THERAPEUTICS

Review: hypericum extracts are safer and lead to fewer adverse effects than older standard antidepressants, but have similar tolerability to SSRIs


Q Are hypericum extracts safe and tolerable in treating people with depression?

Methods

- Design: Systematic review of RCTs with meta-analysis.
- Data sources: Cochrane Collaborative Review Group for Depression (CCDAN), PubMed, plus hand searches of reference lists; the CCDAN was last searched in July 2003, the PubMed search covered the period 1998 to 2003.
- Study selection and analysis: Double blind, randomised, controlled trials comparing hypericum extracts with placebo or standard antidepressant regimens for treatment of depression in adults. Meta-analysis used a fixed effects model as there was no statistical heterogeneity between studies for safety outcomes.
- Outcomes: Dropouts due to adverse effects, numbers reporting adverse effects.

Main results

Thirty-five published RCTs met criteria for inclusion in the review (24 trials comparing hypericum extracts with placebo, seven comparing hypericum extracts with older antidepressants, and six comparing hypericum with selective serotonin reuptake inhibitors (SSRIs)). Compared with placebo, hypericum resulted in similar numbers of dropouts due to adverse effects (24 RCTs, 8/1334 (0.6%) with hypericum vs 15 (1.2%) with placebo, OR 0.61, 95% CI 0.28 to 1.31). There was no significant difference between hypericum and placebo in the number of people reporting adverse effects (236/1123 (21%) with hypericum vs 254/1077 (23.6%) with placebo, OR 0.79, 95% CI 0.61 to 1.03). Compared with older antidepressants, treatment with hypericum led to fewer dropouts for adverse effects and fewer reports of adverse effects (seven RCTs, dropouts for adverse effects: 14/615 (2.3%) with hypericum vs 52/616 (8.4%) with amitriptyline, imipramine, or maprotiline, OR 0.25, 95% CI 0.14 to 0.45; reports of adverse effects: 174/615 (11.1%) with hypericum vs 301/616 (15.6%) with amitriptyline, imipramine, or maprotiline, OR 0.39, 95% CI 0.31 to 0.50). There were no significant differences between hypericum and SSRIs in numbers dropping out for adverse effects or total adverse effects reported, though the trend was for fewer adverse effects with hypericum (dropouts due to adverse effects: OR 0.60, 95% CI 0.31 to 1.15, total numbers reporting adverse effects: OR 0.75, 95% CI 0.52 to 1.08).

Conclusions

With respect to adverse effects, hypericum extracts are better tolerated than older standard antidepressants (amitriptyline, imipramine, or maprotiline), though dropout rates and adverse effects are similar with hypericum, SSRIs, and no treatment.

Notes

Short follow up periods and small sample sizes may increase the chance that potential adverse effects were overlooked in RCTs. The review also included a review of large observational studies and of case series and individual case reports from drug surveillance agencies. Large observational studies in primary care settings found that rates of treatment discontinuation were low and adverse effects were rare. Individual case reports provide evidence that interactions do occur between hypericum and other drugs, but these are rare.

Commentary

The review by Knüppel and Linde addresses recent clinical data on dropout rates and adverse effects of St John’s wort (Hypericum perforatum) using three broad categories of evidence: randomised controlled trials (RCTs), observational studies, and case report information. The overview is a logical extension from existing reports by focusing attention to the frequency of adverse effects, a point that is particularly relevant in light of the potential for adverse drug interactions with hypericum use.

Recent molecular studies have shed light on the mechanism of how hypericum may interact with other therapeutic drugs. Hypericum activates the human pregnane X nuclear receptor (PXR), which is a transcription factor that induces a battery of target genes involved in the transport, biotransformation, and elimination of xenobiotics including one encoding for the enzyme cytochrome P4503A4 (CYP3A), which is responsible for the metabolism of about 60% of therapeutic drugs. Therefore by increasing the rate of metabolism of other drugs, hypericum may accelerate their elimination from the body, consequently reducing their efficacy. Studies examining how hypericum affects the efficacy of a combined oral contraceptive have produced pharmacokinetic findings consistent with this mechanism of interaction.

The Knüppel and Linde review found no reports of adverse drug interactions in RCTs or large observational studies of hypericum, but found published case reports of such interactions. This difference may be attributed to the sample size of RCTs and observational studies, or to stringent inclusion/exclusion criteria in RCTs eliminating people with comorbidities requiring drug treatment. Use of different hypericum extracts, variable reporting procedures for adverse effects in different studies, and inherent differences in the population (for example, genetics, sex) in phase I and phase II biotransformation pathways may also have contributed to this discrepancy.

The metabolic pathways affected by hypericum remain an important factor for consideration by qualified healthcare professionals, and adds to their armamentarium of clinical risk management tools for use when giving advice to individuals who choose to consume hypericum.

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The opinions and conclusions expressed in this article are solely the views of the author and do not necessarily reflect those of the Food and Drug Administration.
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