

ST. JOHN'S WORT EXTRACT IN THE TREATMENT OF DEPRESSION -AN EFFECTIVE AND WELL-TOLERATED ANTIDEPRESSANT

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Introduction

Depression is diagnosed in about 10% of patients who visit a physician ¹. Most of these patients are treated as out-patients by general practitioners. Among those patients only about 10% suffer from a severe depressive disorder .

Currently ICD-10 ² or DSM-IV ³ criteria are employed in the diagnosis of depressive disorders. The cardinal symptoms are a prolonged state (at least two weeks) of melancholy with hopelessness and loss of perspective; sleep disorders are almost always present.

Contrary to previous assumptions the prognosis for depressive patients is rather unfavourable: recurrence is to be expected for two thirds of first-time depressives . The therapeutic emphasis has, therefore, moved from acute treatment to long-term prophylaxis. It is considered to be appropriate after the acute treatment of a first episode to continue maintenance therapy for four to six months. When the course of the disorder has involved several episodes, prophylaxis against recurrence, in the form of continuous treatment, should be carried out for about one to three years ^{4, 5}.

Drug Therapy

There are several possibilities for medication in the treatment of depressive disorders:

Tricyclic and tetracyclic antidepressants
Selective Serotonin Reuptake Inhibitors
(Selective and reversible or nonselective)
Mono-Amino-Oxidase Inhibitors
St. John's Wort (Hypericum)

Extracts of St. John's wort have proved to be a success for the most frequently occurring mild and

moderate depressive disorders ⁶. Hypericum extracts have been shown to influence the dopamine, norepinephrine and serotonin transmitter systems ⁷.

Effects demonstrated in pharmacological EEG

After 4 weeks of treatment with a hypericum preparation the pharmacological EEG revealed a depression in alpha activity with simultaneous increase in slow theta and more rapid beta waves, which is an indication of more rapid information processing. This neurophysiological profile is similar to that of tricyclic antidepressants ⁸. The sleep EEG revealed a prolongation of the proportion of deep sleep; the slight reduction in the total amount of sleep and the increase in the proportion of consciousness indicates the absence of a sedative potential ⁹. Pharmacological EEG investigations of two hypericum extracts containing differing concentrations of hyperforin (WS 5573, 0.5% hyperforin and WS 5572 containing at least 4% hyperforin) both containing the same amount of hypericin, were compared by Schellenberg et al. ¹⁰ with placebo in healthy subjects. Whereas both extracts produced a measurable and reproducible central effect in comparison to placebo, the effects of the extract with the higher concentration of hyperforin were more noticeable.

Clinical efficacy

The efficacy of hypericum extracts has been confirmed in clinical trials. Linde et al. ¹¹ performed a meta-analysis of 23 randomised clinical trials of hypericum extracts with patients who suffered from mild or moderate depressive disorders according to ICD-10 or DSM-IV criteria. Fifteen of the trials were placebo-controlled, eight compared hypericum with another antidepressant. The evaluation was carried out on the basis of the responder rate and the adverse events. The results revealed a significantly higher responder rate under hypericum in compari-

son to placebo and an equal responder rate in compared to other antidepressants. In the reference-controlled studies side effects occurred very much more rarely than was the case with the other antidepressant (in 19.8% of patients receiving hypericum therapy vs. 52.8% of patients receiving other antidepressants), and side effects were about as frequent as with placebo in the placebo-controlled studies (4.1% in the hypericum groups compared to 4.8% in the placebo groups). The authors concluded that, when account is taken of differing dose levels standardizations and methods of evaluation, these results confirm that phytopharmaceuticals prepared from hypericum extracts are efficacious and well tolerated.

This is further supported by the results of recently published clinical trials. The efficacy and tolerability of a hyperforin-rich, standardized hypericum extract WS 5570 was tested in a randomised, placebo-controlled trial where patients with mild to

moderate depressive episodes were included after a placebo-run-in phase in a double-blind treatment phase. They received a film-coated tablet containing 300 mg hypericum extract 3 times a day or placebo for 42 days. The primary outcome variable for evaluation of efficacy was defined as the change in the Hamilton depression scale (HAMD, 17 items), which is an evaluation done by the psychiatrist. At the same time patients filled out the von Zerssen self-rating depression scale (D-S). Furthermore the physician evaluated the patient according to the first and second item of the clinical global impression scale (CGI), whereas the patient made another self-rating with the global patient assessment scale (GPA). The statistical analysis of 72 patients (35 placebo, 37 hypericum) included in the trial showed a statistically significant advantage for the patients treated with hypericum with respect to the HAMD scale (Figure 1) and all secondary outcome variables (Figures 2 and 3) ¹².

