Adverse Effects of St. John's Wort: A Systematic Review

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Objective: To obtain an overview of the available clinical evidence on safety and tolerability of hypericum extracts, we reviewed (1) dropout rates and adverse effects in double-blind randomized trials comparing hypericum extracts and placebo or synthetic standard antidepressants; (2) dropout rates and adverse effects in large-scale observational studies; and (3) adverse effects reported in published cases and to public drug surveillance agencies.

Method: Data on dropout rates and adverse effects were extracted from double-blind randomized trials of hypericum monopreparations collected for a Cochrane review (last search July 2003) and from a PubMed search (text word *hypericum*; search dates 1998–January 2003). Similar data were extracted from uncontrolled observational studies including at least 100 patients identified through a PubMed search (search term *hypericum NOT animal*, last update May 2003), contacts with manufacturers, and screening of review articles. Case reports and case series on adverse events associated with hypericum products were identified through a MEDLINE search (1966–November 2002; search term: *hypericum AND [adverse effects OR interaction]*) and a PubMed search (February 2003) and were collected from 5 public drug surveillance agencies (data through May 2001). All database searches were conducted as English and non–English language searches.

Results: Data from 35 double-blind randomized trials showed that dropout and adverse effects rates in patients receiving hypericum extracts were similar to placebo, lower than with older antidepressants, and slightly lower than with selective serotonin reuptake inhibitors. Dropout rates due to adverse effects in 17 observational studies including 35,562 patients ranged from 0% to 5.7%; interactions or serious adverse effects were not reported in any study. Published cases and cases reported to drug surveillance agencies suggest that interactions with a variety of drugs (particularly cyclosporine in transplant patients) are the most relevant adverse effects of hypericum extracts.

Conclusions: The available evidence suggests that hypericum extracts are well tolerated and safe if taken under control of a physician who is aware of potentially relevant risks in specific circumstances.

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The surveillance agencies providing data used in this review point to the fact that the sources of information are heterogeneous and that a reported event was not necessarily caused by the product used.

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Extracts of St. John's wort (*Hypericum perforatum L.*) are widely used to treat depressive disorders. While the majority of the available double-blind, randomized controlled trials have shown that defined high-quality hypericum extracts are more effective than placebo and similarly effective to standard antidepressants,[1–3] there is still considerable discussion whether this evidence is reliable and how to identify in which patients hypericum extracts might be adequate. In countries with traditional use and registration of hypericum extracts as drugs (such as Germany, Austria, and Switzerland), these extracts are mainly prescribed in patients with mild-to-moderate symptoms.[4] Two recent trials in the United States restricted to U.S. patients with major and often long-lasting depression did not find effects over placebo.[5,6]

In the past, good tolerability has been considered a relevant advantage of hypericum extracts. However, in recent years, an increasing number of adverse effects have been reported, mainly relating to interactions with other drugs.[7,8] While there can be little doubt that hypericum extracts can interact with other drugs and can cause adverse effects, little is known about the frequency of such events.

To obtain an overview of the available clinical evidence on safety and tolerability, we systematically reviewed (1) dropout rates and adverse effects in double-

blind randomized trials comparing hypericum extracts and placebo or synthetic standard antidepressants, (2) dropout rates and adverse effects in large-scale observational studies, and (3) adverse effects reported in published cases and to public drug surveillance agencies.

METHOD

Dropout Rates and Adverse Effects in Double-Blind Randomized Trials

The data used for the presented analysis were collected within the framework of updating a meta-analysis of hypericum extracts for depression performed for the Cochrane Collaboration[2] (update submitted for publication), a worldwide network of health care researchers for systematic reviews in all areas of medicine. The selection criteria for this review included: study design—double-blind, randomized, controlled trial; participants—adult patients treated for depressive disorders; experimental intervention—hypericum monopreparation for at least 4 weeks; control intervention—placebo or a synthetic standard antidepressant; and outcome measure—assessment of symptoms with a depression scale or general assessment of clinical response.

