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ORIGINAL RESEARCH

Patient-Reported Burden of Illness and Unmet Needs in *Demodex* blepharitis

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Background: *Demodex* blepharitis is an ocular disorder caused by the infestation of *Demodex* mites that reside on the eyelash follicles.

Objective: This study assessed the clinical, humanistic, and economic burden of *Demodex* blepharitis from a patient perspective.

Methods: This cross-sectional, observational study used a web-enabled survey to collect data from US adults with *Demodex* blepharitis in 2022. Patients with unique burdens, including those receiving dry eye disease medications, wearing contact lenses, or experiencing cataracts or glaucoma were also examined.

Results: Among 113 patients, mean age was 48.5 years (standard deviation [SD] ± 13.6). Half had private/commercial insurance, and 55% had Medicare and/or Medicaid. Patients had *Demodex* blepharitis for an average of 4.3 years (SD ± 6.7 years) before the study, and 1.2 years (SD ± 3.0 years) elapsed between the appearance of symptoms and diagnosis. Common symptoms, including redness, dryness, itchiness of the eyelids, and itchiness of the eyes, persisted or returned shortly after diagnosis and disease management in most patients, and they were associated with a negative impact on quality of life. Patients visited their healthcare practitioner for *Demodex* blepharitis a mean of 3.9 times (SD ± 4.8) in the preceding year. Patients were often managed with off-label prescription medications, such as medications indicated for dry eye disease, in-office procedures, or over-the-counter management options.

Discussion: Patients with *Demodex* blepharitis reported symptoms impacting their quality of life and activities of daily living, which persisted after diagnosis and disease management. This suggested that the effectiveness of the reported symptom management options was temporary and highlighted an unmet need in treating the root cause of the disease.

Conclusion: Patients with *Demodex* blepharitis were symptomatic, and the commonly used management options for *Demodex* blepharitis lacked long-term symptom relief or mite eradication, demonstrating a high unmet need in treating patients with *Demodex* blepharitis.

Plain Language Summary: *Demodex* blepharitis, a common chronic eyelid disease, was surveyed among US adults. Patients reported several doctor visits for diagnosis. After disease management therapies, patients reported symptoms continued or returned quickly. Unresolved symptoms negatively affected patients' lives, and symptomatic therapy management was a long-term expense that did not provide long-term relief. Patients frequently visited doctors due to recurring symptoms, highlighting a high unmet need in treating patients with *Demodex* blepharitis.

Keywords: *Demodex* blepharitis, burden of illness, disease management, quality of life

Introduction

Blepharitis is a common ocular disorder characterized by inflammation of the eyelid margin, redness, and ocular irritation.[1–3] One of the most common causes of blepharitis is infestation with *Demodex* mites that reside on the eyelash follicles and meibomian glands.[4,5] *Demodex* mites are the most common human ectoparasites, and at high population densities, *Demodex* infestations can cause damage to hair follicles and meibomian glands, disrupt the local microbiome,

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and induce delayed hypersensitivity responses.[6,7] Globally, a wide range of prevalence estimates for *Demodex* blepharitis, from 41% to 70%, has been reported.[8–13] A US-based real-world prevalence study recently revealed that 58% of patients visiting eye care clinics for any reason had *Demodex* blepharitis,[5] suggesting that up to 25 million Americans may be affected by this condition.[14,15] This prevalence among patients presenting for routine visits to ophthalmologists and optometrists also suggests that *Demodex* blepharitis is as common as dry eye disease (DED).[5]

Because an infestation by *Demodex* mites leads to the formation of pathognomonic lash-cuffing collarettes around the base of the eyelashes, *Demodex* blepharitis can be diagnosed if these collarettes are present.[8,16–23] Collarettes can be accurately identified by having patients look down during an examination with a standard slit-lamp,[6,17] (Figure 1) which is used by optometrists and ophthalmologists in routine eye exams.[16] However, despite readily available diagnostic techniques, almost 50% of the patients with collarettes may not be diagnosed with *Demodex* blepharitis, suggesting substantial underdiagnosis resulting from misdiagnosis or missed diagnosis.[5] Assessing patients for *Demodex* blepharitis is currently not part of the routine eye exam, leading to a general lack of awareness among eye care professionals about the importance of identifying collarettes in patients.[5] *Demodex* blepharitis may also be underdiagnosed or misdiagnosed partly due to a substantial overlap of symptoms with DED and other ocular surface disorders.[6]

