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Review article

Efficacy of bilateral OC-01 (varenicline solution) nasal spray in alleviating signs and symptoms of dry eye disease: A systematic review

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ABSTRACT

Purpose: To comprehensively review the efficacy and safety of OC-01 varenicline nasal spray versus vehicle nasal spray (VNS) in the treatment in dry eye disease (DED).

Methods: A systematic review that included full-length randomized controlled studies (RCTs), as well as post hoc analyses of RCTs reporting new findings on OC-01 VNS treatment in three databases, PubMed, Scopus and Web of Science, was performed according to the PRISMA statement. The search period included studies published between December 2021 and September 2023. The Cochrane risk of bias tool was used to analyze the quality of the studies selected.

Results: A total of 8 studies were included in this systematic review. OC-01 VNS treatment achieved higher improvement than vehicle in all reported variables. The mean differences between both groups were in favor of OC-01 VNS treatment and were as follow: eye dryness score base on a visual analogue scale (EDS-VAS) of −7.5 ± 2.2 points [-11.6 to −5.6], Schirmer test (ST) with anesthesia of 6.6 ± 2.3 mm [4.9 to 11.8] and total corneal fluorescein staining (tCFS) of −1.2 ± 0.01 points [-1.2 to −1.1]. Similar improvements were reported with OC-01 VNS 0.03 mg and 0.06 mg. Adverse events (AEs) were 15.5 ± 19.4 % [-13 to 80.5] higher in the OC-01 VNS group with an overall adherence > 93 %.

Conclusions: OC-01 VNS improves dry eye symptoms and signs with a satisfactory tolerability. Therefore, OC-01 VNS seems to be a safe and effective treatment that could be recommended in patients with DED. This new treatment could be particularly useful in those patients who have difficulties with the administration of traditional topical therapies.

1. Introduction

Dry eye disease (DED) is a prevalent and multifactorial condition characterized by an unstable and deficient tear film, resulting in discomfort, visual impairment, ocular surface epitheliopathy, inflammation, and neurosensory abnormalities [1,2]. The impact of DED on patients is substantial, affecting their visual function and quality of life [3,4]. Despite the existing therapeutic options, there remains a need for treatments that target the underlying pathophysiology rather than provide temporary symptom relief [5]. The autonomic nervous system, particularly the efferent parasympathetic and sympathetic nerves, plays a vital role in maintaining the ocular surface and tear film stability [6,7]. Activation of the trigeminal afferent nerves in the cornea, conjunctiva and the nasal cavity leads to stimulation of the efferent sympathetic and

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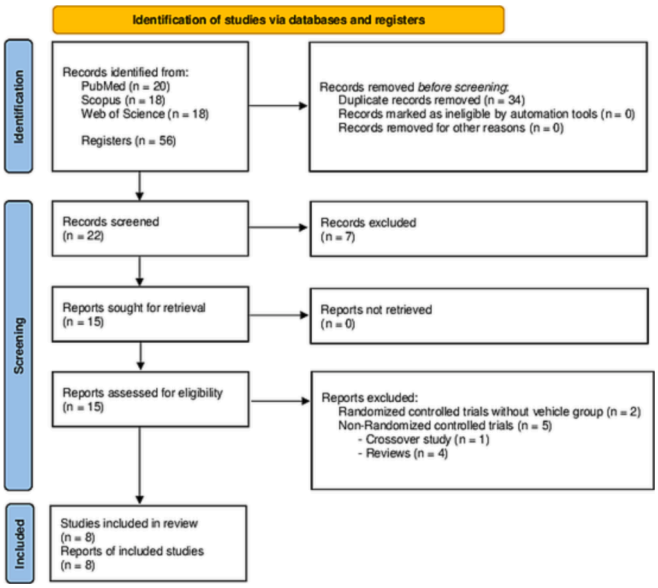

Fig. 1. Flowchart study selection process according to the PRISMA statement.

parasympathetic nerves in the facial nerve [8,9], as well as the trigeminal efferent parasympathetic nerves that innervate the lacrimal functional unit (LFU) [10,11].

Varenicline, a small-molecule nicotinic acetylcholine receptor (nAChR) agonist, has recently been approved as a preservative-free nasal spray (OC-01 VNS) for DED treatment [12]. When administered, OC-01 VNS binds to nAChRs, which are located on the free nerve endings of the nasociliary and maxillary branches of the trigeminal nerve in the nasal mucosa [13,14]. This binding leads to the activation of ligand-gated ion channels and depolarization of the nerve that innervates the LFU, thereby stimulating tear film production [14,15]. However, although some studies have demonstrated the effectiveness of OC-01 VNS in inducing the production of the aqueous component of the tear film [16–23], its impact on goblet cells and meibomian gland function is still unclear.

Therefore, the objective of this systematic review is to evaluate the efficacy and safety of OC-01 VNS treatment in patients with DED, as well as its potential influence on goblet cells and meibomian gland function. Through this review, a comprehensive overview of the current evidence on OC-01 VNS is provided, enabling evidence-based decision making and guiding future research directions.

2. Methods

2.1. Data sources and search strategy

This systematic review (PROSPERO ID: CRD42023469618) was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [24,25]. Fifty-six articles published before September 9, 2023, through the following databases: PubMed, Scopus and Web of science were identified. The data search strategy with Boolean operators was as follows: (varenicline solution OR varenicline nasal spray OR tyrvaya) AND (dry eye disease OR DED OR evaporative dry eye OR EDE OR aqueous deficient dry eye OR ADDE OR meibomian gland dysfunction). The references of the retrieved articles were reviewed to identify other related studies if they met the inclusion criteria.

Table 1
Summary of included studies.

