JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Use of Nonmedicated Control Substances in Randomized Clinical Trials of Patients With Chronic Rhinosinusitis

A Systematic Review and Single-Arm Meta-analysis

Lisa Caulley, MD, MPH; Joel James, BS; Claire Hopkins, BMBCh, DM

IMPORTANCE The effect of nonmedicated control substances in chronic rhinosinusitis remains unclear.

OBJECTIVE To assess the association of nonmedicated control substances in randomized clinical trials with disease outcomes in patients diagnosed with chronic rhinosinusitis.

DATA SOURCES AND STUDY SELECTION In this single-arm systematic review and meta-analysis, the Cochrane Library of Systematic Reviews, Ovid MEDLINE, Embase, PubMed, and ClinicalTrials.gov databases were searched for randomized clinical trials with a preintervention and postintervention design for chronic rhinosinusitis that were published between 1946 and January 23, 2019.

DATA EXTRACTION AND SYNTHESIS Paired reviewers independently extracted data. The analyses used random-effects models and the Cochrane risk of bias assessment to rate the quality of the evidence.

MAIN OUTCOMES AND MEASURES The primary outcomes were the association of nonmedicated control substances with 22-item Sinonasal Outcome Test (SNOT-22) scores or nasal symptom scores when SNOT-22 was not available.

RESULTS A total of 2305 abstracts were identified and screened, 725 articles were reviewed in full text, and 38 articles met the study criteria and were included in the meta-analysis. Among the 38 included studies, a total of 2258 adults (mean age range, 27-53 years; 20.0%-72.5% women) were randomized to receive nonmedicated control substances or sham interventions. Topical nonmedicated control substances were associated with significant reduction in SNOT-22 scores (mean difference [MD], −8.81; 95% CI, −12.60 to −5.03). A subgroup analysis of topical therapies, limited to saline irrigation and nasal spray diluents, found that topical diluents were associated with a greater reduction in SNOT-22 scores (MD, −11.45; 95% CI, −13.50 to −9.41) compared with saline irrigation (MD, −13.60; 95% CI, −19.95 to −7.25). Nonmedicated control substances were associated with a significant reduction in nasal obstruction scores (standardized MD [SMD], −0.42; 95% CI, −0.81 to −0.03). No significant change was found in rhinorrhea scores (SMD, −0.34; 95% CI, −1.37 to 0.69), postnasal drip scores (SMD, −0.96; 95% CI, −2.18 to 0.25), facial pain scores (SMD, −0.57; 95% CI, −1.68 to 0.55), or loss of smell scores (SMD, −0.18; 95% CI, −0.68 to 0.32).

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis of the use of nonmedicated control substances in randomized clinical trials of chronic rhinosinusitis outcomes suggests that the use of nonmedicated control substances is associated with limited improvements in SNOT-22 and nasal obstruction scores. These findings highlight potential areas of future research directions and the importance of randomized clinical trials to accurately estimate treatment effect.

Invited Commentary page 133

Supplemental content

Author Affiliations: Department of Otolaryngology–Head and Neck Surgery, The Ottawa Hospital, University of Ottawa, Ottawa, Ontario, Canada (Caulley); Department of Clinical Epidemiology, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada (Caulley); Department of Epidemiology, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands (Caulley); Department of Undergraduate Medicine, City University of New York School of Medicine, New York, New York (James); ENT Department, Guy's Hospital, London, United Kingdom (Hopkins).

Corresponding Author: Claire Hopkins, ENT Department, Guy's Hospital, Great Maze Pond, London SE1 9RT, United Kingdom (claire.hopkins@gstt.nhs.uk).

JAMA Otolaryngol Head Neck Surg. 2021;147(2):123-133. doi:10.1001/jamaoto.2020.3723
Published online November 12, 2020.

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Erasmus MC - Univ of Rotterdam User on 05/30/2022

A basic principle of randomized clinical trials (RCTs) is that comparing a drug against a placebo, or nonmedicated control, allows researchers to quantify the effectiveness of the drug. Although control groups in RCTs receive an inert or sham intervention, patients in the control arm of RCTs still derive some benefit when compared with groups that receive the active intervention.[1,2] The effect observed in control arms, or placebo effect, is presumed to be related to (1) observation and assessment (ie, Hawthorne effect); (2) performance of a therapeutic ritual; and (3) patient-practitioner interaction, which has the most robust effect in clinical trials.[1,3-5] Increasing evidence suggests that a placebo effect represents a genuine neurobiological phenomenon that is mediated by neurotransmitters and activation of specific, quantifiable, and relevant areas of the brain.[6,7] Furthermore, an estimated 4% to 26% of patients who are randomly assigned to placebos in trials discontinue their use because of perceived adverse or so-called nocebo effects.[7] Consequently, the question of whether nonmedicated controls or sham interventions have a quantitative effect in the treatment of diseases remains.

Chronic rhinosinusitis (CRS) is a long-term sinus disease that affects 1 in 10 adults in the UK.[8] Symptoms of CRS include a blocked and runny nose; loss of smell; facial pain; tiredness; and worsening of breathing problems, such as asthma.[9] A previous study[10] found that sinus disease can have a greater impact on quality of life than heart disease and back pain. Unfortunately, there is a paucity of RCTs, and currently many guidelines base treatment recommendations on outcomes of uncontrolled observational studies. To date, no studies have quantified the effect of nonmedicated control substances on signs and symptoms of CRS. An understanding of the size of the effect of nonmedicated controls on symptom relief will allow observational studies to be better interpreted and will help inform treatment choices.

Key Points

Question Can nonmedicated control substances improve patient-reported and observer-reported outcomes in chronic rhinosinusitis?

Findings This systematic review and meta-analysis of the use of nonmedicated control substances in 38 randomized clinical trials of patients with chronic rhinosinusitis found an improvement in quality-of-life measures (6.21 of 110 points) and in nasal obstruction scores reported using a visual analog scale (0.42 standardized points).

Meaning This study suggests that nonmedicated control substances are associated with limited improvements in the 22-item Sinonasal Outcome Test and nasal obstruction scores.

Methods

The review protocol was registered in PROSPERO International Prospective Register of Systematic Reviews. More detailed information can be found in the eMethods in the Supplement. Because this study was a review of the literature, no ethics approval was required. This study follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[11]

Study Selection

Five electronic databases (Cochrane Library of Systematic Reviews, Ovid MEDLINE, Embase, PubMed, and ClinicalTrials.gov) were searched with the assistance of a trained librarian, without language restriction, to identify publications of RCTs of CRS published between 1946 and January 23, 2019. In addition, ClinicalTrials.gov and references of included studies and systematic reviews were searched. Parallel RCTs of adults 18 years or older that specified a placebo group that received a nonmedicated control or a sham procedure were eligible for inclusion in the review. Inclusion criteria required that all patients in each study were diagnosed with CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP) according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2012,[9] although diagnostic criteria were allowed to vary across individual studies conducted before 2012. Nonmedicated control substances that are known to have a treatment effect in CRS were permitted if the trial was executed as a placebo-controlled trial. Two reviewers (L.C. and J.J.) independently assessed publications for inclusion in the review. A liberal accelerated process was adopted: 1 reviewer was required to include a study but 2 were required to exclude it. The full texts of all records passing level 1 screening were retrieved for level 2 screening to confirm final eligibility. Discrepancies were resolved through discussion by the review team. For more detailed information, see the eMethods in the Supplement.

Data Extraction

Data extraction was performed in Review Manager 5.3 using a standardized data extraction form.[12] Two independent reviewers (L.C. and J.J.) extracted trial details that pertained to the participants, interventions, and results of CRS outcomes. The primary outcome was the association of nonmedicated controls with disease-specific health-related quality of life as measured by the 22-item Sinonasal Outcome Test (SNOT-22) score or disease-severity symptom scores of nasal obstruction, discharge, facial pain, and sense of smell if SNOT-22 was unavailable. SNOT-22 evaluates patient-reported symptom severity and health-related quality of life in sinonasal conditions using a validated instrument on a scale from 0 to 110 (with higher scores indicating poorer outcomes). Other relevant objective outcomes were extracted, such as association with inflammatory markers, Lund-Kennedy endoscopic grading system, Lund-MacKay computed tomography score, generic health-related quality of life as measured by the EuroQol-5D or Medical Outcomes Study 36-Item Short-Form Survey-36 (SF-36), and adverse events. For more detailed information, see the eMethods in the Supplement.

