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EPOMEC
EXPANDING VISION

# The Efficacy and Safety of Varenicline Nasal Spray for the Management of Dry Eye Signs: A Systematic Review and Meta-analysis

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# Introduction

- Dry eye disease (DED) is a disease of multifactorial etiology affecting several tear components leading to persistently unstable tear film [1].
- Tear supplementation is the mainstay of DED management [2]. Other treatments, such as anti-inflammatory and immunosuppressive eye drops, are sparsely used.
- Artificial tear drops have limitations, such as requiring continuous instillation.
- Novel interventions are emerging.

# Introduction

- Nicotinic acetylcholine receptor (nAChR) agonists are mainly used for smoking cessation as patches
- They (varenicline and simpinicline) have been proposed as aqueous nasal sprays for DED
- Varenicline nasal spray (VNS) affects the trigeminal nerve ending within the anterior nasal cavity and activates the nasolacrimal reflux (NLR)
- NLR activation leads to increasing the production of tear films through the lacrimal functional unit (LFU).

# Methods

- Registered in alignment with PROSPERO (CRD42022343175)
- Medline, Embase, CENTRAL were searched
- From databases initiation to **July 6, 2022**
- No restrictions on date or language.
- Selection and Data extraction process
- Quality of RCTs
  - Risk of bias within studies → The revised Risk of Bias 2 (RoB 2) tool
  - Certainty of evidence → GRADE criteria

# Methods

- Inclusion Criteria

Population → DED patients

Intervention → Varenciline nasal spray

Control → Placebo (Vehicle spray)

Outcome → Anesthetized Schirmer test score and safety profile

Study Design → Randomized-controlled trials

- Exclusion Criteria

Studies including subjects with preexistent ocular and conjunctival cofounding conditions

# Methods

**Meta-analysis**

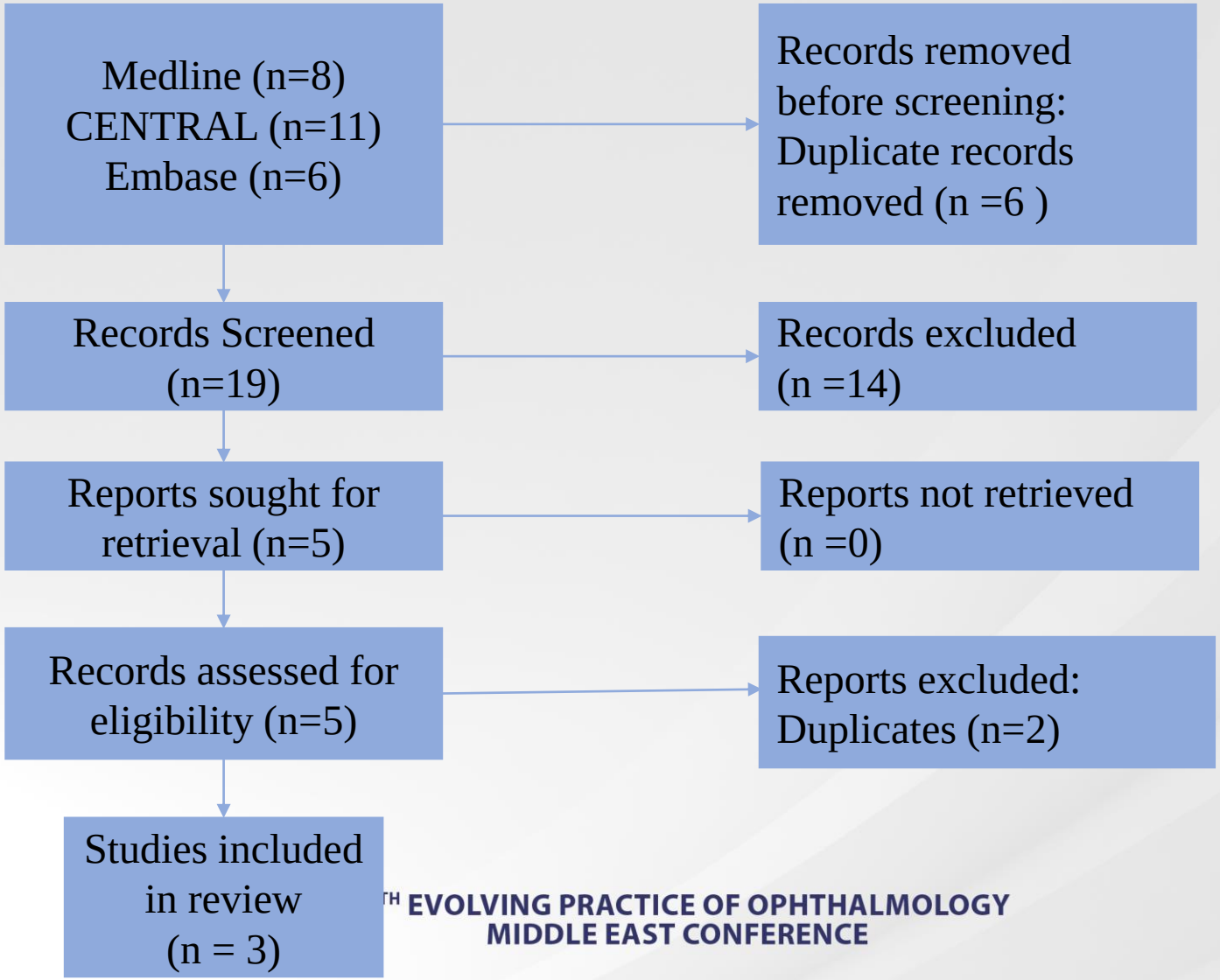
- Random-effects model.
- 95% CI and $p < 0.05$ for statistical significance.
- Statistical heterogeneity ($I^2$)
- Standardized mean Difference (SMD) and risk ratios (RRs) effects
- Inverse variance (IV) weighting method.
- Subgroup analysis of different doses:

