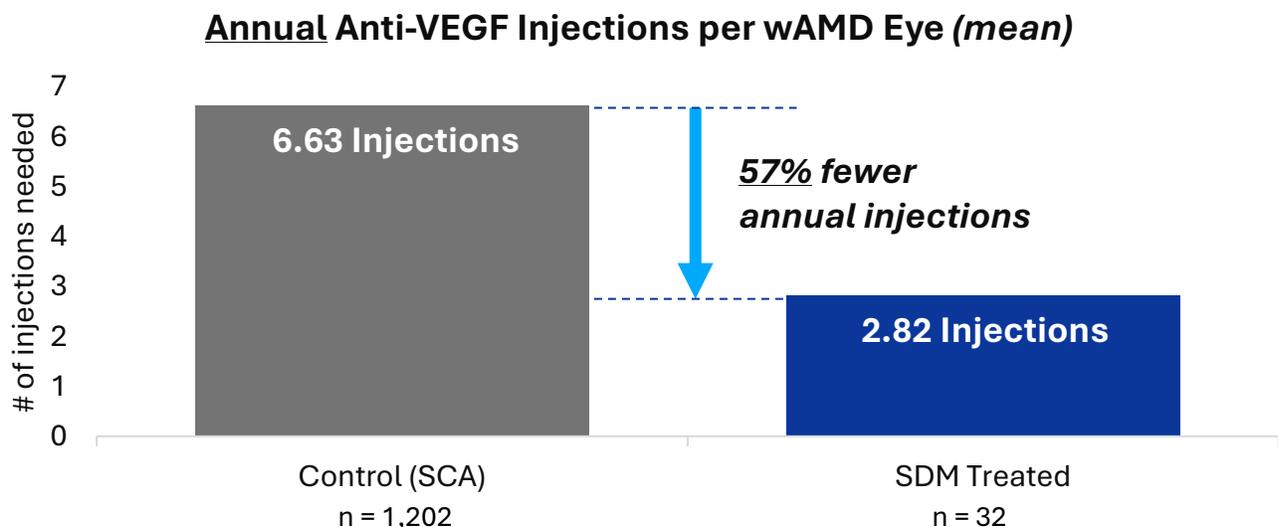The frequent intravitreal injections required for wet AMD management represent a substantial burden for patients, many of whom are elderly and have comorbid conditions that complicate regular visits. This burden includes physical discomfort, anxiety, transportation challenges, caregiver time, and financial costs.

Real-world data suggests that incorporating SDM into wet AMD management may significantly reduce this burden. For patients with drug-tolerant neovascular age-related macular degeneration, SDM has shown promising results. In a study of 13 eyes (12 patients) previously treated with 16–67 anti-VEGF injections (average 34), SDM was followed for 3–7 months (average 5). After SDM and aflibercept resumption, 92% of eyes improved, with full macular exudation resolution in 69%. Visual acuity was stable, while central and maximum macular thicknesses significantly improved. SDM restored drug responsiveness in these patients. [24]

In the 2023 propensity-scored study focusing primarily on dry AMD, investigators noted a secondary finding that patients who developed wet AMD after receiving SDM required 57% fewer anti-VEGF injections than control patients following neovascular conversion.[4] Of patients who converted to wet AMD, those in the SDM group received an average of 2.82 anti-VEGF injections per year, compared to 6.63 injections per year in the SCA group. Due to delayed disease progression in the SDM group, the average follow-up period after conversion to wet AMD was significantly shorter compared to SCA (413.8 days vs. 809.0 days). Since standard anti-VEGF treatment protocol dictates a loading phase with more frequent injections required in initial months, the shorter observation window in the SDM group may disproportionately capture this front-loaded treatment period, potentially inflating the calculation of mean annual injections for the SDM group. This observation further supports the possibility that SDM may modify the underlying disease process in a way that reduces the intensity of treatment required for wet AMD.[4]

**Figure 9:** Number of anti-VEGF injections needed for patients that converted to wet AMD *[Vision Protection Therapy for Prevention of Neovascular Age-Related Macular Degeneration (Nature 2023), Supplemt. Data]*