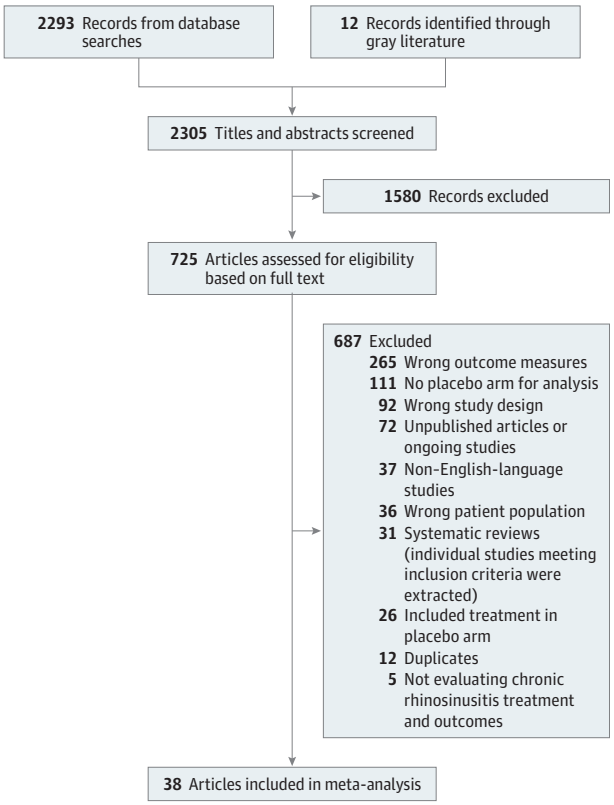
Risk of Bias Assessment

Internal validity of study design and conduct was assessed using the risk of bias tool of the Cochrane Collaboration.[13] Adequate sequence generation, allocation concealment, patient

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Erasmus MC - Univ of Rotterdam User on 05/30/2022

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow Diagram



blinding, addressing incomplete outcome data after randomization, and absence of selective reporting in considering risk of bias were assessed. Two reviewers (L.C. and J.J.) independently judged whether the risk of bias for each criterion was considered low, high, or unclear. Discrepancies were resolved through discussion by the review team.

Data Synthesis

Study results were presented separately for each outcome. Study results extracted from the original publication were transformed into mean differences (MDs) and standardized MDs (SMDs) with the associated 95% CIs or the numbers of participants experiencing an event.[2,12,14-18] For more detailed information, see the eMethods in the Supplement.

Results

A total of 2305 abstracts were identified and screened, 725 articles were reviewed in full text, and 38 articles that followed a pretreatment and posttreatment design were included in the meta-analysis. A flowchart of study retrieval and selection is provided in **Figure 1**. The characteristics of the studies are presented in the **Table**.[19-56] Among the 38 included studies, a total of 2258 adults (mean age range, 27-53 years; 20.0%-72.5% women) were randomized to receive nonmedicated control substances or sham interventions. Study sizes ranged from 8 to 373 participants, and baseline mean nasal polyp scores in studies that included patients with CRSwNP ranged from 3.1 to 7.2. Among patients who had undergone previous surgery, the proportion of participants who had undergone at least 1 prior surgical procedure ranged from 21.0% to 100.0%. Additional details of the included studies are provided in eTable 1 in the Supplement.

Disease-Specific Health-Related Quality-of-Life Outcomes

Eight studies[22,29,30,34,37,42,47,50] reported on the effect of nonmedicated control substances on SNOT-22 scores (eTable 2 in the Supplement). The studies were heterogeneous in the formulation of the controls (oral and topical) and duration of treatment (30 days to 6 months). Nonmedicated controls were associated with a significant reduction in SNOT-22 scores (MD, −6.21; 95% CI, −9.91 to −2.50). A subgroup analysis was performed for the formulation of the therapy (**Figure 2**). Five trials[29,30,34,42,47] used topical controls, 2 trials[37,50] used oral controls, and 1 trial[22] used topical and oral controls. Pooled results from the trials using topical controls showed a significant benefit (MD, −8.81; 95% CI, −12.60 to −5.03), whereas oral controls did not (MD, −1.94; 95% CI, −5.75 to 1.87). Stratification by formulation of topical therapy demonstrated a greater benefit of treatment with topical nasal spray (administered for 4 months) compared with topical irrigation (administered for ≤3 months). A post hoc analysis demonstrated that the 2 studies[34,42] of patients treated with topical nasal spray also had protocols that permitted use of rescue medications in the form of antihistamines after 4 weeks of treatment. Neither study presented details on use of protocol-permitted medications by study participants. There was strong evidence of heterogeneity in the topical irrigation subgroup (I^2 = 74%). The statistical significance and high level of heterogeneity in this subgroup were accounted for by the trial by Tait et al[47] of topical irrigation for 30 days. Exclusion of this trial as an outlier decreased the level of heterogeneity to 0%; the measured effect in patients that received topical irrigation decreased to include the possibility of a null effect (MD, −3.09; 95% CI, −7.20 to 1.03). A subgroup analysis of topical therapies, limited to saline irrigation and nasal spray diluents, demonstrated that topical diluents were more effective in reducing SNOT-22 scores (MD, −11.45; 95% CI, −13.50 to −9.41) reported in 2 studies[34,42] compared with saline irrigation (MD, −13.60; 95% CI, −19.95 to −7.25) reported in 1 study.[47]

Change in Individual Severity Symptom Scores

The change in patient-reported symptom scores was reported in 7 studies[21,25,34,42,48,54,56] (eTable 3 in the Supplement). Topical therapy was associated with a significant reduction in nasal obstruction scores (SMD, −0.42; 95% CI, −0.81 to −0.03) (**Figure 3**). Continued treatment with topical therapy beyond 3 months did not provide any additional benefit (≤3 months: SMD, −0.33; 95% CI, −0.71 to 0.06; 3-6 months: SMD, −0.92; 95% CI, −2.64 to 0.80). A subgroup analysis revealed that the beneficial outcome with topical therapy on nasal obstruction scores was limited to topical nasal spray (nasal irrigation: SMD, −0.16; 95% CI, −0.69 to 0.37; nasal spray: SMD, −0.54; 95% CI, −0.96 to −0.12). Of note, both studies[21,54] in the

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Erasmus MC - Univ of Rotterdam User on 05/30/2022

