Introduction

Depression is one of the most common illnesses and at the same time one of the most frequently unrecognised and wrongly treated disorders. Following the wide-ranging European study of 78,463 adults, it is assumed that 5–10% of the population suffers from depression, only about 1/3 are treated with any medication at all, only of which are effective antidepressants (Le Pine, 1997).

According to a WHO forecast, in 2020 depressive disorders will occupy second place in the worldwide sickness statistics after cardiovascular diseases. It has been proven that the number of days lost through sickness and public health costs will continue to rise. The impairment of health caused by depression – in terms of reduction in quality of life – is comparable to that of other chronic clinical conditions, such as hypertension, diabetes and diseases of the musculo-skeletal system (Lecrubier, 2001). This makes depression the second most expensive disorder after cardiovascular diseases.

Another consideration is that after a first severe episode the risk of relapse is about 50–75%, meaning that depression has to be rated as a potentially chronic illness. Apart from episodes of depression, the various anxiety disorders are common, burdensome illnesses. Some 25% of GP patients suffer from one of the disorders classified under ICD-10 (depressive disorders, generalised anxiety disorder, panic with or without agoraphobia, social and specific phobia). The prevalence of comorbidity of several concomitant anxiety disorders and anxiety disorders with depression is high (Sartorius, 1996). Different figures are quoted for different groups of patients, but as a rule in over 50% of cases anxiety disorders accompany major depression (Melartin, 2002). Comorbid anxiety and depressive disorders are associated with the major impairments in the work process (Lim, 2000). The incidence of depressive disorders with comorbid generalised anxiety disorder is rated as being particularly high.

If the treatment of depressive disorders is inadequate, as stated above, the same applies to generalised anxiety disorder as well (Wittchen, 2002) and consequently even more to comorbid anxiety disorder and depressive disorder.

Treating depression comorbid with anxiety – results of an open, practice-oriented study with St John’s wort WS® 5572 and valerian extract in high doses

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Summary

Depressive disorders in comorbidity with anxiety disorders represent an frequently diagnostic and therapeutic problem. The studies quoted here prove that the symptoms associated with anxiety that severely afflict patients can be clearly improved more quickly with a combination therapy of St John’s wort extract and valerian extract than with St John’s wort monotherapy. The combination therapy was well tolerated, no significant side-effects occurred. Further studies are necessary to compare the combination treatment with other forms of therapy (serotonin- and noradrenalin re-uptake inhibitors).

Key words: Anxiety, depression, treatment, St John’s wort extract, valerian extract
There are several conceivable reasons why depressive disorders and anxiety disorders are medically undertreated:

- Organic symptoms are overrated in diagnostics and therapy, mental symptoms too little analyzed.
- Depression is ‘psychologised’, doctors muster a lot of empathy without taking the next step of therapy with medication above and beyond the psychagogic discussion.
- The comorbidity of several concomitant mental disorders (e.g. depression and addiction) or ‘organic’ disorders with mental disorders (e.g. myocardial infarction and depression) is not recognised.
- The ‘additional’ therapy with anxiolytic and antidepressant medication is regarded as too cost-intensive.
- The side-effects of the drugs are deemed harmful.

With specific regard to the last aspect, a ‘depression manual’ that was recently published advised attaching more importance to side-effects in addition to efficacy, and therefore to start off treating mild to moderately severe depression with serotonin re-uptake inhibitors or St John’s wort extracts, and to continue with the treatment on a long-term basis if it prove effective.

There is sufficient proof of the efficacy of treating mild to moderately severe depressive disorders with St John’s wort extract. Euvegal® Balance contains 500 mg of the extract.  

Study design and participants
The study’s target group were patients suffering from mild to moderately severe depression. This involved collecting 2,462 case report forms (out of 2,500 patients originally) from 521 doctors (of general medicine and specialists) and evaluating them in the period from November 2001 to January 2002.

Three doctor’s visits were evaluated: before treatment, after 3 weeks (on average 20.25 days) and after 6 weeks (on average 46.8 days). The average age of the patients studied was 49.9; 71.7% of them were women and 28.3% men. In 61.4% of the cases it was the patient’s first manifestation, in 33.5% recurring depression and 5.1% chronic depression. Non-psychiatric concomitant illnesses were documented in the case of 55% of patients: high blood pressure (24%), coronary heart disease (7.8%), obesity (10.4%), diabetes mellitus (6.5%) and gastritis (8.3%).

A catalogue of 16 symptoms in total was rated during each doctor’s visit (see Table 1) broken down into 5 grades of severity (not extant – 0, mild – 1, moderate – 2, severe – 3, very severe – 4). The symptoms were listed on a depression sheet analogous with the ICD-10 list of symptoms plus a focal question from the HAMA (Hamilton anxiety scale). The items anxiety/nervousness and tension/dysphoria in particular were accepted as main symptoms of generalized anxiety disorder.

Study medication
The doctors treating the patients were at liberty to opt for the combination of 500 mg valerian extract (1×1 Euvegal® Balance tablet) and 600 mg/day St John’s wort (1×1 Neuroplant® tablet) (Group 1+1) or 1,000 mg valerian extract (2×1 Euvegal® Balance tablet) and 600 mg/day St John’s wort (1×1 Neuroplant® tablet) (Group 2+1).

Drugs: Neuroplant® contains a hydroalcoholic extract from Herba hyperici (extracting agent: ethanol 60% (m/m); drug-extract-ratio 2.5 to 5:1) with standardized contents of 3% to 6% hyperforin and 0.1% to 0.3% hypericin according to high-performance liquid chromatography. Each tablet contains 600 mg of the extract. Euvegal® Balance contains a hydroalcoholic extract from valerian roots (extracting agent: ethanol 60% (m/m); drug-extract-ratio 3 to 6:1). Each tablet contains 500 mg of the extract.

