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Review article

In-office thermal systems for the treatment of dry eye disease

Marie Wangen Beining[a,b,*], *Morten Schjerven Magnø*[a,b,c], *Emily Moschowits*[d], *Jonatan Olafsson, MD*[a,b,e], *Jelle Vehof, MD, PhD*[c,f,g], *Darlene A. Dartt, MD, PhD*[h], *Tor Paaske Utheim, MD, PhD*[b,d,e,i,j,k,l]

[a] *Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway*
[b] *Department of Plastic and Reconstructive Surgery, Oslo University Hospital, Oslo, Norway*
[c] *Department of Ophthalmology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*
[d] *Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway*
[e] *The Norwegian Dry Eye Clinic, Oslo, Norway*
[f] *Department of Twin Research & Genetic Epidemiology, King's College London, St Thomas' Hospital, London, UK*
[g] *Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*
[h] *Department of Ophthalmology, Schepens Eye Research Institute/Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, USA*
[i] *Department of Clinical Medicine, Faculty of Medicine, Bergen, Norway*
[j] *Department of Ophthalmology, Sørlandet Hospital Arendal, Arendal, Norway*
[k] *Department of Ophthalmology, Stavanger University Hospital, Oslo, Norway*
[l] *Department of Computer Science, Oslo Metropolitan University, Oslo, Norway*

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ABSTRACT

Dry eye disease affects millions of people worldwide, causing pain, vision disturbance, and reduced productivity. Meibomian gland dysfunction, a major cause of dry eye, is characterized by chronic glandular inflammation, thickening of the meibum, obstruction of terminal ducts, and glandular atrophy. Treatment of meibomian gland dysfunction can utilize heat and pressure applied to the meibomian glands, increasing meibum expression. With self-treatments, however, not all patients achieve lasting improvement, and compliance is often low. In-office thermal systems offer a second line of treatment and could be a much-needed addition for patients who do not respond to conventional treatment. We critically evaluated the efficacy and safety of LipiFlow, iLux, and TearCare based on existing literature. While the studies found a single in-office thermal treatment to be safe and effective in improving short-term signs and symptoms in patients with dry eye, long-term efficacy needs to be further evaluated. Thus, well-controlled, long-term efficacy studies are warranted to draw clear conclusions. The treatment seemed to provide rapid relief of symptoms that may last

* Corresponding author: Marie Wangen Beining, University of Oslo, PO Box 1072, Blindern, Oslo 0316, Norway. Phone: +47 47360438.
E-mail address: marie.beining@hotmail.com (M.W. Beining).

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up to 1 year, but at a considerably higher cost than the at-home treatments. The choice of treatment depends on cost, compliance with at-home treatment, and personal preference.

1. Introduction

Dry eye disease (DED) is multifactorial and affects millions of people worldwide.[11] Symptoms of DED include ocular surface irritation, pain, and grittiness, and DED often substantially decreases quality of life.[28] Moderate-to-severe DED can even be as debilitating as moderate-to-severe angina.[33]

Despite commonly presenting clinically in mixed forms, DED is often divided into two etiological categories: aqueous-deficient dry eye and evaporative dry eye (EDE).[11] In aqueous-deficient dry eye, the main driver of the disease is the insufficient production of the aqueous layer of the tear film by the lacrimal gland. EDE is caused by a defective lipid layer of the tear film, resulting in evaporation of tear liquid from the ocular surface.[10] EDE is the largest group and characterized by tear film instability and decreased tear film break-up time (TBUT).[10] The main cause of EDE is meibomian gland dysfunction (MGD).[29] The meibomian glands, located in the tarsal plates of the eyelids, produce the meibum making up the protective lipid layer. MGD is characterized by chronic glandular inflammation, thickening of the meibum, obstruction of terminal ducts, and glandular atrophy.[29]

Alterations in the glandular environment are accompanied by changes to the composition of meibum and an increase in the phase-transition temperature.[9] The treatment of MDG induced DED is, therefore, often focused on applying external heat and pressure (Fig. 1) to promote meibomian gland secretion and increase the meibum output. Self-treatments such as warm compresses, eyelid massaging, and eyelid hygiene are important first steps in treatment.[23]

Not all patients, however, achieve lasting improvement with self-treatment, and compliance is often low.[1] A second line of treatment for patients not responding to these methods could be in-office treatments.[20] The LipiFlow Thermal Pulsation System (TearScience, a Johnson and Johnson Vision company, Morrisville, NC) was the first such system intended for treating MGD.[27] LipiFlow aims to soften and squeeze out stagnated meibum through targeted heating of the inner surface of the eyelids and rhythmic compressions to the outer surface of the eyelids (Fig. 2).[27] The system consists of a control unit and a disposable ocular element, composed of a lid warmer and outer eye cup. The lid warmer heats the conjunctival surface of the eyelids to a temperature between 41°C and 43°C.[27] The outer eyecup covers the cutaneous surface of the eyelids and is inflated in a cyclic manner using air pressure.[27] Before the 12-minute treatment session, a topical anesthetic is applied.[27]

LipiFlow was FDA cleared as a medical device for treating MGD in 2011. Since then, further systems have been developed.[2,3,35] TearCare (Sight Sciences, Inc, Menlo Park, CA) is a 510k-exempt device listed by the FDA and commercially available in the United States for treating MGD. It consists

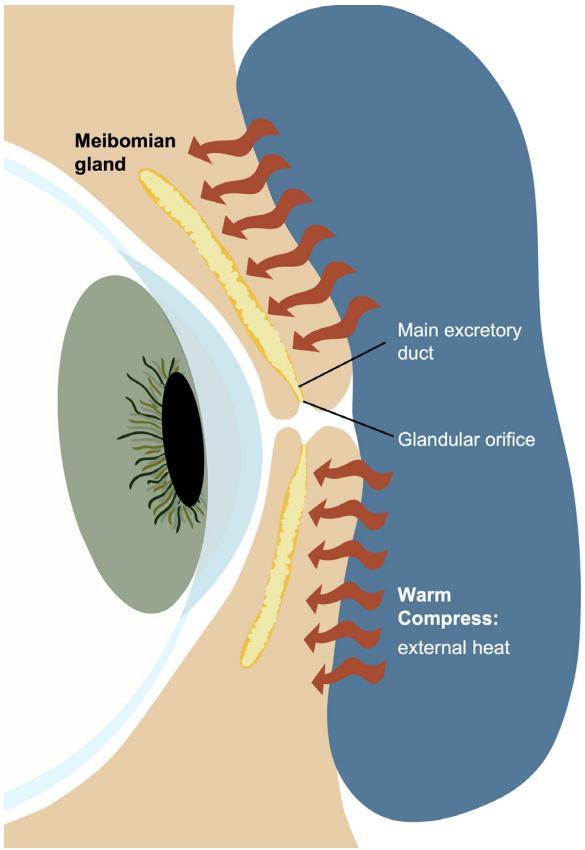

Fig. 1 – External heat applied to outer eyelids through warm compresses melts meibum that is stored in the main excretory duct, which then can be secreted through the meibomian gland ostia onto the ocular surface.