Table. Characteristics of Eligible Randomized Clinical Trials

Source	No. of patients (No. of patients in control arm of RCT)	Diagnosis	No. (%) of patients with nasal polyps	Bilateral endoscopic nasal polyp score, mean (SD)	No. (%) of patients with ≥1 previous sinus surgery	Type of nonmedicated control substances or sham intervention	Composition of nonmedicated control substance	Follow-up duration
Anzić et al,[19] 2017	60 (27)	CRSsNP	0 (0)	0	0 (0)	Oral	NR	8 wk
Bellussi et al,[20] 1990	40 (20)	CRS	NR	NR	NR	Oral	NR	10 d
Ebbens et al,[21] 2006	116 (57)	Mixed	48 (84)	7.2 (3.7)	57 (100)	Topical irrigation	Cernevit, 3.4 mL/L in sterile water containing 2.5% glucose	13 wk
Esmaeilzadeh et al,[22] 2015	34 (16)	CRSwNP	16 (100)	NR	NR	Oral and topical nasal spray	Normal saline and sugar capsules	6 mo
Gevaert et al,[23] 2011	30 (10)	CRSwNP	10 (100)	5.5 (1.65)	8 (80)	Injections	NR	8 wk
Gevaert et al,[24] 2013	23 (8)	CRSwNP	8 (100)	6 (6-8)[a]	6 (75)	Injections	NR	16 wk
Hamilos et al,[25] 1999	21 (11)	CRSwNP	10 (100)	NR	NR	Topical nasal spray	Diluent	4 wk
Hansen et al,[26] 2010	20 (10)	CRSsNP	0 (0)	NR	10 (100)	Topical nasal spray	Aqueous medium containing microcrystalline cellulose and carboxymethyl-cellulose sodium, benzalkonium chloride, EDTA disodium salt dehydrate, dextrose anhydrous, and polysorbate 80	12 wk
Haye et al,[27] 1998	45 (22)	CRSwNP	22 (100)	NR	NR	Oral	NR	12 wk
Hissaria et al,[28] 2006	41 (20)	CRSwNP	20 (100)	NR	13 (65)	Oral	NR	2 wk
Jiang et al,[29] 2015	87 (44)	CRS	16 (41)	4.92 (1.37)	0 (0)	Topical irrigation	Yellowish dye mixed with 60 mL of sterile water	8 wk
Jiang et al,[30] 2018	83 (42)	CRS	14 (38.8)	5.31 (1.43)	0 (0)	Topical irrigation	Yellowish dye mixed with 60 mL of sterile water	8 wk
Keith et al,[31] 2000	104 (52)	CRSwNP	52 (100)	NR	34 (65)	Topical nasal spray	NR	12 wk
Kennedy et al,[32] 2005	53 (28)	CRS	NR	NR	NR	Oral	NR	6 wk
Kirtsreeakul et al,[33] 2011	112 (47)	CRSwNP	46 (100)	3.09 (1.05)	0 (0)	Oral	NR	14 d
Leopold et al,[34] 2019	323 (80)	CRSwNP	80 (100)	3.8 (1.08)	22 (27.5)	Topical nasal drops	Diluent of fluticasone propionate	16 wk[b]
Lildholdt et al,[35] 1995	126 (40)	CRSwNP	40 (100)	NR	NR	Topical nasal spray	Lactose	4 wk
Lund et al,[36] 2004	167 (86)	CRSsNP	0 (0)	0	NR	Topical	NR	20 wk
Mortazavi et al,[37] 2017	38 (19)	CRSwNP	19 (100)	NR	NR	Oral	NR	6 mo
Mösges et al,[38] 2011	60 (35)	CRSsNP	0 (0)	NR	NR	Topical	NR	16 wk
Palm et al,[39] 2017	929 (306)	CRSsNP	0 (0)	NR	NR	Oral	NR	12 wk
Penttilä et al,[40] 2000	142 (47)	CRSwNP	47 (100)	NR	10 (21)	Topical nasal drops	NR	12 wk
Rössberg et al,[41] 2005	65 (19)	CRSsNP	0 (0)	0	4 (21.1)	Sham acupuncture	NA	12 wk
Sindwani et al,[42] 2019	323 (82)	CRSwNP	82 (100)	3.8 (0.94)	52 (63.4)	Topical nasal spray	Diluent of fluticasone propionate	16 wk[b]
Small et al,[43] 2005	354 (117)	CRSwNP	117 (100)	4.25	NR	Topical	Aqueous medium containing glycerin, microcrystalline cellulose, carboxymethylcellulose sodium, sodium citrate, 0.25% wt/wt phenylethyl alcohol, citric acid, benzalkonium chloride, and polysorbate 80	4 mo

(continued)

topical irrigation subgroup used sterile water. A subgroup analysis did not reveal a significant difference in patients by presence of protocol-permitted rescue medications. Two trials[21,56] reported mean change in rhinorrhea scores in

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Erasmus MC - Univ of Rotterdam User on 05/30/2022

Table. Characteristics of Eligible Randomized Clinical Trials (continued)

Source	No. of patients (No. of patients in control arm of RCT)	Diagnosis	No. (%) of patients with nasal polyps	Bilateral endoscopic nasal polyp score, mean (SD)	No. (%) of patients with ≥1 previous sinus surgery	Type of nonmedicated control substances or sham intervention	Composition of nonmedicated control substance	Follow-up duration
Stjärne et al,[44] 2006a	310 (106)	CRSwNP	106 (100)	4.17	NR	Topical nasal spray	Aqueous medium containing glycerin, microcrystalline cellulose, carboxymethylcellulose sodium, sodium citrate, 0.25% wt/wt phenylethyl alcohol, citric acid, benzalkonium chloride, and polysorbate 80	4 mo
Stjärne et al,[45] 2006b	298 (145)	CRSwNP	100 (69.0)	NR	38 (26.2)[c]	Topical nasal spray	Aqueous medium containing glycerin, microcrystalline cellulose, carboxymethylcellulose sodium, sodium citrate, 0.25% wt/wt phenylethyl alcohol, citric acid, benzalkonium chloride, and polysorbate 80	16 wk
Stjärne et al,[46] 2009	162 (82)	CRSwNP	44 (64)	NR	NR	Topical nasal spray	NR	168 +/− 7 d
Tait et al,[47] 2018	74 (34)	Mixed	6 (16)	4.9 (1.9)	12 (32)	Topical irrigation	Normal saline and lactose	4 wk
Vaidyanathan et al,[48] 2011	60 (30)	CRSwNP	30 (100)	4.8 (0.9)	9 (30)	Oral	NR	2 wk
Vento et al,[49] 2012	60 (30)	CRSwNP	30 (100)	NR	20 (66.7)	Oral	NR	9 mo
Videler et al,[50] 2011	60 (31)	CRSwNP	13 (41.9)	NR	NR	Oral	NR	24 wk
Vlckova et al,[51] 2009	109 (55)	CRSwNP	55 (100)	NR	40 (73)	Topical nasal spray	Aqueous medium containing microcrystalline cellulose, carboxymethylcellulose sodium, benzalkonium chloride, EDTA disodium salt dehydrate, dextrose anhydrous, and polysorbate 80	14 wk
Wallwork et al,[52] 2006	64 (35)	CRSsNP	0 (0)	NR	NR	Oral	NR	24 wk
Wang et al,[53] 2015	60 (30)	CRSwNP	30 (100)	4.72 (0.67)	0 (0)	Topical irrigation	Normal saline	14 d
Yousefi et al,[54] 2017	80 (40)	Mixed	6 (15)	NR	0 (0)	Topical irrigation	Sterile water	12 wk
Yu et al,[55] 2017	43 (22)	CRS	NR	NR	0 (0)	Topical irrigation	Normal saline	8 wk
Zhou et al,[56] 2016	748 (373)	CRSwNP	373 (100)	3.7 (1.1)	85 (22.8)	Topical nasal spray	Aqueous medium containing glycerin, microcrystalline cellulose, carboxymethylcellulose sodium, sodium citrate, 0.25% wt/wt phenylethyl alcohol, citric acid, benzalkonium chloride, and polysorbate 80	16 wk

Abbreviations: CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; mixed, chronic rhinosinusitis with and without nasal polyps; NA, not applicable; NR, not reported; RCT, randomized clinical trial.

[a] Median and interquartile range.

[b] Nasal obstruction scores reported at 4 weeks.

[c] Authors reported values for more than 2 previous operations.

patients with CRSwNP following use of nonmedicated control substances with no significant difference observed (SMD, −0.34; 95% CI, −1.37 to 0.69) (eFigure 1A in the Supplement). Similarly, no significant change occurred in postnasal drip scores (SMD, −0.96; 95% CI, −2.18 to 0.25) (eFigure 1B in the Supplement), facial pain scores (SMD, −0.57; 95% CI, −1.68 to 0.55) (eFigure 1C in the Supplement), and loss of smell scores (SMD, −0.18; 95% CI, −0.68 to 0.32) (eFigure 1D in the Supplement).