Typically, symptom management includes off-label prescription medications such as those indicated for DED, antibiotics, and anti-parasitics, alongside in-office lid cleansing measures such as microblepharoexfoliation, and over-the-counter (OTC) lid scrubs and wipes.[6] The use of medications and therapies that do not directly address the mite infestation or lack proven efficacy leads to disease progression, chronic symptoms, and incurring long-term costs.[24]

Chronic symptoms persist among *Demodex* blepharitis patients, with 51% experiencing them for 4 years or more.[25] Untreated, *Demodex* blepharitis has many ocular sequelae including lid and eyelash abnormalities such as trichiasis,

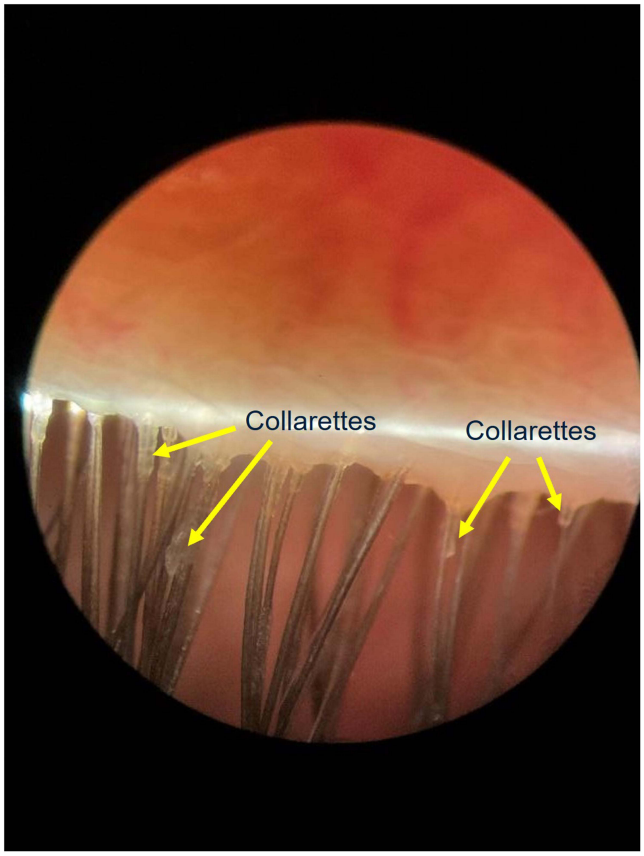

Figure 1 Illustration of Pathognomonic Lash-cuffing Collarettes of *Demodex* Mite Infestation as Identified by Examination with A Standard Slit-lamp.
Notes: Lash-cuffing collarettes are visible at the base of the eyelashes of a patient with *Demodex* blepharitis while looking down during a standard slit-lamp examination. Image Credit: Vance Thompson, MD, Sioux Falls, SD, USA.

misdirected and thinning lashes, noticeable eye and eyelid erythema, corneal ectasia, and contact lens intolerance.[2,4,26–31] Other findings include recurring hordeola and chalazia, meibomian gland disease and meibomian gland atrophy, progressive pterygium, and other corneal and conjunctival complications.[29,32] In a US-based study involving patients with *Demodex* blepharitis across 20 eye care clinics, over 99% of participants reported experiencing at least one symptom.[24] Additionally, 77.4% stated that *Demodex* blepharitis significantly impacted their daily activities.[24]

Efforts to quantify the clinical, humanistic, and economic burden of *Demodex* blepharitis remain scarce. This study sought to characterize the real-world, holistic burden of illness due to *Demodex* blepharitis from a patient perspective, including patient-reported outcomes before and after disease management, unmet need and challenges in diagnosis and current management, impacts on patient's quality of life, and healthcare resource utilization and costs.

Methods

Study Design

This cross-sectional, observational study used a web-enabled survey (developed with a third-party partner, MedSurvey) to collect anonymous information regarding the burden of *Demodex* blepharitis from qualified respondents. The study was conducted in accordance with the 2013 version of the Declaration of Helsinki, and applicable national and local requirements for good pharmacovigilance practices and complied with applicable respondent privacy regulations/guidance as required by local law.[33] Before enrollment of respondents into the study, the protocol, screener, questionnaire, and other written information to be provided to respondents was reviewed and exempted by an independent Institutional Review Board (Advarra, Columbia, MD). All patients provided informed consent to participate in the survey. All survey respondents were identified using a unique identification code to maintain anonymity for study researchers. All data were de-identified, and no diagnostic or therapeutic interventions were used.

