Hypericum perforatum Extract (St. John’s Wort) for Depression

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Depression is a chronic disorder that produces as much functional limitation and morbidity as do chronic diseases such as hypertension and diabetes, and it is one of the costliest illnesses in the United States. A lifetime prevalence rate of approximately 17% and a recurrence rate of more than 50% have been reported for major depression. Depression has been identified in 15% of community-dwelling elderly persons, and major depressive disorder in 1%. Current treatments for depression include electroconvulsive therapy, various forms of psychotherapy, and medications (sometimes combined with psychotherapy). Medications include the tricyclic antidepressants and, more recently, the serotonin and norepinephrine reuptake inhibitors. Extracts of Hypericum perforatum (St. John’s wort; hereafter referred to as hypericum) have also gained a reputation as efficacious and well-tolerated antidepressants. For example, in Germany, hypericum is one of the most widely used antidepressant drugs, with more than 3.7 million prescriptions in 1997 and a market share of more than 25% of all antidepressant prescriptions.

MECHANISM OF ACTION OF HYPERICUM

The precise mechanism of action of hypericum in mild to moderate depression is unknown and the active component or components have not been identified. Hypericum contains a broad range of constituents, of which more than 15 substances may be responsible for the antidepressive effect. Data regarding hypericum’s active compounds are not consistent, and several hypotheses have been proposed regarding its mechanism of action. One active constituent of hypericum that appears to be largely responsible for its antidepressant effect is hypericin, a naphthodianthrone derivative. Accordingly, the production of commercially available drugs from hypericum has been standardized on their hypericin content. However, the role of hypericin in the antidepressive action of hypericum has been questioned.

In 1984, Suzuki et al. reported that, in mice, hypericin and pseudohypericin had a pronounced inhibiting effect on monoamine oxidase, which is involved in the metabolism of serotonin and catecholamine neurotransmitters such as epinephrine, norepinephrine, and dopamine. More recently, however, Yu found that hypericin had a weak inhibitory effect on monoamine oxidase in mice, but that 5-hydroxyindoleacetic acid (5-HIAA) levels were significantly increased in the cerebral cortex, hypothalamus, hippocampus, and caudate 3 hours after treatment with a dose as low as 10 mg/kg. An increase in serotonin levels was also observed in the hypothalamus and the hippocampus. Levels
of 5-HIAA in the brain were not enhanced after the long-term administration of hypericum. Hypericum significantly reduced the plasma levels of tryptophan, the precursor of serotonin. These results are consistent with the notion that the serotonergic system is involved in the actions of hypericum, but that its effects on the levels of 5-HIAA and serotonin in the brain appear to be different from those of classic serotonin reuptake blockers or selective serotonin reuptake inhibitors (SSRIs).

In an in vivo study of rats, Di Matteo et al. demonstrated that hypericum caused a slight but significant increase in dopamine outflow in both the nucleus accumbens and the striatum. The maximum increase of dopamine efflux in the nucleus accumbens occurred 100 minutes after the administration of hypericum. In the striatum, hypericum maximally enhanced dopamine outflow (+24.8 ± 7.5%, relative to the control group) 80 minutes after administration. Extraneuronal dopamine levels were not significantly affected by hypericum, nor (at 1 mg/kg orally) did it produce any significant effect on either serotonin or 5-HIAA efflux in the ventral hippocampus.

This study shows for the first time that hypericum is capable of increasing the in vivo release of dopamine. These results are in accordance with those of Bjerkenstedt et al., who found that in depressed patients treated with citalopram, 5-HIAA was reduced and the dopamine metabolite homovanillic acid was elevated in the cerebrospinal fluid. In depressed patients, zimelidin (an SSRI) has been shown to increase the levels of homovanillic acid in the cerebrospinal fluid, indicating that the monoaminergic systems seem to be interrelated. Fuxe and Dray et al. have shown that the dopamine-containing cell bodies in the mid brain receive a noradrenergic and possibly a 5-hydroxytryptaminergic innervation, suggesting that an effect on one of the systems will also affect the others. Furthermore, central dopamine metabolism might be involved in the pathophysiology of depression.

Hyperforin, another constituent (chloroglucinol derivative) of hypericum, recently attracted interest because it has been shown to be the major reuptake-inhibiting component of hypericum. Laakman et al. reported that among 147 out-patients with mild to moderate depression (per DSM-IV criteria) treated with one of two hypericum preparations differing only in their hyperforin content, significantly greater improvements (Hamilton Rating Scale for Depression scores) were seen for those receiving the preparation with the higher hyperforin content. In a recent in vitro study, Singers et al. found that hyperforin inhibits serotonin uptake by elevating free intracellular Na⁺. Participants at a recent conference on the pharmacology of hypericum concluded that hyperforin seems to be the most important active compound responsible for hypericum’s therapeutic effect.