Generic Health-Related Quality-of-Life Outcomes

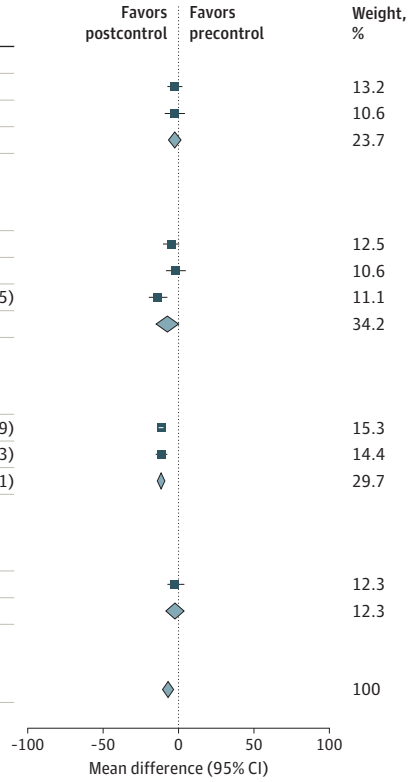
Rössberg et al[41] reported outcomes of EuroQoL-5D visual analog scale in patients with CRSsNP and identified no improvement in scores with sham acupuncture (MD, 5.20; 95% CI, −6.93 to 17.33). However, this study was at high risk for bias because of inadequately concealed allocation and blinding of study personnel. In addition, 2 studies[21,41] reported outcomes for SF-36 component scores (**Figure 4** and eTable 4 in the Supplement). Nonmedicated control was not associated

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Erasmus MC - Univ of Rotterdam User on 05/30/2022

Figure 2. Randomized Clinical Trials of the Association of Nonmedicated Control Substances With the 22-Item Sinonasal Outcome Test (SNOT-22)

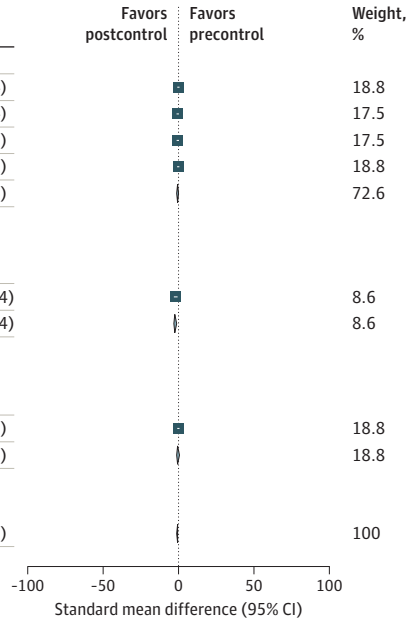
Study	Mean difference (SE)	Mean difference (95% CI)	Weight, %
Oral			
Mortazavi et al,[37] 2017	-1.91 (2.34)	-1.91 (-6.50 to 2.68)	13.2
Videler et al,[50] 2011	-2 (3.49)	-2.00 (-8.84 to 4.84)	10.6
Subtotal		-1.94 (-5.75 to 1.87)	23.7
Heterogeneity: $\tau^2=0$; $\chi^2_1=0$ ($P=.98$); $I^2=0\%$			
Test for overall effect: $z=1.00$ ($P=.32$)			
Topical irrigation			
Jiang et al,[29] 2015	-4.13 (2.64)	-4.13 (-9.30 to 1.04)	12.5
Jiang et al,[30] 2018	-1.28 (3.47)	-1.28 (-8.08 to 5.52)	10.6
Tait et al,[47] 2018	-13.6 (3.24)	-13.60 (-19.95 to -7.25)	11.1
Subtotal		-6.33 (-13.28 to 0.63)	34.2
Heterogeneity: $\tau^2=28.06$; $\chi^2_2=7.84$ ($P=.02$); $I^2=74\%$			
Test for overall effect: $z=1.78$ ($P=.07$)			
Topical nasal spray			
Leopold et al,[34] 2019	-11.7 (1.28)	-11.70 (-14.21 to -9.19)	15.3
Sindwani et al,[42] 2019	-10.96 (1.8)	-10.96 (-14.49 to -7.43)	14.4
Subtotal		-11.45 (-13.50 to -9.41)	29.7
Heterogeneity: $\tau^2=0$; $\chi^2_1=0.11$ ($P=.74$); $I^2=0\%$			
Test for overall effect: $z=10.98$ ($P<.001$)			
Oral and topical nasal spray			
Esmaeilzadeh et al,[22] 2015	-1.7 (2.7)	-1.70 (-6.99 to 3.59)	12.3
Subtotal (95% CI)		-1.70 (-6.99 to 3.59)	12.3
Heterogeneity: not applicable			
Test for overall effect: $z=0.63$ ($P=.53$)			
Total		-6.21 (-9.91 to -2.50)	100
Heterogeneity: $\tau^2=21.63$; $\chi^2_7=35.11$ ($P<.001$); $I^2=80\%$			
Test for overall effect: $z=3.28$ ($P=.001$)			
Test for subgroup differences: $\chi^2_3=26.11$ ($P<.001$); $I^2=88.5\%$			



The SNOT-22 scores ranged from 0 to 110, with higher scores indicating poorer outcomes, and a minimally clinically important difference of 8.90.[58]

Figure 3. Randomized Clinical Trials of the Association of Nonmedicated Control Substances With Symptom Severity Scores for Nasal Obstruction or Congestion Based on a Visual Analog Scale

Study	Standard mean difference (SE)	Standard mean difference (95% CI)	Weight, %
Topical nasal spray <3 mo			
Hamilos et al,[25] 1999	-0.1 (0.38)	-0.10 (-0.84 to 0.64)	18.8
Leopold et al,[34] 2019	-0.54 (0.4)	-0.54 (-1.32 to 0.24)	17.5
Sindwani et al,[42] 2019	-0.49 (0.4)	-0.49 (-1.27 to 0.29)	17.5
Yousefi et al,[54] 2017	-0.21 (0.38)	-0.21 (-0.95 to 0.53)	18.8
Subtotal		-0.33 (-0.71 to 0.06)	72.6
Heterogeneity: $\tau^2=0$; $\chi^2_3=0.90$ ($P=.83$); $I^2=0\%$			
Test for overall effect: $z=1.67$ ($P=.09$)			
Topical nasal spray 3-6 mo			
Zhou et al,[56] 2016	-1.87 (0.63)	-1.87 (-3.10 to -0.64)	8.6
Subtotal		-1.87 (-3.10 to -0.64)	8.6
Heterogeneity: not applicable			
Test for overall effect: $z=2.97$ ($P=.003$)			
Topical irrigation 3-6 mo			
Ebbens et al,[21] 2006	-0.11 (0.38)	-0.11 (-0.85 to 0.63)	18.8
Subtotal		-0.11 (-0.85 to 0.63)	18.8
Heterogeneity: not applicable			
Test for overall effect: $z=0.29$ ($P=.77$)			
Total		0.42 (-0.81 to -0.03)	100
Heterogeneity: $\tau^2=0.07$; $\chi^2_5=7.07$ ($P=.22$); $I^2=29\%$			
Test for overall effect: $z=2.09$ ($P=.04$)			
Test for subgroup differences: $\chi^2_2=6.17$ ($P=.05$); $I^2=67.6\%$			



with physical component scores (MD, 0.62; 95% CI, −1.46 to 2.70) or mental health component scores (MD, 2.06; 95% CI, −0.25 to 4.36). These findings failed to achieve significance with exclusion of the study by Rössberg et al[41] (physical component scores: MD, 1.40; 95% CI, −1.27 to 4.07; mental health component scores: MD, 1.90; 95% CI, −1.06 to 4.86).

© 2020 American Medical Association. All rights reserved.

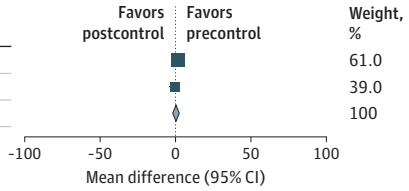
Downloaded From: https://jamanetwork.com/ by a Erasmus MC - Univ of Rotterdam User on 05/30/2022

Figure 4. Randomized Clinical Trials of the Association of Nonmedicated Controls With Medical Outcomes Study 36-Item Short-Form Health Survey SF-36 Scores

A Physical component scores

Study	Mean difference (SE)	Mean difference (95% CI)	Weight, %
Ebbens et al,[27] 2006	1.4 (1.36)	1.40 (-1.27 to 4.07)	61.0
Rössberg et al,[41] 2005	-0.6 (1.7)	-0.60 (-3.93 to 2.73)	39.0
Subtotal		0.62 (-1.46 to 2.70)	100

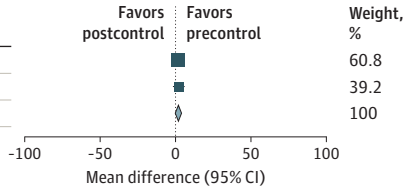
Heterogeneity: $\tau^2 = 0$; $\chi^2_1 = 0.84$ ($P = .36$); $I^2 = 0\%$
Test for overall effect: $z = 0.58$ ($P = .56$)



