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Efficacy and tolerability of *Hypericum perforatum* in major depressive disorder in comparison with selective serotonin reuptake inhibitors: A meta-analysis

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ABSTRACT

Hypericum perforatum is a medicinal plant with established antidepressant properties. The aim of this meta-analysis was to compare the efficacy and tolerability of this antidepressant with selective serotonin reuptake inhibitors (SSRIs) as a group of standard antidepressants. For this purpose, Pubmed, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched for studies comparing efficacy and/or tolerability of *Hypericum* with SSRIs in the management of major depressive disorder (MDD). The search terms were: "Hypericum" or "St. John's wort" and "fluoxetine", "paroxetine", "citalopram", "serteraline", "escitalopram", or "fluvoxamine". Data were collected from 1966 to 2008 (up to June). "Clinical response", "remission", "mean reduction in Hamilton Rating Scale for Depression (HAMD) score from baseline", "total adverse events", and "withdrawals due to adverse events" were the key outcomes of interest.

Thirteen randomized placebo controlled clinical trials met our criteria and were included. Comparison of SSRIs with placebo yielded a significant relative risk (RR) of 1.22 (95% confidence interval: 1.03–1.45, $P=0.02$) for clinical response ($n=4$), a non significant RR of 0.96 (95% CI: 0.71–1.29, $P=0.76$) for remission ($n=4$), and a significant effect size [weighted mean difference (wmd+)] of 1.33 (95% CI: 1.15–1.51, $P<0.0001$) for mean reduction in HAMD score from baseline ($n=3$).

Comparison of *Hypericum* with SSRIs yielded a non significant relative risk (RR) of 0.99 (95% confidence interval: 0.91–1.08, $P=0.83$) for clinical response, a non significant RR of 1.1 (95% CI: 0.90–1.35, $P=0.35$) for remission, and a non-significant wmd+ of 0.32 (95% CI: −1.28–0.64, $P=0.52$) for mean reduction in HAMD score from baseline, a non significant RR of 0.85 (95% CI: 0.7–1.04, $P=0.11$) for any adverse events, and a significant RR of 0.53 (95% CI: 0.35–0.82, $P=0.004$) for withdrawals due to adverse events.

Hypericum does not differ from SSRIs according to efficacy and adverse events in MDD. Lower withdrawal from study due to adverse events by *Hypericum* is an advantage in management of MDD.

1. Introduction

Hypericum perforatum, a perennial herb from the family of Hypericaceae, has been known for its antidepressant activity. Its antidepressant activity has been demonstrated in many clinical trials (Kalb et al., 2001; Kasper et al., 2006; Lecrubier et al., 2002) and several meta-analyses (Linde et al., 2005a,b). The medicinal part of the plant is the whole or cut, dried flowering tops that are harvested during flowering time (ESCOP, 2003; PDR, 2004). It contains a variety of constituents including naphthodianthrons principally hypericin and pseudohypericin, phloroglucinol derivatives mainly hyperforin, adhyperforin and furohyperforin, flavonoids such as kaempferol and luteolin, volatile oil, plant acids, aminoacids, vitamin C, tannins, and carotenoids (Evans, 2002). Its antidepressant activity is attributed to the several bioactive compounds like phloroglucinol derivative hyperforin, naphthodianthrones hypericin and pseudohypericin, and several flavonoids but the exact mechanism of action of these compounds is not understood yet. Suggested mechanisms are inhibition of monoamine oxidase, binding to brain benzodiazepine receptors, and inhibition of neurotransmitters re-uptake such as serotonin, norepinephrine, dopamine and choline (Butterweck and Schmidt, 2007).

It is claimed that the efficacy of *H. perforatum* in the treatment of major depressive disorder (MDD) is comparable to standard antidepressants and it can be used as an alternative for standard therapies. However, the results from clinical trials are conflicting and reported inferiority (Moreno et al., 2006), similarity (Gastpar et al., 2005, 2006) and superiority (Fava et al., 2005; Szegedi et al., 2005) of *Hypericum* in comparison to SSRIs. Result of a meta-analysis published on 2005 suggested that *Hypericum* and standard antidepressants have similar benefit in MDD (Linde et al., 2005b). In that study, preparations of

Abbreviations: CGI, Clinical Global Impression; CI, Confidence Interval; HAMD, Hamilton Rating Scale for Depression; MDD, Major Depressive Disorder; RR, Relative Risk; SSRI, Selective Serotonin Reuptake Inhibitor; wmd, weighted mean difference.

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Hypericum were compared with older antidepressants and selective serotonin reuptake inhibitors (SSRIs) and no significant difference in efficacy was observed between *Hypericum* and standard antidepressants. Although older antidepressants showed better tolerability than *Hypericum*, there was no significant difference in the tolerability between *Hypericum* and SSRIs. In the present meta-analysis, we collected all studies comparing the efficacy and tolerability of *Hypericum* and SSRIs in the period of 1966 to June 2008 to reach a convincing conclusion on the use of *Hypericum* as an alternative to SSRIs.

2. Methods

2.1. Data sources

Pubmed, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched for studies comparing efficacy and/or tolerability of *Hypericum* with SSRIs in MDD. Data were collected from 1966 to 2008 (up to June). The search terms were: "Hypericum" or "St. John's wort" and "fluoxetine", "paroxetine", "citalopram", "serteraline", "escitalopram", or "fluvoxamine". There was no language restriction. The reference list from retrieved articles was also reviewed for additional applicable studies.

2.2. Study selection

Controlled trials comparing the efficacy and/or tolerability of *Hypericum* with SSRIs in patients with MDD were considered. "Clinical response", "remission", "mean reduction in HAMD score", "total adverse events", and "withdrawals due to adverse events" were the key outcomes of interest.

All published studies as well as abstracts presented at meetings were evaluated. Three reviewers independently examined the title and abstract of each article to eliminate duplicates, reviews, case studies, and uncontrolled trials. Studies in which mentioned drugs were administered via topical formulations were excluded and only comparison of oral formulations was considered eligible. Trials were disqualified if they compared *Hypericum* with only placebo or their outcomes had no relation to efficacy and/or tolerability. The reviewers independently extracted data on patients' characteristics, therapeutic regimens, dosage, trial duration, and outcome measures. There was no disagreement between reviewers.

2.3. Assessment of trial quality

The methodological quality of included trials was assessed using the Jadad score, which judges of the descriptions of randomization, blinding, and dropouts (withdrawals) in the trials (Jadad, 1998). This is summarized as follow: a: whether randomized or not (yes = 1 point, No = 0); b: whether randomization was described appropriately or not (yes = 1 point, No = 0); c: double blind (yes = 1 point, No = 0); d: was the double blinding described appropriately (yes = 1 point, No = 0); e: whether withdrawals and dropouts described or not (yes = 1 point, No = 0). The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3.

