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Hyperiforce* tablets for the treatment of mild to moderate depression

A double-blind study to investigate three different concentrations of a standardised fresh-plant extract obtained from the shoot tips of *Hypericum perforatum* L.

With the aim of investigating the efficacy and tolerability of a new standardised preparation of an extract of St. John's Wort in the treatment of mild to moderate forms of depression, a double-blind parallel group comparative study involving 348 patients was carried out. The patients were randomized to receive one of three different doses over a period of 6 weeks. In each group, treatment comprised a 3× daily administration of either 1 tablet of Hyperiforce containing natural extract standardised to 0.33 mg of total hypericin, or a tablet of identical appearance containing either 1/3 or 1/6 of this amount of extract. The study was designed as a multi-centre trial and was conducted in a total of 12 psychiatric specialist practices and 26 general practices in Switzerland and Germany, in compliance with the guidelines of good clinical practice. On conclusion of the study, which lasted from the end of February, 1996 to the middle of March, 1997, the data of 260 patients were available for evaluation of the antidepressive efficacy using the Hamilton Depression Scale. At the end of treatment, a reduction in the average score from an initial 16–17 to 8–9, i.e a relative reduction of about 50%, was observed. The response rates were 68% (high dosage) and 65% and 62% (low dosages), respectively. Overall, the intergroup comparison revealed no significant differences. Tolerability was excellent, with mild adverse reactions (AR) probably causally related to the treatment with *Hypericum* occurring in only 7 of the 348 patients (2%). For antidepressive treatment with Hyperiforce tablets, the following daily dosage can be recommended: 3× one tablet initially, reduced to 1–2× one Hyperiforce tablet daily when there is a good response to treatment.

Depressive states are affective disorders associated with mood disturbances, loss of the capacity to feel pleasure, lack of interest, and a reduction in drive and activity, which can occur even at a young age, and which usually peak in middle age. In the large majority of cases, the victims of depression are women. The biochemical background is suspected to be metabolic disturbances affecting the neurotransmitters serotonin and noradrenaline. A differentiation is made between endogenous and non-endogenous, psychogenic and somatogenic, and masked depression; the symptoms of these different forms, however, often overlap.

To date, no pathological laboratory values or EEG changes are available on which to base the diagnosis of this «disease of a thousand faces» affecting about 10% of the world's population. Instead, the ***Hamilton Depression Scale (HAMD)*** has proved of value as an instrument for objectively assessing the severity of the condition. Since the last four of the 21 items comprising the HAMD **(Table 1)** have relevance almost exclusively for the severe forms of depressive mood disturbances, the HAMD-17 score is preferentially used for assessing mild to moderate depression.

For treatment, ***tri- and tetracyclic antidepressants*** or ***selective serotonin inhibitors*** that prevent the re-uptake from the synaptic gap of norepinephrine and/or serotonin into the presynaptic neurone, are employed. In addition, inhibitors of the monoamine oxidase type A ***(MAO-A inhibitors)*** are also used for therapeutic purposes. With regard to the mild to

moderate forms of depression, however, the use of synthetic antidepressants would appear inappropriate in many cases, since the therapeutic success rate of about 55–70% must be weighed against a not-inconsiderable toxic potential and unpleasant, in part anticholinergic, adverse reactions (e.g. dry mouth, nervousness, restlessness, sleep disorders, nausea, a burning sensation in the stomach, diarrhoea or constipation in up to 30% of the cases) .

Psychotropic phytotherapy

For the treatment of depression, St. John's Wort *(Hypericum perforatum)* is one of the oldest medicinal plants, and was already being used to treat numerous diseases in antiquity. The monograph produced in 1984 by the Commission E of the German Bundesgesundheitsamt (Federal Health Office) quotes the disorders psychovegetative disturbances, depressive mood states, anxiety and nervous restlessness as indications [1]. As three controlled studies have shown [2], the effect of *Hypericum* preparations is comparable with that achieved with synthetic antidepressants, but adverse reactions occur considerably less frequently. In particular, there is no impairment of the patient's reactions [3]. Nor is there any potentiation of the effects of alcohol on psychomotor and/or mental performance [4]. Furthermore, the substance has no potential for addiction, and there is no risk attendant on an overdosage taken with suicidal intention. Finally, no hangover symptoms have ever been observed.

