Continuation and long-term maintenance treatment with Hypericum extract WS[®] 5570 after successful acute treatment of mild to moderate depression – rationale and study design

S. KASPER,¹ A. DIENEL,² M. KIESER³

1 Department of General Psychiatry, Medical University of Vienna, Austria

2 Clinical Trials Group Hypericum, Dr Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany

3 Biometry Department, Dr Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany

Abstract

Unipolar major depression is often a chronic disease that may require lifelong prophylaxis. Recovery from an acute episode is followed by 4-6 months of relapse prevention. After that, long-term maintenance treatment is administered to avoid recurrence.

We present the rationale and design of an ongoing double-blind, randomized, placebo-controlled trial investigating the efficacy of Hypericum extract WS[®] 5570 in relapse prevention in recurrent unipolar depression. An estimated sample of 425 adults with recurrent, mild to moderate major depression (ICD-10 and DSM-IV criteria), ≥ 3 previous episodes (last 5 years) and a total score ≥ 20 points on the 17-item Hamilton Rating Scale for Depression (HAMD) will be included. After a one-week wash out patients receive 3 $\times$ 300 mg/day WS[®] 5570 single-blind for 6 weeks. Responders are randomized to 26 weeks of double-blind continuation treatment with 3 $\times$ 300 mg/day WS[®] 5570 or placebo. Patients completing continuation treatment without relapse enter 52 weeks of double-blind maintenance treatment, where those treated with WS[®] 5570 are re-randomized to 3 $\times$ 300 mg/day WS[®] 5570 or placebo. The primary outcome measure is the time to relapse during continuation treatment (HAMD ≥ 16 , clinical diagnosis of depression, or premature treatment termination for inefficacy).

Hypericum extract, with its favourable tolerability profile, could be an interesting option for long-term prophylaxis. The trial was designed according to current consensus and guidance. Notably, it includes long-term prophylactic treatment with the same drug and the same therapeutic dose applied during acute treatment, uses well-defined outcome measures and provides a clear distinction between relapse and recurrence.

Key words: Hypericum extract, chronic unipolar depression, prophylactic treatment, relapse, recurrence

Introduction

With a lifetime prevalence of approximately 17% in Europe and the US (Kessler, McGonagle, Zhao, Nelson, Hughes, Eshleman, Wittchen and Kendler, 1994; Lépine, Gastpar, Mendlewicz and Tylee, 1997) and a recurrence rate exceeding 50% (Prien and Kupfer, 1986; Keller and Hanks, 1995), unipolar major depression is a very common disease with a high degree of chronicity (Winkler, Tauscher and Kasper, 2002). Disease-related morbidity, with often serious consequences for the patient's social functioning and quality of life, has been found to increase with the number of recurrences (Coryell, Scheftner, Keller, Endicott, Maser and Klerman, 1993; Mintz, Mintz,

Arruda and Hwang, 1992; Montgomery and Kasper, 1998), while the average time interval between two consecutive episodes and the responsiveness to antidepressant drug treatment decrease at the same time (Kasper and Kasper, 1994; Keller and Boland, 1998). Furthermore, the probability of recurrence increases with the number of previous episodes (Keller, 1999). These findings demonstrate a requirement for an effective long-term prophylactic treatment of depression.

Kupfer (1991) has identified three phases in the long-term course and treatment of depression about which there is apparently a consensus among physicians (Kasper and Kasper, 1994; Kasper, Zapotoczky, Stuppäck, König and Wuschitz, 1997; Montgomery,

Reimnitz and Zivkov, 1998; Montgomery and Kasper, 1998). Initial (acute) treatment of the current depressive episode is required for a period of usually 6 to 8 weeks and leads to response (meaningful symptom relief). After remission (complete subsidence of the symptoms to the premorbid state), the patient is believed to be in a state of increased psycho-biological vulnerability that may last for 4 to 6 months, during which antidepressant continuation treatment is applied to prevent relapse of the original episode. This period is followed by maintenance treatment, which helps prevent recurrence of a new episode of depression after recovery (Keller, 1999). Since recurrent depression is now recognized as a lifelong, chronic disease and the underlying risk of recurrence persists and is controlled by antidepressants rather than abolished, maintenance treatment may need to be continued for an indefinite period (Kasper et al., 1997; Montgomery and Kasper, 1998). Clinical experience suggests that the best prophylactic results can be expected when the drug that was used successfully during acute treatment is continued with a therapeutic dose during long-term prophylaxis if tolerated well by the patient (for example, Kupfer, Frank, Perel, Cornes, Mallinger, Thase, McEachran and Grochocinski, 1992; Kasper et al., 1997; Keller and Boland, 1998; Melfi, Chawla, Croghan, Hanna, Kennedy and Sredl, 1998).

