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ORIGINAL RESEARCH

Effectiveness of Intranasal Tear Neurostimulation for Treatment of Dry Eye Disease: A Meta-Analysis

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ABSTRACT

Introduction: To assess the effectiveness and safety of intranasal tear neurostimulation in the treatment of dry eye disease.

Methods: We performed a meta-analysis of four databases from their inception to October 2022 without language restrictions. Randomized controlled trials and non-randomized controlled trials meeting the inclusion criteria were included in this review and were quality appraised. The risk of bias was evaluated by two independent reviewers using the Cochrane Collaboration Tool and Methodological Index for Non-Randomized Studies. The random-effect model or fixed-effect model was adopted to estimate the pooled effect sizes.

Results: Fifteen published studies consisting of 17 clinical trials with a total of 901 patients were analyzed. Schirmer II test scores were significantly higher after intranasal tear neurostimulation in patients with dry eye disease (mean difference = 14.12 mm, 95% confidence intervals (8.93, 19.31), $P < 0.001$). Intranasal tear neurostimulation increased the meibomian gland areas (mean difference = − 251.79 μm^2, 95% confidence intervals (− 348.34, − 155.23), $P < 0.001$), but no significant difference was found in meibomian gland perimeters before and after stimulation (mean difference = 3.72 mm, 95% confidence intervals (− 22.14, 29.59), $P = 0.78$). All adverse events were mild or moderate, and no serious adverse events were reported.

Conclusions: This meta-analysis provides promising evidence for the controversial effectiveness of intranasal tear neurostimulation in the treatment of dry eye disease, along with useful information for guiding intranasal tear neurostimulation in future clinical trials.

Trial Registration: This meta-analysis was registered on the Prospective Register of Systematic Reviews (PROSPERO) (CRD42021284214).

Keywords: Dry eye disease; Intranasal tear neurostimulation; Meta-analysis; Schirmer II test

Zihan Li and Xinglin Wang contributed equally to this work and share first authorship.

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Key Summary Points

Dry eye disease (DED) is one of the most common ocular surface disorders with varying severity and is characterized by a loss of homeostasis of tear film.

Intranasal tear neurostimulation (ITN) is a newly emerging approach for treating DED by delivering minute electrical currents to the anterior ethmoidal nerve, activating the nasolacrimal reflex and thus upregulating the body's natural tear secretion system.

ITN could improve the Schirmer test results and meibomian gland microscopic structures in DED subjects both in short- and long-term studies, with safety assurance for its clinical use.

This first meta-analysis verified that ITN was an effective and safe approach to treat DED both in the long and short term, and further elucidation of the application of ITNs at different intensities and frequencies was greatly in need.

INTRODUCTION

Dry eye disease (DED) is one of the most common ocular surface disorders with varying severity and is characterized by a loss of homeostasis of tear film [1]. The prevalence of DED ranges from 5 to 50% in individuals over the age of 50 [2]. The etiology includes tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities [1]. Patients with DED suffer from a series of clinical symptoms, including eye discomfort, ocular pain, and fluctuating and blurry vision [3], leading to a major decline in their quality of life. Current management for DED can be divided into three aspects: treatment for tear insufficiency, lid abnormalities, and anti-inflammatory therapy [4]. However, these therapies mostly focus on minimizing inflammation and optimizing various components of the tear film to alleviate symptoms [5], such as artificial tears, with only a few aiming to stimulate the associated glands and cells to secrete more natural tears [6].

Intranasal tear neurostimulation (ITN) is a newly emerged approach for treating DED by delivering minute electrical currents to the anterior ethmoidal nerve, which is the alternative afferent pathway to the corneal sensory nerves, activating the nasolacrimal reflex and thus upregulating the body's natural tear secretion system [7–9]. In recent years, a growing number of studies conducted on human subjects showed promising evidence that ITN could lighten the symptoms of DED with improvement of its diagnostic examination results [5, 10], such as the Schirmer test, tear break-up time (TBUT) and changes in functionality, such as meibomian gland parameters on morphological examination.