Although hypericin, the chemical structure of which has certain formalistic similarities with tricyclic monoamine oxidase (MAO) inhibitors [5], has conventionally been considered to be the major mark substance, it has not been possible so far to assign an antidepressive effect to individual constituents of *Hypericum* [6]). It would therefore appear expedient to utilize preparations containing the widest possible spectrum of the constituents of *Hypericum perforatum*. The Hyperiforce tablets are prepared using only the fresh tips of the shoots of St. John's Wort, and their constituents are standardised. Furthermore, the plants are cultivated under biologically controlled conditions and only at suitable sites. Following harvesting, the individual batches obtained are pooled to form large batches.

A single tablet of Hyperiforce contains approximately 60 mg of a plant extract of *Hypericum* (4–5:1) and is standardised to 0.33 mg total hypericin. In comparison with extracts from the whole plant, the extract from the shoot tips has a higher concentration of constituents. This means that an appreciably smaller amount of this plant extract per tablet is needed to achieve an amount of constituents comparable to that obtained with the whole plant extract.

Symptoms	Score (points)
1: Depressed mood	0 – 4
2: Guilt	0 – 4
3: Suicide	0 – 4
4: Insomnia, initial	0 – 2
5: Insomnia, middle	0 – 2
6: Insomnia, delayed	0 – 2
7: Work and interest	0 – 4
8: Retardation	0 – 4
9: Agitation	0 – 4
10: Anxiety (psychic)	0 – 4
11: Anxiety (somatic)	0 – 4
12: Somatic gastrointestinal	0 – 2
13: Somatic general	0 – 2
14: Genital	0 – 2
15: Hypochondrias	0 – 4
16: Loss of weight	0 – 2
17: Insight	0 – 2
18: Diurnal variation (morning, afternoon, evening)	0 – 2
19: Depersonalisation and derealisation	0 – 4
20: Paranoid symptoms	0 – 4
21: Obsessional symptoms	0 – 2

Table 1: The Hamilton Depression Scale (HAMD): symptoms and evaluation.

Study conditions and patient selection

The study was carried out in accordance with good clinical practice (GCP) and in compliance with the guidelines of the Declaration of Helsinki, as well as with the IKS regulations applicable in Switzerland for remedies used in clinical trials, and in Germany in accordance with the AMG; in addition it was approved by the relevant ethics committees. With the aim of assessing the efficacy and tolerability of three different doses of the new fresh-plant preparation, the trial was scheduled to be performed on

patients with mild to moderate depression (HAMD score ≥ 10) aged at least 20 years, who were to receive the study medication three times a day for a total treatment period of 6 weeks. In order to ensure an adequate number of patients for statistical analysis, they were recruited to the multi-centre study by 12 psychiatric specialty practices and 26 general practices. Dropouts were not replaced. Exclusion criteria included a St. John's Wort allergy and treatment with antidepressants, tranquilizers, hypnotics or neuroleptics within the last two weeks immediately prior to the start of the study, as also an acute risk of suicide. Any concomitant treatment had to be continued unchanged throughout the 6-week treatment phase.

A placebo-controlled study would have provided only very modest additional information, since 14 placebo-controlled studies involving a total of 948 patients with depression of mild to moderate severity, have already been carried out [8-21]. The average response rate established in 13 studies was 55% for *Hypericum* preparations and 22% for placebo. This made it appear unethical to withhold treatment from patients in a placebo group. Instead, a dose-controlled study was carried out in accordance with the recommendations in a criteria-supported review and meta-analysis [2].

We therefore conducted a randomized parallel-group comparative study in which patients were given either one tablet of Hyperiforce three times a day, or, as control, a tablet containing, respectively, only 1/3 or 1/6 of the same crude extract. The aim was to investigate the efficacy of the two lower doses in comparison with the daily dose of 1 mg total hypericin; the lowest daily dose of 0.17 mg was just below the amount recommended in Monograph E and the ESCOP guidelines, which cite a mean daily dose of between 0.2 mg and 1 mg total hypericin [1, 7]. Each patient was examined immediately prior to the start of treatment and also after one and six weeks of treatment.

To evaluate efficacy, the HAMD-17 scores were submitted to a statistical analysis. Relevant response was defined either as a decrease in the score to below 10 or a reduction of at least 50%. In addition, an assessment was also made on the basis of the HAMD-21 score, the general clinical impression gained by the physician (CGI) and the self-assessment by the patient on the basis of the HAD (Hospital Anxiety and Depression) Scale.

