Eur Arch Psychiatry Clin Neurosci (2008) 258:59–63 DOI 10.1007/s00406-007-0779-2

ORIGINAL PAPER

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# Efficacy of St. John's wort extract WS® 5570 in acute treatment of mild depression

## A reanalysis of data from controlled clinical trials

Received: 6 July 2007 / Accepted: 16 October 2007 / Published online: 14 December 2007

**Abstract** Based on the original data from two double-blind, randomized, placebo-controlled clinical trials and the acute phase of a long-term study that investigated the antidepressant efficacy of St. John's wort extract WS® 5570, we present a re-analysis of a subset of patients suffering from an acute episode of mild depression according to DSM criteria. Out of a total of more than 1,200 patients included into these trials 217 had a pre-treatment total score ≤20 points on the 17-item Hamilton Rating Scale for Depression (HAMD) and were eligible for our re-analysis. They received 600, 900, or 1,200 mg/day WS® 5570 or placebo for 6 weeks. In patients treated with WS® 5570 the HAMD total score decreased by averages of 10.8 (600 mg/day), 9.6 (900 mg/day), and 10.7 (1,200 mg/day) points between the pre-treatment baseline value and the end of acute treatment, compared to 6.8 points in the placebo group ($p < 0.01$ for all pairwise comparisons of WS® 5570 against placebo). This corresponded to average relative decreases by 49–57% for WS® 5570 and by 36% for placebo. The rates of responders (i.e., patients with a HAMD total score decrease ≥50%) were 73%, 64%, 71%, and 37% for WS® 5570 600 mg/day, 900 mg/day and 1,200 mg/day, and placebo, respectively. At the end of acute treatment 57% of the patients treated with WS® 5570 600 mg/day, 33% in the 900 mg/day group and 62% in the 1,200 mg/day group, as well as 25% in the placebo group were in remission (HAMD total score ≤7 points). The analysis shows that St. John's wort extract WS® 5570 has a meaningful beneficial effect during acute treatment of patients suffering from mild depression and leads to a substantial increase in the probability of remission.

**Key words** St. John's wort · mild depression · acute treatment · efficacy · meta-analysis

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## Introduction

With a point prevalence of 11% estimated in a survey based on a representative sample of 412 primary care practices with a total of 15,081 unselected patients in Germany [20] depression is a very common, but also seriously undertreated disease: According to the first pan-European survey conducted in the European Union only 25% of the patients in need were actually receiving antidepressants [14]. This may be particularly true in milder cases where symptoms may remain unnoticed, or the patient does not consult a physician.

**Table 1** Characteristics of primary trials

| Study | I | II | III |
|---|---|---|---|
| Publication | Lecrubier et al. [13] | Kasper et al. [8], Dienel et al. [2] | Kasper et al. [6] |
| Treatment (acute phase) | 3 × 300 mg/day WS® 5570 or Placebo, 6 weeks | 3 × 300 mg/day WS® 5570, 6 weeks | 1 × 600 or 2 × 600 mg/day WS® 5570 or Placebo, 6 weeks |
| No of patients with mild depression | WS® 5570: 36, Placebo: 36 | WS® 5570: 42 | WS® 5570 600 mg/day: 37, WS® 5570 1,200 mg/day: 42, Placebo: 24 |
| Specific patient selection criteria | Mild or moderate depression (DSM-IV 296.21, 296.22, 296.31 or 296.32); HAMD total score 18–24 points; HAMD item 'Depressed mood' ≥2 points | Recurrent, mild or moderate depression (ICD-10 F33.0 or F33.1, and DSM-IV 296.31 or 296.32); HAMD total score ≥20 points; HAMD item 'Depressed mood' ≥2 points | Mild or moderate depression (DSM-IV 296.21, 296.22, 296.31 or 296.32); HAMD total score ≥18 points; HAMD item 'Depressed mood' ≥2 points |

The antidepressant efficacy of extracts from St. John's wort (*Hypericum perforatum*) has been demonstrated in controlled clinical trials, in out-patients suffering from an acute episode of depression of any severity [15, 18]. Such trials have been performed in patients with mild or moderate, or with moderate or severe intensity of disease. However, none of the trials published to date has investigated the efficacy of St. John's wort extract specifically in mild depression. From a clinical point of view this is quite regrettable as a major part of the total amount of antidepressant drugs is prescribed by primary care physicians among whose patients the milder forms of depression are predominant. It is sometimes argued that particularly in mild, often reactive depression the therapeutic alliance between the patient and the physician can provide enough reassurance to accelerate the natural course of the disease and to achieve remission within an acceptable period of time, so that antidepressant drug treatment may be unnecessary. Proponents of such a position argue that the placebo conditions of clinical trials in depression often show substantial responder and remission rates [9, 21]. We therefore undertook to investigate the efficacy of WS® 5570, a well-defined hydroalcoholic St. John's wort extract, in patients suffering from an acute, mild episode of depression, based on data from controlled clinical trials.

