St John's wort for depression: what's the evidence?

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There is a moderate amount of evidence to suggest that St John's wort is better than placebo in the short-term management of mild to moderate depressive illness, but there is increasing concern over reports of drug interactions. This article examines the scientific evidence and discusses relevant clinical issues.

St John's wort, or *Hypericum perforatum*, is a flowering plant that grows as a common weed in many countries. St John's wort has been used for centuries as a treatment for conditions resembling anxiety and depression. In recent years, a renewed emphasis on complementary medicine and herbal remedies has brought about a huge increase in the recognized use of St John's wort for the treatment of depression.

In 1998 alone, total sales figures in Europe came to US$6 billion, and in the USA sales leaped by approximately 2800% in a single year (Ernst, 1999). In a rapidly expanding market such as this, it is important to critically review the scientific evidence upon which treatment is based.

METHOD

An extensive literature search was performed, using Psyclit (American Psychological Association, 1887–1999), Medline (United States National Library of Medicine, 1985–2000) and the Cochrane Library (1999 edition, Update Software). This was supplemented by tracking back through references from existing review work.

MECHANISM OF ACTION

Hypericum extract contains a minimum of ten biologically active substances including hypericin and pseudohypericin (Gaster and Holroyd, 2000). Initially it was believed that the predominant mechanism of action was similar to that of monoamine oxidase inhibitors, with hypericum extracts seen to inhibit the actions of monoamine oxidase A and B in biological models of depression. However, more recent work shows that hypericum is a very weak inhibitor of the monoamine oxidase system when compared to traditional monoamine oxidase inhibitors used in clinical practice (Cott, 1997; Muller et al, 1997).

It is more likely that the antidepressant properties of hypericum relate to its ability to inhibit re-uptake of numerous neurotransmitters, including serotonin, noradrenaline and dopamine (Nathan, 1999). Indeed, hypericum is probably the only antidepressant agent that inhibits reuptake of all three equally. It also has moderate to high potency for inhibition of uptake of the amino acid neurotransmitters gamma-aminobutyric acid and glutamate (Nathan, 2001).

Furthermore, the pattern of therapeutic response to hypericum is similar to that of other antidepressant agents, with a 3–4-week lag period before apparent clinical benefit and a 6-month optimal treatment period (Wheatley, 2000). Further research is needed in order to fully elucidate the mechanism of hypericum's proposed antidepressant effect.

EFFICACY

A Cochrane review of the use of St John's wort for depression (Linde and Mulrow, 2000) considered 27 randomized clinical trials that compared preparations of St John's wort with placebo or antidepressants. These trials included a total of 2291 patients. Hypericum extracts were found to have an efficacy roughly equal to that of standard antidepressants but significantly greater than that of placebo (rate ratio 2.47; 95% confidence interval 1.69–3.61). Patients treated with hypericum reported significantly fewer side-effects. It was concluded that extracts of hypericum are better than placebo in the short-term treatment of mild to moderate depression, but current evidence is inadequate to establish whether the efficacy of hypericum is equal to that of other antidepressants.

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In 2000 there was a considerable renewal of media interest in St John's wort following the publication, in the *British Medical Journal*, of a randomized controlled trial comparing St John's wort and imipramine (Woelk, 2000). This study randomized 324 outpatients with mild to moderate depression into two treatment groups: one group received imipramine 75 mg twice daily and the other group received hypericum extract 250 mg twice daily, for 6 weeks. Outcome was measured using the Hamilton depression rating scale, clinical global impression scale and patient's global impression scale. At the end of 6 weeks, mean scores on the Hamilton depression scale for the hypericum group had decreased from 22.4 to 12.00, and scores for the imipramine group had decreased from 22.1 to 12.75. It was concluded that hypericum extract had efficacy equivalent to that of imipramine in the treatment of mild to moderate depressive illness, and that hypericum was better tolerated by patients.

There is, therefore, a moderate amount of evidence to suggest that St John's wort is better than placebo in the short-term management of mild to moderate depressive illness (Cott and Fugh-Berman, 1998; Wheatley 1998; Gaster and Holroyd, 2000). However, the efficacy of St John's wort when compared to other antidepressants is not entirely clear (Wheatley, 1997). It also remains unclear whether or not efficacy is maintained at 1 year, or if hypericum has significant prophylactic value. Clearly, more study is needed (Kim et al, 1999).

Hopefully, these issues will be further clarified in 2002 with the completion of a $4.3 million US study of St John's wort funded by the National Institute of Mental Health and the National Institutes of Health Office on Alternative Medicine. This 3-year study will randomize 336 patients with major depression to three treatment groups: hypericum extract, a selective serotonin-reuptake inhibitor and placebo. The results should provide valuable comparisons between the clinical effects of St John's wort and these newer antidepressant agents.

