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Effectiveness of nystatin in polysymptomatic patients. A randomized, double-blind trial with nystatin versus placebo in general practice

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Background. Antifungal therapy has been claimed to be effective in polysymptomatic patients with diffuse symptoms from multiple body systems and even well defined diseases, traditionally not related to fungi. Hypersensitivity to fungus proteins and mycotoxins has been proposed as the cause.

Methods. We conducted a 4-week randomized, double-blind, placebo-controlled study in 116 individuals selected by a 7-item questionnaire to determine whether the antifungal agent nystatin given orally was superior to placebo. At the onset of the study, the patients were free to select either their regular diet or a sugar- and yeast-free diet, which resulted in four different subgroups: nystatin + diet (ND); placebo + diet (PD); nystatin (N); and placebo (P).

Results. Nystatin was significantly better than placebo in reduction of the overall symptom score ($P < 0.003$). In six of the 45 individually recorded symptoms, the improvement was significant ($P < 0.01$). All three active treatment groups reduced their overall symptom scores significantly ($P < 0.0001$), while the placebo regimen had no effect ($P = 0.83$). The benefit of diet was significant within both the nystatin (ND > N) and the placebo groups (PD > P).

Conclusions. Nystatin is superior to placebo in reducing localized and systemic symptoms in individuals with presumed fungus hypersensitivity as selected by a 7-item questionnaire. This superiority is probably enhanced even further by a sugar- and yeast-free diet.

Keywords. *Candida albicans*, general practice, nystatin, polysymptomatic, yeast.

Introduction

It is generally known by primary care physicians that about half of the medical evaluations of out-patient polysymptomatic patients fail to elucidate a specific causative disease. The symptom patterns often suggest the possibility of a systemic disease process involving multiple body systems. The patient may complain of chronic fatigue, poor concentration, impaired memory, respiratory tract symptoms, gastrointestinal distress, pains in muscles and joints, skin problems, recurrent infections, urogenital problems, etc. All too often, the diagnosis given to the patient is in terms such as 'stress', 'psychosomatic symptoms' or an assurance that 'there is nothing physically wrong'.

A number of these patients have been reported to have had an unexpected marked improvement in their symptoms when antifungal drugs were administered to treat various fungal infections. In addition, there are increasing numbers of reports that drugs possessing antifungal activity have been remarkably effective in a number of well-defined diseases.[1] There are also reports of cures of chronic fatigue, allergic conditions including bronchial asthma, pre-menstrual distress, multiple sclerosis and autism[2] with a regimen of diet free from yeasts, moulds and sugars,[3,4] antifungal medication and sometimes desensitization by *Candida* extract.[5] An immunological response to fungal antigens or a reaction to fungal toxins (mycotoxins), yeast-produced alcohols and other metabolic products have all been suggested as an explanation for these phenomena.[3,6]

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Many of the reported benefits have occurred with the use of nystatin, an antifungal agent usually prescribed for the treatment of *Candida albicans* infections, the most common pathogenic fungus in humans. This has led to a belief that *C.albicans* must be the cause of the underlying disorder, a conclusion which has ignored the fact that nystatin is actually a broad spectrum antifungal antibiotic effective against many different species of fungi.

The proponents in the USA for a *C.albicans* aetiology of the involved symptoms and/or diseases have called the phenomena 'The yeast connection', 'Candidiasis hypersensitivity syndrome' and, most recently, 'Candida-related complex' (CRC). In the UK, the entity is often referred to as 'The gut fermentation syndrome'.

The *Candida* hypothesis lacks a specific diagnostic test to support the validity of the concept. The diagnostic methods are limited to a combination of patient history, questionnaires, provocative challenge to yeast antigens and response to a broad treatment programme. There are no published controlled studies supporting a positive effect of antifungal medication or antifungal diet alone on patients thought to have CRC.[7–9]

In this study, we use the term 'fungus-related disease' (FRD) for a condition showing improvement with antifungal treatment. It was not the purpose of this study to identify the specific fungal species that may be playing an aetiological role. Rather, the objectives of our study were to determine whether the antifungal agent nystatin, administered orally to patients with presumed FRD, was superior to placebo as assessed by change in overall symptom score and in specific symptoms from baseline, and to evaluate the influence of diet on the outcome. We believe that our research has provided results which are consistent with the stated objectives of this study.