A reuptake inhibition of norepinephrine and serotonin by hypericum was reported in 1997, suggesting a mechanism of action similar to that of the tricyclic antidepressants and the SSRIs. In an in vitro study, Helgason found that hypericum, unlike serotonergic antidepressants, failed to enhance natural killer cell activity, indicating that it possesses, at best, weak serotonergic activity. According to Hartvig, a combination of low-grade monoamine oxidase inhibition and norepinephrine and serotonin reuptake blockade seems to be involved in hypericum’s antidepressive action. Other candidates that have been proposed for the antidepressant effect are the flavonoids (eg, quercetin), xanthones, and bioflavonoids.

**Efficacy of Hypericum**

For more than 20 years, the antidepressive effects of hypericum have been investigated in several controlled studies. In 1979, Hoffmann and Kühl conducted a 6-week, placebo-controlled, clinical trial of verum, a hypericum preparation, in 60 patients diagnosed as having mild to moderate depression. Since then, more than 30 controlled trials of the efficacy of hypericum in depression have been published; their results have been summarized in several reviews.

Four recent double-blind studies have compared hypericum with a tricyclic antidepressant (imipramine) and SSRIs. Philipp et al. compared hypericum (STEI 300, Steiner Arzneimittel, Berlin, Germany) (1,050 mg/d) and imipramine (10 mg/d) in an 8-week, double-blind, placebo-controlled, randomized study of 263 patients with a current episode of moderate depression.
The two medications were equally efficacious and both were superior to placebo in reducing scores on depression and anxiety scales (ie, the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety, and the Zung Depression Scale). In a multicenter, randomized, double-blind trial, 324 outpatients with mild to moderate depression received hypericum (ZE 117, Bayer Vital, Leverkusen, Germany) (500 mg/d) or imipramine (150 mg/d) for 6 weeks. Both treatments improved scores on the Hamilton Rating Scale for Depression and the Clinical Global Impressions scale, with no significant between-group differences. Hypericum was superior to imipramine on a 5-point scale used to assess tolerability. In a 7-week, double-blind, randomized study of 30 patients with mild to moderate depression, Brenner et al. demonstrated that hypericum (LI 160, Lichtwer Pharma AG, Berlin, Germany) (500 mg/d) was as effective as sertraline (75 mg/d) for this population (per scores on the Hamilton Rating Scale for Depression and the Clinical Global Impressions scale). Both agents were well tolerated. Schrader conducted a randomized, double-blind study of hypericum (500 mg/d) and fluoxetine (20 mg/d) in 240 subjects with mild to moderate depression. After 6 weeks, scores on the Hamilton Rating Scale for Depression were similarly reduced in the two groups, but both the Clinical Global Impressions scale severity score and the responder rate were significantly better in the hypericum group (P < .05). Substantially fewer adverse events were reported for the patients receiving hypericum.

ADVERSE EVENTS AND DRUG INTERACTIONS WITH HYPERICUM

Because most depressed patients are treated as outpatients, it is important that a safe and well-tolerated antidepressant be prescribed to ensure compliance and avoid fatal overdoses. The SSRIs are less toxic than the tricyclics, but are associated with severe adverse events such as sexual dysfunction and gastrointestinal bleeding. Sexual dysfunction can be a serious threat to compliance with treatment. Fatal overdoses of the SSRIs have also been reported.

In general, hypericum has been found to be safe and well tolerated and associated with fewer adverse events than the synthetic antidepressants. In several studies, the overall incidence of side effects with hypericum was found to be comparable to that with placebo. One rare adverse effect of hypericum is phototoxicity after prolonged exposure to sunlight in subjects receiving high or very high doses. Symptoms include dermal erythema, rash, and pruritus. Brockmoller et al. reported a slight increase in dermal sensitivity to solar-stimulated and selective ultraviolet-A irradiation in subjects after 15 days of treatment with 1,800 mg/d of hypericum (twice the normal recommended dose). There is one report of toxic neuropathy in a 35-year-old woman receiving a therapeutic dose of hypericum (500 mg/d) after prolonged exposure to sunlight.

Potential drug interactions include mild serotonin syndrome in patients who combine hypericum with an SSRI, and reduced bioavailability of digoxin, theophylline, cyclosporine (lowering of serum content), and the contraceptive ethinyl estradiol plus desogestrel (breakthrough bleeding) when combined with hypericum. Studies indicate that hypericum may induce certain subenzymes of the cytochrome P-450 enzyme system. Piscitelli et al. recently reported that hypericum reduced the bioavailability of indinavir, a human immunodeficiency virus-1 protease inhibitor, by a mean of 57%. Protease inhibitors are substrates of the CYP 3A4 isozyme. The authors reported that this could lead to drug resistance and treatment failure in patients with human immunodeficiency virus. Ruschitzka et al. reported that hypericum was responsible for acute heart transplant rejection in two patients; the bioavailability of the immunosuppressive agent cyclosporine, which is metabolized by CYP 3A of the P-450 system, was reduced to below the therapeutic range when the patients started to take hypericum.

