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St. John's Wort**An option for the primary care treatment of depressive patients?**

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Abstract This article reviews the historical background, active ingredients of St. John's Wort and the major double-blind placebo-controlled studies. Despite the two major failed clinical trials conducted in American Research Centers, most of the data reviewed support that hypericum extracts are more effective than placebo for the treatment of mild to moderate depressive illness. The authors examine the likely reasons for the failed studies and also describe drug interactions and the side effects of St. John's Wort. Those patients who are prescribed St. John's Wort should be closely monitored.

Key words St. John's Wort · Hypericum · randomised double-blind controlled studies · depression

Introduction

An increasing acceptance of mental illness and consumer awareness of individual health issues has seen an emergence of herbal remedies as an alternative health care measure. A member of the Hypericaceae family, St. John's Wort (SJW) has been used in folk medicine for more than 2000 years. More recently it has gained considerable international awareness and is now successfully competing to take its place as an antidepressant with an increasing market share estimated at \$6 billion in Europe alone (Greeson 2001). A tolerant and more rational approach to phytotherapy, together with the practice of evidence-based herbal medicine, has resulted in several clinical trials of SJW against placebo, tricyclics and the selective serotonin reuptake inhibitors. These trials have not necessarily produced results that help re-

solve the issue of therapeutic efficacy of St. John's Wort fully and decisively. This article aims to provide an updated review of all areas of major interest on SJW in clinical practice.

Historical background

St. John's Wort (*Hypericum perforatum*) is a perennial herb that grows widely in Europe, Western Asia, North Africa and America. Its therapeutic virtues have been known since antiquity. It is named after St. John's Feast Day, which, according to legend, is the day after midsummer's eve, around the time of the summer solstice; the herb commonly blossoms in late June. St. John's Wort would be hung on house and stall doors on St. John's Feast Day to safeguard against demons and their spells, and also against harm and sicknesses to man and livestock. It is a sparse, taut, red-dyed shrub with blossoms which, when they are rubbed between the fingers, release a blood-like sap, for which reason it is also known as *Andro Haimon* (Mar's blood). It is the red liquid that contains the biologically active compounds.

In the 13th century St. John's Wort is mentioned in the medicinal plants list of the medical School of Salerno as *Herba demonis fuga* or "the herb that chases away the devil". In 1525 the plant was established by Paracelsus for the treatment of depression, melancholy and overexcitability. In the early 17th century the Franciscan monks used it as *Fuga Daemonum*. When the therapeutic application of herbal drugs was noticed, the (medicinal) psychotropic effects were attributed to a placebo effect. Its popular use in Germany to overcome fatigue, malaise and depression has led the way for Hypericum extracts to be used and studied under scientific and objective methods. The postulated anti-depressant effects have been observed in earlier clinical studies. Several European countries now recognise SJW more or less as an effective antidepressant in their pharmacopoeias.

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Active ingredients

The genus *Hypericum* consists of more than 370 species; *H. perforatum* itself is divided into four subspecies that are distinguished by the size of their sepals (Schutt & Schulz 1993). The chemical constituents are predominantly accumulated in the flowers. Seven groups of bioactive natural products have been identified from *H. perforatum* (Southwell & Campbell 1991; Bratner et al. 1994; Cellarova et al. 1994). Table 1 gives a summary of the active ingredients of *Hypericum perforatum*.

All antidepressant preparations made from SJW are based on alcoholic extracts, and generally have a herb-to-extract ratio in the range of 4:1 to 7:1. Hyperforin has been considered more important than hypericin in its antidepressant activity. Most clinical trials to date have used *Hypericum* extract LI 160. The crude drug and its alcohol extract contain 10 times more hyperforin (2–6%) than hypericin. Hyperforin is unstable and is subject to oxidative breakdown; in the plant it is protected by the antioxidant properties of flavonoids (Erdelmeier 1998).

