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Effects of a food supplement based on cod liver oil, pollen, royal jelly, glycine, zinc, and vitamins in physical and mental fatigue: a collection of real-life clinical experiences

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Abstract

Many patients come to their family physicians asking for support against tiredness and fatigue. This data collection aimed to evaluate the restorative action of a food supplement based on cod liver oil, pollen, royal jelly, glycine, zinc, and vitamins (Liovital® AD, Pharma Line s.r.l. Milan, Italy) in cases of physical and mental fatigue. Thirty-three physicians participated in this collection of experiences. The following were selected from the patients in our outpatient clinics, subjects (aged 18 to 58 years) who had been experiencing physical and mental fatigue for less than six months. The selected patients assumed Liovital® AD, at a dosage of one vial per day, for 20 consecutive days. The restorative efficacy was assessed by comparing the scores obtained in the Patient Health Questionnaire-9 (PHQ-9) and Fatigue Assessment Scale (FAS), completed by patients at the time of enrollment (T0) and after 20 days of treatment (T20). A total of 326 subjects' data were analyzed. Intake of the product produced an effective restorative action, with a significant decrease in feelings of depression and stress (as measured by the PHQ-9, whose mean score decreases from 12.23 (T0) to 4.45 (T20), $p < 0.0001$) and physical and mental fatigue (in the FAS questionnaire, the mean score drops from 32.9 (T0) to 18.36 (T20), $p < 0.0001$), as well as leading to improvement in management of daily life (in the PHQ-9 additional question "judgment" the score increases from 1.55 (T0) to 2.61 (T20), $p < 0.0001$). The restorative action of the product was also confirmed by the positive judgments on the effectiveness of the treatment expressed at T20 by patients and physicians. Finally, data collection confirmed the safety and tolerability of the food supplement, recording only 5 mild adverse effects out of 326 subjects observed.

Key words: fatigue, restorative, royal jelly, pollen, cod liver oil.

Introduction

Daily life is burdened with highly demanding and stressful situations both on a physical level (e.g. sudden changes in temperature due to the change of seasons), and on the psychological level (e.g., work commitments and family). It is common for patients to experience conditions of fatigue and reduced physical and mental performance, and that they arrive at family physicians' clinics asking for a "tonic".

In medicine, a "tonic" is the definition for a medicinal preparation, for oral or parenteral use, that aims at the complete functional restoration of the body in cases of emaciation or convalescence, or to prevent the consequences of physical or mental overwork[1]. Doctors and patients are constantly searching for effective reconstitutive products that promote the recovery of physical and mental energies in a wide range of situations, with high tolerability and safety, preferably of natural origin.

To this aim, our collection of clinical experiences was structured to evaluate the efficacy and to confirm safety and tolerability of a food supplement based on cod liver oil, pollen, royal jelly, glycine, zinc, and vitamins (Liovital® AD, Pharma Line s.r.l. Milan) in cases of physical and mental fatigue.

Materials and methods

1. Data collection structure

Thirty-three physicians distributed throughout Italy participated in this clinical experiences collection. During the period between February 2022 and July 2022, adult subjects (aged 18 to 58 years) have been selected. Subjects were presenting physical and mental fatigue for less than six months and at the time of the first visit (T0) were not taking restorative therapies or had discontinued them for at least 15 days. To be included in the data collection, the fatigue detected by patients had to be caused by physical or mental stress (e.g., by the change of seasons or by periods of intense work and/or family commitments). **The selected patients tooke the product (formula on the market since 2020, composition in Table 1) at a dosage of one vial daily, preferably away from meals, for 20 consecutive days, at the end of which the patients came back to the attention of the attending physician (T20)**. During the 20 days of administration, patients were asked not to take any other medications, food supplements or medical devices for the treatment of physical and mental fatigue.

The primary outcomes of the data collection were to assess efficacy, through the compilation by the patient of the Patient Health Questionnaire-9 (PHQ-9) and Fatigue Assessment Scale (FAS) at T0 and T20, and confirmation of the safety of the product, by assessing of any adverse events reported by patients at the end of 20 days of intake (T20).

Table 1. Composition of the food supplement Liovital® AD.

