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Systematic Review of Clinical Data with BNO-101 (Sinupret®) in the Treatment of Sinusitis

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Key Words
Sinusitis · Meta-analysis · BNO-101 · Sinupret® · Phytotherapy · Herbal drug · Randomized controlled trials

Summary
Background: The herbal formula BNO-101 (containing Gentianae radix, Primulae flos, Rumicis herba, Sambuci flos and Verbenae herba; ratio 1:3:3:3:3) has been widely employed as a 'mucoactive' agent in Germany for 70 years for the symptoms of respiratory infections. This paper reviews the clinical evidence of BNO-101 in sinusitis. **Methods:** The systematic search identified 22 studies with BNO-101. Out of these, 6 controlled trials on sinusitis were reassessed according to predefined criteria. 4 trials had almost identical designs and could be examined by meta-analysis. **Results:** The database comprised approximately 900 patients, mostly young adult males. After 2 weeks of treatment, verum was significantly superior to placebo (2 RCTs, 159 vs. 160 patients, both add-on to antibacterial treatment). The benefit regards the patients' assessment ('cured': verum = 61.1%, placebo = 34.5%), reduction of drain obstruction, headache and radiological signs (all $p < 0.05$). Comparing BNO-101 to ambroxol (2 RCTs, 151 vs. 150 patients, add-on to antibacterials in 13% of the cases) the patients' assessment after 2 weeks showed no difference, although it favoured BNO-101 in chronic cases ('cured' BNO-101 = 37.1%, ambroxol = 12.5%; $p < 0.05$). It also favoured BNO-101 concerning pyorrhoea and headache ($p < 0.05$). No significant differences were reported in 2 open randomised trials vs. N-acetyl-cysteine and vs. the herbal product Myrtol std. **Conclusions:** BNO-101, combined with standard antibacterial therapy, significantly reduces the acute symptoms and signs of sinusitis. The effects are of the same order of magnitude as observed with other mucoactive agents. In the trials investigated BNO-101 had a favourable risk/benefit ratio, with an incidence of adverse events similar to placebo.

Schlüsselwörter
Sinusitis · Metaanalyse · BNO-101 · Sinupret® · Phytotherapie · Phytopharmakon · Randomisierte kontrollierte Studie

Zusammenfassung
Hintergrund: Die pflanzliche Zubereitung BNO-101 (bestehend aus Gentianae radix, Primulae flos, Rumicis herba, Sambuci flos and Verbenae herba; Verhältnis 1:3:3:3:3) wird in Deutschland seit 70 Jahren häufig als Schleim lösendes Mittel bei Atemwegsinfekten eingesetzt. Diese Arbeit untersucht die Evidence zur klinischen Wirksamkeit von BNO-101 bei Sinusitis. **Methoden:** Die systematische Suche identifizierte 22 Studien mit BNO-101. Von diesen wurden 6 Studien zu Sinusitis nach vordefinierten Kriterien reanalysiert. 4 Studien hatten ein fast identisches Design und wurden auch mittels Metaanalyse untersucht. **Ergebnisse:** Die Datenbasis umfasste zirka 900, hauptsächlich junge männliche Patienten. Nach 2 Wochen war das Verum dem Plazebo (2 RCTs, 159 vs. 160 Patienten, jeweils zusätzlich zu Antibiotika) in der Patienteneinschätzung ('gesund': Verum = 61,1%, Plazebo = 34,5%) sowie der Verringerung von Abflussbehinderung, Kopfschmerz und radiologischen Zeichen signifikant überlegen (alle $p < 0,05$). Im Vergleich mit Ambroxol (2 RCTs, 151 vs. 150 Patienten, in 13% der Fälle zusätzlich zu Antibiotika) war die Patienteneinschätzung nach 2 Wochen Einnahme von BNO-101 insgesamt nicht signifikant besser, jedoch bei chronisch Erkrankten ('gesund' BNO-101 = 37,1%, Ambroxol = 12,5%; $p < 0,05$). BNO-101 war insgesamt besser hinsichtlich Eiterabsonderung und Kopfschmerz ($p < 0,05$). Zwei offene, randomisierte Vergleichsstudien ergaben keine signifikanten Unterschiede zwischen BNO-101 und N-acetyl-cystein bzw. Myrtol std. **Schlussfolgerungen:** BNO-101 verringert signifikant die akuten Symptome und Zeichen der Sinusitis in Kombination mit antibiotischer Therapie. Die Effekte sind von vergleichbarer Grössenordnung wie bei anderen Schleim lösenden Medikamenten. In den untersuchten Studien hatte BNO-101 ein günstiges Nutzen-Risiko-Verhältnis mit einer vergleichbaren Inzidenz unerwünschter Wirkungen wie Plazebo.