    Mid-dose (0.6 mg/mL)

    High-Dose (1.2 mg/mL)

# Results

Figure 1: PRISMA Flowchart



# Results

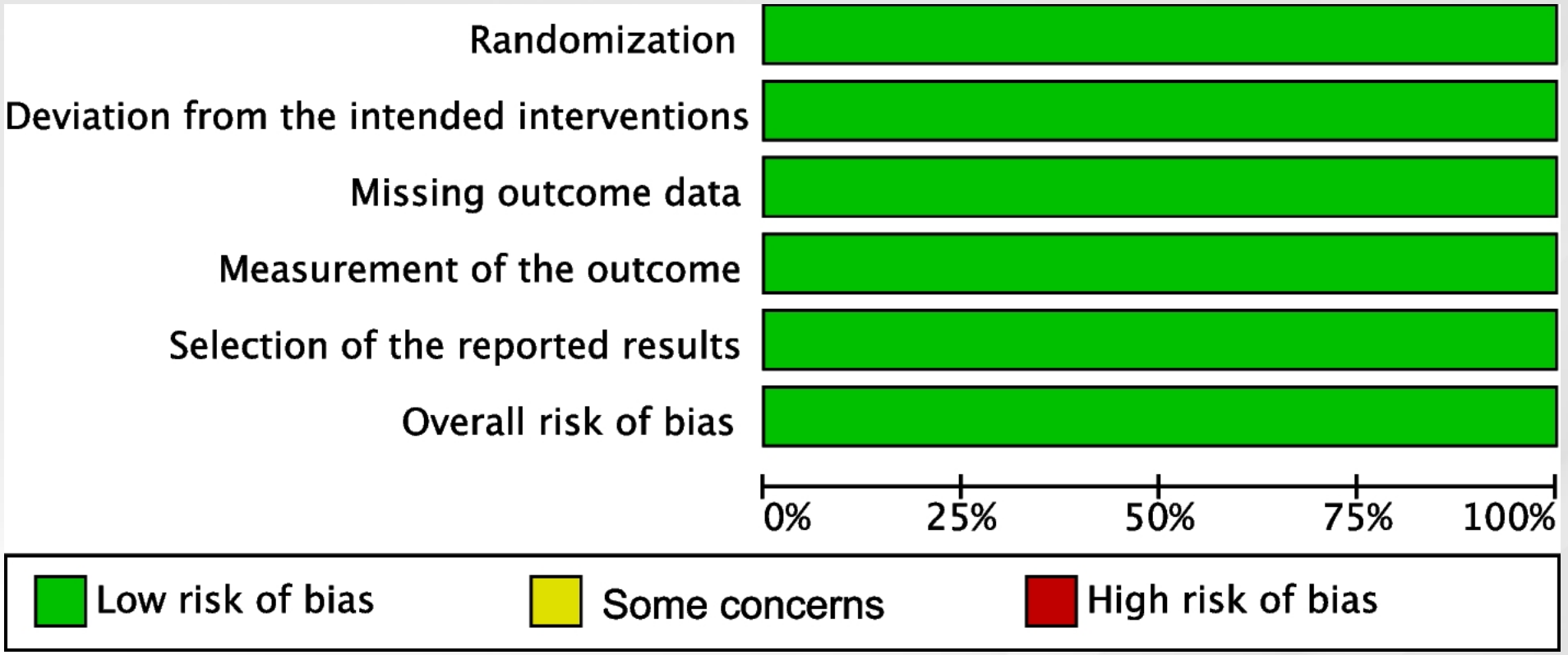
**Table 1** Trial characteristics

| Author, Journal, Study (Reference) | VNS dose (mg/mL) | Number of participants[a] | | Number of participants[b] | | Ethnicity | | Gender | |
|---|---|---|---|---|---|---|---|---|---|
| | | VNS | Placebo | VNS | Placebo | Latino or Hispanic | Not Latino or Hispanic | Male | Female |
| Wirta, Ophthalmology, ONSET-2 [8] | 0.6 | 239 | 228 | 260 | 252 | 100 | 658 | 182 | 576 |
| | 1.2 | 212 | | 246 | | | | | |
| Hugo Quiroz-Mercado, The Ocular Surface, MYSTIC [9] | 0.6 | 36 | 32 | 41 | 41 | 123 | 0 | 23 | 100 |
| | 1.2 | 29 | | 41 | | | | | |
| Wirta, Cornea, ONSET-1 [7] | 0.12 | 47 | 43 | 47 | 43 | 18 | 164 | 45 | 137 |
| | 0.6 | 46 | | 48 | | | | | |
| | 1.2 | 40 | | 44 | | | | | |

[a] Number of participants at randomization

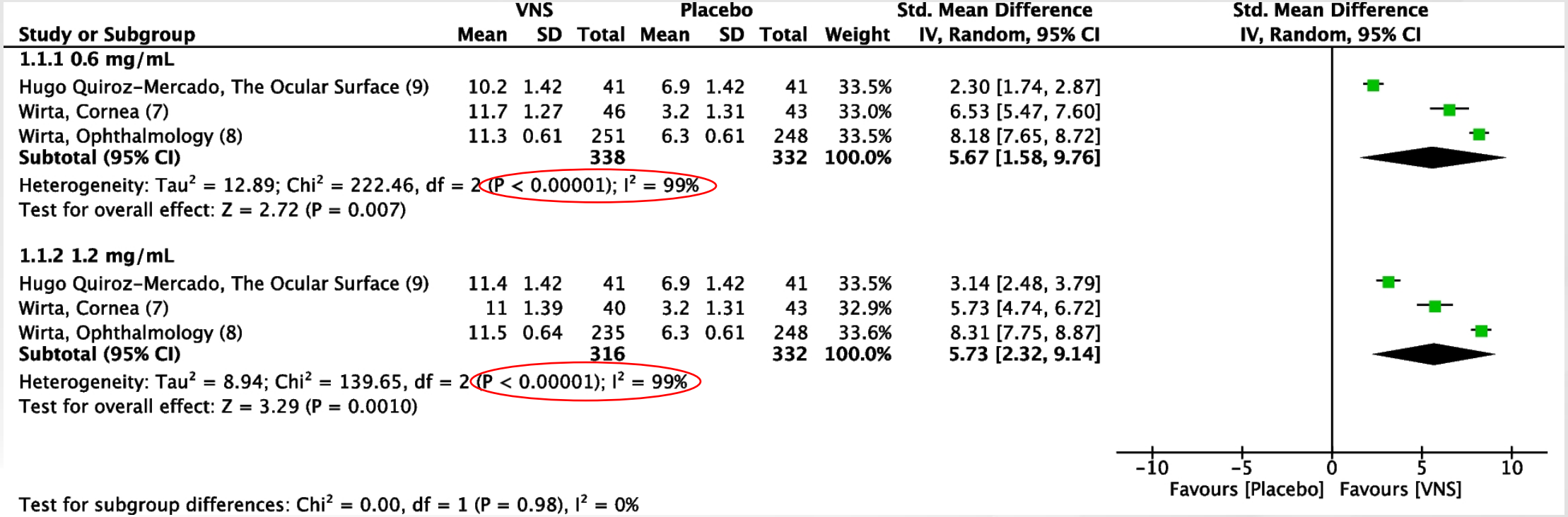
[b] Number of participants at study completion