Methods

The study took place at an urban (Oslo) and a suburban (Mandal) centre. Volunteers were invited through the press from all parts of Norway. FRD was verified by using the questionnaire FRDQ-7 (Table 1). This questionnaire was developed to identify responders to nystatin and/or antifungal diet in an open study based on a historic group of 380 patients previously selected by symptoms and a CRC questionnaire[4] to classify the clinical diagnosis of FRD according to a sustained beneficial effect of nystatin and/or a sugar- and yeast-free diet. In order to determine the relevance of individual items of the CRC scheme, a gradual statistical discrimination analysis was carried out and resulted in the 7-item questionnaire (FRDQ-7) characterizing the historic patient population (H Santelmann, E Laerum and J Roennevig, unpublished).

Selection criteria

Within 3 months, 1620 persons volunteered. Of these, 954 were excluded due to being aged under 18 or over 75 years or because they were pregnant or lactating, dependent on a diet, or taking antibiotics, corticosteroids or other immunosuppressive agents orally or systemically during the 2 weeks prior to the start of the study. They were also excluded if they were receiving oral antimycotics and/or a sugar- and yeast-free diet 2 months prior to assessment of eligibility, or if they were unable to attend for two control evaluations. Five hundred and forty-six volunteers were excluded due to a low FRDQ-7 score (<10 out of 21). Among the 120 persons enrolled, 103 were women and 17 were men, with a mean age of 39 years (range 22–69).

TABLE 1 *Questionnaire FRDQ-7*

		No	Yes
1	Have you, at any time in your life, taken 'broad spectrum' antibiotics?	0	3
2	Have you taken tetracycline or other broad spectrum antibiotics for 1 month or longer ?	0	3
3	Are your symptoms worse on damp, muggy days or in mouldy places?	0	3
4	Do you crave sugar?	0	3
5	Do you have a feeling of being 'drained'?	0	
	occasional or mild		1
	frequent or moderately severe		2
	severe or disabling		3
6	Are you bothered with vaginal burning, itching or discharge (do you have similar symptoms from the penis)?	0	
	occasional or mild		1
	frequent or moderately severe		2
	severe or disabling		3
7	Are you bothered by burning, itching or watery eyes ?	0	
	occasional or mild		1
	frequent or moderately severe		2
	severe or disabling		3

Study design

The study was carried out as a double-blind, randomized placebo-controlled, multicentre trial with block design and diet as block factor. Patients were randomly assigned to receive either nystatin or placebo for a period of 4 weeks (Fig. 1). This part of the study was double-blind and the codes were stored sealed until all data from all patients were delivered to an independent statistical institute for evaluation.

Treatment regimens

Two hundred milligrams of nystatin powder (1 112 000 IU) or cornflour were packaged in transparent gelatine capsules. Blinded observers could not detect any difference between the two types of capsules. Patients were instructed to swallow one capsule unopened, three times a day, after meals, with a non-alcoholic liquid for 4 weeks. In cases of adverse effects, the patients were instructed to decrease the dose to one capsule daily, increase to three capsules within 1 week and continue for 4 weeks altogether.

At the start of the study, patients were free to choose between a modified sugar- and yeast-free diet, in compliance with a food list, or their regular diet for the period of the study. We used this approach because a double-blind diet regimen appeared to be extremely difficult to manage and exceeded the capacity of our study. We chose voluntary selection of diet to enhance compliance. By this means, we obtained four subgroups: nystatin plus sugar- and yeast-free diet (ND), placebo plus sugar- and yeast-free diet (PD), nystatin (N) and placebo (P).

