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St. John's wort extract LI160 for the treatment of depression with atypical features – A double-blind, randomized, and placebo-controlled trial

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ABSTRACT

Preliminary data suggest that hypericum extract LI160 is effective in atypical depression. Reported is the outcome of an 8-week double-blind, placebo-controlled, randomized trial of 600 mg LI160 vs. placebo in patients with vegetative features of atypical depression, i.e. hyperphagia or hypersomnia. One-hundred (100) patients with mild and 100 patients with moderate severity of a major depression according to ICD-10 were randomized. Patients needed to meet a score of 2 in at least one of the items 22–26 of the Hamilton-Depression-Rating-Scale (HAM-D) 28-item version and episode duration of at least 3 months. The primary outcome variable was the relative change of the HAM-D_{17} from Baseline. Secondary outcome variables were the depression sub-score of the Patient Health Questionnaire (PHQ-9), the Clinical Global Impression (CGI), a patient's satisfaction scale, the Hamilton-Anxiety-Scale (HAM-A) and the sum score of atypical vegetative symptoms of the HAM-D_{28}.

The percentage reduction of the HAM-D_{17} for LI160 compared to placebo approached statistical significance ($p = 0.051$) in the Full Analysis Set (FAS)-population. Using the conventional criterion of the absolute reduction of the HAM-D_{17} significance was achieved ($p < 0.05$). No significant benefit could be observed for the sum score of the atypical vegetative items of the HAM-$D_{28;}$ however, the sum score of the hypersomnia items (items 22–24) showed a significant superiority for LI160. The HAM-A, PHQ-9, and CGI-I scales demonstrated superiority of LI160 ($p < 0.01$). Confining the analysis to moderately depressed patients, a highly significant benefit for the primary outcome variable was revealed. The study supports the beneficial effect of LI160 in depression with atypical features and the validity of the definition of atypical depression on the basis of reversed vegetative signs. Further, it identifies the PHQ-9 as a useful outcome variable in this population.

1. Introduction

Major depression is a heterogeneous group of psychiatric disorders. Nevertheless, there is still only limited knowledge about the possibility of differential treatment for patients with more specific depressive syndromes.

The hypericum extract LI160 demonstrated efficacy in some clinical trials, but the overall results are not consistent (Linde et al., 2008). Whereas in populations rich in melancholic patients no relevant benefit could be observed for LI160 (Hypericum-Depression-Trial-Study-Group, 2002; Shelton et al., 2001), earlier studies in mild to moderate depression have demonstrated a significant superiority over placebo (Linde et al., 1996). A more recent study with a similar extract showed a significant differentiation from placebo, but with a relatively small effect size (Lecrubier et al., 2002). There is evidence that fatigue, which is related to hypersomnia (Ferentinos et al., 2009), responds particularly well in patients with neurotic depression as classified by ICD-9 when treated with LI160 in comparison to placebo (Sommer and Harrer, 1994). A more recent study also demonstrated efficacy of LI160 on a trend level vs. placebo and superiority vs. fluoxetine in patients with mild to moderate depression (Fava et al., 2005). This study is of particular interest as for the first time atypical symptoms were recorded in a trial with LI160. A subgroup analysis indicated that the effect size of patients with atypical vegetative symptoms points to a very robust effect of LI160 vs. placebo and vs. fluoxetine (Murck et al., 2005).

Depression with atypical features was defined after the observations that this subgroup responded preferentially to

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monoamine oxidase inhibitors (MAOI), but less to tricyclic antidepressants (Stewart et al., 1989). Following this, the atypical depression specifier was introduced in DSM-IV, which included the presence of mood reactivity, atypical vegetative features hypersomnia and hyperphagia, leaden paralysis of the limbs and rejection sensitivity. However, the specificity of the atypical depression definition according to DSM-IV has been questioned recently (Angst et al., 2005; Benazzi, 2002, 2005; Bruder et al., 2002; Stewart et al., 2003, 2005) by highlighting modifying parameters like: age of onset; hypothalamus-pituitary adrenocortical (HPA) axis activity; electrophysiological parameters; or the determining factor of the vegetative characteristics. In particular, the presence of mood reagibility on the one-hand, and of atypical vegetative symptoms on the other hand define two independent factors in patients diagnosed according to DSM-IV (Benazzi, 2005). This is in line with the findings that vegetative signs of atypical depression are linked to a potentially specific neurobiology, i.e. an underactivity of the HPA axis (Gold and Chrousos, 2002; Levitan et al., 2002; Murck, 2003) and the observation that LI160 increases the activity of the HPA axis in healthy volunteers (Franklin et al., 2006) and in patients with depression in the course of improvement (Holsboer-Trachsler et al., 2001). This definition is also in agreement with findings from the NIMH Treatment of Depression Collaborative Research Program which demonstrate that the presence of at least one reversed vegetative sign is sufficient to discriminate atypical from melancholic depression and to predict differing response to drug treatment (Sotsky and Simmens, 1999) as well as more recent findings from Benazzi (Benazzi, 2002).

