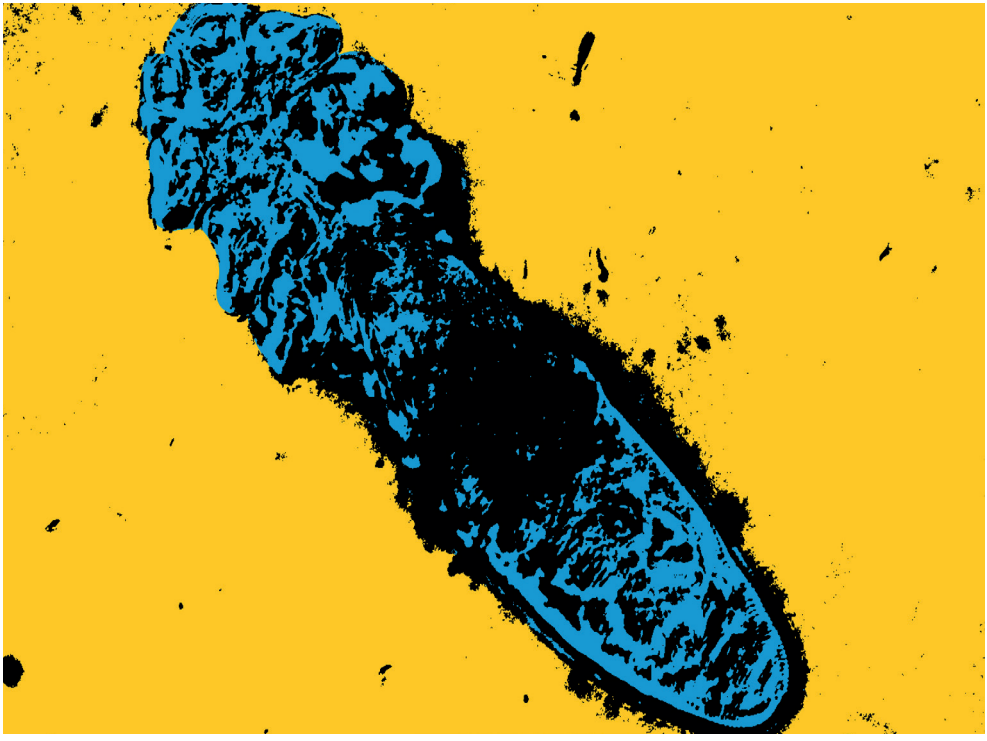
Demodex Blepharitis

A CLINICAL HANDBOOK



Théa
let's open our eyes

PREFACE

Teifi James DO FBCLA FRCP FRCOphth
Consultant Ophthalmologist
Honorary Professor, Cardiff University

This practical guide has been designed to support all eye care professionals in their real-world management of patients suffering with this often under-diagnosed and under-managed condition, *Demodex* blepharitis.

It is over 120 years since *Demodex* was first associated with blepharitis, and despite *Demodex* being the most common ectoparasite in humans, we still have much to understand about the precise role this organism plays in pathogenesis of ocular conditions. It seems to be about overgrowth of *Demodex* populations in follicles and Meibomian glands, with associated risk factors such as age and general health.

What is clear to eye care professionals today, is that there appears to be a subset of patients who present with blepharitis that is unresponsive to conventional therapies; where *Demodex* mites are present, and when you treat with specific treatments to reduce the infestation, symptoms improve considerably.

So, it seems that all blepharitis is not the same...

This clinical handbook has been designed to provide a quick reference guide for ophthalmologists and optometrists, to assist in their daily management of patients with *Demodex* blepharitis.

ABBREVIATIONS

CD
Cylindrical Dandruff

IVCM
In Vivo Confocal Microscopy

LET
Lateral Eyelash Traction

OSDI
Ocular Surface Disease Index

T4O
Terpinen-4-Ol

TOSS
Total Ocular Symptom Score

TTO
Tea Tree Oil

CONTENT

01

Introduction to *Demodex*

WHAT ARE DEMODEX?

Demodex are tiny mites that live in or near the lash follicles and sebaceous glands of mammals. In classification terms they are Arthropods, members of the Arachnida (spider) class and Acari subclass.

Demodex in humans are classified into two distinct species: *Demodex folliculorum* and *Demodex brevis*[1]. In the eyelids, *D. folliculorum* are found in eyelash follicles, and *D. brevis* burrows deep into sebaceous glands and meibomian glands *(Figure 1)*.