B Mental health component scores

Study	Mean difference (SE)	Mean difference (95% CI)	Weight, %
Ebbens et al,[27] 2006	1.9 (1.51)	1.90 (-1.06 to 4.86)	60.8
Rössberg et al,[41] 2005	2.3 (1.88)	2.30 (-1.38 to 5.98)	39.2
Subtotal		2.06 (-0.25 to 4.36)	100

Heterogeneity: $\tau^2 = 0$; $\chi^2_1 = 0.03$ ($P = .87$); $I^2 = 0\%$
Test for overall effect: $z = 1.75$ ($P = .08$)



Endoscopic and Imaging Outcome Measures

The pooled estimate for the 3 included trials[21,47,55] indicated a reduction in the Lund-Kennedy endoscopic score (MD, −1.75; 95% CI, −2.81 to −0.70) (eTable 5 and eFigure 2 in the Supplement) with topical treatment. A subgroup analysis of 2 trials[47,55] of topical irrigation treatment for 3 months or longer revealed significant improvement in Lund-Kennedy scores (MD, −1.91; 95% CI, −3.41 to −0.41). However, there was substantial heterogeneity in this subgroup (I^2 = 95%). One study[21] of topical therapy treatment confirmed a sustained significant improvement in mean Lund-Kennedy scores at 13 weeks (MD, −1.40; 95% CI, −2.36 to −0.44). Placebo treatment was not associated with improved mean Lund-Mackay scores (MD, −0.30; 95% CI, −1.00 to 0.40) (eFigure 3 and eTable 6 in the Supplement).

Inflammatory Markers

Six studies[19,22,25,48,52,54] reported outcomes from nonmedicated controls on inflammatory markers in plasma serum and nasal secretions (eTable 7 in the Supplement). Wallwork et al[52] observed an increase in interleukin 8 (MD, 68.00 pg/mL; 95% CI, 53.03-82.97 pg/mL), fucose (MD, 1.20 µmol/L; 95% CI, 0.27-2.13 µmol/L), and α_2-macroglobulin (MD, 0.25 µg/mL; 95% CI, 0.02-0.48 µg/mL) in nasal lavages of patients with CRSsNP after 12 weeks of oral therapy. Yousefi et al[54] reported a decrease in serum IgE (SMD, −11.49 mg/dL; 95% CI, −22.96 to −0.02 mg/dL) and nasal mucosa eosinophil counts (MD, −1.24/µL; 95% CI, −2.35 to −0.13/µL) after 3 months of topical therapy in 40 patients with CRS. The remaining studies[19,22,25,48] did not identify an effect of nonmedicated control substances on inflammatory markers.

Adverse Events

Eighteen trials[20,21,23,27,28,30-33,36,38-40,45,48,51,55,56] reported on any adverse events (eFigure 4 in the Supplement). There was a high level of variability among studies in the analysis (I^2 = 95%). The rate of adverse events was 31% (95% CI, 13.0%-53.0%) in the topical controls and 41.0% (95% CI, 22.0%-62.0%) in the oral controls.

Thirteen trials[23,26,31,34,35,38-40,48,49,51,53,56] reported on serious adverse events (eFigure 5 in the Supplement). Overall, serious adverse events were rarely observed (0%; 95% CI, 0%-0%), irrespective of type of therapy. Thirteen studies[24-26,28,34,38-40,43-46,56] reported on adverse events that led to withdrawal from trials (eFigure 6A in the Supplement). The pooled estimate of adverse events leading to withdrawal from trials was 2.0% (95% CI, 1.0%-4.0%). A subgroup analysis of duration of therapy revealed that the pooled estimate of adverse events leading to withdrawal for topical nasal sprays was 7.0% (95% CI, 1.0%-17.0%) in patients who received treatment for 3 months or less and 2.0% (95% CI, 1.0%-3.0%) in patients who received treatment for 3 to 6 months. A subgroup analysis revealed no significant difference by nasal polyp status (CRSwNP: 3.0%; 95% CI, 1.0%-5.0%; CRSsNP: 3.0%; 95% CI, 0.0%-12.0%) (eFigure 6B in the Supplement).

The presence of rescue medications or continued baseline medications was not associated with overall adverse events, severe adverse events, or withdrawal from studies because of adverse events.

Risk of Bias

The risk of bias assessment is presented in eFigure 7 in the Supplement. Thirty-four trials (89.5%) were at risk for bias for at least 1 of the following domains. However, 32 (84.2%) adequately generated their randomization sequence, 25 (65.8%) adequately concealed allocation, 32 (84.2%) blinded participants and personnel, and 29 (76.3%) blinded outcome assessors. Potential sources of bias resulted from incomplete outcome data (n = 20 [52.6%] trials) and selective reporting (n = 25 [65.8%] trials).

Discussion

Informed consent requires researchers to provide participants with information about research that is accurate,

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Erasmus MC - Univ of Rotterdam User on 05/30/2022

complete, and understandable, including a detailed description of the effect of nonmedicated control substances. To our knowledge, this study is the first systematic review and meta-analysis of the association of nonmedicated control substances and sham interventions with patient-reported and observed outcomes in CRS. The measurable benefits and harms of nonmedicated control substances in this review highlight the importance of RCTs to accurately estimate the effect of interventions and underscores the need to exercise caution in interpreting noncontrolled observational studies.

The pooled estimates of the association with health-related quality of life varied. Although topical nonmedicated control substances in the form of nasal sprays and saline irrigations were significantly associated with improved SNOT-22 outcomes, the reduction met the criteria for only a minimal clinically important difference (a score reduction of 8.90)[57] in 2 studies[34,42] that used topical nasal sprays in the form of the diluent of fluticasone propionate. Studies of individual symptom severity scores revealed that use of nonmedicated control substances was associated with improvements in nasal obstruction symptoms in topical nonmedicated control substances irrespective of prolonged duration of treatment. Noninert ingredients of the diluent in the topical nasal spray could have an unintended physical effect as another possible explanation for the improvement. The effects of topical diluents may mimic that of xylitol, a 5-carbon sugar alcohol that has gained recent attention as a natural antibacterial agent that can improve symptoms of CRS. Interestingly, the association observed with patient-reported outcomes was limited to local nonmedicated control substances compared with systemic therapy.

Selection of truly inert controls for RCTs of CRS is challenging.[58] Hypotonic solutions are known to cause mucosal damage that exacerbates CRS.[59] As such, it is not surprising that in 4 studies,[21,29,30,54] which used sterile water as a nonmedicated control, no improvement in individual symptom scores was observed. By contrast, isotonic irrigations, which assist in dislodging mucus and restoring mucociliary clearance, are well recognized for their ability to improve symptom-based and endoscopic outcome measures.[9,60] In this analysis, topical irrigations were associated with measured improvements in Lund-Kennedy endoscopic scores, in addition to patient-reported outcomes. This observed benefit in topical placebo therapy is expected because several studies[47,53,55] used saline irrigations in the nonmedicated control arm.

Reported adverse events from nonmedicated control substances ranged from 0% to 64% in trials; the rates were comparable in the oral and topical groups. Serious adverse events were rare. The trend in adverse events that led to withdrawal from trials of topical controls suggests that patient dropout was higher in the first 3 months of therapy (range, 13%-15%). With prolonged topical treatment, rates of withdrawal decreased to 2%.

There is a paucity of literature on the natural evolution of untreated CRS, but this study highlights the need for further research in this domain. A small study[61] of untreated patients with CRS without acute exacerbations identified a trend toward subjective improvement in 25% of patients with CRS during a 4-week period. Notably, there were no changes in endoscopic or radiographic outcomes or inflammatory markers during the same period. The additional benefit in subjective and objective parameters observed in the current systematic review could be related to the effect of the use of nonmedicated control substances or the continued observation of patients during a prolonged period. Further research is needed to differentiate these end points and understand the natural history of CRS.