Despite the new approval of a novel intranasal tear neurostimulator by the United States Food and Drug Administration (FDA), there is no agreement on the recommended frequency and volume of stimulation current, and a comprehensive analysis regarding the safety and efficacy of ITN is still lacking. Here, we conducted a meta-analysis with all available studies to fully evaluate the effectiveness of ITN by the Schirmer II test and meibomian gland parameters. The safety of ITN was also assessed with the incidence of different adverse events (AEs) in this study.

METHODS

This meta-analysis was registered on the Prospective Register of Systematic Reviews (PROSPERO) (CRD42021284214) [11] and performed strictly in accordance with the guidelines presented by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12]. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Literature Search Strategy

We systematically searched four databases, including PubMed, Embase, Cochrane Library databases, and Web of Science, for relevant publications from their inception to October 2022. The following keywords were adopted: "(Tear Stimulation OR Neurostimulation) AND (Dry Eye Disease OR Xerophthalmia OR Keratoconjunctivitis Sicca OR Dry Eye OR Ocular Surface Disease Index OR Schirmer Test)". No language restrictions were applied. In addition, the reference lists of relevant studies were manually reviewed to identify potentially eligible studies. The titles and abstracts were screened by two independent reviewers to identify relevant articles. When disagreement on enrollment of a particular article was present, both reviewers were provided with full text of the study to find more details on the research design to reach a consensus. After screening the titles and abstracts, we downloaded the full-text of relevant articles to collect studies that met the inclusion criteria.

Inclusion and Exclusion Criteria

Studies were considered eligible if they met the inclusion criteria in terms of the following aspects: (1) study types: randomized controlled clinical trials (RCTs) and non-randomized controlled clinical trials (non-RCTs); (2) participants: adults of any sex and age diagnosed with DED due to ocular symptoms and signs [13, 14]; (3) intervention: intranasal tear neurostimulation were given less than 3 min at the front areas of the nasal mucosa; and (4) outcomes: at least one among Schirmer II test, tear break-up time (TBUT), Ocular Surface Disease Index (OSDI), visual analog scale (VAS), tear meniscus height (TMH), or meibomian gland (MG) areas and perimeters were reported in the study. Reviews, meta-analyses, duplicate publications, full texts lacking available raw data and studies with animal subjects were excluded.

Data Extraction, Quality and Assessment of Risk of Bias

Two independent reviewers extracted data from the included trials with a standardized Microsoft Excel form and rechecked them after the first extraction. The following data were extracted from all eligible studies: first authors, publication year, journal, country, study design, methods of intervention, number of participants, mean age and sex of participants, follow-up time, clinical outcomes and number of patients reporting adverse events. To assess the effectiveness of ITN, the clinical outcomes included three parts: diagnostic examination results (Schirmer test or TBUT), ocular symptom evaluations (ODSI or VAS score), and functional improvements (TMH, MG areas and perimeters). If any basic information or outcomes were unclear or deficient, we would ignore these incredible data.

The quality of each article was also assessed by two independent reviewers using the Cochrane Collaboration Tool [15] and Methodological Index for Nonrandomized Studies [16] (MINORS). The Cochrane Collaboration Tool was used to assess the bias of randomized controlled trials. The reviews assessed the following seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each item was judged as "low risk", "unclear risk", and "high risk" based on the full text of each study. We used MINORS to assess nonrandomized trials. Each of the 11 items can score 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The maximum score was 16 for nonrandomized studies, and a higher score indicated better quality. All disagreements were resolved by discussion or by calling in a senior reviewer for arbitration.

Statistical Analysis

We used the RevMan (Version 5.4) software package to perform this meta-analysis. For all variables, mean differences (MDs), standard

differences (SDs) and 95% confidence intervals (CIs) were calculated. The effect size of all results was represented by means with SD. Statistical heterogeneity between studies was assessed using the I^2 test. A random-effect model was used to pool the data when there was significant heterogeneity, indicating that I^2 was greater than 50%; otherwise, a fixed-effect model was used. A sensitivity analysis was performed by removing each study in turn to investigate the impact of individual studies and to test the stability of the pooled results. The results would be shown in the forest plots and line chart.