of four single-use, flexible SmartLid devices that adhere to the external surface of the eyelids and apply external heat (Fig. 3).[2,3] Using a controller, the temperature is adjusted to between 41°C and 45°C.[2] As the device allow the patients to blink during treatment, the melted meibum is naturally excreted from the glands. The thermal treatment is followed by application of topical anesthetic and manual expression of meibum.[2] iLux MGD Treatment System (Alcon, Fort Worth, TX) presents a third option. It is a handheld, battery-powered instrument with a disposable tip.[35] The disposable tip contains two eyelid pads: one inner pad that slides beneath the eyelid and makes contact with the inner surface, and one outer that applies pressure from the external side of the eyelid (Fig. 4).[35] The device uses LEDs to warm the meibomian glands, preferably, between 38°C and 42°C.[35] The LEDs will automatically turn off if the inner surface of the eyelid reaches 44°C or the outer surface reaches 45°C.[35] The instrument has a built-in

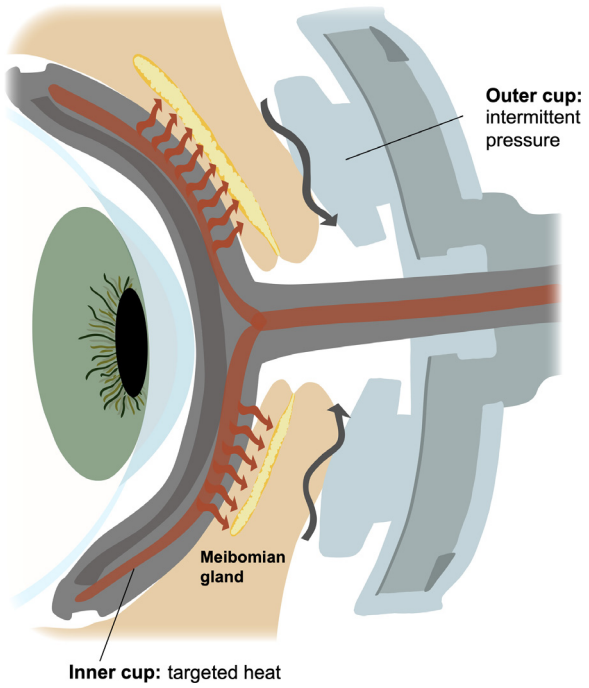

Fig. 2 – LipiFlow system designed to heat lids from the inside while massaging from the outside.

magnifier lens that allows the clinician to view the blocked meibomian gland orifices and manually adjust the temperature and compression.[35] Before treatment, topical anesthetics are applied to the ocular surface.[35]

Several studies examining the effects of in-office thermal systems were published since 2011, when LipiFlow was FDA cleared. Meanwhile, there have only been two review articles focusing on the effects of LipiFlow and in-office thermal treatment.[5,30] In addition to more publications on the efficacy and safety of LipiFlow treatment, new systems, such as TearCare and iLux, have been developed.[2,35] This review focuses on literature describing the efficacy and safety of in-office thermal systems for the treatment of DED.

2. Results

2.1. *Review of existing literature*

The search term "LipiFlow OR (warm* OR heat* OR thermal*) AND (meibomian OR MGD OR eyelid OR "dry eye" OR DED)" yielded 827 results. Many results were from other disciplines or described diagnostics, epidemiology, or other treatment options for DED. Papers with clearly unrelated titles were excluded. After initial screening of titles for relevance, 54 results from PubMed were of interest for further analysis. Review articles were then excluded, leaving only original studies with available English text. Analysis of abstracts and article type resulted in 29 articles of interest, which were narrowed down to 25 articles, excluding three case reports and one article with non-English full text. Any discrepancy between the two authors performing the search was resolved by discussion. An outline of the process is illustrated in Fig. 5.

2.2. *Characteristics of studies*

Among the 25 articles included in this review (Table 1), 10 were randomized, controlled trials (RCTs),[2,6–8,13,21,22,27,34,35] two nonrandomized controlled prospective trials,[37,38] three single-group prospective trials,[15,17,31] and four retrospective studies.[12,16,26,32] Moreover, there were six articles publishing results of later follow-ups on subpopulations of past completed trials.[3,14,18–20,36] Table 1 and Table 2 provide an overview of the key characteristics of articles included, highlighting patient population, study design, sample size, time to follow-up, outcome measures, level of evidence and key takeaways. The included studies were evaluated using the evidence grading scheme described in the Tear Film and Ocular Surface Society's Dry Eye Workshop (TFOS DEWS) II Management and Therapy Report (Supplemental Table 1).[23]

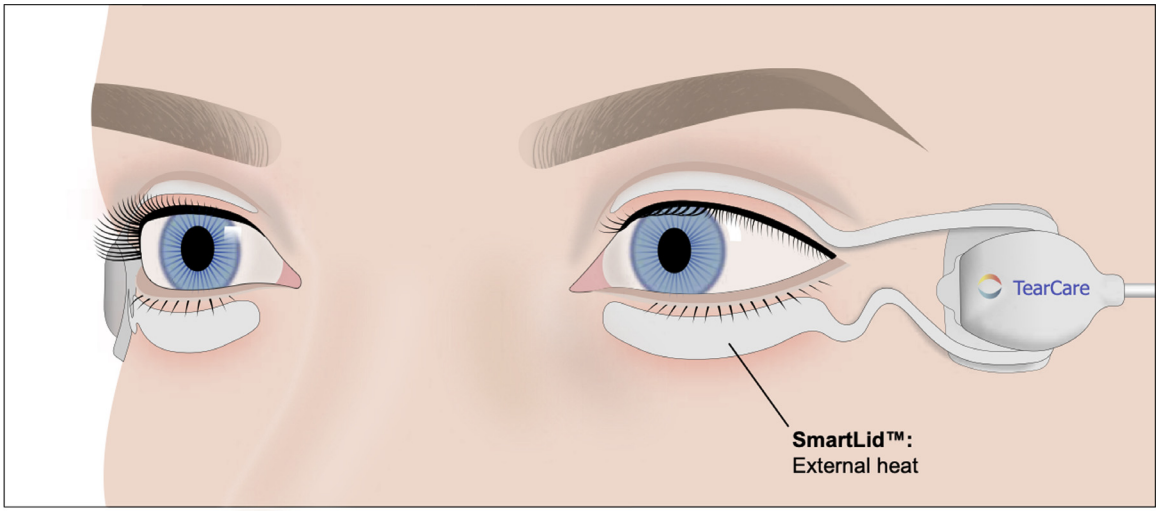

Fig. 3 – TearCare system warming the meibomian glands through the eyelids.

Table 1 – Overview of all included studies.

