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ARTICLE

Hypericum extract in patients with MDD and reversed vegetative signs: re-analysis from data of a double-blind, randomized trial of hypericum extract, fluoxetine, and placebo

Harald Murck[1], Maurizio Fava[2], Jonathan Alpert[2], Andrew A. Nierenberg[2], David Mischoulon[2], Michael W. Otto[2], John Zajecka[3], Marcus Mannel[4] and Jerrold F. Rosenbaum[2]

[1] *Lichtwer Pharma GmbH, Berlin, Germany*
[2] *Depression Clinical and Research Program, Massachusetts General Hospital, Boston, MA, USA*
[3] *Department of Psychiatry, Rush–Presbyterian–St Luke's Medical Center, Chicago, IL, USA*
[4] *Ad libitum Medical Services, Berlin, Germany*

Abstract

Hypericum extract (HE) might be favourably active in depressed patients with reversed vegetative signs (RVS). Therefore, we performed an exploratory subgroup analysis of a three-armed study to compare HE, fluoxetine, and placebo in patients with major depressive disorder (MDD) in a 12 wk trial. A total of 135 patients were randomized to 12 wk treatment with HE LI 160 (900 mg/d), fluoxetine (20 mg/d), or placebo. Patients with RVS were defined in two steps, according to DSM-IV. First, patients with melancholy-related vegetative signs were excluded. Secondly, patients had to have at least one score of 2 for the items 22–26 of the HAMD-28 scale, which are related to hypersomnia and hyperphagia. Twenty-seven patients remained in the group. Analysis of covariance (ANCOVA) was applied using the HAMD-17 score. Secondly a χ^2 test for response was performed, using the same and further an adapted criterium as in recently published studies. ANCOVA revealed a trend to a global difference. Post-hoc analysis showed a trend to superiority of HE compared to placebo and to fluoxetine, but a very large effect size for both differences. Fluoxetine was not different from placebo. The adapted response criterium showed a significant global difference as well as a significant superiority of HE over placebo and over fluoxetine. These data are based on a small sample size and must be considered tentative. A characterization of vegetative features of patients with depression could lead to an overall increased effect size in the treatment with HE.

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Key words: Atypical depression, major depression, reversed vegetative signs, St. John's wort.

Introduction

Some recent studies question the efficacy of hypericum extract (HE) in the treatment of major depressive disorder (MDD) (Hypericum Depression Trial Study Group, 2002; Shelton et al., 2001), whereas others supported the benefit of this drug (Lecrubier et al., 2002). In parallel with these reports, there is a renewed interest in the usefulness of defining subtypes of depression in order to achieve more effective treatment options than in heterogeneous populations (Parker, 2001), especially given that the effect size of antidepressant drugs compared to placebo is quite low in general (Kirsch et al., 2002). In particular, depression with atypical or reversed vegetative features (i.e. hypersomnia and hyperphagia) seems to be a valid subtype of depression, being present in a large proportion of depressed patients, especially in the outpatient population (Nierenberg et al., 1998). This population is, however, often under-represented in clinical trials of antidepressant drugs due to the use of a higher cut off-severity defined by a certain score of the Hamilton Depression scale (HAMD), as 'typical' vegetative signs like sleep complaints and appetite loss, but not the reversed vegetative signs (RVS) add to the score (see Murck, 2003).

Address for correspondence: Dr H. Murck, Laxdale Ltd, Laurelhill Business Park, Stirling, Scotland, UK.
Tel.: ++44 1786 476044 *Fax*: ++44 1786 473137
E-mail: haraldmurck@yahoo.de

Evidence exists from placebo-controlled trials that HE shows efficacy in patients with depressive disorders accompanied by fatigue (Halama, 1991; Sommer and Harrer, 1994), whereas open studies report its effect in seasonal affective disorder (Kasper, 1997; Martinez et al., 1994; Wheatley, 1999). Apart from the RVS, atypical depression is characterized by 'leaden paralysis of the limbs' (i.e. a certain type of somatic complaint), hypersensitivity to rejection, and mood reactivity. Controlled (Hübner et al., 1994) and open studies (Woelk et al., 1994) show the efficacy of HE in depressive disorders accompanied by somatic complaints. A recent placebo-controlled trial could demonstrate its effectiveness in somatoform disorders (Volz et al., 2002). To assess whether HE is effective in MDD patients with atypical features, we performed an exploratory subgroup analysis of the data from a double-blind study in MDD where patients were randomized to HE, fluoxetine, and placebo. The results of the main study have been reported elsewhere (Fava et al., In Press).