Ingredient	Per 1 vial	% NRV*
Vitamin A	1200 µg	150
Vitamin D3	12.5 µg/500 IU	250
Vitamin E	30 mg	250
Vitamin B1	25 mg	2272
Zinc	7.5 mg	75
Glycine	300 mg	--
Cod liver oil	200 mg	--
Pollen d.e.	80 mg	--
Royal Jelly	65 mg	--

* NRV: Nutrient Reference Value

The PHQ-9 is a questionnaire used for the diagnosis, monitoring and determination of the severity of depression. It was chosen to assess the impact of the product intake on the psychological sphere of patients. It is known from the literature that stressed subjects have significantly higher PHQ-9 scores than non-stressed subjects[2]. The PHQ-9 consists of a set of 9 questions covering the two weeks preceding the compilation of the questionnaire: it assigns a value of 0 if a certain condition does not occur "not at all", while it assigns value 3 if it occurs "almost every day". The sum of these values (the PHQ-9 global score) can range between 0 and 27. Scores between 0 and 4 indicate the absence of depressive disorder, between 5 and 9 indicate the presence of mild depressive disorder, between 10 and 14 moderate depressive disorder, between 15 and 19 moderate-severe depressive disorder and between 20 and 27 severe depressive disorder[3]. Furthermore, the PHQ-9 proposes an additional question (judgement) assessing the impact that the dimensions investigated by the questionnaire have on the normal course of the patient's life (score given to the judgement: from 0 = extreme impact, to 3 = no impact). The FAS is a questionnaire consisting of 10 questions to assess chronic fatigue[4]: 5 questions focused on physical fatigue and 5 on mental fatigue. The rating scale for answers is 5 points and ranges from 1 = never, to 5 = always. The overall score can vary between 10 and 50. Scores ≤ 21 are considered normal; scores between 22 and 34 indicate tiredness; scores ≥ 35 indicate extreme tiredness. The secondary objectives consist of the assessment at T20 of the product's level of efficacy by the physician and the patient using a 5-point Likert scale (0 = ineffective, 1 = not very effective, 2 = fairly effective, 3 = very effective, 4 = extremely effective). Finally, at T20, the patient's level of enjoyment of the product was also assessed using another 5-point Likert scale (0 = not at all, 1 = a little, 2 = quite a lot, 3 = much, 4 = very much).

To be included in the data collection, patients at T0 had to present symptoms of physical and mental fatigue attributable to the change of season or to particularly stressful and demanding periods (asthenic symptoms, symptoms of mental and physical fatigue and listlessness, feeling of general debilitation, lack of appetite and sleep disturbances, such as excessive sleep and/or difficulty waking up), accept and sign a regular informed consent for the handling of personal data. Exclusion criteria were the presence of anaemia, chronic fatigue (for more than six months), asthenic symptoms associated with cancer and its treatment, depression or other psychiatric disorders, anorexia, known vitamin deficiency, endocrine disorders, infections or chronic intake of opioid, steroid anti-emetics, beta-blockers, sedatives and psychotropic drugs. Also excluded, subjects already being treated with therapies other than the product under investigation, pregnant or lactating women subjects with psychiatric disorders, known allergies or hypersensitivities to any component of the nutraceutical under study.

Data were collected on 326 patients. The socio-demographic characteristics of the enrolled patients, collected with a special form filled by physicians at T0, are shown in Table 2.

Table 2. Socio-demographic characteristics of patients.

Characteristics	Value
Sex	
Male	143 (43.87%)
Female	183 (56.13%)
Age (years)	37.46 ± 9.79
BMI	23.44 ± 3.38
Co-morbidities	
Yes	66 (20.25%)
No	260 (79.75%)

2. Statistical Analysis

The data of the 326 patients were analyzed using the statistical software Stata14. The Wilcoxon signed-rank test[5] was used for statistical analysis. The Wilcoxon test is a non-parametric test that is used when data are paired, i.e. when you need to investigate on the same subjects the effectiveness of a treatment at two different times (before and after). It was used to compare the scores of the PHQ-9 and FAS questionnaires at T0 and T20, thus assessing the patients' response to taking the product. The Wilcoxon test is significant if the z-test is above the critical value of 1.96 and if the p-value is below the threshold of 0.05.