Recruitment

A multi-modal recruitment approach, using patient panels and eye-care provider (ECP)- referred recruits, was employed to recruit adult patients with *Demodex* blepharitis in the US. The study was conducted from June 6, 2022, until August 16, 2022, during which there were no approved treatments by the US Food and Drug Administration (FDA) for *Demodex* blepharitis. To maintain the anonymity of all patients, study coordinators, and study sponsors were masked through the recruitment process. Qualified respondents who provided informed written consent to participate were asked to complete a screening questionnaire based on the inclusion/exclusion criteria to determine if they met the study eligibility criteria.

Eligibility Criteria

Individuals were eligible for inclusion in this study if they were between 21 and 85 years of age. The lower age limit of 21 was selected to align with the age of majority in Mississippi, where it is 21 years, as compared to 18 years or 19 years in most US states. The upper limit of 85 years was chosen due to the increased likelihood of cognitive impairments in older individuals, which could affect their ability to provide informed consent or accurately complete surveys. Additional inclusion criteria required participants to be currently residing in the US, have a diagnosis of *Demodex* blepharitis provided by a doctor for at least 6 months prior to the survey (to ensure that patients had some treatment experience), can complete the survey in English, and have access to a smartphone and/or computer and internet connectivity to complete the web-enabled questionnaire.

Individuals were excluded from this study if they were directly affiliated with or had immediate family affiliated with an advertising agency in the healthcare area or a market research company in the healthcare area, the US FDA, a pharmaceutical or biotechnology firm, or a health economics and outcomes research company.

Survey Description and Data Collection

The web-enabled questionnaire was designed to collect information about the holistic burden of illness across multiple dimensions, including clinical, psychological, social, humanistic, and economic domains. Before fielding the survey, two telephone-based, 60-minute cognitive or pilot interviews were conducted with eligible respondents to assess

comprehension of the questions as intended; verify that the instrument was appropriately timed; and confirm that questions were appropriately sensitive to patient experiences.

The survey contained custom questions intended to capture patient demographic information; the diagnostic journey starting from the time symptoms prompted the first healthcare provider (HCP) visit; healthcare resource utilization; and therapies used for symptom management including off-label prescriptions, OTC therapies, and in-office management options. Several questions in the survey were answered using a 5-point scale. These included the impacts of symptoms on patient's quality of life and emotional states, for which the 5-point scale ranged from 1 (no impact at all) to 5 (very significant impact). The impact of symptoms experienced before diagnosis with *Demodex* blepharitis was assessed on a scale ranging from 1 (did not experience at all) to 5 (experienced significantly). Finally, the 5-point scale used to assess the willingness of patients to try new treatments for *Demodex* blepharitis ranged from 1 (completely disagree) to 5 (completely agree).

Validated Outcome Measures

The 12-item Ocular Surface Disease Index (OSDI) questionnaire was used to assess the severity of eye dryness and other ocular surface symptoms and their impact on vision-related functioning,[34] and the University of North Carolina Dry Eye Management Scale (UNC DEMS), a 1-item graded scale (1–10) was used to assess symptoms and their effect on patients' quality of life.[35] Impairments to work and daily activities were assessed using the 6-item Work Productivity and Activity Impairment (WPAI) questionnaire.[36,37]

Data Analyses

Data were reported using descriptive statistics, including means and standard deviation (SD) for continuous variables, and medians with interquartile ranges (IQR) for ordinal data, such as those derived from 5-point agreement scales. Frequencies and percentages are provided for categorical variables. Analyses were conducted at the aggregate level, with no patient-level characteristics were included to protect patient identification. All statistical analyses were conducted in Q Research Software 5.12.4.0 (Glebe, Australia).

Results

Patient Demographic and Clinical Characteristics

The survey sample comprised 113 patients with an ECP-confirmed diagnosis of *Demodex* blepharitis for at least 6 months prior to the survey (Supplemental Table 1). Respondents had a mean age of 48.5 years (SD ± 13.6) and included 50% with private/commercial insurance coverage, 55% with Medicaid or Medicare, 1% with other government insurance, and 2% who were uninsured. Patients reported living with clinically confirmed *Demodex* blepharitis for an average of 4.3 years (SD ± 6.7) since their initial diagnosis.

