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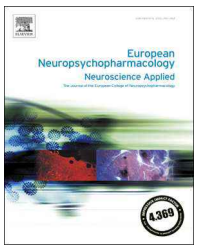

Efficacy of Silexan in mixed anxiety-depression – A randomized, placebo-controlled trial

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Abstract
Mixed anxiety and depressive disorder (MADD; ICD-10 F41.2) is a condition characterized by subsyndromal symptoms of anxiety and depression, neither of which are clearly predominant. Silexan has been demonstrated to be efficacious in subsyndromal and syndromal anxiety disorders and co-morbid depressive symptoms. In this study 318 adult out-patients with MADD according to ICD-10 criteria, a total score ≥ 18 points on the Hamilton Anxiety Rating Scale (HAMA), and at least moderately severe anxious and depressed mood were randomized and received 1×80 mg Silexan or placebo in double-blind fashion for a scheduled period of 70 days. Primary outcome measures were the HAMA and Montgomery Åsberg Depression Rating Scale (MADRS) total score changes between baseline and treatment end. The HAMA total score decreased by 10.8 ± 9.6 points for Silexan and by 8.4 ± 8.9 points for placebo (treatment group difference: $p < 0.01$, one-sided; ANCOVA with factors for treatment and centre and the baseline value as covariate), and total score decreases of 9.2 ± 9.9 and 6.1 ± 7.6 points, respectively, were observed for the MADRS ($p < 0.001$). Compared to placebo, the patients treated with Silexan had a better over-all clinical outcome and showed more pronounced improvements of impaired daily living skills and health related quality of life. Eructation was the only adverse event with a substantially higher incidence under Silexan. The study thus demonstrates that Silexan is efficacious and safe in the treatment of MADD.

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1. Introduction

In clinical practices, notably in primary care, physicians are frequently faced with patients who present with a combination of symptoms of anxiety and depression neither of which are clearly predominant (Das-Munshi et al., 2008; Demyttenaere et al., 2004; Walters et al., 2011). Although these symptoms may not meet the full diagnostic criteria of either a syndromal anxiety or depressive disorder if considered separately, e.g. generalised anxiety disorder (GAD), or a major depressive episode, they may nevertheless cause considerable distress and disability comparable to those observed in patients with a syndromal diagnosis (e.g. Das-Munshi et al., 2008; Kessler et al., 2005; Lewinsohn et al., 2004; Wittchen et al., 2000), bear the risk of exacerbation to a syndromal disorder (e.g. Aune and Stiles, 2009; Cuijpers and Smit, 2004; Forsell, 2007; Haller et al., 2014), and thus warrant clinical recognition and require appropriate treatment (Roy-Byrne et al., 1994). This is why the World Health Organization (WHO), (1992; ICD-10) has included Mixed Anxiety and Depressive Disorder (MADD) as a diagnosis in the International Classification of Diseases although the American Psychiatric Association, (2013; DSM-5) decided not to include MADD into the 5th revision of their Diagnostic and Statistical Manual of Mental Disorders, because the newly proposed DSM-5 criteria for MADD were determined to be not sufficiently reliable (Regier et al., 2013).

There is both neurobiological and phenomenological evidence that depression and anxiety may represent different manifestations of a similar vulnerability (Braam et al., 2014; Tyrer, 2001) that has been linked to a general 'distress' factor (Clark and Watson, 1991; Das-Munshi et al., 2008). Moreover, the genetic matching theory of MADD proposed by Kendler et al., (1992) and based on bivariate twin analysis provides evidence that liability to depressive and anxiety disorder may be influenced by shared genetic factors expressed in vulnerable patients as either depression or anxiety, depending on environmental experiences.