Results

1. Evaluation of the product's effectiveness as a physical and mental restorative

A comparison was made, in terms of mean global score differences, of the questionnaires PHQ-9 and FAS between the start of therapy (T0) and the end of therapy (T20). The mean score of the PHQ-9 at T0 is 12.23 (Tab. 3); this suggests that, on average, the population analyzed presents an altered psychic sphere. After 20 days of treatment, the average PHQ-9 score drops to 4.45, a score which indicates a return to a normal psychic sphere; the difference observed is statistically significant ($p < 0.0001$). In detail, among the total of 326 patients, 178 (54.6%) of them achieve a score of the PHQ-9 at T20 < 5 (Fig. 1). The judgment score, which assesses the impact of the emotional state on the normal course of life of patients (additional question PHQ-9), improved significantly ($p < 0.0001$) from an average value at T0 of 1.55 (score denoting difficulty in managing daily life) to a value of 2.61 at T20 (score denoting little or no difficulty) (Tab. 3).

The mean FAS score at T0 is 32.9; this suggests that on average, the analyzed population is fatigued. At T20, the average score improves significantly ($p < 0.0001$) to 18.36, a score that is below the threshold (≤ 21) needed to indicate the presence of fatigue (Tab. 3, Fig. 2). Table 3 summarizes the results of the questionnaires given to patients at T0 and T20.

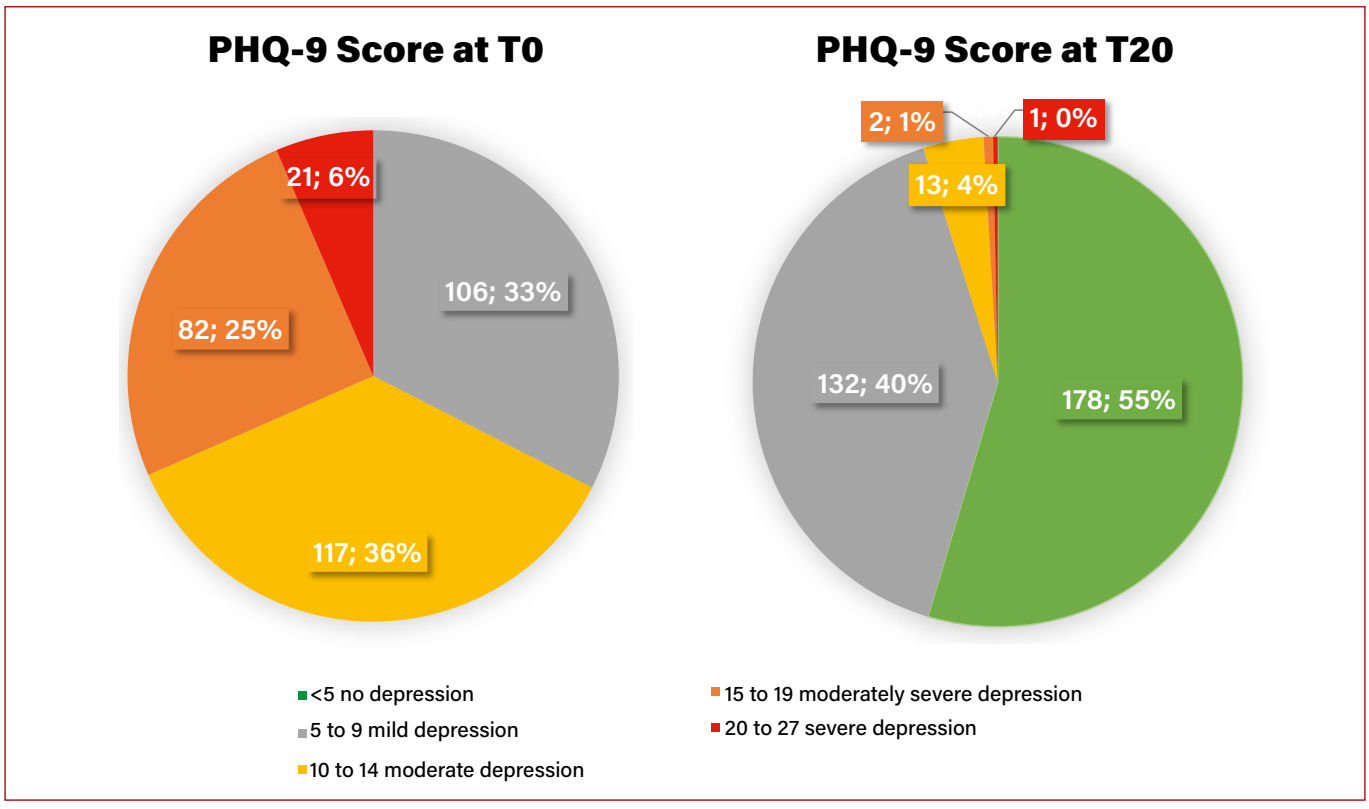

Figure 1.
Distribution of PHQ-9 scores at T0 and T20 (no. of subjects; %) out of total patients.