# Results




Risk of bias summary

# Results

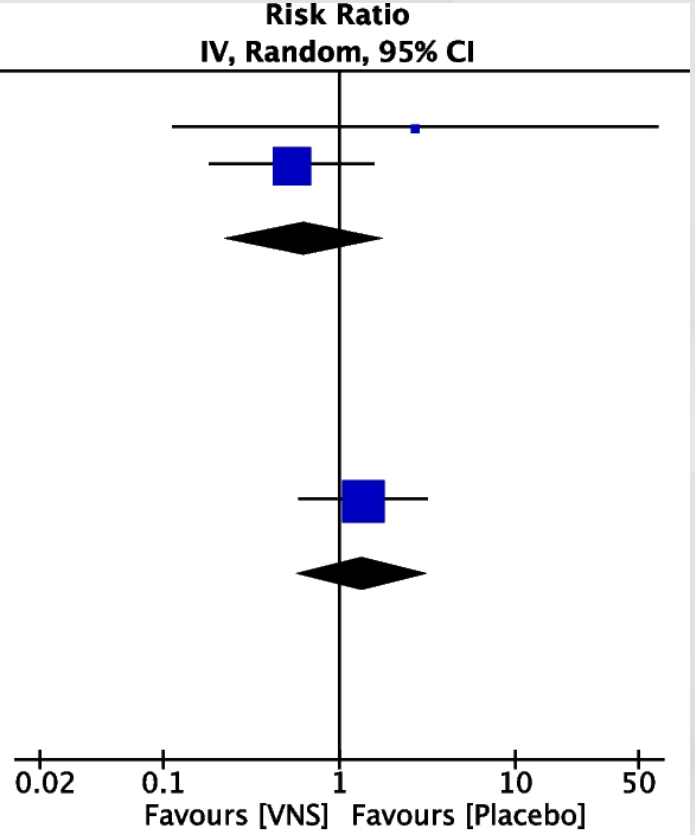



Forest plot of the mean change of Schirmer test score from baseline at day 28

# Results

| Study or Subgroup | VNS Events | VNS Total | Placebo Events | Placebo Total | Weight | Risk Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| **1.2.1 0.6 mg/mL** | | | | | | | |
| Wirta, Cornea (7) | 1 | 48 | 0 | 43 | 10.4% | 2.69 [0.11, 64.43] | 2022 |
| Wirta, Ophthalmology (8) | 5 | 260 | 9 | 251 | 89.6% | 0.54 [0.18, 1.58] | 2022 |
| Hugo Quiroz-Mercado, The Ocular Surface (9) | 0 | 41 | 0 | 41 | | Not estimable | 2022 |
| **Subtotal (95% CI)** | | **349** | | **335** | **100.0%** | **0.63 [0.23, 1.76]** | |
| Total events | 6 | | 9 | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.89$, df = 1 (P = 0.35); $I^2 = 0\%$ | | | | | | | |
| Test for overall effect: Z = 0.87 (P = 0.38) | | | | | | | |
| **1.2.2 1.2 mg/mL** | | | | | | | |
| Hugo Quiroz-Mercado, The Ocular Surface (9) | 0 | 41 | 0 | 41 | | Not estimable | 2022 |
| Wirta, Ophthalmology (8) | 12 | 245 | 9 | 251 | 100.0% | 1.37 [0.59, 3.18] | 2022 |
| Wirta, Cornea (7) | 0 | 44 | 0 | 43 | | Not estimable | 2022 |
| **Subtotal (95% CI)** | | **330** | | **335** | **100.0%** | **1.37 [0.59, 3.18]** | |
| Total events | 12 | | 9 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 0.72 (P = 0.47) | | | | | | | |