In this paper, we review several common issues of trials investigating the long-term prophylactic effect of antidepressant drugs in continuation and maintenance treatment. Then we present the rationale and design of a currently ongoing trial investigating the prophylactic effect of Hypericum extract WS® 5570 in patients suffering from mild to moderate recurrent unipolar depression. We close with a brief discussion.

Methodological issues of studies investigating the prevention of relapse and recurrence

The prophylactic efficacy of an antidepressant drug is its ability to reduce the risk for relapse during continuation treatment and the risk for a new episode of depression during maintenance treatment in patients with recurrent illness (Montgomery, 1989; Montgomery, 1994). Trials investigating prophylactic efficacy must therefore reflect the different stages of recovery and remission. In that context several methodological issues need to be considered:

- For an adequately powered trial it is essential to

include a random sample of patients from a population in which the predicted morbidity is sufficiently high. This can be achieved by defining a certain minimum number of prior episodes of depression, preferably within a pre-specified period of time, as an entry criterion, since the number of previous episodes has been found to be one of the most predictive variables of future recurrence (Montgomery, 1994; Montgomery and Kasper, 1998). In clinical practice, long-term prophylactic treatment has been recommended for patients with two or three previous episodes of major depression within 5 years (see, for example, Blacker, 1996; Kasper et al., 1997; Keller and Boland, 1998; Keller, 1999).

- To distinguish between relapse (reappearance of symptoms of an inadequately treated episode) and recurrence (a new episode of depression), the time of completion of acute treatment should be known and patients should receive at least 4 to 6 months of continuation treatment followed by maintenance treatment. Furthermore, patients included into continuation treatment must have responded to acute treatment and patients included into maintenance treatment must have completed continuation treatment without relapse (Montgomery, 1994). In order to avoid bias from experimental loss during previous stages of the trial, randomization should be performed at the beginning of the treatment phase that is being investigated (Montgomery and Kasper, 1998).
- The duration of maintenance treatment should be chosen so that a clinically meaningful prophylactic effect can be derived and that recurrence is sufficiently likely to occur if prophylactic treatment is not effective. In an observational study reported by Lavori and colleagues (1994), with a follow-up duration of more than 10 years, the rate of recurrence in patients without prophylactic treatment was 28% during the first year after recovery from the panel episode, 15% during the second year and 9% during the third year (resulting in a cumulative rate of 52% after 3 years). While longer study periods might be preferable, a well-designed trial may thus uncover a meaningful treatment effect after one or two years (counted from the end of continuation treatment).
- In order to obtain uniform standards, it is essential to define response and remission by scores of

standardized rating scales that represent substantial improvement over the pre-treatment state or are comparable to those of a population of normal individuals, respectively. Although certainly not the only meaningful definition, a depression scale total score reduction by at least 50% versus baseline has become a widely accepted standard criterion for response (Nierenberg and DeCecco, 2001). Furthermore, well-defined and sensitive criteria for relapse and recurrence are required (Angst, Bech, Bruinvels, Engel, Ferner, Guelfi, Lingjaerde, Müller-Oerlinghausen, Paes de Sousa, Paykel, Rimon, Rzewuska, Saletu, Spiegel, Stassen, Stoll, Wiesel, Woggon and Zvolsky, 1994; Montgomery and Kasper, 1998; Nierenberg and DeCecco, 2001) – for example, a return to a state in which the patient again fulfils the trial's entry criteria at baseline.