First author/year	Patient pop.	Study design	Sample size	Follow-up	Outcome measurements	Level of evidence	Key takeaways
iLux							
Tauber 2020[35^]	MGD	Open-label, multicenter RCT	LipiFlow (70pt) iLux (71pt)	2 w, 4 w	MGS, TBUT, OSDI, OSS, BSCVA, IOP, pain	Level 1.	MGS, TBUT and OSDI were improved at 2 and 4 w in both groups. There was no diff between the groups.
TearCare							
Badawi 2019[3]	Subpop Badawi 2018	Retreatment and follow-up on Badawi 2018	TearCare (12 pt)	1 mo, 3 mo, 6 mo	TBUT, MGS, OSS, OSDI, SPEED, SANDE, IOP, BCVA	Level 3.	Retreatment with TearCare was well tolerated and did improve TBUT, MGS, OSS and symp compared with baseline values before first treatment.
Badawi 2018[2]	DED	Open-label single center RCT	TearCare (12 pt) WC-controls (12 pt)	1 d, 2 w, 4 w, 3 mo, 6 mo	TBUT, MGS, OSS, SPEED, OSDI, SANDE, IOP, BCVA	Level 1.	TBUT, MGS, OSS and symp were improved with TearCare at 6 mo follow-up. No adverse events.
Lipiflow							
Booranapong 2020[8]	MGD	Single-masked, RCT, split-face control	LipiFlow (28 eyes), WC-controls (28 eyes)	1 d, 1 w, 1 mo, 6 w, 3 mo, 6 mo	SPEED, MGYLS, LLT	Level 1.	No diff between groups. Both improved SPEED score, but in LipiFlow group the improvement was maintained at 6 mo.
Tauber 2020[35^]	MGD	Open-label, multicenter RCT	LipiFlow (70pt) iLux (71pt)	2 w, 4 w	MGS, TBUT, OSDI, OSS, BSCVA, IOP, pain	Level 1.	MGS, TBUT and OSDI were improved at 2 and 4 w in both groups. Both were similar in efficacy.
Tauber 2019[34]	MGD	Single-masked, RCT	Lifitegrast (25 pt) LipiFlow (25 pt)	0 d, 21 d, 42 d	Symp, MGS, LLT, BCVA, MMP-9, OSS	Level 1.	Both improved self-reported symptoms and MMP-9 values. Neither improved LLT or MG function.
Blackie 2018[7]	Contact lens wearers with MGD	Open-label, multicenter RCT	LipiFlow + blink exercises (29 pt) Untreated controls (26 pt)	1 mo, 3 mo	MGS, MGYLS, MG atrophy, SPEED, TBUT, LWE, LIPCOF, OSS, comf. Contact lens use, OTC drop use	Level 1.	Improvement of MGS and SPEED in LipiFlow group compared to control. Comfortable contact lens use increased with 4hrs/day.
Godin 2018[17]	SS	Single-group, prospective	Lipiflow (13 pt)	2 mo, 1 year	OSDI MG oil flow, TBUT, osm, OSS	Level 2.	Patients with SS showed improvement of MG oil flow, OSS, and TBUT at 1 year. No improvement in osm. or OSDI.
Hagen 2018[21]	MGD	Single-masked, RCT	LipiFlow (14 pt) Doxycycline (14 pt)	3 mo	SPEED, MGYLS TBUT, OSS	Level 1.	All measurements improved in LipiFlow group. Both improved MG function. SPEED was better in LipiFlow group.
Jaccoma 2018[22]	MGD	Open-label RCT, split-face control	LipiFlow (10 eyes) Pellevé (10 eyes)	1 mo, 3 mo	SPEED, OSDI, MGS, TBUT, osm, Sch1, ML score, wax plugs, OSS, LLT	Level 1.	Pellevé and LipiFlow both improved OSDI, SPEED, and MG function. Only ML score was better in Pellevé group.
Epitropoulos 2017[12]	MGD, with pos or neg SS marker	Retrospective, controlled study	LipiFlow: SS pos (23 pt) SS neg (36 pt)	8 w	SPEED, TBUT, MGS	Level 2.	Improvement in both groups. Only improvements in MGS was greater in patients without SS.
Gibbons 2017[16]	MGD	Retrospective chart review	Lipiflow (49 pt)	4 mo	Symptoms	Level 3.	Lower tear production, higher OSS score and osm are associated with positive symptom response to treatment.

(*continued on next page*)

Table 1 (*continued*)

First author/year	Patient pop.	Study design	Sample size	Follow-up	Outcome measurements	Level of evidence	Key takeaways
Kim 2017[26]	DED	Retrospective chart review	LipiFlow (98 pt)	Ave 77 d	Osm, MMP-9, TBUT, OSDI	Level 3.	Improvement of TBUT, OSDI and MMP-9. In the subset of patients with osm > 307 mOsm/L, there was an improvement in osm.
Schallhorn 2017[32]	DED after LASIK or PRK	Retrospective chart review	LipiFlow (57 pt)	43-121 d	SPEED, OSS, TBUT, MGD score	Level 3.	Improvement of LASIK related DED symptoms, as well as objective measurements.
Blackie 2016[6]	MGD	Open-label, multicenter RCT	LipiFlow (101 pt) WC-controls (99 pt)	1 mo, 3 mo, 6 mo, 9 mo, 12 mo	OSDI, MGS	Level 1.	LipiFlow group showed reduction in OSDI and MGS compared to control. Higher baseline MGS and shorter history with symptoms showed greater improvement.
Greiner 2016[20]	Subpop. Lane 2012	Follow-up on Lane 2012	LipiFlow (20 pt)	3 years	OSDI, SPEED, MGS, MGYLS, TBUT, OSS, BSCVA	Level 3.	SPEED and MGS improvements maintained 3 years after LipiFlow treatment. TBUT and OSDI improvements returned to baseline values after 1 and 2 years, respectively.
Yeo 2016[36]	MGD	Supplemental study of Zhao. Yang 2016	Hot towel (22 pt) Eyegiene (22 pt) Blephasteam (22 pt) LipiFlow (24 pt)	1 mo, 3 mo	TE	Level 2.	LipiFlow reduced TE. A higher baseline TE was associated with greater improvement.
Zhao. Yang 2016[37]	MGD	Open-label, prospective	LipiFlow (25 pt) Hot towel (25 pt)	1 mo, 3 mo	SANDE, TBUT, Sch I, LLT, MGYLS, BSCVA	Level 2.	No diff between groups. A session with LipiFlow was similar in effect to 3 months of twice daily WC.
Zhao. Yinying 2016[38]	MGD	Single-masked, prospective, split-face control	LipiFlow (29 eyes) Untreated controls (29 eyes)	3 mo	SPEED, OSDI, TBUT, Sch I, LLT, MGYLS, OSS, PB ratio, MG dropout	Level 2.	LipiFlow improved symptoms and MG function. No improvement in MG dropout. Only MGYLS and TBUT were better in LipiFlow.
Satjawatcharaphong, 2015[31]	MGD	Single-group, prospective	LipiFlow (32 pt)	21-84 d,	SPEED, LLT, TBUT, OSS, LWE, blink ratio, MGS, meiboscore	Level 2.	Male sex, higher SPEED score and more secretory grade 0 MGS at baseline increased likelihood of improvement with LipiFlow.
Finis, 2014[14]	Subpop. Finis 2014	Follow-up on Finis 2014	LipiFlow (26 pt)	6 mo	OSDI, SPEED, MGS, MGYLS, TBUT, LLT, osm, TMH, Sch I, OSS, LIPCOF	Level 3.	SPEED, OSDI, MGYLS, and LLT were improved at 6 mo. TBUT, osm and Sch I remained unchanged.
Finis, 2014[13]	MGD	Single-masked RCT	LipiFlow (17 pt) WC-controls (14 pt)	1 mo, 3 mo	OSDI, SPEED, MGYLS, TBUT, LLT, osm, OSS TMH, Sch I, LIPCOF	Level 1.	Both treatments improved MGYLS. OSDI improved in the LipiFlow group only.
Greiner, 2013[19]	Subpop. Lane 2012	Follow-up on Lane 2012	Lipiflow (18 pt)	12 mo	OSDI, SPEED, MGS, TBUT	Level 3.	Improvement in MGS, SPEED, and OSDI maintained at 12 mo follow-up. TBUT was no longer sign.
Greiner, 2012[18]	Subpop. Lane 2012	Follow-up on Lane 2012	LipiFlow (21 pt)	9 mo	OSDI, SPEED, MGS, TBUT	Level 3.	The improvement in SPEED, OSDI, MGS, and TBUT was sustained at 9 mo.

