

Pharmaton Capsules in the Treatment of Functional Fatigue: a Double-blind Study Versus Placebo Evaluated by a New Methodology

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A new method for the evaluation of the complaints reported by patients suffering from functional fatigue was investigated in the course of a multicentre, comparative, double-blind, clinical study of Pharmaton Capsules versus placebo in a total of 232 patients aged between 25 and 60 years. The principle of the study was to allow the patient to choose, from a pre-established list of 20 suggestions, the five items that best described his complaints. An individual Fatigue Score was calculated for each patient on the basis of the sum of the scores given by the patient for each of the five items selected (each item was evaluated according to a 4-point time scale). This score was calculated on day 0 and after 21 and 42 days treatment.

The analysis of the Fatigue Scores at the end of the study showed a statistically significant difference in favour of the Pharmaton group. The global assessment of the efficacy of the treatment (given by the investigators and by the patients) demonstrated the superior effect of the Pharmaton Capsules, whereas the global assessment of the tolerability showed no difference between the two treatments.

Pharmaton Capsules proved their efficacy in improving the various complaints experienced by patients suffering from fatigue, with tolerability comparable to that of placebo.

Keywords: functional fatigue; quality of life; new methodology; individual fatigue score; Pharmaton Capsules; double-blind.

INTRODUCTION

To feel exhausted, 'worn out', 'dead tired', 'empty'... the vocabulary is rich for the description of the same complaint: fatigue. It spares nobody and is one of the most frequent complaints in medical practice (Van Berkestijn, 1992). Confronted with a fatigued patient, the physician has to be a good interpreter of the reported complaints as every patient has his own way of expressing his fatigue and the resulting discomfort. Fatigue is a complex and polymorphous phenomenon characterized by objective aspects which are difficult to measure (diminution of physical and/or mental performance), and, moreover, by an important subjective aspect.

Nosologically, one can distinguish in a quite theoretical way different types of fatigue: somatic fatigue, physical fatigue and reactive fatigue (Bugard, 1989; Cathebras and Rousset, 1988). In practice, the physician may often diagnose an association of minor somatic, physical and reactive factors without being able to determine a precise origin of the reported fatigue. We defined this state as functional fatigue.

Faced with the different causes of fatigue, the doctor disposes of a great variety of therapies. The states of functional fatigue which do not seem to depend on a

somatic or physical disorder may be improved by multi-vitamin preparations, mild stimulants or combination preparations of amino acids, phosphorus and trace elements (Krivitsky, 1982). Pharmaton** Capsules, which contain 9 vitamins, 8 minerals, standardized ginseng extract G115 and deanol, can be classified, without doubt, among them. The efficacy of Pharmaton Capsules was evaluated starting from objective criteria judged by the investigators: diminution of heart rate (Tesch *et al.*, 1987), lactate levels (Pieralisi *et al.*, 1991; Tesch *et al.*, 1987) and degree of fatigue, measured after exercise on the ergometric bicycle (Pieralisi *et al.*, 1991; Tesch *et al.*, 1987), as well as improvement of psychomotor capacities (Garay Lillo, 1987; Garay Lillo *et al.*, 1992).

However, all those tests that are normally needed to prove the effect of a treatment take little or no account of the patient's own opinion, nor of the many different types of complaints associated with fatigue.

The aim of the study that we carried out was to prove the efficacy of Pharmaton Capsules with regard to the complaints reported by patients suffering from fatigue. In order to evaluate this we used a method inspired by that devised and validated by Guyatt (Department of Epidemiology and Biostatistics, Ontario, Canada) in the study of asthma and rhinitis (Guyatt *et al.*, 1987a, 1987b; Juniper and Guyatt, 1991). This methodology

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consists of asking the patient to select, from a pre-established list of 20 suggestions, the five items that best describe his symptoms and which he considers are associated with the fact that he is fatigued. The Fatigue Score calculated in this way makes it possible to only take into account those complaints from which the patient is suffering and the areas in which he is most affected.