Mechanism of anti-depressant action

Hypericum extract has been extensively studied in small animals (rodents) with respect to pharmacological interactions and induced behavioural changes such as learned helplessness or despair (Porsolt et al. 1991). While *Hypericum* LI 160 is only a weak inhibitor of MAO-A and MAO-B activity (Cott 1997), it inhibits the synaptosomal uptake of serotonin, dopamine and norepinephrine with about equal affinity (Perovic & Müller 1995; Müller et al. 1997, 1998). This implies that *Hypericum* affects the central monoamine concentration, and indicates that *Hypericum* extract acts via similar biochemical mechanisms to other antidepressants, e. g. tri-

cyclics (Müller et al. 1998) and particularly the SSRIs (Greeson et al. 2001).

The long-term adaptation effects of chronic *Hypericum* administration on the 5-HT_{1A} and 5-HT_{2A} affinity and density have been examined within the rat central nervous system for 26 weeks with a commercially available *Hypericum* extract (2700 mg/kg LI 160). There was a significant down-regulation of β -receptors without a change in receptor affinity, an up-regulation of 5-HT_{1A} post synaptic receptors without a change in receptor affinity, and an up-regulation of 5-HT₂ receptors (Müller et al. 1997; Teufel-Mayer & Gleitz 1997).

5-HT_{1A} receptor findings are consistent with a modification of the expression levels of serotonergic receptors caused by other antidepressants, whereas 5-HT₂ receptor expression is in contrast to the effect of SSRIs. However, this modulation does resemble the action of repeated electroconvulsive treatments on 5-HT₂ receptor expression (Müller et al. 1997; Nathan 1999).

Quantitative electroencephalographic studies with *hypericum* in humans show an increase in the serotonergic (alpha activity), noradrenergic (theta activity) and the cholinergic (delta activity) neurotransmissions (Dimpfel et al. 1999; Schellenberg et al. 1998). Changes in the pattern indicative of improved cognition and relaxation (Dimpfel et al. 1999) as well as an increase in the latency of rapid eye movement in human sleep have also been observed with the use of *Hypericum* (Sharpley et al. 1998).

Hypericum perforatum extracts also increase locomotor activity, affect exploratory behaviour and exert anxiolytic effects when studied in well-validated animal behaviour models of depression. Treatment with hyperforin was associated with improved resistance to stress in the forced swimming test and the learned helplessness test (Bhattacharya et al. 1998; Chatterjee et al. 1999).

In conclusion, there is some indirect evidence that *Hypericum* extracts exert antidepressant activity by a) synaptic inhibition of 5-HT reuptake, noradrenalin reuptake and dopamine reuptake, and b) modulation of neurotransmitter receptor density and sensitivity by down-regulation of beta receptors and up-regulation of 5-HT₁ and 5-HT₂ receptors, pharmacological effects that are also seen with the old tricyclics and with the new generation of antidepressants.

Clinical studies

The therapeutic efficacy of *Hypericum perforatum* extracts in the treatment of depressive illness has been examined in clinical studies since the late 1970s. So far approximately 40 different clinical trials have been reported. Ernst (1995) reviewed 12 randomised controlled clinical trials of *Hypericum* extracts and concluded that there was adequate evidence that *Hypericum* extracts were effective in the treatment of depressive illness. Linde et al. (1996) performed a meta-analysis of 23 randomised clinical trials of *Hypericum*

Table 1 *Hypericum perforatum*: Biologically Active Compounds. (Nahrstedt & Butterweck, 1997)

