

Prescript-Assist™ Probiotic–Prebiotic Treatment for Irritable Bowel Syndrome: A Methodologically Oriented, Two-Week, Randomized, Placebo-Controlled, Double-Blind Clinical Study

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ABSTRACT

Background: The symptomatic efficacy of Prescript-Assist™ (Safer Medical, Inc., Fort Benton, Montana), a treatment combining probiotic and prebiotic components, has previously been evaluated clinically only in an open-label study in patients with various gastrointestinal conditions, including irritable bowel syndrome (IBS).

Objectives: This study was conducted primarily to compare the effects of Prescript-Assist with placebo in patients with a diagnosis of IBS. Toward this objective, a secondary methodologic goal was to determine the number and nature of symptom clusters (“subsyndromic factors”) that characterize IBS.

Methods: This was a double-blind, placebo-controlled clinical study in which patients were randomly assigned to receive either Prescript-Assist one 500-mg capsule BID or 1 placebo capsule BID for 2 weeks. Thirteen IBS symptoms identified from the clinical literature were embedded in a larger research instrument. Using a scale from 0 to 5, patients rated the intensity of these symptoms for the 7-day period immediately before the start of treatment, at the end of each study week, and after each of the 2 subsequent weeks (during which all patients received open-label Prescript-Assist as part of a larger study evaluating methodologic approaches to enhancing assessments of medication efficacy/safety). The symptom-intensity data were subjected to maximum likelihood factor analysis with varimax rotation to identify any IBS subsyndromic factors, and the effect of treatment on each of the identified factors was evaluated using analyses of covariance with appropriate baseline-week assessments as covariate controls.

Results: The study included 25 patients with IBS (23 women, 2 men; age range, 20–70 years). Three subsyndromic factors were identified that together accounted for 60.2% of total IBS symptom variance: factor 1, general ill feelings/nausea; factor 2, indigestion/

flatulence; and factor 3, colitis. Treatment with Prescript-Assist was associated with significant reductions in each of the subsyndromic factors. Factor 1 was significantly reduced by 0.35 standard score units ($F_{1,46} = 4.26$; $P = 0.042$), factor 2 by 0.54 standard score units ($F_{1,46} = 7.83$; $P = 0.008$), and factor 3 by 0.83 standard score units ($F_{1,46} = 10.20$; $P = 0.003$).

Conclusions: This study identified 3 subsyndromic factors of IBS: general ill feelings/nausea, indigestion/flatulence, and colitis. In this methodologically oriented double-blind study in patients with IBS, combined probiotic–prebiotic treatment with Prescript-Assist was associated with significant reductions in these factors. (*Clin Ther.* 2005;27:XXX–XXX) Copyright © 2005 Excerpta Medica, Inc.

Key words: irritable bowel syndrome, subsyndromes, double-blind, probiotic, prebiotic, efficacy, methodology.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic, episodic gastrointestinal disorder characterized by abdominal discomfort and pain, bloating and gas, and altered bowel habits, particularly diarrhea, constipation, or alternation between these symptoms.^{1–3} IBS affects ~10% to 15% of the population in Western countries and twice as many women as men.^{3–6} The etiology of IBS is uncertain but is thought to be multifactorial, with contributions from altered gastrointestinal motility; altered visceral perception in the small bowel, colon, and intestine; and psychosocial factors.^{2,7}

Prescript-Assist™ (Safer Medical, Inc., Fort Benton, Montana) is a probiotic–prebiotic complex that has

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shown early promise for reducing the signs and symptoms of several gastrointestinal disorders, including IBS. The probiotic component is a complex of 29 soil-based microorganisms, all of which are class I etiologic agents (ie, presenting “no or minimal hazard under ordinary conditions”⁸ [when taken orally]). This component was developed in 1992 and marketed as a nutraceutical supplement under various names (most recently as FloraStat, Safer Medical, Inc.). The prebiotic component is a combination of several substances, the most prominent of which is leonardite, a complex of high- and low-molecular-weight humic substances that constitutes a nutritional source enhancing the proliferation of soil-based organisms.^{9,10}

The efficacy of Prescript-Assist has previously been evaluated clinically in an open-label study in patients with various gastrointestinal conditions, primarily IBS (data on file, Safer Medical, Inc., Report CS-01-05). The present study was conducted primarily to compare the effects of Prescript-Assist with placebo in patients with a diagnosis of IBS. Toward this objective, a secondary methodologic goal was to determine the number and nature of symptom clusters (“subsyndromic factors”) that characterize IBS.