RESULTS

Literature Search and Study Characteristics

Using the search strategy of "(Tear Stimulation OR Neurostimulation) AND (Dry Eye Disease OR Xerophthalmia OR Keratoconjunctivitis Sicca OR Dry Eye OR Ocular Surface Disease Index OR Schirmer Test)", a total of 1070 studies were obtained, with 427 in PubMed, 89 in Embase, 102 in Cochrane Library, and 452 in Web of Science. After 248 duplicated studies being excluded, 746 studies were further excluded for the following reasons: reviews, meta-analyses and patent (n = 144), studies not relevant to subjects (n = 412), trials conducted on animal subjects (n = 149), trials lacking data (n = 34), and studies without intranasal neurostimulation implementation (n = 7). More details of the selection process can be found in Fig. 1.

In the final sample, we retained the results of 901 subjects pooled from 15 studies, which consisted of 17 clinical trials, with eight of seventeen RCTs and the rest on non-RCTs. According to the descriptions of the study design and the locations of the institutional review board, we found that most studies (16 of 17) were performed in America, and the remaining one was performed in Australia. The sample sizes of the trials varied from 10 to 185, and the majority (73.8%) of the subjects were female. The characteristics of each study were listed in Table 1. The rate of loss to follow-up was 2.1%. Ten clinical trials used the TrueTear as the intervention and the detailed information on the devices and methods of ITN were listed in Table S1.

Quality Assessment

The risk of bias assessment for eight included RCTs was performed using the Cochrane Collaboration Tool by two individual reviewers. Five studies were assessed as having a low risk of selection bias [17–21], while the others were assessed as having an unclear risk [22–24]. For detection bias, reporting bias and other bias, all trials had unclear risk. More detailed information is shown in Fig. 2A.

The Methodological Index for Nonrandomized Studies (MINORS) was used to assess the quality of nine non-RCTs, and the results are shown in Fig. 2B. Total scores ranged from 12 to 15, which was of high quality. All trials received 'two points' for Questions 1, 2, 3 and 8. Farhangi [25], Green [26], Passi [27] and Sheppard [20] received '0 points' for question 5.

Schirmer II Test

The Schirmer II test was used in these studies to evaluate changes in dry eye condition between pre- and poststimulation. Six studies had detailed patient parameters on the Schirmer II test before and after one stimulation. In three long-term trials, pre- and poststimulation Schirmer II test data were collected on day 0, day 7, day 14, day 30, day 60, day 90 and day 180.

The forest plot (Fig. 3A) showed that there was a significant difference between the pre- and poststimulation values. The mean difference was 14.12 mm, and the 95% CI was from 8.93 to 19.31 mm ($P < 0.001$). There was heterogeneity among these studies (I^2 = 95%), so a random-effect model was applied for analysis. In these 6 trials, the highest mean difference was 19.80 mm, and the 95% CI was from 16.51 to 23.09 mm in Patter's [23]; the lowest mean difference was 7.10 mm, and the 95% CI was from 5.83 to 8.37 mm in Lilley's study [21].