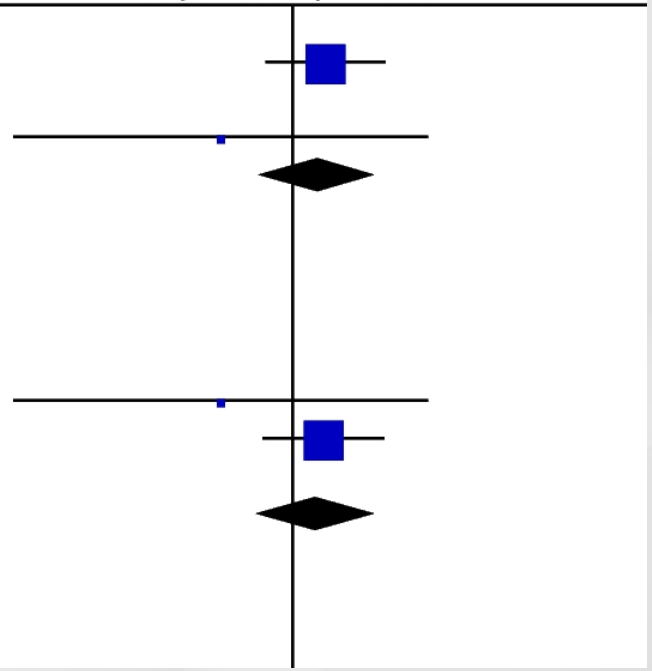
Test for subgroup differences: $Chi^2 = 1.29$, df = 1 (P = 0.26), $I^2 = 22.2\%$




Forest plot of serious adverse events.