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Introduction

Although in most cases sinusitis is a self-limiting disease, it represents a major health burden both in personal and in social terms [1]. For example, in the USA and Germany, every year about 7–9% of the population consult a physician because of sinusitis; the prevalence of sinusitis appears to be increasing [2, 3]. However, review of the evidence reveals few rigorous studies which can guide clinicians in recognition and appropriate treatment. The Agency for Healthcare Research and Quality (AHRQ) [2] sponsored a systematic review of the diagnosis and treatment of acute bacterial sinusitis. That review concluded that most studies were flawed. The AHRQ concluded that sinus radiographs were moderately sensitive (76%) and specific (79%); plain radiographs and sinus computed tomographic (CT) scans were non-specific and insensitive to the presence or absence of clinical sinusitis. Sinus aspirations were accurate but infrequently used because they are costly and invasive. The German Consensus Group of the Deutsche Gesellschaft Hals-Nasen-Ohrenheilkunde, Kopf- und Hals-Chirurgie (DG-HNO – German Society for Otorhinolaryngology, Head and Neck surgery) [3] proposed a more differentiated diagnostic approach, guided by the symptomatology of the patient and stressing the importance of an endoscopic examination. Ultrasound has been reported to be slightly less accurate than radiography when both were compared to sinus puncture [4]. The AHRQ showed that more patients were cured or more quickly improved with antibiotic therapy compared to placebo; nevertheless, two thirds of patients receiving placebo recovered spontaneously. In addition, serious complications of bacterial sinusitis were rare.

Sinusitis may be classified as follows: acute sinusitis involves symptoms that last <4 weeks, usually preceded by a viral upper respiratory infection. Subacute sinusitis involves symptoms that last 4–12 weeks that resolve completely after treatment. Recurrent acute sinusitis is characterised by ≥4 episodes of obstruction per year, with complete resolution of symptoms and a return to normal mucosa between episodes. Chronic sinusitis involves symptoms that last ≥12 weeks and may include acute exacerbations. A subset of chronic sinusitis patients have acute on chronic sinusitis [5]. Chronic sinusitis is a multifactorial disease; microorganisms play a significant role in the persistence and origination of the inflammatory process, albeit the exact role of these organisms in the pathogenesis of chronic sinusitis remains unclear [6].

The evidence as reviewed by the Cochrane Collaboration [7] and the AHRQ suggests that the initial antibiotic choice can either be amoxicillin or a folate inhibitor. The length of therapy and the use of adjunctive treatments such as decongestants, mucoactive substances or saline irrigations have not been adequately studied. The aim of general treatment is to establish a more normal nasal environment through moisturization and humidification, and a reduction in the viscosity of mucus and in local swelling. The current recommendations are 10–14 days of antibiotic therapy and adjunctive treatment to improve drainage. The German Consensus Group DG-HNO [3] considers phytomedicines such as BNO-101 to be 'possibly effective'.

BNO-101 is a herbal medicinal product which has been widely employed as a 'mucoactive' agent in Germany for almost 70 years. Experimental studies have shown that BNO-101 and its individual components have secretolytic properties [8]. More recently, it has been shown that prophylactic administration of BNO-101 increases resistance to respiratory tract infection by intranasal application of Sendai virus (Parainfluenza viridae) in mice. It has been reported that the individual ingredients contribute to the overall pharmacological profile of the combination with secretolytic, antiinflammatory, immunomodulating and antiviral effects [9]. Based on a large epidemiological survey, the herbal medicinal product BNO-101 seems devoid of teratogenic potential in humans [10].

Methods

The primary objective of this review was to assess the efficacy and safety of BNO-101 (Sinupret®) from a clinical point of view taking into account clinically relevant end-points. The guidelines provided by the Cochrane Collaboration Handbook for Reviews [11] were applied in the analysis of the clinical data.

Search Strategy

Among the data sources consulted in the identification of trials were bibliographic databases (TOXLINE, MEDLINE, HealthSTAR, AIDSLINE and CANCERLIT, Embase, AMED, Cochrane Col.; search terms: sinusitis, respiratory infection, sinupret, BNO-101, herbal), reference lists from pertinent review articles and books, and personal contacts with experts active in the area and the manufacturer up to April 2005. Full disclosure of the product documentation including requested statistical and official reports by the manufacturer in Germany eliminated a publication bias. All papers were screened and any dealing with prospective clinical trials was retained for classification. To be eligible for the meta-analysis studies had to be randomised controlled trials (RCT) in which raw data were made available by the manufacturer or the investigators. All trials rendered eligible were summarized in tabulated form by one reviewer (R.B.). The standard table included a full reference, a quality rating, the type of sinusitis studied, demographic data and treatments, end-points (e.g. patients' global assessments) and adverse events. These tables were discussed and verified with the other authors until consensus was reached. No formal validation process was employed.

Statistics

The current analysis was limited to trials in which raw data were available. As a consequence, the data presented here are not necessarily identical to those published or reported. The studies were reanalysed following current standards and reported as 'intent to treat' (ITT) and last observation carried forward (LOCF), applying the same criteria to all of them. The trials had almost identical designs, thus making it easier to compare and pool data.

Since neither validated ratings nor common standardised procedures were used in the trials, the analysis is based on the patient's global assessment and the 'most bothersome symptom' approach; that is, the worst symptom score is considered representative of the patient's condition. This avoids the construction of artificial sum scores. The following criteria were defined 'a priori':

Table 1. Summary of trials selected

Study	Design	Intervention			
		BNO-101, n	control, n	galenics	comparator
Berghorn, 1990 [17]	RCT	71	69	drops	placebo
Neubauer, 1987 [18]	RCT	88	91	tabl.	placebo
Wahls, 1990 [20]	RCT	80	80	drops	Ambroxol
Simm, 1992 [19]	RCT	71	70	drops	Ambroxol
Kraus, 1986 [22]	open random.	67	67	tabl. vs. caps.	Myrtol std.
Braum, 1986 [21]	open random.	80	80	tabl. vs. granulate	NAC
All trials combined		457	457		

NAC = N-acetyl-cysteine.

