Efficacy and tolerability of *Hypericum* extract for the treatment of mild to moderate depression

Siegfried Kasper, Filippo Caraci, Bruno Forti, Filippo Drago, Eugenio Aguglia

Department of General Psychiatry, Medical University of Wien, MUV, Austria
Department of Experimental and Clinical Pharmacology, University of Catania Medical School, Catania, Italy
CSM, Belluno, Italy
Department of Clinical Psychiatry, University of Catania School of Medicine, Catania, Italy

Received 13 May 2010; received in revised form 13 July 2010; accepted 20 July 2010

**KEYWORDS**

Depression; *Hypericum*; St. John's wort; Efficacy; Review

**Abstract**

Depression is a common condition in the community with a significant impact on affected individuals, their relatives and society. Many patients with depression do not seek treatment and are often concerned about the possible adverse effects of antidepressant drugs. Extract of *Hypericum perforatum* (St. John's wort) has long been recognized as a treatment for depression. Several published trials and meta-analyses have demonstrated the efficacy and tolerability of *Hypericum* extract for mild to moderate depression. Recent comparative trials of *Hypericum* extract and other antidepressants, including selective serotonin reuptake inhibitors (SSRIs), provide support for *Hypericum* extract efficacy. However, since the constituents of *Hypericum* extract differ between the individual manufacturers, the efficacy cannot be extrapolated from one extract to another. In this review, WS 5572, LI 160, WS 5570 and ZE 117 *Hypericum* extracts have been shown to be significantly more effective than placebo with at least similar efficacy and better tolerability compared to standard antidepressant drugs.

© 2010 Elsevier B.V. and ECNP. All rights reserved.

**1. Introduction**

Depression is a common condition in the community and the most prevalent form of psychiatric morbidity, although figures depend on the population studied and diagnostic criteria used. Studies that employ Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria of major depression provide lower prevalence estimates than those that allow more self-reporting of depressive symptoms and less stringent diagnostic criteria (Battaglia et al., 2004; Mulsant and Ganguli, 1999; Olsen et al., 2004; Wilhelm et al., 2003). A large-scale survey of 5566 individuals assessed using the modified-Mini-International Neuropsychiatric Interview (MINI) showed that the prevalence of major depression in Italy was 10.8% (Battaglia et al.,...
2004), a figure that corresponds with those from other epidemiological studies (Mulsant and Ganguli, 1999). However, the actual impact of such depressive disturbances is likely to be underestimated as patients may not be sufficiently severe to meet standard diagnostic criteria (Aguglia and Forti, 2001).

One of the most important factors in treatment of mild to moderate depression is the tolerability of pharmacological therapy, since the majority of patients have to continue normal work activities (Sommer and Harrer, 1994). Side effects of psychoactive drugs, such as dependence and mood alterations, are often feared by patients, which is thought to lead to an overall low rate of acceptance of standard pharmacological treatment (Röder et al., 2004). Moreover, the presence of somatic symptoms in mild forms of depression may cause further problems with compliance because of the side effects of antidepressant therapy (Vorbach et al., 1994). Thus, treatment of patients with mild to moderate depression represents a particularly clinically challenging problem.

Extracts of Hypericum perforatum, commonly called St. John's wort, have been used for centuries in herbal medicine and have been clinically studied since the early 1990s (Röder et al., 2004). Drugs based on Hypericum extract are widely employed in Europe and are gaining popularity in the United States (Kasper and Dienel, 2002; Lecrubier et al., 2002). Hypericum extract contains at least 10 active constituents that may contribute to its pharmacological effects (Wagner and Bladt, 1994). Components known, or suspected, to play a role in antidepressant activity include phloroglycin (e.g. hyperforin), naphthodianthrones (e.g. hypercin) and the flavonoids (e.g. quercitrin). Although the labeling of extracts indicates that several of the products studied should be pharmaceutically equivalent, dissolution under biorelevant conditions revealed that they have quite different release profiles and cannot be considered switchable (Westerhoff et al., 2002). Clinical evaluation and comparison of Hypericum extracts is problematic due to the differences in study design, inclusion criteria and extract used and, in many earlier studies, the Hypericum preparations are not adequately characterized. In some studies, the preparations are standardized by either their hypericin or hyperforin content or, occasionally, both. Although these individual substances alone have been shown to have antidepressant activity, the total extract appears to be more effective (Reichling et al., 2003). Some more recent studies use several active components or the whole extract to characterize a preparation.

The mechanisms of action of Hypericum extract are not fully understood (Butterweck, 2003), although some authors have hypothesized that hyperforin is the main active principle responsible for the antidepressant activity (Mennini and Gobbi, 2004). The antidepressant activity of Hypericum extract has been demonstrated in different animal models of depression (Butterweck, 2003). Hypericum extracts can inhibit the synaptosomal uptake of noradrenaline, serotonin and GABA in a concentration-dependent manner (Butterweck, 2003; Schrader, 2000). In particular it has been hypothesized that non-selective inhibition of monoamines occurs in part via modulation of Na⁺ gradient membranes, with Hypericum extract causing sodium influx into the neuron, which finally leads to the release of intracellular calcium (Singer et al., 1999; Marsh and Davies, 2002). In vivo studies have demonstrated that Hypericum extracts lead to a downregulation of β-adrenergic receptors (Butterweck, 2003), a common biochemical marker of antidepressant efficacy (Simbrey et al., 2004). Furthermore Hypericum extract is known to increase dopaminergic activity in the prefrontal cortex (Yoshitake et al., 2004).

Stress and hypothalamic–pituitary–adrenal (HPA) axis abnormalities have a central role in the pathogenesis of depression, with an impaired negative feedback of glucocorticoids on the activity of the HPA axis, which results in elevated cortisol levels (Krishnan and Nestler, 2008). H. perforatum significantly attenuated restraint stress-induced increases in plasma ACTH and corticosterone levels (Kumar et al., 2010; Grundmann et al., 2010; Butterweck and Schmidt, 2007). Studies in healthy male volunteers have found that Hypericum extracts can modulate salivary and serum cortisol levels (Franklin et al., 2006; Schule et al., 2001). Further studies are needed to better understand the molecular mechanisms underlying the antidepressant activity of H. perforatum and the specific effects of the different Hypericum preparations.

Much of the heterogeneity seen in Hypericum clinical trial data can be explained by the differences in extract preparation. The aim of this review is to examine clinical evidence related to the efficacy and tolerability of available Hypericum extracts for the treatment of depression of mild to moderate severity, and to compare the efficacy and tolerability of specific preparations of Hypericum extract with standard antidepressant drugs and allows individual extracts to be evaluated on a peer-extract basis. We will focus our attention on patients with mild to moderate depression which is the population most likely to benefit from Hypericum extract therapy due to the favourable tolerability profile. Relevant studies were selected from literature sourced using comprehensive Medline searches for articles on Hypericum extract from 1993 to the present using the following search terms: Hypericum, St. John's wort, Johanniskraut, Johanniskrautextrakt, and depression. Additional manual searches were also performed in the reference lists of published meta-analyses and randomized controlled trials identified in the literature search. Most active control studies in this review were designed to determine non-inferiority with standard antidepressant treatment in terms of efficacy and to examine the tolerability of Hypericum extract in comparison to standard antidepressant drugs.

2. Clinical evidence for efficacy and tolerability of Hypericum extract

The clinical studies were selected for this review on the basis of the patients' baseline clinical status. Only studies of patients with mild to moderate depression were included. Mild to moderate depression is defined by a baseline Hamilton Depression Rating Scale (HAMD) score of 16–24 or mean HAMD score of 16–24 or by The Tenth Revision of the International Classification of Diseases and Related Health Problems (ICD-10), F32.0, F32.1, F33.0 and F33.1.

Of the various extracts available, LI 160, with a hypericin content of 0.72–0.96 mg in a 900 mg dose, has been the most frequently studied. Other studies have used extracts WS 5570, WS 5572, WS 5573, STEI300, ZE 117, psychotinin,
esbericum, LoHyp-57, calmigen, STW3, and an unnamed extract from the Swiss Herbal Remedies Company, which have differing hypericin and hyperforin contents (Table 1). Clinical studies have been reviewed by the specific preparation of Hypericum extract used, to determine whether some extracts might have a greater antidepressant effect than others.