We searched for studies published in English and non–English language, as well as published and unpublished trials indexed in the register of the Cochrane Collaborative Review Group for Depression, Anxiety and Neuroses (CCDAN; last search July 2003) and PubMed (text word *hypericum*; search dates 1998–January 2003). We also checked reference lists of trials and reviews, contacted manufacturers and experts in the field, and relied on prior extensive searches.[1,2]

To assess adverse effects and tolerability, at least 2 reviewers extracted the number of patients dropping out for adverse effects (primary outcome measure), the total number of patients dropping out, the number of patients reporting adverse effects, and the number of patients randomly assigned to hypericum extract, placebo, or standard antidepressants. The data were entered into the Cochrane Collaboration's software RevMan (version 4.2, Oxford, England), and odds ratios and their respective 95% confidence intervals were calculated. Both fixed effects and random effects pooled summary estimates were calculated. As there was no statistical heterogeneity among trials for all 3 safety parameters (contrary to the analysis of efficacy measures), only fixed effects estimates are presented in this article.

A total of 37 trials met our inclusion criteria. However, for 2 studies, which are available only as an abstract[9] or in a report from an oral presentation,[10] no data on dropouts or adverse effects could be extracted. Therefore, 35 trials were included in the analyses relevant to this paper. The 35 trials include a total of 37 comparisons (2 three-armed trials): 24 comparisons with placebo, 7 with older standard antidepressants, and 6 with selective serotonin reuptake inhibitors (SSRIs).

Dropout Rates and Adverse Effects in Large, Uncontrolled Observational Studies

To be included for this analysis, investigations had to meet the following criteria: study design—prospective observational (phase IV) studies; participants—at least 100 human patients treated for preventative or curative purposes; intervention—hypericum extract for at least 4 weeks; studies on combinations of hypericum extracts with other plant extracts were excluded; reporting of data for at least one of the following outcome measures—number of patients dropping out for adverse effects, total number of patients dropping out, number of patients reporting adverse effects. All references obtained from a general PubMed search (search terms *hypericum NOT animal*, last update May 2003) were screened, but this strategy yielded only 4 eligible studies. All other studies were identified through inquiries to manufacturers, contact with researchers, checking review articles and publications of clinical trials of hypericum extracts, and handsearching proceedings of herbal medicine congresses.

Included studies were read by both reviewers. Extraction of information on patients, interventions, and outcomes was performed by one reviewer (L.K.) using a pretested form and checked by the second reviewer (K.L.). Both reviewers extracted the number of patients with adverse events (defined as any undesired event during the study), the total number of adverse events, the number of patients reporting adverse effects (defined as adverse events with a possible causal link to hypericum treatment), the total number of adverse effects, the number of patients dropping out, and the number of patients dropping out for adverse effects. We identified 20 observational studies of hypericum preparations including more than 100 patients. Three studies were excluded, as they investigated combinations of hypericum and other plant extracts.[11–13] A detailed review of the included observational studies will be published elsewhere.[106]

Suspected Adverse Reactions Reported in Published Cases and to Drug Surveillance Agencies

For this part of the review, we collected original case reports or case series on suspected adverse reactions associated with the treatment with hypericum extracts that were published in the literature or reported to public drug surveillance agencies. We did not include experimental studies on adverse effects or interactions (for example, studies in healthy volunteers studying plasma levels) or reviews of case reports. Published case reports were identified through searches in MEDLINE (1966–November 2002; search terms: *hypericum AND [adverse effects OR interaction]*) and through screening the bibliographies of published review articles. In February 2003, an additional

PubMed search was performed to include recent publications. To obtain information on cases reported to public drug surveillance agencies, we wrote in May 2001 to the U.K. Medicines and Healthcare products Regulatory Agency (MHRA, formerly MCA/CSM), the Australian Adverse Drug Reactions Advisory Committee (ADRAC), the Swedish Medical Products Agency (MPA), the German Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), and the WHO Collaborating Centre for International Drug Monitoring in Sweden. These institutions kindly provided data on suspected adverse reactions to hypericum preparations available up to May 2001.