(*continued on next page*)

Table 1 (*continued*)

First author/year	Patient pop.	Study design	Sample size	Follow-up	Outcome measurements	Level of evidence	Key takeaways
Lane, 2012[27]	MGD	Open-label, multicenter RCT	LipiFlow (69 pt) WC-controls (70 pt)	1 d, 2 w, 4 w	MGS, MGYLS, TBUT, SPEED, OSDI, pain, OSS, IOP, BSCVA	Level 1.	LipiFlow improved MGS, TBUT, SPEED and OSDI, and all improvements were better than WC at 2 w. Effect maintained at 4 w.
Friedland, 2011[15]	MGD	Open-label, prospective, split-face control	LipiFlow prototype (14 eyes) Lipiflow prototype + additional treatment (14 eyes)	1 w, 1 mo, 3 mo	MGS, MGYLS, TBUT, OSS, SPEED, OSDI, IOP, pain	Level 2.	No diff between the eyes receiving LipiFlow only and eyes receiving additional expression. MG function, TBUT, CFS and symptoms were improved in both groups.

MGD: meibomian gland dysfunction, DED: dry eye disease, WC: warm compress, RCT: randomized controlled trial, pt: participant, d: day, w: week, mo: month, diff: difference, OSDI: ocular surface disease index, SPEED: standard patient evaluation for eye dryness, SANDE: symptom assessment in dry eye, MGS: meibomian gland secretion score, MGYLS: meibomian gland yielding liquid secretion, TBUT: tear film break-up time, OSS: ocular surface staining, CFS: corneal fluorescein staining, OTC: over the counter, LWE: lid wiper epitheliopathy, LIPCOF: lid-parallel conjunctival folds, Osm: tear film osmolarity, Sch I: Schirmer I. TE: tear evaporation, PB ratio: partial blink ratio, LLT: lipid layer thickness, BSCVA: best spectacle-corrected visual acuity, IOP: intraocular pressure, TMH: tear meniscus height, ML: Marx Line, SS: Sjögren's syndrome, pos: positive, neg: negative, Pellevé: A system delivering radiofrequency-based energy to gel-covered skin in the periocular area for the treatment of MGD (called the ThermaLid procedure).

^ study including both LipiFlow and iLux and therefore shown twice in the table.

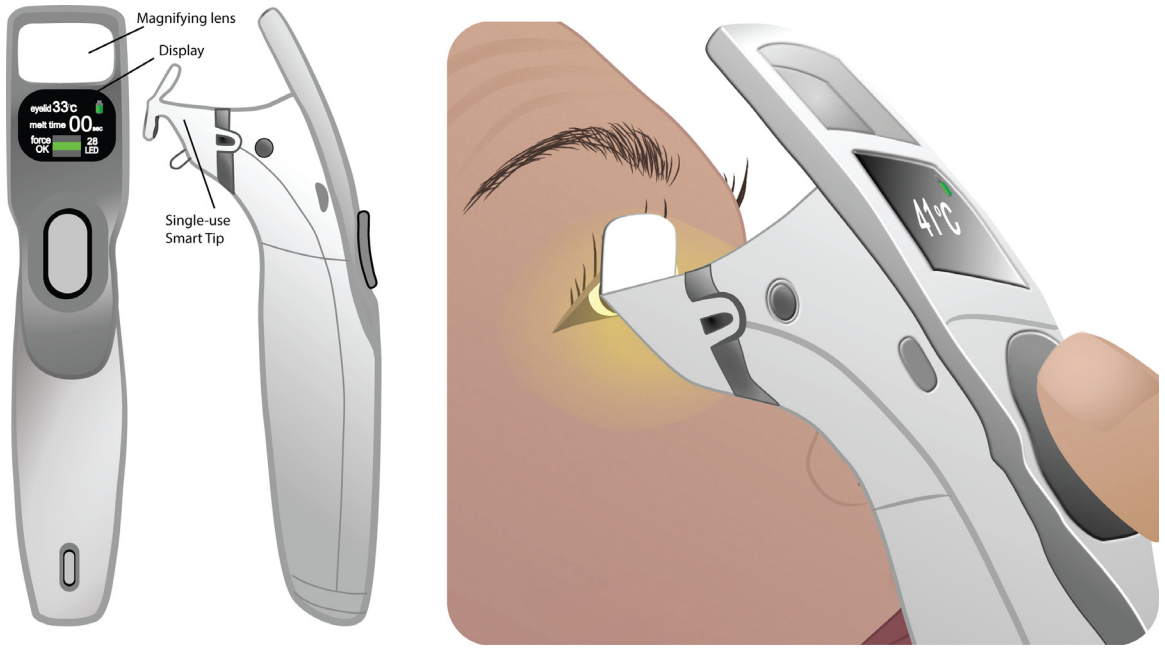

Fig. 4 – iLux system, a handheld eyelid heating device.

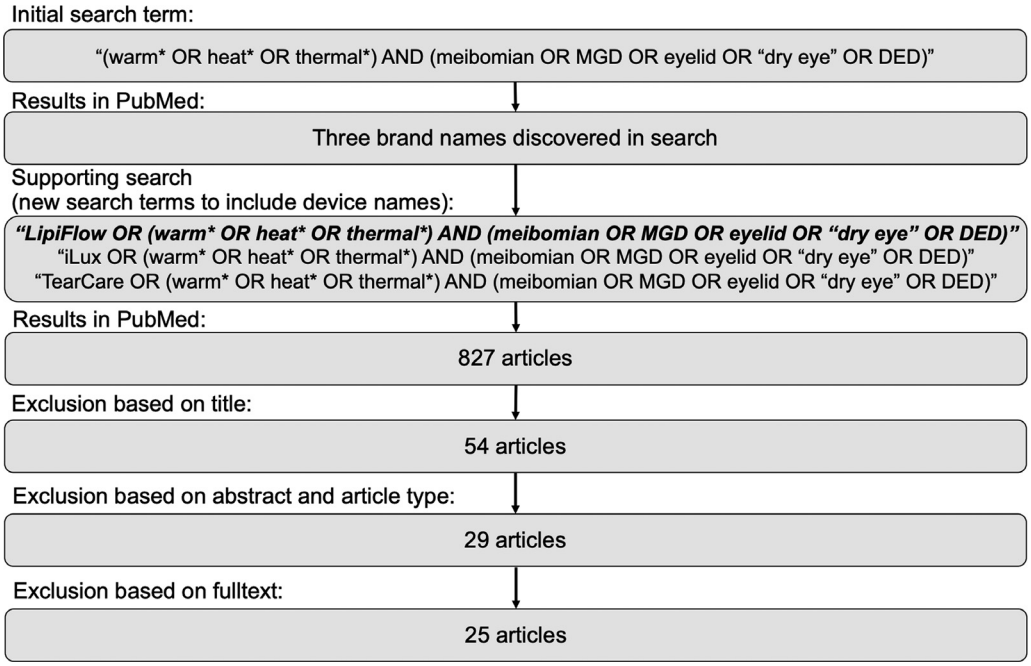

Fig. 5 – Visual flowchart of data extraction.

Studies reporting the effect of treatment with LipiFlow and TearCare compared to existing alternatives are presented in Table 3. Inclusion criteria, mean age of participants and severity are further described in Supplemental Table 2.