Methods

Following a 1-wk, single-blind wash-out, patients with MDD diagnosed by the Structured Clinical Interview for DSM-IV (SCID-I/P) (APA, 2000) were randomized to 12 wk double-blind treatment with St. John's wort extract LI 160 (300 mg t.i.d.; daily dose 900 mg/d), fluoxetine (20 mg/d), or placebo. The study was conducted at two sites (Boston and Chicago). It was approved by the local Ethics Committees.

For inclusion and exclusion criteria we would refer to the original study (Fava et al., In Press). In brief, patients of either sex and any ethnic origin were primarily recruited from general advertising and clinician referrals. They were between 18 and 65 years of age, had a current major depressive episode according to DSM-IV, and a HAMD-17 score of $\geqslant$16 at both screen and baseline. All patients gave written informed consent.

Exclusion criteria were especially a current, serious suicidal or homicidal risk (according to investigator's judgement), a history of seizure disorder, organic mental disorders, substance use disorders, including alcohol within the last 6 months, schizophrenia, delusional disorder, psychotic disorders not elsewhere classified, bipolar disorder, mood-congruent or mood-incongruent psychotic features. Patients had to be drug-free at baseline or, within the specified timeframe before baseline, they had to be free from other psychotropic drugs for 14 d and to the investigational psychotropic drug for 40 d. Furthermore, a failure to respond during the course of current major depressive episode to at least two adequate antidepressant trials defined as 8 wk or more of treatment with either:

- $\geqslant$150 mg of imipramine (or its tricyclic equivalent), or
- $\geqslant$60 mg phenelzine (or its MAO inhibitor equivalent), or
- $\geqslant$20 mg fluoxetine [or its selective serotonin reuptake inhibitor (SSRI) equivalent]

led to exclusion.

After the screening and the baseline visit, further visits were performed after 1, 2, 4, 6, 8, and 12 wk. For the instruments used in the study, see the report by Fava et al. (In Press). As in the main study, the HAMD-17 scale was used as the primary efficacy instrument. For the definition of patients with RVS we used a two-step definition, according to criterium C of the definition of atypical depression of DSM-IV. First, we excluded patients with melancholic vegetative features, defined as a score of 2 of the HAMD: item 6 (late insomnia), item 12 (decreased appetite) and item 16 (weight loss). In the next step, we used items 22–26 of the HAMD-28 item scale (item 22, hypersomnia, early bedtime; item 23, hypersomnia, oversleeping; item 24, hypersomnia, napping; item 25, increased appetite; item 26, weight gain). We defined an atypicality score (atyp) as the maximum score of items 22–26. Patients were included when atyp was 2 (i.e. at least one of the items had a score of 2), according to findings from the NIMH Treatment of Depression Collaborative Research Program (Sotsky and Simmens, 1999). In that study, it was shown that the inclusion of at least one RVS defines a group of patients differing in the response to pharmacotherapy, in this case with imipramine, compared to patients without this feature. The authors demonstrated further, that the criteria 'leaden paralysis' and 'rejection sensitivity' did not lead to a better differentiation of the groups.