Patients in the diet groups obtained a list of foods to avoid, those containing sugars, yeasts or moulds, i.e. honey, jam, sweets, ice cream, lemonade, fruit juices (except freshly prepared), alcohol, cheese, and breads and pastries containing yeast. Additionally, they were asked not to consume more than half a glass of milk or yoghurt daily. Artificial sweeteners such as aspartame, saccharin and xylitol, and bread made with baking powder were allowed.

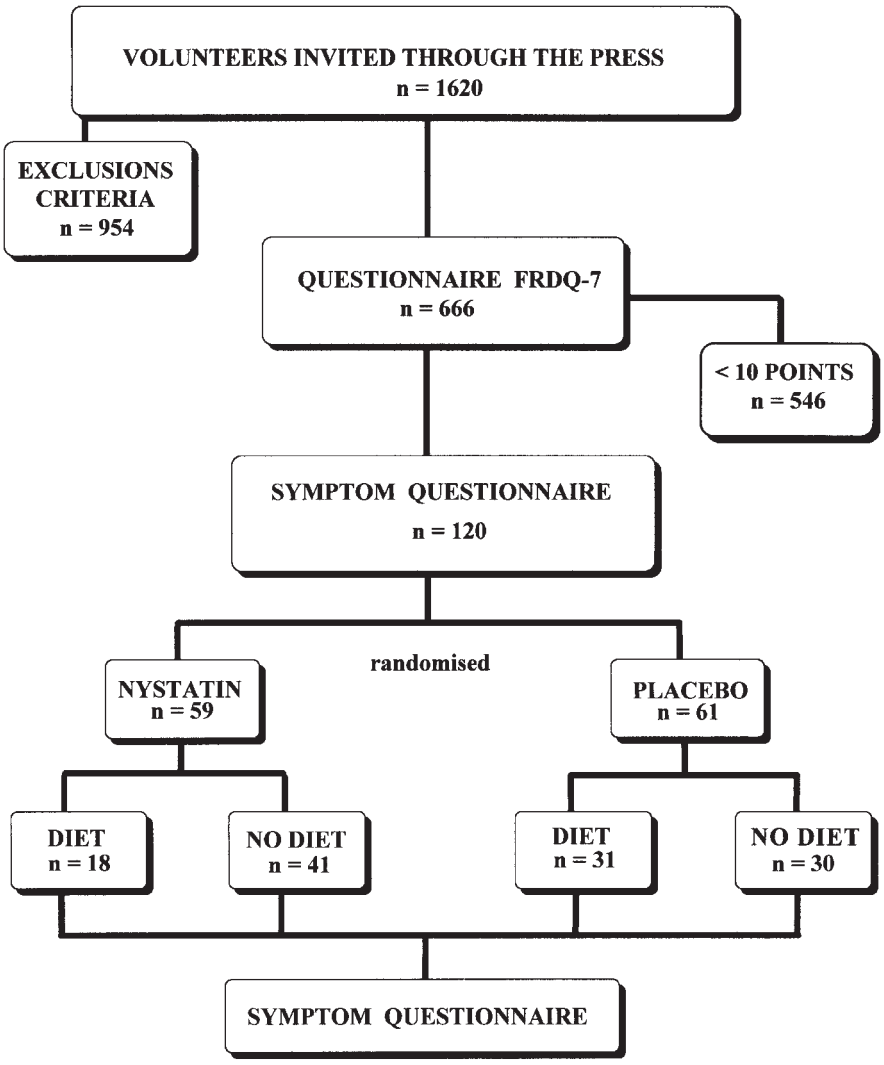

FIGURE 1 *Study design*

Evaluation

Upon entry to the study and 4 weeks after starting the capsules, the patients filled in a questionnaire referring to 45 different symptoms derived from the 70 questions in the CRC questionnaire which were related to localized and systemic symptoms (Table 3). The scores ranged from 0 to 3 (absent, mild, moderate or severe). Improvement in individual symptoms was noted on the basis of a decline in the severity grade. The overall symptom score was calculated as the sum of the severity grades of all 45 symptoms. Since deterioration resulted in a higher score after treatment, it was conceivable that patients could achieve negative symptom scores.

