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IAN MAIDMENT

The use of St John's Wort in the treatment of depression

AIMS AND METHOD

To assess and update the data on the use of St John's Wort as an antidepressant. A Medline search was conducted for the period January 1985 to December 1999. The search included other aspects of the usage of St John's Wort, such as side-effects, mechanism of action and drug interactions.

RESULTS

While two overviews and four clinical trials have recently been published, there is little data comparing St John's Wort against therapeutic doses of standard antidepressants.

CLINICAL IMPLICATIONS

St John's Wort is generally well tolerated, and an effective antidepressant. The current evidence indicates that it is less effective than standard antidepressants for severe depression. While some of the available data suggests equivalent efficacy as sub-therapeutic doses of tricyclic antidepressants in mild to moderate depression this requires further confirmation. One recently published paper suggests that St John's Wort has equivalent efficacy to fluoxetine in mild to moderate depression. The appropriate therapeutic dose needs clarification.

Usually known as St John's Wort, extracts of the plant *Hypericum perforatum*, have been used as an antidepressant for over 2000 years. In Germany St John's Wort is licensed for depression, anxiety and insomnia. There is increasing interest in the use of St John's Wort in the popular media (Bestic, 1999).

Mechanism of action

The mechanism of action of St John's Wort is unclear (Wong *et al*, 1998). It contains at least 10 different chemicals, which may have antidepressant efficacy (Linde *et al*, 1996). Most studies have concentrated on the antidepressant activity of the two naphthodianthrons (hypericin and pseudohypericin). Other biologically active chemicals could include hyperforin xanthones, proanthocyanidins, carotenoids, bioflavonoids and flavonoids (for example, quercetin; Pepping, 1999). These different components may work in different ways.

It has been suggested that St John's Wort inhibits monoamine oxidase (MAO) (Bennett *et al*, 1998). A number of studies, however, have been unable to confirm this (Wong *et al*, 1998). St John's Wort has been shown to affect serotonin, γ-aminobutyric acid (GABA), dopamine and noradrenaline neurotransmitter systems (Wheatley, 1998). It has, therefore, been suggested that this combined action on several transmitters, each insufficient for activity, accounts for the antidepressant effect of St John's Wort (Bennett *et al*, 1998).

Clinical studies

Most of the published trials on the usage of St John's Wort originate from Germany. One major limitation of all the data is that only generally hypericin is considered to have antidepressant activity.

Linde *et al* (1996) published an overview and meta-analysis of the randomised trial data. The paper identified 37 randomised trials that used preparations containing hypericin. Fourteen trials were excluded for various reasons, for example, the lack of a placebo or antidepressant control. Twenty-three trials, fifteen placebo-controlled and eight versus another antidepressant or a benzodiazepine involving 1757 out-patients with mainly mild or moderately severe depression were reviewed. Twenty trials were double-blind, two were open and one was single-blind.

There were 13 trials that compared hypericin with placebo. In the hypericin group 55.1% of patients responded, this compared with 22.3% in the placebo group (pooled rate ratio 2.67; 95% CI 1.78–4.01). There were three trials of hypericin and two trials of combination preparations containing hypericin against standard antidepressants. The results showed that 63.9% of patients taking hypericum alone responded compared with 58.5% of patients on standard antidepressants (pooled rate ratio 1.1; 95% CI 0.93–1.31). Whereas 67.7% of patients on combination products responded, compared with 50% of patients on standard antidepressants (pooled rate ratio 1.52; 95% CI 0.78–2.94).

Linde *et al* (1996) noted major limitations with the meta-analysis. First, some trials were published more than once. Second, the study format of the various trials varied considerably. The studies did not classify depression consistently, used heterogeneous patients and various rating scales, most frequently the Hamilton Depression Rating Scale (HAM–D; Hamilton, 1960) and the Clinical Global Impression (CGI; Guy, 1976). Seven different hypericin products and two different combination products were used. There was a large range in the daily doses of hypericin and St John's Wort extract (0.4–2.7 mg, and 300–1000 mg respectively). Lastly, although most of the trials were double-blind, hypericum has a characteristic taste, which could lead to unblinding.