Because of these possible drug interactions, caution is warranted and clinicians should warn patients not to mix herbal and pharmaceutical drugs. Clinicians should routinely ask patients whether they use alternative medicines, such as herbal drugs, before prescribing other drugs. Furthermore, if hypericum is to be discontinued,
extra caution must be taken. The enzyme induction by hypericum makes it necessary to first reduce the dose of other drugs to avoid toxic reactions.

In his analysis of the clinical safety of hypericum, Ernst commented that, “It is not possible to know to what extent the use of different products and dosages may produce different outcomes in terms of adverse drug reactions.” Different preparations of hypericum, standardized to different concentrations of hypericin and administered in various dosages, have been used in clinical trials. Thus, double-blind, placebo-controlled comparisons with active controls must be performed for each antidepressant based on hypericum, as concluded in the meta-analyses of Linde et al. and Kim et al.

CLINICAL TRIALS OF HYPERICUM

One of the main indications for hypericum is mild to moderate depression. Until approximately 10 years ago, these subtypes of major depression were not pharmacologically treated at all. The indications for the SSRIIs have been expanded from severe to moderate and even mild depression to other disorders such as panic disorder, obsessive-compulsive disorder, and bulimia.

Patients with mild to moderate depression generally appear in the offices of general practitioners, not at psychiatric clinics. Thus, most investigators in clinical trials of hypericum have been general practitioners. The primary measures of antidepressive efficacy have been such rating scales as the Hamilton Rating Scale for Depression, the Montgomery–Asberg Depression Rating Scale, and the Zung Depression Scale. However, general practitioners generally do not have the basic knowledge of how to apply these scales.

As noted recently by Thornett, the education of general practitioners to recognize different types of depression and to treat them is urgently needed. For instance, it is extremely important to screen patients for a history of hypomania, mania, or cycling of mood states before starting treatment with hypericum. In many of the studies of the efficacy of hypericum, the quality of the investigators’ training is not evident (e.g., there are no data on inter-rater reliability).

As can be seen from the tables in the results sections of the reports of clinical trials, the standard deviations of the rating variables are greater than expected, from which it can be inferred that there is insufficient training of the investigators. As a consequence, the statistical power of the studies is undermined with an increased risk for type II errors (a decreased chance of rejecting a false null hypothesis).

Depression rating scales are not congruent with the diagnostic system of the DSM-III-R or the DSM-IV. Thus, the Hamilton Rating Scale for Depression is overloaded with items that measure sleep disturbances, and the Montgomery–Asberg Depression Rating Scale contains no item regarding psychasthenia. Furthermore, depression rating scales do not adequately emphasize the core symptoms of depression, namely sadness and a loss of initiative. The items are arbitrarily summarized into global scores that can contain any of the items. More sophisticated ratings scales of depression are urgently required.

In clinical studies, hypericum is usually compared with another antidepressive drug. This is not an adequate design. Equivalent efficacy of two drugs cannot be interpreted as an efficacy of both drugs because the efficacy of tricyclics or SSRIIs has not been demonstrated in mild to moderate depression. Neither drug might be efficacious. Thus, a three-armed study (hypericum, an active control, and placebo) is essential, as in the study by Philipp et al. A high placebo response has been reported in patients with depression. In an analysis of more than 80 studies, the authors reported mean response rates of 50% for antidepressants and 32% for placebo in patients with major depression. Shelton et al. recently published a study in which hypericum was compared with placebo for patients with major depression (score on the Hamilton Rating Scale for Depression of at least 20). The authors reported no significant difference between the two treatments. The methodology of the study (particularly the two-arm design and patient selection) has since been criticized.

CONCLUSION

There are several reasons to believe that the prevalence of depression and its treatment will
increase. In the Western world, the number of elderly individuals is growing, and the prevalence of depression increases with age. Many agents are now available for the treatment of depression. The results of two studies published in 1997 suggest that a reduced suicide rate in Sweden resulted from a more generous pharmaceutical treatment of depression.

Newer antidepressant agents include selective inhibitors of the reuptake of serotonin (SSRIs), noradrenaline, or both; drugs with distinct neurochemical profiles, such as mirtazapine, nefazodone, and moclobemide; and substance P antagonists. Meanwhile, several other potential therapeutic targets are being explored. Hypericum will no doubt have a place in this antidepressant armamentarium on the grounds of its efficacy, tolerability, and cost-effectiveness in the management of mild to moderate depression.

REFERENCES
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