2.1. Hypericum extract vs. placebo

Numerous studies have compared the efficacy of Hypericum extract with placebo in patients with major depression (Hänsgen and Vesper, 1996; Hübner et al., 1994; Hypericum Depression Trial Study Group, 2002; Kalb et al., 2001; Laakmann et al., 1998; Lecrubier et al., 2002; Lehrl and Woelk, 1993; Philipp et al., 1999; Schmidt and Sommer, 1993; Schrader et al., 1998; Shelton et al., 2001; Sommer and Harrer, 1994; Witte et al., 1995; Kasper et al., 2006, 2008a,b). A summary of these studies including responder rates is shown in Table 2. In the majority of studies, the responder rate is defined as the proportion of patients with a HAMD score of <10 at endpoint or a ≥50% reduction in HAMD score from baseline to endpoint. Studies comparing LI 160 and placebo, all conducted in Germany, showed a significantly greater response with LI 160 vs. placebo. Two studies, both conducted in the US (Hypericum Depression Trial Study Group, 2002; Shelton et al., 2001), showed no significant difference between LI 160 and placebo. However, the greater severity of depression of the patients included in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Preparation details of Hypericum extracts used in clinical trials.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extract</td>
<td>Daily dose (mg)</td>
</tr>
<tr>
<td>LI 160</td>
<td>900 (3×300) (Bjerkenstedt et al., 2005; Brenner et al., 2000; Hänsgen and Vesper, 1996; Harrer et al., 1994; Hubner et al., 1994; Hypericum Depression Trial Study Group, 2002; Sommer and Harrer, 1994)</td>
</tr>
<tr>
<td>WS 5570</td>
<td>900 (3×300) (Kasper et al., 2004; Lecrubier et al., 2002)</td>
</tr>
<tr>
<td>WS 5572</td>
<td>900 (3×300) (Kalb et al., 2001; Laakmann et al., 1998) or 3×600 (Szegedi et al., 2005)</td>
</tr>
<tr>
<td>WS 5573</td>
<td>900 (3×300)</td>
</tr>
<tr>
<td>ZE 117</td>
<td>200–240 (Witte et al., 1995) 500 (2×250) (Schrader, 2000; Schrader et al., 1998; Woelk, 2000)</td>
</tr>
<tr>
<td>STEI300</td>
<td>1050 (3×350) (Philipp et al., 1999)</td>
</tr>
<tr>
<td>Esbericum</td>
<td>75–300 (1–4×75) (Shaper and Brummer, 2005)</td>
</tr>
<tr>
<td>LoHyp-57</td>
<td>800 (4×200) (Harrer et al., 1999)</td>
</tr>
<tr>
<td>Calmigen</td>
<td>300 (2×150) (Behnke et al., 2002)</td>
</tr>
<tr>
<td>Unnamed extract from Swiss Herbal Remedies</td>
<td>900 (3×300) (van Gurp et al., 2002)</td>
</tr>
<tr>
<td>STW3/Laif 600</td>
<td>612 (Gastpar et al., 2005)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td><strong>Placebo as comparator</strong>&lt;br&gt; (Lehr and Woelk, 1993)</td>
<td>DB, R</td>
</tr>
<tr>
<td>(Schmidt and Sommer, 1993)</td>
<td>DB, R</td>
</tr>
<tr>
<td>(Hubner et al., 1994)</td>
<td>DB, R, SC</td>
</tr>
<tr>
<td>(Sommer and Harrer, 1994)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Hänsgen and Vesper, 1996)</td>
<td>DB, R</td>
</tr>
<tr>
<td>(Shelton et al., 2001)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Hypericum Depression&lt;br&gt;Trial Study Group, 2002)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Lecrubier et al., 2002)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Laakmann et al., 1998)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Kalb et al., 2001)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Witte et al., 1995)</td>
<td>DB, R</td>
</tr>
<tr>
<td>(Schrader et al., 1998)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Philipp et al., 1999)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Kasper et al., 2006)</td>
<td>DB, R</td>
</tr>
<tr>
<td>Study</td>
<td>Comparator</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Placebo as comparator</strong> (Kasper et al., 2008b)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td><strong>Tricyclic as comparator</strong> (Vorbach et al., 1994)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Wheatley, 1997)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Bergmann et al., 1993)</td>
<td>DB</td>
</tr>
<tr>
<td>(Woelk, 2000)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Philipp et al., 1999)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td><strong>SSRI as comparator</strong> (Brenner et al., 2000)</td>
<td>DB, R</td>
</tr>
<tr>
<td>(Hypericum Depression Trial Study Group, 2002)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Harrer et al., 1999)</td>
<td>DB, R, MC</td>
</tr>
<tr>
<td>(Schrader, 2000)</td>
<td>DB, R, MC</td>
</tr>
</tbody>
</table>

(continued on next page)
Table 2 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Disease severity at baseline</th>
<th>Hypericum extract (mg/day)</th>
<th>Comparator (mg/day)</th>
<th>Populationa</th>
<th>N</th>
<th>Responders n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRI as Comparator</strong> (Behnke et al., 2002)</td>
<td>DB, R, MC</td>
<td>Mild to moderate: mean HAMD 20–21</td>
<td>Calmigen (300)</td>
<td>Fluoxetine (40)</td>
<td>ITT</td>
<td>70</td>
<td>16/35 (45.7)c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21/35 (60.0)</td>
</tr>
<tr>
<td>(van Gurp et al., 2002)</td>
<td>DB, R, MC</td>
<td>HAMD ≥16, mean HAMD 19</td>
<td>Swiss Herbal Remedies (900–1800)</td>
<td>Sertraline (50–100)</td>
<td>EP</td>
<td>90a</td>
<td>20/45 (44.5)c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22/45 (48.9)</td>
</tr>
<tr>
<td>(Gastpar et al., 2005)</td>
<td>DB, R, MC</td>
<td>Moderate: ICD-10 F32.1, F33.1; HAMD 20–24, mean HAMD 22</td>
<td>STW3/Laif 600 (612)</td>
<td>Sertraline (50)</td>
<td>PP</td>
<td>200d</td>
<td>70/102 (68.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(12 weeks)</td>
<td></td>
<td>69/98 (73.5)</td>
</tr>
<tr>
<td>(Szegedi et al., 2005)</td>
<td>DB, R, MC</td>
<td>Moderate to severe: HAMD ≥22, mean HAMD 25.5 (44% had moderate depression, HAMD 22–24 but data are shown for the whole cohort since separate data for the moderate subgroup were not provided)</td>
<td>WS 5570 (900–1800)</td>
<td>Paroxetine (20–40)</td>
<td>ITT</td>
<td>86/122 (70.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>73/122 (59.8)</td>
</tr>
<tr>
<td>(Bjerkenstedt et al., 2005)</td>
<td>DB, R, MC</td>
<td>Mild to moderate major depressive disorder DSM-IV Mean HAMD 24–25</td>
<td>LI 160 (900)</td>
<td>Fluoxetine (20)</td>
<td>ITT</td>
<td>163</td>
<td>22/54 (40.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fluoxetine 20/54 (37%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo 21/55 (38.1%)</td>
</tr>
<tr>
<td>(Fava et al., 2005)</td>
<td>DB, R, MC</td>
<td>Mild to moderate major depressive disorder DSM-IV HAMD score (17 items) Mean HAMD 22</td>
<td>LI 160 (900)</td>
<td>Fluoxetine (20)</td>
<td>ITT</td>
<td>135</td>
<td>17/45 (37.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fluoxetine 14/47 (29.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo 9/43 (20.9%)</td>
</tr>
<tr>
<td>(Moreno et al., 2006)</td>
<td>DB, R, MC</td>
<td>Mild to moderate major depressive disorder DSM-IV HAMD score 14–17</td>
<td>Hypericum extract Iperisan 3×1 (900 mg)</td>
<td>Fluoxetine (20)</td>
<td>ITT</td>
<td>66</td>
<td>4/20 (20%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fluoxetine 11/20 (55%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo 11/26 (42.3%)</td>
</tr>
<tr>
<td>(Gastpar et al., 2006)</td>
<td>DB, R, MC</td>
<td>Moderate depression: ICD-10 F32.1, F33.1 mean HAMD 22</td>
<td>STW3-VI (900)</td>
<td>Citalopram (20)</td>
<td>PP</td>
<td>388</td>
<td>71/131 (54.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(12 weeks)</td>
<td></td>
<td>Citalopram 71/127 (55.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo 51/130 (39.2%)</td>
</tr>
</tbody>
</table>

aITT/EP/PP data are presented where available; bData are taken from the review of Linde et al. (2005a,b); cITT data were not reported; dPP data not reported; eThe PP analysis (data not reported) was undertaken and yielded similar results to the ITT analysis; fThe ITT analysis (data not reported) was undertaken and yielded similar results to the PP analysis. DB = double-blind; EP = evaluable patients (safety analysis population); HAMD = Hamilton Depression Rating Scale; ITT = intention to treat population; MC = multicenter; NS = not significant, p > 0.05; PP = per protocol (protocol compliant) population; R = randomized.
these studies limits the generalization of these findings; whereas many other well designed studies have demonstrated positive results for *Hypericum* extract in mild depression patients.

Of the other placebo-controlled studies, two, using extract WS 5572, showed a significant response compared with placebo (Kalb et al., 2001; Laakmann et al., 1998) and, in a larger study, WS 5570 extract was shown to be significantly more effective than placebo (Lecrubier et al., 2002). Findings from a study comparing two *Hypericum* extracts with different concentrations of hyperforin (WS 5572, 5% and WS 5573, 0.5%) suggest that the efficacy of *Hypericum* extract in mild to moderate depression might depend on the hyperforin content (Laakmann et al., 1998).