## Methods

We present a re-analysis of the pooled original data from two randomized, placebo-controlled clinical trials and the acute phase of a long-term study investigating the antidepressant efficacy and tolerability of St. John's wort extract WS® 5570[1] in primary care settings. Study I was performed in France, study II in Germany and Sweden, and study III in Germany. The principles of Good Clinical Practice and the Declaration of Helsinki were adhered to in all trials included in our analysis. The main characteristics of the studies are presented in Table 1.

The studies were performed in a total of more than 1,200 male and female (full analysis set, FAS), adult out-patients who suffered from a single or recurrent acute episode of mild or moderate depression according to DSM-IV diagnostic criteria. All primary trials included an acute treatment phase of 6 weeks' duration. In studies I and III the acute phase was double-blind, randomized and placebo-controlled. Study II was designed to investigate relapse prevention after recovery from the acute episode of depression; the acute phase was single-blind and uncontrolled, and treatment responders were randomized to double-blind continuation treatment with WS® 5570 or placebo after completing the acute phase.

WS® 5570 is a methanolic extract from Herba hyperici (drug-to-extract ratio 3–7:1) with defined contents of 3–6% hyperforin and 0.12–0.28% hypericin. Coated tablets containing 300 or 600 mg of the extract were used. In the acute phase of studies I and III an identically matched placebo was available (the success of blinding was evaluated by examining the drugs before distribution).

At each visit the patients' severity of depression was assessed by means of the 17-item version of the Hamilton Rating Scale for Depression (HAMD) [3]. The primary endpoint of studies I and III was the absolute change of the HAMD total score between the beginning and end of acute treatment whereas study II investigated the time until relapse during continuation treatment. Safety was assessed during each visit primarily by questioning the patients for adverse events (without asking for specific events). Patient inclusion and all clinical assessments were performed by the investigators who had participated in a rater training before the beginning of patient inclusion to assure uniform diagnostic and rating standards.

All FAS eligible patients with a pre-treatment HAMD total score ≤20 points were included into our re-analysis. A HAMD total score between the trials' lower limits for inclusion and 20 points was accepted as an indicator of mild depression [1]. We assessed HAMD total score change between the pre-treatment baseline value and the end of acute treatment at week 6 (in patients terminating acute treatment prematurely the last available post-baseline value was carried forward). In addition to absolute and relative change, analyses of response and remission were performed. Response was defined as a HAMD total score decrease by at least 50% of the baseline value. Remission was assumed in case of a HAMD total score ≤7 points at the end of the analyzed treatment period [16, 17].

## Results

The re-analysis is based on a total of 217 patients with mild depression (for details see Table 1).

Table 2 shows the treatment groups' average HAMD total scores at baseline as well as average change. It demonstrates that the average baseline impairment in all groups was comparable. During the 6 weeks of acute treatment the HAMD total score in patients treated with WS® 5570 decreased by averages of between 9.6 and 10.8 points compared to 6.8 points

[1]Manufacturer: Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany.

**Table 2** Baseline HAMD total score and absolute change versus baseline (mean ± SD, median, range)

| Treatment | Baseline | Change[a] |
|---|---|---|
| Placebo ($n$ = 60) | 19.2 ± 0.8 | −6.8 ± 6.4 |
| | 19.0 | −6.5 |
| | 18–20 | −20 to 7 |
| WS® 5570 600 mg/day ($n$ = 37) | 19.0 ± 0.8 | −10.8 ± 5.3 |
| | 19.0 | −12.0 |
| | 17–20 | −19 to 2 |
| WS® 5570 900 mg/day ($n$ = 78) | 19.7 ± 0.5 | −9.6 ± 5.5 |
| | 20.0 | −11.0 |
| | 18–20 | −20 to 6 |
| WS® 5570 1,200 mg/day ($n$ = 42) | 18.7 ± 1.2 | −10.7 ± 5.6 |
| | 19.0 | −12.5 |
| | 13–20 | −19 to 1 |

[a]Negative values denote HAMD total score decrease

**Table 3** $p$-Values for treatment group comparisons, WS® 5570 versus placebo (number of patients as in Table 2)

| | HAMD total score change (absolute)[a] | Responder rate[b] | Remitter rate[b] |
|---|---|---|---|
| WS® 5570 600 mg vs. placebo | <0.01 | <0.01 | <0.01 |
| WS® 5570 900 mg vs. placebo | <0.01 | <0.01 | 0.20 |
| WS® 5570 1,200 mg vs. placebo | <0.01 | <0.01 | <0.01 |