For an assessment of tolerability and the response rate, the overall group was considered (intention to treat analysis), while efficacy was evaluated only in the patients actually complying with the protocol (per protocol analysis). The comparison of groups was carried out with the aid of a three-factor variance analysis of the HAMD-17 score, the first factor being the treatment groups, the second the repeat measurements, and the third factor the test centre. For the statistical description of the data, the Wilcoxon test for pair differences, the chi-square and the Z-test were also employed.

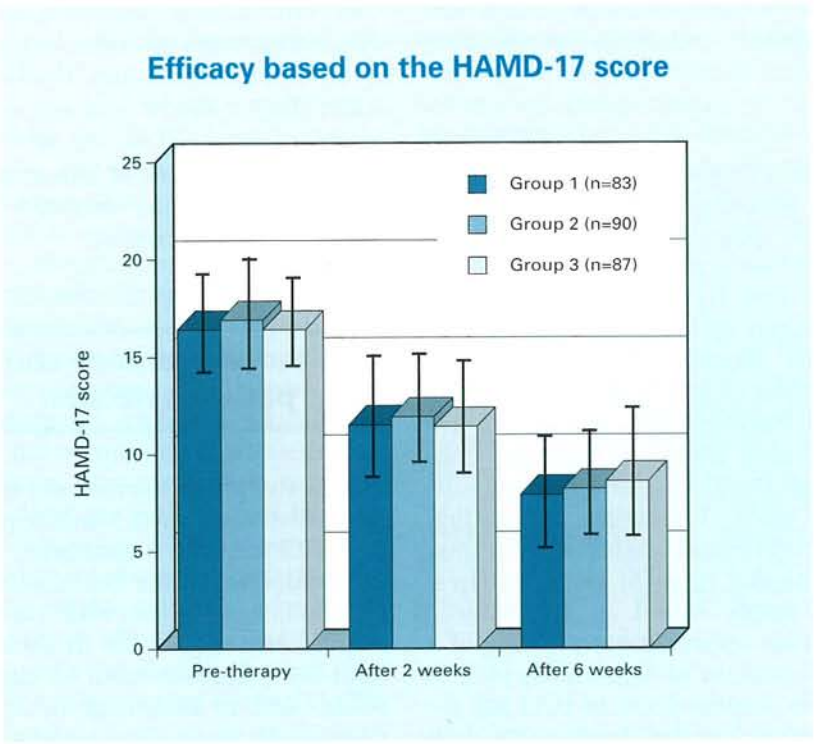

Figure 1: Randomized double-blind study in patients with mild to moderate depression: treatment with Hyperiforce tablets over a period of 6 weeks. Evolution of the HAMD-17 score in the 3 treatment groups.

Group 1 = Dose: 1 mg total hypericin/day in natural extract
Group 1 = Dose: 0.33 mg total hypericin/day in natural extract
Group 3 = Dose: 0.16 mg total hypericin/day in natural extract

Results

A total of 259 women (74%) and 89 men (26%) aged between 19 and 94 years, were recruited to the double-blind study by 38 test centres in Germany and Switzerland. The participants were randomized to one of three treatment groups, and received the fresh-plant preparation of *Hypericum* containing total hypericin at a dose of either 1 mg/day, 0.33 mg/day or 0.17 mg/day. The initial diagnosis (and indication) for treatment with Hyperiforce was, in accordance with ICD-10, depressive episodes in 122 patients, recurrent depressive disor-

ders in 134 patients, persistent affective disorders in 16, anxiety disorders in 21, and stress and adjustment disorders in 44 patients, while in the remaining 11 patients other conditions with accompanying affective mood disorders presented.

A total of 88 of the 348 patients failed to complete the study in conformity with the protocol. 41 patients withdrew prematurely from the study for medical or other reasons, while in 60 there were major deviations from the protocol, such as inadequate compliance, missed or unpunctual visits, violations of good clinical practice or the impermissible use of other medications. The mean compliance rate was better than 90%. The three treatment groups showed no significant differences in terms of deviations from the protocol or mean compliance.

For the analysis of efficacy, therefore, the data of 260 patients were thus available. For the evaluation of the response rate and tolerability the data of all 348 patients were utilized.

During the course of the 6 weeks of treatment, the HAMD-17 score decreased appreciably in all three groups ($p < 0.001$, Wilcoxon test) **(Figure 1)**.

Already after 14 days, the relevant reduction in the HAMD-17 score was about 30% for all groups, and about 50% at the end of the treatment phase. Related efficacy was about 4% better in the highest dose group than in the group receiving the lowest dose. The three-factor variance analysis, however, showed no significant differences **(Figure 2)**.

