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REVIEW ARTICLE

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Adverse effects profile of the herbal antidepressant St. John's wort (*Hypericum perforatum* L.)

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Abstract *Objective*: This paper provides a systematic review of adverse drug reactions (ADRs) associated with the use of extracts of the herb St. John's wort (*Hypericum perforatum* L.) for the treatment of mild to moderate depression.
Methods: Searches of four computerized literature databases were performed for records of (ADRs). Manufacturers of hypericum products, the international drug monitoring centre of the World Health Organization (WHO) and the national drug safety monitoring bodies of Germany and the United Kingdom were also contacted for information.
Results: Information on (ADRs) originates from case reports, clinical trials, post-marketing surveillance and drug monitoring studies. Collectively, the data suggest that hypericum is well tolerated, with an incidence of adverse reactions similar to that of placebo. The most common adverse effects are gastrointestinal symptoms, dizziness/confusion and tiredness/sedation. A potential serious adverse effect is photosensitivity, but this appears to occur extremely rarely.
Conclusions: Hypericum has an encouraging safety profile. However, as most of the current data originate from short-term investigations, more long-term studies are desirable.

Key words *Hypericum perforatum* · Depression · Adverse drug reaction

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Introduction

Depression is a condition with an unknown aetiology and high prevalence [1]. It also is a serious affliction with a high morbidity leading to impairments in family and social functioning. Acute episodes of depression are associated with unemployment, absenteeism and decreased work capacity. Sales of conventional antidepressants have doubled in the last 10 years [2]. These drugs are invariably burdened with adverse effects, which decrease quality of life and lead to "poor concordance with treatment" [3].

Hypericum perforatum (St. John's wort), may offer another approach to the treatment of depression. It has been shown to alleviate symptoms of mild to moderate depression [4], and seems to offer significant advantages over conventional antidepressants in that it is associated with fewer adverse reactions. The aim of this paper is to determine whether this notion can be upheld in the light of all the data available on the subject.

Method

Systematic literature searches were made using the following four computer databases: Medline, AMED (Alternative and Allied Medicine Database, British Library Medical Information Centre, search performed July 1997), Cochrane Library 1997 issue 2, Embase (all from their inception to September 1997). The search terms employed were: adverse drug reaction, adverse effects, adverse events, side-effects, drug interaction, hypericum, safety, St. John's wort, tolerability, toxicity. No language restrictions were imposed. Further publications were identified by checking all reference lists, through discussions with colleagues and by searching our own, extensive files. In addition, the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, the drug safety bodies for the United Kingdom (Committee on Safety of Medicines) and Germany (Bundesinstitut für Arzneimittel und Medizinprodukte), plus 12 German manufacturers of hypericum products were contacted and asked for any information held on ADRs associated with hypericum.

To be included, reports had to relate to the administration of monopreparations of hypericum and had to be published in the peer-reviewed literature. Data were included regardless of whether

they were based on case reports, clinical trials, drug monitoring studies or other types of investigation. Data were extracted in a predefined fashion. Discrepancies were settled through discussions.

Results

Placebo-controlled trials of hypericum in depression

Fourteen randomized, placebo-controlled trials [5–18] were identified. Most of these have recently been submitted to systematic review [19] and meta-analysis [4]. The duration of these trials ranged from 4 to 8 weeks and sample sizes ranged from 40 to 120 participants (Table 1). In seven of these 14 trials it was explicitly stated that no ADRs were observed, two trials gave no information on ADRs, and five trials reported a total of seven patients who experienced mild ADRs (Table 2). In total, only one patient in the hypericum group dropped out of a study because of an ADR, which in this particular case was nausea [6]. This compares with one patient in the placebo groups (unspecified ADR [17]).

Trials comparing hypericum with conventional antidepressants in depression

To date, seven randomized comparative studies have been published of hypericum and other anti-depressants (Table 3), which included a total of 797 (sample sizes ranged from 30 to 209) patients [20–26]. Where data were available, the incidence of ADRs in the groups treated with hypericum was less than 50%, whereas the incidence of ADRs in those treated with reference medication ranged from 32 to 103%. The most frequent ADRs were gastrointestinal symptoms followed by dizziness/confusion, tiredness/sedation and dry mouth (Table 4). For the synthetic antidepressants used in these trials, the ADR profile differs markedly from that of hypericum. In this category, tiredness/sedation and dry mouth are by far the most common ADRs (Table 4).

