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Is Sinupret (BNO 1016- herbal combination) an effective treatment for the symptoms of acute and chronic rhinosinusitis compared to non-treatment in male and female adults ages 18-75?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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In

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Department of Physician Assistant Studies
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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not Sinupret (BNO 1016- herbal combination) is an effective treatment for the symptoms of acute and chronic rhinosinusitis compared to non-treatment in male and female adults ages 18-75?

Study Design: This is a systematic review of three randomized controlled trials (RCTs) regarding Sinupret treatment for sinonasal symptoms. All RCTs were published in the English language in peer-reviewed journals in 2011, 2015, and 2017.

Data Sources: Three randomized controlled trials were found using PubMed and CINAHL databases.

Outcomes Measured: Symptom relief of acute and chronic rhinosinusitis was measured via major symptom score (MSS) of rhinorrhea, post-nasal drip, congestion, headache, and facial pressure by participants (measured by mean change from baseline). Assessment of responders vs. non-responders to treatment as designated by “cured/improved” vs. “unchanged/deteriorated.” Improvement of olfactory function per phenylethanol odor testing as well as odor discrimination and identification testing.

Results: Jund et al.³ showed a greater decrease in acute viral sinusitis symptoms (MSS decrease) with Sinupret treatment than with placebo-treated group ($p < 0.0001$) as well as a NNT of 10. Palm et al.⁶ showed similar reduction in MSS in the use of Sinupret for chronic sinusitis ($p < 0.0015$). Reden et al.⁷ showed improvement in olfactory function in sinusitis patients withdrawing from prednisolone with the use of Sinupret, but failed to show statistical significance ($p = 0.67$).

Conclusions: Two of the three studies reviewed studies revealed that Sinupret, herbal combination, can be used as an effective treatment in adults 18-75 years old for decreasing the symptoms of acute viral and chronic sinusitis at a faster rate than no treatment at all. Multiple studies suggested expanding the study population beyond German participants.

Keywords: sinusitis, rhinosinusitis, herbal treatment, common cold

INTRODUCTION

Acute viral rhinosinusitis (AVRS) and chronic rhinosinusitis (CRS) are common diseases that involve inflammation of the nasal passageways and paranasal sinuses. They lead to the familiar symptoms of rhinorrhea, congestion, facial pain, fatigue, post-nasal drip, and headache.¹ Rhinosinusitis is a condition accounting for more than 16 million visits to primary care physicians in the United States.² It is a major contributing disease to the overprescribing and overuse of antibiotics.

AVRS is also known as the “common cold” and is designated as the most prevalent infectious disease in the United States, causing an average of two to three episodes per year in individual adults.³ It is usually caused by viruses- rhinovirus, coronavirus, and influenza virus being some of the most common.⁴ Being so prevalent, AVRS is a major cause of increased health care costs as well as lost productivity costs in the US. It accounts for 40% of total time lost from jobs in employed persons and an estimated \$39 billion annually.² CRS occurs in individuals in which sinusitis symptoms lasts greater than 12 weeks and was found to effect 2-16% of U.S. adults.⁵ CRS can develop as a sequela from multiple acute infections, chronic autoimmune processes, or allergies.⁶

No gold standard of treatment exists for AVRS and CRS. Common methods used are for symptomatic treatment only. These include over-the-counter analgesics, antipyretics, irrigation (nasal saline sprays and Neti Pots), intranasal corticosteroids, antihistamines, decongestants, and mucolytics (guaifenesin). As previously stated, antibiotics are overused in the treatment of non-bacterial sinusitis. One study by Sharp et al⁷ researched and tracked medical prescriptions for sinusitis diagnoses in primary care settings; their findings suggested that although only 3-5% of sinusitis cases have bacterial causes, four out of five patients were treated by with antibiotics.

This denotes sinusitis as a major contributor to antibiotic resistance. There are many symptomatic treatments for sinusitis, however, there has been a demand for more naturally derived remedies that can be obtained over-the-counter at a low cost.

With sinusitis being incredibly common and lacking a gold standard treatment, it has remained a popular area of research. Sinupret, BNO 1016, is a new herbal remedy for sinusitis that was released in 2012 from Binorica AG Pharmaceuticals in Germany^{3,9} The company has released many herbal formulations in the past for the treatment of bronchitis, tonsillitis, and flu prevention; they are used as over-the-counter treatments throughout Europe. Sinupret is an oral tablet, containing an herbal dry extract combination of gentian root, primula flower, sorrell herb, verbana herb, and elder flower. The manufacturers of Sinupret report that it can be used to decrease the duration of symptoms of AVRS and CRS by enhancing the body's natural defense mechanisms while reducing inflammation and excess mucus production in the nasal cavity.^{6,9} The company claims that the herbal combination is effective in that: primula delivers anti-inflammatory and expectorant properties, gentian root provides an anti-inflammatory effect, elderberry provides an expectorant effect, sorrel herb delivers anti-inflammatory and anti-bacterial effects, and that verbana herb provides expectorant and anti-viral properties.⁹ However, the sources of these claims were not listed by Binorica. This systematic review is designed to evaluate three randomized control trials which studied the use of Sinupret herbal combination in patients with sinusitis.