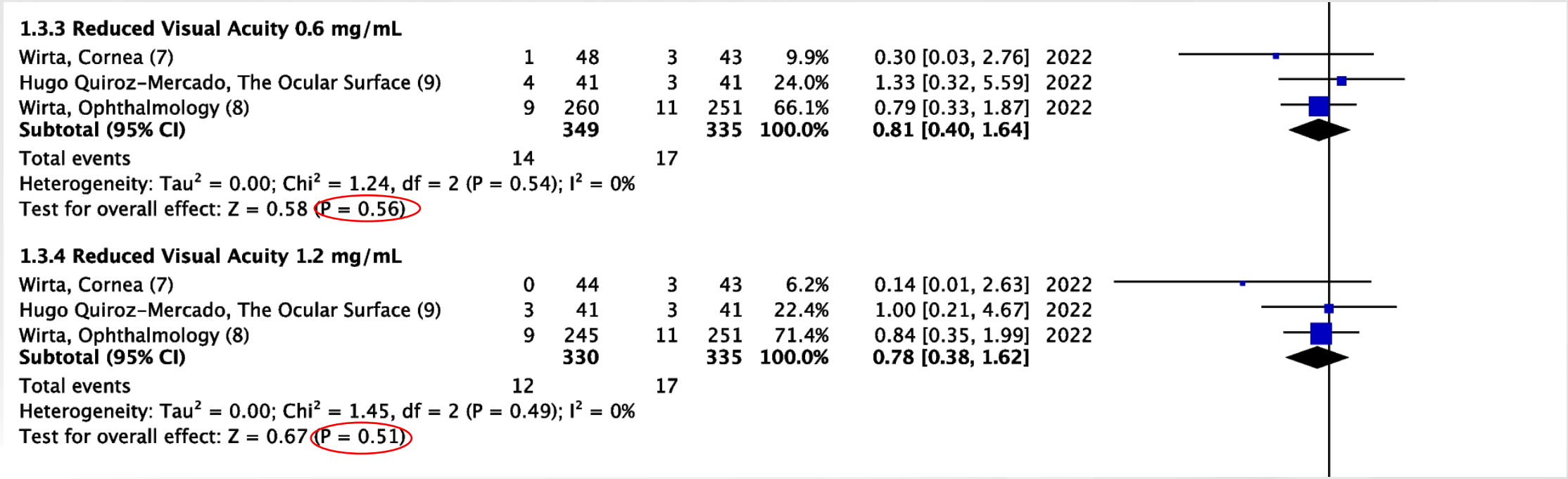
# Results

| Study or Subgroup | VNS Events | VNS Total | Placebo Events | Placebo Total | Weight | Risk Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| **1.3.1 Conjunctival Hyperaemia 0.6 mg/mL** | | | | | | | |
| Wirta, Ophthalmology (8) | 12 | 260 | 7 | 251 | 92.3% | 1.65 [0.66, 4.14] | 2022 |
| Wirta, Cornea (7) | 0 | 0 | 0 | 0 | | Not estimable | 2022 |
| Hugo Quiroz-Mercado, The Ocular Surface (9) | 0 | 41 | 1 | 41 | 7.7% | 0.33 [0.01, 7.95] | 2022 |
| **Subtotal (95% CI)** | | **301** | | **292** | **100.0%** | **1.46 [0.61, 3.53]** | |
| Total events | 12 | | 8 | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.90$, df = 1 (P = 0.34); $I^2 = 0\%$ | | | | | | | |
| Test for overall effect: Z = 0.85 (P = 0.40) | | | | | | | |
| **1.3.2 Conjunctival hyperaemia 1.2 mg/mL** | | | | | | | |
| Hugo Quiroz-Mercado, The Ocular Surface (9) | 0 | 41 | 1 | 41 | 7.9% | 0.33 [0.01, 7.95] | 2022 |
| Wirta, Ophthalmology (8) | 11 | 245 | 7 | 251 | 92.1% | 1.61 [0.63, 4.08] | 2022 |
| Wirta, Cornea (7) | 0 | 0 | 0 | 0 | | Not estimable | 2022 |
| **Subtotal (95% CI)** | | **286** | | **292** | **100.0%** | **1.42 [0.58, 3.47]** | |
| Total events | 11 | | 8 | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.87$, df = 1 (P = 0.35); $I^2 = 0\%$ | | | | | | | |
| Test for overall effect: Z = 0.77 (P = 0.44) | | | | | | | |