Table 2 Incidence and nature of ADRs with hypericum in randomized placebo-controlled trials. *ADRs* adverse drug reactions

Trial	Incidence	Nature of ADRs
Halama	1/25	Unspecified stomach complaint
Hänsgen	1/36	Sleep disturbance
Harrer	1/60	Nausea (withdrew from trial)
Schmidt	3/32	Skin rash, pruritus, drowsiness
Sommer	2/52	Skin reddening, itching and tiredness

Data from drug safety bodies and manufacturers of hypericum products

The WHO provided data from its Collaborating Centre for International Drug Monitoring. Since 1968, the centre has received summary clinical reports about individual suspected adverse reactions to pharmaceutical products from National Centres in countries participating in a Collaborative Programme. The WHO stresses that the information is not homogeneous with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction, and that the information does not represent the opinion of the WHO.

Up until May 1998, 57 reports had been received from the National Centres of Sweden, Ireland, Germany and Bulgaria relating to monopreparations of hypericum extract and a further 49 reports for multi-ingredient products of which hypericum was an ingredient. Of those associated with the monopreparations, the largest number of reports was for nervousness (5) followed by eczema, sleep disorders and paraesthesia (3 each).

Table 1 Randomized, placebo-controlled trials of hypericum for the treatment of depression. *ADRs* adverse drug reactions, *NA* information not available

Trial	Total number of subjects	Hypericum preparation (trade name)	Hypericum extract (mg per day)	Total hypericin (mg per day)	Treatment duration (weeks)	Number of patients with ADRs	
						Hypericum	Placebo
Halama	50	Jarsin	900	1.08	4	1	0
Hänsgen	72	Jarsin 300	900	2.70	6	1	2
Harrer	120	Psychotonin M	500	0.75	6	1	0
Hoffmann	60	Hyperforat	NA	0.60	6	0	0
Hübner	40	Jarsin 300	900	2.70	4	0	0
Lehrl	50	Jarsin	900	1.08	4	NA	NA
Osterheider	46	Psychotonin M	500	0.75	8	NA	NA
Quandt	88	Psychotonin M	500	0.75	4	0	0
Reh	50	Neuroplant	500	1.00	8	0	0
Schlich	49	Psychotonin M	350	0.50	4	0	0
Schmidt	40	Jarsin 300	500	0.75	4	0	0
Schmidt	65	Jarsin	900	1.08	6	2	3
Sommer	105	Jarsin 300	900	2.70	4	2	3
Witte	97	Psychotonin forte	220	1.10	6	0	1

Table 3 Randomized controlled trials comparing hypericum with conventional antidepressant drugs in depression. *NA* information not available, *ADRs* adverse drug reactions

Trial	Total number of subjects	Hypericum preparation	Hypericum extract (mg per day)	Total hypericin (mg per day)	Other drug (mg per day)	Treatment duration (weeks)	Percentage of patients with ADR(s)		Number of ADRs/number of patients	
							Hypericum	Reference drug	Hypericum	Reference drug
Bergmann	76	Esbericum®	NA	0.75	amitriptyline 30	6	24	58	NA/38	39/38
Harrer	102	Jarsin®300	900	2.7	maprotiline 75	4	25	35	25/51	44/51
Kugler	80	Psychotonin®M	500	0.75	bromazepam 6	4	38	75	18/40	49/40
Vorbach (1994)	135	Jarsin®300	900	2.7	imipramine 75	6	12	16	11/67	22/68
Vorbach (1997)	209	Jarsin®300	1800	5.4	imipramine 150	6	23	41	37/107	83/102
Werth	30	Psychotonin®M	500	0.75	imipramine 50	2	20	7	NA/15	NA/15
Wheatley	165	Jarsin®300	900	2.7	amitriptyline 75	6	37	64	27/87	70/78

Table 5 displays the number of ADRs reported for different classes of disorder.

Data were also obtained from the national drug safety bodies in Germany (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) and the United Kingdom (Committee on Safety of Medicines, CSM). The data originate from the post-marketing surveillance programmes of these institutions. From 1989 to August 1997 the BfArM had received eight spontaneous reports of possible ADRs related to hypericum. Six of these reports involved multi-ingredient products administered parenterally, which resulted in pain at the site of injection and local skin reactions. All patients were receiving other medications concurrently. There were two reports of ADRs following oral administration of multi-ingredient products: one case of a pustular rash, and one report of nausea, nervousness, increased sweating, weight loss and anorexia. In the latter case, the patient was also receiving appetite suppressants and moclobemide simultaneously. As of March 1998, the CSM had received no reports of suspected ADRs associated with hypericum.

Twelve German manufacturers of hypericum products were contacted and asked for any records of possible ADRs. Replies were received from seven companies, but no data were provided beyond that which was already published and known to us. The exception was one comment that unpublished clinical trials had shown non-specific gastrointestinal symptoms in a small percentage of the subjects, but that this figure did not differ from that reported for placebo. No further details were provided.

