Acupoint selection for the treatment of dry eye: A systematic review and meta-analysis of randomized controlled trials

QING-BO WEI1,2, NING DING1,2, JIAO-JIAO WANG1,2, WEI WANG3 and WEI-PING GAO1,2

1Ophthalmology Department of Traditional Chinese Medicine, The First Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210023; 2Ophthalmology Department, The Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210029, P.R. China; 3School of Healthcare Sciences, Cardiff University, Cardiff, CF10 3AT, UK

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Abstract. The effectiveness of acupuncture in the treatment of dry eye has been confirmed, but the association between acupoint selection and therapeutic effect has remained to be elucidated. In the present study, a systematic review and meta-analysis were performed to evaluate the effect of periocular acupoints and periocular acupoints plus body acupoints compared with AT for the treatment of dry eye disease (DED). The primary outcomes, including tear break-up time (BUT), Schirmer’s I test (SIT) result and Symptom scores were analyzed. A total of 12 studies comprising 900 participants were included. In the primary meta-analysis, a significant improvement in the BUT (95% CI: 0.56-1.84, P<0.00001) and SIT result (95% CI: 1.33 to -0.72, P=0.0001) was obtained to evaluate the clinical efficacy of acupuncture and AT. Furthermore, periocular acupoints plus body acupoints were more effective in the treatment of DED. However, the total sample size of subjects with only periocular acupoints in the treatment of DED was too small to get any firm conclusions. Further large RCTs are warranted.

Introduction

In 2017, the Tear Film and Ocular Surface Society International Dry Eye Workshop II revised the definition of dry eye disease (DED) and pointed out that its major pathology includes tear film instability, hyperosmolarity, ocular surface inflammation, damage and neurosensory abnormalities (1). Multiple risk factors for the development of dry eye have been repeatedly identified, including increasing age and female sex (particularly post-menopausal females) (2,3) long-term contact lens wear, (4) months after laser-assisted in situ keratomileusis (LASIK), (5) prolonged use of video display screens, (6) and exposure to dry environments (8). Due to the decrease of tear film stability and the high osmolarity of tears, patients may complain of burning, pricking, foreign bodies, tearing, eye fatigue and dryness (9,10).

DED has been one of the most common and prevalent eye disorders for which ophthalmological intervention is sought (11). Several studies have revealed that the prevalence of DED ranges from 2 to 50% in different regions of the world, with a higher incidence among older adults and females, particularly menopausal and post-menopausal females (4,12-14). The number of patients with DED has consistently increased in recent years (15,16). As the population ages and the use of VDTs increases, the direct and indirect cost of managing DED exerts enormous pressure on the health care system (17). It has been reported that the annual economic burden of DED in the US is $55.4 billion dollars (18).

Belmonte and Gallar (19) reported that weakening of nerve stimulation function and a decrease in tear secretion produced corneal surface dryness. Decreased tear secretion, coupled with loss of epithelial cell viability, leads to a decrease...
in ocular surface neurotrophins. Nerve growth factor, a vital component of neurotrophins, is essential for the development and survival of sympathetic neurons. It also has a significant role in nutritional support after nerve injury (20). Tear evaporation has a crucial role in the pathogenesis of DED. It decreases the corneal temperature and repeatedly stimulates the cold-sensitive corneal nerves. Continuous long-term stimulation changes the function of thermal sensors to nociceptors (pain sensors) (21).

Acupuncture is widely known as one of the common forms of complementary and alternative medicine. A large number of randomized controlled trials (RCTs) and systematic reviews have indicated that acupuncture is effective in the treatment of various conditions, including vomiting, dental pain, chronic pain, lower back pain and eye disease (22-25). In addition, several systematic reviews have confirmed that acupuncture is effective for DED (26-28). Lee et al (26) reported that the effect of acupuncture on dry eye was better than that of artificial tears (AT) as indicated by the results of Schirmer's I test (SIT), tear break up time (BUT) test, response rate and corneal fluorescein staining (CFS). The study by Kim et al (27) is principally based on the analysis of results of SIT, BUT and Ocular Surface Disease Index (OSDI) (28), and confirmed that acupuncture was more effective than AT in the treatment of dry eye. Subgroup analysis was also performed to further prove the efficacy of acupuncture. Yang et al (29) indicated the effectiveness of acupuncture in the treatment of dry eye by comparing the results of SIT and the BUT prior to and after treatment. Acupuncture has been proven to promote the secretion of tears, relieve discomfort and improve visual function by modulating ocular surface inflammation in DED (30, 31). However, to the best of our knowledge, no systematic summary of the therapeutic effect of multi-acupoint selection on DED has so far been provided. Therefore, a systematic review and meta-analysis were performed in the present study to evaluate the efficacy of periorcular acupoints, as well as periorcular acupoints plus body acupoints, with the latest literature on DED. On this basis, it was attempted to determine the optimal acupoints for acupuncture treatment of DED.