Intent-to-treat (ITT) analysis was conducted, using the last observation carried forward method for missing values. The primary ITT included all subjects, who completed their baseline visit, were deemed eligible to continue the study, and were, therefore, randomized to double-blind treatment. Univariate analysis of covariance (ANCOVA) for the HAMD-17 at outcome was used with the factors gender and type of drug (drug), i.e. HE, fluoxetine or placebo, as factor and baseline HAMD-17 score and age as covariate. Further a χ^2 test to assess differences in response was performed in this post-hoc analysis with the same definition of response used in two recent studies of HE in depression (Hypericum Depression Trial Study

Group, 2002; Shelton et al., 2001), i.e. responders having a Clinical Global Impression – Improvement (CGI-I) of much improved or very much improved, or a HAMD-17 reduction of $\geqslant 50\%$ or a HAMD-17 score at outcome of $\leqslant 12$ (criterium 1). Because the present study used as an inclusion criterium a HAMD-17 score of $\geqslant 16$, whereas the earlier studies used a cut off of $\geqslant 20$, we used in addition a slightly modified and more strict criterium, where the cut off of 12 as in the previous definition was reduced to $\leqslant 10$ (criterium 2). A per protocol analysis, i.e. an analysis of the completers of the trial without major protocol violations, was not performed due to the small number of patients in each subgroup. The level of significance was set as $p < 0.05$. To complement traditional significance testing, we also computed between-group effect sizes ($d = \text{mean}_{\text{treatment1}} - \text{mean}_{\text{treatment2}} / \text{S.D.}_{\text{pooled}}$) for continuous outcome measures.

Results

A total of 135 patients (57% women, mean age 37.3 ± 11.0 yr, mean HAMD 19.7 ± 3.2) were randomized to double-blind treatment and were included in the ITT analyses. After excluding patients with melancholy-related vegetative signs, 79 patients remained for the ITT analysis, 63% of them female. From these, 27 patients had an atyp score of 2, 12 in the placebo group, 9 in the fluoxetine group and 6 in the HE group, and were the group of interest for further analysis. In total, 78% of the patients in this group were female. Of these, 15 completed the trial, six from the placebo group, four from the fluoxetine group and five from the HE group.

ANCOVA revealed a trend to a global effect of drug for the group with atyp = 2 ($F = 2.4$, $p = 0.12$). For the covariates and factors the significance levels were: baseline score ($p = 0.005$), age ($p = 0.16$), gender ($p = 0.23$). The adjusted HAMD-17 in the ITT sample was reduced to 13.9 ± 1.8 (mean $\pm$ S.E.M.) after placebo treatment ($n = 12$), to 14.9 ± 1.6 after fluoxetine ($n = 9$) and to 8.5 ± 1.8 after HE ($n = 6$). Post-hoc analysis revealed a trend to superiority of HE compared to placebo ($F = 4.9$, $p = 0.068$), that reflected a very large, between-group effect size ($d = 0.94$) for post-treatment differences according to Cohen's standards (Cohen, 1977). Further a trend to a superiority occurred compared to fluoxetine ($F = 3.6$, $p = 0.088$) that also reflected a very large effect size ($d = 1.37$). Fluoxetine was not different from placebo ($F = 0.2$, $p = 0.64$, effect size -0.17). The time-course of the changes is shown in Figure 1.

Using a definition of responders according to criterium 1 (CGI-I of much improved or very much improved or a HAMD-17 reduction of $\geqslant 50\%$ or a HAMD-17 score at outcome of $\leqslant 12$), i.e. the same one than in two recently published trials (Hypericum Depression Trial Study Group, 2002; Shelton et al., 2001), the χ^2 test revealed a strong trend to a global effect [Pearson's $\chi^2 = 5.41$, p (two tailed) $= 0.067$; Table 1]. The direct comparison of the treatment groups revealed no effect of fluoxetine vs. placebo ($p = 0.195$) and no effect of HE vs. placebo ($p = 0.171$), but a significant superiority of HE vs. fluoxetine (Pearson's $\chi^2 = 5.40$, $p = 0.02$). Because of the lower minimal HAMD-17 score for inclusion of patients, which was 16 in the present study compared to 20 in the earlier ones, an adapted and stricter criterium seemed more suitable. With this (criterium 2, similar to the first but with a criterium of HAMD-17 at outcome $\leqslant 10$) a significant global effect was revealed (Pearson's $\chi^2 = 6.1$, $p = 0.048$) with a significant superiority of HE