2.4. Statistical analysis

Data from selected studies were extracted in the form of 2×2 tables. All included studies were weighted and pooled. The data were analyzed using Statsdirect (2.7.2). Relative risk (RR) and 95% confidence intervals (95% CI) were calculated using the Mantel-Haenszel and DerSimonian-Laird methods and effect size (weighted mean difference) meta-analysis have been done using the Mulrow-Oxman and DerSimonian-Laird methods. The Cochran Q test was

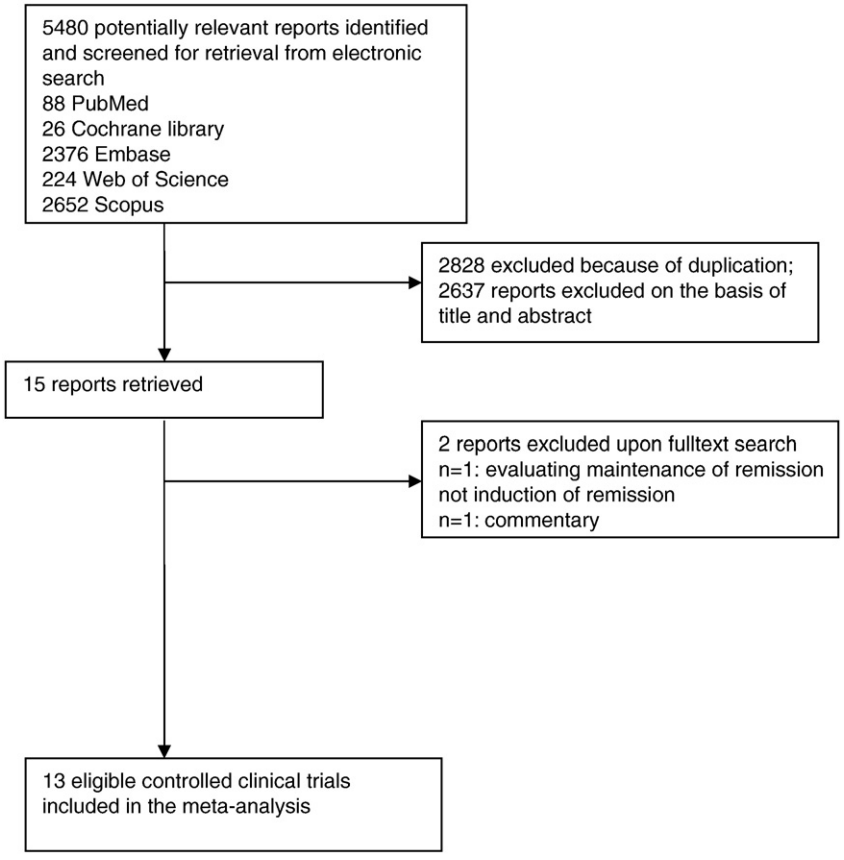

Fig. 1. Flow diagram of the study selection process.

Table 1
Jadad quality score of randomized controlled trial included in the meta-analysis

Study	Factors and Jadad score			
	Randomization	Blinding	Withdrawals and dropouts	Total Jadad score
Papakostas et al. (2007)	1	1	0	2
Gastpar et al. (2006)	2	2	1	5
Bjerkenstedt et al. (2005)	1	1	1	3
Moreno et al. (2006)	1	1	1	3
Szegedi et al. (2005)	2	2	1	5
Gastpar et al. (2005)	1	2	1	4
Fava et al. (2005)	1	2	1	4
Hypericum Depression Trial Study Group (2002)	2	2	1	5
Behnke et al. (2002)	1	1	1	3
van Gurp et al. (2002)	2	1	1	4
Brenner et al. (2000)	1	1	1	3
Schrader (2000)	1	2	1	4
Harrer et al. (1999)	1	1	1	3

used to test heterogeneity. The event rate in the experimental (intervention) group against the event rate in the control group was calculated using L'Abbe plot as an aid to explore the heterogeneity of effect estimates. Funnel plot analysis was used as publication bias indicator.

3. Results

The electronic searches yielded 5480 items; 88 from Pubmed, 26 from Cochrane Central, 2376 from Embase, 224 from Web of Science, and 2652 from Scopus. Of those, 15 trials were scrutinized in full text. Two reports were considered ineligible. Thus, 13 trials were included in the analysis (Behnke et al., 2002; Bjerkenstedt et al., 2005; Brenner et al., 2000; Fava et al., 2005, Gastpar et al., 2005, 2006; Harrer et al., 1999; Hypericum Depression Trial Study Group, 2002; Moreno et al., 2006; Papakostas et al., 2007, Schrader, 2000; Szegedi et al., 2005; van Gurp et al., 2002) (Fig. 1). From these 13 studies, 12 obtained Jadad score of 3 or more (Behnke et al., 2002; Bjerkenstedt et al., 2005; Brenner et al., 2000; Fava et al., 2005, Gastpar et al., 2005, 2006; Harrer et al., 1999; Hypericum Depression Trial Study Group, 2002; Moreno et al., 2006; Schrader, 2000; Szegedi et al., 2005; van Gurp et al., 2002) and remaining one gained Jadad score of 2 (Papakostas et al., 2007) (Table 1). Regarding the Cochran Q test for heterogeneity, it was found that this study does not cause heterogeneity in our meta-analysis and thus, it was not excluded. *Hypericum* was compared with fluoxetine in 7 studies (Behnke et al., 2002; Bjerkenstedt et al., 2005; Fava et al., 2005, Harrer et al., 1999; Moreno et al., 2006; Papakostas et al., 2007, Schrader, 2000), with citalopram in 1 (Gastpar et al., 2006), with sertraline in 4 (Brenner et al., 2000; Gastpar et al., 2005; Hypericum Depression Trial Study Group, 2002; van Gurp et al., 2002), and with paroxetine in 1 (Szegedi et al., 2005). Duration of treatment ranged between 4 and 12 weeks in various studies. Patients' characteristics, diagnosis criteria, *Hypericum* preparation, type and daily dosage of SSRIs, daily dosage of *Hypericum*, duration of treatment, and study setting have been demonstrated in Table 2. Definition of clinical response and remission in each study has been shown in Table 3. Mean reduction in HAMD score from baseline and percent of reduction have been reported in Table 4.