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

Patients with a diagnosis of ongoing IBS were eligible for study participation. For inclusion, patients had to both (1) be currently experiencing abdominal discomfort or pain characterized by ≥ 2 of the following: relieved by defecation, onset associated with a change in stool frequency, and onset associated with a change in the form or appearance of stool; and (2) have experienced these symptoms for >12 weeks in the preceding 12 months (ie, historically met the Rome II criteria).¹¹ Patients meeting the foregoing criteria were recruited from the 3 participating practices. The Rome II criteria do not require that the patient currently be experiencing an episode of IBS; however, in keeping with the guidelines, the diagnosis of IBS in the present study was predicated on clinical evaluations that excluded structural or other explanations for the symptoms, particularly for such “red flag” symptoms as abnormal findings on physical examination and pain and/or diarrhea that disrupts sleep.

Informed consent was obtained from all participants after they had read materials describing the study and been briefed verbally on the double-blind

nature of the study, the treatment conditions, the evaluative instrument, and the study procedures. Dietary changes and/or controls were not part of the research protocol. (If they asked, patients were told to eat as usual.)

Study Design and Procedures

This was a randomized, double-blind, placebo-controlled study. Patients received either Prescript-Assist one 500-mg capsule BID or 1 placebo capsule BID for 2 weeks. All participants were provided with Prescript-Assist for 2 weeks after the double-blind study period as part of a larger study evaluating methodologic approaches. The study drug was supplied by the manufacturer, whose institutional review board approved the protocol.

A broad research instrument was developed by one of the authors (R.M.C.) for use in psychometric explorations of patient well-being across multiple studies. This instrument was based primarily on lists of the most frequently identified (5–15) adverse effects associated with several families of antibiotics (particularly those taken orally) and psychoactive agents (including atypical antipsychotics, selective serotonin reuptake inhibitors, and other classes of antidepressants), as well as lists of prominent symptoms associated with perceptual-conflict conditions and IBS. Through 2 independent content analyses of the prospective symptom descriptions, the instrument was reduced to 64 items, divided for convenience into 11 sections: body as a whole (4 items); cardiovascular (3 items); dermatologic (4 items); gastrointestinal (11 items); metabolic (4 items); nervous system (12 items); respiratory (4 items); special senses (4 items related to auditory, visual, and taste disturbances); urogenital (5 items); musculoskeletal (3 items); and body pain/inflammation (10 items).

The target IBS symptoms, drawn from the clinical literature,^{1–3,7} were embedded in the larger instrument. They were general ill feelings/malaise; general drowsiness/sleepiness; overall feelings of weakness; flu-like syndrome; indigestion/dyspepsia; nausea/vomiting; constipation; decreased appetite; flatulence; colitis; dark stools; diarrhea; and decreased concentration/memory impairment. This final item was included based on its empiric and neurologic linkage with nausea and other symptoms associated with gastrointestinal distress (see Discussion).

Patients assessed the intensity of the 13 IBS symptoms in answer to the question “Have you had this

symptom during the past week, and if so, how intense was it on a scale from 0 to 5, where 0 = no and 5 = high?" These assessments were performed at baseline (for the 7-day period immediately before the start of treatment), at the end of each of the 2 study weeks, and after each of the 2 subsequent weeks of open-label treatment.

Data on the 13 IBS symptoms and the 51 similarly scored non-IBS symptoms collected as part of the 64-item instrument allowed basic analysis of the safety profile, in that any significant increase in an IBS or non-IBS symptom with treatment would point toward an adverse effect or tolerability concern. Analyses of the non-IBS symptoms data also were conducted using the methods described in the following section; however, the results are not presented, as no safety/tolerability concerns emerged.