A study investigating the long-term prophylactic effect of Hypericum extract WS® 5570 in recurrent depression

Long-term prophylactic trials in patients suffering from major depression have been published for many of the widely used antidepressant drugs, including selective serotonin reuptake inhibitors (SSRIs), norepinephrine reuptake inhibitors, monoamine oxidase (MAO) inhibitors and tricyclic antidepressants. In a recent review, Geddes and colleagues (2003) have identified 37 randomized, placebo controlled trials investigating the efficacy of prophylactic treatment aimed at preventing relapse or recurrence after successful acute treatment of an episode of major depression. Although they included a total of 5,032 patients, the majority of the 37 trials were quite small: 20 had fewer than 50 and only 10 had at least 100 patients in the 'active' treatment group. Data were available for 31 trials; out of these, 7 provided information for 6 months' follow-up, 11 at 12 months, 3 at 18 months and 10 at 24 or 36 months.

There has been considerable research activity in relapse and recurrence prevention involving synthetic antidepressants, but no trials have been completed in these areas to date for Hypericum extract, the leading herbal antidepressant (De Smet and Nolen, 1996; Müller and Kasper, 1997; Brevoort, 1998). The antidepressant efficacy of Hypericum extract in acute treatment of mild to moderate major depression is well established (see recent reviews and meta-analyses by

Kim, Streltzer and Goebert, 1999; Linde and Mulrow, 2000; Kasper and Dienes, 2002). The drug has been found to be safe and well tolerated in acute and long-term treatment (see, for example, Ernst, Rand, Barnes and Stevinson, 1998; Wheatley, 1998). Evidence published to date does not permit definitive conclusions regarding recently suspected drug-drug interactions involving Hypericum extract that are believed to be caused by an induction of the CYP-3A4 enzyme system (Schulz, 2001 – in this study any concomitant medication suspected to interact with Hypericum extract was excluded; DeAngelis and Fontanarosa, 2003).

In an ongoing trial, the prophylactic efficacy and safety of Hypericum extract WS® 5570 (Dr Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany) are investigated in patients with mild to moderate, recurrent major depression. WS® 5570 is a hydroalcoholic extract from *Herba hyperici*, with a drug-to-extract ratio of 4–7 : 1, 0.12% – 0.28% hypericin and a standardized content of 3% to 6% hyperforin. Its antidepressant efficacy was proven in acute treatment of mild to moderate major depression at a dose of 3 × 300 mg/d given for 6 weeks (Lecrubier, Clerc, Didi and Kieser, 2002).

Our double-blind, randomized, placebo-controlled, multicenter trial was approved by the responsible independent ethics committees and is conducted with full adherence to the principles of Good Clinical Practice (International Conference on Harmonization, 1996) and the Declaration of Helsinki (in the 1996 revision of Somerset West, the current version at the start of the clinical part of the trial), current scientific standards and to applicable national law. The study is conducted in psychiatric and general primary care practices in Germany and Sweden. Investigators were eligible for trial participation if they were well familiar with the psychiatric rating scales to be administered, and if the centre's patient pool included a sufficiently large number of suitable patients (the minimum and maximum number of patients in each centre was not laid down in advance). To ensure uniform diagnostic and rating standards, a rater training was performed by the first author (investigators entering the trial at a later time underwent a videotaped training session). The participating patients are adults of either sex suffering from a recurrent episode of major depression of mild to moderate severity. The major specific selection criteria are summarized in Table 1.

Table 1. Main inclusion and exclusion criteria

- Male and female outpatients 18–65 years of age, treated by a psychiatrist or general practitioner.
- Recurrent episode of mild to moderate major depression (ICD-10 F33.0 or F33.1, and DSM-IV 296.3).
- History of three previous episodes of depression according to ICD-10 and DSM-IV criteria within the last 5 years before study inclusion.
- Hamilton Rating Scale for Depression (HAMD), 17-item version: total score ≥ 20 and item score for 'depressed mood' ≥ 2 (to be fulfilled at both screening and start of acute treatment).
- Exclusion of the following psychiatric conditions:
 - schizophrenia;
 - acute anxiety disorder;
 - adjustment disorder;
 - chronic or psychotic depression;
 - bipolar disorder;
 - acute post-traumatic stress disorder;
 - substance abuse (except nicotine and caffeine).
- Exclusion of patients with high suicidal risk (for example, HAMD item 'suicide' ≥ 2) or previous attempted suicide.
- Exclusion of any concomitant medication that has an effect on the CNS (except low-dose oxazepam, temazepam and valerian during acute treatment, and chlorhydrat up to 500 mg/d during the entire study period; these drugs were disallowed during the last 3 days before each visit) as well as non-medical antidepressant treatment (for example, specific psychotherapy).