2.3. *Effect of in-office treatment*

2.3.1. *Meibomian gland function and dry eye symptoms*

Most articles evaluated improvement of symptoms and meibomian gland function following a single in-office thermal treatment (Table 2) Table 2. provides further details on included studies. Improvement in symptom scores from LipiFlow, iLux, or TearCare treatment was observed in all but one study (Table 2).[17] The study without improvement included only thirteen patients with Sjögren syndrome.[17] Similarly, meibomian gland function, assessed as either meibomian gland fluid quality or number of expressible glands, improved in all but one study (Table 2).[8] Booranapong and coworkers followed 28 patients with moderate MGD and found no significant improvement in glandular expression at

Table 2 – Improvement above baseline at last follow-up visit for patients receiving in-office thermal treatment.

First author / year	Last follow-up	System	Study design	Symp	MGS	MGYLS	TBUT	Sch. I	LLT	OSS	Tear osm.	LWE
iLux												
Tauber, 2020[35] ^	4 w	iLux	Open-label RCT	↑[1]	↑	ND	↑	ND	ND	↑	ND	ND
TearCare												
Badawi, 2018[2]	6 mo	TearCare	Open-label RCT	↑[1,2,3]	↑	ND	↑	ND	ND	↑	ND	ND
LipiFlow												
Booranapong, 2020[8]	6 mo	LipiFlow	SM RCT, Split-face	↑[2]	ND	—	ND	ND	—	ND	ND	ND
Tauber, 2020[35] ^	4 w	LipiFlow	Open-label RCT	↑[1]	↑	ND	↑	ND	ND	↑	ND	ND
Blackie, 2018[7]	3 mo	LipiFlow	Open-label RCT	↑[2]	↑	↑	↑	ND	ND	—	ND	↑
Godin, 2018[17] *	1 year	LipiFlow	Single-group Prospective	—1	ND	ND	↑	ND	ND	↑	—	ND
Hagen, 2018[21]	3 mo	LipiFlow	SM RCT	↑[2]	ND	↑	↑	ND	ND	↑	ND	ND
Jaccoma, 2018[22]	3 mo	LipiFlow	SM RCT, Spilt-face	↑[1,2]	↑	ND	—	—	—	—	—	ND
Epitropoulos, 2017[12]	8 w	LipiFlow	Retrospective	↑[2]	↑	ND	↑	ND	ND	ND	ND	ND
Kim, 2017[26]	Ave 77 d	LipiFlow	Retrospective	↑[1]	ND	ND	↑	ND	ND	ND	—	ND
Schallhorn, 2017[32] #	43-121d	LipiFlow	Retrospective	↑[2]	ND	ND	↑	ND	ND	↑	ND	ND
Blackie, 2016[6]	1 year	LipiFlow	Open-label RCT	↑[1]	↑	ND	ND	ND	ND	ND	ND	ND
Zhao, Yang, 2016[37]	3 mo	LipiFlow	SM Prospective	↑[3]	ND	↑	—	—	—	ND	ND	ND
Zhao, Yinying, 2016[38]	3 mo	LipiFlow	SM Prospective, Split-face	↑[1,2]	ND	↑	↑	↑	—	↑	ND	ND
Satjawatcharaphong, 2015[31]	21-84 d	LipiFlow	Single-group Prospective	↑[2]	↑	ND	↑	ND	—	—	ND	—
Finis, 2014[14]	3 mo	LipiFlow	SM RCT	↑[1]/—[2]	ND	↑	—	—	—	—	—	ND
Lane, 2012[27]	4 w	LipiFlow	Open-label RCT	↑[1,2]	↑	↑	↑	ND	ND	↑"	ND	ND
Friedland, 2011[15]	3 mo	LipiFlow prototype	Open-label, prospective split-face	↑[1,2]	↑	↑	↑	ND	ND	↑	ND	ND

*Patients with Sjögren's disease, #patients undergoing laser vision correction, ^patients from same study.
"Only corneal staining improved, conjunctival staining did not,
↑significant improvement above baseline, $P < 0.05$, — no significant difference.
SM: single masked, RCT: randomized controlled trial, d: day, mo: month, Ave: average, Symp: symptoms.
[1]Ocular Surface Disease Index.
[2]Standard Patient Evaluation of Eye Dryness.
[3]Symptom Assessment in Dry Eye), MGS: meibomian gland score, MGYLS: meibomian glands yielding liquid secretion, TBUT: tear film break-up time, Sch. I: Schirmer I, LLT: lipid layer thickness, OSS: ocular surface staining, Tear osm: tear film osmolarity, LWE: lid wiper epitheliopathy.

any time-point during the 6-month study.[8] Taken together, all in-office thermal treatment options improved symptoms and meibomian gland function in patients with DED.

2.3.2. *Duration of improvement*

While all the studies reported an initial response to treatment, only six separate patient groups were followed for six months or more.[2,3,6,8,14,17–20] Symptom improvement was found to last for 6[2,14], 9[18], and 12 months[6,17,19] after treatment. Greiner followed up on a subpopulation of Lane and coworkers at 9, 12, and 36 months after a single LipiFlow treatment. OSDI and SPEED improved during the first 9 to 12 months but decreased thereafter.[18–20] While SPEED scores remained improved for 3 years, OSDI scores had returned to baseline value at the 12-month follow-up.[20] Meibomian gland function also improved the first months following treatment and remained so after 3 years.[20] Badawi, who followed patients receiving treatment with TearCare, noted an improvement in TBUT, symptoms, MGS, and ocular surface staining after 6 months;[2] however, the improvement declined after an initial peak between the first and the third month.[2] Badawi extended the study and re-treated all twelve patients.[3] All measurements improved and were maintained six months after retreatment.[3] The long-term effects of iLux treatment are not known, as the longest follow-up was 4 weeks.[35] Across studies, the immediate positive effects after in-office treatment were shown to decline over time; however, some metrics remained elevated even after 3 years.

2.3.3. *Lipid layer thickness and TBUT*

While meibomian gland function improved in nearly all studies, the lipid layer thickness did not[8,15,24,34,37,44,45], with one exception: a follow-up study on a subset from an earlier completed trial.[14] Ten out of the thirteen studies investigating the effect of LipiFlow treatment, and both studies using iLux or TearCare, found short-term improvement in TBUT (Table 2). Overall, markers for tear film stability showed mixed results. While lipid layer thickness was not affected, TBUT generally improved after in-office thermal treatment.

2.4. *Short-term efficacy*

To show the trend of the data, graphs of the changes in commonly reported parameters were created. Outcomes that were frequently assessed and included in the analysis were SPEED, OSDI, TBUT, MGYLS, and MGS. Only one study assessed the effect of iLux and TearCare, respectively, thus only graphs for studies assessing LipiFlow treatment were generated.[2,35] The