Using a pretested form, one reviewer (L.K.) extracted information on patient characteristics, interventions used, and reported clinical events for all published case reports and all reports from the ADRAC and the MPA. The WHO, the MHRA, and the AkdÄ provided only basic information on the type of adverse reactions reported.

RESULTS

Dropout Rates and Adverse Effects in Double-Blind Randomized Trials

In the 24 randomized trials including a placebo control group,[5,6,14–35] 1334 patients were randomly assigned to treatment with hypericum extracts and 1292 to placebo (Table 1). The number of patients dropping out due to adverse effects was 8 (0.6%) with hypericum and 15 (1.2%) with placebo (fixed effects odds ratio [OR] = 0.61, 95% confidence interval [CI] = 0.28 to 1.31). The total number of dropouts in the 23 trials reporting this information was slightly lower in the hypericum groups (136 [10.7% of 1274]) than in the placebo groups (154 [12.5% of 1232]; OR = 0.82, 95% CI = 0.64 to 1.06). Twenty trials reported patients experiencing adverse effects: the number of such patients was 236 (21.0% of 1123) among those receiving hypericum extracts and 254 (23.6% of 1077) among those receiving placebo (OR = 0.79, 95% CI = 0.61 to 1.03). The proportion of patients reporting adverse effects (regardless of group) differed greatly between trials due to some trials documenting adverse events rather than adverse effects.

In the 7 trials comparing hypericum extracts with older standard antidepressants (amitriptyline 30–75 mg, imipramine 75–150 mg, maprotiline 75 mg),[25,36–41] 14 (2.3%) of 615 and 52 (8.4%) of 616 patients, respectively, dropped out due to adverse effects (OR = 0.25, 95% CI = 0.14 to 0.45). The total number of dropouts was 68 (11.1%) in patients with hypericum treatment compared with 96 (15.6%) in patients with older standard antidepressants (OR = 0.65, 95% CI = 0.46 to 0.92), the number of patients reporting adverse effects was 174 (28.3%) with hypericum treatment compared to 301 (48.9%) with older standard antidepressants (OR = 0.39, 95% CI = 0.31 to 0.50).

Trends for fewer dropouts due to adverse effects (OR = 0.60, 95% CI = 0.31 to 1.15) and lower numbers of patients reporting adverse effects (OR = 0.75, 95% CI = 0.52 to 1.08) with hypericum extracts in the 6 trials including SSRIs[5,42–46] were observed, but the differences were not statistically significant. The total number of dropouts for both treatments was similar (OR = 0.95, 95% CI = 0.65 to 1.40).

The most frequently described adverse effects in clinical trials were gastrointestinal complaints such as nausea, itching, fatigue, sleep disorders, and headache.

Dropout Rates and Adverse Effects in Large-Scale Observational Studies

The 17 selected studies[47–62] included a total of 35,562 patients (range, 101–11,296 patients) (Table 2). With the exception of 1 study, in which patients suffered from neurovegetative dysfunction,[55] all studies observed the treatment of mainly mild-to-moderate depressive disorders. One study was of children under 12 years[51]; all others were of adults. All studies originated from German-speaking countries and were performed in private primary care practices. The majority of studies were published in non–peer-reviewed German practitioner journals. Most studies focused on short-term treatment (typically 4–6 weeks); however, in 2 studies,[52,61] long-term treatment (52 weeks) was investigated.

Dropout rates ranged from 1.5% to 17.1% in the short-term studies. A dropout rate of 19.8% for any reason was reported in the only long-term study reporting these data.[52] The rates of dropouts due to adverse effects ranged from 0% to 2.8% in the short-term studies, and 3.4% to 5.7% in the studies lasting 1 year. The proportion of patients reporting adverse effects was generally very low, ranging from 0% to 5.9%. Some studies only reported data on adverse events. These varied from 0.7% to 17.0%. Several publications mentioned that only spontaneously reported adverse events or effects were documented. The most frequently reported side effects or adverse events were gastrointestinal symptoms. Increased sensitivity to light and dermal symptoms in general were the second most frequent group of reported side effects. A variety of nervous symptoms such as agitation or restlessness were also described in several studies. Serious adverse effects (making hospitalization necessary) or interactions with other drugs were not reported in any study.