The screening procedures included a thorough anamnesis and a non-standardized psychiatric interview focused on the assessment of compliance with the study's selection criteria. After determining their eligibility for the trial and obtaining informed consent, the patients enter a 1-week single-blind placebo washout

phase (Figure 1; MAO inhibitors and non-medical psychiatric treatment within 2 weeks before enrolment, SSRIs within 1 week and fluoxetine within 5 weeks are not permitted for inclusion). Patients still meeting the diagnostic entry criteria (cf. Table 1) at the end of the washout phase, notably the minimum required scores in the Hamilton Rating Scale for Depression (HAMD – Hamilton, 1967), enter a single-blind acute treatment phase during which they receive 3×300 mg/day WS® 5570 for 6 weeks. Those who respond to acute treatment are then randomized at a ratio of 2:1 to 26 weeks of double-blind continuation treatment with 3×300 mg/day WS® 5570 or placebo. Response is defined as a score of 2 or 1 (much or very much improved) in the improvement scale of the Clinical Global Impressions (CGI) (National Institute of Mental Health, 1976) and a reduction of the HAMD total score by at least 50% compared to the start of acute treatment. Upon completion of continuation treatment, patients who do not show relapse enter a 52-week phase of double-blind maintenance treatment. While the patients randomized to placebo during continuation treatment are maintained on the same treatment regimen, those treated with WS® 5570 are re-randomized at a ratio of 1:1 to maintenance treatment with 3×300 mg/day WS® 5570 or placebo (Figure 1).

The study schedule includes two visits during acute treatment (every 3 weeks), five visits during continuation treatment (every 4 or 6 weeks) and eight visits during maintenance treatment (every 4, 6 or 8 weeks). At each visit the patients' severity of depression is assessed by means of the HAMD, the Beck Depression

Figure 1: Study flow chart.

Inventory (BDI) (Beck and Steer, 1984) and the CGI. Relapse during continuation treatment is defined by a HAMD total score of ≥ 16 points, or clinical diagnosis of a depressive episode according to any of the ICD-10 criteria, or premature treatment termination related to lack of efficacy. The same criteria apply for recurrence of depression during maintenance treatment. Patients showing relapse or recurrence during any of the intermediate visits have to be withdrawn from the trial.

The primary endpoint of the investigation is the time until relapse during continuation treatment, which will be analysed by a log rank test using Kaplan-Meier survival estimates. Secondary endpoints include time until recurrence during maintenance treatment as well as relapse and recurrence rates and HAMD, BDI and CGI scores at the individual last visit during continuation and maintenance treatment. Safety is assessed during each visit primarily by questioning the patients for adverse events.

The sample size was calculated to show a significant difference between the treatment groups for the primary outcome measure assuming relapse rates of 20% for WS[®] 5570 and 40% for placebo, using a two-sided error level of $\alpha = 0.05$ with a power of 90%. A design with an equal expected number of events in both treatment groups, which is advantageous in terms of power (Hsieh, 1992), was implemented by choosing a randomization ratio of 2:1 leading to a required total sample size of 219 efficacy evaluable patients (WS[®] 5570 146; placebo 73). The sample size was derived by using the formula published in Freedman (1982). Based on an expected responder rate of 65% during acute treatment and an expected dropout rate of approximately 20%, a total of 425 patients were planned to be recruited.

The design includes a blinded sample size review based on the overall relapse rate (Gould, 1992) after 50 patients have completed continuation treatment, with the option of re-calculating the sample size if the initial assumptions regarding the over-all relapse rate should turn out to be not valid. As a consequence of this review the final sample size may be adjusted. The investigators will not be informed about the results of the data review.