Author (date)	Design	F/U[a]	Patients (TG/CG)	Age[b] (TG/CG)	Sex (F/M)	Eyes	Inclusion criteria	Intervention	Control	Posology[c]	CoI
Wirta et al. [16] 2021[a]	MT DM	1	139 / 43	65.5 ± 10.8	137 / 45	182	OSDI ≥ 23 points tCFS ≥ 2 points ST ≤ 10 mm	OC-01 VNS (0.006 mg / 0.03 mg / 0.06 mg)	Vehicle nasal spray (Phosphate-buffered saline)	12	Yes
Quiroz-Mercado et al. [17] 2021	MT DM	3	82 / 41	53.8 ± 12.8	100 / 23	123	tCFS ≥ 2 points ST ≤ 10 mm	OC-01 VNS (0.03 mg / 0.06 mg)	Vehicle nasal spray (Phosphate-buffered saline)	12	Yes
Wirta et al. [18] 2021b	MT DM	1	506 / 252	58.8 ± 13	576 / 182	758	OSDI ≥ 23 points tCFS ≥ 2 points ST ≤ 10 mm	OC-01 VNS (0.03 mg / 0.06 mg)	Vehicle nasal spray (Phosphate-buffered saline)	12	Yes
Dieckmann et al. [19] 2022	MN DM	–	12 / 6	61.4 ± 13.4	14 / 4	18	OSDI ≥ 23 points tCFS ≥ 2 points ST ≤ 12 mm	OC-01 VNS (0.06 mg)	Vehicle nasal spray (Phosphate-buffered saline)	12	Yes
Katz et al. [20] 2022	MT DM	1	597 / 294	59.9 ± 12.8	676 / 215	1782	OSDI ≥ 23 points ST ≤ 10 mm	OC-01 VNS (0.03 mg / 0.06 mg)	Vehicle nasal spray (Phosphate-buffered saline)	12	Yes
Nijm et al. [21] 2022	MT DM	1	222 / 227	59.6 ± 11.6	449 / 0	449	Menopausal status OSDI ≥ 23 points ST ≤ 10 mm	OC-01 VNS (0.03 mg)	Vehicle nasal spray (Phosphate-buffered saline)	12	Yes
Sheppard et al. [22] 2022	MT DM	1	308 / 294	59.9 ± 12.7	521 / 81	602	OSDI ≥ 23 points tCFS ≥ 2 points ST ≤ 10 mm	OC-01 VNS (0.03 mg)	Vehicle nasal spray (Phosphate-buffered saline)	12	Yes
Schallhorn et al. [23] 2023	MT DM	1	597 / 294	60.1 ± 11.9	676 / 215	891	Autoimmune disease OSDI ≥ 23 points ST ≤ 10 mm	OC-01 VNS (0.03 mg / 0.06 mg)	Vehicle nasal spray (Phosphate-buffered saline)	12	Yes

CG = Control group; CoI = Conflict of interest; DM = Double-masked; DED = Dry eye disease; F = Female; F/U = Follow-up; M = Male; MN = Monocentric; MT = Multicenter; OSDI = Ocular surface disease index; OC-01 VNS = Varenicline nasal spray; SM = Single-masked; ST = Schirmer test; tCFS = Total corneal fluorescein staining; TG = Treatment group.

[a] Expressed as months.

[b] Expressed as mean ± SD, years.

[c] Varenicline administration in each nostril expressed as hours per day.

Table 2
Intra-group and inter-group differences outcomes.

Author (Date)		OC-01 VNS group EDS (0–100)	ST, mm	tCFS (0–15)	Vehicle group EDS (0–100)	ST, mm	tCFS (0–15)	**Inter-group differences[a]** EDS (0–100)	ST, mm	tCFS (0–15)	F / A
Wirta et al. [16] 2021a	Baseline	60.9 ± 20.3	5.1 ± 2.9	6.7 ± 2	65.2 ± 17.7	4.5 ± 2.9	6.7 ± 2.4	**−11.6***	**7.6***	**−1.1**	F
	Last visit	43.7 ± 21.3	16.4 ± 4.3	7.9 ± 2.5	59.6 ± 18.1	8.2 ± 3.9	9 ± 3.2				
	Difference	**−17.2***	**11.3***	**1.2**	**−5.6**	**3.7**	**2.3**				
	LV-B										
Quiroz-Mercado et al. [17] 2021	Baseline	NR	5.5 ± 2.4	5.3 ± 2.6	NR	5.3 ± 2	5.8 ± 3.8	–	**4.9***	–	F
	Last visit	NR	16.4 ± 3.3	NR	NR	11.3 ± 3.5	NR				
	Difference	**–**	**10.9***	**–**	**–**	**6**	–				
	LV-B										
Wirta et al. [18] 2021b	Baseline	58.9 ± 22.4	5.3 ± 2.9	6.4 ± 2.2	58.1 ± 22.4	4.9 ± 2.9	6.2 ± 2.1	**−5.6***	**5.1***	**−1.2**	F
	Last visit	37.9 ± 20.4	16.7 ± 3.7	5.6 ± 2.8	42.7 ± 22.6	11.2 ± 3	5.8 ± 2.8				
	Difference	**−21***	**11.4***	**−0.8**	**−15.4**	**6.3**	**−0.4**				
	LV-B										
Dieckmann et al. [19] 2022	Baseline	58.8 ± 26.7	6.6 ± 4.4	NR	66.3 ± 17.4	4.5 ± 3.9	NR	**–**	**–**	**–**	F
	Last visit	NR	NR	NR	NR	NR	NR				
	Difference	**–**	**–**	**–**	**–**	**–**	**–**				
	LV-B										
Katz et al. [20] 2022	Baseline	58.8 ± 22.1	7.8 ± 5.1	6.3 ± 2.4	59.1 ± 21.8	7.4 ± 5.6	6.1 ± 2.3	**−6.5***	**6.1***	–	F
	Last visit	43.3 ± 23.2	16.6 ± 5.5	NR	50.1 ± 19.4	10.1	NR				
	Difference	**−15.5***	**8.8***	**–**	**−9**	**2.7**	**–**				
	LV-B										
Nijm et al. [21] 2022	Baseline	61.8 ± 20.6	4.5 ± 2.9	NR	58.8 ± 21.7	4.6 ± 2.9	NR	**−6.4***	**5.1***	–	F
	Last visit	40.7 ± 19.2	15.1 ± 4.4	NR	44.1 ± 22.1	10.1 ± 2.5	NR				
	Difference	**−21.1***	**10.6***	**–**	**−14.7**	**5.5**	**–**				
	LV-B										
Sheppard et al. [22] 2022	Baseline	59.3 ± 21.6	5.1 ± 2.9	6.5 ± 2.2	59.1 ± 21.8	4.8 ± 2.9	6.2 ± 2.2	**−5.7***	**5.5***	–	F
	Last visit	44.9 ± 20.5	15.5 ± 5	NR	50.1 ± 20.3	9.7 ± 3.6	NR				
	Difference	**−14.7***	**10.4***	**–**	**−9**	**4.9**	**–**				
	LV-B										
Schallhorn et al. [23] 2023	Baseline	59.2 ± 26.1	5.6 ± 2.8	NR	52.7 ± 24.4	4.2 ± 3.4	NR	**−9.3***	**11.8***	**–**	F
	Last visit	39.6 ± 24.2	19.2 ± 4.8	NR	42.4 ± 23.6	6 ± 3.1	NR				
	Difference	**−19.6***	**13.6***	**–**	**−10.3**	**1.8**	–				
	LV-B										
	Mean ± SD	**−18.2 ± 2.5[b]**	**11 ± 1.3[b]**	**0.2 ± 1[b]**	**−10.6 ± 3.4[b]**	**4.4 ± 1.6[b]**	**1.4 ± 0.9[b]**	**−7.5 ± 2.2[c]**	**6.6 ± 2.3[c]**	**−1.2 ± 0.01[c]**	

B = Baseline; EDS =

[a]Defined as (OC-01 VNS group $_{\text{Last visit - Baseline}}$) – (Vehicle group $_{\text{Last visit - Baseline}}$).
[b]Mean ± SD values of the difference $_{\text{LV-B}}$ for each variable.
[c]Mean ± SD values of the inter-group difference for each variable.
*$p < 0.05$.