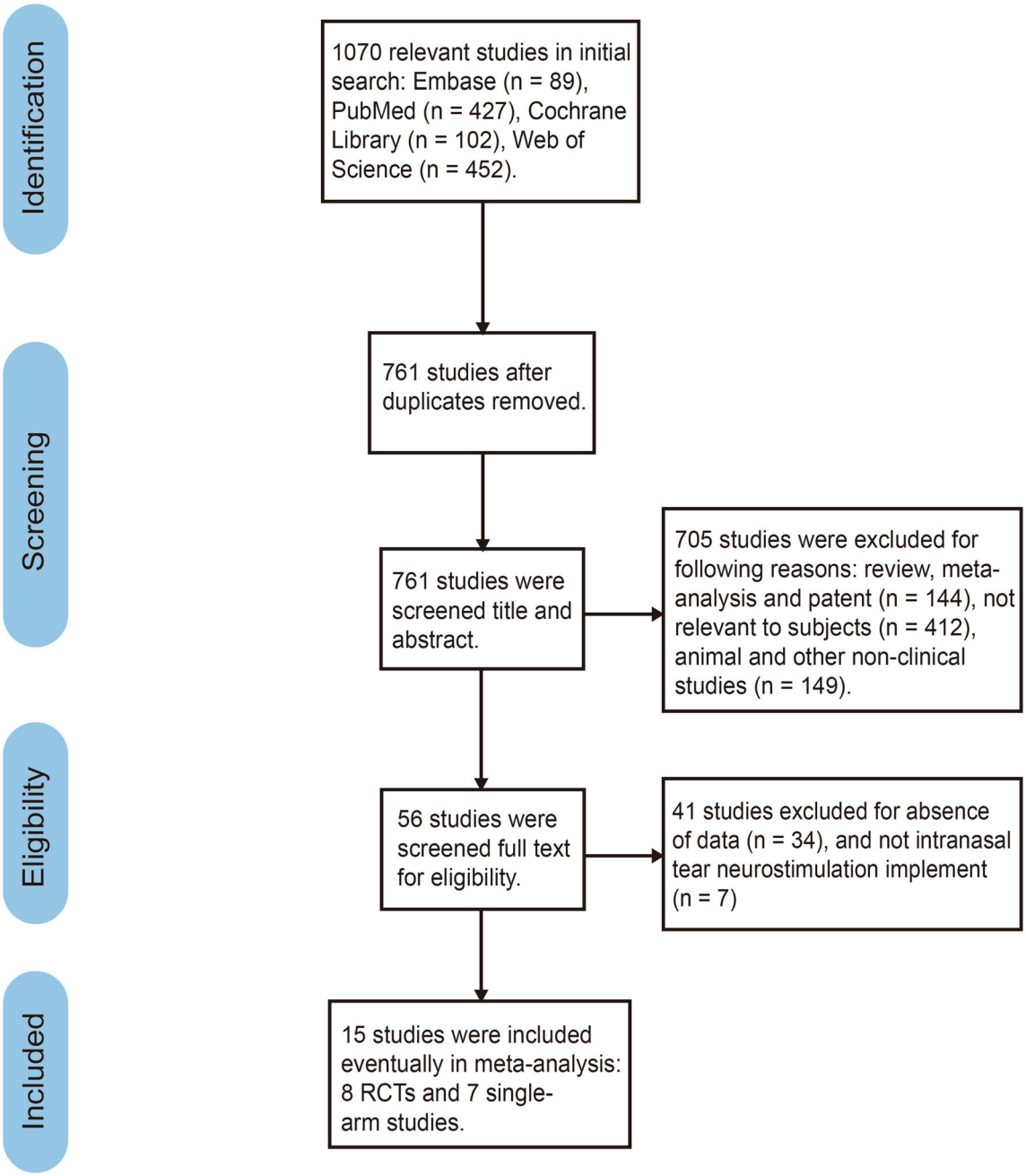


Fig. 1 Flow chart of studies collection process

For the sensitivity analysis, omitting each study showed no changes in the significant output from the meta-analysis for the Schirmer II test. The mean difference ranged from 12.95 mm (95% CI (7.76 mm, 18.14 mm), $P < 0.001$) to 15.65 mm (95% CI (11.43 mm, 19.87 mm), $P < 0.001$).

In long-term studies, 226 patients participated in the long-term studies. They spent at least 90 days and no more than 180 days using intranasal neurostimulation, and their Schirmer II test data were recorded at marked timing. All groups observed significant differences between pre- and poststimulation on each follow-up day.