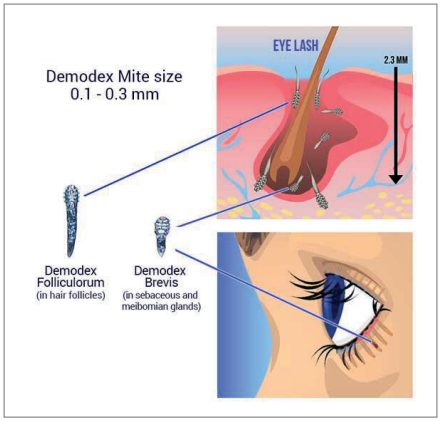


Figure 1 Demodex species around the eye (reproduced by kind permission of David Crystal)

HOW MANY PEOPLE HAVE DEMODEX IN THEIR EYELIDS?

The short answer is most of us...but not all of us have enough to cause a clinical problem as a result *(Figure 2)*. Almost 2/3 of us would seem to have *D. folliculorum* in hair follicles within our skin, and almost a 1/4 will have *D. brevis* in the skin's sebaceous glands[2]. Prevalence appears to increase with age; by the time we are in our 70s, 95-100% of us will exhibit skin *Demodex*[3,4].

But what about the eyelids? Clearly, *Demodex* on the face are able to migrate during darkness and this seems to be reflected in similar values for prevalence, which again appear to increase with age[5-8]. Amongst people with blepharitis the prevalence of *Demodex* from eyelash sampling is reported to be between 54% and 70%[7].

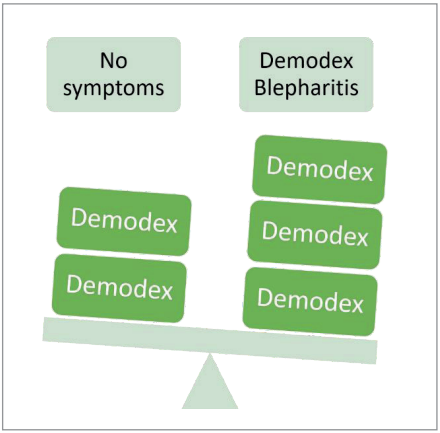


Figure 2 Over-infestation in some people appears to cause symptoms

How many *Demodex* is too many?

Think of them as 'opportunistic pathogens' that proliferate when the environment is favourable[4].

How do you get *Demodex* in the first place?

We are not born with them, but they are acquired soon after from close skin contact with adults[9,10].

The use of the term '*Demodex* blepharitis' is reserved for where the infestation with *D. folliculorum* and/or *D. brevis* is thought to be implicated in the pathogenesis and subsequent management of anterior and posterior blepharitis[11].

WHAT DO *DEMODEX* DO ALL DAY (AND NIGHT)?

They eat *Demodex* mites feed on sebum and skin cells that accumulate around the lid margin, and possibly the keratin for their exoskeleton[12]. They probably also feed on the skin commensal bacteria around the lashes[13].

They move *Demodex* move slowly at 8-16mm/hr, and are more mobile in the dark; bright lights seem to make them recede into follicles[3,9], which is relevant to detection techniques *(see Chapter 2)*.

They reproduce At night the adult mites mate on the lid margins, then the female lays 10-12 eggs in the follicles or sebaceous glands[13]. The life cycle is between 14 and 18 days from egg through larval and nymph stages, followed by 5 days as an adult mite. This life cycle of around 21 days is relevant to topical treatment regimens *(see Chapter 3)*. When mites die they simply decompose within the follicles or glands, and away from their host, their survival is severely limited, particularly in dry conditions[14].

Are they friend or foe?

Sometimes called 'commensal' or 'symbiotic', but sometimes called a 'parasite' – it depends whether harm is being done to the human host.

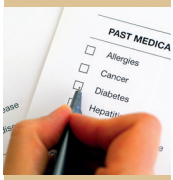
02

Diagnosing *Demodex* Blepharitis

Diagnosing *Demodex* blepharitis step by step

1 Assess patient risk factors

- Age, sex, contact lens wear, history of chalazia, diabetes, living conditions, immunity problems

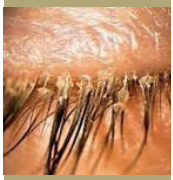


2 Identify key symptoms

- Unresolved persistent blepharitis
- Lid margin itching
- Symptoms questionnaires

3 Look for classical signs

- Cylindrical Dandruff (CD)
- 'Pounting' lash follicles
- Swollen lid margins
- Madarosis



4 Diagnostic techniques

- Remove dandruff to see tails
- Lateral Eyelash Traction (LET)

RISK FACTORS

The high prevalence of *Demodex* would suggest that most patients in ophthalmology and optometry will have them, but do not suffer ill-effects.