Published Cases and Detailed Case Reports From 2 Public Drug Surveillance Agencies (ADRAC, MPA)

A total of 55 case reports (in 36 publications[63–98]) were identified through the literature search. Information with sufficient detail for a further evaluation was also available for the 35 cases reported to the Swedish MPA and the 35 cases reported to the Australian ADRAC. Four cases were reported both in the registers and in publications; there-

Table 1. Dropouts and Number of Patients Reporting Adverse Effects in Randomized Trials of Hypericum Extract vs. Placebo or Standard Antidepressants

	N		Dropout Due to Adverse Effects, N		All Dropouts, N		Patients Reporting Adverse Effects, N	
First Author (by drug class)	Hypericum	Control	Hypericum	Control	Hypericum	Control	Hypericum	Control
Hypericum extracts vs placebo								
Halama[14]	25	25	0	0	0	0	1	0
Hänsgen[16]	53	55	0	0	2	4	1	2
Harrer 1991[15]	60	60	1	0	NA	NA	1	0
HDTSG[5]	113	116	2	3	31	32	100	109
Hoffmann[17]	30	30	0	0	0	0	NA	NA
Hübner[18]	20	20	0	0	0	1	0	0
Kalb[19]	37	35	0	0	0	0	3	2
König[20]	55	57	2	5	6	7	12	16
Laakmann[21]	49	49	0	1	2	3	14	15
Lecrubier[22]	186	189	2	2	18	25	57	70
Lehrl[23]	25	25	0	0	1	0	1	0
Osterheider[24]	23	24	0	0	7	6	NA	NA
Philipp[25]	106	47	0	0	13	9	23	9
Quandt[26]	44	44	0	0	3	2	1	0
Reh[27]	25	25	0	0	0	0	0	0
Schlich[28]	22	24	0	0	3	0	0	0
Schmidt 1989[30]	20	20	0	0	4	8	0	0
Schmidt 1993[29]	32	33	0	1	2	3	2	3
Schrader 1998[31]	81	81	0	1	1	2	6	5
Shelton[6]	98	102	1	1	15	13	NA	NA
Sommer[32]	52	53	0	1	8	8	2	3
Volz[33]	70	70	0	0	1	4	12	19
Winkel[34]	60	59	0	0	10	14	NA	NA
Witte[35]	48	49	0	0	9	13	0	1
Pooled	1334	1292	8	15	136	154	236	254
OR fixed effects (95% CI)			0.61 (0.28 to 1.31)		0.82 (0.64 to 1.06)		0.79 (0.61 to 1.03)	
Hypericum extracts vs older antidepressants								
Bergmann[36]	40	40	2	2	2	2	11	24
Harrer 1993[37]	51	51	0	2	7	9	13	18
Philipp[25]	106	110	0	1	13	11	23	51
Vorbach 1993[39]	67	68	0	0	1	4	8	11
Vorbach 1997[38]	107	102	1	8	9	14	25	42
Wheatley[40]	87	78	7	13	21	24	32	50
Woelk[41]	157	167	4	26	15	32	62	105
Pooled	615	616	14	52	68	96	174	301
OR fixed effects (95% CI)			0.25 (0.14 to 0.45)		0.65 (0.46 to 0.92)		0.39 (0.31 to 0.50)	
Hypericum extracts vs SSRIs								
Behnke[42]	35	35	2	2	6	3	22	20
Brenner[43]	15	15	2	2	7	3	NA	NA
Harrer 1999[44]	77	84	6	8	8	16	12	17
HDTSG[5]	113	111	2	5	31	32	100	103
Schrader 2000[45]	126	114	0	1	1	1	18	28
van Gurp[46]	45	45	3	7	16	17	34	32
Pooled	411	404	15	25	69	72	186	200
OR fixed effects (95% CI)			0.60 (0.31 to 1.15)		0.95 (0.65 to 1.40)		0.75 (0.52 to 1.08)	

Abbreviations: HDTSG = Hypericum Depression Trial Study Group, NA = not available, OR = odds ratio, SSRIs = selective serotonin reuptake inhibitors.