Justification of the design, conclusions

A consensus conference sponsored in 1996 by the US National Depressive and Manic Depressive Association concluded that fewer than 10% of

patients with unipolar major depression receive adequate antidepressant treatment as regards dosage and duration (Hirschfeld, Keller, Panico, Arons, Barlow, Davidoff, Endicott, Froom, Goldstein, Gorman, Marek, Maurer, Meyer, Phillips, Ross, Schwenk, Sharfstein, Thase and Wyatt, 1997). According to information derived from pharmacological inventory databases, anecdotal evidence and clinical experience, the percentage of patients treated for at least 6 months may be less than 5% (Keller and Boland, 1998). Adequate treatment of recurrent depression should provide symptom relief for the current episode, protect against relapse and prevent recurrence (for example, Montgomery, 1994; Kasper et al., 1997; Keller, 1999; Keller and Boland, 1998). The observation that the prevention of relapse or recurrence is often neglected may be attributable to the fact that many patients are reluctant to take (or physicians are reluctant to prescribe) long-term prophylactic treatment with antidepressant drugs with sometimes burdensome side effects after the acute symptoms of depression have disappeared (Keller and Boland, 1998; Montgomery and Kasper, 1998). Lower than therapeutic doses of antidepressant drugs are frequently used in long-term treatment to overcome side effects that might jeopardize patient compliance. However, this approach has been found to be often inadequate to attain long-term benefit (Keller and Boland, 1998; Montgomery and Kasper, 1998) and drugs that can be recommended for prophylaxis should offer good long-term tolerability at the full therapeutic dose. Due to its favourable safety profile (Woelk, Burkard and Grünwald, 1994; Ernst et al., 1998; Wheatley, 1998; Rychlik, Siedentop, Von den Driesch and Kasper, 2001), Hypericum extract can be an interesting, previously neglected option in this context.

Despite its striking popularity (for example, in Germany, Hypericum extract had a market share of 25% of all antidepressant prescriptions in 1997 and outsold fluoxetine by a factor of 4 (Müller, Kasper, 1997; Harrison, 1998) the prophylactic effect of the herbal drug has so far not been investigated systematically. The design features of this first confirmatory trial with Hypericum extract in long-term prophylaxis of mild to moderate major depression are in accordance with the demands of current consensus statements and guidance (Center for Drug Evaluation and Research, 1978; Kasper et al., 1997; Committee for Proprietary Medical Products, 2002).

The disease-specific inclusion criteria define a population of mildly to moderately depressed patients and thus reflect the clinical group in which *Hypericum* extract is predominantly used and in which most of the trials investigating the drug's efficacy in acute treatment have been performed. A history of three well-defined previous episodes of depression within the last 5 years before study inclusion is required to obtain a patient sample with sufficient predicted morbidity to provide reasonable power for a comparison of relapse (Montgomery and Kasper, 1998). Our initial sample size estimate is based on a rate of relapse of 40% in the placebo group. Considering expected rates around 50% in patients receiving no continuation treatment (Priem and Kupfer, 1986) on the one hand and a certain 'therapeutic' effect in the placebo group (Montgomery, 1999) on the other, our assumption appears to be well founded, but it will also be reassessed (and modified if required) during a blinded data review that is part of the trial's biometrical concept.

A dosage of 3×300 mg/day given for 6 weeks has been confirmed to be effective in acute treatment of depression with WS[®] 5570 and a comparable *Hypericum* extract (Laakmann, Schüle, Baghai and Kieser, 1998; Kalb, Trautmann-Sponsel and Kieser, 2001; Lecrubier et al., 2002). Patients randomized to WS[®] 5570 receive the same dose during long-term treatment as well.

In contrast to what Geddes and colleagues (2003) have observed for most of the studies included in their review, our trial provides a clear distinction between continuation and maintenance treatment, and thus also between relapse and recurrence. Since randomization is performed only at the beginning of the study period to which it applies, the validity of the treatment comparison for a specific phase is not compromised by selection bias resulting from the outcome of the preceding period (Möller, 1986; Montgomery, Kasper, 1998). With 26 weeks of randomized continuation treatment, the duration of the phase referring to the confirmatory hypothesis test is consistent with Kupfer's (1991) widely accepted model of the long-term course of depression as well as with findings from trials investigating the optimal length of continuation therapy (Priem and Kupfer, 1986; Reimherr, Amsterdam, Quitkin, Rosenbaum, Fava, Zajecka, Beasley, Michelson, Roback and Sundell, 1998), so that the efficacy of WS[®] 5570 in preventing

relapse can be validly assessed. Furthermore, the subsequent maintenance phase of 52 weeks will provide valuable information about the drug's efficacy in long-term recurrence prevention since a substantial rate of recurrences can be expected in untreated patients during the first year after recovery from an acute episode (Lavori et al., 1994).