Given the importance of the subjective component of fatigue and its method of evaluation, and recognizing the importance of the doctor-patient relationship and the need for treatment, the efficacy of Pharmaton Capsules was compared with that of placebo.

MATERIAL AND METHOD

This study was carried out according to a double-blind design, Pharmaton Capsules versus placebo, by 52 general practitioners, between 19 November 1992 and 14 May 1993. The trial protocol received the approval of the CCPPRB (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) in Lyon.

Patients. The patients included in the study were men and women aged from 25 to 60 years, suffering from functional fatigue for at least 15 years and who had given their informed consent, in writing, to participate in the study. Excluded from the study were patients suffering from an acute or chronic disease (endocrine, neurological, infectious, malignant) that could have been responsible for the fatigue, or from liver disease, calcium lithiasis or psychiatric illness, especially depression (HARD score >20) (Ferreri and Ruffin, 1984). Also excluded from the study were alcoholic patients and alcoholics undergoing detoxication therapy, patients being treated with psychotropic drugs

Table 1. List of suggested items for calculation of the Fatigue Score and number of patients selecting each item (each patient had to select five items)

Difficulty in getting up in the morning	136
Not in good form—poor physical condition	111
Feeling of being exhausted and 'all in'	106
Easily becoming angry and nervous	83
Lack of spirit	68
Difficulty in concentrating	66
Pain in back, abdomen or stomach	56
Somnolence during the day	55
Lapses of memory	49
Lack of efficiency at work	48
Difficulty in moving and getting things done	45
Lack of motivation	39
Difficulty in sleeping	38
Difficulty in facing up to the worries of daily life	36
Difficulty in paying attention	36
Heaviness in the legs	32
Difficulty in tolerating others (children, spouse . . .)	28
Loss of libido	23
Difficulty in looking after the children	22
Loss of appetite	18
Each of the five chosen items is evaluated by means of a time scale with 4 points: 0 = not at all, 1 = from time to time, 2 = most of the time, 3 = always.	

(antidepressants, anxiolytics), antibiotics or antiasthenic preparations, including vitamins, trace elements and homeopathy, pregnant women or those likely to become pregnant and women who had given birth less than 3 months before or who were still breast-feeding.

Each patient included in the study was treated for 42 days, according to the randomization plan, with either Pharmaton Capsules or placebo in the dosage of two capsules per day (one in the morning and one with the midday meal). A clinical assessment was carried out at each of three visits: at the time of inclusion in the study (Visit 1), after 21 days (Visit 2) and after 42 days of treatment (Visit 3). At each visit, the investigating physician recorded the frequency and the severity of the disturbances caused by the fatigue on the list of 20 items (Table 1), the signs and symptoms described by the patient, the concomitant treatments and any possible unwanted effects, in order to assess the tolerability of the treatments. At the end of the study the investigator and the patient gave their global assessment of the efficacy of the treatment on the one hand and the tolerability on the other, using a 4-point scale, from 'excellent' to 'poor'.

Fatigue score. A list of 20 complaints was compiled on the basis of a review of literature and interviews with ten general practitioners. This list contains the complaints most often reported by fatigued patients, in the areas that they consider important. At the first visit the investigator asked the patient to select the five items which most corresponded to his state of fatigue and which were the most troublesome to him.

Each of the five items selected was evaluated using a 4-point time scale: 0 = not at all, 1 = from time to time, 2 = during most of the time, 3 = always (Ferreri and Ruffin, 1984). An individual Fatigue Score was calculated on the basis of the sum of the points obtained for each of the five items selected. This score could thus vary, for each patient, from 0 (no complaints) to 15 (maximum complaints).

For each patient, the degree of the overall complaint, based on the five items selected, was evaluated at the time of inclusion in the study (Visit 1) in order to be able to then follow the development of the individual Fatigue Score under placebo and under the treatment with Pharmaton Capsules.

Study medication. Pharmaton Capsules are dark brown and are available in blister packs of 15, 30, 60 and 90 capsules.