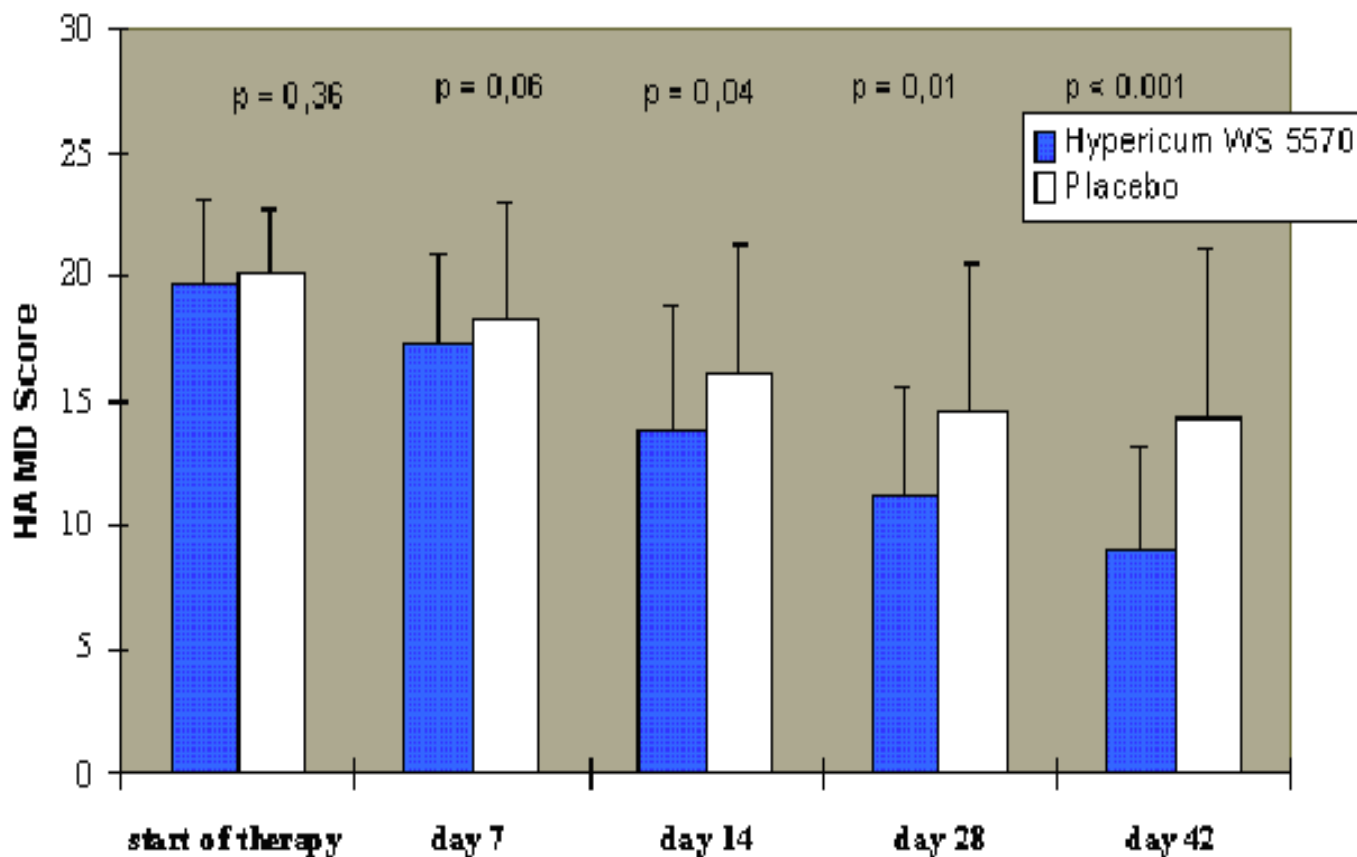


Figure 1. Changes in HAMD total score (means and 95% confidence interval)