Materials and methods

Databases and search strategy. The PubMed, Cochrane Library, Embase, Ovid, China National Knowledge Infrastructure (CNKI), Chongqing VIP Information, Co., Ltd. (CQVIP) and Wanfang databases were searched from inception through to 10 July 2018. CNKI, CQVIP and Wanfang are Chinese databases. The following medical search terms were used: ‘dry eye’, ‘dry eye syndrome’, ‘ophthalmoxerosis’, ‘keratoconjunctivitis sicca’, ‘xerophthalmia’, ‘acupuncture’, ‘electroacupuncture’, ‘Gan Yan’ (DED), ‘Gan Yan Zheng’ (DED), ‘Zhen Jiu’ (acupuncture and moxibustion), ‘Zhen Ci’ (acupuncture) and ‘Dian Zhen’ (electroacupuncture). To identify additional articles, reference lists of selected reviews and studies were manually searched. There were no language restrictions.

Study selection. The two authors independently selected eligible studies and discussed any emerging inconsistencies amongst each other. The specific study inclusion criteria were as follows: i) RCTs of patients with DED; ii) acupuncture or electroacupuncture compared with several alternatives, including AT, other non-acupuncture therapies or conventional treatment; iii) acupuncture treatment combined with other interventions (including AT or other non-acupuncture therapies) and comparison with the other interventions; iv) outcomes included SIT results, BUT, Symptoms score, CFS and visual analogue scale (VAS); and v) full text available.

Studies fulfilling the following criteria were excluded: i) Participants with Sjögren's syndrome; ii) acupuncture combined with other treatments, including Chinese herbal, warming-promotion needling and moxibustion, including thunder-fire miraculous moxa; ii) control group treated with acupuncture therapy only or combined with other interventions (including AT or other non-acupuncture therapies); iv) animal studies or studies lacking a control group, or articles published as case reports, reviews, commentaries or letters.

Data extraction and risk of bias assessment. Two independent reviewers (QBW, ND) read the full texts of all selected articles and used a standardized collection form to extract the following content: First author name and year of publication, participant information, sample size, study selection (inclusion and exclusion criteria), treatment protocol (acupoints, duration, treatment sessions and frequency of treatment) and major outcome data (BUT, SIT results, Symptoms score, CFS, OSDI and VAS).

The risk-of-bias assessment of the included RCTs was independently performed according to the Cochrane Collaboration Tool (31). The following items were included in the risk-of-bias assessment: Random sequence generation, allocation concealment, blinding (participants and personnel, outcome assessment), incomplete outcome data, selective reporting and other biases (31). Two reviewers (QBW, ND) independently assessed the quality of the articles and discussed any emerging inconsistencies with a third reviewer (JJW).

Data synthesis and statistical methods. The statistical software Review Manager 5.3 for Windows (provided by the Cochrane Collaboration) was applied for data synthesis and statistical analysis. To evaluate the effect of acupoint selection on DED, the weighted mean difference (WMD) with 95% CIs were used to analyze subgroup continuous data. Heterogeneity in studies was assessed using the $\chi^2$ test and Higgins I² test (32). A fixed-effect model was used for homogeneity (considered significant at $P>0.1$); a random-effect model was used for heterogeneity ($P<0.1$).