Forest plot of conjunctival hyperemia

# Results

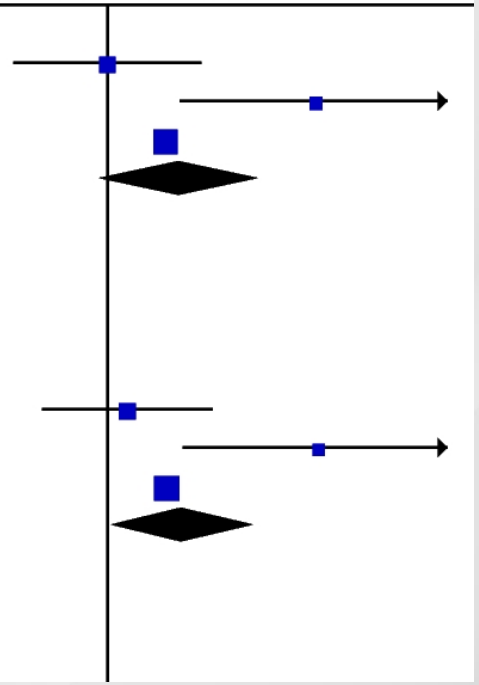


| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **1.3.3 Reduced Visual Acuity 0.6 mg/mL** | | | | | | | |
| Wirta, Cornea (7) | 1 | 48 | 3 | 43 | 9.9% | 0.30 [0.03, 2.76] | 2022 |
| Hugo Quiroz-Mercado, The Ocular Surface (9) | 4 | 41 | 3 | 41 | 24.0% | 1.33 [0.32, 5.59] | 2022 |
| Wirta, Ophthalmology (8) | 9 | 260 | 11 | 251 | 66.1% | 0.79 [0.33, 1.87] | 2022 |
| **Subtotal (95% CI)** | | **349** | | **335** | **100.0%** | **0.81 [0.40, 1.64]** | |
| Total events | 14 | | 17 | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.24$, df = 2 (P = 0.54); $I^2 = 0\%$ | | | | | | | |
| Test for overall effect: Z = 0.58 (P = 0.56) | | | | | | | |
| **1.3.4 Reduced Visual Acuity 1.2 mg/mL** | | | | | | | |
| Wirta, Cornea (7) | 0 | 44 | 3 | 43 | 6.2% | 0.14 [0.01, 2.63] | 2022 |
| Hugo Quiroz-Mercado, The Ocular Surface (9) | 3 | 41 | 3 | 41 | 22.4% | 1.00 [0.21, 4.67] | 2022 |
| Wirta, Ophthalmology (8) | 9 | 245 | 11 | 251 | 71.4% | 0.84 [0.35, 1.99] | 2022 |
| **Subtotal (95% CI)** | | **330** | | **335** | **100.0%** | **0.78 [0.38, 1.62]** | |
| Total events | 12 | | 17 | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.45$, df = 2 (P = 0.49); $I^2 = 0\%$ | | | | | | | |
| Test for overall effect: Z = 0.67 (P = 0.51) | | | | | | | |