### Annual Anti-VEGF Injections per wAMD Eye *(mean)*

Control (SCA): 6.63 Injections, n = 1,202

SDM Treated: 2.82 Injections, n = 32

57% fewer annual injections

Across all published studies of SDM for wet AMD, no adverse treatment effects have been reported. This favorable safety profile represents an important consideration for patients who may already be experiencing anxiety about their vision prognosis. The non-damaging nature of SDM, confirmed by multiple imaging modalities including spectral-domain optical coherence tomography, fundus autofluorescence, and fluorescein angiography, provides reassurance regarding both short and long-term safety.[14,24,25]

# Real-World Evidence vs. Randomized Clinical Trials in Evaluating SDM for AMD

## The Complementary Value of Different Evidence Types

While randomized controlled trials (RCTs) have long been considered the gold standard for establishing treatment efficacy, there is growing recognition that real-world evidence (RWE) provides critical and complementary insights, particularly for chronic conditions like AMD that affect diverse patient populations over extended periods. The current evidence base for SDM consists primarily of real-world studies, which offer several advantages for evaluating this therapeutic approach, with recent validation involving over 500,000 eyes providing unprecedented scale of evidence.

Real-world data (RWD) studies analyze information gathered from routine clinical practice rather than the highly controlled environment of conventional trials. The FDA defines RWD as *"data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources"*.[9] When rigorously analyzed, RWD yields real-world evidence about how a therapy performs in ordinary practice settings.

Between 2019 and 2021, 70% of oncology drug submissions to the FDA included RWD to support efficacy or safety, indicating increasing regulatory acceptance of real-world evidence. Both FDA and EMA have issued guidance on incorporating real-world evidence into regulatory decision-making. [9]

## Strengths of Real-World Evidence for Evaluating SDM

1. **Broader Patient Representation:** RWD studies typically include patients who would be excluded from RCTs, such as those with multiple comorbidities, very advanced age, or complex disease presentations. The SDM studies discussed in this paper included patients with a median age of 84 years and multiple risk factors for progression—a population often underrepresented in traditional clinical trials. This high-risk population is precisely the group most in need of effective interventions.

2. **Long-Term Outcomes:** AMD is a chronic, progressive disease requiring years of follow-up to capture meaningful outcomes. RWD studies often follow patients for extended periods in real clinical settings. The studies of SDM have included follow-up of up to 9 years, providing important insights into the durability of treatment effects.

3. **Functional Visual Outcomes:** Beyond traditional endpoints like visual acuity, RWD studies can capture a broader range of patient-centered outcomes that reflect daily visual function. The SDM studies have assessed outcomes including contrast sensitivity, microperimetry, and patient-reported scotoma changes—measures that connect more directly to quality of life than conventional trial endpoints.

4. **Minimal Treatment Burden:** RWD studies reflect the real-world impact of treatment on patients' lives, including convenience, compliance, and economic considerations. The observed reduction in anti-VEGF injection frequency with SDM represents a meaningful patient benefit that might be missed in a short-term RCT focused primarily on efficacy.

5. **Proven Safety Profile**: With larger patient numbers and longer follow-up, RWD studies are superior for detecting rare adverse events or long-term effects. The consistent absence of adverse effects across multiple SDM studies strengthens confidence in its safety profile.