The trial was designed with special attention to a consensus statement issued by the Austrian Society for Neurology and Psychiatry (Kasper et al., 1997). In accordance with current European and American guidance (Center for Drug Evaluation and Research, 1978; Committee for Proprietary Medical Products, 2002), the use of relapse and recurrence rates as primary outcome measures in continuation treatment and long-term trials is recommended, albeit without providing an operational definition of relapse and recurrence with respect to psychiatric scales or other diagnostic criteria.

Our response criterion for acute treatment, which also serves as an eligibility criterion for continuation treatment, combines well-defined clinical improvement and a halving of the initial HAMD total score. In a population of patients with major depression of mild to moderate intensity this warrants that responders will have scores that are not relevantly different of what can be expected in a normal population and that are substantially lower than what is required for relapse or recurrence. A 17-item HAMD total score of 16, one of our relapse/recurrence criteria, indicates mild depression requiring treatment and has thus been used as an entry criterion in many clinical trials (for example Reimherr et al., 1998; Kalb et al., 2001). By contrast, we chose a HAMD total score of 20 for inclusion into acute treatment in order to obtain a patient sample with a higher degree of pathology so that a sufficient number of 'terminal events' during the continuation and maintenance phases can be expected.

This is the first trial investigating the long-term prophylactic efficacy of *Hypericum* extract after recovery from an acute episode of major depression. Recently Linde and Mulrow (2000) have suggested to compare the antidepressant efficacy of *Hypericum* extract with standard antidepressants in well defined groups of patients over longer periods of observation as well as to study different extracts and doses (for a discussion of therapeutic alternatives to *Hypericum* extract in long-term prophylaxis of depression, see

Winkler et al., 2002). These recommendations are highly welcome, but several trials, each with a large number of patients, will be needed until definitive conclusions can be drawn.