A double-blind, randomized, placebo-controlled, multicenter clinical trial (Kasper et al., 2006) has demonstrated the superior antidepressant efficacy of WS 5570 600 mg/day (in one dose) and of WS 5570 1200 mg/day (in two daily doses) compared to placebo in the treatment of patients with a mild or moderate major depressive episode after 6 weeks of treatment. Interestingly the primary outcome measure, the HAMD total score change vs. baseline after 6 weeks, indicates no significant differences in efficacy between WS 5570 600 mg/day and 1200 mg/day, although the number of patients who experienced remission was higher in the WS 5570 1200 mg/day group than the WS 5570 600 mg/day group.

The antidepressant efficacy of *Hypericum* extracts has been studied in different controlled clinical trials performed in patients with mild or moderate, or with moderate or severe depression. No studies have been specifically conducted in mild depression patients. In view of the high response rate normally seen in mild depression, the efficacy of *Hypericum* extracts in this subtype of depression has been questioned, also considering the large and unpredictable response to placebo.

Interestingly a recent sub-analysis of data from three different controlled clinical trials has clearly shown that St. John's wort extract WS 5570 has a significant beneficial effect during acute treatment of patients suffering from mild depression (Kasper et al., 2008a). A subgroup of 217 patients with a pre-treatment total score ≤ 20 points on the 17-item HAMD was selected for the sub-analysis from a total of more than 1200 patients included into these trials. The rates of responders (i.e., patients with a HAMD total score decrease ≥ 50%) were 73%, 64%, 71%, and 37% for WS 5570 600 mg/day, 900 mg/day and 1200 mg/day, and placebo, respectively. These data suggest that *Hypericum* extracts, compared to placebo, were significantly able to reduce depression severity in mild depressed patients. Furthermore this study shows that treatment with WS 5570 leads to a substantial increase in the probability of remission within 6 weeks of treatment (Kasper et al., 2008a).

Continuing treatment with antidepressant drugs has been considered as the most accepted strategy to prevent relapse in major depression (Geddes et al., 2003). Different trials have investigated the efficacy of antidepressant drugs in the short-term treatment of an acute episode, whereas a paucity of methodologically adequate studies have analyzed the effect of such drugs during long-term prophylaxis (Fava et al., 2003). Interestingly recent studies have been performed to assess the long-term efficacy and safety of *Hypericum* extracts in treatment of depression. (Kasper et al., 2004, 2007, 2008b).

A double-blind, randomized, placebo-controlled trial has also been recently conducted to analyze the prophylactic efficacy and safety of *Hypericum* extract WS 5570 900 mg/day (3–6% hyperforin) compared to placebo in preventing relapse during 6 months' continuation treatment and 12 months' long-term maintenance treatment after recovery from an episode of recurrent depression (Kasper et al., 2004, 2008b). Patients who continued treatment with WS 5570 were at a 30% lower risk of relapse during the first six months than those in whom the antidepressant medication was replaced by placebo after recovery from the acute episode. Interestingly, the prophylactic effect of WS 5570 during long-term maintenance treatment was particularly pronounced in patients with an early onset and consequently with a more extended history of depression. Furthermore the tolerability of WS 5570 in long-term maintenance treatment was on the placebo level (Kasper et al., 2008b).

Placebo-controlled studies showed *Hypericum* extracts to be well tolerated with no noticeable differences between *Hypericum* preparations. Typically, adverse events were reported at incidences similar to placebo. Schmidt and Sommer (1993) specifically assessed cognitive effects and reported that no impairment of any cognitive functions occurred. In an LI 160 study, no notable side effects were reported in either group (Sommer and Harrer, 1994). In the ZE 117 study by Schrader et al. (1998) adverse events, similar in both groups, were described as transient, self-limiting and, in the case of ZE 117, mainly non-specific gastrointestinal complaints. A placebo-controlled study showed a greater incidence of specific adverse events with *Hypericum* extract vs. placebo (Hypericum Depression Trial Study Group, 2002). However, these events were mild in severity and thought to be due to spurious associations created in the analysis process. In an LI 160 study by Shelton et al. (2001) LI 160 was well tolerated; only headache was reported in more patients taking LI 160 than placebo: in 39/95 (41%) and 25/100 (25%), respectively (p = 0.02).

### 2.2. *Hypericum* extract vs. tricyclic antidepressants

A number of studies have compared *Hypericum* extracts with the older tricyclic antidepressants for depression and shown them to be at least as effective and better tolerated than tricyclics (Table 2) (Bergmann et al., 1993; Harrer et al., 1994; Philipp et al., 1999; Vorbach et al., 1994; Wheatley, 1997; Woelk, 2000).

In a double-blind study comparing *Hypericum* extract LI 160 was as effective as maprotiline in reducing HAMD score at 4 weeks and the responder rates were similar (61% and 67% for LI 160 and maprotiline, respectively, based on the per-protocol analysis). A higher proportion of patients experienced adverse events in the maprotiline group (13 [25%] and 18 [35%] with LI 160 and maprotiline, respectively) (Harrer et al., 1994). Increased tiredness, dryness of the mouth and cardiac complaints were more commonly reported with maprotiline than with LI 160. In a 6-week, double-blind study comparing *Hypericum* extract LI 160 with imipramine...
(Vorbach et al., 1994), patients treated with LI 160 (N=67) showed a reduction in HAMD score from 20.2 to 8.8, similar to that seen in the imipramine-treated group (from 19.4 to 10.7; N=68); both significant reductions from baseline (p<0.001). Interestingly, in a subgroup analysis of patients with a baseline mean HAMD score ≥21, LI 160 (N=26) was significantly more effective than imipramine (N=25) in terms of HAMD and Clinical Global Impression (CGI) severity reduction (p<.05). Patients receiving LI 160 had a lower frequency and severity of adverse effects compared with imipramine.

One criticism made of the above study (Vorbach et al., 1994) was that the interpretation of similar efficacy was not based on an adequately priori planned statistical hypothesis. This shortcoming was addressed in another LI 160 study using amitriptyline as the chosen comparator (Wheatley, 1997). Patients were randomized to receive *Hypericum* extract LI 160 (N=87) or amitriptyline (N=78). At 6 weeks, the responder rate was statistically similar in both treatment groups (p= .064; per =protocol analysis), and adverse effects were reported significantly less frequently among LI 160-treated patients (37% vs. 64% for amitriptyline; p≤0.05) with the most common side effect in the amitriptyline group being dry mouth and in the LI 160 group, headache. In total, 24% of patients discontinued treatment in the LI 160 group, compared with 31% with amitriptyline; the most common reason for discontinuation in both groups was adverse events. In a comparative trial, *Hypericum* extract ZE 117 was at least as effective as imipramine (Woelk, 2000); the reduction in mean HAMD scores in patients receiving ZE 117 was similar to imipramine at 6 weeks (12.00 and 12.75, for ZE 117 and imipramine, respectively). Doses were chosen to avoid possible criticism from using overly low doses of synthetic antidepressants. Interestingly, at endpoint, the mean score on the anxiety-somatization subscale of the HAMD was significantly lower in the *Hypericum* extract group (3.79) than the imipramine group (4.26) (p=.03). As with LI 160 in the previous study, *Hypericum* extract ZE 117 was significantly better tolerated than the tricyclic comparator (p<0.01); adverse effects were observed in 39% of patients given *Hypericum* extract and in 63% of patients administered imipramine, with 3% and 16% discontinuing treatment because of adverse events, respectively.

The finding that *Hypericum* extract had an efficacy at least equal to that of imipramine confirmed data from an earlier study using *Hypericum* extract STEI 300 (Philipp et al. 1999) carried out the first trial in which *Hypericum* extract was compared with tricyclic antidepressants and placebo. Patients were randomized to STEI 300, imipramine or placebo for 6 weeks followed by 2 weeks follow-up. STEI 300 was significantly more effective than placebo and at least as effective as imipramine in terms of responder rate at 6 weeks, and significant greater improvements in quality of life (using the SF-36 scale) were also observed with STEI 300 vs. placebo. No safety concerns with STEI 300 were noted, with the most frequent adverse effect in the imipramine group being dry mouth (38% [13% with placebo]) and in the STEI 300 group, nausea (8% [2% with placebo]).

In a meta-analysis by Röder et al. (2004), (N=1231) the mean responder rates were 55.0% for *Hypericum* extract and 53.9% for tricyclic antidepressants (p=.13). The responder rate ratio [RR], defined as the ratio of the responder rates observed with comparator and *Hypericum* extract was 0.98 (95% CI=0.87–1.10, p=.70) (Röder et al., 2004). The number of adverse events was significantly lower in patients administered *Hypericum* extract than those receiving tricyclics; the proportion of patients reporting adverse effects was 49.0% vs. 28.3% for tricyclics vs. *Hypericum* extract, respectively (p<.00001). Consequently, the frequency of therapeutic discontinuation was 3.6 times higher in patients treated with tricyclics than those treated with *Hypericum* extract.

Overall studies suggest that *Hypericum* extracts, when compared to tricyclic antidepressants, demonstrate a similar efficacy and a more favourable side-effects profile.