Clinical Burden of *Demodex* blepharitis

Patients reported persistent symptoms over time, from before being diagnosed with *Demodex* blepharitis to the time of the diagnosis (Table 1). The responses revealed that 1% (1/113) of patients had no eye symptoms. In other words, nearly all (99%) of patients reported at least one symptom, and the most common symptoms included redness, dryness, itchiness of the eyelids, and itchiness of the eyes. At the time of diagnosis, patients reported symptoms occurring multiple times a day, including burning or stinging in eyes (32%; 7/22), dryness of the eyes throughout the day (24%; 10/42), and crusted eyes/eyelashes (24%; 4/17) (Supplemental Figure 1).

Despite the use of management options, patients reported that many symptoms from before *Demodex* blepharitis diagnosis recurred multiple times, specifically crusted eyes/eyelashes throughout the day, dryness of eyes upon waking in the morning, redness of the eyes, sensitivity to light, and eye inflammation (Figure 2). Further, patients reported the impact of their recurring eye symptoms on several outcomes using a 5-point scale of severity, from 1 (did not experience at all) to 5 (experienced significantly). Moderate-to-severe impacts (scores 3–5) were most frequently reported for unrefreshing sleep (74%; 84/113), irritation (71%; 80/113), fatigue (70%; 79/113), headaches (68%; 77/113), difficulty in falling asleep, staying asleep, or waking on time (67%; 76/113), and anxiety (65%; 74/113) (Supplemental Figure 2).

Table 1 Percentage of Patients with *Demodex* Blepharitis Symptoms Over Time

Symptom, n (%)	*Prior to diagnosis* N = 113	*At diagnosis* N = 113
Redness of the eyes	55 (49%)	55 (49%)
Dryness of the eyes throughout the day	54 (48%)	49 (43%)
Itchy eyes	49 (43%)	47 (42%)
Itchy eyelids	51 (45%)	43 (38%)
Eye inflammation	43 (38%)	42 (37%)
Swollen eyelids	40 (35%)	41 (36%)
Burning or stinging in the eyes	34 (30%)	40 (35%)
Crusted eyes/eyelashes upon waking up in the morning	40 (35%)	39 (35%)
Dryness of the eyes upon waking up in the morning	34 (30%)	37 (33%)
Watery eyes	35 (31%)	36 (32%)
Crusted eyes/eyelashes throughout the day	29 (26%)	34 (30%)
Sensitivity to light	35 (31%)	32 (28%)
Difficulty driving at night	25 (22%)	30 (27%)
Blurry vision	30 (27%)	26 (23%)
Flaking of the skin around the eyes	27 (24%)	20 (18%)
Presence of collarettes/mites but no other eye symptoms	1 (1%)	1 (1%)

Notes: This question was multi-select and respondents may have provided more than one response, as appropriate (eg, presence of more than one symptom prior or at diagnosis).

Challenges in Obtaining *Demodex* blepharitis Diagnosis

On average, patients visited an HCP 3.5 times (SD ± 2.8) before receiving a confirmed diagnosis of *Demodex* blepharitis, and 37% of patients noted that the original HCP sent them to another specialist (Supplemental Figure 3). Of the overall study sample, 45% (51/113) visited an ophthalmologist and 42% (47/113) visited an optometrist before being diagnosed with *Demodex* blepharitis (Supplemental Table 2). Similarly, 44% of patients were ultimately diagnosed by an ophthalmologist and 40% by an optometrist. On average, the time between the appearance of symptoms and a *Demodex* blepharitis diagnosis was 1.2 years (SD ± 3.0).

Disease Management in *Demodex* blepharitis

Patients used off-label prescription medications at higher rates before being diagnosed with *Demodex* blepharitis (Figure 3). Although the proportion of patients using off-label prescription medications declined after diagnosis, off-label medication use persisted in a subset of patients ranging from 5% (6/113) for varenicline nasal spray up to 16% (18/113) for cyclosporine eye drops. The use of OTC therapies before the diagnosis of *Demodex* blepharitis and at the time of the survey included warm eye compresses, lubricating eye drops or artificial tears, at-home eyelid wipes or washes, tea tree eyelid cleanser, tea tree oil, oral supplements, eye inserts, and hypochlorous acid cleansers (Supplemental Figure 4). In-office therapies and procedures were reported in <10% of patients to manage *Demodex* blepharitis, including microblepharoexfoliation (7% before diagnosis and 8% currently), intense pulsed light therapy (7% before diagnosis and 6% currently), heating therapies (6% before diagnosis and 9% currently), punctal plugs (6% before diagnosis and 4% currently), and in-office eyelid scrub (5% before diagnosis and 6% currently). Overall, 5% of patients reported never using any form of therapeutic management for their *Demodex* blepharitis symptoms.