Table 1 Description of the characteristics of included studies

Study	Region[a]	Study type	N, *n*	Male/female, *n*/*n*	Follow-up time (days)
Cohn (2018) [18]	Australia	RCT	32	5/27	90
Dieckmann (2017) [37]	America	Non-RCT	15	NA	1
Farhangi (2020) [25]	America	Non-RCT	75	55/20	1
Friedman (2016) [35]	America	Non-RCT	40	6/35	180
Green (2017) [26]	America	Non-RCT	55	NA	1
Gumus (2017) [19]	America	RCT	10	1/9	1
Lilley (2021) [21]	America	RCT	35	0/35	1
Orrick (2017) [22]	America	RCT	25	NA	1
Passi (2020) [27]	America	Non-RCT	21	4/17	1
Patter (2020) (1) * [23]	America	RCT	185	47/138	1
Patter (2020) (2) [23]	America	Non-RCT	57	14/43	45
Pondelis (2017) [36]	America	Non-RCT	12	NA	1
Pondelis (2020) [30]	America	Non-RCT	15	5/10	1
Senchyna (2018) [17]	America	RCT	185	44/141	1
Sheppard (2019) (1) # [20]	America	RCT	16	9/39	1
Sheppard (2019) (2) [20]	America	Non-RCT	97	18/71	180
Watson (2017) [24]	America	RCT	25	NA	1

NA not applicable, *RCT* randomized controlled trial, *non-RCT* non-randomized controlled trial

[a]Where the study was conducted according to the descriptions of its study design and the locations of the institutional review board

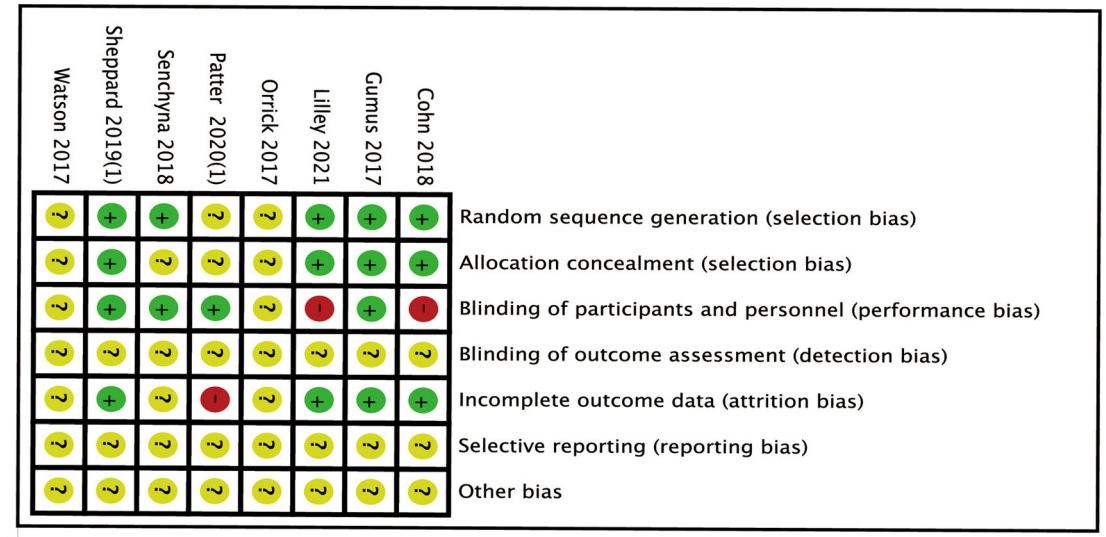
*,#These two articles included two clinical studies and each was separated into two trials

Detailed information on pre-stimulation mean Schirmer II test scores was as follows: D0 = 7.89 mm, D7 = 8.16 mm, D14 = 9.58 mm, D30 = 9.27 mm, D60 = 11.30 mm, D90 = 8.63 mm, and D180 = 9.42 mm. The mean Schirmer II test scores poststimulation on each follow-up day were D0 = 24.81 mm, D7 = 20.94, D14 = 18.23, D30 = 17.29, D60 = 17.30, D90 = 16.83, and D180 = 18.12. The line chart was shown in Fig. 4.

Meibomian Gland (MG) Areas and Perimeters

Two trials reported pre- and poststimulation data of meibomian gland (MG) areas and perimeters. For MG areas, there was no significant difference between the studies by the heterogeneity test ($I^2 = 0$). The differences between pre- and post-stimulation were statistically significant using a fixed-effect model. The mean difference was − 251.79 μm^2, and the 95% CI was from − 348.34 to − 155.23μm^2 ($P < 0.001$) (Fig. 3B). For MG perimeters, there was heterogeneity in these studies ($I^2 = 68\%$), and a random-effect model was applied to perform the meta-analysis. No differences were found between pre- and post-stimulation. The mean difference was 3.72 μm, and the 95% CI was from − 22.14 to 29.59 mm ($P = 0.78$) (Fig. 3C).