Two questionnaires, the EPQ[10] and the GHQ-28[11], were administered on entry to assess more objectively the presence of special characteristics such as neuroticism, dissimulation or depression, and to control for homogeneity of the groups. At the end of the treatment, the remaining capsules were counted and the patients asked to report adverse effects related to the capsules, their compliance with the chosen diet and any use of other medication during the trial. They were also asked to guess whether they had received nystatin or placebo. All participants were evaluated at the two centres by one person (HS).

Statistical analysis

Baseline comparability between the treatment groups with regard to possible co-factors and other baseline characteristics was assessed by analysis of variance (ANOVA). The ANOVA model included nystatin/placebo, diet/no diet and possible interaction between the two effects. In addition, analysis of covariance, with the baseline symptom score and age as co-factors, was applied.

The nystatin and placebo mean values were compared statistically, as well as the means in the four subgroups derived from treatment and diet. This was assessed by using Duncan's multiple-range test and Dunnett's test.[12] The changes within each group were analysed using the one-sample *t*-test. Fisher's exact test for contingency tables larger than 2×2[13] was applied when comparing subgroups with regard to categorical variables. To reduce multisignificance, the significance level was set to 1% in tests, and a test power of 80% was planned for. The test power was based on assumptions of a difference in proportional improvement in symptom score between the nystatin and placebo groups of at least 10% and an SD of 20% (hence an efficacy size of 0.5). All tests were applied two-sided. Continuously distributed variables were presented as mean values, and the primary variable also with a 95% confidence interval (CI). Categorical variables were presented as rates. The data management and the statistical analysis were carried out with Statistical Analysis System (SAS®).

Ethics

The study was performed in accordance with the most recent revision of the Declaration of Helsinki (Hong Kong, 1989). The local ethical committee approved the trial. Volunteers were entitled to indemnity according to Norwegian legal requirements.

Results

Study population

Four of the 120 enrolled patients were excluded on completion of the study and review of the files because of treatment with antibiotics ($n = 2$), corticosteroids ($n = 1$) and hospitalization ($n = 1$) during the trial. Five patients from the diet groups were transferred to groups N and P, as appropriate, due to deviations from the sugar- and yeast-free diet. Three patients in each group did not comply with the treatment as a consequence of side effects, but were included in the analysis; thus 116 patients could be evaluated; ND 18, N 38, PD 30 and P 30 (Fig. 1). A comparison of the baseline data between the nystatin and placebo groups did not reveal any significant differences (Table 2). The enrolled patients showed no special characteristics regarding dissimulation, neuroticism, extroversion–introversion, general somatic symptoms, anxiety, depression and social dysfunction compared with normal populations.[10,11] The four subgroups were statistically comparable with regard to patient characteristics and baseline symptom score.

Outcomes

Within the nystatin groups, the mean proportional improvement in overall symptoms was 23% (95% CI 18–28%) ($P < 0.0001$). The corresponding value within the placebo groups was 12% (95% CI 7–18%) ($P < 0.0001$). The difference between the nystatin groups

TABLE 2 *Initial data, mean (SD)*

	Groups ND and N	Groups PD and P
Number	56	60
Age	37.4 (10.2)	38.2 (10.1)
FRDQ-7	14.5 (2.4)	14.4 (2.1)
Baseline symptoms	67.6 (17.6)	67.8 (18.8)
EPQN	11.7 (5.1)	11.3 (4.7)
EPQL	6.7 (3.7)	8.7 (4.1)
GHQ-28	30.2 (12.3)	29 (12.0)
Somatizing	9.8 (3.8)	10 (3.8)
Anxiety	8.2 (4.0)	7.8 (3.8)
Social dysfunction	9.3 (3.6)	8.8 (3.8)
Depression	3.2 (3.9)	2.6 (3.0)

FRDQ-7 = Fungus-related Disease Questionnaire-7;
EPQN = Eysenck Personality Questionnaire, 'neurotic' scale;
EPQL = Eysenck Personality Questionnaire, 'lie' scale;
GHQ-28 = Goldberg's General Health Questionnaire-28.