OBJECTIVE

The objective of this selective evidence based medicine review is to determine whether or not Sinupret (BNO 1016- herbal combination) is an effective treatment for the symptoms of acute and chronic rhinosinusitis compared to non-treatment in adults ages 18-75.

METHODS

Criteria: All three RCTs examined populations of adults with diagnosed AVRS/CRS as well as anosmia. The three studies were deemed reliable as they were randomized, conducted in a double-blind, placebo controlled manner, the trials were appropriate length for the AVRS/CRS disease course, and the intervention and control groups were similar prior to starting the interventions. Inclusion criteria for this systematic review included double-blind randomized control trials, evaluating the Sinupret intervention in AVRS/CRS specifically, articles published in English, and the need for the RCTs to be published 10 years prior to February 1st 2018. The intervention used in these studies, Sinupret, 160 mg oral tablet three times a day, was compared in efficacy to an oral placebo pill taken three times a day. Outcomes measured included mean reduction of symptoms of AVRS/CRS using the Multiple Symptom Score (MSS), determining responders vs. non-responders to Sinupret treatment, and through olfactory function testing (TDI score).

Data Sources: Data sources were researched by this author through PubMed, CINAHL, and Cochrane in the years 2017 and 2018. Key words used included “Sinusitis” (MeSH), “Herbal”, “Rhinitis”, and “BNO 1016” (Sinupret). Each article was selected based on its relevance to Sinupret and sinusitis as well as on having outcomes that would affect the quality of life of the patient (POEMs). Each study included widely-accepted statistical analyses like p-values, ANOVA, standard deviations, numbers needed to treat (NNT), t-tests, and post-hoc sensitivity analyses.

TABLE 1: DEMOGRAPHICS AND CHARACTERISTICS OF INCLUDED STUDIES

STUDY	TYPE	# PTS	AGE (yr)	INCLUSION CRITERIA	EXCLUSION CRITERIA	W/D	INTERVENTIONS
Jund et al., 2015 ³	RCT	589	18-75	ARS (acute rhinosinusitis) with ≥ 3 main symptoms, MSS (symptom score) classified as moderate to severe	Pts who were treated with corticosteroids/ abx within 4 weeks of trial, use of “common cold” medication within 7 days of trial, pregnant/lactating women, pts with kidney, liver, neurological/psych distress	11	Oral treatment with Sinupret 160 mg (BNO1016- herbal combination of Gentian root, Primula flower, Sorell herb, Elder flower, and Verbana herb) TID x 15 days VS. placebo pill (non-treatment) TID x 15 days.
Palm et al., 2017 ⁶	RCT	929	18-75	Bilateral CRS (chronic rhinosinusitis) without nasal polyps confirmed by endoscopy, sxs present for ≥ 12 weeks, total MSS (symptom score) within 6-12 at start of study, moderate –severe), symptoms must include rhinorrhea and pain	Sinus surgery within past 2 yrs, CRS due to allergies, treatment with systemic or nasal corticosteroids within past 4 weeks, treatment with decongestant preps, mucolytics, antihistamines, and other “common cold” OTC meds within 7 days of trial	81 pts	Oral treatment with 2 different doses of Sinupret in 2 different groups: 80 mg oral tablet TID and 160 mg oral tablet TID (BNO1016- herbal combination of Gentian root, Primula flower, Sorell herb, Elder flower, and Verbana herb) TID x 12 weeks VS. placebo pill (non-treatment) TID x 12 weeks.
Reden et al., 2011 ⁷	RCT	36	22-67	Pts must have olfactory dysfunction as determined by ENT –specialist, must have sinonasal inflammation determined by endoscopy of the nasal cavity.	Pts with TDI score (for olfactory function) that did not improve by 3 points after 7 day prednisolone treatment could not continue in the study.	0	Sinupret oral herbal supplement: BNO1016 combination of primrose, gentian root, verain, elder flower, and Sorrell 160 mg TID x 2 months POST 1 week of 30 mg Prednisolone QD VS placebo (160 mg non-treatment) POST 1 week of 30 mg Prednisolone QD