The results of this study add to the limited evidence that suggests an effect of nonmedicated control substances on chronic diseases. Studies[62,63] have found that people are willing to try open-label placebo treatments if given enough information from their health care practitioners. There is a possibility of reporting bias in these trials because patients are aware of their allocation, so the true effect may be difficult to estimate. Multiple randomized trials of open-label placebo treatments in various conditions have demonstrated that open-label treatments can improve symptoms when compared with treatment as usual or no treatment arms in cancer-related fatigue, back pain, allergy symptoms, and irritable bowel disease symptom severity.[64-73] The studies of placebo effect on rhinology are limited. One trial in patients with allergic rhinitis found active treatment of oral phenylephrine hydrochloride noninferior to open-label placebo treatments in relieving nasal congestion in adults.[74] Open-label placebo treatments are not effective in wound healing, suggesting that the effect of open-label placebos is limited to pain and symptom relief.[75]

Limitations

This study has limitations. Heterogeneity associated with pooled estimates for patient-reported quality of life, endoscopic outcomes, and adverse events among trials may have reduced evidence quality. Subgroup analyses were performed when possible to try to understand the source of heterogeneity in these studies. Too few studies reported details on the use of protocol-permitted medications in their results to allow for subgroup analyses. Studies are needed to determine whether additional treatment is an effect modifier for the placebo. The pooled estimate of the pre-effect and posteffect sizes cannot differentiate between the effects of treatment and natural processes. Research is needed to understand whether there is a role for the use of nonmedicated control substances that complements the natural history of untreated CRS. Studies of the compositions of nonmedicated control substances may also lend insight into the potential effect of active ingredients in controls in CRS.

Repeated measurements introduce the risk of regression to the mean. Therefore, pre-effect and posteffect sizes are at risk for bias because the pretest and posttest outcome measures are not independent of each other.[76] To account for this, our analysis imputed the SD within groups and corrected for the correlation between the paired observations. Most trials did not report both measurement variances and change variances, so the assumed correlation was 0.5, which is a reasonable assumption given that the mean correlation for 2 trials that reported both measurement variances and change variances for SNOT-22 was 0.54.[17,47,50]

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Erasmus MC - Univ of Rotterdam User on 05/30/2022

Conclusions

This study provides an estimate of the effect of nonmedicated control substances in CRS to fill a knowledge gap and guide future research directions. The pooled effect estimate identified settings in which nonmedicated control substances can influence patient-reported quality-of-life assessments as well as endoscopic outcome measures. The significant effect of nonmedicated control substances is further evidence to support cautious interpretation of results from noncontrolled observational studies.

ARTICLE INFORMATION

Accepted for Publication: August 21, 2020.

Published Online: November 12, 2020. doi:10.1001/jamaoto.2020.3723

Author Contributions: Drs Caulley and Hopkins had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Hopkins.
Acquisition, analysis, or interpretation of data: Caulley, James.
Drafting of the manuscript: Caulley, James.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Caulley, James.
Administrative, technical, or material support: Caulley, Hopkins.
Supervision: Hopkins.

Conflict of Interest Disclosures: Dr Hopkins reported performing consultancy work for Sanofi, Smith and Nephew, and Medtronic.

Additional Contributions: Risa Shorr, MLIS, Ottawa Hospital Learning Services, assisted in the preparation and execution of the search algorithm for this systematic review. Tim Ramsay, PhD, and Jordi Pardo, PhD, Ottawa Hospital Research Institute, advised on the statistical analysis for this study. No compensation was received for their contributions.

REFERENCES

1. Kaptchuk TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ*. 2008;336(7651):999-1003. doi:10.1136/bmj.39524.439618.25

2. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev*. 2010;(1):CD003974. doi:10.1002/14651858.CD003974.pub3

3. Kaptchuk TJ. Powerful placebo: the dark side of the randomised controlled trial. *Lancet*. 1998;351(9117):1722-1725. doi:10.1016/S0140-6736(97)10111-8

4. Miller FG, Kaptchuk TJ. The power of context: reconceptualizing the placebo effect. *J R Soc Med*. 2008;101(5):222-225. doi:10.1258/jrsm.2008.070466

5. Hróbjartsson A. What are the main methodological problems in the estimation of placebo effects? *J Clin Epidemiol*. 2002;55(5):430-435. doi:10.1016/S0895-4356(01)00496-6

6. Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. *Lancet*. 2010;375(9715):686-695. doi:10.1016/S0140-6736(09)61706-2

7. Kaptchuk TJ, Miller FG. Placebo effects in medicine. *N Engl J Med*. 2015;373(1):8-9. doi:10.1056/NEJMp1504023

8. DeConde AS, Soler ZM. Chronic rhinosinusitis: epidemiology and burden of disease. *Am J Rhinol Allergy*. 2016;30(2):134-139. doi:10.2500/ajra.2016.30.4297

9. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012: a summary for otorhinolaryngologists. *Rhinology*. 2012;50(1):1-12. doi:10.4193/Rhino50E2

10. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg*. 1995;113(1):104-109. doi:10.1016/S0194-5998(95)70152-4

11. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. doi:10.1136/bmj.b2535

12. *Review Manager (RevMan)*. [computer program]. Version 5.3. The Nordic Cochrane Centre, The Cochrane Collaboration; 2014. Accessed October 5, 2020. https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman

13. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons; 2008. doi:10.1002/9780470712184

14. Freeman M, Tukey J. Transformations related to the angular and the square root. *Annals of Mathematical Statistics*. 1950;21:607-611. doi:10.1214/aoms/1177729756

15. Rousseau MJ, Evans JC. Key statistical assumptions and methods in one-arm meta-analyses with binary endpoints and low event rates, including a real-life example in the area of endoscopic colonic stenting. *Cogent Med*. 2017;4(1):1334318. doi:10.1080/2331205X.2017.1334318

16. Higgins J, Deeks JJ, Altman DG. Special topics in statistics. In: Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. The Cochrane Collaboration; 2011. https://handbook-5-1.cochrane.org/

17. Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol*. 1992;45(7):769-773. doi:10.1016/0895-4356(92)90054-Q

18. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. *Effect Sizes Based on Means: Introduction to Meta-Analysis*. John Wiley & Sons Ltd; 2009:21-32. doi:10.1002/9780470743386.ch4

19. Anzić SA, Turkalj M, Župan A, Labor M, Plavec D, Baudoin T. Eight weeks of omeprazole 20 mg significantly reduces both laryngopharyngeal reflux and comorbid chronic rhinosinusitis signs and symptoms: randomised, double-blind, placebo-controlled trial. *Clin Otolaryngol*. 2018;43(2):496-501. doi:10.1111/coa.13005

20. Bellussi L, Manini G, Buccella MG, Cacchi R. Evaluation of the efficacy and safety of sobrerol granules in patients suffering from chronic rhinosinusitis. *J Int Med Res*. 1990;18(6):454-459. doi:10.1177/030006059001800602

21. Ebbens FA, Scadding GK, Badia L, et al. Amphotericin B nasal lavages: not a solution for patients with chronic rhinosinusitis. *J Allergy Clin Immunol*. 2006;118(5):1149-1156. doi:10.1016/j.jaci.2006.07.058

22. Esmaeilzadeh H, Nabavi M, Aryan Z, et al. Aspirin desensitization for patients with aspirin-exacerbated respiratory disease: a randomized double-blind placebo-controlled trial. *Clin Immunol*. 2015;160(2):349-357. doi:10.1016/j.clim.2015.05.012

23. Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol*. 2011;128(5):989-95.e8. doi:10.1016/j.jaci.2011.07.056

24. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013;131(1):110-116.e1. doi:10.1016/j.jaci.2012.07.047

25. Hamilos DL, Thawley SE, Kramper MA, Kamil A, Hamid QA. Effect of intranasal fluticasone on cellular infiltration, endothelial adhesion molecule expression, and proinflammatory cytokine mRNA in nasal polyp disease. *J Allergy Clin Immunol*. 1999;103(1 Pt 1):79-87. doi:10.1016/S0091-6749(99)70529-4

26. Hansen FS, Djupesland PG, Fokkens WJ. Preliminary efficacy of fluticasone delivered by a novel device in recalcitrant chronic rhinosinusitis. *Rhinology*. 2010;48(3):292-299. doi:10.4193/Rhin09.178

27. Haye R, Aanesen JP, Burtin B, Donnelly F, Duby C. The effect of cetirizine on symptoms and signs of nasal polyposis. *J Laryngol Otol*. 1998;112(11):1042-1046. doi:10.1017/S0022215100142422