**Strengths of SDM Real World Evidence**

1) Broader Patient Representation

2) Improved Long-Term Outcomes

3) Functional Visual Outcomes

4) Minimal Treatment Burden

5) Proven Safety Profile
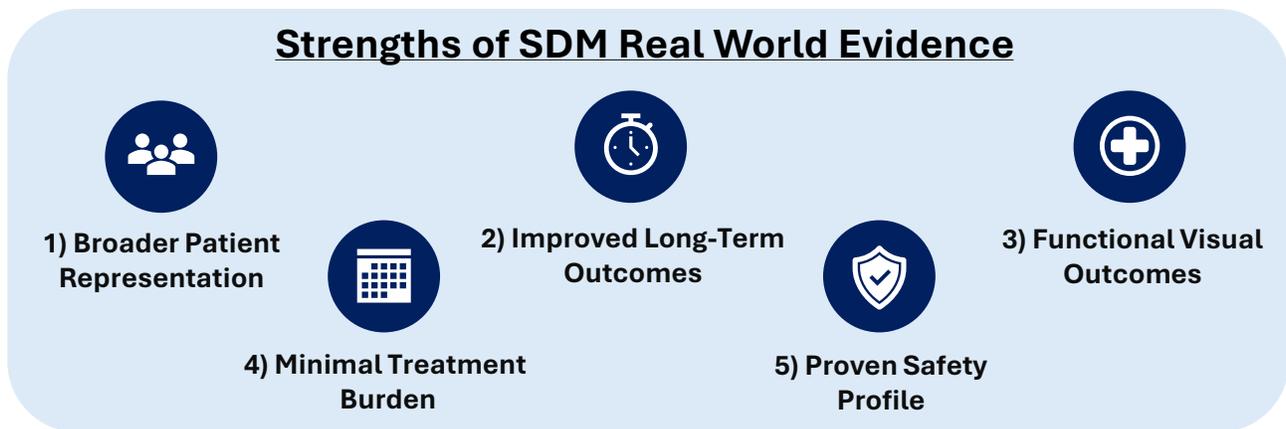
## Methodological Rigor in Real-World Studies

Modern RWD studies employ sophisticated analytical techniques to address potential biases that might arise from the non-randomized nature of the data. The most recent SDM studies have used propensity score matching to balance known risk factors between treatment groups, creating statistically comparable cohorts that minimize selection bias.[3,4]

Propensity score methods can balance study groups with respect to variables used in the model. In the 2022 & 2023 studies of SDM, these variables included key risk factors for neo-vascular conversion such as age, AREDS category, presence of reticular pseudodrusen & fellow eye status. This methodological approach strengthens the validity of the observed treatment effects.

## Limitations and the Need for Multiple Evidence Types

Despite their strengths, RWD studies have inherent limitations. They cannot eliminate the possibility of unmeasured confounding variables & may be affected by documentation quality & completeness in clinical records. These limitations stress the complementary role of different evidence types in building a comprehensive understanding of treatment effectiveness.

For SDM, confirmatory RCTs would provide valuable additional evidence, particularly for regulatory purposes. However, the consistent results observed across multiple real-world studies using different methodological approaches including high-quality statistical analyses such as propensity scoring provide a compelling case for the effectiveness of this treatment approach in routine clinical practice.[9,10]

Recent research has found that well-designed observational studies with appropriate analytical methods (e.g., propensity scoring) often yield results consistent with RCTs.[11] The Cochrane Collaboration, in "*Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials" (2014),* found no significant difference in the results of RCTs compared to those from large RWD studies with robust results.[12] This finding supports the validity of the real-world evidence currently available for SDM.

# Clinical Application of SDM

## Patient Selection and Personalized Approach

SDM has been offered to patients with a variety of indications related to AMD:

A. **Intermediate to advanced dry AMD** (AREDS category 2 or higher) to reduce the risk of neovascular conversion and slow geographic atrophy progression

B. **Early dry AMD with concerning risk** factors such as reticular pseudodrusen or abnormal dark adaptometry

C. **Neovascular AMD with drug tolerance** to anti-VEGF medications

D. **Neovascular AMD with ongoing anti-VEGF treatment** to potentially reduce injection burden

In published studies, acceptance rates for SDM have been exceptionally high (97% of eligible patients), suggesting good tolerability and patient comfort with the therapy.[2] This high acceptance rate may reflect patients' desire for proactive management options beyond nutritional supplements and monitoring.