2.2. Study selection

All those 56 articles identified through the search strategy were considered and analyzed. Duplicate studies were removed by DistillerSR software (DistillerSR Inc., Ottawa, Canada) [26]. The remaining studies underwent additional screening stages, which included title screening, abstract screening, and full-text screening. Studies unrelated to the topic were excluded from the review during title and abstract screening. Full-text screening studies that did not include OC-01 VNS treatment were also excluded from the review. These studies were reviewed by two investigators (ABS and JMSG) who selected them according to the inclusion and exclusion criteria. The inclusion criteria were as follows: prospective randomized controlled trials (RCTs), as well as post hoc analyses of RCTs comparing the safety and efficacy of OC-01 VNS treatment with vehicle nasal spray. The exclusion criteria included non-English publications and unindexed journals. There were no restrictions placed on the country in which the study was performed, the follow-up period, the sample size, the age of the participants and the results of the studies.

2.3. Quality assessment and data extraction

The data from each study were collected and summarized independently in tables designed by two researchers (ABS and JMSG). The following information was obtained from each article: (1) author and date of publication (year), (2) study design, (3) mean follow-up of all

Table 3
Intra-group and inter-group differences outcomes at different Varenicline concentrations.

Author (Date)		OC-01 VNS group						Inter-group differences[a]		
		OC-01 VNS 0.03 mg			OC-01 VNS 0.06 mg					
		EDS(0–100)	ST, mm	tCFS (0–15)	EDS (0–100)	ST, mm	tCFS (0–15)	EDS (0–100)	ST, mm	tCFS (0–15)
Wirta et al. [16] 2021a	Baseline	63.7 ± 18.4	4.8 ± 2.7	6.7 ± 2.1	53.5 ± 22.4	5.5 ± 3	6.9 ± 2.4	**−3.6**	**0.3**	**−0.8**
	Last visit	44.7 ± 17.6	16.2 ± 4	7.5 ± 1.9	38.1 ± 19.5	16.6 ± 4.7	8.5 ± 2.2			
	Difference $_{LV-B}$	**−19***	**11.4***	**0.8**	**−15.4**	**11.1***	**1.6**			
Quiroz-Mercado et al. [17] 2021	Baseline	NR	5.5 ± 2.4	4.6 ± 1.9	NR	5.4 ± 2.4	6 ± 3.3	–	**−0.2**	–
	Last visit	NR	16.3 ± 4.3	NR	NR	16.4 ± 3.8	NR			
	Difference $_{LV-B}$	–	**10.8***	–	–	**11***	–			
Wirta et al. [18]2021b	Baseline	58.5 ± 22.1	5.1 ± 3	6.4 ± 2.2	59.3 ± 22.6	5.4 ± 2.9	6.3 ± 2.2	**2.4**	**−0.2**	**0.3**
	Last visit	38.7 ± 20.3	16.4 ± 5	5.8 ± 2.4	37.1	16.9 ± 3.5	5.4 ± 2.8			
	Difference $_{LV-B}$	**−19.8***	**11.3***	**−0.6**	**–22.2***	**11.5***	**−0.9**			
Katz et al. [20]2022	Baseline	59.3 ± 21.6	7.2 ± 5	6.4 ± 2.3	58.4 ± 22.6	8.3 ± 5.2	6.2 ± 2.5	**1.5**	**−0.1**	–
	Last visit	44.6 ± 22.5	15.9 ± 4.8	NR	42.2	17.1 ± 4.3	NR			
	Difference $_{LV-B}$	**−14.7***	**8.7***	–	**−16.2***	**8.8***	–			
	Mean ± SD	**−17.8 ± 2.2[b]**	**10.5 ± 1.1[b]**	**0.1 ± 0.7[b]**	**−17.9 ± 3[b]**	**10.6 ± 1.1[b]**	**0.4 ± 1.3[b]**	**0.1 ± 2.6[c]**	**−0.1 ± 0.2[c]**	**−0,3 ± 0.6[c]**

[a]Defined as (OC-01 VNS 0.03 mg $_{Last\ visit\ -\ Baseline}$) – (OC-01 VNS 0.06 mg $_{Last\ visit\ -\ Baseline}$).
[b]Mean ± SD values of the difference $_{LV-B}$ for each variable.
[c]Mean ± SD values of the inter-group difference for each variable.
*$p < 0.05$.

patients in the whole procedure (expressed in months), (4) number of patients, (5) mean age of the patients (expressed in years), (6) patient sex (male/female), (7) number of eyes involved, (8) study group intervention, (9) control group intervention, (10) OC-01 VNS posology and (11) conflicts of interest.

Regarding the results of the studies, the following date were collected: (12) eye dryness score based on a visual analog scale (EDS-VAS, values from 0 to 100); (13) Schirmer test with anesthesia (ST, expressed in millimeters, mm) [27]; (14) total corneal fluorescein staining (tCFS), which was defined as the sum of fluorescein staining in 5 areas (inferior, superior, central, nasal and temporal) with a maximum score of 15 points [28]. Fluorescein staining in each area was assessed with the National Eye Institute scale from grade 0 (no staining) to grade 3 (heavy staining) [29]; (15) ocular and non-ocular adverse events (AEs) (expressed as percentages); and finally (16) authors judgment expressed by commenting in favor or against of OC-01 VNS treatment. Data synthesis was performed according to the Cochrane guideline for synthesis without *meta*-analysis (SWiM) [30]. Baseline and last visit values for all these variables were collected in the OC-01 VNS and vehicle groups. Intra-group clinical outcomes were defined as "Last visit (LV) – Baseline (B) differences". Inter-group clinical outcomes were defined as "OC-01 VNS $_{(LV–B)}$ – vehicle group $_{(LV–B)}$ differences". Mean ± SD, were calculated to report intra-group and inter-group clinical outcomes.

The literature that remained after full-text screening was examined to assess the quality of the studies. To avoid the risk of bias, two dependable authors created a synopsis based on the Cochrane risk of bias tool [31], which includes the following items: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting and (7) other sources of bias. A third non-blinded assessor decided the quality of the studies when disagreements occurred between the two assessors.

3. Results

3.1. Study characteristics

The study selection process of this systematic review is presented with a flowchart diagram in Fig. 1. The design of the included studies was prospective RCTs published between 2021 and 2023. This systematic review included 1972 eyes from 1081 patients with a mean age of 59.9 ± 3 years. The sex distribution was 827 females (76.5 %) and 254 males (23.5 %). Patient follow-up, expressed in months, ranged from 1 month [16,18,20–23] to 3 months [17], with a mean follow-up of 1.3 ± 0.7 months. Regarding study and control group intervention, all studies used OC-01 VNS (Oyster Point Pharma Inc., Princeton, USA) and vehicle nasal spray, respectively [16–18,20–23]. In addition, all studies also had conflicts of interest by the authors (Oyster Point Pharma Inc., Princeton, USA) [16–18,20–23]. More detailed study characteristics and nasal spray composition are presented in Table 1.