28. Hissaria P, Smith W, Wormald PJ, et al. Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. *J Allergy Clin Immunol*. 2006;118(1):128-133. doi:10.1016/j.jaci.2006.03.012

29. Jiang RS, Hsu SH, Liang KL. Amphotericin B nasal irrigation as an adjuvant therapy after functional endoscopic sinus surgery. *Am J Rhinol Allergy*. 2015;29(6):435-440. doi:10.2500/ajra.2015.29.4246

30. Jiang RS, Twu CW, Liang KL. Efficacy of nasal irrigation with 200 µg/mL amphotericin B after functional endoscopic sinus surgery: a randomized, placebo-controlled, double-blind study. *Int Forum Allergy Rhinol*. 2018;8(1):41-48. doi:10.1002/alr.22033

31. Keith P, Nieminen J, Hollingworth K, Dolovich J. Efficacy and tolerability of fluticasone propionate nasal drops 400 microgram once daily compared with placebo for the treatment of bilateral polyposis in adults. *Clin Exp Allergy*. 2000;30(10):

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Erasmus MC - Univ of Rotterdam User on 05/30/2022

1460-1468. doi:10.1046/j.1365-2222.2000.00932.x

32. Kennedy DW, Kuhn FA, Hamilos DL, et al. Treatment of chronic rhinosinusitis with high-dose oral terbinafine: a double blind, placebo-controlled study. *Laryngoscope*. 2005;115(10):1793-1799. doi:10.1097/01.mlg.0000175683.81260.26

33. Kirtsreesakul V, Wongsritrang K, Ruttanaphol S. Clinical efficacy of a short course of systemic steroids in nasal polyposis. *Rhinology*. 2011;49(5):525-532. doi:10.4193/Rhino11.140

34. Leopold DA, Elkayam D, Messina JC, Kosik-Gonzalez C, Djupesland PG, Mahmoud RA. NAVIGATE II: randomized, double-blind trial of the exhalation delivery system with fluticasone for nasal polyposis. *J Allergy Clin Immunol*. 2019;143(1):126-134.e5. doi:10.1016/j.jaci.2018.06.010

35. Lildholdt T, Rundcrantz H, Lindqvist N. Efficacy of topical corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. *Clin Otolaryngol Allied Sci*. 1995;20(1):26-30. doi:10.1111/j.1365-2273.1995.tb00007.x

36. Lund VJ, Black JH, Szabó LZ, Schrewelius C, Akerlund A. Efficacy and tolerability of budesonide aqueous nasal spray in chronic rhinosinusitis patients. *Rhinology*. 2004;42(2):57-62.

37. Mortazavi N, Esmaeilzadeh H, Abbasinazari M, et al. Clinical and immunological efficacy of aspirin desensitization in nasal polyp patients with aspirin-exacerbated respiratory disease. *Iran J Pharm Res*. 2017;16(4):1639-1647.

38. Mösges R, Bachert C, Rudack C, et al. Efficacy and safety of mometasone furoate nasal spray in the treatment of chronic rhinosinusitis. *Adv Ther*. 2011;28(3):238-249. doi:10.1007/s12325-010-0105-7

39. Palm J, Steiner I, Abramov-Sommariva D, et al. Assessment of efficacy and safety of the herbal medicinal product BNO 1016 in chronic rhinosinusitis. *Rhinology*. 2017;55(2):142-151. doi:10.4193/Rhin16.103

40. Penttilä M, Poulsen P, Hollingworth K, Holmström M. Dose-related efficacy and tolerability of fluticasone propionate nasal drops 400 microg once daily and twice daily in the treatment of bilateral nasal polyposis: a placebo-controlled randomized study in adult patients. *Clin Exp Allergy*. 2000;30(1):94-102. doi:10.1046/j.1365-2222.2000.00695.x

41. Rössberg E, Larsson PG, Birkeflet O, Söholt LE, Stavem K. Comparison of traditional Chinese acupuncture, minimal acupuncture at non-acupoints and conventional treatment for chronic sinusitis. *Complement Ther Med*. 2005;13(1):4-10. doi:10.1016/j.ctim.2005.01.002

42. Sindwani R, Han JK, Soteres DF, et al. NAVIGATE I: randomized, placebo-controlled, double-blind trial of the exhalation delivery system with fluticasone for chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy*. 2019;33(1):69-82. doi:10.1177/1945892418810281

43. Small CB, Hernandez J, Reyes A, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. *J Allergy Clin Immunol*. 2005;116(6):1275-1281. doi:10.1016/j.jaci.2005.07.027

44. Stjärne P, Mösges R, Jorissen M, et al. A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. *Arch Otolaryngol Head Neck Surg*. 2006;132(2):179-185. doi:10.1001/archotol.132.2.179

45. Stjärne P, Blomgren K, Cayé-Thomasen P, Salo S, Søderstrøm T. The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: a randomized, double-blind, placebo-controlled study. *Acta Otolaryngol*. 2006;126(6):606-612. doi:10.1080/00016480500452566

46. Stjärne P, Olsson P, Alenius M. Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. *Arch Otolaryngol Head Neck Surg*. 2009;135(3):296-302. doi:10.1001/archoto.2009.2

47. Tait S, Kallogjeri D, Suko J, Kukuljan S, Schneider J, Piccirillo JF. Effect of budesonide added to large-volume, low-pressure saline sinus irrigation for chronic rhinosinusitis: a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. 2018;144(7):605-612. doi:10.1001/jamaoto.2018.0667

48. Vaidyanathan S, Barnes M, Williamson P, Hopkinson P, Donnan PT, Lipworth B. Treatment of chronic rhinosinusitis with nasal polyposis with oral steroids followed by topical steroids: a randomized trial. *Ann Intern Med*. 2011;154(5):293-302. doi:10.7326/0003-4819-154-5-201103010-00003

49. Vento SI, Blomgren K, Hytonen M, Simola M, Malmberg H. Prevention of relapses of nasal polyposis with intranasal triamcinolone acetonide after polyp surgery: a prospective double-blind, placebo-controlled, randomised study with a 9-month follow-up. *Clin Otolaryngol*. 2012;37(2):117-123. doi:10.1111/j.1749-4486.2012.02455.x

50. Videler WJ, Badia L, Harvey RJ, et al. Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. *Allergy*. 2011;66(11):1457-1468. doi:10.1111/j.1398-9995.2011.02693.x

51. Vlckova I, Navrátil P, Kana R, Pavlicek P, Chrbolka P, Djupesland PG. Effective treatment of mild-to-moderate nasal polyposis with fluticasone delivered by a novel device. *Rhinology*. 2009;47(4):419-426. doi:10.4193/Rhin09.024

52. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope*. 2006;116(2):189-193. doi:10.1097/01.mlg.0000191560.53555.08

53. Wang C, Lou H, Wang X, et al. Effect of budesonide transnasal nebulization in patients with eosinophilic chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2015;135(4):922-929.e6. doi:10.1016/j.jaci.2014.10.018

54. Yousefi J, Akhavan A, Hoseini-Motlagh R, Banaei-Boroujeni S, Panahi Y, Khosravi MH. Effect of amphotericin b on treatment of chronic rhinosinusitis: a double-blind randomized clinical trial. *Razavi International Journal of Medicine*. 2017;5(4):e64550.