Preclinical studies indicate that an increased release of neurotransmitters such as glutamate and norepinephrine caused by enhanced Ca^{2+}-influx mainly through N and P/Q type voltage dependent calcium channels (VOCCs; Musazzi et al., 2011) and variations in serotonin-1A (5-HT_{1A}) receptor binding (Akimova et al., 2009; Savitz et al., 2009) may play a role in both anxiety and depression. The interpretation is supported by the fact that drugs with proven efficacy in the treatment of depression have been demonstrated to be efficacious in anxiety disorders as well. This is particularly true for selective serotonin reuptake inhibitors (SSRIs) whose efficacy in anxiety and depression has been linked to their agonistic action on the 5-HT_{1A} receptor subtype (Berk, 2000; Stahl, 1997). Consequently SSRIs, that were originally developed as antidepressants (Bauer et al., 2013), are now also recommended as first line treatment for anxiety disorders (e.g. Bandelow et al., 2012), and there is also evidence that SSRIs are efficacious in MADD where studies have been performed for sertraline (Carrasco et al., 2000), fluvoxamine (Rausch et al., 2001) and citalopram (Moin et al., 2008).

Silexan[‡] is an active substance produced from *Lavandula angustifolia* flowers, which has been shown to be a potent inhibitor of VOCCs in synaptosomes, primary hippocampal neurons and stably overexpressing cell lines (Schuwald et al., 2013), attenuating the overreaching, situationally inadequate stress response of the central nervous system associated with anxiety and mood disorders (e.g., Satpute et al., 2012). Moreover, Baldinger et al., (2014) showed that Silexan significantly reduces the 5-HT_{1A} binding potential in the brain clusters encompassing the temporal gyrus, the fusiform gyrus, the hippocampus, the insula and the anterior cingulate cortex, leading to an increase of extracellular serotonin levels. Since 2009, Silexan has been registered as a medicinal product in Germany for the treatment of restlessness related to anxious mood, with a recommended daily dose of 1×80 mg. Randomized, double-blind, controlled clinical trials have demonstrated that Silexan has a strong anxiolytic effect in patients suffering from GAD (Kasper et al., 2014; Woelk and Schläfke, 2010), subsyndromal anxiety disorder (Kasper et al., 2010) as well as in anxiety related restlessness and agitation (Kasper et al., 2015). In all trials the effect of Silexan on co-morbid depression was assessed as a secondary efficacy outcome measure, and the results indicate that Silexan may also have an antidepressant effect (Kasper and Dienel, 2013).

We present the results of a randomized, placebo-controlled clinical trial that investigated the efficacy and safety of Silexan in patients suffering from MADD.

2. Experimental procedures

2.1. Objectives, design overview and ethical conduct

The objective of this double-blind, randomized, placebo-controlled, parallel-group multicentre trial was to demonstrate the efficacy and to investigate the safety and tolerability of Silexan in patients suffering from MADD. The study protocol was reviewed and approved by an independent ethics committee. All patients provided written informed consent. The principles of Good Clinical Practice and the Declaration of Helsinki were adhered to.

Participants underwent a 3–7day screening period. Eligible patients were then randomized at a ratio of 1:1 to 10 weeks' double-blind treatment with Silexan or placebo. Efficacy and safety assessments were performed at 1 and 2 weeks $\pm$ 2 days as well as at 4, 7, and 10 weeks $\pm$ 7 days after baseline. Patients terminating their participation in the trial prematurely were to participate in the examinations scheduled at week 10 unless they were lost to follow-up or revoked their informed consent.

2.2. Participants

Male and female out-patients of any ethnic group between 18 and 65 years of age, were asked for participation if they suffered from MADD in accordance with the diagnostic criteria of ICD-10 category F41.2 (World Health Organization, 1992). The diagnosis had to be established by a specialized psychiatrist. A standardized checklist of symptoms and complaints, adapted from the WHO Diagnostic and Management Guidelines for Mental Disorders in Primary Care (World Health Organization, 1996), was used by all investigators during their interviews with the patients to assure the diagnosis of MADD. For randomisation patients had to present with a total score ≥ 18 points on the Hamilton Anxiety Rating Scale (HAMA; Hamilton, 1976) and with minimum scores of 2 points (indicating at least moderate symptom intensity) for HAMA items 'Anxious mood' and 'Depressed mood' at both study inclusion and baseline. Patients with any previous suicidal attempts or clear auto-aggressive