OUTCOMES MEASURED

Sinupret and AVRS were studied by Jund et al. over a treatment period of 15 days.³ In the study by Palm et al.⁶, Sinupret was used in the treatment of CRS over a treatment period of 12 weeks. Reden et al.⁷ studied Sinupret's effect on olfactory dysfunction returning after a 7 day course of corticosteroids over a treatment period of 3 months in patients with CRS. Studies by Jund et al. and Palm et al. used similar means of measurement outcomes for AVRS/CRS symptom improvement. The Multiple Symptom Score (MSS), a self-reported symptom rating per the participants, included five symptoms of rhinorrhea, post-nasal drip, congestion, headache, and facial pain, each rated on a scale from 0-7 at each visit.⁶ The total scores were calculated and averaged and the mean change from baseline in MSS was determined at the end of the treatment period. The above mentioned studies also measured responders vs. non-responders to treatment (symptoms cured/improved vs. unchanged/deteriorated compared to previous visit). The final study by Reden et al. took a different approach and measured Sinupret's improvement of olfactory dysfunction in patients with sinusitis using the TDI score (Threshold, Discrimination, and Identification olfactory testing). This involved the use of "Sniffin Sicks" in which participants undertook phenylethanol odor threshold, odor discrimination, and odor identification testing⁷. A decrease in TDI scores signals the individual's olfactory function decreased.

RESULTS

RCT 1- Jund et al. (2015)³: This 589 person study took place in 37 health clinics of otorhinolaryngology, internal medicine, and family medicine in Germany and attempted to determine the effectiveness of Sinupret treatment on AVRS symptoms over 14 days. The study showed statistically significant clinical results. The MSS showed improvement in symptoms by an average of 7.55 points in the treatment group and only by an average of 6.24 points in the

placebo group by day 14 of treatment, meaning there was a larger decrease in symptoms (MSS) in the treatment group compared to placebo. The authors found that this greater decrease of symptoms with Sinupret was statistically significant at $p < 0.0001$. This author (Boyle) also calculated a numbers needed to treat of 10 based on participants being “responders vs. non-responders” to treatment. On day 14 of treatment, 90.8% of the Sinupret experimental group were responders to treatment while on the same day only 80.7% of the placebo group were responders. This NNT signifies that 10 patients would need to be treated with Sinupret for one more patient to see a positive treatment effect compared to control. The study reports that all data was analyzed using SAS statistical software and included p-values, standard deviation analyses, and ANOVAs. Jund et al. also determined that no serious adverse events occurred during the duration of the study. They reported 9.8% minor adverse events in the Sinupret treated group and 14.1% in the placebo-treated group, indicating a reliable safety profile of the treatment. The nature of the minor adverse events was not explicitly identified.

Table 2: Reduction in average MSS score from day 0 to day 14

	Sinupret (BNO1016) 480 mg	Placebo
Day 0	10.02	9.87
Day 14	2.47	3.63
p-value	<0.0001	<0.0001

Table 3: NNT on day 14 calculated using responders vs. non-responders to treatment

Ree4CER	EER	$\frac{EER - CER}{CER}$	EER-CER	1/ARI
.807	.908	.125	.101	10
p-value	p<0.0002			

RCT 2- Palm et al. (2017)⁶: This 929 participant study focused on the treatment of CRS with Sinupret herbal over 12 weeks at 67 centers of otorhinolaryngology, internal medicine, and family medicine throughout Germany. An important criteria for patient selection was the determining of CRS for a duration of 12 weeks without nasal polyps confirmed by endoscopy.⁶ MSS at consecutive visits was also measured as an outcome in this study. The RCT demonstrated an average decrease in symptoms of 5.4 MSS points for the 480 mg Sinupret treatment group and only a decrease of 4.0 MSS points for the placebo group at week 8 with a p-value of $p < 0.0015$. NNT could not be calculated because data were non-dichotomous and presented in continuous forms. P-values, ANCOVAs, and a post-hoc sensitivity analysis were used to determine significance of data. Safety profiles of the two different doses of Sinupret were compared to placebo. No serious adverse events (SAEs) were reported, but the study did find minor to moderate AEs in 4.4% of the Sinupret group and 3.9% in the placebo group.⁶ The most commonly reported AEs in all three groups were abdominal pain, diarrhea, and headache. The relative similarities between the AEs found between the groups indicates a reliable safety profile of Sinupret treatment.

Table 4: Reduction in average MSS in chronic rhinosinusitis over 12 weeks

	Sinupret 480mg	Placebo
Day 1	10.7	10.8
Week 12	5.3	6.8
p-value	$p=0.0015$	$P=0.0015$

RCT 3- Reden et al. (2011)⁷: This 36 person study took place at the Taste Clinic at the University of Dresden Medical School in Germany. It evaluated the effects Sinupret had in improving olfactory function following a 7 day course of prednisolone in patients with CRS and coinciding olfactory dysfunction. Olfactory function was measured via TDI score prior to and after treatment with Prednisolone and then after treatment with Sinupret vs placebo at the 2 month mark. A higher TDI score is indicative of improved olfactory function. The study determined that the mean decrease in TDI was 8.4 points in the placebo group-indicating the expected worsening of olfactory function after stopping Prednisolone. The TDI score in the Sinupret treated group was only decreased by 6.8 points – indicating return olfactory dysfunction, although less symptomatic than in the placebo group. Statistical measures such as p-values, t-tests, and ANOVA were used; however, the study found that these results were not statistically significant ($p=0.67$). No adverse health events were reported by the authors of this RCT.