Results

Search results. A total of 484 entries of potential relevance were identified from the database search. After excluding duplicate studies, screening of article titles and abstracts, 59 potentially relevant studies were retrieved. After reviewing the full texts, 47 studies were excluded for the following reasons: i) Clinical trials but not RCTs (n=20); ii) studies including patients Sjögren's syndrome as participants (n=16); iii) commentaries (n=2); iv) outcome assessment did not meet the inclusion criteria (n=3); v) inadequate data (n=4); vi) acupuncture or electroacupuncture used in the control groups (n=2). A flow
A total of 12 studies with 900 participants were included in this review. A majority of the studies compared manual acupuncture with AT (33-43). An applied form of acupuncture was used in 4 of the studies, including 1 study using silver spike point electro-therapy (35), 1 study using electroacupuncture (44) and 2 studies using combined acupuncture at the phenomaxillary ganglia with acupoints (41,42). Participants in the study by Zeng et al (40) were patients who experienced DED for >1 month after LASIK. Furthermore, 2 studies focused on DED in post-menopausal or peri-menopausal females (38,43). Regarding the sensation of acupoints, 4 studies reported on de-qi (soreness, numbness, sensation of heaviness or swelling) associated with the needling (35,37,40,44). A total of 10 of the studies were performed in China (34-36,38-44). Detailed descriptions of the studies and the acupuncture treatments are provided in Tables I and II.
Table I. Baseline characteristics of the randomized controlled trials included in the meta-analysis that investigated the effects of acupuncture in dry eye disease.

| First author (year) | Country | Sample size* | Gender (M/F) | Mean age (range) | Duration (m or y)** | Treatment regime in intervention group | Treatment regime in control group | Major outcomes (Refs.) |
|---------------------|---------|--------------|--------------|------------------|---------------------|----------------------------------------|-------------------------------|------------------------|
| Nepp (1998)         | Austria | 52 (30/22)   | NA           | NA               | NA                  | Acupuncture                          | AT                            | BUT, SIT, drop frequency (33) |
| Wang (2005)         | China   | 45 (15/15/15)| Intervention 1 (7/8) | Intervention 1: 51.7 (27-75) | Intervention 1: 6m-10y | Acupuncture                          | AT                            | BUT, SIT, and CFS (34) |
| Tseng (2006)        | China (Taiwan) | 43 (17/17/9) | Intervention 1 (4/13) | Intervention 1: 52.24 | Intervention 1: 2.65±1.80 y | Intervention 1: SSP + AT, Intervention 2: Acupuncture + AT | AT | BUT, SIT, VAS, overall score of eye condition (35) |
| Shi (2012)          | China   | 68 (33/35)   | Intervention 1 (14/19) | Intervention 1: 47.4 (29-63) | NA                  | Acupuncture                          | AT                            | Eye condition, ST, BUT, tear lactoferrin (36) |
| Kim (2012)          | South Korea | 150 (75/75) | Intervention 1 (22/53) | Intervention 1: 47.95 | NA                  | Acupuncture                          | AT                            | OSDI, VAS, BUT, SIT, QOL (37) |
| Liao (2013)         | China   | 40 (0/40)    | Intervention 1 (0/20) | Intervention 1: 47.95 | NA                  | Acupuncture + AT                      | AT                            | BUT, SIT, symptoms score, VRQOL (38) |
| Nan (2014)          | China   | 60 (30/30)   | Intervention 1 (12/18) | Intervention 1: 47.56 | Intervention 1: 9.15 m (2 m-8 y) | Intervention 1: SSP + AT | AT | Eye acupuncture + AT, ST, BUT, total score (39) |
| Zeng (2014)         | China   | 52 (28/24)   | Intervention 1 (13/15) | Intervention 1: 47.56 | Intervention 1: 4-14 | Acupuncture + AT                      | AT                            | BUT, SIT, FLS (40) |
| Shang (2015)        | China   | 148 (72/76)  | Intervention 1 (40/32) | Intervention 1: 47.56 | Intervention 1: 4-14 | Acupuncture + AT                      | AT                            | Symptoms score, VAS (41) |
| Xiang (2016)        | China   | 88 (44/44)   | Intervention 1 (20/24) | Intervention 1: 47.56 | Intervention 1: 4-14 | Acupuncture + AT                      | AT                            | OSDI, BUT, SIT, FLS (42) |
| Liu (2017)          | China   | 28 (14/14)   | Intervention 1 (0/14) | Intervention 1: 47.56 | Intervention 1: 4-14 | Acupuncture + AT                      | AT                            | Symptoms score, BUT, SIT, FLS (43) |
| Huang (2013)        | China   | 126 (64/62)  | Intervention 1 (23/41) | Intervention 1: 47.56 | Intervention 1: 4-14 | Acupuncture + AT                      | AT                            | Symptoms score, BUT, SIT, FLS (43) |