3.2. Outcomes

Regarding efficacy outcomes, 6 studies reported dry eye symptom outcomes using the EDS-VAS [16,18,20–23]. Seven studies also reported dry eye sign outcomes [16–18,20–23], of which all evaluated ST [16–18,20–23], while only 2 studies assessed tCFS [16,18] Regarding safety outcomes, 3 studies reported ocular AEs [16,17,19], while non-ocular AEs was reported by 5 studies [16–20].

Intra-group and inter-group clinical outcomes are presented in Table 2. Regarding OC-01 VNS group, EDS-VAS and ST achieved an improvement of −18.2 ± 2.5 points and 11 ± 1.3 mm, respectively. However, tCFS remained unchanged with a value of 0.2 ± 1 points. Inferior improvements were achieved in the vehicle group with an EDS-VAS and ST of −10.6 ± 3.4 points and 4.4 ± 1.6 mm, respectively. In addition, tCFS showed an increase of 1.4 ± 0.9 points. Regarding inter-group clinical outcomes, all outcomes were in favor of the OC-01 VNS group with an EDS-VAS, ST and tCFS of −7.5 ± 2.2 points, 6.6 ± 2.3 mm

Table 4
AEs inter-group differences.

Author (Date)		Varenicline group	Vehicle group	**Inter-group Differences** [a]
Wirta et al. [16] 2021a	Ocular AEs, %	3	16	**−13**
	Non-ocular AEs, %	92.5	12	**80.5**
Quiroz-Mercado et al. [17] 2021	Ocular AEs, %	10.9	9.8	**1.1**
	Non-ocular AEs, %	14.6	22	**−7.4**
Wirta et al. [18] 2021b	Ocular AEs, %	NR	NR	–
	Non-ocular AEs, %	98.3	57	**41.3**
Dieckmann et al. [19] 2022	Ocular AEs, %	0	0	**0**
	Non-ocular AEs, %	50	16.7	**33.6**
Katz et al. [20] 2022	Ocular AEs, %	NR	NR	–
	Non-ocular AEs, %	33.3	6.6	**26.7**
Nijm et al. [21] 2022	Ocular AEs, %	NR	NR	–
	Non-ocular AEs, %	NR	NR	–
Sheppard et al. [22] 2022	Ocular AEs, %	NR	NR	–
	Non-ocular AEs, %	NR	NR	–
Schallhorn et al. [23] 2023	Ocular AEs, %	NR	NR	–
	Non-ocular AEs, %	NR	NR	–

AEs, Adverse events.
[a] Defined as (Varenicline group) – (Vehicle group).

and −1.2 ± 0.01 points, respectively.

Intra-group and inter-group clinical outcomes of OC-01 VNS at different concentrations are presented in Table 3. Regarding OC-01 VNS 0.03 mg group, EDS-VAS and ST achieved an improvement of −17.8 ± 2.2 points and 10.5 ± 1.1 mm, respectively. However, tCFS remained unchanged with a value of 0.1 ± 0.7 points. Similar results were reported in the OC-01 VNS 0.06 mg with an EDS-VAS, ST and tCFS of −17.9 ± 3 points, 10.6 ± 1.1 mm and 0.4 ± 1.3 points, respectively. Regarding inter-group clinical outcomes, all outcomes were in favor of both OC-01 VNS concentrations with minimal EDS-VAS, ST and tCFS differences of 0.1 ± 2.6 points, −0.1 ± 0.2 mm and −0,3 ± 0.6 points, respectively.

Ocular and non-ocular AEs are presented in Table 4. The most common ocular and non-ocular AEs in both groups were blurred vision and sneeze, occurring in 2.9 ± 3.4 % and 43.4 ± 36.7 %, respectively. In addition, the OC-01 VNS group reported that ocular AEs was 3.9 ± 6.4 % lower than the vehicle group. However, non-ocular AEs was 34.9 ± 28 % higher in the OC-01 VNS group compared to the vehicle group. Overall, adherence to OC-01 VNS treatment was > 93 %.

3.3. Risk of bias

The risk of bias summary of the included studies is presented in Fig. 2. Risk of bias assessment was classified into three evidence level groups: (1) studies with a low risk of bias (Wirta et al. 2021a [16], Wirta et al. 2021b [18], Katz et al. [20], Nijm et al. [21], Sheppard et al. [22] and Schallhorn et al. [23]), (2) studies with an unclear risk of bias (Quiroz-Mercado et al. [17]) and (3) studies with a high risk of bias (Dieckmann et al. [19]). The overall risk of bias summary of the domains used in each study is presented in Fig. 3. The items used to assess the risk of bias showed an overall low risk of bias, which was 75 %. Therefore, no study was excluded due to risk of bias. The Robvis tool (NIHR, Bristol, UK) was used to create risk of bias assessment figures [32].

4. Discussion

This systematic review of the literature demonstrated that OC-01 VNS treatment achieved a higher reduction in the symptoms and signs of DED compared to vehicle nasal spray, reporting AEs that were well tolerated.

4.1. OC-01 VNS efficacy

All studies included in this systematic review that evaluated dry eye symptoms used the EDS-VAS. This questionnaire is based on a visual analog scale that quantifies both the severity and frequency of dry eye symptoms and it is significant correlated with OSDI score [35,36]. Although EDS-VAS has a high degree of sensitivity and discriminating capacity, the minimal clinically important difference has been defined recently by Pattar et al. [37], concluding that intra-group changes in EDS-VAS > 13 points would be clinically meaningful. Wirta et al. (2021a) [16], Wirta et al. (2021b) [18], Katz et al. [20], Nijm et al. [21], Sheppard et al. [22] and Schallhorn et al. [23] reported that patients who received OC-01 VNS treatment achieved significant EDS-VAS improvement of −18.2 ± 2.5 points, while the vehicle group achieved non-significant EDS-VAS improvement of −10.6 ± 3.4 points. However, although these results may suggest that OC-01 VNS treatment seems to improve DED symptoms to a clinically meaningful degree compared to vehicle, the benefit of taking OC-01 VNS treatment compared to the vehicle is just 7.6 points, which could be argued to be not clinically significant. Therefore, the effects of OC-01 VNS treatment on DED symptoms should be carefully interpreted.