3.1. Efficacy of SSRIs

The summary RR for clinical response in four trials (Bjerkenstedt et al., 2005; Gastpar et al., 2006; Hypericum Depression Trial Study Group, 2002; Moreno et al., 2006) was 1.22 with a 95% CI of 1.03–1.45 with a significant RR (P=0.022, Fig. 2). The Cochrane Q test for heterogeneity indicated that the studies are homogenous (P=0.39) and could be combined. Thus, the fixed effects for individual and summary of RR were applied. Regression of normalized effect versus precision for all included studies for clinical response among SSRIs vs. placebo therapy was −1.19 (95% CI=−8.83 to 6.45, P=0.57), and Kendall's test on standardized effect vs. variance indicated tau=−0.33 (P=0.33).

Summary RR for remission by SSRIs vs. placebo in long term therapies among the four studies (Fava et al., 2005; Hypericum Depression Trial Study Group, 2002; Moreno et al., 2006; Papakostas et al., 2007) was 0.96 (95% CI=0.71–1.29) indicating a non-significant RR (P=0.76, Fig. 3). The Cochrane Q test for heterogeneity (P=0.33)

Table 2
Characteristics of papers included in the meta-analysis

Study	Sex		Mean age	Diagnosis criteria	Severity of depression	*Hypericum* preparation	Type of SSRI	Daily dosage (mg)		Treatment duration (weeks)	Recruitment of patients
	Male	Female						*Hypericum*	SSRI		
Papakostas et al. (2007)	ND	ND	ND	DSM-IV	Mild to severe	LI-160	Fluoxetin	20	20	12	General advertisement and clinician referrals
Gastpar et al. (2006)	90	168	50	ICD-10	Moderate	STW3-VI	Citalopram	900	20	6	Primary care physicians
Bjerkenstedt et al. (2005)	24	84	49.7	DSM-IV	Mild to moderate	LI-160	Fluoxetine	900	20	4	General practitioners
Moreno et al. (2006)	ND	ND	37.4	DSM-IV	Mild to moderate	Iperisan	Fluoxetine	900	20	8	Affective disorders study group unit at the institute of psychiatry
Szegedi et al. (2005)	76	168	47.2	DSM-IV	Moderate to severe	WS 5570	Paroxetine	900–1800	20–40	6	Psychiatric primary care centers
Gastpar et al. (2005)	51	149	48.9	ICD-10	Moderate	STW3	Sertraline	612	50	12	Primary care physicians
Fava et al. (2005)	58	77	37.3	DSM-IV	Mild to severe	LI-160	Fluoxetine	900	20	12	Depression clinical and research program of general hospital
Hypericum Depression Trial Study Group (2002)	77	147	43.5	DSM-IV	Moderate to severe	LI-160	Sertraline	900–1500	50–100	8	Academic or community clinics
Behnke et al. (2002)	22	47	49.7	ICD-10	Mild to moderate	Calmigen	Fluoxetine	300	40	6	ND
van Gurp et al. (2002)	33	52	40	DSM-IV	Mild to severe	ND	Sertraline	900–1800	50–100	12	articipating Participating doctors
Brenner et al. (2000)	11	19	45.5	DSM-IV	Mild to moderate	LI-160	Sertraline	600–900	50–75	7	Community hospital
Schrader (2000)	83	157	46	ICD-10	Mild to moderate	Ze117	Fluoxetine	500	20	6	Outpatient departments in internal medicine practices
Harrer et al. (1999)	32	129	69	ICD-10	Mild to moderate	LoHyp-57	Fluoxetine	800	20	6	General practitioners

ND=not determined.
CMHC=Community mental health center.

Table 3
Outcomes of efficacy

Study	Clinical response SSRI				Remission			
	Definition	*Hypericum*		Placebo	Definition	*Hypericum*	SSRI	Placebo
Papakostas et al. (2007)	A 50% reduction in total HAMD score	–	–	–	An HAMD score of 7 or less	13/45	16/47	10/39
Gastpar et al. (2006)	An HAMD score of <10 after treatment or an improvement of the initial HAMD score of at least 50%	71/131	71/127	51/130	–	–	–	–
Bjerkenstedt et al. (2005)	Decrease of more than 50% of the HAMD total score relative to baseline	22/54	20/54	22/55	HAMD total score of <8	13/54	15/54	4/55
Moreno et al. (2006)	Decrease of more than 50% of the HAMD total score relative to baseline	4/20	11/20	11/26	HAMD total score of <8	3/20	7/20	12/26
Szegedi et al. (2005)	Decrease of more than 50% of the HAMD total score relative to baseline	86/122	73/122	–	HAMD total score of <8	61/122	43/122	–
Gastpar et al. (2005)	An HAMD score of <10 after treatment or an improvement of the initial HAMD score of at least 50%	70/102	72/98	–	–	–	–	–
Fava et al. (2005)	–	–	–	–	HAMD total score of <8	17/45	14/47	9/43
Hypericum Depression Trial Study Group (2002)	A decrease in the HAMD total score from baseline of at least 50%	43/113	53/109	50/116	A CGI-I score of 1 or 2 and a HAMD total score of 8 or less	27/113	27/109	37/116
Behnke et al. (2002)	A decrease in total score from baseline of at least 50%	16/29	21/32	–	–	–	–	
van Gurp et al. (2002)	A HAMD score of <10 after treatment or an improvement of the initial HAMD score of at least 50%	20/45	22/45	–	–	–	–	–
Brenner et al. (2000)	A decrease in the HAMD total score from baseline of at least 50%	7/15	6/15	–	–	–	–	–
Schrader (2000)	A HAMD score of <10 after treatment or an improvement of the initial HAMD score of at least 50%	57/125	39/113	–	–	–	–	–
Harrer et al. (1999)	A HAMD score of <11 after treatment or an improvement of the initial HAMD score of at least 50%	50/77	57/84	–	–	–	–	–

HAMD=Hamilton rating scale for depression, CGI=Clinical Global Impression.