*Sample size (number in intervention group/number in control group). NA, not available; AT, artificial tears; SIT, Schirmer’s I test; BUT, tear break-up time; CFS, corneal fluorescein staining; OSDI, ocular surface disease index; VAS, Visual Analogue Scale; QOL, Quality of Life; VRQOL, vision-related quality of life; SSP, silver spike point; M, male; F, female; m, months; y, years. **Duration: median (range), mean ± SD, range.
Table II. Details of acupuncture treatment characteristics of the randomized controlled trials included in the present meta-analysis.

| First author     | Acupoints                                      | Duration of acupuncture (min) | Therapeutic course | Treatment frequency | Insertion depth | Needle type | De-qi |
|------------------|-----------------------------------------------|-------------------------------|--------------------|--------------------|-----------------|-------------|-------|
| Nepp (1998)      | Periocular acupoints: GB 1, BL 2, EX-HN2       | 30                            | Control: NA        | Intervention: 1 time per week; | 30 NA           | NA          | NA    |
| Wang (2005)      | Acupuncture: ST 5, LI 4, SI 3, LI 3, KI 6, TE 5 | 20-25                         | Control: NA        | Intervention: 1-3 times per week; | 20 NA           | NA          | NA    |
| Wang (2006)      | Periocular acupoints: ST 2, TE 23, GB 14, ST 1| 30                            | Control: NA        | Intervention: 1-3 times per week; | 30 NA           | NA          | NA    |
| Tseng (2006)     | Periocular acupoints: EX-HN5, TE 23, GB 14, ST 1| 30                            | Control: NA        | Intervention: 1-3 times per week; | 30 NA           | NA          | NA    |
| Shi (2012)       | Acupuncture: LI 11, LI 4, SP 6, KI 3, ST 2    | 20                            | Control: 3-4 times a day | Intervention: 2-3 times a day; | 20 NA           | NA          | NA    |
| Shi (2012)       | Acupuncture: EX-HN5, TE 23, GB 14, ST 1       | 30                            | Control: NA        | Intervention: 1-3 times per week; | 30 NA           | NA          | NA    |
| Shi (2012)       | Acupuncture: GB 1, BL 2, EX-HN5               | 30                            | Control: NA        | Intervention: 1-3 times per week; | 30 NA           | NA          | NA    |
| Nan (2014)       | Eye acupuncture: ST 1, BL 2, TE 23, GB 14     | 30                            | Control: NA        | Intervention: 1-3 times per week; | 30 NA           | NA          | NA    |
| Zeng (2014)      | Acupuncture: GB 1, LI 4, LI 11                | 30                            | Control: NA        | Intervention: 1-3 times per week; | 30 NA           | NA          | NA    |
| Liao (2013)      | Acupuncture: BL 1, BL 2, TE 23, GB 14, ST 1   | 30                            | Control: NA        | Intervention: 1-3 times per week; | 30 NA           | NA          | NA    |
| Liao (2013)      | Acupuncture: EX-HN5, TE 23, GB 14, ST 1       | 30                            | Control: NA        | Intervention: 1-3 times per week; | 30 NA           | NA          | NA    |
| Liu (2017)       | Periocular acupoints: BL 1, BL 2, TE 23, EX-HN5| 30                            | Control: NA        | Intervention: 1-3 times per week; | 30 NA           | NA          | NA    |

Total sample size (number in intervention group/control group); NA, not available/not specified; AT, artificial tears; EA, electroacupuncture.
A total of 10 studies were analyzed to compare the effect of periocular acupoints or periocular acupoints plus body acupoints with those of AT in patients with DED in terms of the results of the BUT test (34-40,42-44). Compared with the AT group, significant improvement was identified among the acupuncture groups (n=1,209, WMD=1.01, 95% CI: 0.49-1.53, P=0.0001). Of note, subgroup analysis indicated no significant advantage of periocular acupoint intervention (P=0.10), but there was a significant difference in periocular acupoints plus body acupoint intervention (P=0.0003; Fig. 4).