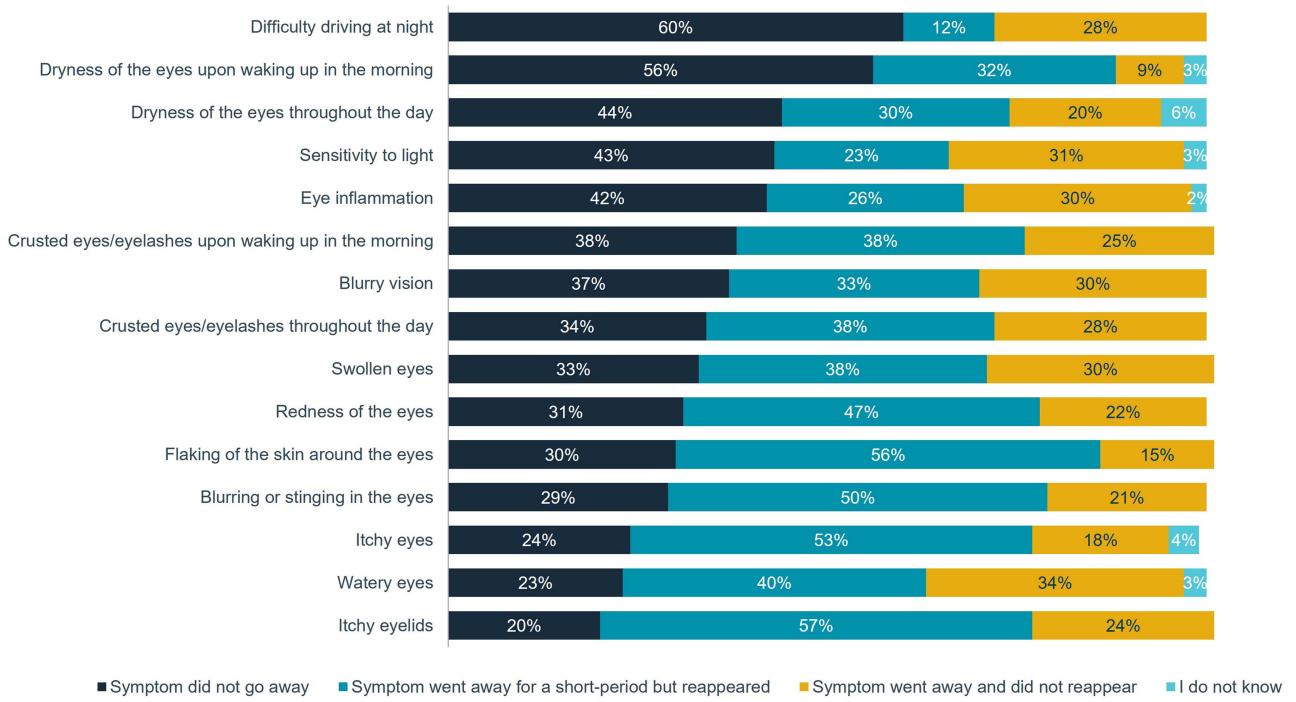

Figure 2 Results of Management of Eye Symptoms Prior to *Demodex* Blepharitis Diagnosis (N=113). Patients reported the results from symptom management therapies on specific symptoms before their diagnosis. For each symptom, patients reported if the symptom went away and did not reappear, went away for a short period but later reappeared, did not go away, or if the patient did not know. Patients also reported the number of times the symptom reappeared before diagnosis with *Demodex* blepharitis.