The response rate established on the basis of the HAMD-17 score was about 39% after 14 days, and 62–68% by the end of the treatment period **(Figure 3)**.

In the assessment of the physicians, the efficacy of the study medication was moderate to good in approximately 70% of the cases, while the severity of the disease, as assessed on the basis of the general clinical impression, decreased on average from moderate to marked

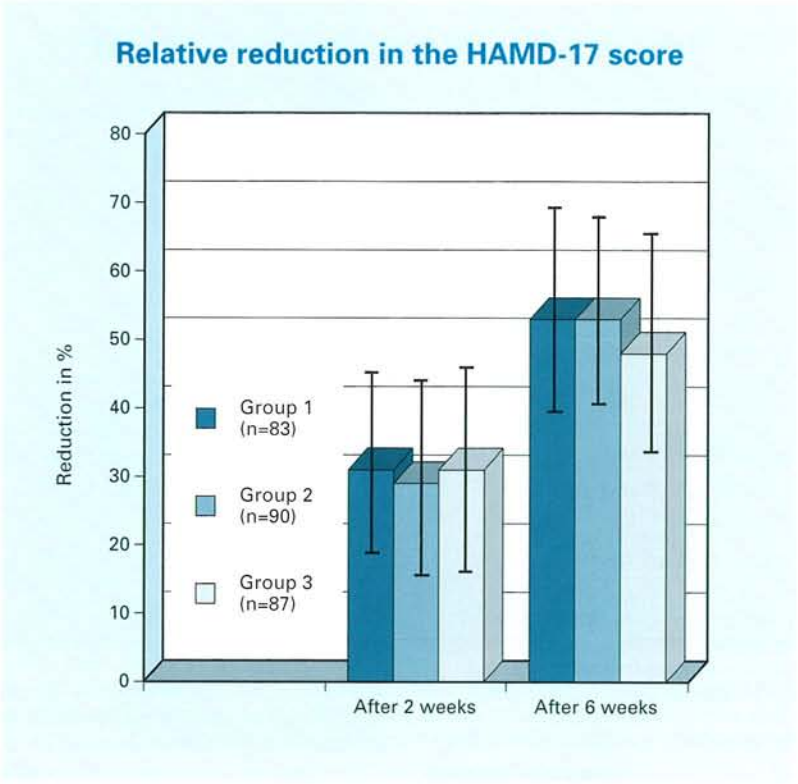

Figure 2: Randomized double-blind study in patients with mild to moderate depression: treatment with Hyperiforce tablets over a period of 6 weeks. Relative reduction in the HAMD-17 score (for a description of the individual treatment groups see caption to Figure 1).

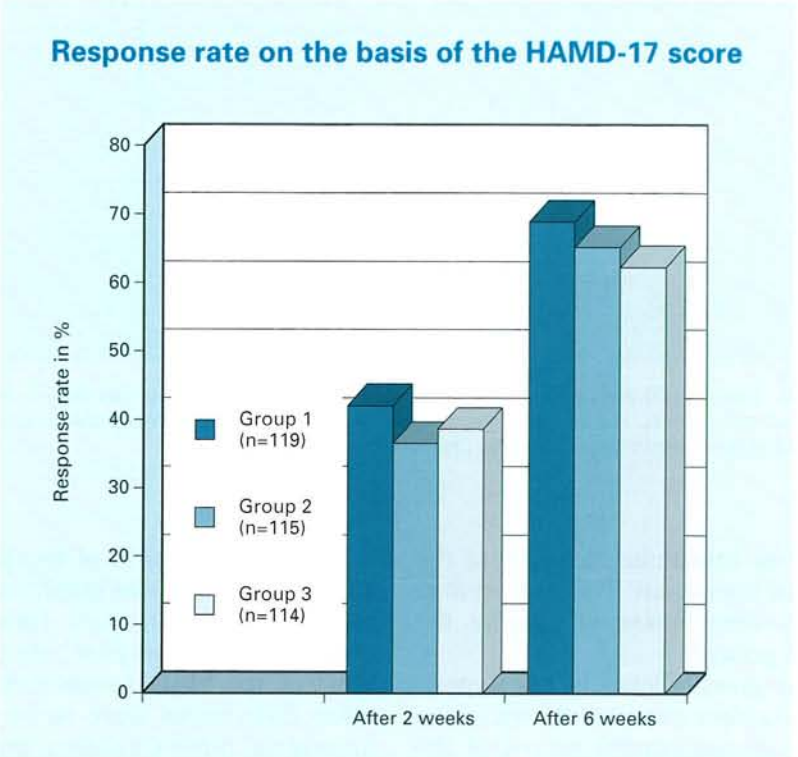

Figure 3: Randomized double-blind study in patients with mild to moderate depression: treatment with Hyperiforce tablets over a period of 6 weeks. Response rate on the basis of the HAMD-17 score (for a description of the individual treatment groups see caption to Figure 1).