A



B

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total
Dieckmann	2	2	2	2	2	1	2	2	15
Farhangi	2	2	2	1	0	1	2	2	12
Friedman	2	2	2	2	1	2	1	2	14
Green	2	2	2	2	0	1	2	2	13
Passi	2	2	2	1	0	1	2	2	12
Patter (2)	2	2	2	2	1	2	2	2	15
Pondelis 2017	2	2	2	2	2	1	2	2	15
Pondelis 2020	2	2	2	2	2	1	2	2	15
Sheppard (1)	2	2	2	2	0	2	1	2	13

Non-RCT, nonrandomized controlled trial. MINORS, Methodological index for nonrandomized studies.

Fig. 2 Quality assessment of included studies. **A** Risk of bias for RCTs: reviewers' judgements about each bias item for each included RCT. **B** Quality scoring component for the nine included non-RCTs

Adverse Events

Adverse events (AEs) were mentioned in seven studies, with a total number of 72 patients who had at least one AE throughout the experiments (Table 2). All AEs were mild or moderate, and no serious AEs were reported, whereas six subjects (1.1%) discontinued the study due to AEs. The 7 included studies reported device-related AEs in details and Table 2 lists some device-related AEs of which the percentage was above 0.5%, including nasal discomfort (n = 15, 2.7%), nosebleed (n = 12, 2.1%), headache (n = 9, 1.6%), transient electrical discomfort (n = 6, 1.1%), trace blood (n = 6, 1.1%), electric jolt (n = 3, 0.5%), and nasal congestion (n = 3, 0.5%). Nasal discomfort (n = 15, 2.7%) was the most common AE observed in 3 trials.

DISCUSSION

Intranasal tear stimulation is a newly emerging approach for treating DED. This meta-analysis consisting of 15 clinical trials aimed at investigating the effectiveness and safety of ITN in the

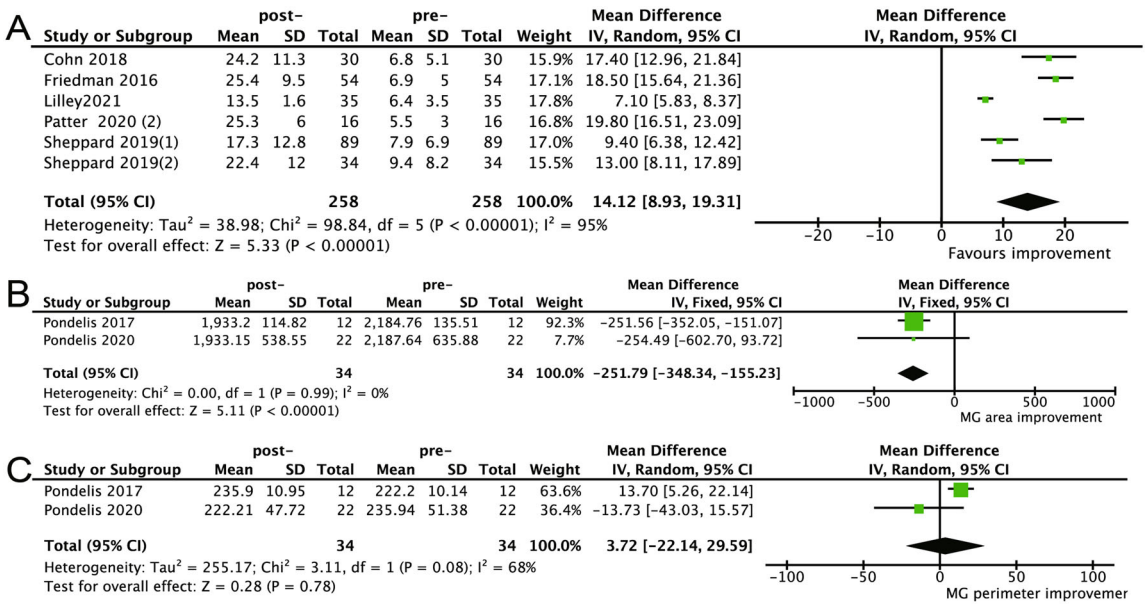


Fig. 3 Forest Plot in studies that compared pre- with post-stimulation. **A** Forest plot of changes in Schirmer II test. **B** Forest plot of changes in meibomian gland area. **C** Forest plot of changes in meibomian gland perimeter