For the results of the SIT, 10 studies were used to compare the effect of periocular acupoints or periocular acupoints plus body acupoints with those of AT in patients with DED (34-40,42-44). Compared with the AT group, significant improvement was determined among the acupuncture groups (n=1,107, WMD=1.98, 95% CI: 0.44-3.34, P=0.01). The subgroup analysis indicated no significant difference in periocular acupoint intervention (P=0.07), but there was a significant difference in periocular acupoints plus body acupoints intervention (P=0.03; Fig. 5).

In addition, five studies were used to evaluate the Symptoms score (34,38,39,42,44). Compared with the AT group, the results indicated a significant difference among acupuncture groups (n=402, WMD=-1.02, 95% CI: -1.33 to -0.72, P<0.00001; Fig. 6).

**Discussion**

The purpose of the present systematic review and meta-analysis was to analyze the difference between each acupuncture modality group (periocular acupoints group and periocular acupoints plus body acupoints group) and the AT group. Although previous systematic reviews and meta-analyses have confirmed that acupuncture may effectively relieve DED (26-28), to the best of our knowledge, the present study was the first systematic review evaluating the therapeutic effects of multi-acupoint acupuncture on DED. In comparison with previous studies, stricter inclusion and exclusion criteria were adopted. After the selection process, the studies included were compared with those of the previous meta-analyses. Certain studies included in the previous meta-analyses were not included in the present study. The entire text of those studies was read and they were found unsuitable, principally because they included patients with Sjogren's syndrome and non-randomized controlled clinical trials. The present...
systematic review and meta-analysis initially included 11 RCTs comprising 848 patients with DED. The overall results indicated that acupuncture significantly improved the BUT, SIT results and Symptom scores compared with AT.

Although there are numerous predisposing factors and various clinical manifestations of DED, the major pathologies include hyperosmolarity, ocular surface inflammation and damage, tear film instability and neurosensory abnormalities (1). Tear film osmolarity has an important role in the pathogenesis of DED. It varies with the changes in internal and external factors, including body hydration, tear film stability, environmental conditions, blink interval, eyelid opening width and characteristics of tear film lipid layer (45). An increase in the osmolarity of the tear film is mainly caused by its excessive evaporation and reduced tear production (46-48). Exposure to tears with high osmolarity may lead to apoptosis of cells, loss of goblet cells, and dysfunction in corneal and conjunctival mucin expression. In addition, tear hyperosmolarity may activate a series of inflammatory events and contribute to further morphological changes in the cornea and conjunctiva. These changes may aggravate tear film instability and persistence of the condition (45,49,50).

In the theory of Traditional Chinese Medicine, acupoints are specific points that reflect the internal state of the body and regulate its function (51). The major purpose of acupoint stimulation includes the regulation of local and systemic effects. In the present study, the additional effect of stimulation of body acupoints in other parts of the body besides the periocular acupoints was examined, mainly for the purpose of distinguishing between the local therapeutic effects and remote sensing therapeutic effects. Histological investigations have confirmed that the local acupoints may be composed of the following parts: High-density nerve endings, high concentration of nerve and vascular elements, and mast cells, which have the function of perceiving stimuli (52). Zhang et al (53) proved that the skin resistance of acupoints in healthy individuals is significantly lower than that in non-acupoint areas. When the acupoints are stimulated, local biological molecules may be released, thus having a role in regulating the local effects (54). Studies have confirmed that acupuncture stimulates the afferent nerves of the skin and muscle at acupoints, and the somatic sensory information is then transmitted to the cerebral cortex and different nuclei of the brain stem and hypothalamus. At the same time, it may regulate the autonomic function of the body (55,56). Therefore, the combination of periocular acupoints and the body acupoints not only increases the local effects but also increases the local therapeutic effects but also increases the remote sensing therapeutic effects, which is more conducive to the treatment of dry eye.