Table 4
Reduction in HAMD score from baseline

Study	*Hypericum*			SSRIs			Placebo		
	No. of patients	Mean reduction	%Reduction	No. of patients	Mean reduction	%Reduction	No. of patients	Mean reduction	%Reduction
Gastpar et al. (2006)	131	11.6±6.3	53	127	11.4±6.5	52.3	130	9.0±6.8	40.9
Bjerkenstedt et al. (2005)	54	9.9±8.1	39.8	54	8.9±8.0	37.4	55	9.7±7.0	38.5
Moreno et al. (2006)	20	–	22.3	20	–	53.9	26	–	32.1
Szegedi et al. (2005)	122	14.4±8.8	57	122	11.4±8.6	45	–	–	–
Gastpar et al. (2005)	102	–	62.3	98	–	63.4	–	–	–
Fava et al. (2005)	45	–	48	47	–	32.1	43	–	36.7
Hypericum Depression Trial Study Group (2002)	113	8.68±0.68	37.6	109	10.53±0.72	40.5	116	9.2±0.67	46.8
Behnke et al. (2002)	35	10.0±5.8	50	35	12.0±6.8	58	–	–	–
van Gurp et al. (2002)	44	9.5±7.1	50.3	43	8.2±7.5	41.6	–	–	–
Brenner et al. (2000)	13	8.4±6.5	39.4	15	9.1±5.2	41.9	–	–	–
Schrader (2000)	125	7.25±1.7	37	113	8.11±1.7	41.6	–	–	–

HAMD=Hamilton rating scale for depression.

indicated that the studies for remission in SSRIs therapy were not heterogeneous and thus fixed effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for remission was 2.42 (95% CI=−6.40 to 11.23, $P=0.36$), and Kendall's test on standardized effect vs. variance indicated tau=0.67 ($P=0.33$).

Effect size [weighted mean difference (wmd+)] for mean reduction in HAMD score from baseline by SSRIs vs. placebo therapy among the three studies (Bjerkenstedt et al., 2005; Gastpar et al., 2006; Hypericum Depression Trial Study Group, 2002) was 1.33 (95% CI=1.15 to 1.51) indicating a significant wmd+ ($P<0.0001$, Fig. 4). The Cochrane Q test for heterogeneity ($P=0.15$) indicated that the studies for mean reduction in HAMD score from baseline in SSRIs therapy were not heterogeneous and could be combined, thus fixed effects for pooling weighted mean difference was applied. Regression of normalized effect vs. precision for all included studies for mean reduction in HAMD score from baseline could not be calculated because of too few strata.

3.2. Efficacy of Hypericum in comparison with SSRIs

Clinical response and remission were evaluated in 11 (Behnke et al., 2002; Bjerkenstedt et al., 2005; Brenner et al., 2000; Gastpar et al., 2005, 2006; Harrer et al., 1999; Hypericum Depression Trial Study Group, 2002; Moreno et al., 2006; Schrader, 2000; Szegedi et al., 2005; van Gurp et al., 2002) and 6 (Bjerkenstedt et al., 2005; Fava et al., 2005; Hypericum Depression Trial Study Group, 2002; Moreno et al., 2006; Papakostas et al., 2007, Szegedi et al., 2005) studies (Table 3).

The summary RR for clinical response in eleven trials (Behnke et al., 2002; Bjerkenstedt et al., 2005; Brenner et al., 2000; Gastpar et al.,

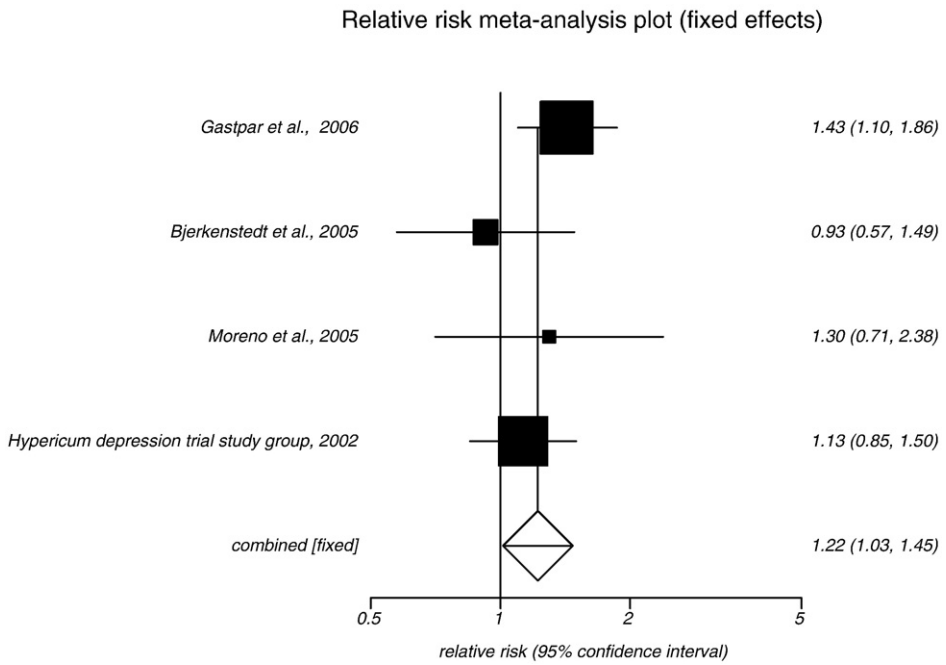

Fig. 2. Individual and pooled relative risk for the outcome of "clinical response" in the studies considering SSRIs vs. placebo therapy.

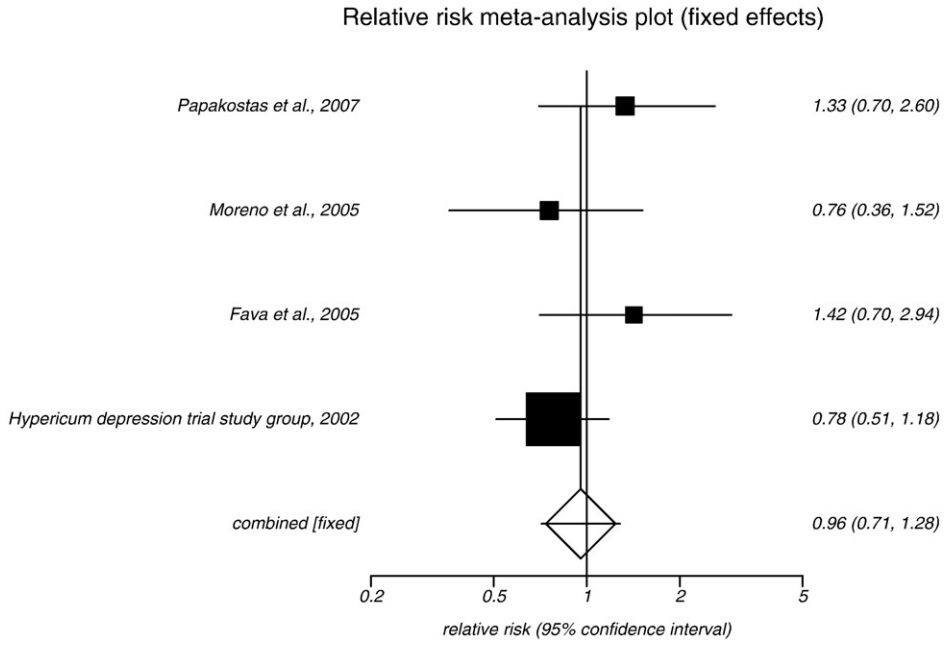

Fig. 3. Individual and pooled relative risk for the outcome of "remission" in the studies considering SSRIs vs. placebo therapy.