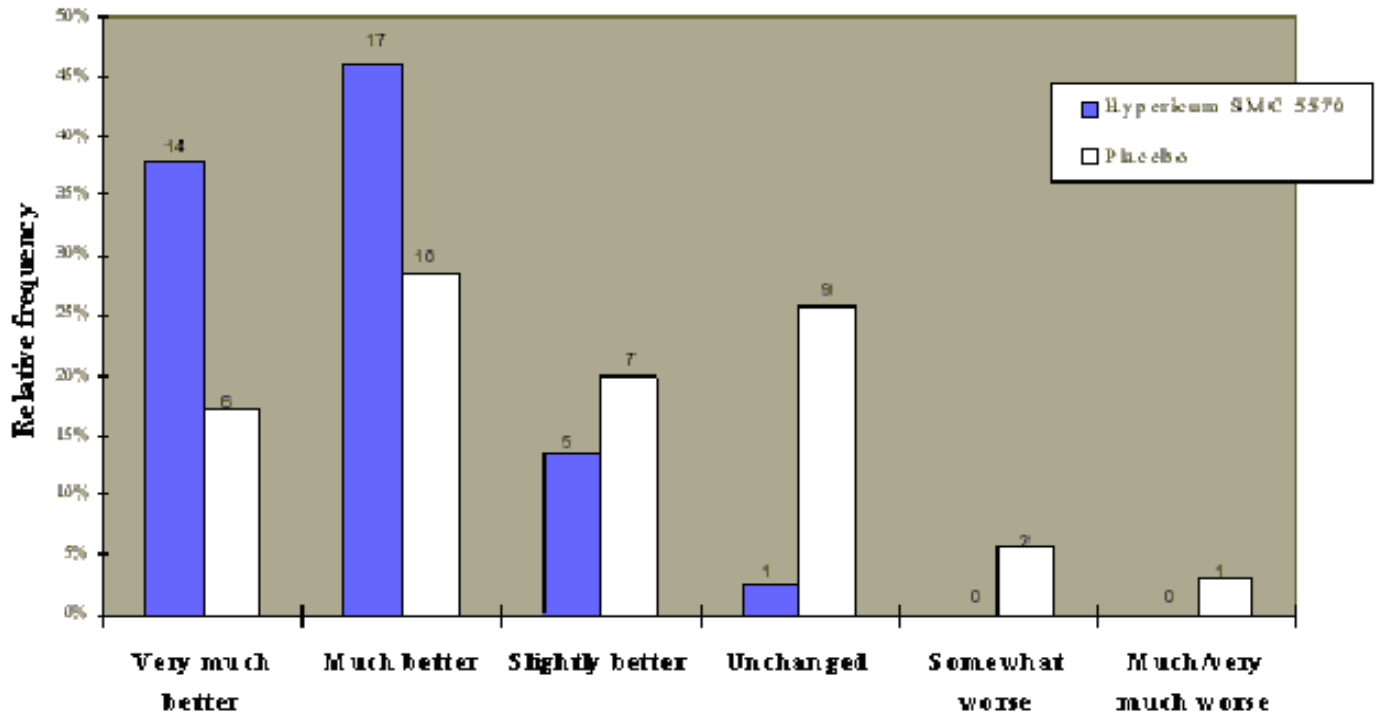


Figure 2. Global evaluation of the change in condition after 6 weeks of treatment (item 2 of the Clinical Global Impression [CGI])