Table 3. Mean score and Wilcoxon test on score comparisons of the PHQ-9 questionnaire (including judgement) and of the FAS questionnaire between T0 and T20.

Assessment scale	Mean score at T0	Mean score at T20	Z test	P-value
PHQ-9	12.23	4.45	15.633	< 0.0001
PHQ-9 Judgement	1.55	2.61	15.262	< 0.0001
FAS	32.9	18.36	15.629	< 0.0001

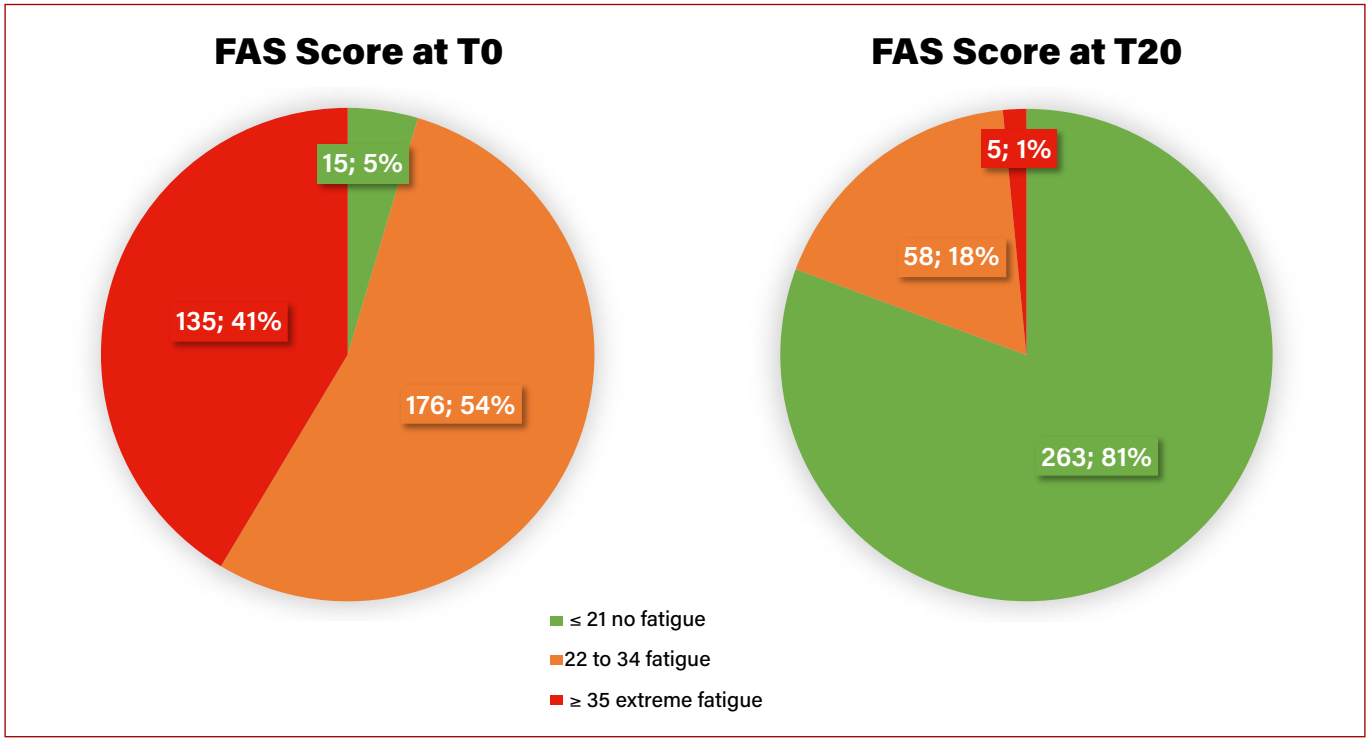

Figure 2.
Distribution of FAS scores at T0 and T20 (no. of subjects; %) out of total patients.