2005, 2006; Harrer et al., 1999; Hypericum Depression Trial Study Group, 2002; Moreno et al., 2006; Schrader, 2000; Szegedi et al., 2005; van Gurp et al., 2002) was 0.99 with a 95% CI of 0.91–1.08 and a non-significant RR (P=0.83, Fig. 5). The Cochrane Q test for heterogeneity indicated that the studies are homogenous (P=0.15) and could be combined. Thus, the fixed effects for individual and summary of RR were applied. Regression of normalized effect versus precision for all included studies for clinical response among *Hypericum* vs. SSRIs therapy was −0.85 (95% CI=−2.78 to 1.08, P=0.34), and Kendall's test on standardized effect vs. variance indicated tau=−0.13 (P=0.54).

Summary RR for remission by *Hypericum* vs. SSRIs therapy among the six studies (Bjerkenstedt et al., 2005; Fava et al., 2005; Hypericum Depression Trial Study Group, 2002; Moreno et al., 2006; Papakostas et al., 2007; Szegedi et al., 2005) was 1.1 (95% CI=0.90–1.35) indicating a non-significant RR (P=0.35, Fig. 6). The Cochrane Q test for heterogeneity (P=0.23) indicated that the studies for remission in *Hypericum* therapy were not heterogeneous and thus fixed effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for remission was −2.54 (95% CI=−4.29 to −0.78, P=0.02), and Kendall's test on standardized effect vs. variance indicated tau=−0.73 (P=0.02).

Effect size [weighted mean difference (wmd+)] for mean reduction in HAMD score from baseline by *Hypericum* vs. SSRIs therapy among the eight studies (Behnke et al., 2002; Bjerkenstedt et al., 2005; Brenner et al., 2000; Gastpar et al., 2006; Hypericum Depression Trial Study Group, 2002; Schrader, 2000; Szegedi et al., 2005; van Gurp et al., 2002) was 0.32

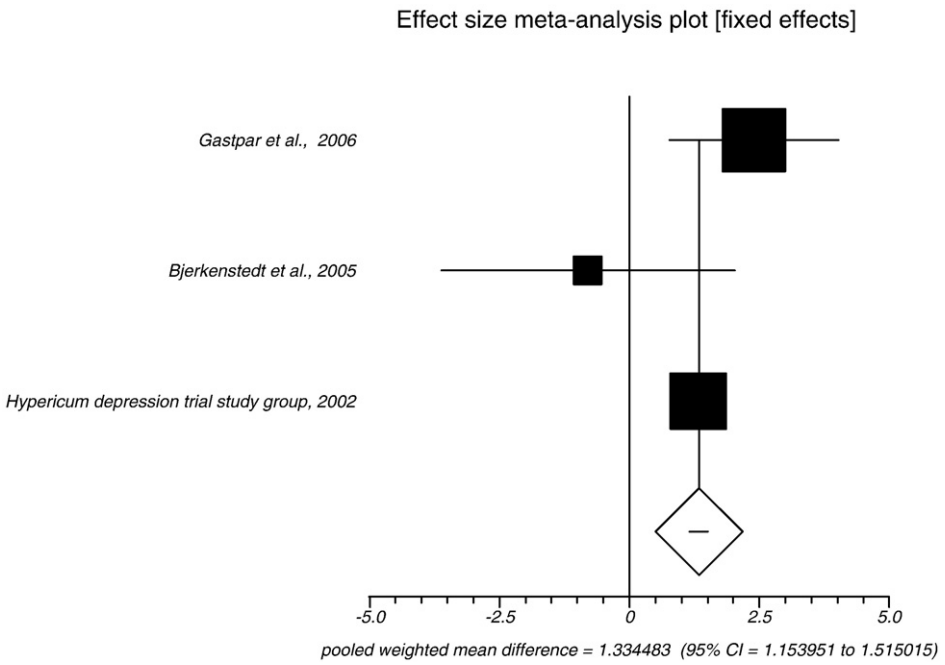

Fig. 4. Pooled weighted mean difference for the outcome of "mean reduction in HAMD score from baseline" in the studies considering SSRIs vs. placebo therapy.

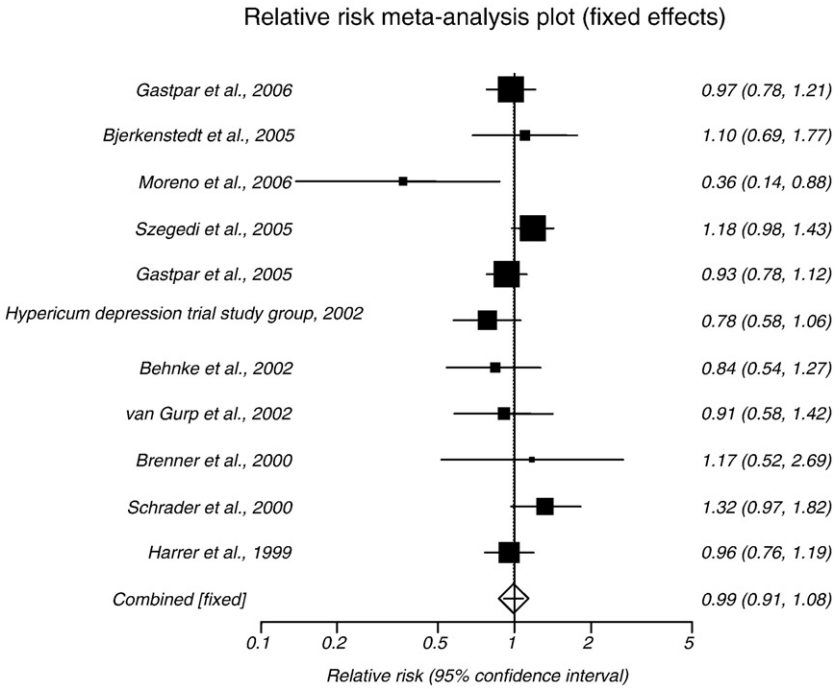

Fig. 5. Individual and pooled relative risk for the outcome of "clinical response" in the studies considering *Hypericum* vs. SSRIs therapy.