### 2.3. *Hypericum* extract vs. SSRIs

There have been a number of comparative studies between *Hypericum* extract and SSRIs, with recent studies incorporating more rigorous methodology and greater patient numbers than earlier trials as with the other studies described (Table 2) (Behnke et al., 2002; Brenner et al., 2000; Gastpar et al., 2005; Harrer et al., 1999; *Hypericum* Depression Trial Study Group, 2002; Schrader, 2000; Szegedi et al., 2005; van Gurp et al., 2002; Fava et al., 2005; Bjerkenstedt et al., 2005; Moreno et al., 2006; Gastpar et al., 2006; Papakostas et al., 2007).

Several trials have compared *Hypericum* extract with sertraline. In a small preliminary study comparing *Hypericum* extract LI 160 with sertraline in 30 outpatients with mild to moderate depression (Brenner et al., 2000), a clinical response was seen in 54% of patients receiving LI 160 and 40% of those receiving sertraline (p=NS, ITT analysis) and both treatments were well tolerated. In a randomized controlled trial in primary care, 90 patients with major depression (HAMD ≥16) were randomized to treatment with either sertraline (50–100 mg/day) or an unnamed *Hypericum* extract containing 0.3% hypericin (900–1800 mg/day) (van Gurp et al., 2002). Assessments were carried out at entry and at weeks 2, 4, 8 and 12. At week 12, *Hypericum* extract achieved similar improvements in HAMD and Beck Depression Inventory (BDI) scores to sertraline (18.9–9.4 and 19.5–12.1 for *Hypericum* extract vs. 19.7–11.5 and 18.4–12.0 for sertraline, for HAMD and BDI respectively; p=NS). During the early stages of treatment, significantly more adverse effects were reported among sertraline-treated patients than among those receiving *Hypericum* extract. The authors concluded that *Hypericum* extract has a role as a first treatment option for mild to moderate depression in primary care settings.

In another recent study, 123 patients with moderate depression (ICD-10 F32.1 or F33.1, HAMD 20 to 24) were randomized to *Hypericum* extract STW3 (612 mg) and 118 patients to sertraline (50 mg) with approximately 100 patients in each group being treated for a period of 12 weeks followed by 12 weeks follow-up (Gastpar et al., 2005). At 12 weeks, reductions in HAMD scores were similar between groups and responder rates were 68.6% and 73.5% for STW3 and sertraline, respectively (p value not stated, PP analysis). At 24 weeks, in the 161 patients who continued on treatment for the 12-week follow-up (81 patients receiving STW3 and 80 receiving sertraline), responder rates were
84.0% in STW3 recipients and 81.3% in the sertraline group (p value not stated). Overall, tolerability was deemed ‘good’ or ‘very good’ in most patients (99.2% and 94.9% of patients with STW3 and sertraline, respectively). Adverse events attributed to study medication and discontinuations due to adverse events were more common with sertraline than STW3; treatment-related adverse events occurred in 12 [9.8%] and 16 [13.6%] patients treated with STW3 and sertraline, respectively, with drug-related discontinuations seen in 5 (4.1%) and 10 (8.5%) patients, respectively. One of the strengths of this study is that the sample size was calculated to ensure adequate power to demonstrate the non-inferiority of STW3 compared with sertraline.

In the Hypericum Depression Trial; neither Hypericum extract (LI 160; 900–1500 mg/day) nor sertraline (50–100 mg/day) were shown to have significantly greater effect on HAMD score or significantly greater responder rate (based on HAMD and CGI scores) than placebo (Hypericum Depression Trial Study Group, 2002). However, Linde et al. (2002) suggest that as patients had relatively long-term chronic depression, this lack of efficacy vs. placebo might be due in part to a high proportion of the patients being treatment resistant (Cott and Wisner, 2002; Linde et al., 2002; Wheatley, 2002). Since patients significantly related to the treatment arm to which they had been randomized, loss of blinding may have been another limitation of this study. Other authors have suggested that unsuitable outcome measures (Spielmans, 2002; Volp, 2002), and overoptimistic effect sizes are the cause of these unexpected findings (Linde et al., 2002). Adverse events reported at a significantly greater rate with sertraline than placebo and LI 160 were diarrhoea, nausea, anorgasmia, and sweating. However, the authors note that these events, inconsistent with Hypericum’s previously reported safety profile, were all mild, and multiple comparisons may have produced spurious associations.

Several studies have compared Hypericum extract with fluoxetine. A study comparing Hypericum extract LoHyp-57 800 mg/day and fluoxetine 20 mg/day was carried out in 161 elderly patients with mild to moderate depressive episodes (ICD-10 F32.0 and F32.1) (Harrer et al., 1999). Efficacy in terms of improvement in HAMD score and responder rate was similar with Hypericum extract and SSRI. LoHyp-57 was better tolerated than fluoxetine with a total of 12 undesirable events considered to be possibly or probably related to study drug observed in the LoHyp-57-treated group compared with 17 in the group treated with fluoxetine.

In a similar comparative, randomized study in 240 patients, Hypericum extract ZE 117 was at least as effective as fluoxetine for mild to moderate depression in terms of HAMD score reduction, and achieved a significantly greater responder rate (P = .005) and significantly greater improvements in CGI item 1 (P = .03) than fluoxetine (Schrader, 2000). ZE 117 had a superior tolerability profile with a lower global incidence of adverse effects (14% vs. 25%, respectively; P < .07). No patients discontinued due to adverse events with ZE 117. In a study comparing the Hypericum extract calmigen with fluoxetine (Behnke et al., 2002), both treatments were significantly effective with no differences between groups in any of the efficacy or tolerability endpoints. Other studies have compared Hypericum extracts with fluoxetine (Fava et al., 2005; Bjerkenstedt et al., 2005; Moreno et al., 2006; Papakostas et al., 2007).

Bjerkenstedt et al. (2005) conducted a 4-week, multicenter, double-blind, randomized controlled study comparing LI 160 900 mg/day and fluoxetine 20 mg/day in 163 patients affected with mild to moderate depression. Unfortunately both active treatments failed to prove superiority over placebo regarding the primary efficacy measure, the HAMD total score reduction from baseline to 4 weeks of treatment. The number of responders was not significantly different in the three groups (Table 2). Nevertheless, considering the stricter criterion of remission (final HAMD < 8) to assess treatment success, both Hypericum (24%) and fluoxetine (28%) were significantly superior to placebo, but Hypericum was significantly better tolerated than fluoxetine. One of the limits of this study is the duration of treatment (4 weeks), which seems to be too short, considering that separation of active drug from placebo may require 6 and more weeks of treatment.

Similar results have been observed in an 8-week double-blind trial in patients with mild to moderate depression, assessing the efficacy and safety of H. perforatum in comparison with fluoxetine (Moreno et al., 2006). Outcome was monitored using the HAMD, Montgomery-Asberg depression rating scale, CGI. The mean HAMD score was low compared to other studies (14–17) and only 66 patients completed the study. The authors found no differences between the groups regarding mean HAMD changes and the lowest response to treatment in the Hypericum group, when compared with both placebo and fluoxetine groups. The number of patients included in this study does not allow definitive conclusions due to the statistical power of the sample size.

In a 12-week, randomized, active- and placebo-controlled, parallel-group, double-blind study Fava et al. (2005) have analyzed the efficacy and safety of H. perforatum (LI-160 900 mg/die) relative to both placebo and fluoxetine (20 mg/die) in a population of 135 outpatients with mild to moderately severe MDD. The primary efficacy end point for this study was the final HAMD-17 total score after 12 weeks of randomized treatment on end point. The mean HAMD score in the three groups was 19. Interestingly the authors found that St. John’s wort treatment was associated with a significantly (P < 0.05) greater decrease in HAMD-17 scores compared with fluoxetine and showed a trend toward statistically significant superiority over placebo. An higher rate of remission (HAMD-17 < 8) was observed in the St. John’s wort group (38%) compared with the fluoxetine group (30%) and the placebo group (21%). There were no adverse events related treatment discontinuations in the Hypericum group and placebo-treated patients, whereas 4% (2/47) of the fluoxetine-treated patients dropped out because of side effects. Surprisingly in this study fluoxetine lacked of efficacy and St. John’s wort treatment was not significantly superior to placebo. The authors suggest that these data may be explained with the smaller than planned sample size. Recruitment was stopped before planned sample size was reached due to decision of the sponsor. Larger studies are therefore needed to fully compare the efficacy of H. perforatum vs. fluoxetine in the treatment of mild to moderate depression.
One of the most discussed issues in the field of antidepressant trial is the relationship between timing of clinical improvement and resolution of depressive symptoms during the treatment of major depressive disorder (Papakostas et al., 2007). Some authors have proposed that patients showing a significant symptom improvement during the first 2 weeks of treatment, might not respond to antidepressant drugs per se, but they might have a ‘placebo’ pattern of response (Stewart et al., 1998; Nierenberg et al., 2004). On the contrary other authors have demonstrated that a clinical response during the first 2 weeks of treatment can highly predict a greater drug vs. placebo difference in depressive symptoms improvement at endpoint (Stassen et al., 1998; Szegedi et al., 2003).