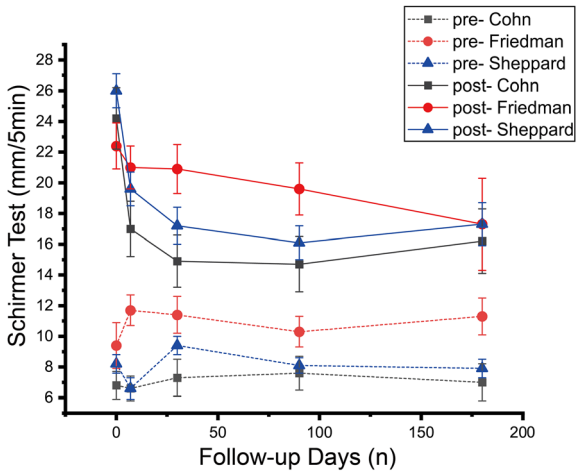


Fig. 4 Line chart of the long-term studies comparing pre- with post-stimulation Schirmer II Test. The same shape represents the same study. The *solid line* represents data of pre-stimulation and the *dotted line* represents data of post-stimulation

management of DED and demonstrated that ITN could improve the Schirmer II test results and meibomian gland microscopic structures in DED subjects, with safety assurance for its clinical use.

Two related studies on animals have investigated whether long-term ITN should treat dry eye disease by stimulating the anterior ethmoid nerve [28, 29]. The anterior ethmoid nerve, which is located at the upper nasal mucosa [30], is an accessory afferent pathway that contributes to tearing and replaces the sensory receptor of lacrimal functional unit (LFU)—a tear-secreting apparatus which is a vital part in the homeostasis of ocular surface by retaining the stability and integrity of the cornea and conjunctiva [7, 31], The external stimuli generated by ITN is transmitted onto the trigeminal nerve, through the trigeminal nucleus in the brain stem and reach the efferent part of the loop which embodies parasympathetic and sympathetic fibers [31–33]. Secretion of mucin, aqueous and lipid is elevated after ITN stimulation under the moderation of these secretomotor parasympathetic postganglionic nerves [3, 8, 34]. The intranasal tear neurostimulator named TrueTear was approved by FDA in 2017 and has been widely used in the experimental studies and in the treatment of DED in clinic. Three randomized controlled clinical trials [19, 20, 23] reported the efficiency of TrueTear in different outcomes, including Schirmer test

Table 2 Adverse events and discontinuations due to AEs

	All subjects (n = 561)
Adverse events (device-related)	
Number of AEs	72
Number (%) of at least one AE	59 (10.5%)
Nasal discomfort	15 (2.7%)
Nosebleed	12 (2.1%)
Headache	9 (1.6%)
Trace blood	6 (1.1%)
Transient electrical discomfort	6 (1.1%)
Electric jolt	3 (0.5%)
Nasal congestion	3 (0.5%)
Discontinuations due to AEs	6 (1.1%)

AE adverse events

both in long- and short-term, OSDI and changes of meibomian parameters and whole surrounding outcomes announced great improvement of dry eye condition as well as the relief of clinical symptoms. However, being limited by the specific device of this treatment, only a few patients can benefit from it and the high production cost is such a burden for both patients and Allergan.