Table 2. Summary of examinations and variables in the selected trials

Examinations	Berghorn [17]	Neubauer [18]	Wahls [20]	Simm [19]	Braum [21]	Kraus [22]
Control visits at day(s)	7, 14	14	7, 14	7, 14	7, 14	7, 14
Radiology	yes[c]	yes	yes	yes	yes	yes
Ultrasonography	yes	–	–	yes	–	yes
Rhinomanometry	yes	–	–	yes	–	–
Rhinoscopy						
– Mucosa	–	yes	yes	–	yes	–
– Irritation[a]	–	yes	yes	–	yes	yes
– Turbinates	–	yes	yes	–	yes	–
– Drain obstruction	yes	yes	yes	yes	yes	yes
– Pyorrhoea	yes	yes	yes	yes[d]	yes	yes
Examen, anamnesis[b]	yes	yes	yes	yes	yes	yes
Global assessment	yes	yes	yes	yes	yes	**

[a]Reddening, livid, negative.
[b]See table 3.
[c]Only at admission to the trial.
[d]Mucus streaming down in upper pharynx and nasal cavity.
**Replaced by algorithm: If at last visit sum [difficult respiration, headache, pyorrhoea, mucosa, mucus] ≥ 2, the score is 2; if sum [difficult respiration, headache, pyorrhoea, mucosa, mucus] ≥ 1, score is 1; otherwise the score is 0.

Primary end-point:
– The patient's global assessment ('unchanged', 'improved', 'cured') as reported.

Secondary end-points:
– Number of patients free of any subjective symptom (mucus, headache, local/pressure or pain, difficult respiration);
– Number of patients free of any objective sign of sinusitis (radiology, ultrasonography, rhinoscopy: mucosa, blood irrigation, turbinates, drain obstruction, pyorrhoea);
– Number of patients free of any subjective symptom or objective sign, i.e. medically 'healed'.

Descriptive results: Changes in ratings of symptoms or signs (in patients ever presenting the symptom or sign) and absolute ratings.

In the case of pooled studies, confirmatory multiple stepwise regression analysis was performed taking trial, sex, treatment, age, weight, presence of chronic or acute sinusitis, duration of disease (0.5 weeks assumed for acute cases), and known allergic component as independent variables and global assessments, absence of any symptom, absence of any sign and medically 'healed' at the final visit as dependent variables.

The studies were tabulated and analysed in WinSTAT™ with Excel Version 2001.1 (an SPSS-validated program). The data were summarised in tables and statistically analysed: in the case of dichotomous data, the odds ratio and the rate difference according to Peto Mantel-Haenszel were employed; ordinal data were analysed with the χ^2-trend [12] or an equivalent method. Sensitivity analyses were performed in the event of significant results and appropriate software [13] was employed in the validation of results. Significances were calculated using 2-sided tests, the threshold of significance being $p \leq 0.05$ (demographics: values between $p > 0.05$ and $p \leq 0.1$ were reported as trends).

Results

Material Scrutinised

The literature search identified 22 trials with BNO-101, but only 2 comparative studies. 6 further unpublished clinical studies were identified through other channels and duly scrutinised. 2 studies [14, 15] were excluded because of incomplete data-sets. 6 studies with raw data (table 1) could be retained as relevant trials with 4 meeting all the inclusion criteria and being regarded as 'key' trials.

Table 3. Comparison of AHRQ criteria for 'a strong history for acute sinusitis' (present with ≥ 2 major factors or 1 major and 2 minor factors) and symptoms rated in the selected trials

Criteria	Berghorn [17]	Neubauer [18]	Wahls [20]	Simm [19]	Braum [21]	Kraus [22]
Major factors						
Facial congestion or fullness	–	–	–	–	–	–
Nasal obstruction or blockage	–	yes	yes	–	yes	yes
Nasal discharge	yes	yes	yes	yes	yes	yes
Purulence or discoloured postnasal discharge*	yes	yes	yes	yes	yes	yes
Facial pressure or pain	–	–	–	yes	yes	–
Hyposmia or anosmia	–	–	–	–	–	–
Fever	–	–	yes	–	–	–
Minor factors						
Headache	yes	yes	yes	yes	yes	yes
Halitosis, fatigue, dental pain, cough, ear pain	–	–	–	–	–	–

*Including purulence in the nose on examination.

Table 4. Patients' global assessment, BNO-101 vs. placebo – individual and pooled trials