Other limitations included inadequate trial durations. The maximum duration was 12 weeks, and the majority of trials lasted six or less weeks. The comparison antidepressants were tricyclic agents such as imipramine, amitriptyline, maprotiline and desipramine. The doses of tricyclics ranged from 30–150 mg, with the majority of trials using sub-therapeutic daily doses of 75 mg or less.

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None of the trials compared hypericum with selective serotonin reuptake inhibitor (SSRI) antidepressants, where underdosing is less common. Linde *et al* (1996) concluded that while there is good evidence that St John's Wort is more effective than placebo in treating depression, future trials should involve standard antidepressants.

Volz (1997) reviewed the literature and came to a similar conclusion, expressing similar concerns about the studies.

Since the Linde *et al* (1996) review was printed, four studies which compared St John's Wort with standard antidepressants have been published (Vorbach *et al*, 1997; Wheatley, 1997; Harrer *et al*, 1999; Philipp *et al* 1999). Unfortunately, only two studies used therapeutic doses of standard antidepressants (Vorbach *et al*, 1997; Harrer *et al*, 1999).

A recent randomised, double-blind six-week study compared 1800 mg daily of a special extract of St John's Wort called LI160 with 150 mg daily of imipramine (Vorbach *et al*, 1997). The trial involved 209 patients, 107 received LI160 and 102 received imipramine. There were no significant differences between the two groups. Every patient in the trial had an ICD–10 F 33.2 diagnosis (severe episode of major depression, recurrent without psychotic symptoms; World Health Organization, 1992). Patients did not receive any other medication except chloral hydrate for insomnia, they were also allowed to continue taking lithium.

The HAM–D, the CGI and the Von Zerssen Depression Scale (VZD; Zerssen *et al*, 1974) were taken at Days −3, 0, 7, 14, 28 and 42 to measure depressive symptoms. In the comparison between treatments Vorbach *et al* assumed equivalent efficacy if the difference in the results was within a 25% deviation (i.e. they were within 25% of each other). After six weeks the HAM–D score for the patients taking LI160 had dropped from 25.3 to 14.4. In the imipramine group the score had decreased from 26.1 to 13.4. This result and the changes in the CGI and VZD scales were not statistically equivalent within the 25% deviation interval. In all cases there were greater improvements in the imipramine group.

The results were analysed to identify the number of patients in each group who showed a 50% and 33% reduction in the total HAM–D score. In the LI160 group there were 35.3% and 57.9% responders respectively; this compared with 41.2% and 62.7% response rates in the imipramine group. These results were statistically equivalent within the 25% deviation interval.

One major limitation of the trial was the lack of a placebo. While acknowledging the superior efficacy of imipramine in severe depressive disorders, Vorbach *et al* suggested that the low incidence of side-effects with St John's Wort may improve compliance and therefore the treatment of depression.

One recent eight-week study, which received a great deal of media attention compared placebo and sub-therapeutic doses of imipramine (100 mg daily) with St John's Wort (Philipp *et al*, 1999). The study involved 263 patients with moderate depression, and used standard rating scales including the HAM–D. The results showed that St John's Wort was as effective as imipramine in the treatment of depressive symptoms.

A six-week double-blind study compared LI160 990 mg daily (n=83) with amitriptyline 75 mg daily (n=73) in the treatment of mild to moderate depression (Wheatley, 1997). The HAM–D, the CGI and the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) were used to measure response at the start and end of a 3–7 day placebo trial, and after two, four and six weeks. If the HAM–D score decreased by 25% or more during the placebo period, the patient was excluded from active therapy.