2. Confirmation of safety

Among 326 subjects observed, 5 patients (1.5%) reported minor side effects (mild nausea, two cases of occasional heartburn, diarrhoea, headache). All subjects completed the 20-day treatment period. The product is therefore confirmed to be safe and well tolerated.

3. Evaluation of efficacy and acceptance

At T20, medical doctors rated the treatment as effective, giving it an average overall score of 2.69 on a 5-point Likert scale (0 = ineffective, to 4 = extremely effective). The distribution of responses is shown in Figure 3A. The patients' assessment of effectiveness (expressed at T20 using the same Likert scale) is superimposable to that stated by the physicians, with an overall average of 2.69 (Fig. 3B).
Finally, at T20, patients were asked to express a rating of liking for the restorative product taken. Again, a 5-point Likert scale was used (from 0 = not at all, to 4 = very much), resulting in an average score of 2.74. The distribution of the answers is shown in Figure 4.

Discussion

To the best of our knowledge, this collection of real-life clinical experiences is the first that use the PHQ-9 and FAS questionnaires to evaluate the efficacy of a food supplement with restorative action on a fair number of patients. The international literature amply supports the beneficial properties of the single ingredients of the formula. In the scientific literature, among the natural substances with

a recognized restorative action, royal jelly, pollen and cod liver oil stand out in particular. Cod liver oil is extracted from the liver of *Gadus morhua* and other cod species. It contains large amounts of vitamins A, D and omega-3 fatty acids [eicosapentaeonic acid (EPA) and docosahexaenoic acid (DHA)][6]. Historically, cod liver oil was used to treat rickets in children. Pollen has an extremely rich composition: it contains vitamins, amino acids, lipids, minerals enzymes, coenzymes and hormones. The pollen used in Liovital® AD is Graminex® G63®, a standardized extract and allergen-free rye pollen extract supported by several clinical studies in many different fields[7]. Graminex® can be used as nutritional support for children, adults[8] and the elderly. Its effects include counteracting asthenia, regaining appetite, weight gain and increasing resistance to fatigue. In addition, Graminex® can be used: to aid concentration; against stress; for improving physical condition and endurance in athletes; to prevent influenza and colds[7]. Royal jelly is a secretion produced by worker bees to feed the larvae and queen bee. It is the hive's richest product: it contains sugars, fats, proteins, vitamins (A, B, C), trace elements (Fe, Zn, Cu), enzymes and natural antibiotics, and is therefore considered a 'superfood'. Royal jelly is a vitamin product and a natural anabolic stimulant commonly used as a supplement for various diseases, including cancer, diabetes, cardiovascular disease, and Alzheimer's disease[9]. Approximately 80-90% of its lipid fraction consists of an extremely rare unsaturated fatty acid and with an unusual structure: 10-hydroxy-*trans*-2-decenoic acid (10H2DA or 10-HDA), which exists only in royal jelly and to which many properties of this extraordinary foodstuff are ascribed. 10-HDA is a modulator of the innate immune response[10]. The freeze-dried royal jelly contained in Liovital® AD is titrated to 4% 10-HDA, an indication of high quality. The formula of Liovital® AD is further enhanced by the presence of glycine, zinc, and vitamins A, D3, E, B1.

Efficacy of the product as a physical and mental tonic

Analyzing the results of the PHQ-9 questionnaire (Fig. 1) shows that at T0 223 subjects (68.4%) have scores between 5 and 14, indicating the presence of mild or moderate depressive disorder, while 103 patients (31.6%) have scores between 15 and 27, indicating moderate to severe depressive disorder At T20, out of a total of 326 patients, as many as 178 (54.6%) achieve a score < 5 and thus fell into a normal mental picture, while 145 (44.5%) had a score between 5 and 14 (mild or moderate depressive disorder). At T20 the group of people who still show moderately severe or severe depressive disorder is drastically reduced to only 3 patients (0,9%). This confirms the great efficacy of the product in improving the psychic sphere of patients, bringing more than 54% of them back to normal. In the additional PHQ-9 question "judgement" at T0, only 23 patients (7%) stated that their emotional state did not cause difficulties in everyday life (score = 3), while as many as 207 subjects (63.5%) achieved this result after treatment. At T0, 138 subjects (42.3%) declared an extreme or very significant impact (score 0-1) of their negative psychic state during their lives, whereas at T20 only 6 patients (1.8%) still had this perception (data not shown). This is reflected in a better and easier management of daily life by the subjects, as the improved psychic state makes it easier to cope with daily challenges.