Adverse events (AE) and causal relationship

Body system	Pro	Pos	Imp	Σ
Skin		3	7	10
Skeleton/muscles			4	4
Nerves	2	5	12	19
Psyche	1	1	3	5
Gastrointestinal tract	4		8	12
Liver/biliary system			1	1
Cardiovascular system			2	2
Airways/lungs			3	3
Blood			1	1
Kidneys/urinary tract			1	1
Reproductive organs			3	3
Neoplasms			2	2
Organism as a whole		2	17	19
Σ	**7**	**11**	**64**	**82**

Table 2: Randomized double-blind study in patients with mild to moderate depression: Body systems affected by adverse events, and causal relationship to the study medication (**Pro:** probable or certain; **Pos:** possible or perhaps possible; **Imp:** improbable or questionable).

Severity of AE, and causal relationship

	Mild			Moderate			Severe			Σ		
Group	Pro	Pos	Imp	Pro	Pos	Imp	Pro	Pos	Imp	Pro	Pos	Imp
1	1	4	10	2	2	4	0	0	17	3	6	31
2	0	1	8	1	0	4	0	0	11	1	1	23
3	1	3	9	2	1	0	0	0	1	3	4	10
Σ	2	8	27	5	3	8	0	0	29	7	11	64

Table 3: Randomized double-blind study in patients with mild to moderate depression: Severity of the adverse events, and causal relationship to the study medication.(**Pro:** probable or certain; **Pos:** possible or perhaps possible; **Imp:** improbable or questionable).

prior to treatment, to mild at the end of treatment. No clear differences were observed among the three groups.

The good efficacy of the Hyperiforce tablets was also shown by the two self-assessment scores of the patients for anxiety and depression (HAD), which, during the course of treatment decreased appreciably in all treatment groups.

In the assessment of the physicians tolerability was good, namely 84% (high dose), 95% (medium dose) and 90% (low dose). As in the case of the HAD assessment, no clear differences were to be seen among the three treatment groups. A total of 82 adverse events (AE) were observed in 74 patients, affecting in particular the nervous system, the gastrointestinal tract, and the general state of well-being of the patient **(Table 2)**.

A causal relationship of such events to the study medication was considered to be improbable or questionable in 64 cases, and as possible or perhaps possible in 11 cases. In six cases, the causal relationship to the study medication was considered to be probable: there were two mild adverse events taking the form of sleepiness or nausea, and 4 moderate adverse events taking the form of gastric pain, nausea, a tendency to cry, increased anxiety and migraine. All these adverse events were of a temporary nature and cleared up again after discontinuing treatment, or during the further course of therapy. In the case of one adverse event evaluated as moderate, the causal relationship to the study medication was considered certain: here, nausea, headaches and dizziness was experienced after every medication use, but cleared up again on discontinuation of treatment.

In the high-dose group, significantly more AE with a questionable or improbable causality relationship to the test medication were observed as compared with the lower-dose groups. With respect to AE with possible or probable causality, however, no differences were found among the treatment groups **(Table 3)**.

Discussion and conclusions

The response rates of between 62% and 68%, including that of the lowest daily dose of 0.17 mg total hypericin, were better than the 55% reported by other *Hypericum* studies employing 0.5–2.7 mg hypericin/day. It is possible that this reflects the advantage of using only the fresh shoot tips of St. John's Wort.

On the basis of these results, it may be recommended that treatment with Hyperiforce tablets could be started at a dose of 1 tablet 3 times a day, and then – when a good anti-depressive effect is

achieved – continued over the long-term with 1 to 2 tablets a day. Recent pharmacokinetic data [22], appear to indicate that even at the reduced dosage a constant level of the active substance can be ensured over the long term.

Hyperiforce proved to be well tolerated at all three doses. The number of patients experiencing undesired adverse events is comparable with that reported in 6 other *Hypericum* studies [2]. The few adverse events that probably had a causal relationship with the study medication in 2% of the cases were mild gastrointestinal, psychic or nervous symptoms which, however, may equally well be accompanying symptoms of the depression itself.

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