Study	Treatment group	Cured n (%)	Improved n (%)	Unchanged n (%)	Missing n	Significance ('cured'), p
Berghorn	*All patients*					
[17]	BNO-101	44 (62)	24 (33.8)	3 (4.2)	0	0.093
	Placebo	32 (46.4)	35 (50.7)	2 (2.9)	0	
	Acute sinusitis					
	BNO-101	40 (64.5)	20 (32.3)	2 (3.2)	0	0.090
	Placebo	28 (49.1)	27 (47.4)	2 (3.5)	0	
Neubauer	*All patients*					
[18]	BNO-101	44 (60.3)	25 (34.2)	4 (5.5)	15	0.001
	Placebo	19 (24.1)	40 (50.6)	20 (25.3)	12	
	Acute sinusitis					
	BNO-101	38 (63.3)	20 (33.3)	2 (3.3)	11	0.001
	Placebo	16 (26.7)	28 (46.7)	16 (26.7)	11	
Pooled trials	*All patients*					
	BNO-101	88 (61.1)	49 (34)	7 (4.9)	15	<0.001
	Placebo	51 (34.5)	75 (50.7)	22 (14.9)	12	
	*Acute sinusitis**					
	BNO-101	78 (63.9)	40 (32.8)	4 (3.3)	11	<0.001
	Placebo	44 (37.6)	55 (47)	18 (15.4)	11	
	*Chronic sinusitis**					
	BNO-101	8 (40)	9 (45)	3 (15)	4	0.539
	Placebo	7 (24.1)	19 (65.5)	3 (10.3)	1	

*Patients without data about chronicity are not stratified.

All examined studies are briefly described and the most relevant data included in the tabulated summaries. 6 comparative studies, 4 of which randomised double blind and 2 open randomised, were retained for closer analysis (table 1); of these, only the trial by Neubauer [18] has been published [16]. The selected studies deal with more than 900 patients, half of which were treated with the study medication as drops or as sugar-coated tablets. Each double blind studies lasted 14 days and included at least one radiological examination and a rating of subjective symptoms. In one trial [22] the global assessment was missing and therefore replaced by an algorithm (details see table 2). The patients had to present radiologic and/or ultrasonographic signs of sinusitis in order to be eligible for the trials. The comparison between the AHRQ [2] criteria for 'a strong history for acute sinusitis' and the symptoms rated in the selected studies showed the validity of the symptoms rated although several AHRQ criteria were not specifically mentioned (but probably reflected to some extent in the global assessments, table 3).

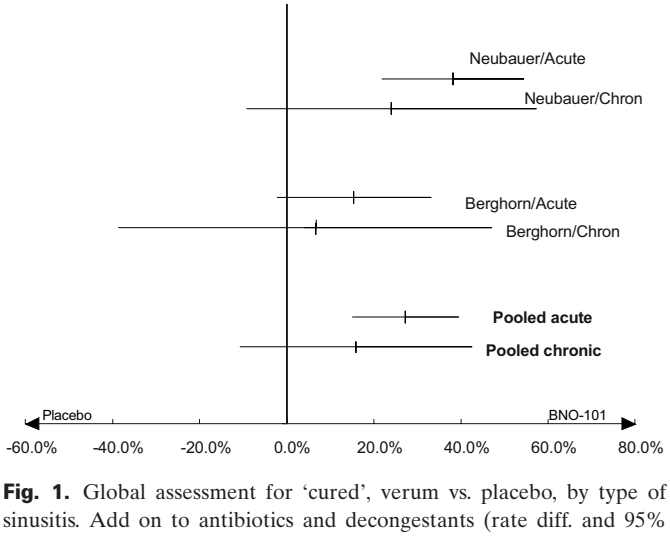

Fig. 1. Global assessment for 'cured', verum vs. placebo, by type of sinusitis. Add on to antibiotics and decongestants (rate diff. and 95% confidence interval (CI).

Individual Studies vs. Placebo

Berghorn [17]: 85% males (more females in the placebo group, $p < 0.05$); mean age: verum = 29.1 ± 11.6 years vs. placebo = 29.5 ± 14; body weight: verum = 75.9 ± 10.1 kg vs. placebo = 77 ± 16.4 kg. The treatment was 3 × 50 drops per day of the active medication or the corresponding placebo for 14 days. An allergic component was reported in 4 patients in the verum group vs. 7 patients in the placebo group. All patients received antibiotics and decongestants. As shown in table 4, ≥95% of the patients improved but, comparing treatments, no variable reached the threshold of significance.

Neubauer [18]: All males; mean age: verum = 23.4 ± 5.2 years vs. placebo = 24.9 ± 7.2 years; mean body weight: verum = 73.7 ± 5.8 kg vs. placebo = 72.7 ± 5.9 kg). Patients were treated with 3 × 2 sugar-coated tablets of verum daily or the corresponding placebo for 14 days; there was no intermediate visit after 1 week. An allergic component was reported in 8 patients in the verum group vs. 7 patients in the placebo group. The frequency of comedications prescribed was for antibiotics 99% of the patients vs. 96%; decongestants 98% of the patients vs. 97%. There were more patients with chronic sinusitis and pyorrhoea in the BNO-101 group ($p < 0.05$).

The patients' global assessments favoured verum (table 4); that is, both the patients reporting to be 'cured' ($p < 0.001$) and the entire rating scale (χ^2-trend $p < 0.01$). These outcomes were similar when the analysis was restricted to patients with acute sinusitis, but did not reach significance when restricted to patients with chronic sinusitis (small number of patients). Considering absence of any symptom after 2 weeks, verum was significantly better ($p < 0.05$; LOCF: verum = 35% of patients vs. placebo = 21%). Also, improvements of individual symptoms were more frequent with the active therapy; that is, drain obstruction, x-rays and headache (all $p < 0.05$).

Pooled Data vs. Placebo

The above mentioned 2 studies compared 159 BNO-101 treated patients with 160 placebo patients. The frequency of comedications prescribed was 99% vs. 98% of the patients for antibiotics and 99% vs. 98% of the patients for decongestants; thus, these studies are to be considered as 'add-on to standard care' trials.