Acupuncture therapy has a long history in the treatment of ophthalmic diseases. Systematic reviews have confirmed that acupuncture is effective in the treatment of myopia, amblyopia and optic atrophy (57-59). In recent decades, the use of acupuncture therapy for the treatment of DED has aroused interest and its efficacy has been actively explored (60). Although acupuncture treatment of dry eye has yielded encouraging results, rigorous clinical trials are required to confirm its therapeutic effect (26). Numerous studies have confirmed that acupuncture is useful for the treatment of dry eye, but the mechanism of action remains elusive. It is thought that acupuncture stimulates the lacrimal gland to secrete tears (61), promote corneal wound healing (62), reduce tension and reduce pain intensity or increase the pain threshold (63), regulate the autonomic nervous system and immune system (64,65), reduce local inflammatory response (43) and increase the flow velocity of the ophthalmic artery (66). Most of the acupuncture treatments for dry eye are based on the acupoints around the eyes, but there is no further research on the selection of acupoints. The most commonly used periocular acupoints include EX-HN5, BL1, GB1, BL2, ST1 and TE23.
Most clinicians still rely on conventional diagnostic tests, including the BUT test and SIT, for the diagnosis of DED (67). The measurement of tear film stability is usually performed by the BUT test (28), while the tear capacity is reflected by the SIT. Most patients seek ophthalmological intervention due to ocular discomfort. Although DED is usually diagnosed based on symptoms, there is no correlation between symptoms and signs of DED. The ability to quantify ocular surface symptoms helps to establish an additional medical assessment for dry eye. They have a critical guiding role in monitoring the development of DED and the prognosis after treatment (28).

Therefore, in the present meta-analysis, the BUT, SIT results and Symptoms score were used as the outcome indexes, which may reflect the effect of acupuncture treatment from different angles. The present meta-analysis indicated that the BUT and SIT result of patients with DED exhibited statistically improvement in the acupuncture group, and the treatment effect of periocular acupoints plus body acupoints was more efficient than that using periocular acupoints only. At the same time, the present meta-analysis indicated that the symptoms score of patients with DED exhibited statistically improvement in the acupuncture group.

The present study indicated that the acupuncture group exhibited significant improvements in BUT, SIT result and Symptoms score compared with those in the control group. However, high heterogeneity was noted in the BUT (I^2=91%) and SIT results (I^2=96%). To reduce the heterogeneity of the present results, the studies were screened more strictly than in previous meta-analyses, excluding those studies on patients with Sjögren's syndrome and on acupuncture combined with other treatments, including moxibustion, Chinese herbal medicine, warming-promotion needling or thunder-fire miraculous moxa. However, the problem of high heterogeneity was not completely resolved. Different acupuncturists, different AT and the frequency of AT administration are important contributors to the high heterogeneity and affect the evaluation of the present results.

The present systematic review and meta-analysis has several limitations. The RCTs included in the present study exhibited a variation in acupuncture intervention programs (including acupoint selection, duration of treatment and course of treatment) and patient characteristics (including age, sex, ethnicity, environment and severity of DED). Due to insufficient data from RCTs, it was impossible to perform in-depth investigations of specific changes. Thus, individual patient data are required for future meta-analyses. Further limitations include the lack of standard protocols and the lack of high-quality RCTs. Only three studies reported on adverse reactions to acupuncture in the treatment of dry eye (36,37,40). Follow-up evaluation of...
acupuncture treatment for dry eye is necessary (37). Although the present study confirmed that acupuncture is more effective than AT, the latter has the advantage of being convenient to use, while needling is time-consuming and inconvenient for most patients with DED. A previous study indicated that the effect of acupuncture lasts longer than that of AT (37). Further large-cohort studies are required to confirm the long-term efficacy of acupuncture treatment.

In conclusion, the present meta-analysis revealed that in terms of BUT and SIT results, the effect of acupuncture is better than AT. However, due to the relatively small sample size, short treatment duration, lack of a sham-acupuncture control and insufficient observation of long-term efficacy, further large-sample RCTs are required to evaluate the efficacy of acupuncture in the treatment of DED.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors’ contributions

Conception and design: WPG and QBW. Literature search and data extraction: QBW, WW, ND and JJW. Drafting of the manuscript: QBW and WW. Data interpretation and research supervision: WPG. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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