References

- Angst J, Bech P, Bruinvels J, Engel RR, Ferner U, Guelfi JD, Lingjaerde O, Müller-Oerlinghausen B, Paes de Sousa M, Paykel E, Rimon R, Rzewuska M, Saletu B, Spiegel R, Stassen HH, Stoll KD, Wiesel FA, Woggon B, Zvolsky P. Report on the Fifth Consensus Conference: methodology of long-term clinical trials in psychiatry. *Pharmacopsychiatry* 1994; 27: 101–7.
- Beck AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. *Journal of Clinical Psychology* 1984; 40: 1365–7.
- Blacker D. Maintenance treatment of major depression: a review of the literature. *Harvard Review of Psychiatry* 1996; 4: 1–9.
- Brevoort P. The booming US botanical market. *Herbalgram* 1998; 44: 33–48.
- Center for Drug Evaluation and Research. Guidelines for the clinical evaluation of antidepressant drugs. Report No. HEW (FDA) 77-3042. Rockville, Maryland: Food and Drug Administration, 1978.
- Committee for Proprietary Medical Products. Note for Guidance on the Clinical Investigation of Medical Products in the Treatment of Depression. Report No.: CPMP/EWP/518/97. London: European Agency for the Evaluation of Medicinal Products, 2002.
- Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL. The enduring psychosocial consequences of mania and depression. *American Journal of Psychiatry* 1993; 150: 720–7.
- De Smet PA, Nolen WA. St John's wort as an antidepressant. *British Medical Journal* 1996; 313: 241–2.
- DeAngelis CD, Fontanarosa PB. Drugs alias dietary supplements. *Journal of the American Medical Association* 2003; 290: 1519–20.
- Ernst E, Rand JJ, Barnes J, Stevinson C. Adverse effects profile of the herbal antidepressant St John's wort (*Hypericum perforatum* L.). *European Journal of Clinical Pharmacology* 1998; 54: 589–94.
- Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. *Statistics in Medicine* 1982; 1: 121–9.
- Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet* 2003; 361: 653–61.
- Gould AL. Interim analyses for monitoring clinical trials that do not materially affect the type I error rate. *Statistics in Medicine* 1992; 11: 55–66.
- Hamilton M. Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology* 1967; 6: 278–96.
- Harrison P. Herbal medicine takes root in Germany. *Canadian Medical Association Journal* 1998; 158: 637–9.
- Hirschfeld RM, Keller MB, Panico S, Arons BS, Barlow D, Davidoff F, Endicott J, Froom J, Goldstein M, Gorman JM, Marek RG, Maurer TA, Meyer R, Phillips K, Ross J, Schwenk TL, Sharfstein SS, Thase ME, Wyatt RJ. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. *Journal of the American Medical Association* 1997; 277: 333–40.
- Hsieh FY. Comparing sample size formulae for trials with unbalanced allocation using the logrank test. *Statistics in Medicine* 1992; 11: 1091–8.
- International Conference on Harmonization. ICH topic E6 – Good clinical practice – consolidated guidance. London: European Agency for the Evaluation of Medicinal Products, 1996.
- Kalb R, Trautmann-Sponsel RD, Kieser M. Efficacy and tolerability of hypericum extract WS 5572 versus placebo in mildly to moderately depressed patients. A randomized double-blind multicenter clinical trial. *Pharmacopsychiatry* 2001; 34: 96–103.
- Kasper S, Dienes A. Cluster analysis of symptoms during antidepressant treatment with Hypericum extract in mildly to moderately depressed out-patients. A meta-analysis of data from three randomized, placebo-controlled trials. *Psychopharmacology* 2002; 164: 301–8.
- Kasper S, Kasper A. Langzeitbehandlung affektiver Störungen. *Nervenarzt* 1994; 65: 577–89.
- Kasper S, Zapotoczky HG, Stuppäck C, König P, Wuschitz A. Diagnostik und Therapie der Depression – Konsensus-Statement. *Neuropsychiatrie* 1997; 11: 59–67.
- Keller MB. The long-term treatment of depression. *Journal of Clinical Psychiatry* 1999; 60 Suppl 17: 41–5; discussion 46–8.
- Keller MB, Boland RJ. Implications of failing to achieve successful long-term maintenance treatment of recurrent unipolar major depression. *Biological Psychiatry* 1998; 44: 348–60.
- Keller MB, Hanks DL. Anxiety symptom relief in depression treatment outcomes. *Journal of Clinical Psychiatry* 1995; 56 Suppl 6: 22–9.
- Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994; 51: 8–19.
- Kim HL, Streltzer J, Goebert D. St John's wort for depression: a meta-analysis of well-defined clinical trials. *Journal of Nervous and Mental Disease* 1999; 187: 532–8.