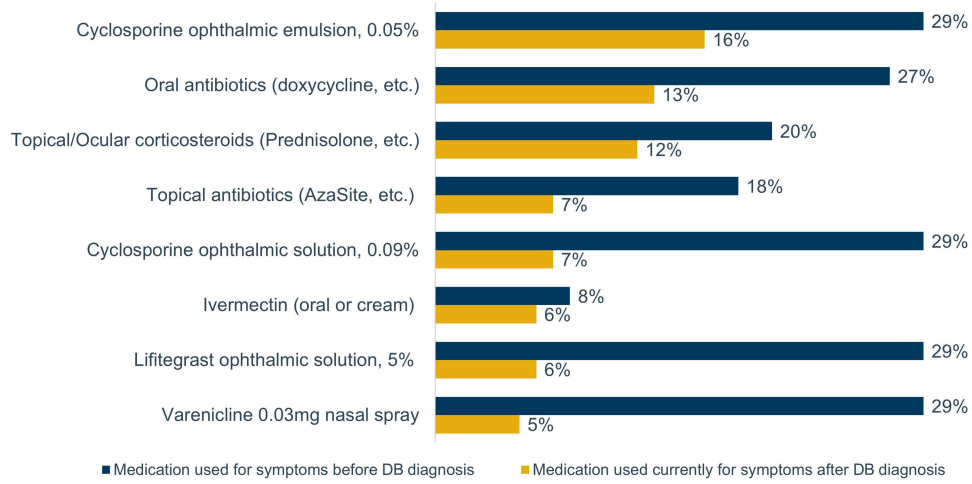

Figure 3 Off-label Prescription Medications used in the Management of *Demodex* Blepharitis Across Time (N=113). Patients reported receiving various prescription medications before receiving a confirmed diagnosis of *Demodex* blepharitis, or currently after receiving a confirmed diagnosis of *Demodex* blepharitis.
Notes: DB, *Demodex* blepharitis. This question was multi-select and respondents may have provided more than one response, as appropriate (eg, respondent was taking multiple medications at one time).

DED Therapies and Symptom Severity in Patients with *Demodex* blepharitis

Overall, patients with *Demodex* blepharitis reported using any type of prescription medication for DED at rates of 29% (33/113) before diagnosis and 21% (24/113) at the time of the survey. More than half of the patients currently taking prescription DED medications (54%; 13/24) did not have a diagnosis of DED, consequently more than 10% (13/113) of all patients in the study were currently taking an off-label prescription medication for DED at the time of the survey.

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All patients were assessed with the OSDI questionnaire and UNC DEMS scale to assess the severity and impact of eye symptoms. Based on the OSDI, 62% of patients with *Demodex* blepharitis could be classified as having severe DED based on symptom severity, with 17% classified as moderate and 11% classified as mild DED. Scores on the UNC DEMS showed that 17% of patients reported their symptoms had a high impact on their quality of life (score: 8–10), 69% indicated a moderate impact (score: 4–7), and 14% indicated a low impact (score: 1–3).

Comorbidities with *Demodex* blepharitis

Patient subgroups had substantial differences from the overall patient population in some results regarding the clinical burden of *Demodex* blepharitis. Patients with cataracts (n = 22) had a longer average interval since their diagnosis with *Demodex* blepharitis, mean 6.3 years (SD ± 8.1), than the overall population (4.3 years [SD ± 6.7]). Likewise, those with glaucoma (n = 11) reported an average of 6.6 years (SD ± 7.2) since being diagnosed with *Demodex* blepharitis. Patients also visited ophthalmologists prior to their diagnosis more often if they had cataracts (68%) or glaucoma (82%) than the overall study sample (45%; 51/113). A small number of patients in these subgroups also reported indirect as well as direct clinical burdens of *Demodex* blepharitis. Half (7/14) of patients with cataracts experienced delays in cataract treatment, and 25% (2/8) of those who required cataract surgery experienced post-surgery complications due to their *Demodex* blepharitis. Likewise, 67% (4/6) of patients with glaucoma felt that their *Demodex* blepharitis had resulted in a need to pursue surgery for their glaucoma.

Several subgroups had a longer interval from symptom appearance to diagnosis. For all patients, the average time was 1.2 years (SD ± 3.0) and required 3.5 HCP visits (SD ± 2.8). Patients with cataracts waited an average of 2.9 years from the appearance of their symptoms to their diagnosis with *Demodex* blepharitis, and those with glaucoma waited 3.5 years, while patients who wore contact lenses averaged 4.6 visits to an HCP before receiving a diagnosis.

Finally, patients with glaucoma reported receiving in-office therapies at a higher rate (54%; 6/11) than the overall patient population before the diagnosis of *Demodex* blepharitis (15%; 17/113).