Despite the consistent conclusion that ITN could alleviate patients' ocular suffering under the burden of DED, both subjective and objective parameters used in the evaluation of the effectiveness of ITN still varied in recent studies [10]. Friedman [35] reported the first clinical study on ITN in 2016, which enrolled 40 patients in a prospective, single-arm study and used the Schirmer II test, TBUT and VAS as outcomes to demonstrate ITN effectiveness. Six other studies used the OSDI to evaluate ocular symptoms. The quantified assessment of DED has become more diverse, and many novel parameters have been introduced in the evaluation of ITN effectiveness. In 2017, Pondelis [36] conducted a study assessing ITN efficacy by comparing changes in meibomian gland perimeters and areas pre- and post-stimulation; and perfected the trial in 2020 [30]. Green [26], Gumus [19], and Orrick [22] used TMH as a new assessment tool, and it underwent an increase of 28–166% following the use of ITN; in Gumus's [19], Green's [26] and Dieckmann's [37] studies, immunofluorescence staining, tear total lipid concentration and morphological analysis were used to qualify goblet cells and meibomian glands. The diversity of metrics in the estimation of ITN effectiveness is in line with the diagnosis of DED, which is greatly based on subjective symptoms and lacks the golden unbiased standard.

To overcome this dilemma, we applied the most-used parameter, Schirmer II test, as a unified standard to validate the effectiveness of ITN while accommodating the inadequate number of related studies. Changes in Schirmer test between pre- and post-stimulation of ITN were analyzed and the mean difference was 14.12 mm (95% CI 8.93–19.31 mm, $P < 0.001$), which showed significant difference following the use of ITN and verified the evidently positive impact of short-term ITN use. Besides, some longitudinal studies were enrolled to estimate the effectiveness of daily application of long-term ITN use. The gap between pre- and post-ITN Schirmer test results was analyzed at each follow-up, ranging from 6.00 to 16.92 mm. It is noteworthy that the 'instant effect' of ITN facilitated tear production profusely in the first 2 weeks, which stabilized at a level slightly greater than day 0. A reasonable hypothesis for this interesting fact is that the immediate response of tear production is aroused by the combination of mechanism stimulation and neurostimulation, and in time, the body eventually adapts to the insertion of ITN equipment and its electric signals after the 2-week period [18, 20].

Moreover, in this meta-analysis, we first assessed the safety of ITN in a systematic way by analyzing the categories, frequency, percentage of whole events and discontinuations: adverse events were separated into device-related and non-device-related events, and we noticed that nose-related adverse events, such as nasal discomfort (n = 15, 2.7%), nosebleed (n = 10, 1.7%), and runny nose (n = 2, 0.3%), were the main parts.

There were some limitations of this meta-analysis. First, except for 8 RCTs, several studies included in this review used single-arm, open-label trials, which provided evidence at a lower level. Some selection bias is inevitable, and readers should apply caution when utilizing our uncertainty because of the biases of non-RCTs. For those RCTs, as with any meta-analysis, there were some factors that influenced our research results and great heterogeneity was observed in this meta-analysis because of the different controlled settings and eligible criteria. Furthermore, we could only include published studies that introduced publication bias, and it is inevitable that data collected in the same clinic center are duplicated and used in different trials. Third, subgroup analyses of stimulation intensity, length, and frequency were lacking in this meta-analysis but should be performed in future trials, and although we assessed the Schirmer test and meibomian gland parameters, the evaluation of changes in ocular symptoms was not included. Thus, the evidence we provided was limited and not sufficient.

CONCLUSIONS

This meta-analysis verified that ITN was an effective and safe approach to treat DED both in the long and short term. This preliminary yet promising application should be further validated at different intensities and frequencies in future studies, with unified and solid assessment tools for DED.

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Author Contributions. Zihan Li and Xinglin Wang participated in the design and review of the meta-analysis; Zihan Li collected and analyzed the data and generated the figures; and Xinglin Wang assisted in the data collection and literature screening. All authors (Zihan Li, Xinglin Wang, Xuemin Li) were involved with the manuscript development and reviewed and approved the final version of the manuscript.

Disclosures. Zihan Li, Xinglin Wang, and Xuemin Li declare that they have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. All data generated or analyzed during this study are included in this published article. The data that support the findings of this study are available from the corresponding author, Xuemin Li, upon reasonable request.

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