Risk factors for *Demodex* blepharitis:

- Increasing age[5,7,15,16]
- Male sex[2,17,18]
- Contact lens wear[19,20]
- People with chalazia[21-25]
- Diabetes[26]
- Poor and/or crowded living conditions[4,6]
- Where local or systemic immunity is compromised by medication, malnutrition or illness[4,27,28]
- Pre-existing conditions such as rosacea, acne, eczema, oily skin where mite numbers will be higher on skin generally[13]

SYMPTOMS

There is a strong correlation between the number of *Demodex* and the severity of general ocular discomfort[5]. Symptoms are similar to those of blepharitis related to other causes (seborrhoea, staphylococcal overload), and whilst there is limited evidence relating symptoms specifically to *Demodex* blepharitis, clinicians generally agree that there are two significant complaints to listen out for:

- a chronic history of blepharitis that has been unresponsive to standard treatments,
- moderate/severe itching localised to the lid margin area *(Figure 3)*.

Figure 3 Eyelid margin scratching

LISTEN for patients who complain of itching specific to the lid margin area

Scoring symptoms in *Demodex* blepharitis

A correlation between Ocular Surface Disease Index (OSDI) scores and *Demodex* mite numbers on epilated lashes has been observed[5], but there are few questionnaires that have been specifically designed or validated for *Demodex* blepharitis symptoms. One potentially useful questionnaire is included in Appendix.

LOOKING FOR SIGNS

Given the size of these mites, they are invisible to the naked eye, and magnification of at least 25x is required: magnification of 40x on the slit lamp is ideal, but it can still be challenging to see them. However, there are some characteristic signs that *Demodex* may be present which are easier to spot.

- Cylindrical Dandruff or CD - A KEY SIGN[15,29,30,31]
- 'Pouting' around lash follicles
- Telangiectasia,
- Swollen lid margins
- Madarosis

How to differentiate between types of blepharitis?

STAPHYLOCOCCAL BLEPHARITIS	SEBORRHEIC BLEPHARITIS	*DEMODEX* BLEPHARITIS
Scaly, dry crusts	Greasy, oily crusts	Cylindrical Dandruff (CD)
Skin usually clear	Look for seborrheic dermatitis Flaky skin in eyebrows & scalp	Look for Rosacea
Eventual loss, misdirection of lashes	Lash loss is rare	Lash loss more likely
Typically in slightly younger patients	Tend to be older patients	Prevalence increases dramatically with age
Significant inflammation on lid margins	Less inflammation	Minimal inflammation on margins
Can be associated with Hordeola and conjunctivitis	Crusts more adherent to lashes than lid margin	Dandruff stay around lash base
Responds to lid hygiene	Responds to lid hygiene	Often unresponsive to standard lid hygiene
Manage with lid hygiene +/- antibiotic treatment	Manage with lid hygiene +/- steroids	Manage with Tea Tree Oil (TTO) lid wipes

Table 1 Adapted, with kind permission of Sarah Farrant

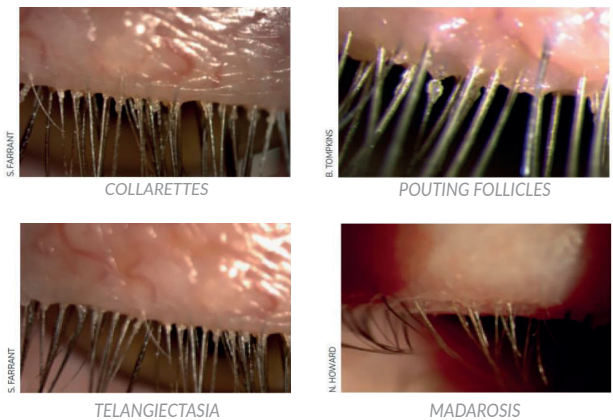


Figure 4 Classical signs of Demodex infestation

TOP TIP: 40x magnification is ideal for spotting *Demodex* tails

Collarettes, cylindrical dandruff and crusts - What's the difference?