Examining the results of the FAS questionnaire in detail (Fig. 2), at T0 as many as 135 patients (41.4%) have a score ≥ 35, indicating extreme fatigue, while only 15 subjects (4.6%) had an initial score ≤ 21, indicating no fatigue. At T20, however, most of the population analyzed no longer detect the feeling of physical or mental fatigue. In particular, 263 patients (80.7%) have a score ≤ 21 and therefore no longer feel fatigue. We can therefore state that the product was very effective in reducing patients' perceived physical and mental fatigue. Analysis of the data, summarized in Table 3, shows **the product resulted in a restorative action with a very significant decrease in feelings of depressive mood and stress (PHQ-9), physical and mental fatigue (FAS), as well as leading to an improvement in life management (PHQ-9 judgement)**.

The product's pronounced restorative action was also confirmed by the positive feedback on the effectiveness of the treatment expressed at T20 by patients and doctors. In particular, 210 patients (64.4%) rated the treatment with the product as very or extremely effective (score 3-4). The physicians rated the treatment as very or extremely effective in 206 cases (63.2%).

Conclusions

The results of this collection of real-life clinical experiences demonstrate the restorative efficacy of Liovital® AD in cases of physical and mental fatigue caused by stressful periods, such as the change of season or particularly intense commitments and situations. The product made it easier for patients to cope with everyday life (the PHQ-9 judgment increased from 1.55 (T0) to 2.61 (T20), p < 0.0001), significantly reduced feelings of depressive mood and stress (mean PHQ-9 score reduced from 12.23 (T0) to 4.45 (T20), p < 0.0001), physical and mental fatigue (mean FAS score drops from 32.9 (T0) to 18.36 (T20), p < 0.0001). This can also be seen in the efficacy and satisfaction ratings expressed by the patients at the end of the treatment (T20) and by the efficacy found by the investigating physicians. The data collection also confirmed the safety and tolerability of the product, recording only 5 mild adverse effects out of 326 subjects treated for 20 days with one vial/day.

Based on the analysis of the data collected, we can state that, thanks to its complete formulation, Liovital® AD is an effective restorative to counteract stress conditions that alter the body's normal functions (e.g. change of season, physical and/or psychic overwork, etc.) and to promote rapid recovery from physical and mental fatigue.