<ul style="list-style-type: none"> • Phenylpropane <ul style="list-style-type: none"> – Chlorogenic acid – Caffeic acid • Flavonol Glycosides <ul style="list-style-type: none"> – Quercetin – Quercitrin – Hyperoside – Kaempferol – Luteolin • Biflavones <ul style="list-style-type: none"> – Amentoflavone 	<ul style="list-style-type: none"> • Tannins and Proanthocyanidins • Xanthones <ul style="list-style-type: none"> – 1,3,6,7-Tetrahydroxyxanthone • Phloroglucinols 2–5 % Flower buds Hyperforin • Naphodianthrones <ul style="list-style-type: none"> – Protohypericin – Hypericin – Pseudoprotohypericin – Pseudohypericin – Cyclopseudohypericin – Emodinanthrone • Essential Oils • Amino Acid (e. g. GABA)
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extracts including a total of 1757 outpatients with mild to moderate depressive illnesses. Fifteen of these clinical trials were placebo controlled, and 8 had compared Hypericum with another antidepressant. The authors concluded that there was evidence that Hypericum extracts were more effective than placebo for the treatment of mild to moderately severe depressive disorders. However, Kunze and Priebe (1998) challenged these conclusions on the grounds that these studies were mostly performed in Germany and lacked objective outcome measures. While most clinical studies pointed towards some antidepressant activity of Hypericum extracts, criticism was further made that the performed trials were not necessarily rigorous in their design, inclusion criteria and methodology. The studies lacked diagnostic rigor, the comparator medicine was used in sub-therapeutic doses, there was a high placebo response (indicative of recruitment of patients with mild transient depressive episodes), and, finally, data on side effects were insufficiently analysed (Deltito & Beyer 1998).

Kim et al. (1999) performed a meta-analysis of six well-designed clinical trials with regard to DSM-III-R, DSM-IV or ICD-10 as the inclusion criteria and the Hamilton Depression scale to review the severity ratings. These authors highlight methodological concerns, for example that psychiatric assessments were conducted by the family practitioners, study duration was inadequate, and objective outcome measures were lacking. Linde & Mulrow (2000) conducted another meta-analysis and concluded that Hypericum extracts were more than twice as effective as placebo (56% vs. 25%), as effective as the tricyclic antidepressants (50% vs. 52%), and safer with respect to the incidence of side effects. Gaster and Holroyd (2000) reported that while Hypericum extracts were effective in the treatment of depression, the response rate was 6–18% lower than the rate for patients treated with the tricyclic antidepressants.

The most recent review was conducted by Whiskey et al. (2001). These authors identified 22 randomised controlled trials. Using a random effect size model, their meta-analysis showed that SJW is significantly more effective than placebo, with a response of 1.98 (CI 95%, 1.49–2.62), i.e. almost twice that with placebo but not significantly different in efficacy from active antidepressants. The authors sub-analysed 10 studies with more strict methodology. They found no publication bias. Adverse effects occurred more frequently with standard antidepressants than with SJW. Six of the placebo-controlled and four active comparator-controlled studies (Whiskey et al. 2001) of the 22 analysed by these authors, and an additional three studies that have since appeared in publications, are described in Tables 1 and 2. These studies are considered to satisfy methodological requirements.

In order to advance the debate on the efficacy of SJW and in view of the two recent failed clinical trials of SJW in the treatment of depression, we will comment in considerable detail on some of these studies.

The therapeutic efficacy and tolerability of St. John's Wort in the treatment of mild to moderate depression has been established in recent, well-designed studies, including Phillip et al. (1999), Schrader et al. (1998) and Laakman et al. (1998). All these studies were placebo controlled and the study by Phillip et al. also included an imipramine control. However, some criticism has been made by Linde (Phillip et al. 1999) of the relatively low dose of imipramine (100 mg/day) used in this study.

The mass of positive evidence obtained from several more-or-less methodologically adequate studies is questioned by the negative results of some other studies performed in large samples of patients. These negative clinical trials are reviewed in somewhat more detail to try to detect possible reasons for their negative outcome.

In a multicentre study, Shelton et al. (2001) failed to demonstrate therapeutic efficacy of SJW versus placebo on both primary and secondary efficacy criteria. These criteria included as the primary outcome measure a change in the severity in the Hamilton Depression Rating Scale during the period of study. The secondary measures included the Beck Inventory (BDI), Hamilton Rating Scale for Anxiety (HAM-A), the Global Assessment of Function (GAF) scale, and the Clinical Global Impression-Severity and -Improvement scales (CGI-S and CGI-I). The response rates in the intention-to-treat analysis sample during the eight-week period did not differ significantly between the two treatment groups (26.5% for SJW vs. 18.6% for placebo; $p=0.02$). However a significantly higher remission rate was recorded for St. John's Wort (14.3% with SJW vs. 4.9% with placebo). It is noteworthy that this trial included patients referred from tertiary care clinics in academic medical centres and that a baseline score of 20 on the HDRS 17-item scale was an inclusion criterion. Furthermore, the average duration of major depression was two years. Thus, from the nature of the referral system and the inclusion criteria it would appear that many of these patients had moderate to severe recurrent depressive illness, and that they had perhaps also failed to respond to previous treatments and were generally difficult-to-treat patients. The authors themselves infer that the outcome of the trial could have been different if it had been performed in patients who were not chronically ill or who had been recruited from different referral systems.