Drug monitoring and post-marketing surveillance studies

Woelk et al. reported a drug monitoring study involving 3250 moderately or mildly depressed patients monitored by 663 German physicians [27]. All were treated with hypericum extract (Jarsin®300) 300 mg three times

Table 4 Percentage of patients with ADRs from randomized controlled trials of hypericum and conventional antidepressants. *ADR* adverse drug reaction

ADR	Hypericum (n = 352)	Conventional drug (n = 339)
Gastrointestinal symptoms	8.5	9.4
Dizziness/confusion	4.5	6.5
Tiredness/sedation	4.3	20.4
Dry mouth	4.0	19.8
Restlessness	2.6	1.8
Headache	1.7	2.4
Insomnia	0.9	0.6
Tremor	0.6	1.2
Pruritus	0.6	0.3
Photophobia	0.6	0.3
Apathy	0.3	1.2
Allergic skin reaction	0.3	1.2
Others	4.8	14.2

Table 5 Reports from WHO Collaborating Centre for International Drug Monitoring[a] of suspected ADRs in patients taking monopreparations of hypericum up to May 1998. *ADR* adverse drug reaction

Type of ADR	Number of reports	Type of ADR	Number of reports
Allergies and skin disorders	16	Platelet, bleeding and clotting disorders	4
Psychiatric disorders	15	Liver and biliary system disorders	4
Central and peripheral nervous system disorders	5	Gastrointestinal system disorders	2
Respiratory system disorders	4	Others[b]	7

[a] Information from the WHO drug monitoring database is not homogenous with respect to origin or likelihood that the product caused the adverse reaction and does not represent the opinion of the WHO

[b] Bradycardia (1), cerebral haemorrhage (1), nephritis interstitial (1), oedema (2), therapeutic response decrement (1), conjunctivitis (1)

daily. ADRs were spontaneously reported by 79 (2.4%) patients during 4 weeks of treatment. Gastrointestinal symptoms were the most frequently reported ADRs ($n = 18$, 0.6%) followed by allergic reactions ($n = 17$, 0.5%) and fatigue ($n = 13$, 0.4%). There were 48 (1.5%) drop-outs, most frequently due to insufficient therapeutic effect ($n = 11$, 0.3%) and allergic reaction ($n = 10$, 0.3%).

In another study of Jarsin®300, involving 1060 patients [28], adverse events were reported by 21 (2%) patients. Gastrointestinal symptoms ($n = 12$) were most common, followed by confusion/restlessness/anxiety ($n = 4$) and increased sweating ($n = 2$). All ADRs were mild or moderate except two, which were considered serious. One of these was a case of abdominal pain which was thought to be unrelated to treatment. The other was a case of tiredness. A total of eight (0.8%) patients withdrew from the study due to adverse effects.

A further drug monitoring study evaluated the effects of treatment with Kira® for 5 weeks (a lower strength version of Jarsin®300) on 114 patients [29]. ADRs were reported by seven individuals (6.1%) and all were mild, moderate or transient. Three patients reported gastrointestinal complaints (nausea, stomach pains, meteorism), while the remaining four experienced nervousness, restlessness or other physical symptoms.

In another smaller scale study [30], 163 patients given 500 mg twice daily of a new hypericum extract for an average of 66 days, were monitored by four physicians. Nine patients (6%) reported ADRs, with no more than two individuals experiencing each of the following symptoms: aggravation of clinical symptoms, dry mouth, constipation, skin allergies, gastrointestinal symptoms.

Photosensitivity

Consumption of large quantities of St. John's wort by light-skinned grazing animals has been associated with the development of photosensitivity [31]. On exposure to bright sunlight, the affected animals develop skin blisters similar to those of burns, as well as signs of psychomotor agitation. In a few severe cases haemolysis, epileptic fits and death may occur.

Literature searching undertaken for this review has identified two cases of photosensitivity reactions in humans associated with the ingestion of hypericum. A case of delayed hypersensitivity or photodermatitis following the ingestion of herbal tea made from the leaves of St. John's wort has been reported (Benner 1979 quoted in Newall 1996, but reference details untraceable [32]). An instance of reversible photosensitivity after taking 240 mg hypericum extract (containing 0.3 mg hypericin) daily for 3 years has also been recorded [33]. The patient developed itching erythematous lesions in light-exposed areas, but recovered on withdrawal of the medication.

A randomized, placebo-controlled, multiple crossover study has been carried out in 13 subjects to investigate the relationship between dermal photosensitivity and plasma concentrations of hypericin and pseudohypericin [34]. The volunteers received a single dose of placebo or standardized hypericum extract 900, 1800 or 3600 mg containing 2.8, 5.6 mg and 11.3 mg total hypericin, respectively. Before and 4 h after drug intake subjects were exposed to solar and UVA light irradiation. Hypericum extract did not lead to an increase in solar light sensitivity, and UVA sensitivity increased only after the highest dose. In the same paper [34], another experiment is reported involving 50 volunteers taking hypericum extract 600 mg three times daily. After 15 days there was a slight but significant increase in solar and UVA light sensitivity. The increase was such that it would be compensated by reducing exposure time by 21%. The number of ADRs reported even with these excessive doses of hypericum, was equal to that seen with placebo.