Table 5: Average change in TDI score after 2 months

	Sinupret 480 mg	Placebo
7 days post prednisolone	27.8	27.4
2 months	21.0	19.0
p-value	$p=0.67$	$p=0.67$

DISCUSSION

Sinusitis, both chronic and acute, stands as a major contributor to high health care costs, decreased quality of life, and missed productivity. It can lead to facial pain, rhinorrhea, congestion, fatigue, headache, and anosmia; leaving patients feeling unlike themselves. To this

day, health care providers still have trouble attributing a cause for AVRS and even more so, CRS. In addition to this there is no gold standard therapy, and the majority of treatment methods remain symptomatic. The current most effective treatment for sinonasal inflammation is systemic corticosteroids.⁸ However, in CRS, the symptoms typically quickly return after cessation and in AVRS/CRS chronic treatment with oral steroids is not feasible as prolonged steroid treatment is known to have detrimental adverse effects on the body.

This systematic review evaluated three randomized control studies in which two of the three showed that Sinupret herbal combination can be used to decrease the symptoms of AVRS/CRS with statistical significance. Results showed decreased symptom scores (MSS) in the treatment groups, as well as increased TDI scores compared to placebo-treated groups; indicating reduction of sinusitis symptoms and improvement in olfactory function with the use of Sinupret. The percentage of adverse health events that occurred with Sinupret were reported to be non-severe in nature and infrequent in studies by Jund et al. and Palm et al. They found that the side effect profile of the herbal remedy was found to be similar, if not improved, compared to the placebo groups- indicating a dependable safety profile.^{3,6}

Where would Sinupret fit in with the other symptomatic treatments of AVRS and CRS? In their study, Jund et al. compared Sinupret to intranasal corticosteroids, a popular treatment recommended by practitioners for sinusitis, which was recently pushed over-the-counter in the U.S. Noted in their discussion, was the fact that mometasone (Nasonex) intranasal corticosteroid, had a NNT for AVRS of 11, while Sinupret was found to have a NNT of 10.³ This suggests a similar clinical profile of the efficacies of the two drugs and a place for Sinupret as an adjunctive herbal therapy in symptomatic treatment of sinusitis. Many authors also discussed how Sinupret

and other symptomatic treatment options could potentially allow for the reduction of the over-prescribing of antibiotics.³

Despite compelling evidence, the studies reviewed had notable inadequacies. For example, all three of the studies took place at health centers in Germany and studied German populations, putting the generalizability of the results into question. Another limitation regarding the reliability of these studies is the fact that Binorica, the company that manufactures Sinupret, was the major funding source for the trials and publications, suggesting a possible source of bias. Other limitations include subjective self-reporting of symptoms and olfactory function by participants in all three studies, as well as lack of a standard for the level of severity of sinusitis symptoms required in patients to participate in the studies. The study by Reden et al., is not as robust in showing the effects of the intervention as the other two RCTs due to the fact that it only studied a sample size of 36 and did not find clinically significant data. Studies by Palm et al. and Jund et al. saw significant results with large sample sizes, indicating robust, more generalizable results. Despite some downfalls, the results found by Jund et al. and Palm et al. are promising and suggest that Sinupret's herbal combination could be considered as an adjunct in the treatment of sinonasal diseases through its proposed mechanism of suppressing inflammation, mucus production, and pathogen growth.

CONCLUSION

This systematic review offered insight into three studies using an herbal oral combination, Sinupret, for the treatment of sinusitis. Due to the thorough nature, large population size, and clinically significant results of two of the studies,^{3,6} it was determined that Sinupret is an effective treatment when compared to placebo, and worthwhile for patients to attempt in the treatment of sinusitis. It was found to have similar efficacy to an intranasal corticosteroid in

reducing inflammatory symptoms.³ The common cold may never have a “gold standard” treatment due to many different and undefinable etiologies, but further pharmaceutical research is being conducted to discover ways to combat the symptoms of AVRS/CRS that affect so many Americans every day. This will ultimately allow less health care dollars spent and less missed productivity days. Herbal medicine is increasingly gaining attention with new research developing for its use in many different disease states; from psychological disorders, to diseases of the bowel and bladder, to sinusitis.⁹ Although research efforts should be continued, Sinupret presents itself as an effective and safe option to reduce symptoms and recover more rapidly from sinonasal diseases.

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