Table 1. Cross-tabulation of the responders vs. non-responders in the different treatment groups with an atyp score of 2 (criterium 1: CGI-I of much improved or very much improved or HAMD-17 reduction of $\geqslant 50\%$ or HAMD-17 score at outcome of $\leqslant 12$)

	Responders	Non-responders	Total
Placebo	6 (50%)	6 (50%)	12
Fluoxetine	2 (22%)	7 (78%)	9
Hypericum extract	5 (83%)	1 (17%)	6
Total	13	14	27

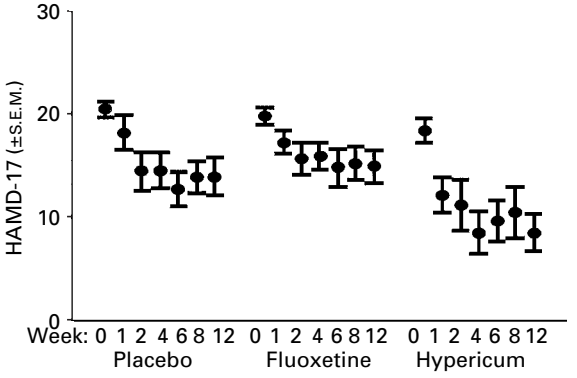

Figure 1. Comparison of the time-course of the HAMD-17 score in patients with reversed vegetative signs in the different treatment groups. Whereas the patients in the fluoxetine and placebo group could not be distinguished, the patients receiving hypericum extract showed a rapid and marked improvement over time compared to the other groups.

Table 2. Cross-tabulation of the responders vs. non-responders in the different treatment groups with an atyp score of 2 (criterium 2: CGI-I of much improved or very much improved or HAMD-17 reduction of $\geqslant 50\%$ or HAMD-17 score at outcome of $\leqslant 10$)

	Responders	Non-responders	Total
Placebo	4 (33%)	8 (67%)	12
Fluoxetine	2 (22%)	7 (78%)	9
Hypericum extract	5 (83%)	1 (17%)	6
Total	11	16	27

over placebo (Pearson's $\chi^2 = 4.0$, $p = 0.046$) and over fluoxetine (Pearson's $\chi^2 = 5.4$, $p = 0.020$) (Table 2).

The groups with an atyp score of 1 ($n = 28$) also showed qualitatively similar, but less pronounced changes, which were not statistically significant ($p > 0.1$, data not shown).

Discussion

The main finding of this analysis of treatment response in subgroups of depressed patients was that, in a group of MDD outpatients with RVS, HE showed a trend towards greater efficacy compared to fluoxetine, and placebo using ANCOVA. Using a χ^2 test, HE also showed a trend to superiority compared to placebo, and a significant superiority compared to fluoxetine, using the same response criterium as two recently published trials (Hypericum Depression Trial Study Group, 2002; Shelton et al., 2001), and a significant superiority over placebo and fluoxetine with a slightly more strict response criterium, which seems to be more suitable due to differences in the inclusion criteria for the trials. We obtained a number of findings that reflected effect sizes far in advance of Cohen's standard ($d = 0.8$) for a 'large' effect (Cohen, 1977). Due to sample size constraints, these large-sized effects did not consistently reach significance. However, the study utilized small sample sizes. Accordingly, results must be considered as tentative. Further, the patients were not randomized into this post-hoc-defined group, therefore, a bias of the inclusion of patients into the medication groups cannot be excluded. These preliminary data could suggest that HE has a pronounced efficacy in patients with RVS. This points to the possibility that in particular the patients with RVS contribute to the effect of the total group, which showed a trend to a superiority of HE compared to placebo and a significant superiority compared to fluoxetine (Fava et al., In Press).

