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Comments on:

Hypericum Depression Trial Study Group (2002) Effect of *Hypericum perforatum* (St. John's Wort) in Major Depressive Disorder. A Randomized Controlled Trial. JAMA 287: 1807-14.

This original paper, which was published on 10th April 2002 in the *Journal of the American Medical Association (JAMA)*, reports the results of an American clinical trial investigating the antidepressant efficacy of a Hypericum extract compared to the synthetic Standard preparation sertraline versus placebo. The study, which received public funding (approx. 4 million US\$), ended in a fiasco: The main outcome measure, i.e. the change in the Hamilton Depression Score (HAMD), showed no significant difference between the 3 treatment groups. For this reason, the expensive study was almost worthless.

The authors consequently attempted to provide a justification, particularly for the lack of evidence for the efficacy of the FDA approved antidepressant sertraline. In this quandary, the authors pointed out that the reduction in HAMD score at least showed a somewhat more favourable "trend" for sertraline than for placebo or Hypericum, and, in addition, that a statistically significant difference in favour of sertraline was found for a secondary outcome measure (CGI-I score).

This attempted justification does not take further pertinent data into account, however. On page 1811 of the publication under the subheading: *Assessment of Blindness to Treatment* is stated: *Correct guesses for clinicians totalled 66 % for sertraline, 29 % for hypericum, and 36 % for placebo (p = 0.001)*. In other words: the physicians knew the group allocations for 52 of the 79 patients who were treated with sertraline! However, alone the FDA-approved antidepressant would have been expected to be effective by the study investigating physicians. The difference of approx. 2 HAMD scores in Figure 2 of the paper can thus be explained as the result of a **clear unblinding effect**. The positive correlation between efficacy and the Proportion of unblinded side effects was already established and published by Kirsch and Sapirstein in 1998; Schulz called attention to the consequences for Hypericum as early as three years ago (Schulz 1999).

If during antidepressant pharmacotherapy, psychodynamic factors are more important for efficacy than pharmacodynamic effects, the selection of the preparation should be directed primarily towards tolerability and price, which would be very favourable for Hypericum extracts (Schulz 2002). Since 1998, this has provided sufficient grounds for Professional circles to argue about the phenomenon in numerous publications and podium discussions. It thus appears even stranger that **the unblinding ratio for sertraline reported by the investigating physicians as 66 % of the patients** is not discussed in a single sentence in the final "Comment". Moreover, the third sentence of the text under *Assessment of Blindness to Treatment* appears to be a little misleading. Here, it is pointed out that, **with regard to the patients**, the Proportion of unblinded cases had no effect on the results. This was not actually possible in the study because the main outcome measures HAMD and CGI are not self-assessment scales but observer assessment scales, so that the evaluation of efficacy was not performed by the patients at all but only by the physicians. The

authors make no comment on the comparison of efficacy between those cases which were recognised and those which were not recognised by the physicians, possibly because after 8 weeks, only 27 unrecognised cases remained.

Another passage also appears to be misleading. Under "Comment", the 5th paragraph states: *Although a dose-effect relationship within the therapeutic range (50 - 200 mg/d) has not been demonstrated, one may wonder whether the study dose limitation up to 100 mg was too restrictive...*

This sentence is a contradiction in terms. Furthermore, a recent meta-analysis of 33 studies investigating dose-dependent efficacy of antidepressants showed that efficacy does not continue to increase with higher dosages, but, on the contrary, decreases again, possibly owing to the increasing number of undesirable side effects (Bollini et al, 1999). This "reversal phenomenon" in dose-effect has also been observed for more well tolerated antidepressants such as fluoxetine and sertraline. The limitation to 100 mg sertraline per day in the trial protocol was therefore well-founded and should not be a subsequent cause for pseudo-discussion.