The patients' global assessments favoured verum; that is, both considering the patients reporting to be 'cured' (table 4) and for the entire rating scale (χ^2-trend, $p < 0.01$) (fig. 1).

Considering the secondary variables verum was better concerning absence of any symptom and absence of any objective sign at the final visit (LOCF; $p < 0.05$; verum = 51% vs. placebo = 39% of patients, and verum = 36% vs. placebo = 24%, respectively) and for the rates of medically 'healed' (verum = 34% vs. placebo = 24%). Regarding changes in individual signs and symptoms at the final visit, verum was better in reducing drain obstruction ($p < 0.01$) and headache ($p < 0.05$) (fig. 2).

The results were similar when the analysis was restricted to cases with acute sinusitis. Considering only those cases with chronic sinusitis, the differences did not reach significance.

Confirmatory analysis: Multiple stepwise regression analysis confirmed that there was a highly significant difference between treatments and between trials in the dependent variables mentioned above.

Individual Studies vs. Ambroxol

Simm [19]: All males; mean age: 40.5 ± 19.2 years in the verum group vs. 43.4 ± 22.5 years in the ambroxol group; mean body weight: 65 ± 12.1 kg in the verum group vs. 66.6 ± 12 kg in the ambroxol group. Patients were treated with 50 or 100 drops of BNO-101 or ambroxol 3 × daily for 14 days. Chronic sinusitis was diagnosed in the BNO-101 group in 18 cases vs. 7 in the ambroxol group ($p < 0.05$). An allergic component was reported in 7 patients in the BNO-101 group vs. 11 patients in the ambroxol group. The frequency of comedications prescribed was 55% of the patients vs. 62% for antibiotics and 49% of the patients vs. 51% for decongestants, respectively.

The patients' global assessments favoured BNO-101 (table 5); that is, both considering the patients reporting to be 'cured' ($p < 0.05$) and the entire rating scale (χ^2-trend $p < 0.05$). However, there were no significant differences between treatments considering the secondary variables with the exception of headache at the final visit (more frequently improved with BNO-101; $p < 0.05$). The results remained essentially similar when the analysis was restricted to cases with acute sinusitis, but were not significant in patients with chronic sinusitis (Fisher test, $p = 0.2$).

Wahls [20]: All males; mean age: BNO-101 = 22.8 ± 5.3 years vs. ambroxol = 23.3 ± 5.6 years; mean body weight: BNO-101 = 76 ± 9.6 kg vs. ambroxol = 75.3 ± 9.1 kg). Patients were treated with 50 or 100 drops of BNO-101 or ambroxol 3 × daily for 14 days. An allergic component was reported in 9 patients in

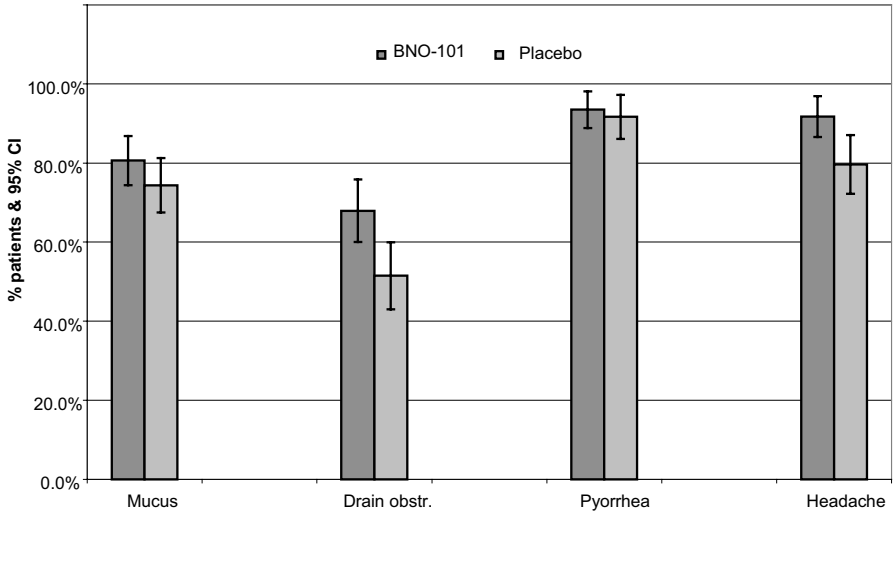

Fig. 2. Patients with symptom improved as percentage of patients ever having had the symptom, verum vs. placebo.

Table 5. Patients' global assessment, BNO-101 vs. ambroxol – individual and pooled trials