fore, the total number of cases reported in these sources is 121. Thirty-one cases were classified as interactions, 26 as possible interactions, 24 as adverse effects possibly related to an interaction, 26 as adverse effects, and 14 as questionable adverse effects (Table 3). The most frequently reported single events were serotonin syndrome (18 cases), decrease of plasma cyclosporine concentration in transplant patients (15 cases), increased international normalized ratio (INR) or prothrombin time (13 cases), mania (10 cases), light erythema or phototoxic reactions (9 cases), allergic reactions (8 cases), breakthrough bleeding (5 cases), psychotic episodes (3 cases), and blood pressure problems (3 cases). A pregnancy in patients taking oral contraceptives was reported twice.

For 90 cases, sufficient information was available to assess the necessity of an intervention. Three cases were classified as life-threatening. Two of these were cases of pulmonary embolism for which a causal link with hypericum treatment, however, appears unlikely. The third case was an acute transplant rejection reaction after liver transplantation due to a decreased plasma cyclosporine concentration that could only be controlled by giving ste-

Table 2. Dropouts and Adverse Effects (AE) in Nonrandomized Observational Studies of Hypericum Extracts

First Author	N	Extract	Daily Extract Dose (mg)	Treatment Duration, Weeks	Dropouts for Any Reason, N (%)	Dropouts Due to AE, N (%)	Patients With AE, N (%)	Total No. of AE
Albrecht[47]	1060	LI 160	900	4	63 (5.9)	8 (0.8)	21 (2.0)	NR
Grube[48]	114	Kira	405–675	5	3 (2.5)	NA	7 (5.9)	7
Schmidt[49]	3902	HY51K1	850	6	NA	NA	28 (0.7)	36
Holsboer-Trachsler[50]	647	LI 160	900	6	84 (13.0)	18 (2.8)	111 (17.0)	NR
Hübner[51]	101	LI 160	300–1800	6	NR	NR	0 (0.0)	0
Kalb[52]	313	LI 160	900	52	62 (19.8)	10 (3.4)	15 (4.8)	35
Lemmer[53]	6382	WS 5572	600–900	6	691 (10.7)	5 (0.1)	8 (0.1)	10
Meier[54]	170	ZE 117	500	1–33	7 (4.1)	0 (0.0)	1 (0.6)	1
Müller 1999[56]	607	HYP 811	425–850	6	104 (17.1)	2 (0.3)	3 (0.5)	3
Mueller 1998[55]	758	HYP 811	425–850	6	60 (7.9)	2 (0.3)	2 (0.3)	2
Rychlik[57]	2199	WS 5572	600–1200	6–7	86 (3.9)	4 (0.2)	9 (0.4)	13
Schakau[58]	2414	STEI 300	360–720	4–6	69 (2.9)	8 (0.3)	23 (1.0)	23
Sepehrmanesh[59]	1606	TEXX 300	600–900	4	NA	3 (0.2)	10 (0.6)	10
Spitzner Arzneimittel[a]	303	Neuroplant	NR	6	26 (8.6)	4 (1.3)	19 (6.3)	19
Woelk 1994[60]	3250	LI 160	900	4	48 (1.5)	30 (0.9)	79 (2.4)	79
Woelk 2000[61]	440	ZE 117	500	52	NR	25 (5.7)	22 (5.4)	34
Zeller[62]	11,296	Laif 600	600	NR	NR	NR	2 (< 0.1)	2

[a]Spitzner Arzneimittel, Ettlingen, Germany, unpublished data, 1991.
Abbreviations: NA = not available, NR = not reported.

roids and increasing the cyclosporine dose.[68] In 3 further cases of interaction with cyclosporine in transplant patients, the authors explicitly referred to a rejection reaction.[64,72] In 1 patient with a kidney and pancreas transplant, the rejection became chronic and the patient had to return to dialysis.[64] In a further 50 patients, some intervention was necessary (for example, increasing dosages); in 23 patients, the only action was to stop hypericum treatment. A causal link to hypericum treatment was considered certain in 28 cases, likely in 14, and possible in 73. In 6 cases, an assessment was not considered possible. Most published case reports are missing detailed information on the type, daily dose, and duration of hypericum treatment.

