



Gisela Pfister-Hotz
Deryk Shah
Silvia Bommer

Hyperiforce*: Treatment of depressive states

Clinical study of a fresh-plant extract in patients with mild to moderate forms of depression

In recent years, the incidence of depression has been on the increase throughout the world. Women are more likely to be affected than men. Throughout the course of their lifetime, between 10% and 20% of our population will suffer from this condition at some time or other. More than one half of all attempted suicides are undertaken while the person concerned is in a depressed state. For this reason, depression is always to be considered a condition that requires treatment.

Causes and forms of depression

Quite a lot of attempts have been made to explain the reasons for depression. Although in recent years some light has been cast on the biochemical background of the disease, there are still many gaps in our knowledge. One of the things under discussion is a disturbance in the metabolism of the brain, which, admittedly has not been described in any great detail [9, 10]. If, instead of the depressive mood being in the foreground, physical complaints predominate in the patient's field of consciousness, the condition is referred to as masked depression. In such a case, the physical complaints dominate the overall picture to such an extent

The aim of the present clinical trial involving 32 patients with depressive syndrome was to document the therapeutic action on mild depression and psychosomatic disorders associated with anxiety and nervous states of the preparation Hyperiforce (alcoholic extract of the freshly gathered plants St. John's Wort, Balm and Hops) In addition, the tolerability of the preparation was to be investigated. The exclusion criterion was current medication with antidepressive agents, tranquilizers, neuroleptic agents or lithium. The study was designed as an open, uncontrolled prospective trial and was carried out over a period of four weeks. All the patients had to take a dose of 30 drops of Hyperiforce three times daily. The depressive states of the patients were recorded on three occasions using psychometric methods, and then quantified: prior to the start of treatment and then after the start of treatment at two-weekly intervals. The tolerability of the preparation was also assessed. The trial was initiated in August, 1991, and terminated in April, 1994.

A clinical effect of the treatment was registered in 74% of the patients on the basis of the Hamilton Depression Scale (HAMD-17-Item Score). The differences between the mean HAMD-17-item scores of the patients prior to treatment and also at two and four weeks after treatment, were statistically significant ($p < 0.05$). During the treatment phase, 42% of the patients complained of mild physical symptoms. In 6%, the treatment was thereupon terminated. Among the remaining 35% no causal relationship was to be recognized, and the complaints cleared up again spontaneously. In the present study concerning the treatment of mild to moderate depressive states in the doctor's office, Hyperiforce proved to be a highly effective and well tolerated preparation.

that the psychic symptoms are often overlooked.

Symptoms of depression

In addition to pathological melancholy, depression is often also associated with a disturbance of such vital functions as sleep, appetite and sexuality. Such accompanying symptoms as, for example, heart complaints, sweating, noises in the

ear and also general weakness, are not uncommonly found to be in the forefront of the complexity of symptoms in depression. Depressive states occur in particular in patients in the younger and middle age groups who are in the middle of their working lives. During depression, all those qualities and skills which have daily to be applied in the working world, dry up

as it were. As a result of the depressive state, therefore, the sufferer's ability to go about his/her work is often severely impaired.

Treatment of depression

For hundreds of years, ever new treatment concepts have been tried in an effort to overcome or manage depression. Over and beyond the synthetic antidepressants, phytotherapeutic agents are increasingly gaining in importance in this area, since not only do they have a good positive effect on mild to moderate depressive states, but they also have virtually no side effects, and no potential for addiction. In particular the bothersome side effects of the synthetic psychopharmaceutical drugs, such as fatigue, dry mouth and constipation, which may develop in as many as 50% of the cases, and the risk of addiction developing, have all combined to prompt a continued search for more effective and more readily tolerable alternative remedies.

Reports from the area of folk medicine, which for hundreds of years have attributed an anxiolytic, harmonising action to St. John's Wort, were rediscovered [1, 2]. They also prompted the implementation of controlled clinical studies aimed at putting the antidepressive action of certain extracts of St. John's Wort on a scientific footing [4, 5, 6, 7, 8, 11]. For a number of years now, extracts of St. John's Wort have been successfully used to treat depressive mood. In particular a rapid improvement in the psychovegetative accompanying symptoms such as sleep disturbances, cardiac complaints, headaches and exhaustion, all of which frequently have a prominent place in depression, has been reported.