Study	Treatment group	Cured n (%)	Improved n (%)	Unchanged n (%)	Missing n	Significance ('cured'), p
Simm	*All patients*					
[19]	BNO-101	52 (77.6)	13 (19.4)	2 (3)	4	0.035
	Ambroxol	42 (60.9)	20 (29)	7 (10.1)	1	
	Acute sinusitis					
	BNO-101	37 (82.2)	7 (15.6)	1 (2.2)	4	0.052
	Ambroxol	37 (64.9)	13 (22.8)	7 (12.3)	1	
Wahls						
[20]	*All patients*					
	BNO-101	13 (19.7)	32 (48.5)	21 (31.8)	14	0.892
	Ambroxol	14 (20.3)	35 (50.7)	20 (29)	11	
	Acute sinusitis					
	BNO-101	11 (22.4)	24 (49)	14 (28.6)	13	0.763
	Ambroxol	13 (25)	28 (53.8)	11 (21.2)	9	
Pooled trials	*All patients*					
	BNO-101	65 (48.9)	45 (33.8)	23 (17.3)	18	0.170
	Ambroxol	56 (40.6)	55 (39.9)	27 (19.6)	12	
	*Acute sinusitis**					
	BNO-101	48 (51.1)	31 (33)	15 (16)	17	0.460
	Ambroxol	50 (45.9)	41 (37.6)	18 (16.5)	10	
	*Chronic sinusitis**					
	BNO-101	13 (37.1)	14 (40)	8 (22.9)	1	0.036
	Ambroxol	3 (12.5)	12 (50)	9 (37.5)	2	

*Patients without data about chronicity are not stratified.

the BNO-101 group vs. 15 patients in the ambroxol group. The frequency of comedications prescribed was for antibiotics 1% of the BNO-101 patients vs. 3% in the ambroxol group; decongestants 99% of BNO-101 patients vs. 96% in the ambroxol group. At admission, pyorrhoea was somewhat more frequent in the BNO-101 group, while headache was more frequent in the ambroxol group (both $p < 0.1$). There were no significant differences between treatments considering the primary (table 5) or the secondary variables.

Pooled Data vs. Ambroxol

The two studies compared 151 patients treated with BNO-101 and 150 male patients treated with ambroxol. Chronic sinusitis was diagnosed in the BNO-101 group in 36 cases vs. 26 in the ambroxol group. An allergic component was reported in 16 patients in the BNO-101 group vs. 26 patients in the ambroxol group ($p < 0.1$). Antibiotics were co-prescribed to 12% of the BNO-101 patients vs. 15% of the ambroxol patients; 75% of the patients of both groups received decongestants. No sig-

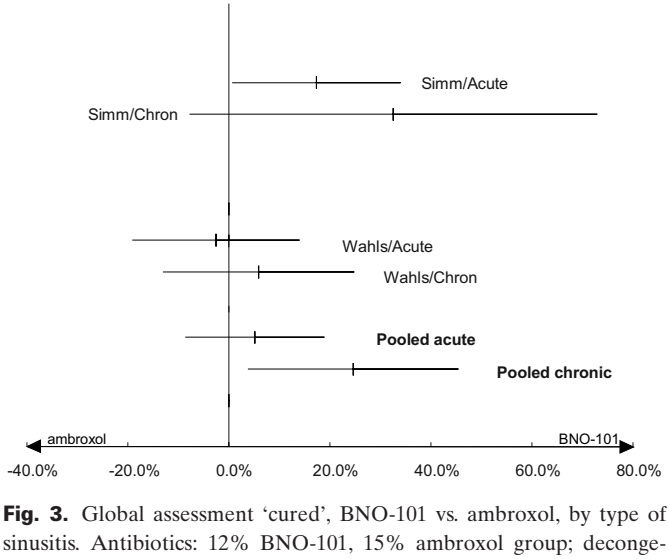

Fig. 3. Global assessment 'cured', BNO-101 vs. ambroxol, by type of sinusitis. Antibiotics: 12% BNO-101, 15% ambroxol group; decongestants: 75% in both groups (rate diff. and 95% CI).

nificant differences in demographics were observed, with the exception of duration of chronic sinusitis (BNO-101 = 67.8 ± 55.6 months vs. ambroxol = 36.0 ± 35.1 months; $p < 0.05$).
There were no significant differences between treatments considering the patients' global assessments (table 5, fig. 3).
Regarding the symptomatology, there were no significant differences between treatments with the exception of pyorrhoea at day 7 and of headache at the final visit (both more frequently improved with BNO-101; $p < 0.05$; fig. 4). The results were similar regardless of concomitant treatment with antibiotics or decongestants.
Confirmatory multiple stepwise regression analysis showed a highly significant difference between trials but not between treatments.
The subgroup of chronic patients merited closer scrutiny (fig. 3). Except for the duration of the disease and for weight, the two groups were comparable. The patients' global assessments (primary end-point) significantly favoured BNO-101, although there were no significant differences between treatments considering the secondary variables. These findings in the chronic cases would require confirmation by a larger prospective trial.

Open Randomised Study vs. N-acetyl-cysteine (NAC)
Braum [21]: All males; mean age: BNO-101 = 23.2 ± 5.7 years vs. NAC = 23.7 ± 6.4 years; mean body weight: BNO-101 = 75.6 ± 9.5 kg vs. NAC = 76.2 ± 10 kg. Patients were treated with 6 sugar coated tablets of BNO-101 or 600 mg NAC per day. In the BNO-101 and the NAC groups, 44 and 48 patients, respectively, were treated with antibiotics; decongestants were not reported. An allergic component was reported in 11 patients in the BNO-101 group vs. 6 in the NAC group. There were no differences between groups at baseline, with the sole exception of headaches which were reported more frequently in the NAC group ($p < 0.1$). Although about two thirds of the patients reported an improvement, there were no significant differences between treatments considering patients' global assessments (primary end-point; table 6) or the secondary variables with the exception of headache at the intermediate visit (day 7, more frequently improved with BNO-101; $p < 0.05$).