(95% CI = −1.28 to 0.64) indicating a non-significant wmd+ (P=0.52, Fig. 7). The Cochrane Q test for heterogeneity (P<0.0001) indicated that the studies for mean reduction in HAMD score from baseline in *Hypericum* therapy were heterogeneous and thus random effects for pooling weighted mean difference was applied. Regression of normalized effect vs. precision for all included studies for mean reduction in HAMD score from baseline was 2.20 (95% CI = 0.145 to 4.25, P=0.04), and Kendall's test on standardized effect vs. variance indicated tau = −0.07 (P=0.72).

3.3. Safety

Number of patients reported adverse events and withdrawal due to adverse events were evaluated in 8 (Behnke et al., 2002; Bjerkenstedt et al., 2005; Gastpar et al., 2005, 2006; Harrer et al., 1999; Schrader, 2000; Szegedi et al., 2005; van Gurp et al., 2002) and 11 (Behnke et al., 2002; Bjerkenstedt et al., 2005; Brenner et al., 2000; Fava et al., 2005, Gastpar et al., 2005, 2006; Harrer et al., 1999;

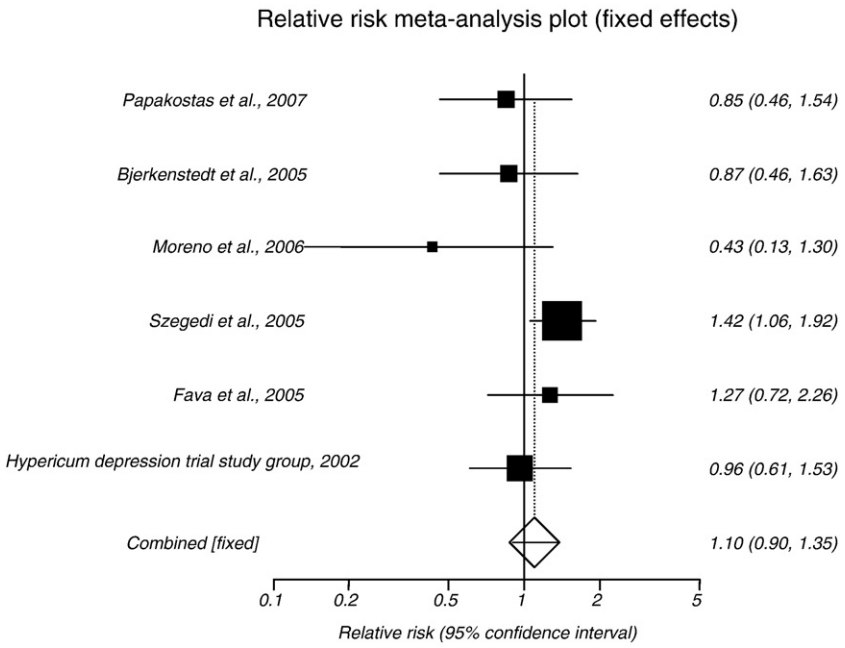

Fig. 6. Individual and pooled relative risk for the outcome of "remission" in the studies considering *Hypericum* vs. SSRIs therapy.

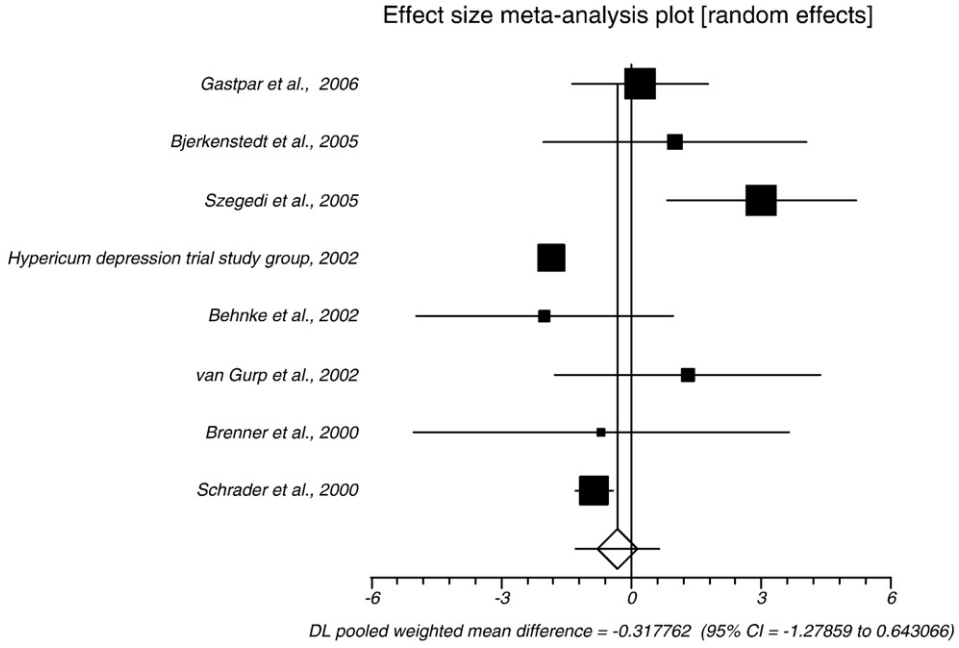

Fig. 7. Pooled weighted mean difference for the outcome of "mean reduction in HAMD score from baseline" in the studies considering *Hypericum* vs. SSRIs therapy.

Hypericum Depression Trial Study Group, 2002; Schrader, 2000; Szegedi et al., 2005; van Gurp et al., 2002) trials (Table 5).

The summary RR for adverse events of *Hypericum* vs. SSRIs therapy among 8 trials (Behnke et al., 2002; Bjerkenstedt et al., 2005; Gastpar et al., 2005, 2006; Harrer et al., 1999; Schrader, 2000; Szegedi et al., 2005; van Gurp et al., 2002) was 0.85 with a 95% CI of 0.7–1.04, indicating a non-significant RR for *Hypericum* intake (P=0.11, Fig. 8). The Cochrane Q test for heterogeneity indicated that the studies are significantly heterogeneous (P=0.004, Fig. 9) and thus the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for any adverse events among *Hypericum* vs. SSRIs therapy was −0.96 (95% CI=−5.14 to 3.21, P=0.59), and Kendall's test on standardized effect vs. variance indicated tau=−0.14 (P=0.55).