TABLE 3 *Analysis of individual symptoms after adjustment for baseline symptom score and age*

Symptom	Treatment groups with mean proportional improvement	
	ND + N	PD + P
Fatigue or lethargy	21	13
Feeling of being 'drained'	22	16
Depression	16	4
Poor memory	10	8
Feeling 'spacy' or 'unreal'	23	14
Inability to make decisions	20	16
Unco-ordinated	19	5
Dizziness/loss of balance	26	6*
Inability to concentrate	15	0
Irritability or jitteriness	14	7
Frequent mood swings	15	2
Attacks of anxiety or crying	27	6*
Insomnia	17	15
Shaking or irritable when hungry	26	0*
Headache	12	0
Pressure above ears	19	8
Burning or watery eyes	26	–3*
Spots in front of eyes or erratic vision	22	8
Nasal congestion or post-nasal drip	14	7
Nasal itching	9	13
Dry mouth or throat	10	4
Rash or blisters in mouth	14	13
Sore throat	11	20
Laryngitis, loss of voice	14	13
Cough or recurrent bronchitis	11	15
Pain or tightness in chest	13	14
Bad breath	4	16
Indigestion or heartburn	10	11
Abdominal pain	15	–2
Constipation and/or diarrhoea	19	3*
Mucus in stools	16	6
Rectal itching	17	13
Bloated feeling, belching or intestinal gas	17	4
Food sensitivity or intolerance	7	–9
Chronic rashes or itching	25	8*
Numbness, burning or itching	26	17
Foot, hair or body odour not relieved by washing	1	16
Muscle aches	20	6
Muscle weakness or paralysis	17	14
Pain and/or swelling in joints	12	18
Vaginal burning, itching or discharge	31	15
Loss of sexual desire or feeling	11	11
Urinary frequency or urgency	22	6
Burning on urination	24	11
Cold hands or feet and/or chilliness	13	4

TABLE 3 *Continued*

*$P < 0.01$. Values were estimated by analysis of covariance.
ND = nystatin + diet; N = nystatin; PD = placebo + diet; P = placebo.

and the placebo groups was statistically significant ($P < 0.003$). As shown in Figure 2, the overall symptom scores were significantly reduced ($P < 0.0001$) in each of the three active treatment groups (ND, N and PD), while no changes were detected in the placebo group (P) ($P = 0.83$). In the diet groups (ND versus PD), the difference in actual improvement (24.3:16.5) was statistically significant ($P < 0.05$), while the difference in proportional improvement (34.3:25.8) was not. Significant differences were found between the nystatin groups and the placebo groups for six of the 45 individual symptoms (Table 3). Almost all of the non-significant differences favoured nystatin.

Other findings

The proportion of patients identifying their medication correctly after 4 weeks of treatment was 31% for the nystatin groups and 60% for the placebo groups. Seventeen (30%) of the patients in the nystatin groups and 13 (22%) of the patients in the placebo groups reported minor side effects (bloated feeling, headache, pruritus and tiredness) during the first week of treatment only.