55. Yu MS, Kim BH, Kang SH, Lim DJ. Low-concentration hypochlorous acid nasal irrigation for chronic sinonasal symptoms: a prospective randomized placebo-controlled study. *Eur Arch Otorhinolaryngol*. 2017;274(3):1527-1533. doi:10.1007/s00405-016-4387-5

56. Zhou B, He G, Liang J, et al. Mometasone furoate nasal spray in the treatment of nasal polyposis in Chinese patients: a double-blind, randomized, placebo-controlled trial. *Int Forum Allergy Rhinol*. 2016;6(1):88-94. doi:10.1002/alr.21650

57. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol*. 2009;34(5):447-454. doi:10.1111/j.1749-4486.2009.01995.x

58. Bachmann G, Hommel G, Michel O. Effect of irrigation of the nose with isotonic salt solution on adult patients with chronic paranasal sinus disease. *Eur Arch Otorhinolaryngol*. 2000;257(10):537-541. doi:10.1007/s004050000271

59. Kim CH, Hyun Song M, Eun Ahn Y, Lee JG, Yoon JH. Effect of hypo-, iso- and hypertonic saline irrigation on secretory mucins and morphology of cultured human nasal epithelial cells. *Acta Otolaryngol*. 2005;125(12):1296-1300. doi:10.1080/00016480510012381

60. Rudmik L, Soler ZM. Medical therapies for adult chronic sinusitis: a systematic review. *JAMA*. 2015;314(9):926-939. doi:10.1001/jama.2015.7544

61. Kuehnemund M, Ismail C, Brieger J, Schaefer D, Mann WJ. Untreated chronic rhinosinusitis: a comparison of symptoms and mediator profiles. *Laryngoscope*. 2004;114(3):561-565. doi:10.1097/00005537-200403000-00032

62. Bishop FL, Aizlewood L, Adams AE. When and why placebo-prescribing is acceptable and unacceptable: a focus group study of patients' views. *PLoS One*. 2014;9(7):e101822.

63. Hull SC, Colloca L, Avins A, et al. Patients' attitudes about the use of placebo treatments: telephone survey. *BMJ*. 2013;347:f3757.

64. Hoenemeyer TW, Kaptchuk TJ, Mehta TS, Fontaine KR. Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. *Sci Rep*. 2018;8(1):2784. doi:10.1038/s41598-018-20993-y

65. Kaptchuk TJ, Miller FG. Open label placebo: can honestly prescribed placebos evoke meaningful therapeutic benefits? *BMJ*. 2018;363:k3889. doi:10.1136/bmj.k3889

66. Carvalho C, Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. *Pain*. 2016;157(12):2766-2772. doi:10.1097/j.pain.0000000000000700

67. Kam-Hansen S, Jakubowski M, Kelley JM, et al. Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Sci Transl Med*. 2014;6(218):218ra5. doi:10.1126/scitranslmed.3006175

68. Kaptchuk TJ, Friedlander E, Kelley JM, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One*. 2010;5(12):e15591. doi:10.1371/journal.pone.0015591

69. Kelley JM, Kaptchuk TJ, Cusin C, Lipkin S, Fava M. Open-label placebo for major depressive disorder: a pilot randomized controlled trial. *Psychother Psychosom*. 2012;81(5):312-314. doi:10.1159/000337053

70. Locher C, Frey Nascimento A, Kirsch I, Kossowsky J, Meyer A, Gaab J. Is the rationale more important than deception? a randomized controlled trial of open-label placebo analgesia. *Pain*. 2017;158(12):2320-2328. doi:10.1097/j.pain.0000000000001012

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Erasmus MC - Univ of Rotterdam User on 05/30/2022

71. Schaefer M, Harke R, Denke C. Open-label placebos improve symptoms in allergic rhinitis: a randomized controlled trial. *Psychother Psychosom*. 2016;85(6):373-374. doi:10.1159/000447242

72. Schaefer M, Sahin T, Berstecher B. Why do open-label placebos work? a randomized controlled trial of an open-label placebo induction with and without extended information about the placebo effect in allergic rhinitis. *PLoS One*. 2018;13(3):e0192758. doi:10.1371/journal.pone.0192758

73. Zhou ES, Hall KT, Michaud AL, Blackmon JE, Partridge AH, Recklitis CJ. Open-label placebo reduces fatigue in cancer survivors: a randomized trial. *Support Care Cancer*. 2019;27(6):2179-2187. doi:10.1007/s00520-018-4477-6

74. Meltzer EO, Ratner PH, McGraw T. Oral phenylephrine HCl for nasal congestion in seasonal allergic rhinitis: a randomized, open-label, placebo-controlled study. *J Allergy Clin Immunol Pract*. 2015;3(5):702-708. doi:10.1016/j.jaip.2015.05.007

75. Mathur A, Jarrett P, Broadbent E, Petrie KJ. Open-label placebos for wound healing: a randomized controlled trial. *Ann Behav Med*. 2018;52(10):902-908. doi:10.1093/abm/kax057

76. Cuijpers P, Weitz E, Cristea IA, Twisk J. Pre-post effect sizes should be avoided in meta-analyses. *Epidemiol Psychiatr Sci*. 2017;26(4):364-368. doi:10.1017/S2045796016000809

Invited Commentary

Controls for Clinical Trials of Intranasal Medications for Chronic Rhinosinusitis

Who Nose What to Do?

Ahmad R. Sedaghat, MD, PhD; Katie M. Phillips, MD

Clinical trials are designed as uncontrolled or controlled studies. Controlled studies, with the highest quality and level of evidence coming from randomized controlled studies, judge the efficacy of an experimental treatment against an alternative treatment, or control. Controls may be broadly categorized as placebo, active treatment, or best available therapy.[1] A placebo, by definition, has no therapeutic benefit and is intended to provide only a psychological treatment effect. In comparison, active treatment or best available therapy controls have intrinsic therapeutic benefit.

Related article page 123

In this issue of *JAMA Otolaryngology–Head & Neck Surgery*, Caulley and colleagues[2] perform a systematic review of clinical trials of chronic rhinosinusitis (CRS) treatments with the primary objective of studying the associations of nonmedicated control substances in clinical trials of CRS treatments with outcomes, with a focus on both general and disease-specific quality of life, symptom severity scores, endoscopic and imaging scores, inflammatory markers, and adverse events. Their study very nicely highlights the difficulty in choosing inert, yet appropriate, controls for CRS trials. While many clinical trials of CRS have claimed to include a placebo control, many are in fact active treatments with known therapeutic effect for CRS, including saline and topical diluents (which frequently contain carbohydrate solutions with known therapeutic effects). In the 8 included randomized clinical trials (RCTs) using the 22-item Sinonasal Outcome Test (SNOT-22) as an outcome measure, 5 RCTs used topical controls while 3 used oral controls. There was no net therapeutic benefit for oral controls, while topical controls—which included saline and topical diluents—were associated with an 8.8-point decrease in SNOT-22 score. Subgroup analyses of topical controls also identified interesting findings. The therapeutic benefit of topical spray formulations was noted to be greater than irrigations, with the positive therapeutic outcomes of irrigation controls dominantly driven by 1 trial, which acted as an outlier and, if excluded, reduced the benefit of irrigation controls to insignificant. Moreover, topical diluent controls were associated with a greater improvement in SNOT-22 score than saline. In the 7 included RCTs that measured patient-reported symptom severities with a visual analog scale, topical controls were associated with a reduction in nasal obstruction that was limited to spray formulations, although control irrigations in this group of studies used sterile water, and it has been shown that hypotonic solutions may cause severe damage to the nasal epithelium[3] that may then lead to enhanced symptoms such as nasal congestion. Topical controls had no association with change in symptoms of rhinorrhea, postnasal drip, facial pain, or loss of smell. These results suggest several conclusions. First, the only true placebos that were included in this study—nontherapeutic oral control medications—had no significant association with CRS outcomes. Second, the nonmedicated intranasal solutions—typically consisting of saline or spray diluent, which have known therapeutic benefit—that were used as controls were associated with modest improvement in CRS outcomes.

The recent development of novel treatments for CRS has made more timely a discussion on the need for well-designed clinical studies. This study by Caulley et al[2] provides the opportunity to ponder the appropriate use of controls in clinical trials for CRS. In their study, Caulley et al[2] introduce their work with a discussion of placebos, but their work ultimately focuses on nonmedicated intranasal control substances, which highlights the difficulty in finding true placebos for intranasal application. While a placebo has no inherent therapeutic benefit and is intended entirely to account for psychological effects, intranasal application of even inert substances, such as saline, has been found to have potentially therapeutic effects. While Caulley et al[2] show oral placebos to have no therapeutic benefit on sinonasal symptomatology, oral placebos would not be appropriate in the study of an intranasal medication. Thus clinical trial design for study of intranasal medications is limited by the lack of true placebos with only modestly active treatments available as the least potent control options.

However, the question may be asked why placebo controls may be required for clinical trials of medications for CRS in general. Presently, there is level 1 evidence for the efficacy of intranasal corticosteroid sprays (ICS) for the treatment of all

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Erasmus MC - Univ of Rotterdam User on 05/30/2022