After six weeks 67 patients (81%) were still receiving LI160 and 54 patients (74%) amitriptyline. The mean decreases in the HAM–D and MADRS rating scales were significantly greater in the amitriptyline group ($P<0.05$). There was a significant improvement in the CGI scale in both groups ($P<0.001$), but no significant difference between the two groups. Wheatley (1997) then classified patients as either responders (>50% reduction or a HAM–D score <10) or non-responders. In the LI160 group 59.7% of patients responded, compared with 77.8% in the amitriptyline group, and it was concluded there was no significant difference in the number of patients who responded (P=0.064). Limitations of this study included the short duration, relatively low dose of tricyclic antidepressant, and the lack of a placebo group.

One recent randomised double-blind trial compared 20 mg daily of the SSRI antidepressant fluoxetine, with 800 mg of the St John's Wort extract LoHyp-57 (Harrer *et al*, 1999). The six-week study involved 149 patients with mild to moderate depression according to ICD–10 criteria (World Health Organization, 1992). The primary outcome measure was the HAM–D scale. Secondary outcome measures included the CGI scale. Depressive symptoms, rated with the HAM–D scale indicated that there was equivalent efficacy. Interestingly, there was a trend towards a greater improvement with St John's Wort in mild depression, and fluoxetine in moderate depression. These differences did not reach statistical significance. The improvements in the CGI scale were greater in the patients on fluoxetine.

Side-effects

St John's Wort appears generally to be very well tolerated. In an open study involving 3250 patients by Woelk *et al* (1994), the most common side-effects were gastrointestinal symptoms (0.6%), allergic reactions (0.5%) and fatigue (0.4%).

In one clinical trial 25 (23%) patients taking LI160 reported adverse effects (Vorbach *et al*, 1997). This compared with 42 (41%) of patients on imipramine. This result was not equivalent within the 25% deviation interval, and indicated that LI160 caused fewer adverse events. The Linde *et al* (1996) study also reported that St John's Wort was well tolerated. The drop-out rate in patients having hypericum (4.1%) was comparable to placebo (4.8%).

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St John's Wort has been reported to cause photosensitivity (Brockmoller *et al*, 1997). There is a report of subacute neuropathy in the sun-exposed skin of a 35-year-old woman who had been taking St John's Wort for four weeks (Bove, 1998). The condition improved after St John's Wort was discontinued.

Drug interactions

All the trials used St John's Wort as monotherapy. St John's Wort affects levels of serotonin and noradrenaline in the central nervous system, therefore there is a theoretical risk of a serotonin syndrome reaction when taken with conventional antidepressants (Pepping, 1999). A recent paper has reported a possible serotonin syndrome in five separate patients taking St John's Wort and SSRI antidepressants (Lantz *et al*, 1999). Concomitant administration of St John's Wort and monoamine oxidase inhibitors should also be avoided.

A recent review suggested that St John's Wort possessed enzyme-inducing properties, which could account for the reports of St John's Wort reducing plasma levels of concomitant medication including warfarin, theophylline and cyclosporin (Ernst, 1999).

St John's Wort is available from health food shops and pharmacies. Clinicians should advise patients not to self-medicate with St John's Wort while on standard antidepressants.

Comment

Interest in the use of St John's Wort as an antidepressant is increasing. There are major limitations with most of the currently published studies. There is, therefore, an urgent need for controlled trials of sufficient duration against therapeutic doses of standard antidepressants.

There is good evidence suggesting St John's Wort is more effective than placebo. The current data, however, indicates that St John's Wort is not as effective as therapeutic doses of standard antidepressants in severe depression. In clinical practice its use may be restricted to mild or moderate depression, where some data have shown St John's Wort to have equivalent efficacy to low doses of conventional antidepressants. For such patients a possible advantage of St John's Wort is that it causes relatively few side-effects.

The effective therapeutic dose and pharmacologically active components of St John's Wort require confirmation.

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Ian Maidment Clinical Pharmacist, Pharmacy Department, Hellesdon Hospital, Drayton High Road, Norwich NR6 5BE

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