**Methodology**

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Results

Course of symptoms

Table 1 shows that not only did the ‘core symptoms’ of depression recede significantly, but also the main symptoms of anxiety disorder (sleep disorders, tension/dysphoria and anxiety/nervousness) quickly receded well. It is further noticeable that precisely these symptoms represented the most severe impairment for the patients at the beginning of their treatment (over half the patients’ degree of severity was at least ‘moderate’, Fig. 3 and 4).

The doctor’s decision on treatment

The severity of the illness at the start of treatment (rated according to CGI Item 2) was moderate to severe in 78% with the single dose (1+1) and moderate to severe in 87% with the standard dose (2+1). The type of illness was recorded as recurrent in 29% with the low dosage and as recurrent in 36% with the high dosage. It follows from this that the attending doctors treated the more severe and recurring disorders with higher doses. In contrast, the improvement at the end of the study was similar in the two groups: still moderate to severe disorder in 9% of the cases with low dosage therapy, in 10% with high dosage therapy. The conclusion from this is that a higher dosage can result in greater improvement (Fig. 1 and 2).

The doctor described the onset of the effect as follows: in 10.4% of the patients by Day 5, in 39.6% by Day 10, in 41.7% after Day 10 and in 8.3% with uncertain effect. A perceptible onset of effect was reported in 50.5% of the low-dose patients and in 49.9% of the high-dose patients by Day 10 of treatment.

Global Rating by doctors and patients

The doctors rated efficacy as ‘very good’ or ‘good’ in 87.2% of the cases, and as ‘poor’ in 1.6%. Tolerability was assessed as ‘very good’ or ‘good’ in 96.8% of the cases (Table 2).

In the comparison between the first and third examination, overall 83.2% of the patients in the treatment groups rated the efficacy as markedly or very markedly improved, 0.2% referred deterioration (Table 3).

Changes in dose, Differences between the sexes

Twenty-one changes in dose were indicated between the 1st and the 2nd doctor’s visit, and the same number between the 2nd and 3rd visit, the differences within Groups 2+1 and 1+1 not being significant.

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Fig. 1. Results. Severity of illness at the start of treatment (rates according to CGI: Item 2 mean: 2.1.).

Fig. 2. Course of treatment. Severity of illness at contact 3 (46 days of treatment).

Fig. 3. 600 mg Hypericum extract SW® 5572 + 1,000 mg/d Valerian extract improves the symptom sleep disorders more quickly than WS® 5572 alone (data from Rychlik, 2001).

Fig. 4. 600 mg Hypericum extract WS® 5572 + 1,000 mg/d Valerian extract improve the symptom sleep tension/dysphoria more quickly than hypericum alone (data from Rychlik, 2001).

The outcome of testing distributions (chi-square test, all doses) in relation to sex was a p-value of 0.322 for changes in degree of severity and 0.748 for onset of effect, i.e. there was no evidence of any differences.

**Discussion**

In summary, the following results can be derived from evaluating the 2,462 case report forms of 500 patients: Treatment with St John’s wort extract and two doses of valerian extract is well tolerated (side-effects on level...
Drowsiness was not increased, even with high-dosage valerian therapy. A multicentre practice research study (Rychlik, 2001) of 2,166 patients with St John’s wort special extract WS® 5572 (Neuroplant®) showed also a clinically relevant improvement in the depressive symptoms of 83.7% of the patients on a daily dose of 600 mg and of 86.9% of the patients on a daily dose of 1,200 mg. Doctors described tolerability as good or very good in 99% of the cases. We find that both forms of treatment resulted in a highly significant improvement up until Day 46 of treatment. At the end of the observation period, results (frequency and degree of expression of the symptoms) were comparable. The doctors were at liberty to choose the dose. At the beginning, ‘severe’ and ‘recurring’ courses of illnesses were more frequently treated with high doses, i.e. patients were assessed as manifestly more seriously ill. This indicates that a higher dose can bring about greater improvement. The onset of effect on the core symptoms of depression (depressed mood, cheerlessness, exhaustion) through additional valerian therapy is comparable in terms of time with St John’s wort monotherapy (2–3 weeks) (Laakmann, 1998). The crucial benefit of additional valerian treatment is the evident, quicker improvement in anxiety symptoms (tension/dysphoria, anxiety/nervousness, sleep disorders, see Fig. 3 and 4). Treating these symptoms as part of depression therapy acquires particular importance insofar as sleep disorders have been proven to comprise a key factor in restricted quality of life especially in depression (Katz and Horney, 2002). In the long term there should be a greater focus on the complex therapy of the symptoms of anxiety and depression (the concept of ‘anxious depression’ Malhi et al. 2002). It was thus observed in a series of studies that the original figure of 39% concomitant depressive disorders with generalized anxiety disorder rose to 65% after four years and to 74% after 8 years (Bruce, 2001).

We come to the conclusion, that the combination of the two preparations as the basic therapy for mild to moderate depression comorbid with anxiety is effective. In cases of severe depression comorbid with anxiety, treatment should be done with serotonin re-uptake inhibitors (including paroxetine) (Wagstaff, 2002) or serotonin/noradrenalin re-uptake inhibitors (venlafaxine) (Sramek, 2002; Spalletta, 2002). From economic viewpoints, additional treatment with Euvegal® Balance 500 (€ 0.48/day) is also recommended.

### References


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