Patient selection should consider individual risk factors, prognosis with standard care alone, and patient preferences regarding preventive interventions. Patients with high-risk features such as intermediate or advanced dry AMD, reticular pseudodrusen, or fellow eye CNV may derive the greatest benefit from SDM, as suggested by subgroup analyses showing the highest-risk eyes benefiting most from treatment.[2-5]

# Treatment Protocol and Technical Considerations

The standardized approach to SDM – using identical laser parameters, treatment area, and spot application pattern in all eyes – makes it technically straightforward to perform compared to conventional photocoagulation and creates a "dose-like" treatment that minimizes the influence of surgeon skill and experience.[26]

**Table 1: Examples of the evolution of panmacular SDM laser parameter**

| SDM Laser Parameters | IOVS 2016 | Current / Sci Rep 2024 |
|---|---|---|
| Laser wavelength | 810 nm | 810 nm |
| Lens | Mainster contact lens | 90 D noncontact lens |
| Number of spot applications | 1800-3000 | 400-450 |
| Retinal spot size | 200 µ[3] | 300 µ[4] |
| Duty cycle | 5% | 5% |
| Power | 1.4 W | 1.73 W |
| Duration | 0.15 sec | 0.3 sec |
| Fluence[1] | $3.34 \times 10^{-7}$ fluence units | $3.67 \times 10^{-7}$ fluence units |
| Panmacular treatment time | 8 minutes | 2.5 minutes |
| ED 50/50[2] | 2 watts | 15 watts |

1. Fluence=Power X pulse duration X duty cycle / Pi (spot diameter/2)^2
2. Laser power required to reach 50/50 risk of thermal retinal injury / damage.
3. Retinal spot size with Mainster macular contact lens = aerial spot size 200um x 1.05 magnification factor = 210um
4. Retinal spot size with 90D lens = aerial spot size 300um x 1.32 magnification factor = 396um.

*(Table courtesy of David Browning, MD, Dept of Ophthalmology, School of Medicine, Wake Forest University)*

**Table 1.** *Table 1 above Illustrates that the usual measure of laser intensity, "fluence", fails to reflect key attributes of microsecond pulsed laser therapy such as SDM, including treatment time, therapeutic range, and safety margins of different laser parameter sets. SAPRA™ has exploited the unique biophysics of pulsed lasers to optimize the SDM treatment parameters to apply automated panmacular treatment in just 2 seconds with a 25 watt therapeutic range while simultaneously precluding the possibility of surgeon error, to eliminate treatment risk.*

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## Safety Profile and Patient Monitoring

The safety profile of SDM is one of its most noteworthy features. Across all published studies involving thousands of treated eyes, there have been no reported adverse treatment effects, including:

- ⊗ No laser-induced retinal damage

- ⊗ No treatment-associated visual loss

- ⊗ No accelerated disease progression

- ⊗ No increase in neovascular conversion (in contrast to some other laser modalities)

This exceptional safety profile is attributable to the fundamental design of SDM, which delivers laser energy at levels that activate HSPs but remain below the threshold for cellular damage. The absence of anatomic alterations resulting from LIRD makes SDM more akin to a medical treatment rather than a surgical procedure.[26]

Patient monitoring following SDM typically includes regular comprehensive eye examinations with optical coherence tomography to assess macular status. Functional testing with microperimetry or pattern electroretinography can provide additional objective measures of treatment response, though these specialized tests may not be available in all clinical settings.

# Future Directions and Research Priorities

## Advancing the Evidence Base

While the current evidence for SDM is promising, several research priorities would strengthen the foundation for its broader adoption:

**Randomized Controlled Trials:** Prospective, controlled studies comparing SDM to standard care would provide additional evidence regarding efficacy and optimal treatment protocols.

**Biomarker Identification:** Research to identify predictors of treatment response could help refine patient selection and personalize treatment regimens.

**Optimized Treatment Parameters:** Studies comparing different treatment intervals, laser settings, and application patterns could potentially enhance treatment effects.

**Combination Therapy Approaches:** Investigation of SDM in combination with other emerging therapies for AMD, such as complement inhibitors for geographic atrophy or sustained-release anti-VEGF formulations for wet AMD.