A summary RR for withdrawal due to adverse events by *Hypericum* vs. SSRIs intake among 11 studies (Behnke et al., 2002; Bjerkenstedt et al., 2005; Brenner et al., 2000 Fava et al., 2005, Gastpar et al., 2005, 2006; Harrer et al., 1999; Hypericum Depression Trial Study Group, 2002; Schrader, 2000; Szegedi et al., 2005; van Gurp et al., 2002) was 0.53 (95% CI=0.35–0.82) indicating a significant RR (P=0.004, Fig. 10). The Cochrane Q test for heterogeneity indicated that the studies for withdrawal due to adverse

Table 5
Outcomes of tolerability

Study	Adverse events		Withdrawal due to adverse events	
	Hypericum	SSRI	*Hypericum*	SSRI
Gastpar et al. (2006)	39/131	53/127	4/131	11/127
Bjerkenstedt et al. (2005)	20/57	31/56	4/57	4/56
Moreno et al. (2006)	–	–	–	–
Szegedi et al. (2005)	69/125	96/126	4/125	8/126
Gastpar et al. (2005)	74/123	60/118	1/123	2/118
Fava et al. (2005)	–	–	0/45	2/47
Hypericum Depression Trial Study Group (2002)	–	–	2/31	5/32
Behnke et al. (2002)	22/35	20/35	2/35	4/35
van Gurp et al. (2002)	34/45	32/45	3/45	7/45
Brenner et al. (2000)	–	–	2/15	2/15
Schrader (2000)	18/125	28/114	0/125	1/114
Harrer et al. (1999)	12/77	17/84	6/77	8/84

events by *Hypericum* vs. SSRIs therapy in MDD was homogenous (P=0.98) and could be combined. Thus, the fixed effects for individual and summary of RR were applied. Regression of normalized effect vs. precision for withdrawal due to adverse events among *Hypericum* vs. SSRIs therapy was −0.51 (95% CI=−1.73 to 0.70, P=0.36). The Kendall's test on standardized effect vs. variance indicated tau=−0.018 (P=0.88).

4. Discussion

In the current meta-analysis, the efficacy and tolerability of *Hypericum* were compared with SSRIs. At the first step, the efficacy of SSRIs in comparison to placebo was evaluated in 6 of eligible studies (Bjerkenstedt et al., 2005; Fava et al., 2005; Gastpar et al., 2006; Hypericum Depression Trial Study Group, 2002; Moreno et al., 2006; Papakostas et al., 2007). The results 4 meta-analyzed articles showed that SSRIs are effective in induction of clinical response with MDD. Furthermore, results of 3 trials demonstrated effectiveness of SSRIs in reduction of HAMD score in patients with MDD. Clinical remission was not different between SSRIs and placebo.

Data for comparison of clinical remission between SSIRs and placebo was available in five study but they were heterogeneous. Heterogeneity was assessed because of one of the studies that its duration of drug therapy was shorter than other studies and made variation, thus only four studies with long-term therapy were included in the meta-analysis.

The results from comparing *Hypericum* with SSRIs demonstrated that rate of clinical response and remission and reduction of HAMD score was similar between *Hypericum* and SSRIs. Moreover, the number of patients reporting adverse events was not different between *Hypericum* and SSRIs. Withdrawal due to adverse events by SSRIs was higher than *Hypericum*. Although statistically significant, the advantage of SSRIs over placebo in this dataset is at the lower margin of clinical utility meaning that when specific efficacy is relatively weak, the advantage in tolerability favoring *Hypericum* is relatively more important.

The results obtained from current meta-analysis supports the previous meta-analysis (Linde et al., 2005b) except for withdrawal due to adverse events, which was reported to be similar between two groups in that meta-analysis. In the study of Linde et al. (2005b), only 6 papers were included while the current meta-analysis included 13 trials with larger study patients causing the present data more convincing.

All included trials in the current meta-analysis were randomized and double blinded and patients were diagnosed with MDD according to DSM-IV or ICD-10 criteria. Severity of disease among population in each study was determined according to HAMD score. The quality of trials was assessed by Jadad score and all trials have acceptable quality except one which obtained Jadad score of 2 (Papakostas et al., 2007) but Cochran Q test showed no heterogeneity. Among the included studies, 5 (Bjerkenstedt et al., 2005; Fava et al., 2005; Hypericum Depression Trial Study Group, 2002; Moreno et al., 2006; Papakostas et al., 2007) compared SSRIs and *Hypericum* with placebo additionally. Three of them (Bjerkenstedt et al., 2005; Fava et al., 2005; Papakostas et al., 2007) concluded that *Hypericum* and SSRIs cause higher remission rate than placebo and 2 (Hypericum Depression Trial Study Group, 2002; Moreno et al., 2006) concluded that remission rate in placebo group is higher than *Hypericum* and SSRIs. Of course, the

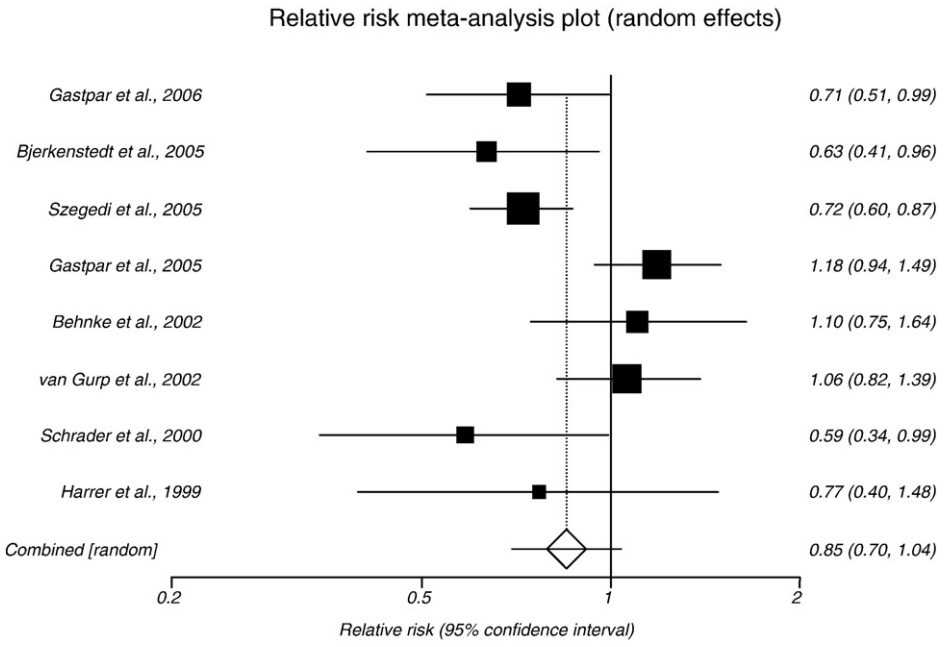

Fig. 8. Individual and pooled relative risk for the outcome of "adverse events" in the studies considering *Hypericum* vs. SSRIs therapy.