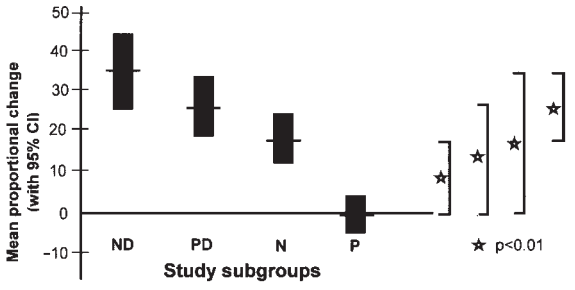

FIGURE 2 *Mean proportional improvement in overall symptom score from baseline to the end of the 4-week study period. Each line with a bar represents the mean proportional change with the 95% CI. Brackets with stars denote significant differences at the 1% level between subgroups*

Age did not interfere significantly with the proportional reduction of symptom score ($P = 0.12$). However, there was a tendency among younger patients in the placebo groups to respond better. The main diagnoses of the evaluated patients and the proportional improvement within the diagnoses groups are listed in Table 4.

Discussion

In the 116 patients selected by the FRDQ-7 questionnaire, nystatin therapy reduced overall symptoms significantly as compared with placebo, even after correction for sugar- and yeast-free diet. When assessing individual symptoms for proportional improvement only, six of the 45 were significant. Nystatin showed the most striking effect for mental, abdominal and urogenital complaints. Since we did not perform microbiological studies in the patients and the positive effect of nystatin may be due to its effect on other fungi, a connection between *C.albicans* and FRD remains unproved.

Nystatin is well known for its antifungal effect on *C.albicans* which is found in all segments of the gastrointestinal tract in 10–80% of humans,[14,15,19] as well as on other yeasts and moulds.

Studies of *C.albicans* have revealed findings which might explain some symptoms found in patients with FRD: *C.albicans* can disturb the immune system at different levels:[15,16–18] it is a polyantigenic organism containing at least 30 different antigens;[19,20] it cross-reacts with baker's yeast and brewer's yeast;[21] it can induce production of autoantibodies and endocrinopathy;[22] it produces IgA proteases;[23] it contains glycoproteins which stimulate the mast cells to release histamine and apparently prostaglandin;[24,25] it assimilates all sugars except lactose;[26] it depresses the activity of lactase;[27,28] and it has a synergistic effect with *Staphylococcus aureus*.[29]

Table 4 *Main diagnoses and proportional improvement*

Diagnoses	*n*	ND + N	PD + P
Non-specific	24	25%	20%
Fibromyalgica	24	18%	10%
Depression, neurosis	13	27%	12%
Asthma	10	24%	28%
Colitis, IBS	9	35%	9%
Allergy	7	16%	–2%
Rheumatism, PCP	7	13%	5%
Recurrent vaginitis	6	36%	11%
Eczema	5	16%	67%
Recent lower respiratory tract infection	2	10%	–
Pruritus	2	19%	–
Multiple sclerosis	2	64%	15%
Migraine	2	37%	–38%
Cutaneous candidiasis	2	30%	0%
Bulimia	1	13%	–

Since previous studies did not reveal intestinal overgrowth of *C.albicans* in patients with presumed FRD[30,31] and since oral nystatin works only on the intestinal stream and gut wall colonization, we would speculate that the beneficial effect of nystatin in our study is due to a reduction in the overall fungal colonization in the gastrointestinal tract in patients sensitive to fungus antigens or toxins, rather than a control of a *Candida* infection.

The benefit of diet was significant within both the nystatin groups (ND > N) and the placebo groups (PD > P) (Fig. 2). Patients following a sugar- and yeast-free diet, in addition to taking nystatin, achieved a proportional improvement in overall symptom score of 35% as compared with placebo. As already suggested by others,[8,32] the avoidance of foods containing yeasts or moulds and the reduction of dietary carbohydrates, which are fungal growth promoters and associated with increased adherence of *Candida* species to mucosal epithelial cells, seem to be essential components of therapy. Of course, these data must be interpreted cautiously, keeping in mind that the diet regimens have not been administered in a double-blind way. In addition, the fact that the patients have not been randomly assigned to diets, resulting in a disparity between the numbers in the two nystatin groups, might compromise the ability of the study to address the role of diet in the treatment of FRD adequately. Until further studies are completed, we find it difficult to ascertain whether the effect of diet is due to the avoidance of fungus antigens, a decreased intake of mycotoxins, a placebo effect or a combination of these and other factors. We recommend that later trials on patients with presumed FRD include a controlled double-blind provocation test with encapsulated food items in connection with an elimination diet, as one of the authors has used in his general practice (HS).