Published Case Series

In addition to the cases described above, 3 articles reporting series of cases have been published. These series differ from the case reports in that they are partly retrospective data collections in institutions regularly documenting plasma levels of drugs applied for treatment. Breidenbach et al. report in 2 articles[99,100] on a total of 35 kidney and 10 liver transplant patients taking hypericum extracts, in whom a decrease of the cyclosporine plasma concentration was observed. In 1 patient, a rejection reaction occurred. De Maat et al.[101] report on 5 patients with human immunodeficiency virus (HIV)–1 infection, in which intake of hypericum extracts was the most likely explanation for an increased clearance of antiretroviral therapy.

Cases Reported to Other Public Drug Surveillance Agencies (WHO, MHRA, AkdÄ)

A total of 722 case reports on suspected adverse reactions were provided from the WHO, MHRA, and AkdÄ. However, from the databases of these agencies, we received only basic information; therefore, a detailed evaluation was not possible. Table 4 summarizes the reported events classified according to classes of symptoms. The largest groups are general, unspecific symptoms (191 cases), mental or psychic symptoms (106 cases), and dermal symptoms (97 cases). Table 5 lists the most frequently reported single symptoms. Interactions with other drugs and a variety of skin reactions seem to be the most frequent specific adverse events associated with the intake of hypericum products. The MHRA also provided an additional list of the 36 cases in which an interaction was suspected. The most frequently reported events on this list were unwanted pregnancies in women taking oral contraceptives (7 cases), intermenstrual bleeding (6 cases), and INR changes (2 patients with an increased and 2 patients with a decreased INR) in patients under warfarin treatment.

DISCUSSION

The results of this review show that (1) in randomized trials, the rate of adverse effects and dropouts due to adverse effects among patients receiving hypericum extracts or placebo is similar, while compared with older antidepressants the rates are clearly lower and compared with SSRIs the rates are slightly lower; (2) rates of treatment discontinuation due to adverse effects in nonrandomized observational studies of hypericum extracts in routine primary care are low even in long-term studies, and the adverse effects reported are mild and mostly unspecific apart from skin reactions; and (3) case reports, case series, and data from public drug surveillance agencies provide clear evidence that clinically relevant interactions be-

Table 3. Suspected Adverse Reaction to Hypericum Extracts Reported in Published Case Reports (55 Cases), to the Australian Adverse Drug Reactions Advisory Committee (35 cases), and to the Swedish Medical Products Agency (35 cases)[a]

Type of Event	Number of Events
Interactions	31
Cyclosporine (lowering of plasma levels in transplant patients)	15
Tacrolimus (lowering of plasma level in kidney transplant patient)	1
Coumarins/warfarin (increased prothrombin time/INR)	13
Theophylline (lowering of blood level)	1
Clozapine (increased level)	1
Possible interactions	26
With oral contraceptives (2 pregnancies, 4 intermenstrual flow, 2 amenorrhea)	8
With SSRIs (serotonin syndrome)	18
Adverse effects possibly related to an interaction	24
Psychic reactions (4 mania, 1 mental confusion, 1 compulsive disorder; comedications: SSRI, lithium, nortriptyline, other)	6
Acute hypertension (2 multiple comedications, 1 thiamine-enriched nutrition)	3
Prolonged anesthesia; cardiovascular problems (comedication: multiple anesthetics)	2
Sexual dysfunction (comedication: sertraline; multiple medications)	2
Erythema (comedication: dothiepin; ALA-induced protoporphyrin)	2
Other singular events, often with multiple comedications	9
Adverse effects	26
Skin/allergic reactions (erythema, dermatitis, urticaria, hyperesthesia, neuropathy)	17
Mania	6
Psychotic episode	2
Anxiety	1
Questionable adverse effects	14

[a]Four published cases were also reported to 1 of the 2 agencies (total no. of cases = 121).
Abbreviations: ALA = aminolevulinic acid, INR = international normalized ratio, SSRIs = selective serotonin reuptake inhibitors.

tween hypericum extracts and other drugs can and do occur, but they seem to be relatively rare or limited to specific groups of patients.