Composition:

1 capsule contains:

Highly concentrated, standardized

Ginseng extract G115	40 mg
Dimethylaminoethanol bitartrate	26 mg
Retinol palmitate	4000 I.U.
Thiamine mononitrate	2 mg
Riboflavine	2 mg
Pyridoxine hydrochloride	1 mg
Cyanocobalamin	1 µg
Ascorbic acid	60 mg
Nicotinamide	15 mg
Ergocalciferol	400 I.U.
D,L- α -tocopherol acetate	10 mg
Copper sulphate monohydrate	2.80 mg
Manganese sulphate monohydrate	3.10 mg

Zinc oxide	1.25 mg
Calcium fluoride	0.42 mg
Potassium sulphate	9 mg
Magnesium sulphate	50.7 mg
Iron sulphate	50 mg
Dicalcium phosphate	352 mg

The placebo did not contain any of the above active ingredients.

Excipients: Lecithin (powder), vegetal oils, ethyl vanillin

Composition of capsule shell: gelatin, glycerol, potassium sorbate (0.3 p. 100 of shell weight)

Colouring agents: Red iron oxide, black iron oxide

Statistical method. The statistical analysis was carried out on the basis of the observations in the patients who had met the criteria for inclusion in the study. The Fatigue Score was calculated at the first visit and after 21 and 42 days respectively. Tolerability was evaluated for all the patients.

The Fatigue Scores in the two treatment groups were

compared by means of an analysis of covariance, taking the score value at Visit 1 as the covariable. The other parameters were compared by means of a χ^2 test or a Fisher's Exact test for the nominal qualitative variables, a Mantel Haenszel χ^2 test for the ordinal qualitative variables and a Student's *t*-test for the quantitative variables.

RESULTS

A total of 232 patients were included in the study, 117 in the Pharmaton group and 115 in the placebo group. Thirteen patients (5.6%), 7 in the Pharmaton group and 6 in the placebo group, could not be taken into account in the analysis of the efficacy of the treatment, due either to violation of the inclusion criteria (4 cases) or the lack of any evaluation after the start of treatment (9 cases). The efficacy could thus be evaluated for 219 cases, 110 from the Pharmaton group and 109 from the placebo group.

Before the start of treatment the two patient groups were comparable with regard to both the demographic and clinical criteria (Table 2). At the first visit, at the time of inclusion in the study, a total of 46 signs or symptoms related to fatigue were recorded in 28 patients of the Pharmaton group, and 52 in 29 patients of the placebo group.

The five items used to calculate the Fatigue Score which were most often selected by the patients were: difficulty in getting up in the morning (136); not in good form—poor physical condition (111), feeling of being exhausted, and 'all in' (106), easily becoming angry or nervous (83) and lack of spirit (68) (Table 1). After the start of treatment the Fatigue Score reflecting the complaints associated with fatigue had improved in both treatment groups. At the end of the study the score was statistically significantly better in the Pharmaton group (Fig. 1).

At the second visit, 16 patients (14.5%) of the Pharmaton group and 22 patients (20.2%) of the placebo group reported signs and symptoms, of which 18 and 20 of 31 in the two groups, respectively, were associated with fatigue. At the end of the study 6 patients (5.7%) of the Pharmaton group and 16 patients (15.2%) of the placebo group reported signs or symptoms, of which 4 of 6 and 14 of 25, respectively, were associated with fatigue; the difference between the groups was statistically significant ($p = 0.023$).

The different signs or symptoms associated with fatigue that were observed at each of the visits are reported in Table 3. These were reduced not only in frequency but also in severity (Fig. 2).