To increase the body of evidence, more recently an important multicentre trial of SJW was performed in the USA supported by the National Centre for Complementary and Alternative Medicine and the National Institute of Mental Health (Davidson 2002). Three hundred and forty adult patients suffering from major depression participated in this double-blind, randomised study of SJW extract LI 160 versus sertraline and placebo. Outpatients older than 18 with a current diagnosis of major depression DSM-IV who scored at least 20 on the HDRS and had a maximum score of 60 on the Global Assessment of Functioning scale (GAF) at screening were considered eligible to enter the 8-week comparative study after a 1-week run-in period. The patients were ran-

Table 2 Randomised, double-blind, controlled studies of SJW extracts

Author	Clinical trial design and duration	SJW extract comparator medicine	Results	Comments
Vorbach et al. (1997)	Severe depressive episode ICD-10 F32.2 Double-blind, randomised 18–70 years 6 weeks 209 patients, 18–75 years	Jarsin 300 1800 mg Imipramine 150 mg	No statistically significant difference in efficacy between Hypericum and imipramine	Baseline HAMD score not defined. Original number of patients not mentioned 209 patients in final analysis.
Harrer et al. (1999)	Mild to moderate depression. ICD-10 F 32.0 and F 32.1 Double-blind, randomised HDRS-17 item 6 weeks 149 patients, 60–80 years	SJW LoHYP-57 – 800 mg Fluoxetine 20 mg	LoHYP57 71.4 % Fluoxetine 72.2 % Hypericum extract LoHYP57 Equivalent efficacy to fluoxetine	The authors have provided separate analyses for mild – moderate – severe depressives. The adverse events with Hypericum extract LoHYP57 were as high as with fluoxetine. Drop-out rates were also equal in both groups.
Phillipp et al. (1999)	Moderate depression ICD-10 F32.1 F33.1 HDRS-17 item 18 Zung CGI 8 weeks 263 patients, 18–65 years.	Hypericum STEI extract 1050 mg Imipramine 100 mg	Hypericum more effective than placebo and as effective as imipramine	The authors report Quality of Life ratings SF-36 and found that with Hypericum differences were large in the mental component of the scale. Hypericum extract superior to placebo in the physical component. Higher rate of side effects with imipramine quoted as the reason.
Woelk (2000)	Moderate depression ICD-10 F32.0 F32.1 F33.0 F33.1 HDRS 17 items 18 Zung CGI 6 weeks 324 patients, > 18 years	Hypericum ZE 117, 500 mg Imipramine 150 mg	No statistically significant difference in efficacy between Hypericum and imipramine Hypericum tolerated better than imipramine $P < 0.01$	Adverse events occurred in 63 % patients taking imipramine with 16 % dropping out. 39 % of the Hypericum-treated patients reported adverse events with 3 % dropping out.
Hypericum Depression Trial Study Group (2002)	Moderate to severe depression Double-blind, randomised DSM-IV HDRS-17 item 20 scores 8 weeks controlled 340 patients, > 18 years	Hypericum perforatum extract LI-160900–1500 mg. Placebo and sertraline 50–100 mg	Neither Hypericum nor sertraline were better than placebo	The adverse effects of sertraline were consistent with its profile, with nausea, diarrhoea and orgasmia, swelling and frequent urination relative to placebo. Similar adverse events occurred in the Hypericum group but less frequently.
Halama (1991)	ICD-9, 300.4 309.0 Double-blind, randomised Placebo-controlled HAMD 16–20 4 weeks 50 patients, 20–64 years old	Jarsin 900 mg	Hypericum extract is superior to placebo	HAMD total score result not reported.
Reh et al. (1992)	Double-blind, randomised Placebo-controlled 8 weeks 50 patients, 38–60 years old	Neuroplant 900 mg	Hypericum extract is superior to placebo	Heterogenous patient group included.
Laakman et al. (1998)	Double-blind, randomised Placebo-controlled DSM-IV 6 weeks 147 patients, 18–65 years old	Hyperforin 5 % WS 5572	Hypericum extract is superior to placebo	
Schrader et al. (1998)	Mild to moderate depression ICD-10 F32.0 F32.1 Double-blind, randomised Placebo-controlled 6 weeks 162 patients, > 18 years old	Z E-117 500 mg	Hypericum extract is superior to placebo	14% patients reported side effects with Hypericum and 25 % with fluoxetine ($P < 0.007$).
Montgomery et al. (2000)	Moderate depression Double-blind, randomised Placebo-controlled DSM-IV 296.2x 296.3x 12 weeks 247 patients, 18–65 years old	Jarsin 300 900 mg	At week 6 and after the exclusion of 2 centres due to very high placebo rates (more than 70 %), a high number of patients in the LI 160 group as compared to the placebo group were responders in both the intention-to-treat and per protocol population at week 6 ($p < 0.05$)	The exclusion of the two centres with high placebo response may be considered to minimise the placebo response, however, in recent years as an increasing number of clinical trials have failed to show the difference from placebo for the anti-depressant drug perhaps a mid-term analysis is the right thing to do.