Forest plot of reduced visual acuity

# Results

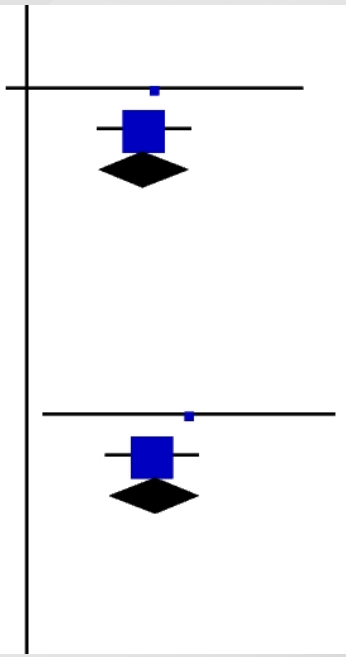
| Study or Subgroup | VNS Events | VNS Total | Placebo Events | Placebo Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.4.1 Sneezing- 0.6 mg/mL** | | | | | | |
| Hugo Quiroz-Mercado, The Ocular Surface (9) | 2 | 41 | 2 | 41 | 29.6% | 1.00 [0.15, 6.76] |
| Wirta, Cornea (7) | 38 | 48 | 0 | 43 | 20.4% | 69.14 [4.38, 1092.33] |
| Wirta, Ophthalmology (8) | 247 | 260 | 73 | 251 | 50.0% | 3.27 [2.69, 3.97] |
| **Subtotal (95% CI)** | | **349** | | **335** | **100.0%** | **4.30 [0.85, 21.70]** |
| Total events | 287 | | 75 | | | |
| Heterogeneity: $Tau^2 = 1.36$; $Chi^2 = 6.17$, df = 2 (P = 0.05); $I^2 = 68\%$ | | | | | | |
| Test for overall effect: Z = 1.76 (P = 0.08) | | | | | | |
| **1.4.2 Sneezing 1.2 mg/mL** | | | | | | |
| Hugo Quiroz-Mercado, The Ocular Surface (9) | 3 | 41 | 2 | 41 | 29.9% | 1.50 [0.26, 8.51] |
| Wirta, Cornea (7) | 37 | 44 | 0 | 43 | 18.0% | 73.33 [4.65, 1157.62] |
| Wirta, Ophthalmology (8) | 237 | 245 | 73 | 251 | 52.1% | 3.33 [2.74, 4.04] |
| **Subtotal (95% CI)** | | **330** | | **335** | **100.0%** | **4.58 [1.08, 19.44]** |
| Total events | 277 | | 75 | | | |
| Heterogeneity: $Tau^2 = 1.04$; $Chi^2 = 5.63$, df = 2 (P = 0.06); $I^2 = 64\%$ | | | | | | |
| Test for overall effect: Z = 2.06 (P = 0.04) | | | | | | |