The effect of OC-01 VNS on tear volume was evaluated by the ST with topical anesthesia, which is more objective and reliable in DED detection [27,38]. Wirta et al. (2021a) [16], Quiroz-Mercado et al. [17], Wirta et al. (2021b) [18], Katz et al. [20], Nijm et al. [21], Sheppard et al. [22] and Schallhorn et al. [23] reported that patients who received OC-01 VNS treatment achieved anesthetized ST improvement of 11 ± 1.3 mm compared to the 4.4 ± 1.6 mm achieved in the vehicle group. This difference between both groups may be considered large enough for patients to move to “normal” tear production, reducing DED severity [1]. Regarding ST long-term efficacy, Quiroz-Mercado et al. [17] was the only study to report ST long-term outcomes with OC-01 VNS treatment. Their results may be compared with long-term outcomes of other DED therapies such as topical cyclosporine and lifitegrast. Topical cyclosporine studies have shown that anesthetized ST improvements of 2.5 mm may take up 6 months to manifest in patients with DED [34,39,40]. Similar results were reported by topical lifitegrast studies, with anesthetized ST improvements < 2 mm at 3-months follow-up [41–43]. However, Quiroz-Mercado et al. [17] reported anesthetized ST improvement of 10.9 mm at 3-months follow-up, which suggest a rapid initial response to OC-01 VNS treatment. The OC-01 VNS effects in EDS-VAS and ST were also evaluated in populations with high DED

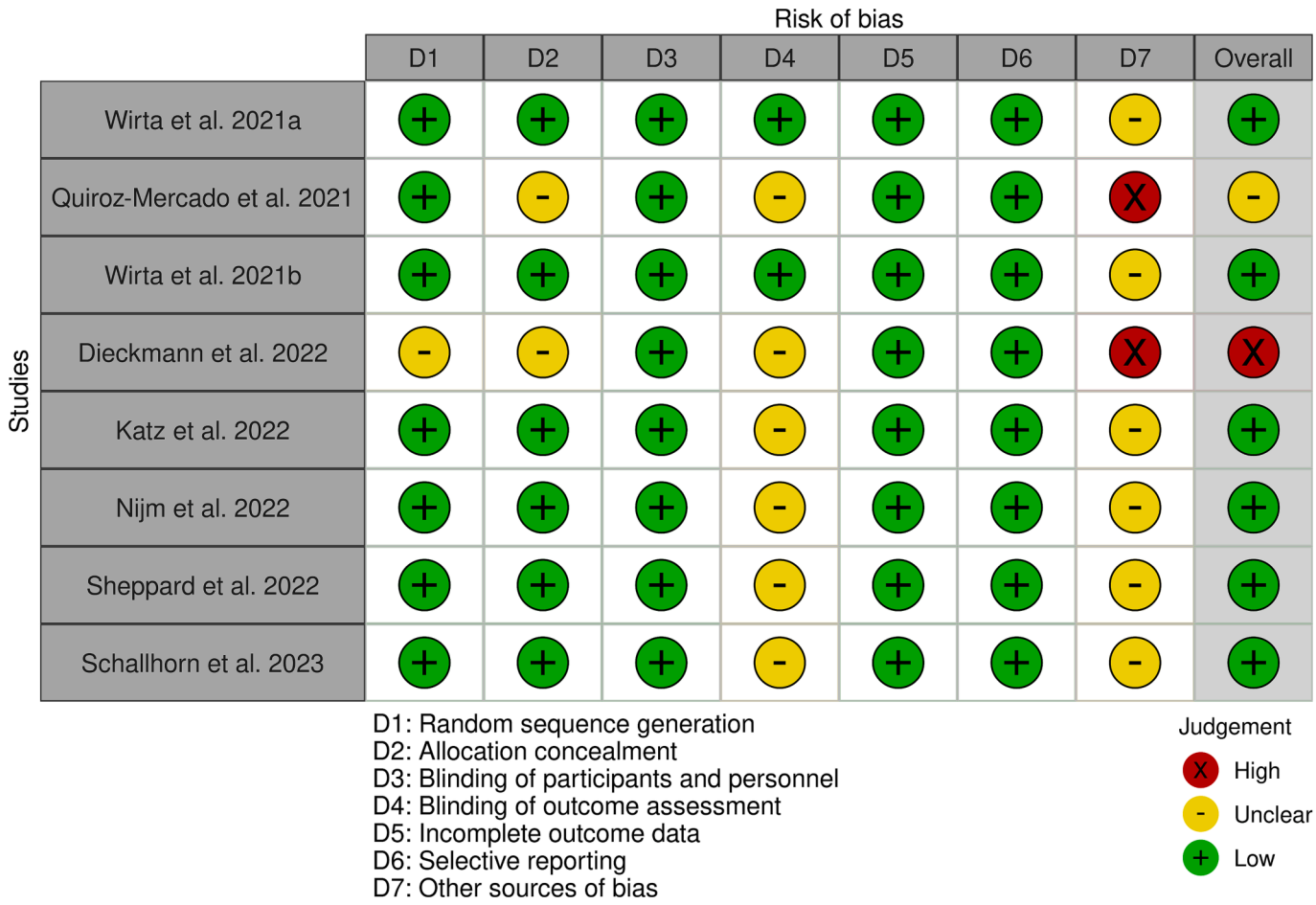

Fig. 2. Risk of bias summary of the included studies with traffic light plot. The traffic lights represent the author's risk of bias judgment in each domain (D) used to assess the quality of the studies.

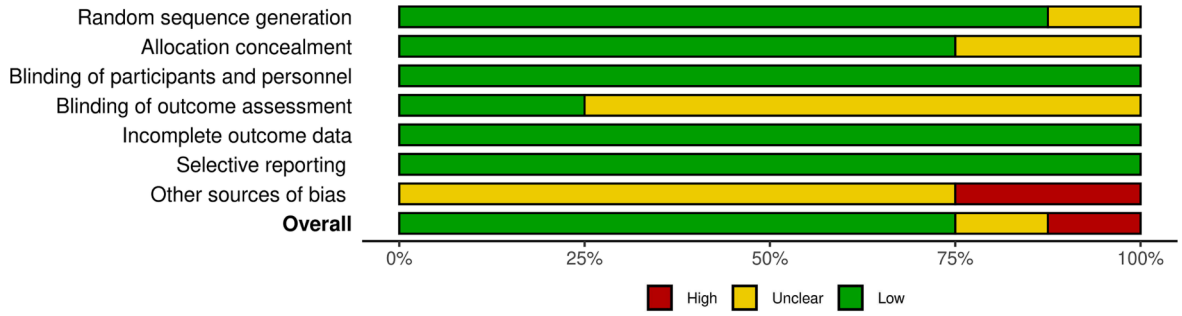

Fig. 3. Overall risk of bias summary of the domains with bar plot. Bars represent the overall author's risk of bias judgment in each domain presented as percentages.

prevalence, such as patients with autoimmune diseases [44] and menopausal women [45,46]. Schallhorn et al. [23] reported that patients with autoimmune diseases who received OC-01 VNS treatment achieved significant EDS-VAS and ST improvements of −9.3 points and 11.8 mm compared to those who received vehicle, respectively. Similar results were achieved by Nijm et al. [21] reporting that menopausal women who received OC-01 VNS treatment achieved significant EDS-VAS and ST improvements of −6.4 points and 5.1 mm compared to those who received vehicle, respectively. In addition, Sheppard et al. [22] demonstrated that OC-01 VNS treatment significantly improves EDS-VAS and ST in patients with different DED severity. Therefore, these results suggest the potential efficacy of OC-01 VNS for DED regardless of the study population. Regarding ocular surface staining, Wirta et al. (2021a) [16] and Wirta et al. (2021b) [18] reported that patients who received OC-01 VNS treatment achieved tCFS improvement of -1.2 ± 0.01 mm compared to the vehicle group. Although these results suggest that OC-01 VNS treatment could reduce corneal damage due to DED, interpretation could be limited by the anesthesia used for ST evaluation, which may increase corneal staining [47]. This is consistent with the non-significant tCFS slight increase of 1.2 points reported by Wirta et al. (2021a) [16] in the OC-01 VNS group. It is important to emphasize that in these studies the type of dry eye was not specified, which would have been of interest to determine in which type of dry eye the OC-01 VNS treatment is more effective.