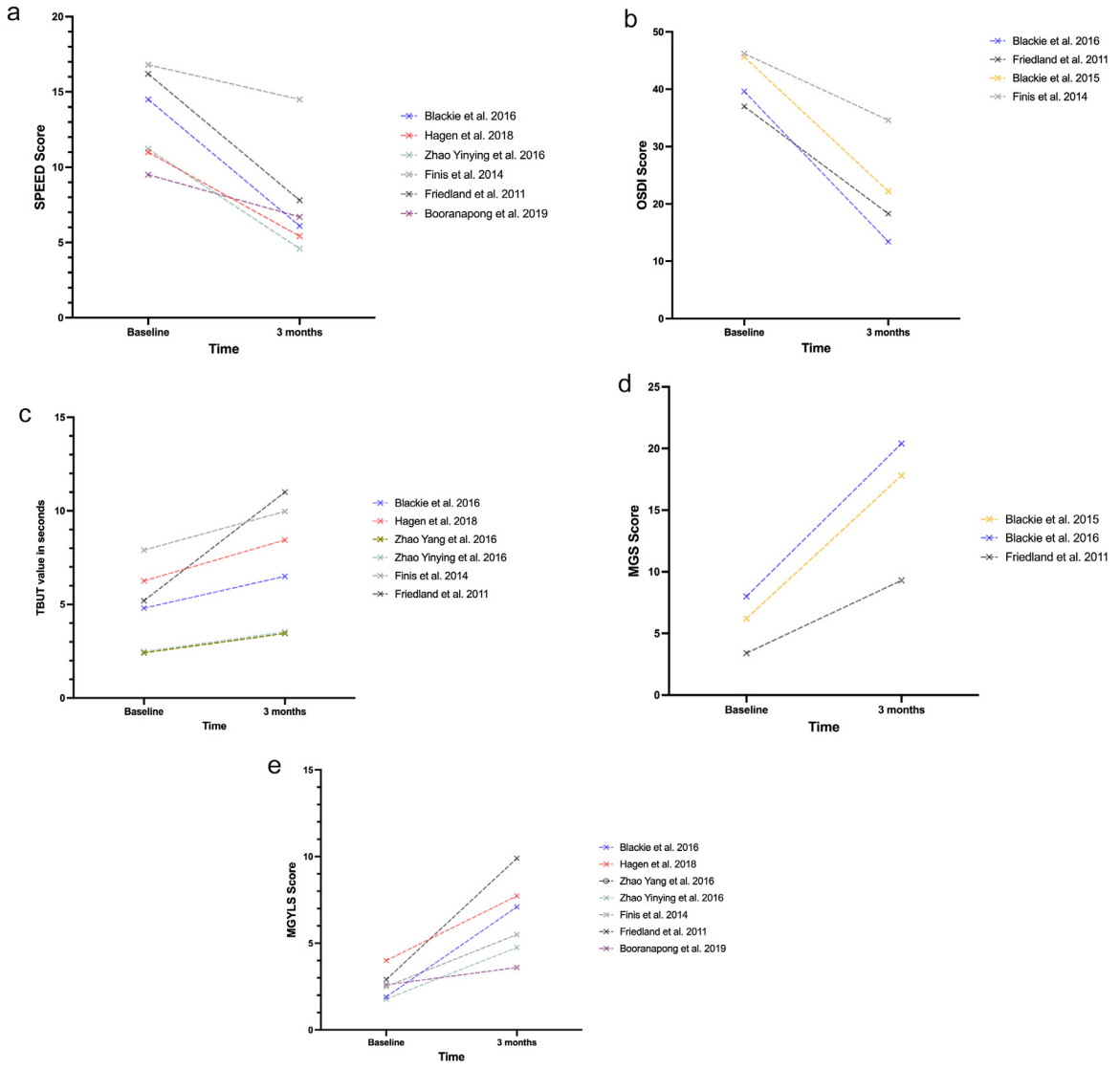

Fig. 6 – (A) The mean Standard Patient Evaluation of Eye Dryness (SPEED) score at baseline and 3 months after a single treatment with the LipiFlow system in six individual studies. Decrease in score indicates improvement. (B) The mean Ocular Surface Disease Index (OSDI) scores at baseline and 3 months after a single treatment with the LipiFlow system in four individual studies. Decreased score indicates improvement. (C) The mean tear film break-up time (TBUT) values, measured in seconds, at baseline and 3 months after a single treatment with the LipiFlow system in six individual studies. Increased score indicates improvement. (D) Mean meibomian gland secretion (MGS) scores at baseline and 3 months after a single treatment with the LipiFlow system in 3 individual studies. Increased score indicates improvement. (E) Mean meibomian glands yielding liquid secretion (MGYLS) at baseline and 3 months after a single treatment with the LipiFlow system in six individual studies. Increased score indicates improvement.

values at baseline and 3 months after treatment were extracted and are presented in Fig. 6.

2.5. *Comparison of in-office treatment to other treatments for MGD*

Six studies compared in-office thermal devices to at-home treatment with warm compresses (Table 3). Important characteristics of these studies are summarized in Table 3. Lane and coworkers (2012) conducted the first open-label RCT, consisting of 139 patients with MGD.[27] The control group was instructed to do a 5-minute daily treatment with iHeat portable warm compress for at least ten days, while the test group received a single 12-minute LipiFlow treatment.[27] Subjects in the control group were shown the technique and completed the first treatment with the instructor; they received a log to record daily use.[27] Measurements at the 2-week follow-up showed improvement in MGS, TBUT, SPEED, and OSDI in the LipiFlow group, while only OSDI and SPEED improved in the control group.[27] Similarly, in a study by Badawi, the control group was instructed to apply warm compresses, MGDRx (The Eye Bag Company, Halifax, UK) warmed by microwaving for 30 seconds, 5 minutes daily for 4 weeks, while the intervention group received TearCare treatment.[2] The participants filled

Table 3 – Observed improvement in patients receiving in-office thermal treatment compared to controls receiving warm compresses.

First Author	Study Design	System (n)	Control (n)	Follow-up	Symp	MGS	MGYLS	TBUT	Sch. I	LLT	OSS
TearCare											
Badawi, 2018[2]	Open-label RCT	TearCare (12 pt)	5-min WC with MGDRx bags heated in a microwave for 30 s x1 daily for 4 w (12 pt)	1 d, 2 w, 4 w, 3 mo, 6 mo	↑[1,2]/⟷[3#]	↑	ND	↑	ND	ND	↑
LipiFlow											
Finis, 2014[13]	SM RCT	LipiFlow (17 pt)	5-min 45C WC x2 daily for 3 mo (14 pt)	1 mo, 3 mo	↑[1]/⟷[2]	ND	⟷	⟷	⟷	⟷	⟷
Booranapong, 2020[8]	SM RCT, Split-face	LipiFlow (28 pt)	5-min WC with towels heated in warm water x2 daily for 3 mo (28 pt)	1 d, 1 w, 1 mo, 6 w, 3 mo, 6 mo	⟷[2]	ND	⟷	ND	ND	⟷	ND
Blackie, 2016[6]	Open-label RCT	LipiFlow (101 pt)	10-min WC with EyeGiene® Insta-WarmthTM System x2 daily for 3 mo (99 pt)	3 mo	↑[1]	↑	ND	ND	ND	ND	ND
Lane, 2012[27]	Open-label RCT	LipiFlow (69 pt)	5-min with iHeat portable WC x1 daily for 14 d (70 pt)	2 w	↑[1,2]	↑	↑	↑	ND	ND	↑
Zhao, Yang, 2016[37]	Prospective	LipiFlow (69 pt)	10-min WC with towels heated in warm water x2 daily for 3 mo (70 pt)	1 mo, 3 mo	⟷[3]	ND	ND	⟷	⟷	ND	ND

#Not significant at 3-month follow-up.
↑significant greater improvement compared to controls receiving warm compresses.
⟷ no significant difference between treatment with in-office thermal system compared to warm compresses.
SM: single masked, RCT: randomized controlled trial, Symp: symptoms.
[1]Ocular Surface Disease Index.
[2]Standard Patient Evaluation of Eye Dryness.
[3]Symptom Assessment in Dry Eye), MGS: meibomian gland score, MGYLS: meibomian glands yielding liquid secretion, TBUT: tear film break-up time, Sch. I: Schirmer I, LLT: lipid layer thickness, OSS: ocular surface staining, WC: warm compress, min: minute, d: day, mo: month, pt: participant, x1: once, x2: twice.