[a]Two-sided $t$-test
[b]Two-sided $\chi^2$-test

in the placebo group. In pairwise comparisons of all WS® 5570 doses versus placebo the associated two-sided $p$-values were always smaller than 0.01 (Table 3) while the differences between WS® 5570 600 mg/day, 900 mg/day, and 1,200 mg/day were negligible in this subset of mildly depressed patients (WS® 5570 600 mg/day versus 900 mg/day: $p$ = 0.28; 600 mg/day versus 1,200 mg/day: $p$ = 0.96; 900 mg/day versus 1,200 mg/day: $p$ = 0.29; two-sided).

The corresponding relative HAMD total score changes between the beginning and end of acute treatment are shown in Fig. 1. On average, the scores decreased by 57% ± 29% in the WS® 5570 1,200 mg/day group, by 49% ± 27% in the WS® 5570 900 mg/day group, by 56% ± 27% in the WS® 5570 600 mg/day group, and by 36% ± 33% in the placebo group (mean ± SD).

Figure 2 shows the percentages of patients whose HAMD total score decreased by at least 50% of the pre-treatment value ('responders') as well as of those with a HAMD total score ≤7 points ('remitters'). For the pooled data of all subsets treated with WS® 5570, the ratio of the responder rates for the herbal extract and placebo was 1.9:1. In pairwise comparisons the treatment group differences between the responder rates of the three doses of WS® 5570 and placebo were always substantial (Table 3) whereas only negligible differences were observed between the various doses of WS® 5570 ($p \geq 0.4$).

Regarding remission rates, a ratio of 1.9:1 in favor of WS® 5570 was observed as well. For the pairwise treatment group comparisons Table 3 again shows substantial differences between WS® 5570 600 mg/day and 1,200 mg/day on one hand and placebo on the other.

After completing the 6-week acute treatment phase patients of study III who were classified as responders (according to the criteria above) were offered continuation of the trial in an optional 4-month, double-blind maintenance phase during which they received the same treatment as before. Among the patients with initially mild depression 31 treated with WS® 5570 and eight patients randomized to placebo continued into maintenance treatment. When leaving the trial at the end of continuation treatment one patient treated with WS® 5570 (3.2%) and three patients in the placebo group (37.5%) showed a deteri-