Table 2 *Continued*

Author	Clinical trial design and duration	SJW extract comparator medicine	Results	Comments
Shelton et al. (2001)	Major depression, moderate to severe DSM-IV HAMD > 20 Randomised Placebo-controlled BDI, GAF HAMA CGI 200 patients, > 18 years old	Jarsin 300 900–1200 mg	SJW was not effective for the treatment of major depression	SJW was well tolerated with more than 80 % of both the SJW and placebo groups completing the study and only 1 % discontinuing due to adverse effects. Treatment-emergent adverse events occurred in 10 % of patients with abdominal discomfort, insomnia and headaches.
Lecrubier et al. (2002)	Mild to moderate depression Double-blind, randomised Placebo-controlled DSM-IV 296.21, 296.22, 296.31, 296.32 HAMD 17- items score 18–25 MADRS Symptom Check List-58 CGI 375 patients, 8–65 years old	SJW extract WS5570 Standardised 3–6 % Hyperforin and 0.12–0.28 % Hypericin	Hypericum extract WS5570 was found to be safe and more effective than placebo for the treatment of mild to moderate depression	30.6 % of the Hypericum-treated patients experienced adverse events compared to 37 % in the placebo group. The type of adverse events and their severity did not indicate any treatment emergent risks with WS 5570.

domly assigned to receive one of the three treatments in a 1:1:1 ratio. The primary efficacy criterion for full response was defined as a CGI score of 1 or 2, and a decrease in the HAMD total score of 8 or less. SJW Lichtwater extract LI 160 standardised to between 0.12 % and 0.28 % hypericin at a dose of 900–1200 mg was compared to sertraline 50–100 mg and a placebo equivalent. The number of patients allocated to each of the treatment groups was similar, as were the drop-out rates from these groups during the trial. Full clinical improvement as defined in protocol occurred in 31.9 % of the placebo-treated patients, 23.9 % of the Hypericum-treated patients ($p = 0.021$) and 24.8 % of the sertraline-treated patients ($p = 0.26$). On the two primary efficacy measures HAMD and the CGI-I score, neither sertraline nor the Hypericum extract was significantly different from placebo. Sertraline was better than placebo on the CGI improvement scale ($p = 0.02$), which was a secondary measure in the study. The study was adequately powered to detect moderate effect sizes (i.e. at least 0.41 on the CGI-I effect enhanced the lack of statistical significance on the primary outcome measure). Previous studies with sound methodology and a large population (Vorbach et al. 1997; Phillip et al. 1999; Woelk 2000) had sufficient power to find a 15–20 % difference (Whiskey et al. 2001) and were able to separate placebo from the active medicines.