Forest plot of sneezing

# Results

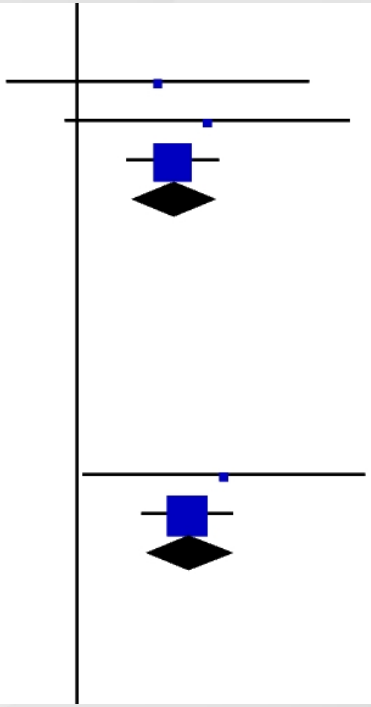
| | | | | | | |
|---|---|---|---|---|---|---|
| **1.4.3 Cough – 0.6 mg/mL** | | | | | | |
| Wirta, Cornea (7) | 6 | 48 | 0 | 43 | 9.1% | 11.67 [0.68, 201.30] |
| Wirta, Ophthalmology (8) | 49 | 260 | 5 | 251 | 90.9% | 9.46 [3.83, 23.36] |
| **Subtotal (95% CI)** | | **308** | | **294** | **100.0%** | **9.64 [4.08, 22.82]** |
| Total events | 55 | | 5 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 5.16 (P < 0.00001) | | | | | | |
| **1.4.4 Cough 1.2 mg/mL** | | | | | | |
| Wirta, Cornea (7) | 11 | 44 | 0 | 43 | 9.3% | 22.49 [1.37, 370.10] |
| Wirta, Ophthalmology (8) | 54 | 245 | 5 | 251 | 90.7% | 11.06 [4.50, 27.19] |
| **Subtotal (95% CI)** | | **289** | | **294** | **100.0%** | **11.82 [5.02, 27.83]** |
| Total events | 65 | | 5 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.22$, df = 1 (P = 0.64); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 5.65 (P < 0.00001) | | | | | | |



Forest plot of cough

# Results

| | | | | | | |
|---|---|---|---|---|---|---|
| **1.4.5 Throat Irritation – 0.6 mg/mL** | | | | | | |
| Hugo Quiroz-Mercado, The Ocular Surface (9) | 2 | 41 | 0 | 41 | 7.8% | 5.00 [0.25, 101.04] |
| Wirta, Cornea (7) | 7 | 48 | 0 | 43 | 8.8% | 13.47 [0.79, 229.07] |
| Wirta, Ophthalmology (8) | 35 | 260 | 5 | 251 | 83.4% | 6.76 [2.69, 16.97] |
| **Subtotal (95% CI)** | | **349** | | **335** | **100.0%** | **7.01 [3.03, 16.26]** |
| Total events | 44 | | 5 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.26$, df = 2 (P = 0.88); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 4.54 (P < 0.00001) | | | | | | |
| **1.4.6 Throat Irritation 1.2 mg/mL** | | | | | | |
| Hugo Quiroz-Mercado, The Ocular Surface (9) | 0 | 41 | 0 | 41 | | Not estimable |
| Wirta, Cornea (7) | 9 | 44 | 0 | 43 | 9.4% | 18.58 [1.11, 309.59] |
| Wirta, Ophthalmology (8) | 44 | 245 | 5 | 251 | 90.6% | 9.02 [3.64, 22.35] |
| **Subtotal (95% CI)** | | **330** | | **335** | **100.0%** | **9.65 [4.07, 22.90]** |
| Total events | 53 | | 5 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 5.14 (P < 0.00001) | | | | | | |



Forest plot of throat irritation

# Results

| Certainty assessment | | | | | | | Certainty |
|---|---|---|---|---|---|---|---|
| Outcome | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | |
| Schirmer test score | randomised trials | not serious | not serious | not serious | not serious | very strong association | ⊕⊕⊕⊕ High |
| Serious adverse events | randomised trials | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ High |
| Conjunctival hyperemia | randomised trials | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ High |
| Reduced visual acuity | randomised trials | not serious | not serious | not serious | not serious | none | ⊕⊕⊕⊕ High |
| Sneezing | randomised trials | not serious | serious[a] | not serious | serious[b] | none | ⊕⊕◯◯ Low |
| Cough | randomised trials | not serious | not serious | not serious | serious[b] | very strong association | ⊕⊕⊕⊕ High |
| Throat irritation | randomised trials | not serious | not serious | not serious | serious[b] | very strong association | ⊕⊕⊕⊕ High |

# Discussion

- Strengths
  - First Systematic review in this topic
  - Only RCTs
  - Novel systematic review and meta-analysis
  - Subgroup analysis
- Limitations
  - 3 RCTs only

# Conclusion

- VNS caused a highly significant improvement versus placebo.
- However, it caused an increased frequency of some nasal cavity-related AEs (i.e., cough and throat irritation).
- It did not cause neither SAEs or ocular AEs.
- Included studies had a low risk of bias

# Implications

- Implications on practice
  - VNS is speculated to be implemented among the prominent management options for DED in the future
- Implications on research
  - More RCTs are needed
  - Different doses with longer follow-up times should be assessed

# Thank you for listening