The clinical effects on EDS-VAS, ST and tCFS may be explained by the mechanism of action of OC-01 VNS. This agent is a cholinergic agonist with high affinity and selectivity at human α3β4, α3α5β4, α4β2, α4α6β2 and α7 nAChRs [13,14], which are present on the trigeminal nerve

within the nasal cavity throughout the nasal mucosa [14]. Tear film production occurs when OC-01 VNS binds to nAChRs that open ligand-gated ion channels and depolarizes the nerve that innervates the LFU [19]. To the best of our knowledge, Dieckmann et al. [19] is the only study to analyze changes in goblet cells and meibomian glands after OC-01 VNS treatment. Regarding goblet cells, significantly reduced goblet cells area and perimeter were reported 10 min after OC-01 VNS administration. These changes induce goblet cells degranulation which results in the release of mucin onto the ocular surface that plays a key role in restoring tear film homeostasis [48,49]. Regarding meibomian glands, no significant changes in meibomian glands area were reported 10 min after OC-01 VNS administration. This may be due to the possibility that OC-01 VNS treatment only influences meibomian gland function [50], but further studies are needed. Overall, is hypothesized that OC-01 VNS induce TTP stimulation through nAChRs present in the nasal mucosa, which mediate afferent signals that may innervate the lacrimal functional upregulating all 3 layers of the tear film [14,19], and consequently ameliorate DED symptoms and signs [16–18].

4.2. OC-01 VNS safety

Wirta et al. (2021a) [16], Quiroz-Mercado et al. [17], Wirta et al. (2021b). [18], Dieckmann et al. [19] and Katz et al. [20] reported AEs after OC-01 VNS treatment. Non-ocular AEs were more common than ocular AEs after OC-01 VNS treatment, which may be expected due its nasal route of administration. Sneeze and blurred vision were the most reported non-ocular and ocular AEs, respectively. However, both were mild and transient, occurring immediately after OC-01 VNS administration. In addition, sneeze reflex from trigeminal nerve stimulation is well documented [51,52]. Therefore, it seems that the AEs of OC-01 VNS treatment do not influence its tolerability, which favors high adherence.

OC-01 VNS safety may be put in context with other DED therapies. Topical cyclosporine and lifitegrast studies have shown that burning after instillation is the most common ocular AEs, reporting an overall discontinuation of 19.8 %[34,39,40] and 8.9 % [41–43], respectively. However, no case of burning occurred after OC-01 VNS administration with an overall discontinuation of 4.6 % [16–18], which included patients who stopped taking the treatment due to improvement in their DED symptoms and signs, as well as patients who did not tolerate the non-ocular AEs. In addition, the nasal route of administration of OC-01 VNS offers the following advantages over traditional topical therapies, which also contribute to increase adherence: (1) reduce the common patient-reported complains of eye drops, (2) can be administered to contact lens wearers and (3) provide a potentially easier delivery method for patients with tremors, neck deformities, and overall difficulty with the administration of eye drops [16–18]. This suggests OC-01 VNS as a potentially safe treatment option in patients with DED.

4.3. Strengths and limitations

The main strength of this systematic review is high quality of reported results since all studies included were RCTs or post hoc analysis of RCTs with an overall low risk of bias. The interventions in both groups, as well as the doses applied per day were essentially the same between the studies; therefore, the methodologies of all of them were substantially similar. In addition, this study provides an update on the topic, including new RCTs and evaluating other variables, such as EDS-VAS and tCFS compared to other systematic reviews [53]. However, there are limitations that may have influenced the results. First, a *meta*-analysis was not performed, which may influence the interpretation of the results. Second, the included studies had a short follow-up period. Therefore, there is a needed for larger, well-designed, strictly blinded, multicenter RCTs evaluating the long-term effect of OC-01 VNS on the LFU at different concentrations, particularly in patients with Sjogren's syndrome (SS) and meibomian gland dysfunction (MGD), which are the main cause of aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE) [33,54], respectively. In addition, it would also be interesting to compare OC-01 VNS with other preservative-free nasal sprays, such as simpinicline (OC-02 SNS), which has been shown to significantly increase tear production and improve dry eye symptoms [55]. Third, the influence of anesthetized TS on the interpretation of tCFS results. Thus, further studies analyzing tear volume by objective and non-invasive tests, such as tear meniscus height (TMH) and tear meniscus area (TMA) are needed to avoid the influence of traditional tests on tCFS. Fourth, the studies included in this systematic review have not considered a nasal endoscopic evaluation to establish as exclusion criteria the absence of nasal pathologies that could alter the administration or absorption of OC-01 VNS. Fifth, although OC-01 VNS 0.03 mg and 0.06 mg have shown to achieve similar results, tear production was only assessed at the time of OC-01 VNS administration. Consequently, it would be interesting to determine the duration of increased tear production after OC-01 VNS treatment at different concentrations. This information could be useful to establish the effective daily dose and concentration of OC-01 VNS. Finally, it is important to mention that all studies included in this systematic review were supported by Oyster Point Pharma; hence, there is an unmet need of further non-industry funded studies.

5. Conclusions

In conclusion, this systematic review has demonstrated that OC-01 VNS treatment achieves better results than vehicle. Despite the AEs, its tolerability is satisfactory, reporting high adherence. OC-01 VNS treatment reduces the symptoms and signs of DED, such as EDS, anesthetized ST and tCFS. Therefore, OC-01 VNS seems to be an effective and safe treatment that may be recommended for patients with DED. In addition, OC-01 VNS may be represented as a novel candidate to treat DED due to its nasal mode of administration, acting on the nerves that innervate the LFU without the commonly AEs of topical ocular application modalities, but further RCTs are needed.