out a daily log documenting the therapy.[2] TBUT, the primary endpoint, had improved in the TearCare group compared to a decline in control group at 4 weeks.[2] Likewise, MGS, ocular surface staining, and symptoms were more improved at all follow-ups in the TearCare group than in the control group.[2]

Four trials evaluated long-term effects of LipiFlow compared to warm compress treatment.[6,8,13,37] The control groups in all four studies were instructed to perform twice-daily lid hygiene and warm compresses for 3 months.[6,8,13,37] The length and use of warm compresses in the control groups varied between the trials and are further described in Table 3. Blackie and coworkers reported significantly greater improvement in OSDI and MGS scores in the LipiFlow group.[6] In contrast, two articles found no significant difference between LipiFlow and controls after 3 months.[13,37] Furthermore, one study used a split face study design and and found no significant difference between the two treatments at any time.[8]

One article compared LipiFlow to three different at-home eyelid-warming treatments.[36] Compared to hot towels, EyeGiene (Eyedetec Medical Inc., Danville, CA) and Blephasteam (Théa Pharmaceuticals, Newcastle-under-Lyme, UK), only LipiFlow significantly reduced tear evaporation rates.[36] Additionally, a case report from 2017 noted that a 12-minute LipiFlow treatment elevated the inner eyelid temperature to therapeutic levels while 10 minutes with the Bruder mask (Bruder Healthcare, Alpharetta, GA) and 10 minutes Blephasteam treatment did not.[25] In two RCTs, LipiFlow showed similar efficacy as the pharmaceutical options lifitegrast and doxycycline.[21,34] Two patients, however, in the doxycycline group (14.3%) withdrew from the study due to stomach illness, illustrating potential side effects of pharmaceutical treatment.[21]In sum, in-office thermal treatment seems to be at least as effective, if not more effective, than at-home treatment options, especially in the short term.

2.6. *Patient populations*

The studies described in this review primarily examine the effect of LipiFlow, iLux, or TearCare in patients with DED stemming from MGD (Supplemental Table 2); however, the severity differed between articles. Most study populations were subjects with moderate-to-severe DED.[2,3,6–8,12–16,18–22,27,35–38] One trial included participants with inflammatory MGD,[8] while four studies did not specify severity in the inclusion criteria[17,26,31,32] (Supplemental Table 2).

Several studies examined which baseline characteristics impacted patients' response to the in-office thermal treatment; however, no clear conclusions can be drawn. Three studies found worse baseline meibomian gland atrophy, lower MGS, and a longer history of symptoms to be tied to lower improvement after treatment.[6,14,38] Conversely, two articles presented opposing conclusions, where worse baseline SPEED scores, lower MGS, and more corneal staining was tied to an improved response to treatment.[16,31]Thus, there are currently no conclusive results on which baseline characteristics may predict patient response to in-office thermal treatment.

2.7. *Safety of treatments*

Transient post-treatment hyperemia, petechial hemorrhages on the eyelid, and vascular injection were reported in patients receiving treatment with LipiFlow or iLux.[6,7,27,31,35,37] One study found that all participants had transient redness in the eyes after the procedure,[37] while another reported similar in only 5% of the participants.[6] All events resolved without treatment within short time.[6,7,27,31,35,37] Some patients treated with LipiFlow or iLux experienced transient ocular discomfort that resolved without treatment;[8,15,27,31,35] however, one patient had to stop the LipiFlow procedure after 10.5 minutes because of severe discomfort[15], while in another article, 5% of patients reported that their symptoms worsened after the procedure with LipiFlow.[31] This was attributed to short fornices, as the scleral shells of the LipiFlow system come in only one size.[8,31] Only Badawi evaluated the safety of retreatment, including assessment of IOP, visual acuity, and eyelid and corneal health after TearCare treatment.[3] Both the first and the second treatment with TearCare were well tolerated and there were no changes in IOP, visual acuity, or adverse events among the 12 subjects included.[2,3]Apart from transient and minor adverse events, treatment with LipiFlow, iLux, or TearCare appears to be safe.

3. Discussion

3.1. *Options for treatment*

Based on literature analyzed in the present review, LipiFlow, iLux, and TearCare all appear to be effective in improving symptoms and clinical signs in patients with DED. While LipiFlow has been FDA cleared for 10 years, and efficacy and safety has been shown in many studies, the newer systems have advantages concerning personalization and portability. The LipiFlow system follows an automated pressure procedure, while iLux and TearCare allow manual control of the pressure and more individualization. iLux additionally has a built-in magnifier lens, so the clinician can visualize the eyelid margin and adjust the treatment.[35] TearCare leverages specialized meibomian gland clearance tool that requires clinicians to address individual gland blockages while using slit lamp biomicroscope; however, with only a limited number of studies assessing these newer in-office systems, further trials are needed to make clear recommendations for clinical use.

In several studies, a single 12-minute in-office treatment with LipiFlow was shown to be mostly equivalent to 3 months of self-administered warm compress treatment.[6,8,13,37] The equivalency indicates a lasting effect of treatment, but also illustrates the efficacy of warm compress treatment when conducted appropriately. Due to inconsistency in methods and reported information of warm compress treatment and compliance, there is still uncertainty about the true difference between treatment with LipiFlow and warm compress;[6,8,13,37] however, this highlights some disadvantages of the latter treatment option, being time-consuming and possibly difficult to comply with.[1] A single treatment with LipiFlow, iLux, and TearCare have repeatedly shown long-lasting improvements. There are currently no trials longer than 6 months that compare these in-office procedures to in-home treatment options. This makes it difficult to predict long-term compliance and lasting effects of in-home treatment. In the event of sustained failure of therapy or lack of compliance, treatment with in-office thermal systems may be effective. Hence, a single in-office thermal treatment is effective in improving signs and symptoms of MGD. The results of these treatments are at least equivalent to the time-consuming traditional treatment options, such as hot towels.

3.2. *Cost and availability of treatment*

Potential drawbacks of the in-office thermal treatment systems are the expense and availability. One study described the costs as "overwhelmingly more expensive than eyelid warming."[37] Despite recent reduction in prices for single-use equipment, United States (US) patients still pay around $400–500 per eye treated with LipiFlow and around $300–400 for binocular treatment with iLux.[39,40] In addition to the expense, accessibility is also an important hurdle. The systems are costly, which may affect their distribution among ophthalmology and optometry clinics. While TearCare has not yet been cleared by the FDA as a treatment (It is cleared as a diagnostic tool), the estimated price in the US is $5,000 for the treatment system and $350 per bilateral treatment in consumables (R.Hill, personal communication, July 7, 2020). Thus, health care professionals need the economic resources to acquire the thermal systems.

In comparison, other treatment options, such as warm compresses only require household items such as towels, water, and a method of heating. Furthermore, LipiFlow treatment is not covered by most US insurance companies or health care plans and are paid out-of-pocket. As most studies found warm compresses, if used regularly and correctly, to be largely equivalent with LipiFlow (Table 3), the value of the convenience of a 12-minute in-office treatment each year versus a twice-a-day eyelid warming routine must be weighed against the potential difference in cost and patient compliance. Selecting the right patients for treatment is therefore essential, and shared decision making should play a major role in choice of treatment.