The phytotherapeutic agent Hyperiforce

Composition

In addition to the alcoholic extract obtained from fresh St. John's Wort (*Hypericum perforatum*), Hy-

periforce contains the plants Balm (*Melissa officinalis*) and the Hop (*Humulus lupulus*), which also have a sedative or calming and harmonising effect. The dose applied is 30 drops of Hyperiforce three times a day [1, 2, 8].

For all three plants there are official manufacturing instructions and quality control guidelines available, which guarantee that a certain minimum standard is always maintained. The objective behind the combination of these three medicinal plants is to potentiate the effects of the individual active constituents in the indication psychosomatic disorders accompanied by anxiety and restlessness. All three plants have a positive monograph in these fields of indication. Psychovegetative disorders, depressive mood states together with anxiety and or nervous unrest, nervous sleep disturbances and functional gastrointestinal complaints can all be subsumed under the term "depressive syndrome".

Active principle

The antidepressive effect of St. John's Wort – suitably prepared and administered at appropriate doses – has long been known. The antidepressive, drive-enhancing effect of *Hypericum* depends, in all probability, on an inhibition of monoamine oxidase [7]. Monoamine oxidase inhibitors have long proven their usefulness in the treatment of depression. One of the specific major constituents of St. John's Wort is hypericin [4, 5, 11].

Indications

The field of application of Hyperiforce is the primary treatment of incipient depression. But *Hypericum* preparations can alternatively be used to manage mild to moderate depressive mood, for which a synthetic antidepressive agent would have too powerful an effect and thus lead to a predominance of the side effects.

Aim and conduct of the study Methodology

The aim of the study was to investigate the efficacy of Hyperiforce, a new combination remedy containing the plants St. John's Wort, Balm and Hops, used in accordance with its field of indication, namely the treatment of depressive syndrome. Since nine out of ten patients suffering from depressive mood are ambulatory and are treated by general practitioners, it appeared only logical to have the present trial carried out by general practitioners. This open, uncontrolled, prospective investigation involving 32 patients was conducted over a period of 4 weeks.

Hamilton Depression Scale

Since depression is a subjective condition, no objective means of assessing it in a scientific sense is available. For the clinical proof of efficacy, we considered the Hamilton Depression Scale (HAMD) – which is frequently used in the psychiatric research setting – to be a suitable objective psychometric method [3]. Consequently, the main parameter employed for the testing of efficacy was the overall HAMD score. The HAMD scale is an instrument, recognized by specialists in the field, which permits the quantified assessment of the course of the illness in depressed patients on an objective basis.

Patient selection, dosage, duration of treatment

A definitive total of 32 patients from among patients being managed by psychiatrists and general practitioners were included in the study.

The exclusion criterion was ongoing treatment with antidepressive agents, tranquilizers, neuroleptic agents or lithium. Simultaneous client-centered therapy was, however, permitted.

The inclusion criterion was the diagnosis "depressive state" with an HAMD score of between 10 and 30 points.

Evaluation for	Number	Sex			Age years	Treatment duration/days
		f	m			
Efficacy	27	15	12	Mean	41.4	27.1 us
				St. dev.	10.8	1.7
				Min-max.	23-67	21-29
Tolerability	31	18	13	Mean	42.2	25.0 us
				St. dev.	12.8	6.3
				Min-max.	23-82	3-29

Table 1. Demographic data and duration of treatment with Hyperiforce

Each patient participating first gave his/her written informed consent to be included in the study.

The dosage used was 30 drops three times a day. The test preparation was to be taken before meals in a little water. The overall duration of the treatment period was four weeks.

Assessment by the physician, and compliance

Prior to the start of treatment and on its termination, the patients were assigned to six groups in accordance with a clinical global impression scale as follows: not ill; borderline; mildly ill; moderately ill; obviously ill; severely ill. The regular use of the medication as instructed was monitored.