Randomized trials of antidepressants can provide only limited data for the assessment of safety. Sample sizes are often too small to detect rare adverse effects, treatment and observation periods are mostly short (up to 12 weeks), and patients with relevant comorbidities receiving potentially problematic comedications are excluded. Furthermore, methods of documenting adverse effects or events differ. Adverse effect rates associated with hypericum extracts are much lower in placebo-controlled trials than in trials with a synthetic antidepressant control group. The most likely explanation is that trials including a synthetic antidepressant more actively explore specific side effects, while placebo-controlled trials primarily rely on spontaneously reported events, as little is known on specific side effects of hypericum preparations. One trial[5] included in our study set reported extremely high event rates; it seems likely that this trial closely reported any minor adverse event. While these variations make it difficult to detect minor qualitative differences in adverse effect profiles, the quantitative comparison of adverse effect and dropout rates with hypericum and placebo or older antidepressants yields clear-cut results. Due to the low adverse effect and dropout rates in most trials, the comparison of hypericum extracts and SSRIs lacks statistical power. Further trials are needed to investigate whether the trend in favor of hypericum extracts is real.

In principle, nonrandomized observational phase IV studies better reflect the routine use of a product and could be more appropriate to investigate the safety in practice. Such studies tend to have larger sample sizes and less rigid inclusion criteria, allowing long-term studies to be easily performed. A major problem of such phase IV studies is often their doubtful quality, as the participation of large numbers of centers and patients makes quality control difficult. Furthermore, such studies are performed not only for scientific reasons but also to promote the use of a product among practitioners. With few exceptions, most of the studies included in our review have not been published in peer-reviewed journals. The methodological quality of the majority of the studies is difficult to assess but often appears low. However, the results of the available studies consistently show a good tolerability of the tested hypericum products even over longer periods if prescribed by physicians.

When extrapolating these findings to hypericum use in other countries, one must remember that all the observational studies included in our review originate from German-speaking Europe (Germany, Switzerland, Austria), where there is a long tradition of using hypericum extracts as drugs. The products used in the studies might have undergone more rigorous quality control than many products available in health food stores. A recent investigation of hypericum products available in Germany[102] has shown that the content of active ingredients was clearly lower in products available in health food stores compared with those from pharmacies. A lower content of active ingredients probably decreases the likelihood of adverse effects but also the likelihood of a therapeutic effect. The addition of other ingredients might change the risk profile of a product containing hypericum. There is no study investigating the effects of self-medication of hypericum products in depressive patients.

Published case reports provide information on unusual, unexpected, or clinically important events but do not necessarily reflect the frequency of adverse events in practice. Cases reported to drug surveillance agencies provide a broader spectrum and give some insight into the relative frequency of events; however, underreporting and selective reporting are also present. It should be noted that

Table 4. Suspected Adverse Reactions to Hypericum Extracts Reported to Drug-Monitoring Agencies by May 2001[a]

Type of Symptoms	Total	%	Germany	United Kingdom	Austria	Canada	Ireland	Netherlands	Spain	United States
General symptoms	191	26	73	37	2	6	1	7	2	63
Changes in blood count ratios	30	4	22	6		1				1
Fertility/gynecologic	41	6	9	18		1		3	1	9
Skin	97	13	57	27	2	1	1			9
Cardiovascular	71	10	22	23		5	1			20
Nervous	79	11	29	31	2	4		3		10
Mental/psychic	106	15	26	29	1	5				45
Visual	14	2	3	6	2	1				2
Gastrointestinal	69	10	34	24		2				9
Hepatobiliary	24	3	13	5						6
Total	722	100	288	206	9	26	3	13	3	174

[a]The data from Germany were provided by the Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), the data from the United Kingdom by the Medicines and Healthcare products Regulatory Agency (MHRA), and the remaining data by the WHO Collaborating Centre for International Drug Monitoring in Sweden (which also receives the data from the AkdÄ and the MHRA).