The way we defined the group of patients with RVS needs some explanation. As mentioned, we chose a two-step definition, first, to exclude patients with melancholic symptoms and secondly to include only patients with RVS, according to the definition of DSM-IV. This approach makes biological sense, as hypersomnia, defining a RVS, might well be the result of (early) insomnia, as defined as a criterium for melancholic depression (Breslau et al., 1996). Therefore, the exclusion of melancholic symptoms before selecting for atypical symptoms seems necessary. Furthermore, we did not choose a sum score, but the presence of maximum score in a number of specific items. This approach is the same as performed in a trial, which was able to differentiate groups responding differentially to a pharmacotherapy with imipramine (Sotsky and Simmens, 1999). The items used could range from 0 to 2. To increase the contrast between the groups and the knowledge that a score of 1 often reflects an unclear situation, we chose only a score of 2 as an inclusion criterium.

In the present study, patients with atypical features or RVS are not responsive to fluoxetine. This is in line with one published placebo-controlled trial on maintenance treatment, showing that RVS are a predictor of relapse during the treatment with fluoxetine (McGrath et al., 2000b). On the other hand the same group showed a superiority of both fluoxetine and impramine over placebo in patients with atypical depression (McGrath et al., 2000a). Comparison studies in patients with atypical depression (Lonnqvist et al., 1994) showed a superiority of moclobemide vs. fluoxetine, whereas other studies showed no difference between fluoxetine and phenelzine (Pande et al., 1996) or moclobemide and sertraline (Sogaard et al., 1999). The latter studies seem to support the clinical efficacy of SSRIs, as the comparators are from the group of monoamine oxidase inhibitors, which show a preferable action in atypical depression (for review see Murck, 2003). Further, in one study comparing fluoxetine with nortriptyline the outcome with fluoxetine was favourable compared to nortripyline (Joyce et al., 2002). Comparison studies without the inclusion of a placebo arm, however, have to be handled with care (Kupfer and Frank, 2002).

A hypothesis for the biological basis of the differential efficacy of drugs in subgroups of depression, especially atypical depression vs. melancholic depression, include a differentially disturbed hypothalamus–pituitary–adrenocortical (HPA)-axis activity (Gold and Chrousos, 1998) with an increase in HPA axis activity in patients with melancholic depression and rather a decrease in patients with atypical

depression or depression with RVS. Accordingly, antidepressive therapy in patients with more severe depression generally leads to a reduction of the activity of the HPA axis, as measured, for example, with the combined dexamethasone suppression corticotropin-releasing hormone (CRH) test (Dex-CRH test) (Nickel et al., 2003). However, HE leads to non-suppression of cortisol in this test, i.e. an activation of the HPA axis, which accompanied clinical improvement of non-melancholic depressed patients (Holsboer-Trachsler et al., 2001). Furthermore, reduced sleep (Antonijevic et al., 2000) and loss of appetite and weight (Casper et al., 1987), vegetative characteristics of severe melancholic depression, are closely related to HPA axis overactivity, whereas hypersomnia and increased appetite are related to hypocortisolism (Casper et al., 1988). Therefore, it has been suggested that the HPA axis activating effect of HE might be related to its preferable efficacy in patients with RVS (see Murck, 2003).

Limitations of the study have to be mentioned. First, the non-response to fluoxetine is an issue. Data from our group suggest that a significant proportion of patients non-responding to 20 mg/d may go on to respond when the dose is increased to 40 or 60 mg/d (Fava et al., 1994, 2002). These studies suggest that 20 mg/d fluoxetine, although typically considered an effective dose in the treatment of MDD, may not be an adequate dose for a significant proportion of patients suffering from MDD. Secondly, none of the analyses performed were pre-specified before breaking the blind. Therefore, all these analyses have to be regarded as exploratory and purely of heuristic value for the design of a prospective, randomized, placebo-controlled trial. This trial is in fact ongoing. In this regard it is important, that the results of the trial do not stand alone, but make sense in a context, which was presented in the Introduction, that HE seems, in fact, to be of particular efficacy in a specific type of patients of the atypical spectrum of depression (Murck, 2003).

To conclude, patients with RVS, as defined in this exploratory study, appear to be a group with a specific susceptibility to the therapeutic effect of HE. Fluoxetine did not separate from placebo in this group. Therefore, the characterization of vegetative features of patients with depression could lead to an overall better distinction of patients having a benefit from specific antidepressant drugs.

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