These terms tend to be used in an interchangeable fashion, yet there are useful differences to observe.

The typical debris around the eyelashes in classic anterior blepharitis are off-white flaky or yellowish greasy 'crusts' *(Figure 5 top)*. These can be located along the length of the lash itself or even speared by it, but tend to grow out as the lash grows. Some clinicians use the term 'collarettes' to describe these 'crusts'[31] attributed to blepharitis that is staphylococcal or seborrheic in nature.

In *Demodex* infestation, it is thought that the mite's claws generate follicular debris[29] which collects at the root of the lashes and envelops the base of the lashes on the lid margin, where it tends to remain located, independent of lash growth, in some cases appearing fused with the lid margin epithelium[32]. These are seen as slightly more transparent, gelatinous sleeves – Cylindrical Dandruff (CD) – often with a slight pouting of the follicle *(Figure 5 bottom)*. Some clinicians call these collarettes, too; hence the confusion! There is a movement towards encouraging consistency in terminology by referring to this specific form as CD.

It is generally accepted that there is a strong relationship between the presence of CD and presence of *Demodex* in an untreated patient[15,29-31].

CLASSICAL ANTERIOR BLEPHARITIS CRUSTS

CYLINDRICAL DANDRUFF

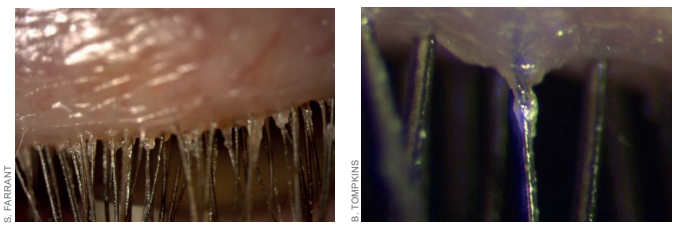


Figure 5 Crusts versus Cylindrical Dandruff

Other signs to watch out for include[34]:

- Misdirected lashes
- Recurrent chalazia

DIAGNOSTIC TECHNIQUES

There are several ways to confirm the diagnosis of *Demodex* blepharitis, with differing levels of invasiveness *(Table 2)*.

TECHNIQUE	Potential discomfort for patient (invasiveness)	Difficulty rating (where 5 is most challenging)	Impact on examination time	Specialist equipment required beyond slit lamp
IDENTIFY CYLINDRICAL DANDRUFF		1	none	no
IDENTIFY MITE TAILS		2	minimal	forceps
LATERAL EYELASH TRACTION (LET)		2	minimal	forceps
LASH ROTATION		3	minimal	forceps
CONFOCAL MICROSCOPY		5	significant	yes
LASH EPILATION		4	significant	yes

Table 2 Diagnostic techniques for Demodex blepharitis

After you have identified CD, follow this step by step guide using simple techniques to confirm the diagnosis of *Demodex* blepharitis…

1. Reveal the mite 'tails'

Demodex tails are normally completely hidden from view under CD and collarette crusts. The mites are 'head-first' in the follicle: once the CD is removed, it is possible to see as many as four tails protruding from a single follicle. Once you have identified 'risk factors' in the patient history, signs and symptoms, this is the first thing to do. Using fine forceps and at least 25x magnification at the slit lamp (preferably 40x), gently pull at the CD to slide it down the lash, away from the lid margin *(Figure 6)*. This is easiest using a repetitive short, 'stroking' method.

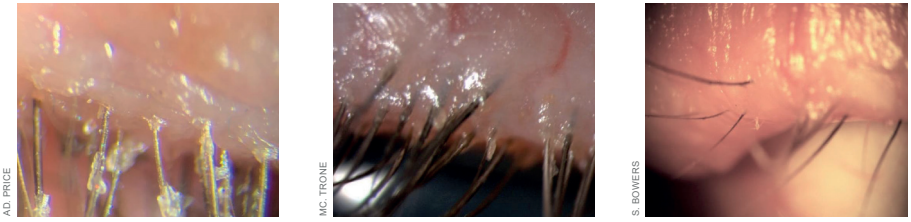


Figure 6 Demodex tails visible from follicle openings, after pulling Cylindrical Dandruff (CD) away from lash base