**Quality of Life and Economic Outcomes:** Formal assessment of the impact of SDM on patient-reported outcomes and healthcare resource utilization would provide important data for patients, clinicians, and payers.

**Treatment Automation:** Development of standardized delivery systems for improved accessibility and efficiency, which is needed to maximize patient acceptance and minimize risk given the vast numbers of patients at risk for vision loss from AMD.

## Integration with Emerging Therapy

SDM can complement any other treatment of any kind to improve clinical outcomes. The AMD treatment landscape continues to evolve, with several promising approaches in development or recently approved. SDM could potentially complement these emerging therapies:

1. **Complement inhibitors:** Recently approved drugs targeting the complement cascade for geographic atrophy may have synergistic effects with SDM cellular protective mechanisms.

2. **Port delivery systems:** Long-acting anti-VEGF implants could be combined with SDM to optimize treatment of neovascular AMD while minimizing the frequency of invasive procedures.

3. **Oral therapies:** Investigational oral medications for AMD could be evaluated in combination with SDM for potentially enhanced efficacy.

The non-invasive nature and favorable safety profile of SDM make it a potentially attractive component of multimodal treatment strategies aimed at addressing the complex pathophysiology of AMD.

## Implementation Barriers and Considerations

Current implementation barriers include the lack of industry (such as pharmaceutical) sponsorship for large randomized controlled trials, as there is limited financial incentive for companies to fund studies of non-proprietary laser treatments. Given the safety profile, significant need, and absence of other comparably safe and effective interventions, it is reasonable to consider SDM for patients with AMD who are sufficiently anxious about age-related vision loss or at high risk for age-related vision loss and who may not be willing, or indeed able, to wait for years for confirmatory RCTs that may never materialize due to funding limitations.

# Conclusion

Panmacular subthreshold diode microsecond pulse laser represents a promising approach to managing age-related macular degeneration. Current evidence from statistically robust large-scale real-world studies involving over 500,000 eyes indicates that retinal laser treatment avoiding tissue damage is the safest and most effective treatment of any kind to prevent progression and vision loss in dry AMD. The real-world evidence accumulated to date suggests that SDM may provide significant benefits for patients with both dry and wet AMD, including 13x reduced risk of neovascular conversion, slowed progression of geographic atrophy, improved visual function, and enhanced response to anti-VEGF therapy.

- **Non-damaging physiologic mechanism**: SDM activates cellular protective mechanisms through heat shock protein upregulation via controlled thermal hormesis, enhancing retinal function without structural changes—distinguishing it from conventional destructive laser treatments with superior safety profiles.

- **Robust real-world evidence**: Multiple studies using sophisticated methodologies, including propensity score matching and quintile analyses detecting 99% of potential biases, demonstrate consistent results across different patient populations with rigorous statistical validation.

- **Clinical advantages for AMD patients**: SDM offers non-invasive, well-tolerated, repeatable treatment that addresses AMD pathophysiology not targeted by current therapies, with improved functional outcomes and reduced treatment burden enhancing quality of life.

- **Optimal treatment approach**: Safety and effectiveness depend on sublethal RPE treatment applied widely over the macula on a regular basis to maintain benefits over time, currently exemplified by panmacular low-intensity/high-density subthreshold diode microsecond pulse laser.

The real-world evidence suggests SDM provides significant benefits for both dry and wet AMD, including 13x reduced risk of neovascular conversion, slowed geographic atrophy progression, improved visual function, and enhanced anti-VEGF response. Given its exceptional safety profile, current AMD management limitations, and potential public health value from prophylactic treatment, SDM deserves serious consideration as a therapeutic addition for this sight-threatening disease.

Retinal Protection Sciences, Inc. is developing SAPRA®, a medical device designed specifically to administer SDM. SAPRA® aims to address critical needs of hundreds of millions globally at risk for AMD and other ocular neurodegenerative diseases requiring regular, lifelong treatment.

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# Retinal Protection Sciences

*Our mission is to prevent vision loss through clinical innovation*

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