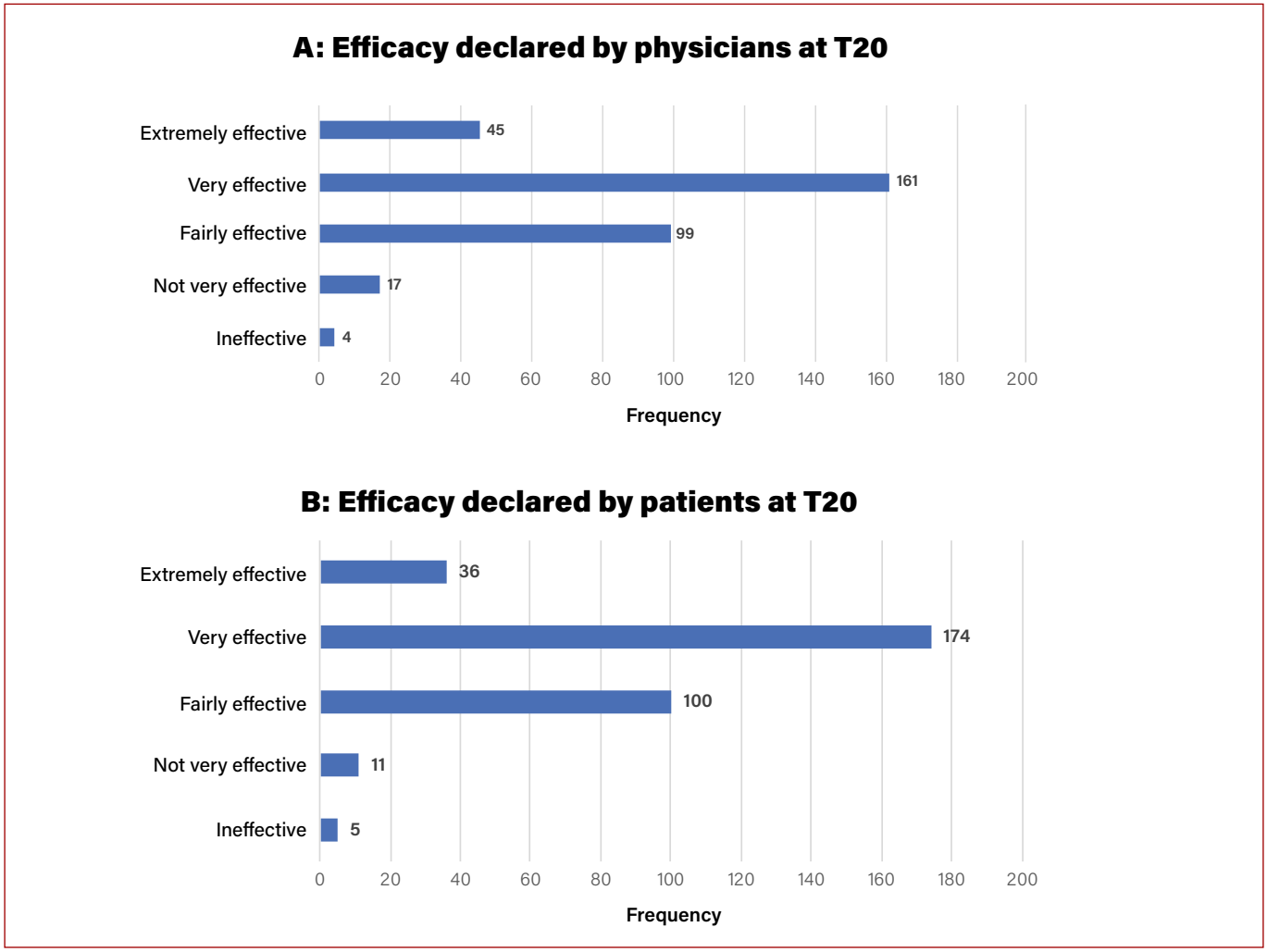

Figure 3.
Distribution of doctors' (A) and patients' (B) responses on treatment efficacy at T20.

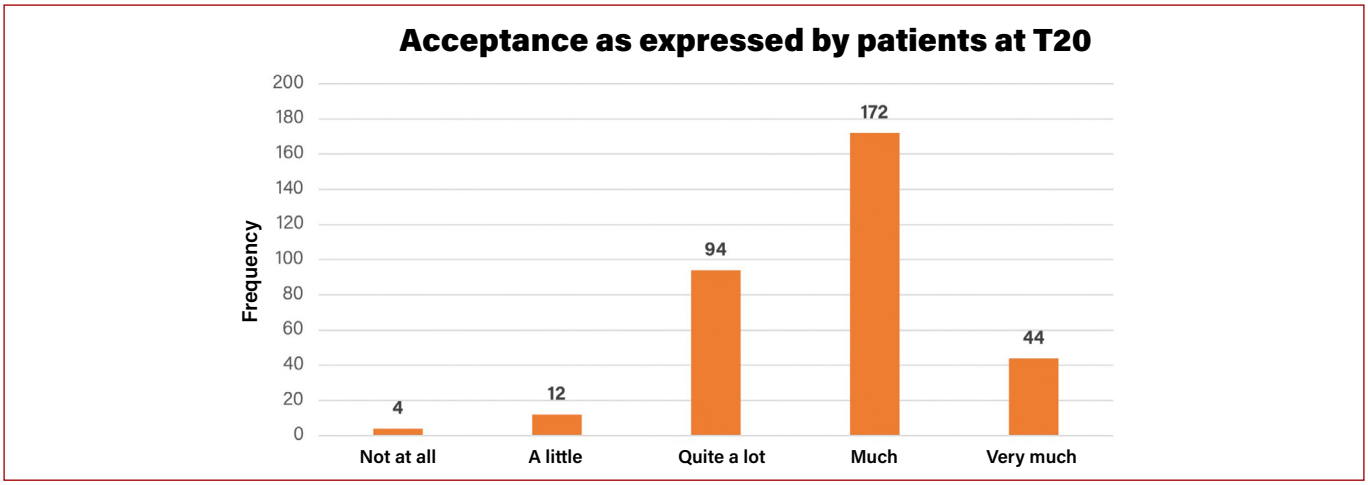

Figure 4.
Distribution of patient responses on liking Liovital® AD.

Conflict of interest

The data collection was financed by Pharma Line s.r.l.

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