2. Manipulate the eyelashes

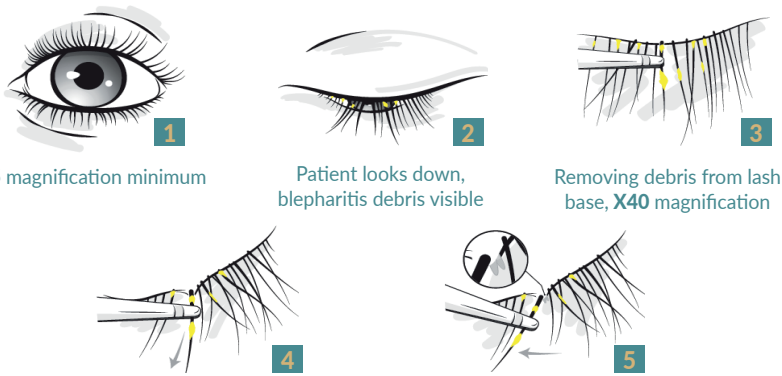
Mites can be buried deep in the follicle, so manipulating the lashes is more effective to confirm their presence. There are two ways to do this:

- LET is a validated technique[33] where you gently pull a lash to one side with fine forceps after CD removal (Figures 7 & 8), using 25-40x magnification at the slit lamp.
- Alternatively you can rotate the lash (Figure 9): Mastrota recommends applying gentle tension and manually rotating the lash slowly with forceps, believing the action of the lash will 'scrape out' *Demodex* residing deep within the follicle[35].

The LET technique appears to yield the highest numbers of mites per eyelash when compared to all other techniques (including lash rotation and lash epilation)[33].

Some clinicians subsequently extract a lash or mite for microscopic examination, depending on local protocols, but it must be remembered that simple lash manipulation techniques have the distinct advantage that no lashes to be sacrificed which is preferable for clinician and patient alike[33].

TOP TIP: Gentle Lateral Eyelash Traction without epilation seems to be the best way to confirm *Demodex*[33]



1 **X25** magnification minimum

2 Patient looks down, blepharitis debris visible

3 Removing debris from lash base, **X40** magnification

4 Applying Lateral Eyelash Traction, **X40** magnification

5 *Demodex* mite tails emerging from the eyelash orifice, **X40** magnification

Figure 7 The Lateral Eyelash Traction technique

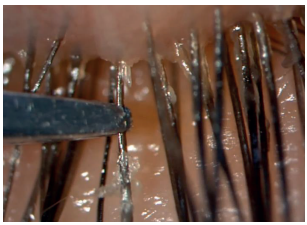


Figure 8 Lateral Eyelash Traction (LET)

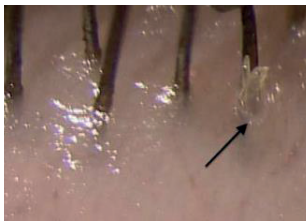


Figure 9 Lash rotation (from Mastrota, 2013) – Note that the tails are more visible after rotation

In Vivo Confocal Microscopy (IVCM)

IVCM has shown promise as a useful technique for detection of *Demodex* in eyelids but is technically difficult. In a study where IVCM was compared to traditional epilation, it was efficient and reliable for the diagnosis of eyelid mite infestation, even for detecting low grades of infestation[36]. However, in eyelids, the reflection from the substantia propria makes it more challenging as a technique, leaving it generally limited to research settings at the time of writing (2019). Indeed, one study found that IVCM failed to offer unequivocal evidence of *Demodex* presence, even in known positive cases[33].

Lash epilation

This is the traditional, *ex-vivo* method, where lashes are selected, removed and examined under a light microscope (high magnification 100-200x) for evidence of mites attached to lashes.

How many *Demodex* is too many?

Think of them as 'opportunistic pathogens' that proliferate when the environment is favourable[4].

STEP BY STEP ROUTINE FOR DIAGNOSIS

LISTEN

be suspicious of *Demodex* in patients with blepharitis who complain of:

- a chronic history of blepharitis that has been unresponsive to standard treatment,
- moderate/severe itching localised to the lid margin area,
- foreign body sensations.

LOOK

observe the patient under 25-40x magnification, and look for:

- CD,
- missing or misdirected lashes,
- 'pouting' around lash follicles,
- telangiectasia, swollen lid margins,
- recurrent chalazia.

MANIPULATE

use fine forceps at the slit lamp to:

- slide the CD down the lash away from the lid margin,
- apply LET to lashes once,
- check a few eyelashes for signs of infestation.