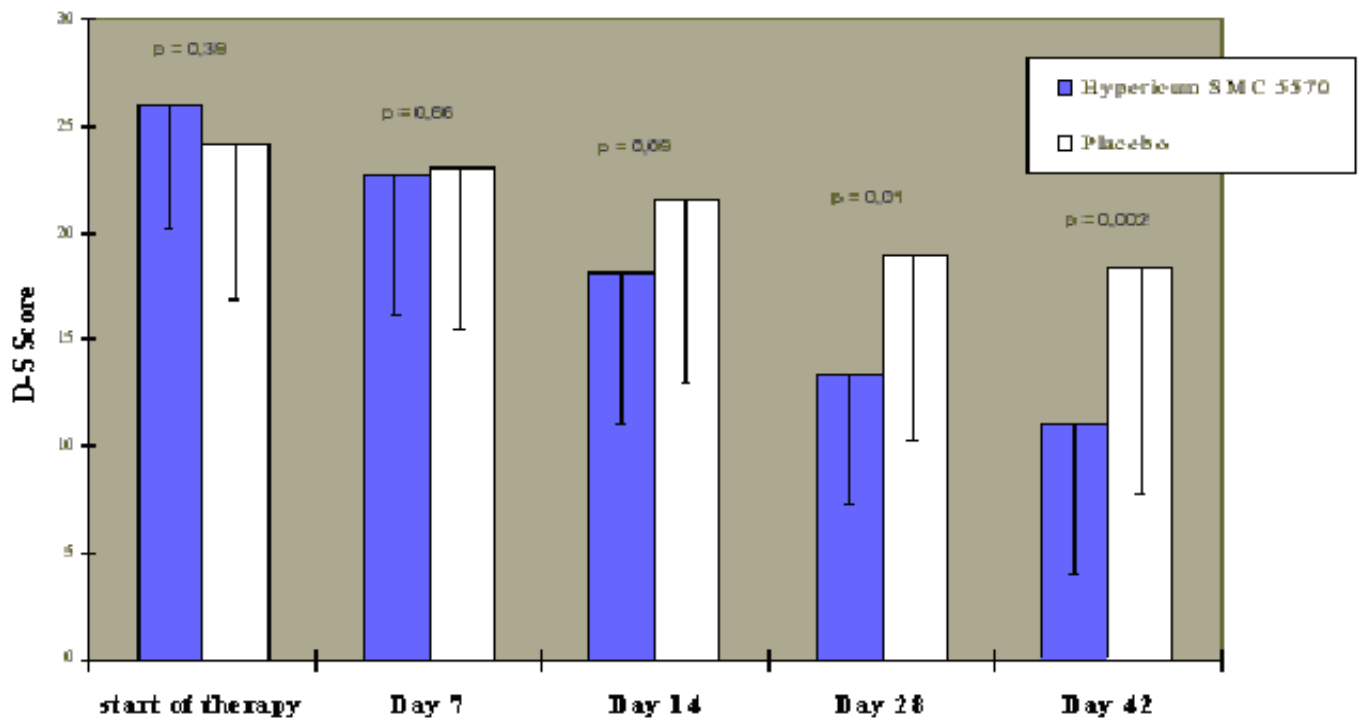


Figure 3. Changes in the total score on the v. Zerssen Depression Scale (mean and standard deviation) during the course of the trial

A further randomised, placebo-controlled study compared St. John's wort extracts containing various concentrations of hyperforin in order to assess the importance of this extract component. A total of 147 patients were treated for 12 weeks with either the special extract WS 5572 (containing at least 4% hyperforin) or extract WS 5573 (hyperforin content 0.5%) or with placebo. There was an appreciable and statistically significant improvement on the

Hamilton Depression Scale from 20.9 to 10.6 (mean) for the WS 5572 group while the extract 0.5% group only exhibited a tendentially better effect than placebo which was not statistically significant. The results of the secondary outcome variables D-S and CGI behaved in a similar manner. The results of this study confirm the clinical relevance of hyperforin¹³. (see Figure 4)