Given the fact that also the active comparator was not superior to placebo in the primary outcome measures, this study has to be seen as a failed study. The reasons for this failure may be complex. Beside quite a high placebo response rate, especially in relation to the lower response rates in the sertraline group, the argument of overrepresentation of refractory patients has to be considered.

The study design of accepting referrals from tertiary centres would allow a number of resistant and partially resistant patients to be included who are not likely to re-

spond to an active treatment (Montgomery 1999; Robinson & Rickels 2000). It is also conceivable that in a large multicentre trial of this magnitude, it may not be possible to achieve a uniform implementation of the inclusion criteria and the performance of assessments strictly in accordance with the protocol requirements. This study gives no details of the inter-rater reliability co-efficient for the 12 academic centres involved in the study for either the inclusion or the primary efficacy criteria. Finally, the authors freely admit that the hyperforin content of the batch used in the study was 3.1 %, and that the formulation was not standardised to hyperforin, which has been considered an important active ingredient with antidepressant efficacy. Lack of standardisation of SJW is a known handicap (Greeson et al. 2001) that should have been considered in a trial of this magnitude.

The study by Montgomery et al. (2000) addresses in a practical manner the issue of recruitment disparities on placebo response in a multicentre trial. In a double-blind, randomised, placebo-controlled study of Jarsin 900 mg/day (LI 160), the authors performed an interim analysis at 6 weeks and found that two of their centres had a high placebo response rate of more than 70 %. When these two centres were excluded for the following six weeks of the double-blind period, a higher number of patients in the SJW extract LI 160 group than in the placebo group were found to be responders in both the intention-to-treat and the per protocol population at 6 weeks (SJW extract LI 160 66 % vs. placebo 45 %, $p < 0.05$). This can be viewed as a problematic statistical manipulation of the placebo response. However in their editorial on concerns about clinical drug trials, Robinson & Rickels (2000) recommend an interim analysis in drug development without compromising the double blindness. They also recommend that if one site is deviant, centre-by-treatment interaction can be tested and,

if present, the data from a particular site can be excluded from that final data analysis, or at least identified as being an outlier. This study also has the advantage that patients were recruited from general practices as well as from psychiatric outpatient clinics. Thus there was a lower risk of including difficult-to-treat patients, as are mostly found in tertiary research hospitals, or patients attracted by invitations to participate in research who may have acute stress reactions or mild to moderate transient depressive episodes.

The methodology in the study by Lecrubier et al. (2002) went a long way to overcome some of the shortcomings of the failed clinical trials. Their selection of patients does not involve referrals from tertiary centres for the enrolment in a double-blind placebo-controlled comparison. The SJW extract WS5570 with standardised contents of 3%–6% hyperforin and 0.12%–0.28% hypericin was used for the trial period. Interrater reliability of the assessments process was also achieved between various investigators from different participating centres to within two standard deviations from the mean rating. Three hundred and seventy five outpatients were enrolled from psychiatric outpatient departments attached to inpatient units or private practices. After 6 weeks of treatment the percentage of responders in the group receiving *Hypericum perforatum* extract was 52.7% versus 42.3% in the placebo group. This difference was significant, demonstrating a moderate effect size.

Comments made here on some of the studies highlight the necessity for a revision of the patient recruitment style and practices to antidepressant drug trials. The two negative American studies do not necessarily represent the last verdict on the therapeutic efficacy of St. John's Wort, as can be seen by the positive results of the two studies performed recently by Montgomery et al. (2000) and Lecrubier et al. (2002).