Along this line Papakostas et al. (2007) have examined data from the 39 responders of the above discussed 12-week double-blind study (Fava et al., 2005) comparing *Hypericum perforatum*, fluoxetine or placebo (Papakostas et al., 2007). The authors defined an early clinical response as a 25% decrease in 17-item HDRS after 2 weeks and found that, among the 39 responders, earlier clinical improvement predicted lower HDRS-17 scores at week 12 in the patients treated with either fluoxetine or *Hypericum*, but not in placebo-treated patients. The small sample size of the study does not allow definitive conclusions and larger studies are needed to demonstrate that an early clinical improvement during treatment can predict a greater symptom resolution at endpoint in depressed patients responding to *Hypericum* or fluoxetine.

Szegedi et al. (2005) conducted a well designed, 6-week, multicenter, double-blind, randomized controlled study comparing WS 5570 900 mg/day and paroxetine 20 mg/day in 251 patients affected with moderate to severe depression. This study has been thought worthy of inclusion in this review because it is the only study to compare *Hypericum* extract with paroxetine and, although patients had a more severe form of depression than the other studies reviewed, nearly half (44%) had a baseline HAMD of 22–24 (moderate depression). To avoid criticisms of inadequate dosing doses were increased to 1800 mg/day WS 5570 or 40 mg/day paroxetine if no response was observed within 2 weeks. Outcome was monitored using the HAMD, the von Zerssen’s Adjective Mood scale and the CGI. The mean HAMD score in the three treatment groups was 22. The authors found a statistical significant therapeutic equivalence of *Hypericum* extract STW3-VI to citalopram and the superiority of this *Hypericum* extract over placebo. Furthermore the percentage of responders at the end of treatment was 54.2% in the Hypericum group, 55.9% in the citalopram group and 39.2% in the placebo group. More adverse events were observed in patients treated with citalopram than in other group treatment, thus suggesting both a non-inferiority in terms of clinical efficacy and a better safety and tolerability of *Hypericum* extract in comparison to citalopram (Gastpar et al., 2006).

### 3. Evidence from meta-analyses

Several systematic reviews and quantitative meta-analyses of *Hypericum* extract trials, compared with both placebo and standard antidepressants, provide a comprehensive overview of clinical studies involving *Hypericum* extract (Table 3) (Kim et al., 1999; Linde et al., 1996, 2005a,b, 2008; Linde and Knuppel, 2005; Röder et al., 2004; Volz and Laux, 2000; Whiskey et al., 2001; Rahimi et al., 2009). In Table 3, in all meta-analyses except Röder et al., the RR was defined as the ratio of the responder rates observed with *Hypericum* extract and comparator, whereas in Röder et al. it is inverted (comparator/*Hypericum*).

Over time, there has been a trend towards an improved quality of meta-analysis relating to *Hypericum* extract in terms of studies included and the criteria used to select studies. Recent meta-analyses of *Hypericum* extract have sought to encompass more methodologically sound studies than those used in earlier meta-analyses, which has been made possible by improvements in the quality of individual clinical studies. This has led to a greater number of large randomized studies with rigorous criteria for major

**Figure 1** Total HAMD scores over time (intention to treat analysis, means and 95% confidence intervals) from a trial comparing the *Hypericum* extract WS 5570 and paroxetine in 244 patients with moderate to severe depression. On day 42 WS 5570 was statistically superior to paroxetine (*p*<0.01, two-sided t-test) (modified from Szegedi et al. (2005) with permission).
depression and higher baseline depression scores. Further evidence for the greater selectivity of included studies in more recent meta-analyses relates to the diagnostic criteria used; in Röder et al. (2004), the majority of studies included used ICD-9 and ICD-10 and DSM (DSM-III, III-R, and IV) criteria. A minimum HAMD score of 16 to 21 was stated as inclusion criteria in 15 studies and, in 7 studies, a maximum score of 20, 24 or 25 was specified. One of the major limitations, however, is the inclusion in all meta-analyses of studies using different preparations of *Hypericum* extract.

Linde et al. (2005a) point out that, compared with trials published before 1995, newer trials have larger sample sizes, are of longer duration, are more likely to use a placebo run-in phase, are more often restricted to patients who met criteria for major depression and tend to include patients with higher baseline scores on depression scales. In addition, documentation of methodology and daily doses are more thorough in the more recent trials. In their most recent meta-analysis Linde et al. (2008) have examined several new well-designed trials restricted to patients with major depression.

Linde and Mulrow (2000) carried out a systematic review and meta-analysis of the efficacy and tolerability of *Hypericum* extract, which was published as a Cochrane review. This was an update of a systematic review carried out in 1996, one of the first for *Hypericum* extract. Only randomized studies were included in which *Hypericum* extract was compared to placebo or conventional antidepressants for the treatment of depression. Outcomes were measured using standardized clinical evaluation scales. Moreover, for inclusion, the methodology of each individual study required assessment by at least two independent observers using the evaluation scale proposed by Jadad et al. (1996). Of 45 studies identified, 27 met the inclusion criteria for a total of 2291 patients. Seventeen of the included trials were placebo-controlled. Ten studies compared *Hypericum* extract (8 *Hypericum* extract alone, two in combination with Valeriana extract) with other antidepressants or sedatives. Among these various trials, diagnostic criteria were quite broad and included dysthymia and also patients with mild symptoms who did not meet criteria for major depression. Other potential drawbacks among these studies include a limited follow-up period, which for the most part did not exceed 4 weeks, and the use of low doses of standard antidepressants in comparative trials. Nonetheless, in spite of these negative aspects, the methodology was considered generally acceptable. Overall, *Hypericum* extracts were significantly superior to placebo (RR 2.47, 95% CI=1.69–3.61) for short-term therapy of mild or moderate depression and were very well tolerated. In this meta-analysis, *Hypericum* was also shown to be at least as effective as standard antidepressants (*Hypericum* extract alone, RR 1.01, 95% CI=0.87–1.16; combined extracts, RR 1.52, 95% CI=0.78–2.94). However, data from this meta-analysis did not allow to establish whether *Hypericum* extract has equivalent clinical efficacy to other antidepressants for the heterogeneity of the studies, the short duration of the observation period and the low proportion of studies using an SSRI as comparator.

In a subsequent meta-analysis by Linde et al., (2005a,b), published in 2005, which is an update to the 2000 systematic Cochrane review, only randomized, controlled, double-blind studies were included; of 68 possible studies identified, 37 trials met the inclusion criteria, including 26 comparisons with placebo and 14 with standard synthetic antidepressants (13 of these provided efficacy data: 6 tricyclics, 7 SSRIs). Responders were defined as those who experienced objective improvement using the HAMD and CGI scales. The studies with placebo involved 3320 patients, many of whom were

**Figure 2** Change from baseline (means and 95% confidence intervals) in the re-scaled cluster 1 (core symptoms of depression) and cluster 2 (mainly anxiety and insomnia-related symptoms) scores in 544 patients with mild to moderate depression treated with *Hypericum* extract for 42 days (Kasper and Dienel, 2002). Re-scaled cluster scores were calculated as the means of the scores of all items included in the cluster re-scaled to a 0–100 scale (where 0=all items in the cluster score 0; 100=all items in the cluster scored the maximum score). Negative values indicate symptom improvement.
Table 3  Overview of several meta-analyses of *Hypericum* extract.