- Kupfer DJ. Lessons to be learned from long-term treatment of affective disorders: potential utility in panic disorder. *Journal of Clinical Psychiatry* 1991; 52 Suppl:12-6; discussion 17.
- Kupfer DJ, Frank E, Perel JM, Cornes C, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ. Five-year outcome for maintenance therapies in recurrent depression. *Archives of General Psychiatry* 1992; 49: 769-73.
- Laakmann G, Schüle C, Baghai T, Kieser M. St John's wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. *Pharmacopsychiatry* 1998; 31 Suppl 1: 545-9.
- Lavori PW, Keller MB, Scheftner W, Fawcett J, Mueller TI, Coryell W. Recurrence after recovery in unipolar MDD: an observational follow-up study of clinical predictors and somatic treatment as a mediating factor. *International Journal of Methods in Psychiatric Research* 1994; 4: 211-29.
- Lecrubier Y, Clerc G, Didi R, Kieser M. Efficacy of St John's wort extract WS 5570 in major depression: a double-blind, placebo-controlled trial. *American Journal of Psychiatry* 2002; 159: 1361-6.
- Lépine JP, Gastpar M, Mendlewicz J, Tylee A. Depression in the community: the first pan-European study DEPRES (Depression Research in European Society). *International Clinical Psychopharmacology* 1997; 12: 19-29.
- Linde K, Mulrow CD. St John's wort for depression. *Cochrane Database Syst Rev* 2000; CD000448.
- Melfi CA, Chawla AJ, Croghan TW, Hanna MP, Kennedy S, Sredl K. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. *Archives of General Psychiatry* 1998; 55: 1128-32.
- Mintz J, Mintz LI, Arruda MJ, Hwang SS. Treatments of depression and the functional capacity to work. *Archives of General Psychiatry* 1992; 49: 761-8.
- Möller HJ. Methodological problems of long-term studies in psychopharmacology. *Pharmacopsychiatry* 1986; 19: 156-60.
- Montgomery SA. Prophylaxis in recurrent unipolar depression: a new indication for treatment studies. *Journal of Psychopharmacology* 1989; 3: 47-53.
- Montgomery SA. Long-term treatment of depression. *British Journal of Psychiatry* 1994; Suppl 26: 31-6.
- Montgomery SA. Alternatives to placebo-controlled trials in psychiatry. ECNP Consensus Meeting, September 26, 1996, Amsterdam. European College of Neuropsychopharmacology. *European Neuropsychopharmacology* 1999; 9: 265-9.
- Montgomery SA, Kasper S. Depression: a long-term illness and its treatment. *International Clinical Psychopharmacology* 1998; 13 Suppl 6: S23-6.
- Montgomery SA, Reimitz PE, Zivkov M. Mirtazapine versus amitriptyline in the long-term treatment of depression: a double-blind placebo-controlled study. *Int Clin Psychopharmacol* 1998; 13: 63-73.
- Müller WE, Kasper S. Clinically used antidepressant drugs. *Pharmacopsychiatry* 1997; 30 Suppl 2: 71.
- National Institute of Mental Health. 028 CGI. Clinical Global Impressions. In W Guy, RR Bonato (eds) *Translator and Editor Manual for the EDCEU Assessment Battery*. Chevy Chase MD: US National Institute of Mental Health, Psychopharmacology Research Branch; 1976; pp. 12-1-12-6.
- Nierenberg AA, DeCecco LM. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. *Journal of Clinical Psychiatry* 2001; 62 Suppl 16: 5-9.
- Prien RF, Kupfer DJ. Continuation drug therapy for major depressive episodes: how long should it be maintained? *American Journal of Psychiatry* 1986; 143: 18-23.
- Reimherr FW, Amsterdam JD, Quitkin FM, Rosenbaum JF, Fava M, Zajecka J, Beasley CM, Jr., Michelson D, Roback P, Sundell K. Optimal length of continuation therapy in depression: a prospective assessment during long-term fluoxetine treatment. *American Journal of Psychiatry* 1998; 155: 1247-53.
- Rychlik R, Siedentop H, Von den Driesch V, Kasper S. Johanniskrautextrakt WS 5572 bei leichten bis mittelschweren Depressionen. Wirksamkeit und Verträglichkeit von 600 und 1200 mg Wirkstoff täglich. *Fortschritte der Medizin* 2001; 119: 119-28.
- Schulz V. Incidence and clinical relevance of the interactions and side effects of *Hypericum* preparations. *Phytomedicine* 2001; 8: 152-60.
- Wheatley D. *Hypericum* extract. Potential in the treatment of depression. *CNS Drugs* 1998; 9: 431-40.
- Winkler D, Tauscher J, Kasper S. Maintenance treatment in depression. The role of pharmacological and psychological treatment. *Current Opinion in Psychiatry* 2002; 15: 63-8.
- Woelk H, Burkard G, Grünwald J. Benefits and risks of the *hypericum* extract LI 160: drug monitoring study with 3250 patients. *Journal of Geriatric Psychiatry and Neurology* 1994; 7 Suppl 1: S34-S38.

Correspondence: Siegfried Kasper, Professor and Chairman, Department of General Psychiatry, Vienna Medical University, Währinger Gürtel 18-20, A-1090 Wien, Austria.
 Telephone (+43) 140 4003568.
 Fax (+43) 140 4003099.
 Email sci-genpsy@meduniwien.ac.at.