Another dimension to the argument in favour of the therapeutic efficacy of hypericum is added by Kaspar and Dienel (2002) in their cluster analysis of symptoms response to hypericum in 544 patients taken from three double-blind randomised multicentre trials. These authors found *Hypericum* extract accelerated the recovery from depression in a rather general manner, by influencing both the core symptoms Cluster 1 on the Hamilton Depression Rating Scale, items 1, 2, 3, 7, 8, 12, 13, 14, 14, 16, and Cluster 2, items 4, 5, 6, 9, 10, 11, 15, 17, the latter assessing depression-related anxiety and insomnia. The therapeutic profile of hypericum is thus characterised primarily by its effect on the core symptoms, which was found to be similar to the profile of selective serotonin reuptake inhibitors.

Drug interactions

Moore et al. (2000) have demonstrated that Hyperforin, a lipophilic component and constituent of St. John's Wort, is a potent ligand that regulates the expression of

cytochrome P450 (CYP)3A4 mono-oxygenase (Conney 1986), which plays a central role in the metabolism of many drugs. Clinical experience indicates that *Hypericum* extracts may interfere with the bioavailability of various drugs, including combined oral contraceptives, cyclosporin, indinavir and phenprocoumon (Moore et al. 2000; Piscitelli et al. 2000; Ruschitzka et al. 2000). The Swedish Medical Products Agency has received case reports of a reduced anticoagulant effect of warfarin (reduced International Normalised Ratio, INR) associated with the concomitant use of SJW. The agency has also received reports of inter-menstrual bleeding (break-through bleeding) and altered menstrual bleeding in women aged 23–31 (Yue et al. 2000). Furthermore, plasma levels of concomitant tricyclics may be lowered and there have been cases of Serotonin Syndrome reported by combining the use of St. John's Wort extract with serotonin reuptake inhibitors (Gordon 1998; DeMott 1998). The interaction study with digoxin did not confirm induction of cytochrome P450 by SJW, but suggested induction of the drug transporter P-glycoprotein, which mediates the intestinal absorption, distribution and renal excretion of digoxin (Johns et al. 1999).

The clinical implication is that patients taking *Hypericum* extracts with concomitant prescription of any of the medicines mentioned above run the risk of treatment ineffectiveness due to lowered plasma levels with concomitant use of SJW extracts and drug toxicity in the event of their sudden withdrawal (Baede-van-Dijk et al. 2000).

Concomitant administration of SJW extracts is now contraindicated in patients receiving cyclosporin (which is routinely prescribed in the prevention of graft rejection in kidney, liver and heart transplant patients, for nephrotic syndrome, severe active rheumatoid arthritis when other therapy is ineffective, and for severe psoriasis/atopic dermatitis).

Side effects

On the basis of information originating from reports of clinical trials (Whiskey et al. 2001; Harrer et al. 1999; Philipp et al. 1999; Schrader et al. 1998), post-marketing surveillance and drug monitoring studies, the drug safety monitoring bodies in Germany and Sweden (Yue et al. 2000) conclude in general terms that *Hypericum* is well tolerated with an incidence of adverse drug reactions (ADRs) of 2.4%. The most common adverse events reported are gastrointestinal discomfort, insomnia and headaches (Whiskey et al. 2001; Harrer et al. 1999; Philipp et al. 1999). Shelton et al. (2000) found that treatment-emergent headaches occurred more frequently in patients receiving SJW (41%) than in those receiving placebo (25%).

The study performed by Harrer et al. (1999) was the first double-blind comparative trial of *Hypericum* extract (LoHYP57) versus placebo in an elderly population. This study is unique in that it compared *Hypericum*

ricum extract against fluoxetine in an elderly population. Among its findings, the side effects of Hypericum extract for the elderly population were high and were comparable to the side effects caused by fluoxetine.

The use of St. John's Wort has resulted in several case reports of treatment-emergent classic symptoms of manic illness with and without previous history of similar episodes (Moses & Mallinger 2000; Nierenberg et al. 1999).