Table 5. Most Frequently Reported Single Adverse Events in the Data From the WHO, the MHRA, and the AkdÄ

Frequency	Adverse Event
19	Paresthesia, headache
16	Itching
15	Skin erythema/rash, anxiety, nausea
12	Dyspepsia, decreased therapeutic effect of a comedication, hypertonia
11	Pain; metabolic changes
10	Unwanted pregnancy; nervousness, agitation, tachycardia, palpitation
5–9	Photosensitivity, skin pigmentation, urticaria; sleeping disorders, depression, psychosis, increased depression; increased prothrombin time, coagulation disorder, decreased plasma level of comedication; dizziness, sweating, abnormal vision, gastric pain, diarrhea, fatigue, general sick feeling, dyspnea, myocardial infarction, dysmenorrhea, reaction at site of application

Abbreviations: AkdÄ = Arzneimittelkommission der deutschen Ärzteschaft, MHRA = Medicines and Healthcare products Regulatory Agency, WHO = World Health Organization.

for our review we collected drug surveillance data only until May 2001.

The information collected suggests that the most relevant risk associated with hypericum use is interactions with other drugs. These interactions are probably due to an induction of the isoenzyme 3A4 of the cytochrome oxidase system, which metabolizes a series of pharmaceutical substances, and an induction of P-glycoprotein, which is responsible for an increase in excretion of drugs from the organism.[103] A wide range of drug interactions has been described in the recent past (see Hammerness et al.[8] for a comprehensive review), but the clinical relevance is not clear, as many of these interactions as actual side effects in patients have not yet been observed or reported. The lowering of plasma cyclosporine concentration in transplant patients is obviously of great importance. The large number of cases in a relatively small group of patients suggests that such an interaction regularly occurs in patients receiving cyclosporine and a hypericum extract at the same time. Hypericum extracts should also not be used in HIV-infected patients receiving antiretroviral treatment. In patients receiving anticoagulants of the coumarin type, the use of hypericum is only acceptable if coagulation parameters are regularly monitored. Simultaneous use of hypericum extracts and other antidepressants, particularly SSRIs, is inadequate and can be harmful.

The question whether hypericum extracts interact with oral contraceptives is of major relevance but has been difficult to answer up to now. A recent randomized trial[104] in a limited number of healthy females taking low-dose oral contraceptives found no evidence of ovulation in subjects also taking a hypericum extract, but intracyclic bleeding episodes increased. Patients should be informed that an interaction cannot be ruled out with certainty. Finally, hypericum extracts should be avoided in patients with a known allergy or hypersensitivity to such products.

In conclusion, the available evidence suggests that hypericum extracts are well tolerated and safe if taken under control of a physician who is aware of potential risks in specific circumstances. Self-medication might be acceptable in patients who have very mild depressive symptoms and who are not taking any other medication. As patients often do not disclose the use of complementary and alternative therapies to their physicians,[105] all clinicians should ask patients about herbal products. Also, clinicians need to be aware of the potential sources for drug interaction (see also Hammerness et al.[8]) and, if they are going to prescribe these drugs (e.g., coumarins, cyclosporine), should ask about St. John's wort directly. As available hypericum preparations can differ considerably in composition and even batch-to-batch quality, physicians should preferably prescribe products that have been tested in clinical trials. Products that do not provide important information on the content, such as the amount of total extract (e.g., 900 mg), the extraction fluid (e.g., methanol 80% or ethanol 60%), and the ratio of raw material to extract (e.g., 3–6:1), should be avoided. Publication of case reports should provide more detail on the specific product

used as well as on doses, duration of treatment, and interaction with other medication.

Drug names: amitriptyline (Elavil and others), clozapine (Clozaril, Fazaclo, and others), cyclosporine (Gengraf, Neoral, and others), imipramine (Tofranil and others), lithium (Eskalith, Lithobid, and others), nortriptyline (Aventyl, Pamelor, and others), sertraline (Zoloft), tacrolimus (Prograf and Protopic), theophylline (Elixophyllin, Theo-24, and others), warfarin (Coumadin, Jantoven, and others).

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