On the basis of these observations, this trial was designed to focus on the vegetative features in order to test the efficacy of hypericum extract LI160 prospectively in patients with mild to moderate major depression with atypical characteristics.

2. Materials and methods

2.1. Study design

The study was an 8-week, randomized, double-blind, placebo-controlled, multi-center parallel-group trial to evaluate the efficacy of the *hypericum perforatum* extract LI160 in patients diagnosed with atypical depression. The study design had been developed in compliance with current international guidelines on the investigation of medicinal products in the treatment of depression. It was planned to be carried out in outpatient centers of psychiatrists, neurologists, and general practitioners throughout Germany. Recruitment of patients started in December 2002 and ended in September of 2004. Investigators were trained by an expert in a standardized fashion on the use of diagnostic procedures and rating scales in a 1-day session before the start of the study. The majority of the investigators were experienced in the field of clinical studies in psychiatric illnesses and had participated in several preceding clinical trials in depressive and anxiety disorders.

The design was an 8-week double-blind treatment phase to receive either LI160 (300 mg twice daily, i.e. a daily dose, 600 mg) or matching placebo. The sequence of visits was as follows: Screening (3 days to 4 weeks before Baseline, depending on anti-depressive pre-treatment), Baseline (week 0), Visit 1 (week 2), Visit 2 (week 4), and Visit 3 (week 8). Efficacy ratings, adverse events, concomitant medications, study drug compliance and adherence to the protocol were collected at all visits.

The study protocol and patient information materials had been approved by the federal ethics committees in charge of the participating investigators. The study was conducted in complete compliance with Good Clinical Practice (GCP) Guidelines and the Declaration of Helsinki and its revisions.

2.2. Patients

Subjects between 18 and 70 years of age suffering from atypical depression were screened for selection criteria at assigned private practices of participating investigators, all in Germany. Diagnostic selection was operationalized by means of semi-structured checklists, based on IDCL checklists (Hiller et al., 1993). ICD-10 criteria for mild or moderate depression had to be met, with the adjustment that the duration of symptoms of 3 month was required. A simplified definition of "atypical depression" was used (see introduction): The requirement was of a minimum score of two points for at least one of the five items of the HAM-D_{28} scale (Fava et al., 2005), covering the atypical features hypersomnia, increased appetite and weight gain. According to findings from the NIMH Treatment of Depression Collaborative Research Program (Sotsky and Simmens, 1999), this approach is acceptable to identify atypical depression, since the presence of at least one reversed vegetative sign is sufficient to discriminate from melancholic depression and to predict differing response to drug treatment. Additionally, a maximum score of one point for items 6 (insomnia late), 12 (somatic symptoms, gastrointestinal), and 16 (loss of weight) of the HAM-D_{17} scale were allowed; thereby, excluding subjects exhibiting vegetative features of melancholic depression. Further, the patients were excluded in case of a history of an episode of melancholic depression, alcohol or substance abuse, organic mental disorders, psychotic disorders, personality disorders, seasonal depression, postpartum depression and current serious suicidality risk. Patients had to be free of psychotropic drugs for at least 14 days before randomization and of fluoxetine for at least 28 days. No active psychotherapy was permitted before or during the trial. For the actually randomized patients no placebo washout period was required (all were drug free for at least two weeks before randomization) and eligible patients who had signed written informed consent directly entered the trial. Further exclusion criteria were the use of corticosteroids, including topical, gyrase inhibitors, noradrenergic agonists, and magnesium supplements.

Allocation of patients to treatments occurred randomly with the help of a computer software. Randomization was done in blocks of four, block wise for patients with mild depression and moderate depression, respectively, to ensure the enrollment of comparable numbers of patients with mild and moderate severity of depression. All investigators, personnel of the participating partners and sponsor in the trial were blinded to group assignment until the study database was closed and the blinded review procedure was completed.

2.3. Study medications

Medication for the study was provided by Lichtwer Pharma. Coated tablets (Batch No. 02080277) containing 300 mg of LI160 extract LI160 (drug-extract ratio 3–6:1; extraction solvent: 80% Methanol in water; Batch No. 02019073) or placebo tablets (Batch No. 01010177) that were identical in shape, size, taste and color were administered orally twice daily (morning and evening) with some liquid. The first tablet was taken the day after the beginning of the study and the last tablet in the morning of Visit 3 (after 8 weeks). The entire study supply of SJW extract LI160 and tablets came from one batch. LI160 study medication is marketed in Germany as Jarsin® 300 mg and licensed for the treatment of mild and moderate depressive episodes.