<table>
<thead>
<tr>
<th>Review</th>
<th>Year</th>
<th>Inclusion criteria</th>
<th>Number of studies (total number of patients)</th>
<th>Responder rate ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Linde et al., 1996)</td>
<td>1996</td>
<td>RCT&lt;sup&gt;a&lt;/sup&gt;, depressed patients, single or combination preparation, comparison with placebo or other antidepressants, all clinical outcome measures</td>
<td>15 vs. placebo (1008) 8 vs. antidepressants/sedatives (749)</td>
<td>2.67 (1.78–4.01) for single preparations 1.1 (0.93–1.31) for combinations 1.52 (0.78–2.94) for combinations</td>
</tr>
<tr>
<td>(Linde and Mulrow, 2000)</td>
<td>2000</td>
<td>RCT, depressed patients, single or combination preparation, comparison with placebo or other antidepressants, all clinical outcome measures</td>
<td>17 vs. placebo (1168) 10 vs. antidepressants (1123)</td>
<td>2.47 (1.69–3.61) for single preparations 2.00 (1.14–3.52) for combination 1.01 (0.87–1.16) for single preparations 1.52 (0.78–2.94) for combination</td>
</tr>
<tr>
<td>(Kim et al., 1999)</td>
<td>1999</td>
<td>Blinded/controlled, single preparation, depression (ICD10, DSM-III, DSM-IV), outcomes by HAMD</td>
<td>2 vs. placebo (169) 4 vs. tricyclic antidepressants (482)</td>
<td>1.48 (1.03–1.92) 1.11 (0.92–1.29)</td>
</tr>
<tr>
<td>(Volz and Laux, 2000)</td>
<td>2000</td>
<td>Placebo-controlled trials of <em>Hypericum</em> or fluoxetine in mild depressive disorders (HAMD ≤ 24)</td>
<td>17 <em>Hypericum</em> vs. placebo (1739) 9 fluoxetine vs. placebo (1873)</td>
<td>Responder rate ratio not stated 10.2 (51.4%) 12.5 (55.5%)</td>
</tr>
<tr>
<td>(Whiskey et al., 2001)</td>
<td>2001</td>
<td>RCT, depression, single preparation, comparison with placebo or other antidepressants, outcomes by HAMD</td>
<td>14 vs. placebo 9 vs. antidepressants</td>
<td>1.98 (1.49–2.62) 1.00 (0.90–1.11)</td>
</tr>
<tr>
<td>(Kasper and Dienel, 2002)</td>
<td>2002</td>
<td>Double-blind, RCT, mild to moderate depression, comparison with placebo, outcomes by HAMD</td>
<td>3 vs. placebo (544)</td>
<td>1.35 for cluster 1 HAMD items 1.40 for cluster 2 HAMD items</td>
</tr>
<tr>
<td>(Röder et al., 2004)</td>
<td>2004</td>
<td>Double-blind, RCT, depression, single preparation, comparison with placebo or other antidepressants</td>
<td>19 vs. placebo (2129) 15 vs. antidepressants (2231)</td>
<td>0.66 (0.57–0.78) 0.96 (0.85–1.08)</td>
</tr>
<tr>
<td>(Linde et al., 2005a)</td>
<td>2005</td>
<td>Double-blind, RCT, included patients with depression, single preparations, comparison with placebo or other antidepressant, all clinical outcomes</td>
<td>26 vs. placebo (3320) 14 vs. antidepressants (2283)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.15 (1.02–1.29)&lt;sup&gt;a&lt;/sup&gt; and 2.06 (1.65–2.59)&lt;sup&gt;a&lt;/sup&gt; depression only 1.71 (1.40–2.09)&lt;sup&gt;a&lt;/sup&gt; and 6.13 (3.63–10.38)&lt;sup&gt;a&lt;/sup&gt; including other diagnoses 1.01 (0.93–1.10) overall 0.97 (0.85–1.12) vs. SSRIs 1.03 (0.93–1.14) vs. older antidepressants</td>
</tr>
<tr>
<td>(Rahimi et al., 2009)</td>
<td>2009</td>
<td>Double-blind, RCT, included patients with depression single or combination preparation, comparison with placebo or SSRI, outcomes by HAMD</td>
<td>13 SSRI vs. placebo (1995) 11 <em>Hypericum</em> vs. SSRI (1652)</td>
<td>1.22 (1.03–1.45) 0.99 (0.91–1.08)</td>
</tr>
</tbody>
</table>
Table 3 (continued)

<table>
<thead>
<tr>
<th>Review</th>
<th>Year</th>
<th>Inclusion criteria</th>
<th>Number of studies (total number of patients)</th>
<th>Responder rate ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Linde et al., 2008)</td>
<td>2008</td>
<td>Double-blind, RCT, included only patients with major depression, single preparations, comparison with placebo or other antidepressant, all clinical outcomes</td>
<td>18 vs. placebo (3064) 17 vs. antidepressants (2810)</td>
<td>1.28 (1.10–1.49) in the nine larger trials 1.87 (1.22–2.87) in the nine smaller trials 1.02 (0.90–1.15) vs. tri- or tetracyclic antidepressants 1.00 (0.90–1.11) vs. SSRIs</td>
</tr>
</tbody>
</table>

*The responder rate ratio is the ratio of the responder rates observed with *Hypericum* and comparator (a value > 1 denotes a greater effect with *Hypericum* vs. comparator) with the exception of Röder et al. (2004), where it is inverted and defined as the ratio of the responder rates of comparator and *Hypericum* (in this case a value < 1 denotes a greater effect with *Hypericum* vs. comparator). *Or quasi-randomized (e.g. alteration); ‡five larger trials; §six smaller trials; ¶five smaller trials; ‖13 provided quantitative data. HAMD = Hamilton Depression Rating Scale; RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitor.

Efficacy and tolerability of *Hypericum* extract for the treatment of mild to moderate depression

affected by major depression, and were treated for more than 4 weeks using a mean dose of 800 mg/day *Hypericum* extract. The 14 trials using standard antidepressants as the comparator involved 2283 patients (Linde et al., 2005a; Linde and Knuppel, 2005). The proportion of responders was comparable in *Hypericum* extract-treated patients compared with those seen with both tricyclic antidepressants (RR=1.03, 95% CI=0.93–1.14) and SSRIs (RR=0.98, 95% CI=0.85–1.12). There was a trend towards fewer dropouts for any reason or due to adverse effects in patients treated with *Hypericum* extract compared with placebo and also less dropouts compared with those administered standard antidepressants.

To avoid compromising results by inclusion of studies with weak methodology, Kasper and Dienel (2002) carried out a meta-analysis using trials that also met relatively strict criteria based on patient selection (diagnostic criteria), outcome measures used, design (double-blind, placebo-controlled), period of observation as well as quality of investigator rating. The meta-analysis included three randomized, double-blind, placebo-controlled studies including a total of 544 patients affected by mild to moderate depression who received *Hypericum* extract (3×300 mg/day) or placebo. These studies all utilized standardized and well-defined diagnostic criteria (DSM-IV) of mild to moderate major depression. Primary outcome was measured using the total HAMD score and therapy lasted for 6 weeks.

The objective of the meta-analysis was to evaluate the therapeutic profile of *Hypericum* extract by cluster analysis and determine if *Hypericum* extract has a selective effect on particular signs and symptoms of depression. Cluster analysis is a statistical technique that attempts to overcome potential shortcomings of factor analysis, particularly difficulties in interpretation. For the HAMD, most analyses include two factors, one related to core symptoms of depression (e.g. profound, non-reactive sadness, somatic symptoms, and lethargy) and another to elements such as agitation and anxiety. For this meta-analysis, two clusters were also identified. The first (HAMD items 1, 2, 3, 7, 8, 12, 13, 14, and 16) represented core symptoms of depression including somatic symptoms. The second (HAMD items 4, 5, 6, 9, 10, 11, 15, and 17) was composed primarily of items that evaluated anxiety and insomnia correlated with depression. *Hypericum* extract was found to be particularly efficient in reducing core symptoms of depression in a global manner with a therapeutic profile similar to SSRIs. Fig. 2 shows the change of the cluster scores vs. baseline, and demonstrates that score changes over time were similar for both clusters but the extent of score changes was more pronounced for core symptoms of depression (cluster 1).

The meta-analysis by Röder et al. (2004) examined the available clinical data by considering only the average responder rate to *Hypericum* extract therapy, compared with placebo or other antidepressants. This meta-analysis found that, compared with newer generation antidepressants, the mean responder rate was highly similar in the *Hypericum* extract and antidepressant groups (51.0% vs. 48.0%, respectively) (Röder et al., 2004). This review also differentiated rates of treatment success from *Hypericum* extract or comparator therapy according to subgroups of patients, based on severity. Inclusion criteria for the meta-analysis were a double-blind, randomized design with placebo or other antidepressants as the comparator, diagnosis of depression and use of *Hypericum* extract alone and not in combination with other plant extracts. The quality of the studies was quantified using a scoring system derived from criteria used by the authors. Thirty studies satisfied both the inclusion and quality criteria for the meta-analysis, 12 of which had been previously included in the meta-analysis by Linde et al. (Linde et al., 2005a; Linde and Knuppel, 2005). However, the meta-analysis from Röder et al. (2004) contained more studies using SSRIs as the comparator. The results showed a significantly higher efficacy with *Hypericum* extract compared with placebo (N=2129, RR=0.66, 95% CI=0.57–0.78). The average number of patients responding to therapy was also significantly higher for *Hypericum* extract compared with placebo (53.3% vs. 32.7%, respectively; p<.00001, number needed to treat [NNT]=4.2, 95% CI=3.0–6.6). *Hypericum* extract also showed an efficacy that was similar to standard antidepressants (N=2231, RR=0.96, 95% CI=0.85–1.08) and the average number of patients responding to therapy was also similar for *Hypericum* extract and other antidepressants (52.3% vs. 51.3%, respectively (p = .509)). In the subgroup with mild to moderate depression, *Hypericum* extract showed significantly higher efficacy with respect to standard antidepressants (N=1166, RR=0.85, 95% CI=0.75–0.97, p = .01, NNT=14.3, 1 denotes a greater effect with *Hypericum* vs. comparator (a value > 1 denotes a greater effect with *Hypericum* vs. comparator). *Or quasi-randomized (e.g. alteration); ‡five larger trials; §six smaller trials; ¶five smaller trials; ‖13 provided quantitative data. HAMD = Hamilton Depression Rating Scale; RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitor.