Humanistic Burden of *Demodex* blepharitis: Patient Perspectives and Impact

Patients reported the extent to which *Demodex* blepharitis impeded activities of daily living during the 12 months preceding the survey using a 5-point scale of impact ranging from 1 (no impact at all) to 5 (very significant impact) (Supplemental Figure 5). Activities with a high proportion of patients reporting impacts of 3, 4, or 5 included reading (73%), driving a car (71%), basic housework (64%), ability to work (58%), and wearing glasses or contact lenses (58%). Patients also indicated that *Demodex* blepharitis was detrimental to their sense of confidence about their appearance and even happiness/life satisfaction, with 65% of patients or more reporting an impact of 3, 4, or 5 in all emotional domains queried by the survey (Supplemental Figure 6).

Patients who were working or students at the time of the survey (n = 63) were notably impacted by *Demodex* blepharitis in the previous 7 days as assessed by the WPAI questionnaire, with scores of 75% for overall work impairment, including both impairment and absenteeism, 63% for impairment while working, and 60% for absenteeism. Similarly, patients had a score of 63% for impairment of regular activities outside of work due to *Demodex* blepharitis.

Patients were interested in new disease management options, with most patients (83%) reporting a need for curative treatment, and 78% were willing to use new treatment options if they would improve their symptoms. Nearly as many (76%) expressed a willingness to switch their current treatment if something more effective became available (Supplemental Figure 7).

Economic Burden of *Demodex* blepharitis

Patients in this study visited their HCP due to *Demodex* blepharitis a mean of 3.9 times in the 12 months preceding the survey (SD ± 4.8) and visited urgent care facilities an average of 1.4 times (SD ± 2.2). Importantly, 52% of patients visited an urgent care facility related to their *Demodex* blepharitis in the year before the survey. In-office therapies were associated with the highest average annual out-of-pocket expenses for patients ($368), followed by HCP visits ($192), prescription medicines ($175), and OTC medications or management options ($115).

Discussion

This is the first study to examine the clinical, humanistic, and economic burden of *Demodex* blepharitis and the ability to manage this burden with management options during the time when there were no FDA-approved treatments available in the market for the condition. Almost all (99%) patients with *Demodex* blepharitis reported frequent and bothersome symptoms like blurry vision, crusted eyes, and dryness, persisting even post-diagnosis and disease management. Off-label use of DED medications was a part of reported disease management therapies with notable more than half (54%) of the patients with *Demodex* blepharitis taking DED medications did not have diagnosis of DED. Persistent symptoms had a negative impact on patients' daily life, ability to engage in daily activities, and psychosocial well-being and incurred additional costs to patients. *Demodex* blepharitis potentially complicates the diagnosis and management of comorbid conditions like cataracts and glaucoma, leading to prolonging patients' burden and increased healthcare resource utilization. As there was no standard of care for eradication of the *Demodex* mites at the time of this study, symptom alleviation was temporary, at best, illustrating an unmet need in treating *Demodex* blepharitis.

This study also identified challenges associated with obtaining a *Demodex* blepharitis diagnosis from patients' perspective. More than one-third (37%) of patients were referred to multiple specialists during their diagnosis journey, with an average of 1.2 years from first symptoms to a confirmed diagnosis of *Demodex* blepharitis. The evidence of multiple HCP visits before a definitive diagnosis and the use of off-label prescriptions, such as DED medications, suggests a potentially high percentage of misdiagnoses in these patients.

A major gap in care for *Demodex* blepharitis is the long-term use of off-label use of prescription drugs (ie, medications indicated for DED, or oral ivermectin) and OTC options that lack supporting clinical trial data regarding efficacy and safety in treating patients with *Demodex* blepharitis. Off-label use of oral ivermectin unnecessarily subjects patients to unwanted adverse effects including hepatitis, serious Mazzotti reaction, and Steven-Johnson and Lyell disease.[38–40] Additionally, tea tree oil, or its active ingredient terpinen-4-ol, is a widely available OTC option that is commonly used in *Demodex* blepharitis; however the literature suggests there is uncertainty associated with its effectiveness, and well-documented unwanted adverse effects.[32,41] Tea tree oil was studied in a randomized study involving 281 patients with *Demodex* blepharitis by Koo et al.[42] While the study found 23.6% of patients achieved mite eradication after using tea tree oil for 1 month, patients had to comply with a relatively burdensome regimen of weekly in-office procedure of lid scrubs with highly concentrated 50% tea tree oil applied over 30 minutes following topical anesthesia, in addition to twice-daily at-home lid scrubs. Terpinen-4-ol has also been found to have deleterious effects on meibomian glands observed in vitro.[43] Additionally, in-office procedures such as intense pulsed light (IPL) were often used in the management of *Demodex* blepharitis.[6] However, IPL therapy was utilized by only 7 patients (6%) at the time of the study. Recent studies have found that IPL treatments may reduce the average mite count when used for up to 12 weeks of therapy or used in adjunct with other treatments, but the high cost of IPL treatment may be a major hindrance to patient adoption.[44–46]