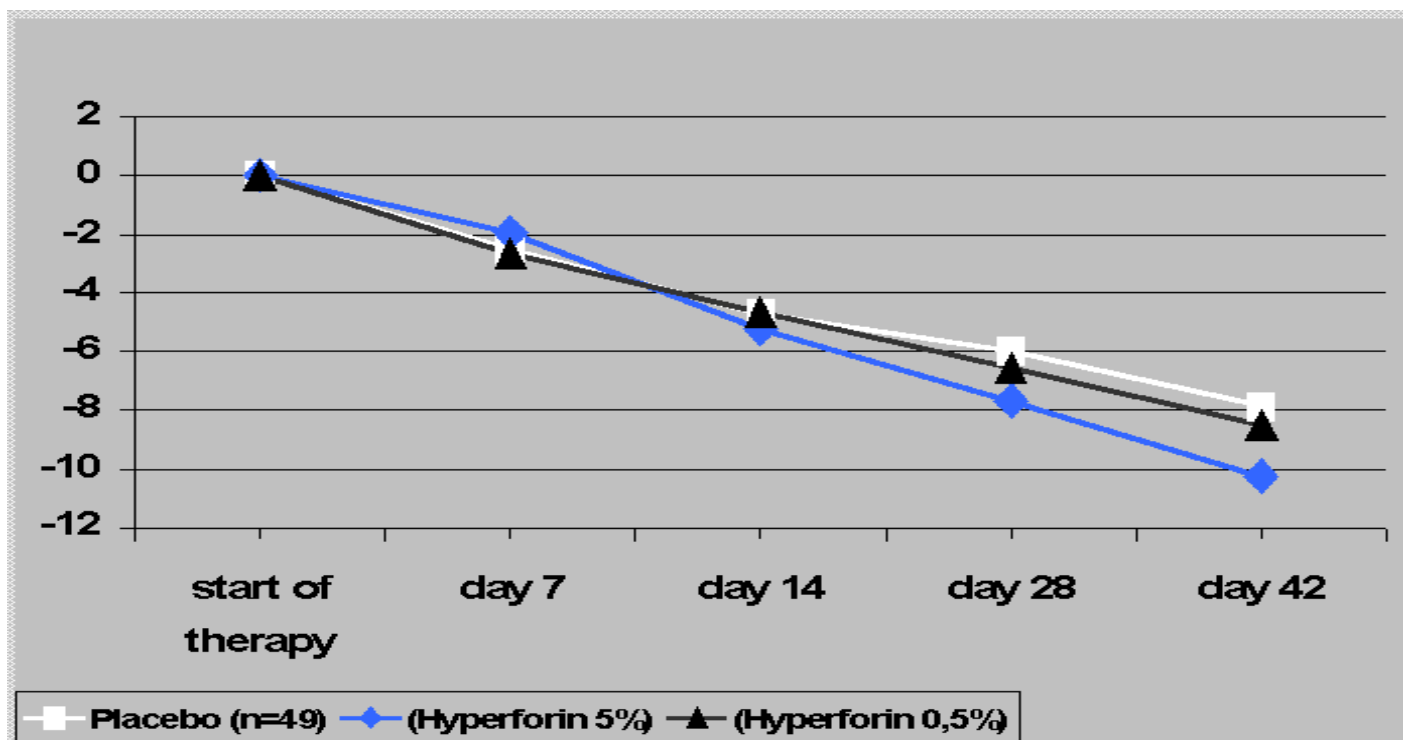


Figure 4. Changes in HAMD total score (differences vs. baseline)

Safety

The antagonistic effect of tricyclic antidepressants on cholinergic receptors explains the not uncommon anticholinergic side effects, such as dry mouth, accommodation disturbances, constipation, micturition disturbances and cardiovascular disturbances with depression of blood pressure, tachycardia and delayed conduction. It is the cardiovascular side effects that are sometimes a lethal danger on overdose with suicidal intent.

The sedation that also occurs with tri- and tetracyclic antidepressants is indeed a desired effect when the patient is agitated, but in many patients it leads to

limitations in daily life, in particular by reducing the ability to drive a car.

Adverse effects of the SSRIs are nausea, vomiting, sleep problems and disturbances of sexual function as well as an anorectic effect. Cardiovascular effects are very rare and there is no sedation. A very severe side effect which occurs very rarely - especially if the SSRI is combined with other drugs - is the so-called serotonin syndrome.

St. John's wort preparations have a favourable side effect profile. Gastro-intestinal complaints, allergic

reactions, fatigue or restlessness can occur on rare occasions. In clinical trials the incidence of adverse events was only slightly higher for the group re-

ceiving the test preparation than it was for the placebo group ¹⁴. (Table 1)

Table 1: Side effects of St. John's wort in clinical trials

	Placebo-controlled trials		Reference-controlled trials	
Patients reporting side effects	Hypericum group:	4.1%	Hypericum group:	19.8%
	Placebo group	4.8%	Placebo group	35.9%
Drop-outs reporting side effects	Hypericum group:	0.4%	Hypericum group:	0.8%
	Placebo group	1.6%	Placebo group	3.0%

Table 2: Adverse events in clinical trials with St. John's wort

	Hypericum	Placebo
Schellenberg et al. 1998	n=48 24 probands with WS 5573 and 24 probands with WS 5572	n=24
	1 x itching* 1 x intermenstrual bleeding 2 x headache 1 x herpes simplex 1 x influenza-like symptoms	1 x itching 1 x anaemia 1 x influenza-like symptoms 2 x headache
Kalb et al. 1998	n=37	n=35
	1 x bronchitis 1 x sinusitis 1 x influenza-like symptoms	1 x bronchitis 1 x gastroenteritis

* possible relationship to study drug (known side effect)

Conclusions for clinical practice

Extracts of St. John's wort are among the accepted possibilities for treatment of mild to moderate depressive disorders. It has been possible to demonstrate that the mechanism of action involves inhibition and influence on the serotonin, noradrenaline and dopamine transmitter systems. The hyperforin component plays an important role here. Controlled clinical trials have demonstrated that it is effi-

cient and well-tolerated. It is particularly this favourable side effect profile, in comparison to other antidepressants, that gives the patient an improved quality of life and retention of occupational performance, which leads in turn to an increase in compliance in the treatment of mild to moderate depressive disorders.

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