The difference in improvement between ND and PD is smaller than the difference between N and P. It could be speculated that nystatin has an inhibiting influence on the effect of diet, possibly caused by a temporary increase in the amount of fungus proteins and mycotoxins.

Surprisingly, group P did not achieve any improvement in the symptom score. A closer look at our data revealed nine patients reporting an improvement, seven without change and 14 reporting an aggravation. We believe that the possibility of gaining minus points on the proportional change from baseline symptom score explains the negative results in group P. Another explanation could be that the patients had gone through several previous treatments without a positive effect on their condition, which might affect their expectations of new treatments. This hypothesis seems to be supported

by our findings that the placebo effect tended to be higher among the patients under the age of 40 years. We also suggest that the placebo effect diminishes with the number of symptoms investigated. In addition, a higher percentage in the placebo groups identified the content of the capsules correctly, apparently due to the fact that they did not register an improvement.

One might ask if the study population had special psychological characteristics, but the two questionnaires EPQ and GHQ-28 did not reveal deviations from normal populations[10,11] with regard to dissimulation, neuroticism, extroversion–introversion, anxiety and depression. The fact that the included patients were attending from different parts of Norway, from both urban and sub-urban regions, should count in favour of a more general applicability of our findings.

Dismukes *et al*., who published a cross-over study on 42 women with presumed candidiasis hypersensitivity syndrome, concluded that there was no reason to support the empirical recommendation of nystatin treatment for patients who are believed to suffer from this condition.[33] However, several objections to the study were made regarding patient selection, study design, statistical analysis and ignoring the importance of diet.[8,32] We included diet regimens and chose a parallel block design because a cross-over design was not found to be appropriate for this study due to carryover effects, which might be a source of error. However, we believe that the most important reason for the contrasting results of the two studies are the different inclusion criteria. In the Dismukes study, only women with a history of *Candida* vaginitis who had been treated previously with nystatin or other local antifungal agents and who were complaining of at least three of the following five additional clinical features were included. The features were: gastrointestinal symptoms of unknown cause lasting for at least 1 year; upper or lower respiratory tract symptoms suggesting respiratory allergy; symptoms of pre-menstrual distress; moderate to severe depression without vegetative or psychotic features; and difficulty with short-term memory or concentration. In contrast, we enrolled patients with a score of >9 out of 21, from seven questions (FRDQ-7), only one of which was similar to those of the previous study (vaginitis). Also, treatment with nystatin 2 months prior to assessment of eligibility was one of our exclusion criteria. As in the study of Dismukes *et al*., we found significantly reduced vaginal symptoms in the nystatin group. Analysis of the other individual symptoms asked for in Dismukes' study reveals that not more than two out of 15 showed a significant improvement in our study (lethargy and inability to concentrate), while most of the symptoms reduced by nystatin in our study (Table 3) were not evaluated by Dismukes *et al*..

A limitation of our study is the lack of well established instruments for measuring the effect of the four regimens. However, the many different, non-specific symptoms presumed to be associated with FRD, and the absence of specific microbiological or chemical tests for this condition, led to our choice of a symptom questionnaire. Moreover, our conclusions refer to a 4-week treatment only; the effect of nystatin and diet in the long term has not as yet been studied.

In summary, our study shows that patients with presumed fungus-related diseases, as selected by the questionnaire FRDQ-7, benefit from both nystatin and probably a diet free from yeasts, moulds and sugars. The findings are significant and indicate that the beneficial effect of nystatin over placebo within the population studied is not due to coincidence. Further controlled studies are needed, addressing both diagnostic criteria and therapy, in order to elucidate more fully the benefits of long-term nystatin treatment and a sugar- and yeast-free diet for patients with presumed fungus-related disease.

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