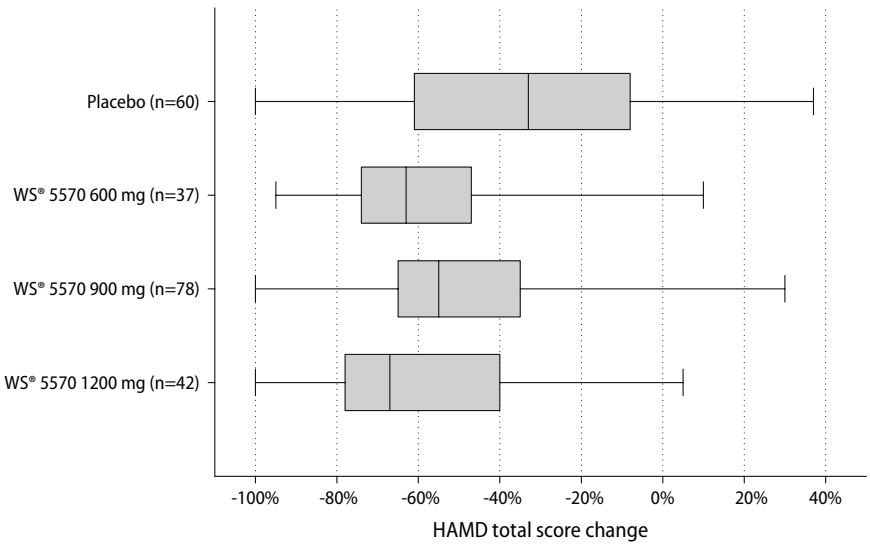


**Fig. 1** Relative HAMD total score change (in % of baseline value; median, quartiles, minimum, maximum)

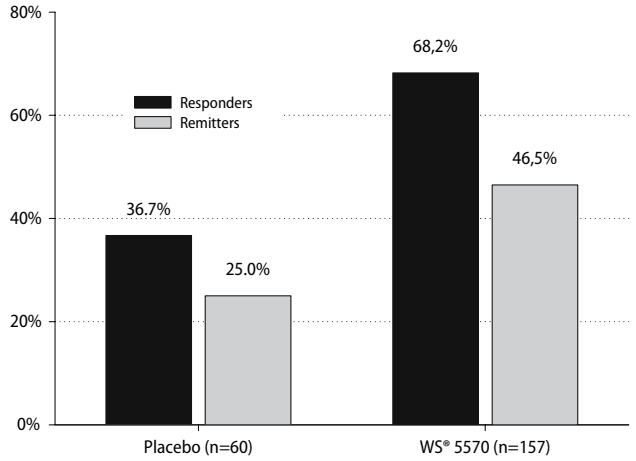


**Fig. 2** Percent of responders and remitters

oration of the HAMD total score by at least five points compared to the end of acute treatment.

## Discussion

In patients suffering from mild depression the sometimes disturbing side effects of antidepressant drugs are often perceived to outweigh their therapeutic effect which some clinicians perceive to be questionable in this population. This may be one of the reasons why depression is still a seriously undertreated condition despite the apparent adverse consequences on social functioning and quality of life [4, 12].

Our analysis suggests that in case of St. John's wort extract WS® 5570 the reluctance to use antidepressant drug treatment in patients who are 'only' mildly depressed is unfounded. Compared to placebo the reduction of depression severity as measured by the HAMD was substantially more pronounced with any of the doses of WS® 5570 investigated. Furthermore, in contrast to placebo to which 37% of the patients responded, more than two thirds of the patients treated with WS® 5570 were responders, and almost half of the depressed patients were in remission at the end of acute treatment compared to only 25% in the placebo group. Many recent clinical trials in depression have been plagued by a large and often unpredictable response to placebo (e.g. [15]) that is favored by the special conditions of a clinical trial which include the patients' as well as the physicians' expectations, more frequent contacts and more extensive examinations than one would expect under daily practice conditions as well as numerous other factors constituting a supportive basic psychotherapy as a 'side effect' of the trial procedures. It is all the more remarkable that the chance of a favorable treatment response to 6 weeks' acute treatment or even remission was on average approximately twice as high when WS® 5570 was administered.

During 4 months of maintenance treatment all patients but one who received WS® 5570 in the extension to study III showed a continued favorable response whereas almost half of those with a beneficial placebo response during acute treatment relapsed. This result is supported by the trial reported by Kasper and colleagues [2, 8] during which acute treatment responders were randomized to double-blind continuation treatment with 900 mg/day WS® 5570 or placebo. Patients treated with St. John's wort extract showed a substantially lower relapse rate than those in the placebo group. The findings suggest that a continuation of WS® 5570 administration beyond the end of the acute depressive episode at the full therapeutic dose is quite likely to support sustained response or remission, whereas continuation treatment with placebo was associated with a substantial risk of relapse.

The observation that the difference in HAMD total score reduction between WS® 5570 900 mg/day and placebo was somewhat smaller (albeit nevertheless highly significant) than in case of WS® 5570 600 mg/day or 1,200 mg/day cannot be fully explained in this analysis due to confounding between the primary trials and the doses administered (the 900 mg/day dose was only investigated in studies I and II, while the 600 and 1,200 mg/day doses were only tested in study III). Lecrubier et al. [13] argue that the rather moderate treatment effect of WS® 5570 in their trial's subset of more mildly depressed patients had to be interpreted in the context of a large and essentially unpredictable response to placebo.

The selection of primary trials for our reanalysis was based on comparability regarding the Hypericum extract administered, patient selection criteria, study schedule, and outcome measures. Two of the three trials from a recent meta-analysis [7] could not be considered here because they included only a small number of patients with mild depression or used different Hypericum extracts [5, 11]. On the other hand, we chose to include study II [2, 8] despite its lack of placebo control during acute treatment (in this trial the patients were randomized to WS® 5570 or placebo only after completing the acute phase) because it contributed a comparatively large number of mildly depressed patients, and because it featured the same Hypericum extract and dose and a very similar acute phase schedule as study I [13] so that we felt that an indirect comparison to the latter trial's placebo control group was justified.

In conclusion, our re-analysis of data from clinical trials shows that St. John's wort extract WS® 5570 has a meaningful beneficial effect during acute treatment of patients suffering from mild depression and leads to a substantial increase in the probability of remission within 6 weeks of treatment. The herbal extract was effective in the entire dose range between 600 and 1,200 mg. However, the data also show that in many mildly depressed patients a once daily dose of 600 mg

WS® 5570 was sufficient to achieve adequate symptom relief.

Considering the very low risk of side effects of St. John's wort extract [10, 19] the drug can be a valuable option for accelerating the process of recovery in the mildly depressed.

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