Study Analyses

The planned data analysis included 2 phases: a maximum likelihood factor (MLF) analysis focused on understanding the multifactorial nature of IBS symptoms, and analyses of covariance (ANCOVAs) conducted primarily to assess the effects on factors identified by the MLF of treatment compared with placebo. During the first phase, the combined set of baseline and weekly symptom ratings were subjected to MLF analysis with an orthogonal varimax rotation.¹²⁻¹⁴ This MLF analysis was intended to determine whether the 13 IBS symptoms could be characterized compactly by a small number of relatively independent subsyndromic (or other) factors that could be used to define factor-score variables capable of capturing the totality of symptoms statistically. If the symptom clusters identified through this analysis were found to provide a compact characterization, they would represent prospective IBS subsyndromic factors to be verified based on (1) their form (ie, patterns of symptom correlation with resultant factors) and (2) the results of the subsequent ANCOVAs. Thus, the factor analysis was considered a statistically efficient means of addressing the multifactorial nature of IBS.^{2,7}

After factor identification, factor-score estimates for individual patients' assessments were computed automatically for each of the resulting factors using the classic regression method.¹⁴ This process resulted in a factor-score variable representing the cluster of symptoms contained within each factor identified in the MLF analysis (ie, capturing the symptom-variable

correlations ["loadings"] for each factor). The subsequent analyses were conducted on the resulting factor scores, which were computed from and replaced patients' weekly assessments of the 13 IBS symptoms. Conservative estimates of reliability for these factor scores also were computed automatically as diagonal elements of the factor-score covariance matrix.^{13,14} Overall, the initial analytic phase was intended to identify prospective subsyndromic factors and representative factor-score variables for use in the subsequent analyses.

The second phase involved ANCOVAs for the effect of treatment, defined as differences between Prescript-Assist and placebo, for each set of factor scores.¹⁴ Other covariates included the effects of week, defined as the difference in treatment effects between week 1 and week 2, and of covariate, controlling for factor scores for the week immediately before study initiation. It was anticipated that any analytically meaningful treatment effects would be statistically significant ($P < 0.05$) with inclusion of the covariate control.¹⁵⁻¹⁹

RESULTS

Of 27 patients initially enrolled, 25 patients with IBS completed the study (23 women, 2 men; age range, 20-70 years). (One patient in each group was discontinued because of administrative difficulties.) Twelve patients received Prescript-Assist one 500-mg capsule BID, and 13 received 1 placebo capsule BID. Most patients well exceeded the entrance criterion of >12 weeks of IBS symptoms in the preceding 12 months, and all reported experiencing symptoms ≥ 4 days a week at the time of enrollment.

Factor Analysis

Based on the MLF analysis with varimax rotation, 3 potential subsyndromic factors were identified that together accounted for 60.2% of the total explained variation across the 13 symptoms¹²: factor 1 was identified as general ill feelings/nausea, factor 2 as indigestion/flatulence, and factor 3 as colitis. **Table I** summarizes the symptom loadings for each factor, which represent the correlation between each set of symptoms and the factor-score variables (where loadings ≥ 0.31 are considered statistically significant).¹³ The reliabilities of the 3 factors were 0.860, 0.798, and 0.998, respectively; this was not surprising given the magnitude of the factor loadings.

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Table I. Results of maximum factor likelihood analysis with varimax rotation to identify subsyndromic components of irritable bowel syndrome (IBS).

IBS Symptoms*	Factors		
	1. General Ill Feelings/Nausea	2. Indigestion/Flatulence	3. Colitis
General ill feelings/malaise	0.783	0.237	0.139
Drowsiness/sleepiness	0.757	0.399	-0.014
Overall feelings of weakness	0.758	0.342	0.050
Flulike syndrome	0.547	0.098	-0.089
Indigestion/dyspepsia	0.222	0.783	-0.019
Nausea/vomiting	0.629	0.107	0.071
Constipation	0.513	0.219	0.197
Decreased appetite	0.498	-0.003	0.248
Flatulence	0.047	0.801	0.237
Colitis	0.012	0.058	0.998
Dark stools	0.261	0.447	-0.002
Diarrhea	0.163	0.199	0.187
Decreased concentration/ memory impairment	0.494	0.330	0.394

*Symptoms were scored by patients on a scale from 0 = none to 5 = high. Factor loadings ≥ 0.31 were statistically significant (Bonferroni $P < 0.05$, 2-tailed).