The analysis of tolerability was performed on the basis of 222 cases, 111 in each group. Compliance with the treatment was assessed as very good for 85/98 patients of the Pharmaton group and for 88/95 patients of the placebo group. In the course of the study, 19 patients (17.1%) of the Pharmaton group and 10 patients (9.0%) of the placebo group reported the appearance of at least one unwanted effect; discontinuation of the treatment proved necessary in 2 cases in the Pharmaton group and in 3 cases in the placebo group. One serious adverse event was reported in the placebo group, the patient requiring hospitalization for

Table 2. Demographic and clinical characteristics

	Pharmaton group n = 110	Placebo group n = 109
Average age (years) m (range)	37.6 (9.2)	38.8 (9.9)
Sex m/f(*)	34/75	34/75
Occupational activity		
active	87	80
inactive	23	29
Marital status		
living as a couple	70	84
others	40	25
Concomitant illness	10	10
HARD score m (range)	9.38 (4.12)	9.21 (4.18)
Fatigue score m (range)	9.27 (2.45)	9.48 (2.61)
Absence from work prescribed	11	14
Average duration of absence from work (days) m (range)	7.0 (3.1)	7.2 (2.9)

*Data missing for one patient of the Pharmaton group.

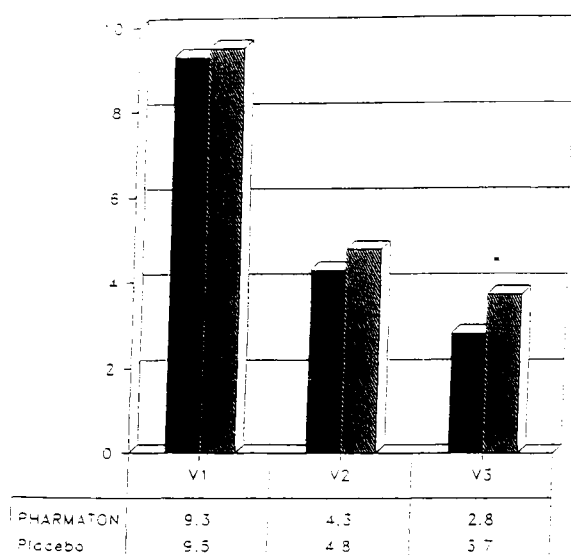
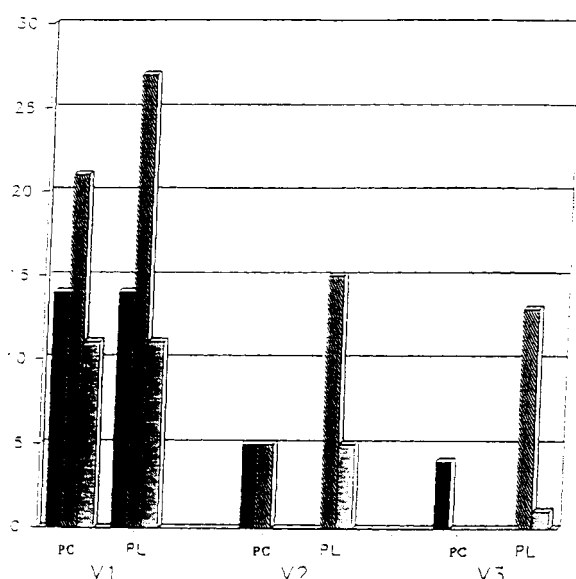


Figure 1. Fatigue score at each visit. It is calculated by adding up the single scores obtained by the five chosen items. It can vary therefore between 0 (no complaints) and 15 (max. complaints). * $p = 0.019$. ■ Pharmaton, ▨ placebo.

Table 3. Signs and symptoms caused by fatigue, reported at each visit

	Visit 1		Visit 2		Visit 3	
	Pharmaton n = 28	Placebo n = 29	Pharmaton n = 16	Placebo n = 22	Pharmaton n = 6	Placebo n = 16
Fatigue	8	11	5	6	3	6
Anxiety/nervousness	5	4	1	1	1	—
Disturbances of memory	—	1	—	—	—	—
Lowering of tone and activity	9	6	2	8	—	3
Poor concentration	3	4	—	1	—	3
Sleep disorders	6	7	1	4	—	2
Pain	4	9	1	—	—	—
Physical and mental slowing-down, depressive syndrome	1	1	—	—	—	—
Various disorders	10	9	—	—	—	—
Total signs and symptoms	46	52	10	20	4	14
Total patients in the study	110	109	110	109	106	105

**Figure 2.** Severity evaluated according to a 3-point score (■ +, ▨ ++, □ +++) for the signs/symptoms observed at each visit. PC, Pharmaton Capsules; PL, placebo.

treatment of an oedema of the uvula, which disappeared under corticotherapy.