Conflicts of interest disclosures

The authors have no financial/non-financial competing interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II definition and classification report. Ocul Surf 2017;15:276–83. https://doi.org/10.1016/J.JTOS.2017.05.008.
[2] Willcox MDP, Argüeso P, Georgiev GA, Holopainen JM, Laurie GW, Millar TJ, et al. TFOS DEWS II tear film report. Ocul Surf 2017;15:366–403. https://doi.org/10.1016/J.JTOS.2017.03.006.
[3] Barabino S, Labetoulle M, Rolando M, Messmer EM. Understanding symptoms and quality of life in patients with dry eye syndrome. Ocul Surf 2016;14:365–76. https://doi.org/10.1016/J.JTOS.2016.04.005.
[4] Sayegh RR, Yu Y, Farrar JT, Kuklinski EJ, Shtein RM, Asbell PA, et al. Ocular discomfort and quality of life among patients in the dry eye assessment and management study. Cornea 2021;40:869–76. https://doi.org/10.1097/ICO.0000000000002580.
[5] Jones L, Downie LE, Korb D, Benitez-del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II management and therapy report. Ocul Surf 2017;15:575–628. https://doi.org/10.1016/J.JTOS.2017.05.006.
[6] Kaido M, Arita R, Mitsukura Y, Tsubota K. Autonomic nerve activity features according to dry eye type. Invest Ophthalmol Vis Sci 2023;64:19. https://doi.org/10.1167/iovs.64.7.19.
[7] Kaido M, Arita R, Mitsukura Y, Ishida R, Tsubota K. Variability of autonomic nerve activity in dry eye with decreased tear stability. PLoS One 2022;17:e0276945.
[8] Labetoulle M, Baudouin C, Calonge M, Merayo-Lloves J, Boboridis KG, Akova YA, et al. Role of corneal nerves in ocular surface homeostasis and disease. Acta Ophthalmol 2019;97:137–45. https://doi.org/10.1111/AOS.13844.

[9] Dartt DA. Neural regulation of lacrimal gland secretory processes: relevance in dry eye diseases. Prog Retin Eye Res 2009;28:155–77. https://doi.org/10.1016/J.PRETEYERES.2009.04.003.

[10] Yu MD, Park JK, Kossler AL. Stimulating tear production: spotlight on neurostimulation. Clin Ophthalmol 2021;15:4219–26. https://doi.org/10.2147/OPTH.S284622.

[11] Dieckmann G, Fregni F, Hamrah P. Neurostimulation in dry eye disease-past, present, and future. Ocul Surf 2019;17:20–7. https://doi.org/10.1016/J.JTOS.2018.11.002.

[12] Frampton JE. Varenicline solution nasal spray: a review in dry eye disease. Drugs 2022;82:1481–8. https://doi.org/10.1007/S40265-022-01782-4.

[13] Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at alpha4beta2 and a full agonist at alpha7 neuronal nicotinic receptors. Mol Pharmacol 2006;70:801–5. https://doi.org/10.1124/MOL.106.025130.

[14] Pflugfelder SC, Cao A, Galor A, Nichols KK, Cohen NA, Dalton M. Nicotinic acetylcholine receptor stimulation: A new approach for stimulating tear secretion in dry eye disease. Ocul Surf 2022;25:58–64. https://doi.org/10.1016/J.JTOS.2022.05.001.

[15] Belmonte C, Nichols JJ, Cox SM, Brock JA, Begley CG, Bereiter DA, et al. TFOS DEWS II pain and sensation report. Ocul Surf 2017;15:404–37. https://doi.org/10.1016/J.JTOS.2017.05.002.

[16] Wirta D, Torkildsen GL, Boehmer B, Hollander DA, Bendert E, Zeng L, et al. ONSET-1 Phase 2b Randomized Trial to Evaluate the Safety and Efficacy of OC-01 (Varenicline Solution) Nasal Spray on Signs and Symptoms of Dry Eye Disease. Cornea 2022;41:1207–16. https://doi.org/10.1097/ICO.0000000000002941.

[17] Quiroz-Mercado H, Hernandez-Quintela E, Chiu KH, Henry E, Nau JA. A phase II randomized trial to evaluate the long-term (12-week) efficacy and safety of OC-01 (varenicline solution) nasal spray for dry eye disease: The MYSTIC study. Ocular Surf 2022;24:15–21. https://doi.org/10.1016/j.jtos.2021.12.007.

[18] Wirta D, Vollmer P, Paauw J, Chiu K-H-H, Henry E, Striffler K, et al. Efficacy and Safety of OC-01 (Varenicline Solution) Nasal Spray on Signs and Symptoms of Dry Eye Disease The ONSET-2 Phase 3 Randomized Trial. Ophthalmology 2022;129:379–87. https://doi.org/10.1016/j.ophtha.2021.11.004.

[19] Dieckmann GM, Cox SM, Lopez MJ, Ozmen MC, Yavuz Saricay L, Bayrakutar BN, et al. A Single Administration of OC-01 (Varenicline Solution) Nasal Spray Induces Short-Term Alterations in Conjunctival Goblet Cells in Patients with Dry Eye Disease. Ophthalmol Ther 2022;11:1551–61. https://doi.org/10.1007/s40123-022-00530-x.

[20] Katz J, Periman LM, Maiti S, Sarnicola E, Hemphill M, Kabat AG, et al. Bilateral Effect of OC-01 (Varenicline Solution) Nasal Spray for Treatment of Signs and Symptoms in Individuals with Mild, Moderate, and Severe Dry Eye Disease. Clin Ther 2022;44:1463–70. https://doi.org/10.1016/j.clinthera.2022.09.013.

[21] Nijm LM, Zhu D, Hemphill M, Blemker GL, Hendrix LH, Kabat AG, et al. Does Menopausal Status Affect Dry Eye Disease Treatment Outcomes with OC-01 (Varenicline Solution) Nasal Spray? A Post Hoc Analysis of ONSET-1 and ONSET-2 Clinical Trials. Ophthalmol Ther 2022;12:355–64. https://doi.org/10.1007/s40123-022-00607-7.

[22] Sheppard JD, O'Dell LE, Karpecki PM, Raizman MB, Whitley WO, Blemker G, et al. Does Dry Eye Disease Severity Impact Efficacy of Varenicline Solution Nasal Spray on Sign and Symptom Treatment Outcomes? Optom Vis Sci 2023;100:164–9. https://doi.org/10.1097/OPX.0000000000001986.

[23] Schallhorn JM, McGee S, Nau J, Macsai M, Gibson A, Blemker G, et al. OC-01 (Varenicline Solution) Nasal Spray for the Treatment of Dry Eye Disease Signs and Symptoms in Subjects with Autoimmune Disease: Integrated Data from ONSET-1 and ONSET-2. Clin Ophthalmol 2023;17:725–34. https://doi.org/10.2147/OPTH.S403953.

[24] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews 2021:89.

[25] Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2020;2021:372. https://doi.org/10.1136/BMJ.N160.

[26] DistillerSR. Version 2.35. DistillerSR Inc.; 2022. n.d. https://www.distillersr.com/.

[27] Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II Diagnostic Methodology report. Ocul Surf 2017;15:539–74. https://doi.org/10.1016/J.JTOS.2017.05.001.

[28] Tauber J, Berdy GJ, Wirta DL, Krösser S, Vittitow JL, GOBI Study Group. NOV03 for Dry Eye Disease Associated with Meibomian Gland Dysfunction: Results of the Randomized Phase 3 GOBI Study. Ophthalmology 2023;130:516–24. 10.1016/j.ophtha.2022.12.021.