SJW extracts lead to an increase in cutaneous photosensitivity which can be compensated by reducing irradiation time by 21 %. Photo-toxic reactions are therefore proportional to the dose of St. John's Wort taken as well as the duration and the area of the body that is exposed to direct sunlight. The adverse reaction to sunlight can be minimised by decreasing the exposure time and the body area (Brockmoller et al. 1997). Lane-Brown (2000) reported three cases first presenting with erythematobullous dermatosis, commencing 20 hours after exposure to sunlight, with a previous history of cutaneous lupus erythematosus. The second patient developed follicular erythema, urticarial oedema and burning pain on receiving phototherapy for pre-existing psoriasis. The third patient had no pre-existing dermatological condition but developed frontal and maxillary bullae after spending a day on the beach. This observation is particularly important for patients living in countries with more intense and longer sunlight.

Czekalla et al. (1997) has reported a small acceleration in heart rate with high doses of Hypericum extract. No significant effect was seen on the PR interval in Hypericum-treated patients, indicating that atrial conduction was unaffected. Further, as there was no prolongation of the QRS complex or QT interval, one may conclude that depolarisation and repolarisation through the ventricles are unaffected.

Hyperalgesia has been reported in a 35-year-old woman who took St. John's Wort (500 mg/day) for mild depression (Bove 1998). SJW extracts may cause lipid peroxidation, and myelin is sensitive to damage via this mechanism (Hadjur et al. 1996). The patient's recovery within 2 months was considered consistent with remyelination in that period.

So far there have been no reports in the literature of unwanted pregnancy due to impaired efficacy of oral contraceptives, or reports of foetal deformities. However, this does not necessarily prove the teratogenic safety of SJW extracts in pregnancy (Grush et al. 1998). In a case report on the analysis of four breast milk samples, hypericin remained undetectable in the infants' plasma, foremilk and the hindmilk, whereas hyperflorin was detectable in the foremilk and hindmilk in very low concentrations (Klier et al. 2002). The milk plasma concentration was far below the lower limit of quantification.

The use of St. John's Wort extracts is on the increase and for reasons of possible drug interaction, as discussed above, it has now become important to routinely inquire about herbal treatment when taking a psychi-

atric history. Similarly, for patients presenting with aggravations of a psychosis or of the underlying illness, or indeed with any presentation, the use of herbal remedies must be elicited.

Conclusion

There is evidence that some Hypericum extracts possess significant therapeutic efficacy in the treatment of mild to moderate depression. It is also reasonable to conclude that Hypericum extracts do not appear to provide any efficacy advantage over classical or modern antidepressants in the treatment of moderate to severe depressive illness. Hypericum extracts are well tolerated and have significantly fewer side effects. The efficacy and tolerability of the Hypericum extracts in the elderly population is not as good and requires care in administration (Harrer 1999).

Since SJW extracts are a natural product, the quality of their supply in a plant is subject to ecological factors, just as wine vintage varies from year to year and from place to place. The nature of the solvent used, extraction and the drying processes, and the quality adjustment by blending the primary extracts together in a way that ensures consistent concentration, are important considerations in the production and quality control (Schulz 2000). With such care and analytical standardisation, further multicentre and multinational clinical studies of standardised extracts of SJW should be undertaken versus placebo and standard anti-depressant therapies to determine the full therapeutic efficacy of Hypericum extracts as antidepressants.

In some countries, for example Germany, the concept of herbal therapies is well accepted by the general population, who believe in the natural and less toxic effects and actions of such remedies. Thus compliance with these medications is generally better than with "chemical drugs". Often patients demand that practitioners prescribe herbal medication, at least as the first step of antidepressant treatment. In turn this leads to a high compliance. The daily treatment costs in Germany, where SJW extracts are on the formulary, is approximately €1.30 for the older antidepressants, €2.50 for the new antidepressants and about €0.90 for St. John's Wort (Schwabe & Paffrath 1999).

Depression is the most common psychiatric illness with a lifetime prevalence of 17 % (Kessler et al. 1994) and a prevalence of 2–5 % for severe depression (World Health Organisation 1998). Epidemiological data indicate that most patients with symptoms of depression are treated by general practitioners. Important criteria for selecting an antidepressant medication in this setting are the lack of side effects, patient adherence to treatment and the acceptable cost. Due to the increasing popularity of SJW it is important that clinical trials in this area continue to excel and advance the understanding of the risks and benefits of this treatment.

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