According to the meta-analysis, *Hypericum* extract therapy was particularly efficient in reducing core symptoms of depression in a global manner with a therapeutic profile similar to SSRIs. This meta-analysis found that, compared with newer generation antidepressants, the mean responder rate was highly similar in the *Hypericum* extract and antidepressant groups (51.0% vs. 48.0%, respectively). This review also differentiated rates of treatment success from *Hypericum* extract or comparator therapy according to subgroups of patients, based on severity. Inclusion criteria for the meta-analysis were a double-blind, randomized design with placebo or other antidepressants as the comparator, diagnosis of depression and use of *Hypericum* extract alone and not in combination with other plant extracts. The quality of the studies was quantified using a scoring system derived from criteria used by the authors. Thirty studies satisfied both the inclusion and quality criteria for the meta-analysis, 12 of which had been previously included in the meta-analysis by Linde et al. (Linde et al., 2005a; Linde and Knuppel, 2005). However, the meta-analysis from Röder et al. (2004) contained more studies using SSRIs as the comparator. The results showed a significantly higher efficacy with *Hypericum* extract compared with placebo (N=2129, RR=0.66, 95% CI=0.57–0.78). The average number of patients responding to therapy was also significantly higher for *Hypericum* extract compared with placebo (53.3% vs. 32.7%, respectively; p<.00001, number needed to treat [NNT]=4.2, 95% CI=3.0–6.6). *Hypericum* extract also showed an efficacy that was similar to standard antidepressants (N=2231, RR=0.96, 95% CI=0.85–1.08) and the average number of patients responding to therapy was also similar for *Hypericum* extract and other antidepressants (52.3% vs. 51.3%, respectively (p = .509)). In the subgroup with mild to moderate depression, *Hypericum* extract showed significantly higher efficacy with respect to standard antidepressants (N=1166, RR=0.85, 95% CI=0.75–0.97, p = .01, NNT=14.3,
95% CI = 8.3–100.0). The mean responder rate was 59.5% in the Hypericum extract group compared with 52.9% for standard antidepressants (p=.14).

Linde et al. (2008) carried out a systematic review and meta-analysis on the efficacy and tolerability of Hypericum extract in major depression, which was published as a Cochrane review. Only randomized studies were included in which Hypericum extract was compared with placebo or standard antidepressants for the treatment of major depression. Outcomes were measured using standardized clinical evaluation scales. Moreover, for inclusion, the methodology of each individual study required assessment by at least two independent observers, using scales developed by Jadad et al. (1996).

Of 79 studies identified, 29 met the inclusion criteria for a total of 5489 patients. Eighteen of the included trials were placebo-controlled. Seventeen studies compared Hypericum extract with other antidepressants. Eight new trials were included since the last update (Linde et al., 2005b) with a total of 1947 patients. The severity of depression was described as mild to moderate in 19 trials, and as moderate to severe in 9 trials. Responders were defined as those who experienced objective improvement using the HAMD and CGI scales. The studies with placebo involved 3064 patients, whereas the seventeen trials using standard antidepressants as the comparator involved 2810 patients. Patients receiving Hypericum extract were significantly more likely to be responders (RR=1.48; 95% CI=1.23–1.77), but placebo-controlled trials were highly heterogeneous. In the nine larger trials the combined response rate ratio for Hypericum extract compared with placebo was 1.28 (95% CI=1.10–1.49), whereas effects in favour of Hypericum extract were more pronounced in the nine smaller trials (RR=1.87 95% CI=1.22–2.87).

In the meta-analysis, Hypericum was also shown to be at least as effective as tricyclic antidepressants (RR=1.02 95% CI=0.90–1.15) or SSRI (RR=1.00 95% CI=0.90–1.11). Interestingly patients treated with Hypericum extract were less likely to drop out from studies due to adverse effects than patients allocated to older standard antidepressants (OR=0.24; 95% CI=0.13–0.46) or to SSRIs (OR=0.53; 95% CI 0.34–0.83).

This meta-analysis examines for the first time only clinical trials conducted in patients with major depression and suggests that Hypericum extract has a modest effect over placebo in a similar range as standard antidepressant drugs, finally showing that Hypericum extracts have fewer side effects than standard antidepressant drugs. However it should be underlined that trials from German-speaking countries have significantly more positive results than trials from other countries. The reasons for the "country effect" are unclear and further studies are needed to investigate this difference.

In a recent meta-analysis Rahimi et al. (2009) have examined all studies comparing the efficacy and tolerability of Hypericum extract and SSRIs. Only randomized and double blinded conducted in patients with major depressive disorder were included. Outcomes were measured using HAMD. Duration of treatment ranged between 4 and 12 weeks in various studies. The methodological quality of included trials was assessed using the Jadad score. 13 eligible controlled clinical trials were included in the meta-analysis. Comparison of SSRIs with placebo yielded a significant relative risk (RR) of 1.22 (95% CI: 1.03–1.45) for clinical response, whereas a non significant RR of 0.96 (95% CI=0.71–1.29) was observed for remission.

In this meta-analysis Hypericum was also shown to be at least as effective as SSRI. The authors, by comparing Hypericum extract with SSRI, found that rate of clinical response (RR=0.99 95% CI=0.91–1.08), remission (RR=1.10 95% CI=0.90–1.35), and reduction of HAMD score (RR=0.32 95% CI=–1.20–0.64), was similar between Hypericum and SSRIs. Lower withdrawal due to adverse events was observed in patients treated with Hypericum extract compared to SSRI (RR=0.53 95% CI=0.35–0.82).

The results obtained from this meta-analysis demonstrate both a similar efficacy of Hypericum extract and SSRI and a better profile of tolerability for Hypericum, finally suggesting that Hypericum extract might be considered as an alternative to SSRIs in the management of mild to moderate depression.

4. Tolerability with Hypericum extract: evidence from meta-analyses and systematic reviews

The absence of adverse effects is an important factor in the treatment of patients affected by mild to moderate depression, given that these patients are less likely to accept drugs with undesirable effects than patients with more severe forms of depression. Poor tolerability has been shown to have a negative impact on compliance, with the potential for worsening of depressive symptoms (Keller et al., 2002). In general, Hypericum extracts have a favourable tolerability profile and are generally better tolerated than standard antidepressant drugs (Ernst et al., 1998; Rahimi et al., 2009).

The meta-analysis by Röder et al. (2004) found a lower incidence of adverse events with Hypericum extract (24.5%) compared to that seen with synthetic antidepressants (32.8%); although this did not reach significance (p=.09), and a similar number of withdrawals due to adverse effects (p=.2). Another methodologically sound overview of the adverse effects of Hypericum extract comes from a systematic review by Knuppel and Linde (2004). Part of this review was performed in the context of updating the meta-analysis of Linde, et al. discussed above (Linde et al., 2005a; Linde and Knuppel, 2005). Overall, the systematic review examined dropout rates and adverse effects in 24 double-blind, randomized trials, 17 large-scale observational studies as well as numerous case reports, case series and data sets from surveillance agencies (Knuppel and Linde, 2004). Based on the results of this review, the authors made several statements regarding the rates of adverse effects and dropouts in patients treated with Hypericum extract. Firstly, in randomized trials, rates were similar for Hypericum extract and placebo, lower for Hypericum extract compared with tricyclic antidepressants and slightly lower for Hypericum extract compared with SSRIs. In non-randomized observational studies, rates of discontinuation due to adverse effects among Hypericum extract-treated patients are low even in long-term studies and effects are generally mild.

Several longer-term studies on Hypericum extract have also been completed, which provide an assessment of the
Efficacy and tolerability of Hypericum extract for the treatment of mild to moderate depression

761

tolerability of this agent over a longer period of follow-up. Data from four large post-marketing surveillance studies with a total of 14, 212 patients taking various preparations of Hypericum extract have been published (Lemmer et al., 1999; Rychlik et al., 2001; Schauk et al., 1996; Woelk et al., 1994). In these studies, the overall incidence of side effects was 0.1–2.4% with 0.1–0.9% of patients discontinuing due to drug-related adverse events (Schulz, 2006).

Linde and Knappel (2005) published a systematic review of 16 large-scale, open-label observational studies on Hypericum extract, including an assessment of methodological quality, involving a total of 34,804 patients. Two studies were long-term (52-week) observational studies including the WS 5572 study (Lemmer et al., 1999) in mild to moderate depression reviewed by Schulz (2006), and a study of Hypericum extract Laif 600 in depressive disorders, published in abstract form (Zeller, 2000). In these two studies, 3.4% and 5.7% of patients discontinued due to adverse effects. All adverse events reported with Hypericum extract were mild and the most common were gastrointestinal symptoms, light sensitivity and other skin problems.

In a 1-year, open-label study on 313 patients with mild to moderate depression according to the DSM-IV scale, the tolerability of Hypericum extract was rated as good or very good after one year by both patients and physicians (Hubner and Arndt, 2000). At the end of the 12-month follow-up period, there were no significant differences between the initial and final parameters concerning EEG, blood pressure, heart rate or haematological parameters. Only 11.2% of cases reported undesirable events during the entire year of therapy, the most frequently reported adverse events being infections of the upper airway, headache and gastrointestinal disturbances.

Acute mania was reported in one patient taking 1800 mg Hypericum extract in a randomized, double-blind comparison with sertraline (van Gurp et al., 2002). Several other cases of acute mania have been reported (Fahmi et al., 2002; Guzelcan et al., 2001; Moses and Mallinger, 2000; Nierenberg et al., 1999). No causal relationship between the use of the extract and the mania has been established but the propensity for affective switching, as seen with synthetic antidepressant use, cannot be ruled out. Hypericum extracts should be therefore avoided in patients with bipolar disorder.