ADVERSE EFFECTS

The side-effects most commonly reported with St John's wort include nausea, fatigue, and rash (Gaster and Holroyd, 2000). Photosensitivity has also been reported (Brockmoller et al, 1997; Miller, 1998). In general, St John's wort is reported as having fewer side-effects than antidepressants to which it has been compared (Linde and Mulrow, 2000). In one study, only 1.1% of patients discontinued St John's wort extract as a result of side-effects (Woelk et al, 1994).

There are no extensive studies comparing the side-effect profile of hypericum with that of selective serotonin-reuptake inhibitors. There is, however, the possibility of severe sedation when hypericum extract is combined with a selective serotonin-reuptake inhibitor (Gordon, 1998). There are also reports of clinically diagnosed central serotonergic syndrome in elderly patients who combined prescription antidepressants with St John's wort (Lantz et al, 1999). It is important to note that at this time little information is available on the safety of hypericum extract in overdosage, or on the issue of withdrawal or discontinuation reactions.

There is considerable concern about the occurrence of drug interactions with hypericum extracts. Evidence suggests that hypericum extracts activate hepatic cytochrome P450, possibly doubling its metabolic activity (Ernst, 1999). There are reports of acute heart transplant rejection as a result of a reported metabolic interaction between hypericum extract and cyclosporin (Ruschitzka et al, 2000). It is also suggested that hypericum may lower serum levels of theophylline and warfarin, and may result in breakthrough bleeding when combined with ethinyloestradiol and desogestrel (Ernst, 1999). There is also evidence for interactions with amitryptiline and digoxin (De Smet and Touw, 2000).

It is clear that both the introduction and discontinuation of hypericum extract may produce significant changes in the pharmacological activity of other medications. A list of clinically important interactions of St John's wort was published by the Committee on Safety of Medicines (*Table 1*; Committee on Safety of Medicines, 2000).

Further study of the mechanism of action of hypericum and further reporting of adverse

TABLE 1.
Clinically important interactions of St John's wort

Human immunodeficiency virus protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir)
Human immunodeficiency virus non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine)
Warfarin
Cyclosporin
Oral contraceptives
Anticonvulsants (carbamazepine, phenobarbitone, phenytoin)
Digoxin
Theophylline
Triptans (sumatriptan, naratriptan, rizatriptan, zolmitriptan)
Selective serotonin-reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)

events or proposed interactions should help advance our knowledge of the therapeutic potential of hypericum.

CONCLUSIONS

There is a moderate amount of evidence to suggest that *Hypericum perforatum* is better than placebo for the short-term management of mild to moderate depressive illness. More study is needed. At present, there is insufficient evidence to draw firm conclusions about usefulness of hypericum in more severe depression or its efficacy or tolerability compared to selective serotonin-reuptake inhibitors.

St John's wort appears to be generally well tolerated, although reports of significant drug interactions necessitate further research. Clinically, the possibility of drug interactions should be actively considered in the case of each individual patient who is taking any preparation of St John's wort. There is a notion that St John's wort is an 'herbal' remedy, and thus less likely to produce adverse events. Current evidence suggests that St John's wort can have adverse effects and can lead to significant drug interactions. Clear information must be provided regarding its use (Jobst et al, 2000).

At present, St John's wort is available in a number of different preparations, ranging from tablets to tea bags. Of course, in countries where hypericum remains an unlicensed herbal remedy, there are no officially approved preparations. In 1998 a newspaper in the USA examined the hypericum content of ten different preparations and found that 30% of products in their sample contained less that 50% of the hypericin content stated on the label, and 50% of products contained less than 80% of the stated hypericin content (Monmaney, 1998). Appropriate regulation of these products in future should help standardize the hypericum content of each product.

At this time, St John's wort appears to be a promising medication, but further study of therapeutic and adverse effects is needed before its role in clinical practice can be clearly defined. **HM**

Conflict of interest: none.

KEY POINTS

- There is a recent upsurge of interest in St John's wort (*Hypericum perforatum*) — a common weed traditionally used for the treatment of anxiety and depression.
- St John's wort inhibits reuptake of serotonin, noradrenaline, dopamine, gamma-aminobutyric acid and glutamate.
- There is a moderate amount of evidence to suggest that St John's wort is better than placebo in the short-term management of mild to moderate depressive illness.
- Side-effects include nausea, rash and photosensitivity. Overall, St John's wort appears to be well tolerated.
- Further study is underway to compare the clinical effects of St John's wort with those of selective serotonin-reuptake inhibitors.
- There is growing evidence of significant drug interactions between St John's wort and a range of other medications.
- Appropriate regulation of commercial preparations of St John's wort would help standardize the hypericum content of these products.
- At this time, St John's wort appears to be a promising medication, but further study of therapeutic effects and adverse effects is needed before its role in clinical practice can be clearly defined.

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