[‡]Silexan® is the active substance of LASEA® (Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany).

behaviour, as well as those with 2 or more points on item 'Suicidal thoughts' (weariness of life with fleeting suicidal thoughts) of the Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) were excluded. The latter criterion was re-assessed during each post-baseline visit, and patients meeting the criteria for increased suicidality were to be withdrawn from further study participation. Moreover, any clinically important psychiatric or neurological diagnosis other than the study indication within 6 months before enrolment including personality disorders, a history of substance abuse, or the administration of any psychotropic drugs within 30 days before randomisation led to exclusion. Concomitant psychotropic medication and psychotherapy were not allowed during study participation.

2.3. Interventions and blinding

Silexan is a patented active substance with an essential oil produced from *Lavandula angustifolia* flowers by steam distillation and complies with the monograph Lavender oil of the Ph. Eur. It exceeds the quality requirements of the European Pharmacopoeia monograph on lavender oil. Batch to batch consistency is assured by a well-defined, standardized manufacturing process. Immediate release soft capsules containing 80 mg of Silexan or identically matched placebo capsules were used. The smell of the investigational treatments was matched by flavouring the capsules containing placebo with 1/1000 of the amount of lavender oil contained in the Silexan capsules. Randomized patients were instructed to administer 1 capsule per day unchewed in the morning. The daily dose was established in accordance with the marketing authorisation of the product.

2.4. Measures of efficacy and safety

The absolute intraindividual changes of the HAMA and the MADRS total scores (observer ratings) between baseline (i. e. start of randomized treatment) and the final examination at week 10 were pre-specified as primary outcome measures of treatment efficacy. Both scales were administered at each visit, and the last valid assessment was used in the primary analysis in patients terminating the trial prematurely. Uniformity of assessments was assured by performing a mandatory rater training before the start of patient inclusion. The training included ratings of 2 standardised, videotaped interviews, with subsequent calculation of inter-rater reliability. After randomisation of about half of the scheduled number of patients all investigators had to participate in a refresher training course.

Efficacy criteria for both scales pre-defined as secondary outcome measures were a total score decrease by at least 50% of the baseline value (as an indicator of a favourable treatment response) and a total score <10 points (HAMA) and ≤ 10 points (MADRS) at treatment end (as an indicator of remission). Further standardized scales assessed as secondary efficacy outcome measures included the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983) as a self-rating of anxiety, the self-rated Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983), the observer-rated Clinical Global Impressions scale (CGI; National Institute of Mental Health, Guy, 1970), as well as the Sheehan Disability Scale (SDS, self-rating; Sheehan et al., 1996) and the SF-36 health survey questionnaire (observer-rating; Ware and Sherbourne, 1992) as measures of quality of life. For the CGI response was pre-defined as an amelioration of disease severity by at least 2 categories of Item 1 (Severity of Illness) and as an assessment of 'much improved' or very much improved' for Item 2 (Global Improvement). Tolerability was assessed based on adverse events (AEs) reported and on physical and ECG examinations, vital signs, and routine laboratory measures.

2.5. Random sequence generation, allocation concealment and implementation

The study drugs were dispensed to the centres in numbered containers. The investigators were instructed to assign the lowest available random number after confirming a patient's eligibility for randomized treatment. The random code was generated by a qualified person of the biostatistical department of the product manufacturer otherwise not involved in the trial, using a validated SAS macro (RANSCH, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany). Randomisation was performed in fixed-size blocks at a ratio of 1:1 with stratification by trial centre. The random block size was withheld from the investigators until completion of the trial in order to reduce the predictability of the randomisation.