Open Randomised Study vs. Myrtol standardised (std. – Gelomyrtol®)
Kraus [22]: All males; mean age: BNO-101 = 22.5 ± 4.5 vs. Myrtol std. = 22.3 ± 3.4 years; mean body weight: BNO-101 = 75.7 ± 11.8 kg vs. Myrtol std. = 74.7 ± 8.1 kg. Patients were treated with 6 sugar-coated tablets of BNO-101 daily or 2–4 capsules of Myrtol std. per day for 21 days. An allergic component was reported in 2 patients in the BNO-101 group vs. 3 in the Myrtol std. group. There were no significant differences in demographics at admission.
There were no significant differences neither between the patients' global assessments of the treatments (63.6% of the BNO-101 patients reported an improvement vs. 70.1% of the Myrtol std. patients; table 7), nor considering the secondary variables.

Safety

The safety evaluation of BNO-101 was performed considering an 'adverse event' to be any undesired event occurring during a study, whether classified as 'adverse event', 'intercurrent disease' or 'side effect'. This analysis concerns the studies reported above (table 8). Older studies than those examined here tend to report about 'side effects' (i.e. symptoms perceived to be possibly linked to the medication) while more recent studies report any event or symptom reported during the trial. The differences of incidences of adverse events in comparative trials showed that a similar number of patients reported adverse events during BNO-101 therapy and placebo. There were no serious adverse events.

Discussion

The two placebo-controlled studies pooled in this analysis examined a predominantly male population of young adults. One trial was performed with tablets [15] while drops were employed in the other [14]. This is the only obvious major difference between the studies which might explain the difference in outcomes. Another aspect that needs to be emphasized is that practically all patients in the placebo controlled trials received antibiotics and decongestants. This could explain the higher rates of 'cured' with BNO-101 in the placebo controlled trials as compared to the trials vs. ambroxol. One may conclude that the active treatment was significantly supe-

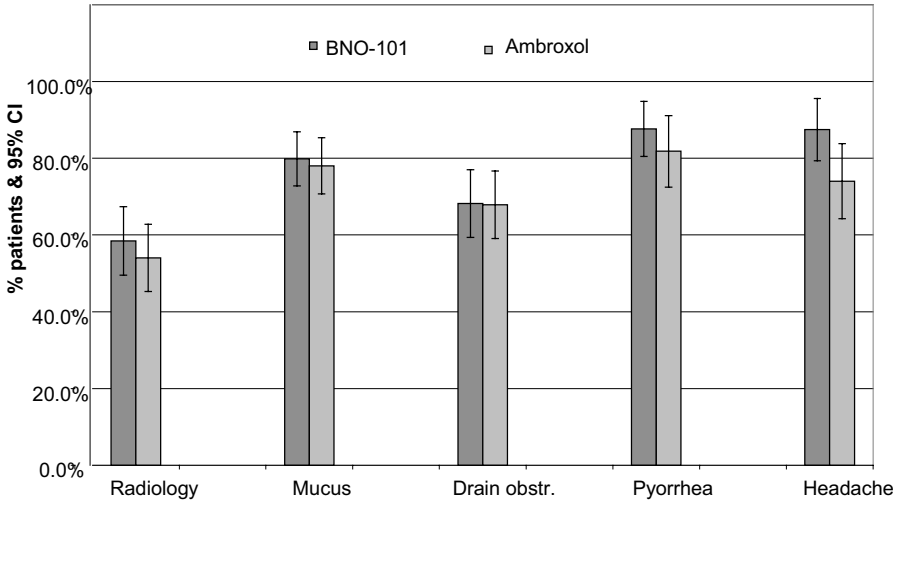

Fig. 4. Patients with symptom improved as percentage of patients ever having had the symptom, BNO-101 vs. ambroxol.

Table 6. Patients' global assessment, BNO-101 vs. NAC [21] (no significant differences)

	Treatment group	Cured n (%)	Improved n (%)	Unchanged n (%)	Missing n
All patients	BNO-101	16 (20.5)	34 (43.6)	28 (35.9)	2
	NAC	17 (21.5)	40 (50.6)	22 (27.8)	1
Acute sinusitis	BNO-101	9 (15.5)	25 (43.1)	24 (41.4)	1
	NAC	6 (12)	27 (54)	17 (34)	1
Chronic sinusitis	BNO-101	7 (35)	9 (45)	4 (20)	1
	NAC	11 (37.9)	13 (44.8)	5 (17.2)	0

Table 7. Global assessment based on algorithm, BNO-101 vs. Myrtol std. [22] (no significant differences)

	Treatment group	Cured n (%)	Improved n (%)	Unchanged n (%)	Missing n
All patients	BNO-101	23 (34.8)	19 (28.8)	24 (36.4)	1
	Myrtol std.	21 (31.3)	26 (38.8)	20 (29.9)	0
Acute sinusitis	BNO-101	16 (42.1)	8 (21.1)	14 (36.8)	1
	Myrtol std.	18 (40.9)	14 (31.8)	12 (27.3)	0