Tolerability and laboratory monitoring

With the aid of an examination journal, the tolerability of Hyperiforce at the start, after two weeks, and at the end, of treatment was investigated. Laboratory investigation were carried out for monitoring purposes.

Results

Patients

Of the 32 patients originally enrolled in the study, 31 proved evaluable for tolerability (one patient was hospitalized and lost to the study), and 27 patients for the investigation of efficacy (incomplete data records in 4 patients) (Table 1).

Compliance

Thirty patients employed Hyperiforce regularly as required, for the duration of the scheduled four weeks. In only a single woman (patient No. 20) was compliance unsatisfactory.

Clinical efficacy

On the occasion of the interview physician/patient, 21 disorders (items) commonly associated with depression were considered and quantified with the aid of a code. For the evaluation proper, only the first 17 items, the classical symptoms of depression, were considered. Special aspects of depression (items 18-21) were not evaluated in this study (Table 2).

The first 17 items are collected together in an overall score, the so-called HAMD-17-item score. An increase in this score indicates a worsening of symptomatology, a decrease an improvement in the symptoms. An effect was considered to have been demonstrated when there was a decrease in the score of at least 20%. A clinically relevant effect of the therapy (treatment responders) was considered to be given when one of the following conditions applied:

- at least a 50% reduction in the HAMD-17-item score, or
- a HAMD-17-item score of less than 10.

As shown by the HAMD-17-item score, an effect, which was dependent upon the duration of treatment, was found in 24 (89%) of the 27 patients; in 20 patients already

Item 1: Depressive mood
Item 2: Feelings of guilt
Item 3: Suicide
Item 4: Difficulty in falling asleep
Item 5: Difficulty in staying asleep
Item 6: Early morning awakening
Item 7: Work and other activities
Item 8: Depressive inhibition
Item 9: Agitation
Item 10: Anxiety - psychic
Item 11: Anxiety - somatic
Item 12: Physical symptoms - gastrointestinal
Item 13: Physical symptoms - general
Item 14: Genital symptoms
Item 15: Hypochondria
Item 16: Loss of weight
Item 17: Insight into the disease condition
Item 18: Daily fluctuations
Item 19: Depersonalisation
Item 20: Paranoid symptoms
Item 21: Obsessive-compulsive symptoms

Table 2: Hamilton Depression Scale (HAMD): symptoms items 1 to 21

after two weeks of treatment, in the remaining four patients by the end of the treatment period.

True treatment responders, that is, patients in whom a clinically relevant positive effect occurred, were, after four weeks of treatment with Hyperiforce, 20 out of 27 patients (74%, confidence level at $p < 0.05$: 53-89%) (Figure 1). In 15 of the 27 patients (56%, confidence level at $p < 0.05$: 35-75%), a clinically relevant effect of the treatment was already to be seen after only two weeks.

The differences in the Student T test between the patients prior to (HAMD-17-item score = 19.3), after two weeks (HAMD-17-item score = 11.0), and after four weeks, of treatment (HAMD-17-item score = 7.5) were found to be statistically significant ($p < 0.05$).