Among the unwanted effects most frequently reported were nausea and/or vomiting in 6 patients of the Pharmaton group and in 1 patient of the placebo group, sleep disorders in 3 patients of each group,

Table 4. Assessment of the efficacy and tolerability of Pharmaton Capsules and placebo by the patients and by the doctors

	Patients' assessment				Doctors' assessment			
	Pharmaton n	Placebo n	Pharmaton %	Placebo %	Pharmaton n	Placebo n	Pharmaton %	Placebo %
Efficacy^a								
Excellent	31	18	29.2	17.3	40	17	37.7	16.3
Good	44	35	41.5	33.7	35	35	33.0	33.6
Moderate	22	31	20.8	29.8	24	34	22.6	32.7
Poor	9	20	8.5	19.2	7	18	6.6	17.3
Tolerability								
Excellent	67	61	63.2	58.1	74	64	69.8	60.9
Good	30	33	28.3	31.4	25	32	23.6	30.5
Moderate	8	11	7.5	10.5	4	9	3.8	8.6
Poor	1	0	0.9	0.0	3	0.0	2.8	0.0

^a χ^2 test according to Mantel Haenszel, $p \leq 0.002$.

abdominal pain, gastralgia and/or distension of the stomach in 3 patients of each group, bowel disorders in 2 patients of the Pharmaton group and headache in 2 patients of the placebo group.

The efficacy of Pharmaton Capsules was assessed as better than placebo by both the patients and the doctors (Table 4).

DISCUSSION

The efficacy of Pharmaton Capsules on the complaints caused by a state of functional fatigue, after 6 weeks' treatment, has been proved by the results of this double-blind multicentre study in 232 patients treated with either Pharmaton Capsules or placebo according to a randomization plan. After 21 days the effect of Pharmaton Capsules was already better, although a statistically significant difference could not be demonstrated. The global tolerability of the two treatments was good, the only serious unwanted effect being reported in the placebo group. The other occasional side effects reported were of the types usually seen in clinical trials.

The fatigue was defined as functional if the general practitioner was able to eliminate any possible somatic or psychic causes. Depressive patients diagnosed with a HARD score of more than 20, in particular, were excluded from the study. The authors of the HARD scale in fact distinguish between mild depressions, with a score of 20 to 34, moderate depressions, with a score of 35 to 49, and severe depressions, with a score of 50 to 72 (Ferrerri and Ruffin, 1984).

Generally, the efficacy of treatments of fatigue is evaluated on the basis of physical and mental performance criteria. Because of the many different forms of fatigue and the important role played by subjectivity in its interpretation, each patient complains in his own particular way. The innovative methodological approach in the present study was to evaluate the state of fatigue not in terms of performance but in terms of the various complaints and symptoms experienced by the patients, taking into account the individual characteristics of each one of them. In fact, each patient's score was individual to him, since it was calculated on the basis of a combination of the five different complaints (items) which he himself had selected as best reflecting how he felt.

The methodology applied for the selection of these items, which was inspired by that devised by Guyatt for the evaluation of quality of life in relation to state of health, made it possible to quantify the subjective nature of the complaints associated with fatigue and to demonstrate the superiority of the effect of Pharmaton Capsules on this parameter.

This method of evaluation of the symptoms experienced by patients suffering from fatigue represents a new means of measuring the efficacy of an anti-fatigue preparation, supplementary to measurements of physical and mental performance. It enables the doctor to measure the relevance of the response of the patient's various complaints to the treatment.

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