Based on the findings of experimental studies on animals and humans, it has been estimated that it would require a dose of hypericum 30–50 times greater than the recommended daily dose taken at one time, to lead to severe phototoxic reactions in humans [35]. Furthermore, in the event of such an overdose, serious complications could be avoided by shielding the patient from all ultraviolet light for one week.

Interactions with other drugs

There has been little investigation of the effects of hypericum in interactions with other drugs. One placebo-controlled RCT examined the effect of alcohol with 32 volunteers [36]. Participants received hypericum extract (Jarsin®300) 300 mg three times daily for 7 days of each treatment phase. Volunteers were challenged with alcohol to produce a blood-alcohol concentration of 0.45–0.8%. Psychometric testing showed no effect of hypericum and the authors therefore exclude an interaction of hypericum and alcohol.

Due to the absence of evidence regarding the safety of hypericum in interactions with other drugs, concurrent use with other medication and in particular with other antidepressant agents is not recommended. However, the avoidance of foods and medicines containing tyramine [32] is considered unnecessary, since MAO inhibitory activity has not been demonstrated with hypericum [37, 38]. There is no evidence on the safety of hypericum during pregnancy or lactation. Its use should therefore be avoided in these conditions [32].

Discussion and conclusions

This overview summarizes the evidence relating to the safety of extracts of hypericum. It has revealed that the overall incidence of ADRs associated with hypericum is low, and in placebo-controlled trials is similar to that reported for placebo. The incidence of hypericum-related ADRs is generally lower than that of ADRs associated with conventional antidepressant agents. However, it is interesting to note that the reported rates of ADRs associated with hypericum are higher in trials comparing it with conventional antidepressants, than in trials comparing hypericum with placebo (Tables 1 and 3). This may be explained by patient expectation. The awareness that they might be taking a synthetic drug, could lead patients to develop some of the adverse effects they expect to experience from a such a drug, even though they are not actually taking it. Along with the observation that the types of ADR reported for hypericum are similar to those reported for placebo [39], this could suggest that some ADRs reported for hypericum should actually be viewed as nocebo effects.

Several different hypericum preparations have been used in clinical trials, standardized to different concentrations of hypericin and administered in various dosages (Tables 1 and 3). It is not possible to know to what extent the use of different products and dosages may produce different outcomes in terms of ADRs.

The majority of ADRs reported for hypericum are minor; current data report few serious ADRs. Photosensitivity seems to be an extremely rare event with recommended dosages of hypericum. Thus, on balance, hypericum has a more favourable short-term safety profile than conventional antidepressants – in the short-term, it is associated with fewer ADRs, and the nature of ADRs associated with hypericum gives less cause for concern, compared with those associated with conventional antidepressants.

However, there is still a paucity of systematic long-term safety data for hypericum. To date, trials of hypericum have been only 4–8 weeks in duration. In particular, a drug monitoring study conducted by Woelk and colleagues [27] of 3250 patients receiving hypericum was not of sufficient duration to allow conclusions to be drawn about its long-term safety, nor was it large enough to identify rare adverse events. Data provided by manufacturers and drug safety bodies are encouraging with regard to long-term safety and serious adverse events. However, spontaneous reporting schemes are notorious for the underreporting of ADRs and the evidence from the WHO suggests that serious adverse effects are possible. There is therefore a need for systematic data from long-term monitoring to provide a more accurate picture of the overall safety of hypericum.

If the safety profile of hypericum was demonstrated to be more favourable than that of conventional antidepressants, it could have advantages in leading to a higher degree of concordance with medication among patients receiving treatment with hypericum, and potentially a better quality of life. It is, however, only meaningful when considered in conjunction with the clinical effectiveness of hypericum, compared with that of conventional antidepressants. Current data suggest that hypericum may be nearly as effective as conventional antidepressant drugs for the symptomatic relief of mild to moderate depression [19, 4, 26]. Thus, the risk-benefit profile of hypericum could be considered to be superior to that of conventional antidepressant drugs. However, it is important to emphasize the caveat that long-term safety data for hypericum are scarce [40].

In conclusion, hypericum may prove to be a relatively safe treatment option for individuals with mild to moderate depression. Further research is needed to establish whether hypericum is as effective as conventional antidepressants, and importantly, future systematic investigations should address the issue of long-term safety.

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