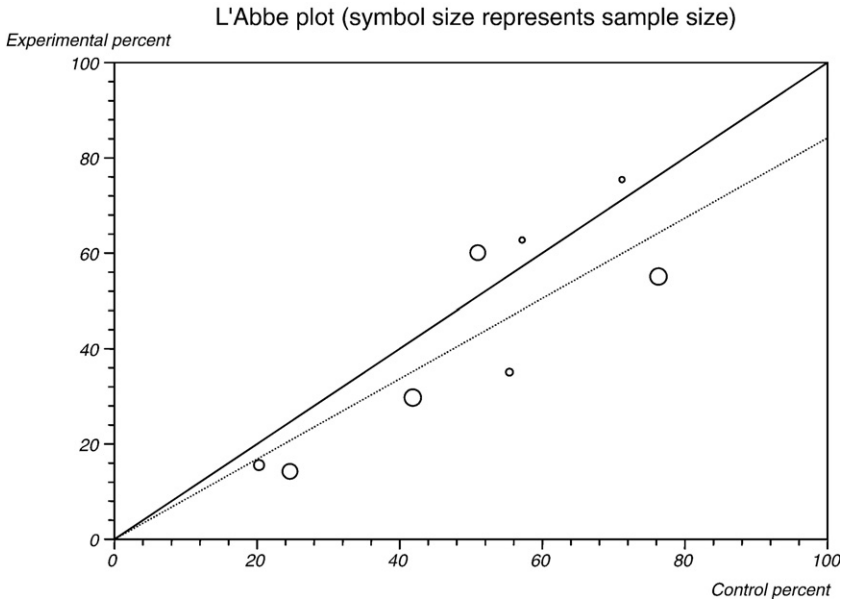

Fig. 9. Heterogeneity indicators for the outcome of "adverse events" for studies including *Hypericum* vs. SSRIs therapy.

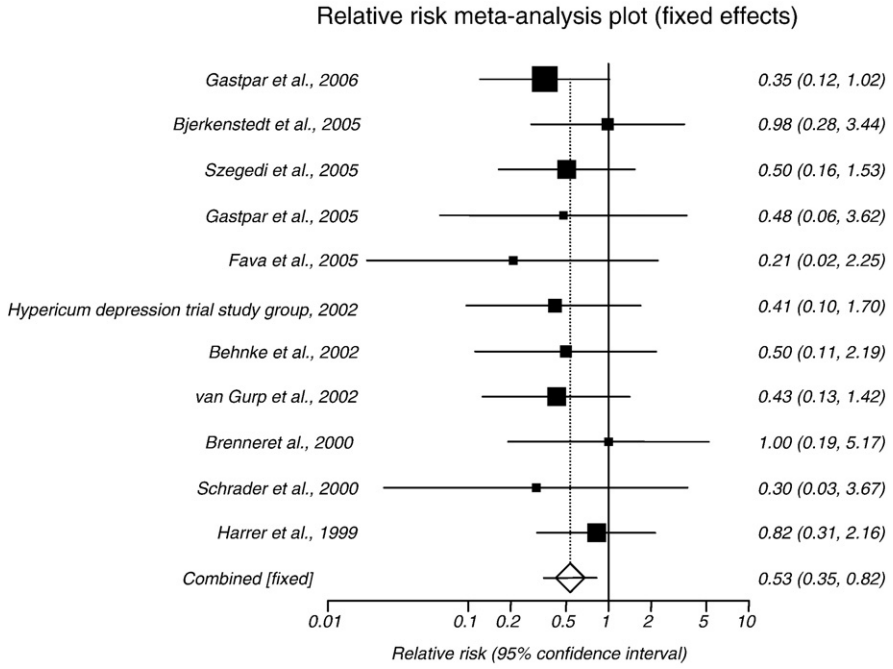

Fig. 10. Individual and pooled relative risk for the outcome of "withdrawal due to adverse events" in the studies considering *Hypericum* vs. SSRIs therapy.

results of a meta-analysis comparing the efficacy of *Hypericum* with placebo in patients with MDD have shown a higher response rate by *Hypericum* (Linde et al., 2005a,b).

The included data in the present study for adverse events was not homogeneous (Fig. 9) and thus random effect model was used for meta-analysis. This heterogeneity is mainly a result of "clinical heterogeneity" among trials (Gastpar et al., 2005; van Gurp et al., 2002) that compared *Hypericum* with sertraline while other studies compared *Hypericum* with other antidepressants (Table 2). This heterogeneity may be partly because of different incidences of adverse events that are usually seen in clinical trials by different SSRIs (Rahimi et al., 2006, 2008a,b).

Some limitations can be numbered for this meta-analysis, such as dissimilarities among characteristics of patients (age, sex, lifestyle, and compliance), different SSRIs, dissimilar *Hypericum* preparations, different doses of drugs, dissimilar durations of treatments, different diagnosis criteria, and different severity of depression.

Hypericum as a medicinal herb has been more interested for its antidepressant properties and thus concomitant use of *Hypericum* and SSRIs may occur in patients with MDD. Furthermore, a number of clinically significant interactions of *Hypericum* have been identified with conventional drugs, including anticancer agents (imatinib and irinotecan), anti-HIV agents (e.g. indinavir, lamivudine and nevirapine), anti-inflammatory agents (e.g. ibuprofen and fexofenadine), antimicrobial agents (e.g. erythromycin and voriconazole), cardiovascular drugs (e.g. digoxin, ivabradine, warfarin, verapamil, nifedipine and talinolol), central nervous system agents (e.g. amitriptyline, buspirone, phenytoin, methadone, midazolam, alprazolam, and

sertraline), hypoglycaemic agents (e.g. tolbutamide and gliclazide), immuno-modulating agents (e.g. cyclosporine and tacrolimus), oral contraceptives, proton pump inhibitors (e.g. omeprazole), respiratory system agents (e.g. theophylline), and statins (e.g. atorvastatin and pravastatin). Both pharmacokinetic and pharmacodynamic components may play a role in the interactions of drugs with *Hypericum*. For pharmacokinetic changes of drugs by *Hypericum*, induction of cytochrome P450 and P-glycoprotein are considered the major mechanism (Di et al., 2008). This necessitates administering of *Hypericum* under careful medical care and awareness of physicians to regularly ask their patients about the use of products containing *Hypericum*.

The results of this meta-analysis are optimistic for the use of *Hypericum* as an alternative to SSRIs in the management of depression.

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