[29] Sall K, Foulks GN, Pucker AD, Ice KL, Zink RC, Magrath G. Validation of a Modified National Eye Institute Grading Scale for Corneal Fluorescein Staining. Clin Ophthalmol 2023;17:757–67. https://doi.org/10.2147/OPTH.S398843.

[30] Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ 2020;368. https://doi.org/10.1136/BMJ.L6890.

[31] Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. The. BMJ 2011;343. https://doi.org/10.1136/BMJ.D5928.

[32] McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods 2021;12:55–61. https://doi.org/10.1002/JRSM.1411.

[33] Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. Ocul Surf 2017;15:438–510. https://doi.org/10.1016/J.JTOS.2017.05.011.

[34] Tuan HI, Chi SC, Kang YN. An Updated Systematic Review With Meta-Analysis Of Randomized Trials On Topical Cyclosporin A For Dry-Eye Disease. Drug Des Devel Ther 2020;14:265. https://doi.org/10.2147/DDDT.S207743.

[35] Amparo F, Schaumberg DA, Dana R. Comparison of Two Questionnaires for Dry Eye Symptom Assessment: The Ocular Surface Disease Index and the Symptom Assessment in Dry Eye. Ophthalmology 2015;122:1498–503. https://doi.org/10.1016/J.OPHTHA.2015.02.037.

[36] Rodriguez-Garcia A, Ruiz-Lozano RE, Bustamante-Arias A, Pantaleon-Garcia J, Hernandez-Quintela E, Navas A. Correlation and Level of Agreement between the Ocular Surface Disease Index and the Symptom Assessment in Dry Eye Questionnaires: A Survey-Based Study. Curr Eye Res 2023. https://doi.org/10.1080/02713683.2023.2211249.

[37] Pattar GR, Jerkins G, Evans DG, Torkildsen GL, Ousler GW, Hollander DA, et al. Symptom improvement in dry eye subjects following intranasal tear neurostimulation: Results of two studies utilizing a controlled adverse environment. Ocul Surf 2020;18:249–57. https://doi.org/10.1016/J.JTOS.2019.09.006.

[38] Li N, Deng XG, He MF. Comparison of the Schirmer I test with and without topical anesthesia for diagnosing dry eye. Int J Ophthalmol 2012;5:478–81. https://doi.org/10.3980/J.ISSN.2222-3959.2012.04.14.

[39] Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. Ophthalmology 2000;107:631–9. https://doi.org/10.1016/S0161-6420(99)00176-1.

[40] Straub M, Bron AM, Muselier-Mathieu A, Creuzot-Garcher C. Long-term outcome after topical ciclosporin in severe dry eye disease with a 10-year follow-up. Br J Ophthalmol 2016;100:1547–50. https://doi.org/10.1136/BJOPHTHALMOL-2015-306930.

[41] Sheppard JD, Torkildsen GL, Lonsdale JD, D'Ambrosio FA, McLaurin EB, Eiferman RA, et al. Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study. Ophthalmology 2014;121:475–83. https://doi.org/10.1016/J.OPHTHA.2013.09.015.

[42] Tauber J, Karpecki P, Latkany R, Luchs J, Martel J, Sall K, et al. Lifitegrast Ophthalmic Solution 5.0% versus Placebo for Treatment of Dry Eye Disease: Results of the Randomized Phase III OPUS-2 Study. Ophthalmology 2015;122:2423–31. https://doi.org/10.1016/J.OPHTHA.2015.08.001.

[43] Holland EJ, Luchs J, Karpecki PM, Nichols KK, Jackson MA, Sall K, et al. Lifitegrast for the Treatment of Dry Eye Disease: Results of a Phase III, Randomized, Double-Masked, Placebo-Controlled Trial (OPUS-3). Ophthalmology 2017;124:53–60. https://doi.org/10.1016/J.OPHTHA.2016.09.025.

[44] Bustamante-Arias A, Ruiz Lozano RE, Rodriguez-Garcia A. Dry eye disease, a prominent manifestation of systemic autoimmune disorders. Eur J Ophthalmol 2022;32:3142–62. https://doi.org/10.1177/11206721221088259.

[45] Gomes JAP, Azar DT, Baudouin C, Efron N, Hirayama M, Horwath-Winter J, et al. TFOS DEWS II iatrogenic report. Ocul Surf 2017;15:511–38. https://doi.org/10.1016/J.JTOS.2017.05.004.

[46] Sullivan DA, Rocha EM, Aragona P, Clayton JA, Ding J, Golebiowski B, et al. TFOS DEWS II Sex, Gender, and Hormones Report. Ocul Surf 2017;15:284–333. https://doi.org/10.1016/J.JTOS.2017.04.001.

[47] Josephson JE, Caffery BE. Corneal staining after instillation of topical anesthetic (SSII). Invest Ophthalmol vis Sci 1988;29:1096–9.

[48] Baudouin C, Rolando M, Benitez Del Castillo JM, Messmer EM, Figueiredo FC, Irkec M, et al. Reconsidering the central role of mucins in dry eye and ocular surface diseases. Prog Retin Eye Res 2019;71:68–87. https://doi.org/10.1016/J.PRETEYERES.2018.11.007.

[49] Alam J, de Paiva CS, Pflugfelder SC. Immune - Goblet cell interaction in the conjunctiva. Ocul Surf 2020;18:326–34. https://doi.org/10.1016/J.JTOS.2019.12.006.

[50] Green KB, Kamat M, Franke M, Holdbrook M, Senchyna M. Tear Total Lipid Concentration in Patients with Dry Eye Following Intranasal Neurostimulation. Invest Ophthalmol vis Sci 2017;58:2693.

[51] Hydén D, Arlinger S. On the sneeze-reflex and its control. Rhinology 2007;45:218–9.

[52] Songu M, Cingi C. Sneeze reflex: facts and fiction. Ther Adv Respir Dis 2009;3:131–41. https://doi.org/10.1177/1753465809340571.

[53] Bashrahil B, Taher N, Alzahrani Z, Alnabihi A, Aldahlawi A, Alkhathlan M, et al. The efficacy and safety of varenicline nasal spray for the management of dry eye signs: a systematic review and meta-analysis. BMC Ophthalmol 2023;23. https://doi.org/10.1186/S12886-023-03069-Y.

[54] Barrientos RT, Godín F, Rocha-De-Lossada C, Soifer M, Sánchez-González JM, Moreno-Toral E, et al. Ophthalmological Approach for the Diagnosis of Dry Eye Disease in Patients with Sjögren's Syndrome. Life (Basel) 2022;12. 10.3390/LIFE12111899.

[55] Torkildsen GL, Pattar GR, Jerkins G, Striffler K, Nau J. Efficacy and Safety of Single-dose OC-02 (Simpinicline Solution) Nasal Spray on Signs and Symptoms of Dry Eye Disease: The PEARL Phase II Randomized Trial. Clin Ther 2022;44:1178–86. https://doi.org/10.1016/J.CLINTHERA.2022.07.006.