The highest positive loadings for factor 1 were general ill feelings/malaise (0.783), overall feelings of weakness (0.758), and drowsiness/sleepiness (0.757). Less positive but significant loadings included nausea/vomiting (0.629) and decreased concentration/memory impairment (0.494). The highest loadings for factor 2 were indigestion/dyspepsia (0.783) and flatulence (0.801). For factor 3, a pronounced positive loading was observed for colitis (0.998). As with factor 1, factors 2 and 3 also had statistically significant loadings (although smaller than their most prominent loadings) for decreased concentration/memory impairment (0.330 and 0.394, respectively). The absence of all but negligible negative loadings (ie, a unipolar structure) for any of the prospective subsyndromic factors is noteworthy (see Discussion).

Analyses of Covariance

The results of the ANCOVAs showed significant reductions in the symptoms associated with the 3 factors and suggested that positive treatment effects occurred within the first week (Table II). For factor 1, treatment with Prescript-Assist was significantly associated with a reduction in factor scores of 0.345 standard score units ($F_{1,46} = 4.26$; $P = 0.042$); in contrast,

the difference in treatment effect between week 1 and week 2 was not statistically significant. Treatment also was associated with significant reductions in factor scores for factors 2 and 3: factor 2 was reduced by 0.544 standard score units ($F_{1,46} = 7.83$; $P < 0.008$), and factor 3 was reduced by 0.826 standard score units ($F_{1,46} = 10.20$; $P < 0.003$). Paralleling the result for factor 1, the differences between week 1 and week 2 were not significant for either factor 2 or factor 3.

DISCUSSION

Based on the analytic results, the symptom clusters identified in this study appear to constitute 3 subsyndromic factors—general ill feelings/nausea, indigestion/flatulence, and colitis—in patients with IBS diagnosed using the Rome II criteria.¹¹ This conclusion is supported by the absence of all but negligible negative loadings for any of the 3 factors. This unipolar structure (all loadings in essentially the same direction) is a primary characteristic of subsyndromic factors when symptoms are scored consistently for adverse directionality (ie, higher symptom scores reflecting greater distress), as in this study. However, a unipolar structure is not a definitive marker of a subsyndromic factor, as it could also represent a cluster of adverse

Table II. Summaries of the analyses of covariance for the 3 subsyndromic factors of irritable bowel syndrome.

Factor 1. General ill feelings/nausea						
Model Terms	Unstandardized Coefficients		β	<i>t</i>	<i>P</i>	
	B	SE				
Constant	0.028	0.431		0.066	0.95	
Treatment	-0.345	0.165	-0.188	-2.093	0.042	
Week	-0.075	0.165	-0.041	-0.454	0.65	
Covariate	0.803	0.093	0.777	8.634	<10 ⁻¹⁰	
Factor 2. Indigestion/flatulence						
Model Terms	Unstandardized Coefficients		β	<i>t</i>	<i>P</i>	
	B	SE				
Constant	0.227	0.466		0.49	0.63	
Treatment	-0.544	0.194	-0.273	-2.80	0.008	
Week	-0.070	0.176	-0.035	-0.40	0.69	
Covariate	0.724	0.109	0.645	6.62	<10 ⁻⁷	
Factor 3. Colitis						
Model Terms	Unstandardized Coefficients		β	<i>t</i>	<i>P</i>	
	B	SE				
Constant	0.540	0.671		0.80	0.43	
Treatment	-0.826	0.259	-0.377	-3.19	0.003	
Week	0.032	0.257	0.014	0.12	0.91	
Covariate	0.654	0.152	0.507	4.29	<0.001	

B = simple regression weight; β = standardized coefficient; *t* = *t* test statistic.

effects associated with the probiotic–prebiotic treatment. This concern was addressed by the ANCOVAs, in which the absence of negative factor loadings implied that any treatment-related reductions in the associated factor scores (as was the case throughout) indicated a broad reduction in IBS symptoms. Indeed, the results of the ANCOVAs support the identified subsyndromic factors, as treatment with Prescript-Assist was associated with significant reductions in each factor-score analysis.