Table 8. Summary of adverse events (AE) in the reviewed trials

Type of AE	BNO-101 n (%)	Placebo n (%)	Ambroxol n (%)	NAC n (%)	Myrtol std. n (%)
Cutaneous allergy	1 (0.2)	–	1 (0.7)	–	–
Headache	1 (0.2)	–	–	–	–
Diarrhoea	1 (0.2)	–	–	–	2 (3.6)
Epigastric discomfort	1 (0.2)	–	–	–	–
Dysgeusia	–	–	–	–	1 (1.8)
Gastroesphageal reflux	–	–	–	–	2 (3.6)
Allergic rhinitis	1 (0.2)	–	–	–	–
Nausea, dysgeusia	–	–	–	–	1 (1.8)
Renal pain	–	–	–	–	1 (1.8)
Not specified	–	3 (1.8)	–	–	–
Hospitalisation*	–	–	–	–	1 (1.8)
Total patients with AE	5 (1.1)	3 (1.8)	1 (0.7)	–	8 (14.5)
Total exposed and reported	445	160	150	80	55

*For invasive diagnostic work up of frontal sinus.

rior to placebo when added to standard antibacterial (and decongestant) treatment. The benefit is seen for both subjective symptoms and objective signs; the benefit of BNO-101 is particularly clear-cut in the reduction of drain obstruction, headache and radiological signs. The global benefit was most evident in cases of acute sinusitis, which accounted for the majority of the cases. However, a non-randomised pilot study with acute sinusitis failed to reveal significant differences between conventional and 'complementary' treatments, including BNO-101, but the number of patients per treatment was small and the dose employed too low [23].

Regarding the comparative trials vs. ambroxol (trans-4-[2-amino-3.5-dibromobenzylamino]-cyclohexane hydrochloride), it is noteworthy that this substance has been reported to have properties similar to the ones described for the components of BNO-101. Since it scavenges oxidants (e.g. OH, HOCl), it stimulates cellular surfactant production and has anti-inflammatory properties owing to its inhibitory effect on the production of cellular cytokines and arachidonic acid metabolites. The two studies pooled in this analysis examined a male population of young adults. Both trials were performed with variable doses of drops, without details of the doses. A few of the patients received antibiotics and the majority received decongestants, without measurable influence on the outcome. There is no obvious major difference between the two studies that may account for the difference in outcomes. Generally, there were no major differences between BNO-101 and ambroxol, even though patients in the BNO-101 group showed greater reduction in some symptoms (i.e. pyorrhoea, headache) than patients in the latter group. In cases of chronic sinusitis, patients' global assessments clearly favoured BNO-101; but these findings would require confirmation by a larger prospective trial with chronic patients.

The two open randomised studies examined BNO-101 in comparison to NAC or to a Myrtol standardised phytomedicine and they suggest similarity between therapeutic effects. However, both the studies' design and the numbers of patients treated preclude any formal conclusion. NAC is a potent antioxidant. It has been reported in previous trials to be effective in sinusitis [24, 25] and it reduces the viscosity of nasal mucus [26]. Myrtol std. contains monoterpenes (e.g. (+)alpha-pinene, d-limonene and 1.8-cineole) that contribute to its anti-inflammatory properties [27]. In patients with sinusitis, Myrtol has been reported in one double blind trial [28] to be superior to placebo.

It is clear that the analysed database has weaknesses concerning the biased selection of patients as well as the methodology of the studies. Although the study population was atypical in that mostly men were included, there are no known gender differences in the incidence, clinical presentation or clinical course of sinusitis [29, 30]. There is a clear need for more and better studies concerning the symptomatic relief of patients with sinusitis. More than 90% of the publications dealing with the treatment of sinusitis in the last few years deal with antibacterial therapies and not with symptomatic relief.

In the study population BNO-101 was well tolerated with an incidence of adverse events that was comparable to that reported with placebo. Data from other sources indicate that in rare cases there are dermatologic/allergic and minor digestive adverse events related to the medication. This profile is in agreement with the results from a Post-Marketing-Surveillance study in bronchitis [31] and with the spontaneous reports of adverse events to the manufacturer and/or the authorities. The incidence of spontaneously reported adverse events is about 1 per 1,000,000 patients treated (Periodic Safety Update Report 1999–2004 provided by the manufacturer). Data on routine haematology and blood chemistry with the study medication have not been reported.

According to the information provided by the manufacturer, rare cases of lesser cutaneous reactions, dyspnoeic episodes and face oedema have been reported and considered as possibly BNO-101 related. There have been isolated reports of serious adverse events (mainly cutaneous eruptions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis) in patients treated with BNO-101, with an approximate incidence of 1 out of 4,000,000 patients related. These eruptions, which may represent variants of the same disease process, could not be attributed with reasonable degree of certainty to BNO-101 (i.e. causal relationship not assessable) due to the preexisting coexistence of predisposing factors, such as infections, auto-immune diseases or drug intake e.g. antibiotics, sulphonamides or NSAIDs.

Conclusions

With some caveats derived from the population of predominantly young healthy males studied, it may be concluded that BNO-101 provides a clinically relevant symptomatic relief in patients with sinusitis, acute and possibly chronic. There is no accepted 'golden standard' supportive therapy for acute or chronic sinusitis; however, there is reasonable evidence that the reference compounds employed in the studies with BNO-101 can provide some degree of symptomatic relief. The results not only indicate that the herbal medicinal product is superior to placebo but that it is also equal or superior to ambroxol and, with major reservations, similar to NAC or Myrtol std.

It is worthwhile to mention that the results with BNO-101 were better when it was combined with an antibacterial treatment. In addition, BNO-101 has a favourable safety profile.

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