3.3. *Safety of in-office thermal treatment*

Although there were reports of minor complications with use of in-office thermal treatment, all complications resolved spontaneously within a few days.[2,8,15,27,31,35] As these complications were only slightly more common than those observed in control groups,[27,35] treatment with the LipiFlow, iLux, or

TearCare system seems to be a safe option for treating DED. This conclusion supports the findings of both the companies' own reviews and the FDA reports, which cleared the LipiFlow device for treatment of MGD in 2011 and the iLux device in 2016. Treatment with TearCare has not yet been cleared by the FDA, nor directly compared to existing thermal treatment systems. Compared to warm compress treatment, however, TearCare was shown to be equivalent in efficacy and safety.[2]

As patients might need additional treatments, future studies on repeated treatments are required. Still, apart from transient complications, a single treatment with in-office thermal treatment devices appears safe.

3.4. *Limitations*

3.4.1. *Limitations of the current review*

The current review has some limitations. First, the review is based on a search in the PubMed database only. Additional articles could possibly have been identified if supplementary databases were included. No additional cited studies, however, were found during the review process while reading the studies included from PubMed, indicating that our search did not miss important studies. Second, the articles included were selected based on title, abstract and last, full text. This process may lead to inappropriate exclusion of articles. Third, inclusion required articles with full text in English. Due to lack of professional translators, articles written in other languages were not included. This resulted in the exclusion of one article written in French.[4]

3.4.2. *Limitations in either studies or treatment*

A major weakness in the included material is the lack of a placebo-controlled double-blind randomized control trial (RCT). To date no trial comparing in-office thermal treatment to placebo has been performed. As the effect of placebo has repeatedly proven to be surprisingly large in DED pharmaceutical treatment studies, such trials should be conducted.[24] Trials so far using LipiFlow, iLux, or TearCare are inherently difficult to design to minimize bias. It is almost impossible to do a double blinded placebo controlled RCT in this context. Therefore, all these results, and especially subjective measurements, could be biased by a placebo effect. Of the studies described, the RCTs using compresses as control group likely have the least biased results (Table 3). The description of the methods used for the control groups did, however, vary between the papers (Table 3). Information regarding temperature and frequency of warm compress therapy were lacking in several studies. These factors should be considered when interpreting the findings of comparative trials.

As DED is a chronic disease[11], long-term effects of in-office thermal treatment need further investigation. Patients may need treatments lasting beyond one year and potentially require repeated treatments.[20] Further studies determining optimal treatment regimens and cost-effectiveness over the long term are therefore warranted.

It is important to note that sample sizes were relatively small in most included articles. The median sample size was 31 participants, while the study with the largest and smallest studies included 200 and 10 participants, respectively.[6,22] The statistical calculations of sample size and description of the method used varied across studies, from number of eyes[35] to number of patients.[8,13,37] This made it difficult to precisely estimate the effects of treatment and compare the findings between studies. In addition, five of the articles followed up on patients who had already been described in other studies.[3,14,18–20] Although it is important to have long-term studies that track the effects of treatment beyond the first few months, these studies could not be treated independently.

3.5. *Future directions*

Larger, multicentered, randomized clinical trials are required to confirm the effectiveness and safety of the different treatment options, as well as studies investigating which patients are most likely to respond to treatment. Among the subtypes of DED, there are currently differing results on what baseline characteristics may impact response of treatment with iLux, TearCare, and LipiFlow. Thus, larger studies investigating the role of meibomian gland atrophy may be of interest. There are currently no studies evaluating the long-term indirect costs and benefits of treatment with in-office thermal treatment systems. While a single in-office treatment costs more than one usage of warm compresses, the cumulative expense and inconvenience of such at-home treatment options have not been considered. Studies including work productivity, time saved, and quality of life would be of particular value for patients and insurance companies in the discussion of therapy and future coverage. Furthermore, assessment of patient satisfaction would be important in recognizing which patients would benefit most from the procedures. Although the improvements after treatment with LipiFlow were sustained for one year, the chronic pattern of DED may trigger a need for repeated treatments. Studies evaluating efficacy and safety of additional treatments are warranted.

4. Conclusion

In-office thermal systems appear safe and effective, but more evidence on long-term outcomes is needed. The effects of LipiFlow appear to be similar or even superior to at-home therapy with warm compresses, and iLux and TearCare could be promising new options. Further studies evaluating the efficacy and safety of in-office thermal systems are warranted. In-office therapy is more expensive and less available than at-home treatment, but could offer an option for patients who prefer one treatment every 6 to 12 months or are not compliant with time-intensive regimens. The final decision between in office and in-home treatment should be guided by extent of insurance coverage, cost, increased difficulty of in-house treatments, personal preference, and the recommendation of health care professionals.

5. Literature search (methods)

A literature search was conducted by two independent authors on June 15th 2020 using the following search term in PubMed: "(warm* OR heat* OR thermal*) AND (meibomian OR

MGD OR eyelid OR "dry eye" OR DED)". All studies with available English full text articles were included for further processing. Through assessing first title, and then abstract, unrelated articles were removed. After conducting this process, three brand-named devices were mentioned in the included articles, and a supporting search was conducted. This search consisted of adding the device names to the initial search term, aiming to ensure inclusion of all relevant articles. The search terms used thus included: "LipiFlow OR (warm* OR heat* OR thermal*) AND (meibomian OR MGD OR eyelid OR "dry eye" OR DED)," "iLux OR (warm* OR heat* OR thermal*) AND (meibomian OR MGD OR eyelid OR "dry eye" OR DED)," and "TearCare OR (warm* OR heat* OR thermal*) AND (meibomian OR MGD OR eyelid OR "dry eye" OR DED)." Only the search term including "LipiFlow" increased the number of articles retrieved, and thus the final search term was: "LipiFlow OR (warm* OR heat* OR thermal*) AND (meibomian OR MGD OR eyelid OR "dry eye" OR DED)."

6. Method of literature search

The databases and search engines used for this review was: PubMed. The search was conducted on the following date: June 15th, 2020.

The search term used was: "LipiFlow OR (warm* OR heat* OR thermal*) AND (meibomian OR MGD OR eyelid OR "dry eye" OR DED)".

All years covered were included. The oldest included article was from 2011. No further articles meeting the inclusion criteria were found cited in the reference list of the included articles or through other sources.

Inclusion criteria were all original studies with full-text evaluating the effect and safety of in-office thermal systems for the treatment of signs and symptoms of dry eye. All results were evaluated through first examining title and then abstract for relevance to the subject and checking against exclusion criteria.

Exclusion criteria were studies not written in English, case reports which did not contribute new information and studies only described as abstracts.

7. Literature search instructure

7.1. *Literature search instructions*

As a service to our readers, we have implemented a policy of including a literature search statement with every review published in Survey of Ophthalmology. This statement should be specific enough to allow for duplication of the search, and it should specify the rationale used for including and omitting references from your list. Please refer to the form below for help in preparing your statement.

1. **Title:** In-Office Thermal Systems for the Treatment of Dry Eye Disease
2. **Databases Searched (circle all that apply):**
   OTHER: PUBMED
3. **Years Searched**
   ALL
4. **Search Words Used (please include an additional sheet if necessary)**

   "LipiFlow OR (warm* OR heat* OR thermal*) AND (meibomian OR MGD OR eyelid OR "dry eye" OR DED)".
5. **Inclusion Criteria (circle all that apply)**
   General inclusion philosophy: We included all relevant peer-reviewed, English language, full-text articles found in PubMed.
6. **Exclusion Criteria (circle all that apply)**
   General exclusion philosophy: Abstracts and nonpeer reviewed articles were excluded, as well as articles not available in English. All material was critically evaluated and therefor complete results needed to be available for review. We excluded case reports if they did not contribute to new information.

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Supplementary materials

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