Phototoxicity has been raised as a potential adverse effect of Hypericum extract. In the official register of spontaneous events (Schulz, 2001), only 1 case per 300,000 treated cases has been reported. Volunteer studies have shown a non-clinically relevant increase in photosensitivity, only detectable using highly sensitive photometric measurement. This might become relevant, but only in fair-skinned individuals, in those with skin disorders or after extended solar irradiation (Schempp et al., 2000) and most individuals would be highly unlikely to experience problems. Investigations in volunteers have also shown that the threshold dose for an increased risk of photosensitization is about 2–4 g/day of a usual commercial extract (equivalent to approximately 5–10 mg of hypericin), considerably more than doses used in clinical practice (Schulz, 2001). It has been estimated that a Hypericum extract dose 30–50 times greater than the recommended daily dose taken at one time would be required to cause severe phototoxic reactions (Ernst et al., 1998). Indeed, only few cases have been reported with respect to a serious phototoxicity reaction necessitating treatment cessation (Bove, 1998; Golsch et al., 1997; Lane-Brown, 2000). In one, a woman developed recurrent erythematous lesions in areas exposed to light following consumption of a commercial Hypericum extract for 3 years. The condition resolved after discontinuation of Hypericum extract (Golsch et al., 1997). In another case, a woman experienced neuropathy after taking Hypericum extract (Bove, 1998) and three cases of severe blistering and burns were reported in patients taking Hypericum extracts (either internally or topically) before exposure to sunlight (Lane-Brown, 2000).

According to Brockmoller et al. (1997), given that photosensitivity is unlikely at doses of up to 1800 mg/day, potential phototoxic effects may only become apparent when Hypericum extract is taken with other drugs with phototoxic effects (Schulz, 2001).

5. Compliance

Compliance with antidepressant medication is essential to ensure treatment response and prevent relapse and symptom recurrence (Keller et al., 2002). However, compliance with antidepressant medication is poor, with one set of published data indicating that between 30% and 60% of patients do not take their medications as prescribed (Demyttenaere et al., 2004), a figure which agrees broadly with other commonly quoted estimates of antidepressant non-compliance (Olivier-Martin, 1986). The rate of onset and poor tolerability of antidepressant drugs has a considerable influence on patient compliance. To illustrate the point, one US study that examined claims data among 2012 patients found that initiating treatment with a tricyclic antidepressant reduced the probability of antidepressant treatment compliance vs. SSRI plus psychotherapy (Tai-Seale et al., 2000). In contrast, Hypericum extract is associated with a good tolerability profile and good compliance. In a placebo-controlled study of Hypericum extract (ZE 117) involving 162 patients, an electronic counter was inserted in the medicinal container in order to evaluate compliance (Schrader, 2000). A high level of compliance was observed, with a therapeutic coverage of 81.7% noted. Adherence to therapy was attributed, at least in part, to a low number of undesirable effects (5 in the placebo group and 6 in the Hypericum extract group), generally limited to acute gastrointestinal complaints. Other investigators have suggested that the superior tolerability of Hypericum extracts relative to other antidepressants, particularly tricyclics, could account for advantages in terms of compliance (Wheatley, 1997).

Finally a recent trial from Kasper et al. (2008b) has demonstrated that long-term treatment with Hypericum extract is not associated with any unexpected drug-specific risks or problems of intolerance (Kasper et al., 2008b). Furthermore the rates of potentially attributable events reported during double-blind treatment with Hypericum were lower than in the placebo group. Recent meta-analyses have also clearly demonstrated that treatment with Hypericum extract is associated with a lower withdrawal due to adverse events when compared to standard antidepressant drugs, thus suggesting an advantage of Hypericum extract in
terms of tolerability and compliance (Linde et al., 2008; Rahimi et al., 2009).

6. Drug interactions with Hypericum extract

Several systematic reviews have examined the published literature on Hypericum extract-mediated drug interactions (Henderson et al., 2002; Izzo, 2004; Mills et al., 2004; Whitten et al., 2006). Izzo (2004) published a review of the clinical evidence related to drug interactions with Hypericum extracts which pulls together many small studies and case reports. Interactions of clinical relevance often relate to the potential of Hypericum extracts for inducing cytochrome P450 enzymes (particularly CYP 3A4) and also increasing expression of P-glycoprotein (Pgp). Current evidence suggests that these effects can be due to hyperforin, one of the main constituents of Hypericum extract, which increases the expression of the pregnane X receptor, and then induces Pgp expression as well as CYP 3A4 activity (Moore et al., 2000). Moreover pharmacodynamic interactions have been described between Hypericum extract and other antidepressants (e.g. serotonin reuptake inhibitors such as paroxetine and sertraline) with the possible occurrence of a serotonin syndrome (Zhou and Lai, 2008).

Izzo (2004) have reviewed the data relating to interactions with oral contraceptives (OCs); several cases have been reported in which women have had breakthrough bleeding while taking Hypericum extract with OCs. In two open-label post-marketing surveillance studies (Hall et al., 2003; Pfrunder et al., 2003) of concomitant OC and Hypericum extract use over 3 months, there was no loss of contraceptive control; endogenous hormone levels showed an absence of ovulation in all patients taking Hypericum extract throughout the study period.

A systematic review was conducted by Whitten et al. (2006) to examine the quality and outcomes of clinical trials analyzing the effect of St. John’s wort extracts on the metabolism of drugs by CYP3A. All of the 19 studies that used high-dose hyperforin extracts (>10 mg=day) had outcomes consistent with CYP3A induction, while the three studies using low-dose hyperforin extracts (<4 mg=day) demonstrated no significant effect on CYP3A (Whitten et al., 2006).

7. Conclusion

Whether examined individually or combined in quantitative meta-analyses, the results of numerous clinical studies strongly support the effectiveness of some Hypericum extracts for the treatment of mild to moderate depression. Study methodology and quality of reporting have increased in recent years, which should make prescribers and patients more confident in choosing Hypericum extract over conventional antidepressants. Although a small number of comparative trials have shown Hypericum extract to be effective in severe depression, the majority do not support this view, and, therefore, weighing current evidence, Hypericum extract is not recommended for patients with severe depression. There is some evidence that Hypericum extract is effective in controlling symp-

toms in patients with disorders associated with or related to depression such as anxiety (Muller et al., 2003), somatoform disorders (Muller et al., 2004; Volz et al., 2002; Woelk, 2000), and obsessive compulsive disorder (Taylor and Kobak, 2000).

Overall, current evidence appears to support the efficacy of Hypericum extract for the treatment of mild to moderate depression; meta-analyses of clinical trials suggest that Hypericum extract is significantly more effective than placebo and at least as effective as standard antidepressants. Those extracts which demonstrate efficacy in clinical trials can and should be recommended for the treatment of mild to moderate depression. Based on our review of individual clinical trials, WS 5572, LI 160, WS 5570 and ZE 117 Hypericum extracts have been shown to be significantly more effective than placebo with similar efficacy to standard antidepressants. Initial studies of extracts LoHyp-57, psychotinin, calmigen, Swiss Herbal Remedies, STW3, STEI 300 and esbericum have produced promising results but further clinical data are needed to confirm their effectiveness in mild to moderate depression.

Considering the favourable safety profile of all extracts studied (equivalent to placebo and better tolerated than standard antidepressants), which also correlated with a lower frequency of dropouts in clinical studies than seen with standard antidepressants, Hypericum extract is a valid therapeutic approach in patients with mild to moderate depression. For these patients, for whom adverse effects of treatment may be difficult to accept, Hypericum extracts provide a high rate of pharmacological compliance. They provide an effective and well tolerated alternative to standard tricyclic and SSRI antidepressants and are advocated for first line therapy of mild to moderate depression.

Role of the funding source

This study was not supported by external funding.

Contributors

All authors have been actively involved in the construction of the paper from the outset and have had full editorial control over its content.

Conflict of interest

Siegfried Kasper has received grant/research support from Eli Lilly, Lundbeck, Bristol-Myers Squibb, GlaxoSmithKline, Organon, Sepra-
cor and Servier; has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Lundbeck, Pfizer, Organon, Schwabe, Sepacor, Servier, Janssen, and Novartis; and has served on speakers’ bureaus for AstraZeneca, Eli Lilly, Lundbeck, Schwabe, Sepacor, Servier and Janssen.

Filippo Caraci has received grants or honoraria as a consultant from Eli Lilly, Janssen, and Innova Pharma.

Bruno Forti and Eugenio Aguglia declare that they have no conflict of interests.

Filippo Drago has served as a consultant or on advisory boards for Eli Lilly, GlaxoSmithKline, AstraZeneca, Novartis, Pfizer, SIFI, Amdipharm, Grunenthal.
Efficacy and tolerability of Hypericum extract for the treatment of mild to moderate depression

763

References


Efficacy and tolerability of Hypericum extract for the treatment of mild to moderate depression


SCHANZ, V., 2006. Safety of St. John's wort extract compared to synthetic antidepressants. Phytomedicine 13, 199–204.


Schulz, V., 2006. Safety of St. John's wort extract compared to synthetic antidepressants. Phytomedicine 13, 199–204.