Fine forceps are key

03

Topical Treatment of *Demodex* Blepharitis

***Demodex* infestation should be specifically treated only in blepharitis resistant to a primary treatment by traditional lid hygiene, and accompanied by a positive identification of *Demodex* mites at the slit lamp.**

Is total 'extermination' the objective of topical treatments?

Given that *D. folliculorum* and *D. brevis* are commensal organisms under normal conditions, total eradication may not be desirable nor achievable. It is suggested that it is only necessary to reduce the overpopulation of mites and bring it back to 'normal' levels[12,37].

Consequently, treatments are frequently judged to be effective when symptoms and mite numbers are reduced, but this may not be because the treatment is actually 'killing' mites, per se[37].

Achieving a balance between tolerance, compliance and efficacy is essential for any successful treatment for long term relief from this condition.

Is standard lid hygiene enough?

Standard lid hygiene regimes are the first line of managing blepharitis but may not be sufficient as the first line treatment alone when *Demodex* infestation has been confirmed.

Is lid scrubbing useful?

Lid scrubbing or debridement has limited evidence to support its use as a standalone treatment; when used alone it may reduce numbers, but is no more effective than a commercial lid cleanser alone[38].

The most successful treatment is one that balances effectiveness from the active ingredient with tolerability, such that the patient can adhere to the treatment without risk of adverse or unpleasant sensations.

Topical treatments

Whilst there is some evidence to support regimens of weekly treatment in the clinic consisting of diluted TTO alongside daily home lid scrubs[39,40], these are time-consuming for both clinician and patient, and tolerability can be an issue. At the time of writing (2019) no commercial preparations exist to match these regimes, and preparations have to be 'home-made' with a suitable diluent.

Natural TTO actually contains over 100 components, most of which are ineffective against *Demodex* but have the potential to irritate. By isolating only the effective components from the other allergenic and ineffective ingredients, it is possible reduce irritation and the potential for allergic reactions/ chemical injury.

One single component of TTO, called Terpinen-4-Ol (T4O) is actually the most potent ingredient within TTO for killing *Demodex* mites, meaning that less can be applied. T4O has a kill time of 12.3 minutes with just a 10% concentration, 32.1 minutes for 5% concentration, and 87.6 minutes for 1 % concentration[41]. *In vitro* anti-demodectic efficacy has been observed to be similar between undiluted TTO and T4O[42].

How long should a treatment last?

Considering the life cycle of the *Demodex* mite, it is logical to treat for a minimum of one life cycle, and many clinicians advocate two life cycles. In practice this means 4-6 weeks.

4-6 weeks of topical treatment may be necessary

Is re-treatment necessary?

Re-infestation after successful treatment may be necessary if favourable conditions persist. In patients with recurrent symptomatic infestations, it may be proposed to maintain a regular lid hygiene with lid wipes impregnated with TTO extract, in relay with gentle micellar cleansing wipes.

Maintenance between treatments

Whilst lid hygiene alone may be not sufficient as first line treatment, it should be considered as permanent, ongoing maintenance treatment after the active treatment period for *Demodex* blepharitis. It can be used in relay with 'active' topical therapy, to maintain clean eyelids and reduce the bacterial load on the lids[43]. Switching to a maintenance treatment as soon as symptoms are controlled (or sufficient life cycles have passed) once or twice a day is recommended by experts[31].

A relay treatment with standard lid hygiene should be maintained after the end of the anti-*Demodex* treatment

APPENDIX

The Total Ocular Symptom Score (TOSS) questionnaire. The TOSS is well-accepted for assessing the frequency of four symptoms commonly associated with allergic conjunctivitis: itching, redness, tearing, and swelling. Because symptoms of blepharitis, dry eye, and allergic conjunctivitis share common symptomatic traits, the TOSS questionnaire has been applied in *Demodex*-infested and control patients. In one study, scores for *Demodex* patients exhibited a large difference compared to controls[44]. This TOSS questionnaire has also been adapted for clinical trials (Figure 10).

Have you experienced any of the following in the past week ?	All of the time (4)	Most of the time (3)	Half of the time (2)	Some of the time (1)	None of the time (0)
Itchy eyelids					
Eyelid redness					
Red eyes generally					
Swollen (puffy eyes)					
Tearing (eyes watering)					
Crusting around the lashes					
Burning or stinging sensations					
Noticed eyelash loss					

Figure 10 Adapted Total Ocular Symptom Score (TOSS) questionnaire

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