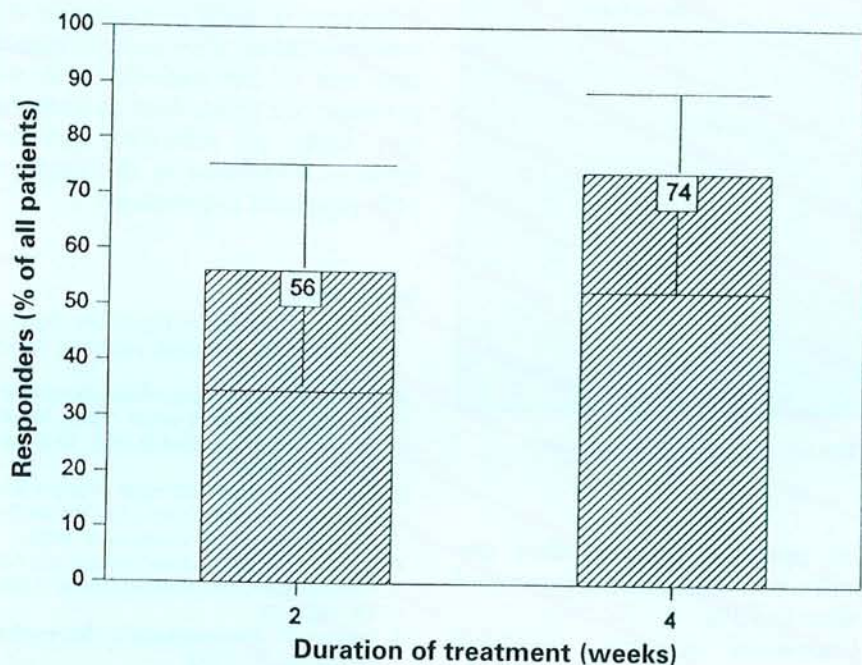


Figure 1: Responders to treatment with Hyperiforce in accordance with HAMD-17-item score. Number of responders as a percentage of patients investigated (n = 27) with confidence level ($p < 0.05$)

decreased from 17 (63%) prior to treatment to 13 (48%) patients after termination of the treatment phase. Ten (37%) of the patients were considered to be no longer ill by the end of the treatment period.

Tolerability

Of the 32 patients admitted to the study, 31 proved evaluable for efficacy (Table 3).

The 20 undesired side effects occurred in 13 different patients. Apart from two cases, these were only mild in nature, did not lead to abandonment of the trial, and disappeared spontaneously. Two (6%) of the 31 patients abandoned treatment with Hyperiforce on account of fatigue or a burning sensation in the stomach. No undesired side effects caused by MAO-inhibition, as have been noted with synthetic antidepressive agents, were observed. For the most part, the undesirable side effects did not differ from those that have also been noted with placebos. The symptoms could, at least in part, be interpreted as somatic symptoms accompanying depressive mood.

Laboratory monitoring

Monitoring of the laboratory parameters revealed no differences greater than 10% vis-a-vis the normal values, and thus confirmed the high level of tolerability of Hyperiforce.

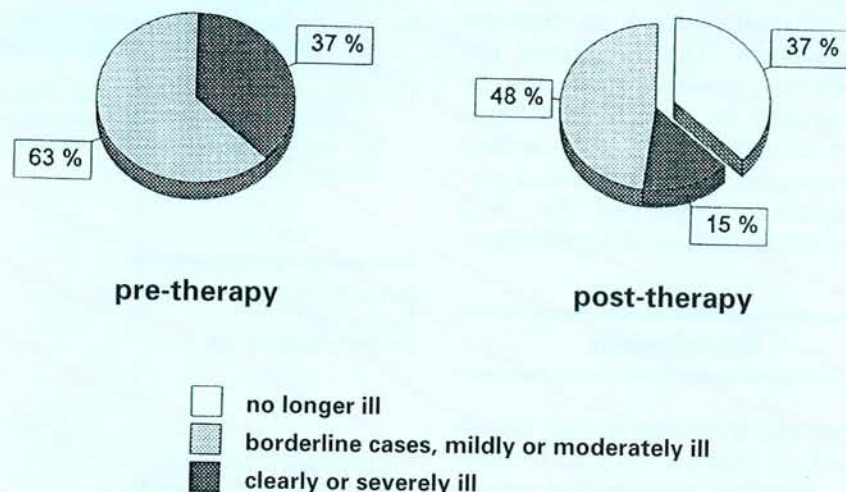


Figure 2: Severity of illness: assessment by the care-providing physicians prior to and after treatment with Hyperiforce. Number of patients divided up in accordance with severity of illness as percentages of the total number of patients investigated (n = 27)

Assessment by the care-providing physicians

In agreement with the HAMD-17-item score, the subjective assessment of disease severity by the care-providing physicians during treatment with Hyperiforce also revealed an improvement in the depressive

symptomatology (Figure 2). While 10 (37%) of the 27 patients were assessed to be clearly or severely ill prior to treatment, on termination of the therapy, only four were thus categorized (15%). The percentage of borderline cases and mild to moderately ill patients also

In the present investigation, the use of Hyperiforce led to a significant improvement in depression, the extent of which depended on the duration of treatment. The appreciable effect on depressive states of treatment with Hyperiforce is compatible with the results of other current clinical studies involving *Hypericum* preparations which have demonstrated an unequivocal positive effect.