The economic burden of *Demodex* blepharitis is under-recognized. Payers were exposed to costs for DED medications and other prescription medications that did not treat *Demodex* blepharitis, as well as the increased healthcare resource utilization from repeated office visits for chronic symptom management therapies. Additionally, self-reported out-of-pocket costs from patients may not accurately reflect the full financial burden of the disease, particularly when factoring in insurance contributions. These self-reports, for both off-label prescription medications and OTC management options, might substantially underrepresent the actual costs incurred by both payers and patients for what amounts to ineffective or temporarily effective disease management.

Published estimates of the economic burden of *Demodex* blepharitis are unavailable; however, a 2011 study reported direct costs of treating DED of $3.84 billion per year for symptom management, physician visits, and nutritional supplements. Indirect costs were estimated at $55.4 billion yearly for productivity loss.[47] A substantial portion of this cost may be associated with *Demodex* blepharitis given the reported rates of misdiagnosis and off-label DED treatments prescribed to patients with *Demodex* blepharitis.

Together, these results suggest that underdiagnosis, misdiagnosis, and ineffective disease management options contribute to the overall high cost and high burden of illness in *Demodex* blepharitis. An observational, prospective study, by O'Dell et al reported frequent and bothersome symptoms experienced by patients and that 80% of patients with

Demodex blepharitis experienced a negative impact on their psychosocial well-being.[25] Trattler et al 2022 study found that more than half of the patients presenting for cataract surgery had *Demodex* blepharitis, suggesting *Demodex* blepharitis lead to worsening of eye health post cataract surgery.[5] The negative effects of *Demodex* blepharitis on the outcomes of comorbid conditions aligns with the results in this study.

Study Limitations

A cross-sectional study design was used for this study, making interpretation of the results subject to several limitations. Convenience sampling was used for this survey and included patients who were willing and able to participate in an online study, possibly skewing the sample population. While many demographic characteristics were collected for this study (eg, age, race, etc)., patient's sex or gender was not collected. This could be a potential limitation of the study; however, *Demodex* blepharitis is commonly reported among both males and females in the U.S.[6] Responses to the survey may have been subject to recall bias. Additionally, patient-reported clinic visit frequency, and out-of-pocket costs were collected across a mixed population of commercial, Medicare, Medicaid, and uninsured patients, which may not accurately reflect healthcare resource utilization and cost analysis at a national level. Finally, responses may have been subject to social desirability bias with an underreport of socially undesirable attitudes and overreport of socially desirable attitudes, such as infrequent use of prescribed treatments, which can lead to a distorted understanding of treatment compliance. Conversely, they may overreport behaviors that are viewed positively, such as frequent healthcare visits or diligent use of OTC therapies.

Conclusion

The burden of illness study of patients with *Demodex* blepharitis underscored a substantial burden across clinical, humanistic, and economic domains. Patients faced multiple challenges in obtaining *Demodex* blepharitis diagnosis, visited health care providers multiple times for recurring symptoms, and received management options that lacked long-term symptom relief or mite eradication, highlighting the high unmet need in diagnosing and treating patients with *Demodex* blepharitis.

Abbreviations

DB, *Demodex* Blepharitis; DED, Dry Eye Disease; ECP, Eye-Care Provider; FDA, Food and Drug Administration; HCP, Healthcare Provider; IQR, Interquartile Ranges; OSDI, 12-item Ocular Surface Disease Index; OTC, Over-the-Counter; SD, Standard Deviation; UNC DEMS, University of North Carolina Dry Eye Management Scale; US, United States; WPAI, Work Productivity and Activity Impairment.

Ethics Approval and Informed Consent

Ethical approval was granted by the Advarra Institutional Review Board (Columbia, MD; https://www.advarra.com/) as an exemption under 45 CFR 46.104(d)(2) prior to study initiation. The research team confirms that this study did not cause any physical or mental harm to participants and adhered to the principles outlined in the Declaration of Helsinki. Electronic consent was obtained from all participants through specific questions in the instrument screener.

Consent for Publication

Study participants consented to the publication of their data anonymously on an aggregate basis.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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