The patterns of correlation between individual symptoms and the 3 factors (ie, factor loadings) were generally consistent with expectations. Before conduct of the study, it was conjectured that decreased concentration/memory impairment would load on an IBS subsyndromic factor similar to those previously reported

in studies of ship motion^{15,20} and consistent with patterns associated with chemical, mechanical, and other irritations to the stomach and perceptual-conflict illnesses.^{21–23} This conjecture was predicated on IBS sharing with the above-mentioned conditions the “prophylactic inactivation” and behavioral components addressed by Treisman²³ and others.^{20,22} In fact, the data for factor 1 strongly supported this conjecture, with a pattern of loadings (including 0.494 for decreased concentration/memory impairment) similar to that reported elsewhere.¹⁵ Decreased concentration/memory impairment also was found to load on factors 2 and 3 (0.330 and 0.394, respectively), possibly pointing toward more complex interactions with this cognitive symptom than was initially anticipated. These findings warrant further

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study of the 3 IBS subsyndromic factors in larger samples.

Methodologic Considerations

In pursuing its primary interest in the efficacy of Prescript-Assist, this study also found support for the efficacy of its methodologic tools, the 64-item questionnaire and the use of a covariate control. As noted earlier, the 64-item questionnaire had not been previously validated; however, information on reliability and validity was derived in the course of the study. In particular, the MLF analysis yielded conservative estimates for the reliability of the factor scores for the 3 subsyndromic factors: 0.860 for factor 1, 0.798 for factor 2, and 0.998 for factor 3. These represent conservative “concurrent reliabilities” for the 3 sets of factor scores. To some extent, cross-week (nonconcurrent) test–retest reliabilities are also represented by the results of the 3 ANCOVAs, in which each covariate β represented the reliability over the 2 weeks of the study from baseline with subsequent assessments (0.777, 0.645, and 0.507 for factors 1, 2, and 3, respectively). The pattern of these results was not surprising in the authors’ experience of test-reliability and other psychometric evaluations.²⁴ Two types of validity—factor-construct validity and external validity—were also represented by the study results. The strongest evidence for external validity was provided by the statistical significance of treatment across the 3 ANCOVAs ($P < 0.05$), in which the 3 factor-score variables were statistically independent (orthogonal) according to their MLF construction.

The covariate-control approach used in this study was effective in removing individual variations from the treatment–control comparison, as was anticipated based on studies conducted in other domains.^{15–19} As indicated by the magnitude of the covariate β in each of the 3 analyses, the factor scores for the week before the study controlled for a respective 60.4%, 41.6%, and 25.7% of variation in the 3 ANCOVAs (as the respective β^2 values reflect the proportions controlled).^{13,17} The first of these values (60.4%) suggests that the sample size would have to be increased by a factor of 2.5 to achieve equal sensitivity without use of the covariate control.¹⁷ This 2.5-fold increased sensitivity and the analogous sensitivity increases in the other analyses suggest a benefit to using similar covariate controls in future studies.

Combined Probiotic–Prebiotic Treatment

Treatment with Prescript-Assist was associated with significant reductions across the analyses of the 3 subsyndromic factors ($P < 0.05$). These results were obtained without discernible adverse effects, based on the lack of increase in any IBS symptom during treatment. In addition, none of the analyses found any significant differences in treatment effects between week 1 and week 2. This suggests that the effects of treatment were manifested within the first week and were maintained during the second week. However, this finding should be interpreted with caution, as questions of continuing efficacy and/or maintenance requirements call for a longitudinal investigation.

CONCLUSIONS

This study identified 3 relatively independent subsyndromic factors of IBS: general ill feelings/nausea, indigestion/flatulence, and colitis. Combined probiotic–prebiotic treatment with Prescript-Assist was associated with significant reductions in the symptoms of these factors in this small double-blind study in patients with IBS.

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