To demonstrate the clinical efficacy of Hyperiforce in the treatment of depressive states, the study

Discussion

Side effects	Number
Gastrointestinal complaints	6
Fatigue	6
Dizziness	2
Restlessness/nervousness	1
Headache, pain and episodes of sweating	1
Unusual sensation in the ears	1
Influenza	1
Apathy	1
Skin irritation	1
Total in 13 patients	20

Table 3: Incidence of undesired side effects during treatment with Hyperiforce (n = 31)

employed the Hamilton Depression Scale – an objective method for assessing the course of a depression which is recognized by specialists in the field – as the psychometric method. The quantitative analysis of the HAMD is a validated method for assessing the action profile of drugs used to treat depression. Normally, the effect of these drugs is tested using the HAMD-17-item score, which includes the classical symptoms of depression.

The positive results of treatment with Hyperiforce, as documented with this objective method in 74 percent of the patients, and the appreciable improvement in the global assessment of the course of the illness by the care-providing physician, serve as a good basis for ascribing to Hyperiforce a good positive effect on depressive states. In 56% of the patients, a clinically relevant improvement in the depressive state was observable already from the third week of treat-

ment onwards, which, after the fourth week of treatment increased further to 74%.

Undesired adverse reactions caused by MAO inhibition, which are commonly observed with synthetic antidepressive agents, were not noted with Hyperiforce. For the most part, the data on undesired side effects correspond to those that also occur under placebo, such as mild gastrointestinal or nervous disturbances. The symptoms observed can, at least in part, also be interpreted as somatic accompanying conditions within the setting of depressive mood. Laboratory investigations confirmed the high level of tolerability of Hyperiforce.

Conclusion

Overall, Hyperiforce can be assessed as being a very well tolerated effective preparation whose

primary role is in the ambulatory treatment of mild to moderate depressive states. Since approximately nine out of ten patients with depression are treated on an ambulatory basis, an effective, low-risk form of treatment is of considerable practical importance.

References

1. Roth L.: *Hypericum, Hypericin*. Botanik, Inhaltsstoffe, Wirkung. ecomed, Landsberg, 1990.
2. Wichtl M.: *Teedrogen*, Wissenschaftliche Verlagsgesellschaft mbH 1989: Hopfen S. 242, Johanniskraut S. 257, Melissenblätter S. 327.
3. Collegium Internationale Psychiatriae Sclorum: *Internationale Skalen für Psychiatrie*. Belz Test, Weinheim, 1986.
4. Schulz V. et al.: *Johanniskraut als Antidepressivum*. *Der informierte Arzt* 1992; 19: 1687–90.
5. Harrer G. (Herausgeber): *Nervenheilkunde* Nr. 12, 1993
6. König C. et al.: *Der informierte Arzt* 1992: 1691–94.
7. Sparenberg B. et al.: *Untersuchung über antidepressive Wirkstoffe von Johanniskraut*. *Pharm. Ztg. Wiss.*, Nr. 2, 138 (1993).
8. Reuter H. D.: *Hypericum perforatum L.* Kooperation Phytopharmaka 1994.
9. Arieti S., Bemporad J.: *Depression*. Klett-Cotta 1983.
10. Bergener M.: *Depressive Syndrome im Alter*. Georg Thieme Verlag Stuttgart 1989.
11. Becker S.: *Das Johanniskraut (Hypericum perforatum) – Antidepressivum aus der Natur*. *Schweiz. Zschr. Ganzheits-Medizin* 6 (2): 92–97 (1994).

Address for correspondence:

Dr. med. Friedrich H. Degenring
Bioforce AG
CH-9325 Roggwil TG

* Trademark in the USA:
St. John's Wort Complex