Controlled clinical trials of hypericum extracts in depressed patients: an overview

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Authors' objectives
To assess the antidepressant efficacy of hypericum extracts.

Searching
The author searched MEDLINE (search dates and keywords not reported). Additional data was obtained by asking all manufacturers of hypericum extracts to supply the author with scientific information.

Study selection
Study designs of evaluations included in the review
Controlled double-blind clinical trials either versus placebo or an active comparator. Treatment duration ranged from 4-8 weeks.

Specific interventions included in the review
Hypericum extracts (also named St John's wort). Treatment groups received: Jarsan (300 mg/1.08 mg total hypericin, 3 times per day), Jarsin/-300 (300 mg/2.7 mg total hypericin, 3 times per day), Hyperforat drops (30 drops/0.6 mg total hypericin, 3 times per day), Neuroplan (1/1.0 mg total hypericin, 4 times per day), Esbericum (1/0.75 mg total hypericin, 3 times per day), Psychotonin (300 mg/2.7 mg total hypericin, 3 times per day), and Psychotonin M (20 or 30 drops/0.75 mg total hypericin, 3 times per day). Control groups received imipramine (25 mg, 3 times per day), maprotiline (25 mg, 3 times per day), amitryptiline (30 mg per day), or placebo.

Participants included in the review
Patients with varying degree of depression (mild to major) classified either by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-III or DSM-III-R), International Classification of Diseases, 9th and 10th revisions (ICD-9 or -10), or a Hamilton Depression Scale (HAMD) score greater than 15 in 13 of the 15 included studies.

Outcomes assessed in the review
Scores for rating levels of global and mental states (not stated whether change or end points were used), measured by various rating scales (e.g. HAMD, D-S, CGI, HAMA, BL, WDG, BEB, GE, and BF-S), and the occurrence of any adverse events measured by tolerability results.

How were decisions on the relevance of primary studies made?
The author does not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The author does not report the method used to assess quality, or how the quality assessment was performed.

Data extraction
The author does not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The studies were not combined in a statistical analysis and quantitative results are not stated. The individual studies and
their results are presented in a table and the authors discuss two of the studies (Jarsan-300 versus placebo and Jarsan-300 versus maprotiline) in depth in the text. Summaries of the changes in HAMD scores for the two studies are reported in graph format.

How were differences between studies investigated?
The author does not state how differences between the studies were investigated.

Results of the review
Fifteen trials were included in the review with 1,126 participants: 12 studies compared hypericum extracts (400 participants) with placebo (413 participants), and 3 trials compared hypericum extracts (156 participants) with active comparators (157 participants).

The hypericum extract Jarsan-300 (9 studies) was reported to be more effective than the placebo in 6 out of 7 studies and as effective as the active control in two studies. Tolerability results were equal for both groups. Adverse events reported were unspecific gastrointestinal disturbances, erythema, tiredness, itching and sleep disturbances.

The hypericum extract Psychotonin-M (3 studies) was reported to be more effective than the placebo in 2 out of 3 studies. Tolerability results were equal for both groups. Adverse effects were 1 drop-out due to nausea.

In the remaining 3 interventions of Hyperforat and Neuroplan versus placebo (2 studies) reported greater efficacy for the treatment group versus placebo and Esbericum versus amitryptiline (1 study) reported equal efficacy between the groups. Adverse events were reported for Esbericum and included stomach disturbances, dizziness and tiredness.

Authors' conclusions
The antidepressive action of hypericum is only sufficiently documented for Jarsin 300. Strong indicators of an antidepressive efficacy of Psychotonin-M also exist. No dose finding studies have been conducted and studies on inpatients with severe depression and endogenously depressed patients are also lacking. Since most trials have been conducted over only a short period of time, a longer treatment duration (longer than 6 weeks) cannot be recommended.

CRD commentary
The author has stated the research question and some inclusion criteria for the review. The literature search is poor because the author has searched only the MEDLINE database and does not report the dates and keywords used. It is not stated whether there were any language restrictions, hence it is possible that relevant studies may have been missed.

The author has not reported on how the articles were selected, or how the quality of the included studies was assessed and there is no report as to who, or how many of the reviewers, selected the articles or extracted the data. The studies are not statistically combined, although the study designs are controlled double-blind trials. The results table does not report measurements of change in the outcome measures. There is no discussion or test for homogeneity. The author mentions several drawbacks about the quality and design of the individual studies, including the inclusion scores for HAMD being set too low, the length of treatments being too short, and the doses of active controls being too low (75 mg/day, rather than the usual 150 mg/day) which could influence the strength of the reported results. The reported outcomes should be viewed with caution.

Implications of the review for practice and research
Practice: The author states that in slight to modest depressions on the outpatient sector, a therapy restricted in time (no longer than 6 weeks) with hypericum extract can be attempted, taking into account the favourable side-effect profile. Hypericum extracts are not recommended in complicated depressive courses, including therapy resistance, suicidal tendencies, delusions and severe depression.

Research: The author states that further studies are needed to improve methodological quality of studies on hypericum extract and to investigate maintenance therapy (3 months duration) and recurrence prophylaxis (at least 1 year).
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