2.6. Statistical methods and sample size

Confirmatory testing of the 2 primary outcome measures, HAMA and MADRS total score change versus baseline, was performed using analysis of covariance (ANCOVA) with treatment and centre as factors and the baseline total score of the applicable scale as a covariate. Multiplicity caused by testing 2 primary outcomes was controlled by a-priori ordering of hypotheses (Maurer et al., 1995) according to which the null hypothesis referring to the HAMA was to be tested first, and the null hypothesis referring to the MADRS was to be tested second, and only under the condition that the null hypothesis referring to the HAMA had been rejected. The study was planned and performed with an adaptive interim analysis (Bauer and Köhne, 1994) with options for sample size re-assessment and hypothesis testing using a local type I error level of $\alpha_1=0.0152$ (one-sided) for null hypothesis rejection and an upper bound of $\alpha_0=0.20$ for stopping for futility applied to each of the two confirmatory tests in the interim analysis. This procedure assured that an over-all, studywise type I error level of $\alpha=0.025$ (one-sided) was not exceeded (Kieser et al., 1999).

The analysis population for confirmatory testing was the full analysis set (FAS) which included all patients who had received the randomized treatment at least once and who had at least one post-baseline outcome assessment for one or both primary outcome measures. Patients terminating their participation in the trial prematurely were also to be retained in the FAS if the reason for termination was lack of efficacy or an adverse event for which a causal relationship with the investigational treatment could not be excluded, even if no post-baseline efficacy data were available. For the primary outcome measures missing data were replaced by carrying the last observation forward (LOCF). Sensitivity analyses assessing the impact of missing data imputation were performed using observed cases analysis (i.e. without imputation), and mixed models for repeated measures (MMRM) that included the fixed effects of treatment, centre, visit and treatment by visit interaction, the baseline value of the dependent variable as well as the baseline by visit interaction as covariates, and in which the within-patient errors were modelled using an unstructured covariance matrix. Moreover, a per protocol (PP) analysis was performed as a sensitivity analysis assessing the impact of protocol deviations. No missing data imputation was applied to all other outcome measures. All decisions regarding patient eligibility for the different analysis data sets were obtained before code breaking. Secondary efficacy and safety measures were analysed descriptively. All p-values are two-sided unless otherwise noted; two-sided p-values ≤ 0.05 are considered descriptively significant. The results presented below apply to the FAS unless otherwise noted.

The sample size calculation was based on a clinically relevant treatment group mean value difference of 3 points (Bandelow, 2006; Montgomery, 1994) and an expected common standard deviation 7.5 points for both primary outcome measures. A sample size of at least 157 patients in each treatment group was assumed

to provide a power of 90% for rejecting the first null hypothesis and a power of 81% for subsequently rejecting the second null hypothesis using two independent samples *t*-tests, each with a local, one-sided type I error level of $\alpha=0.0152$.

This report presents the results of the interim analysis after which the pre-specified conditions for the stopping of the trial (Kieser et al., 1999) were met.

3. Results

3.1. Recruitment and participant flow

The clinical part of the trial was performed between November 2012 and February 2014. A total of 348 patients were included and assessed for eligibility in 35 psychiatric practices in Germany, and 318 (Silexan 160; placebo 158) were randomized and treated. Figure 1 presents the reasons for non-randomisation and premature withdrawal, an overview of serious protocol deviations as well as the resulting analysis data sets defined before code breaking. All randomized patients were analysed for safety. Three patients (Silexan 1, placebo 2) who left the trial before the first post-baseline visit for reasons evidently unrelated to efficacy or tolerability issues could not be analysed for efficacy since they did not provide any post-baseline efficacy data. All other randomized study participants were assessed for efficacy at post-baseline at least once. Out of the 15 (Silexan) and 13 (placebo) premature terminators 7 in each group were retained in the PP analysis data set because an association between withdrawal and lack of efficacy or tolerability could not be excluded. Among the protocol deviations that occurred after randomisation treatment and visit schedule non-compliance were somewhat more frequent in the placebo group as compared to Silexan.

3.2. Baseline data

The treatment groups' baseline demographic and anthropometric data were essentially comparable (Table 1). More than 2/3 of the patients were female. All participants were Caucasians except for one Asian and one African patient who were both randomized to placebo. Thirty-four and

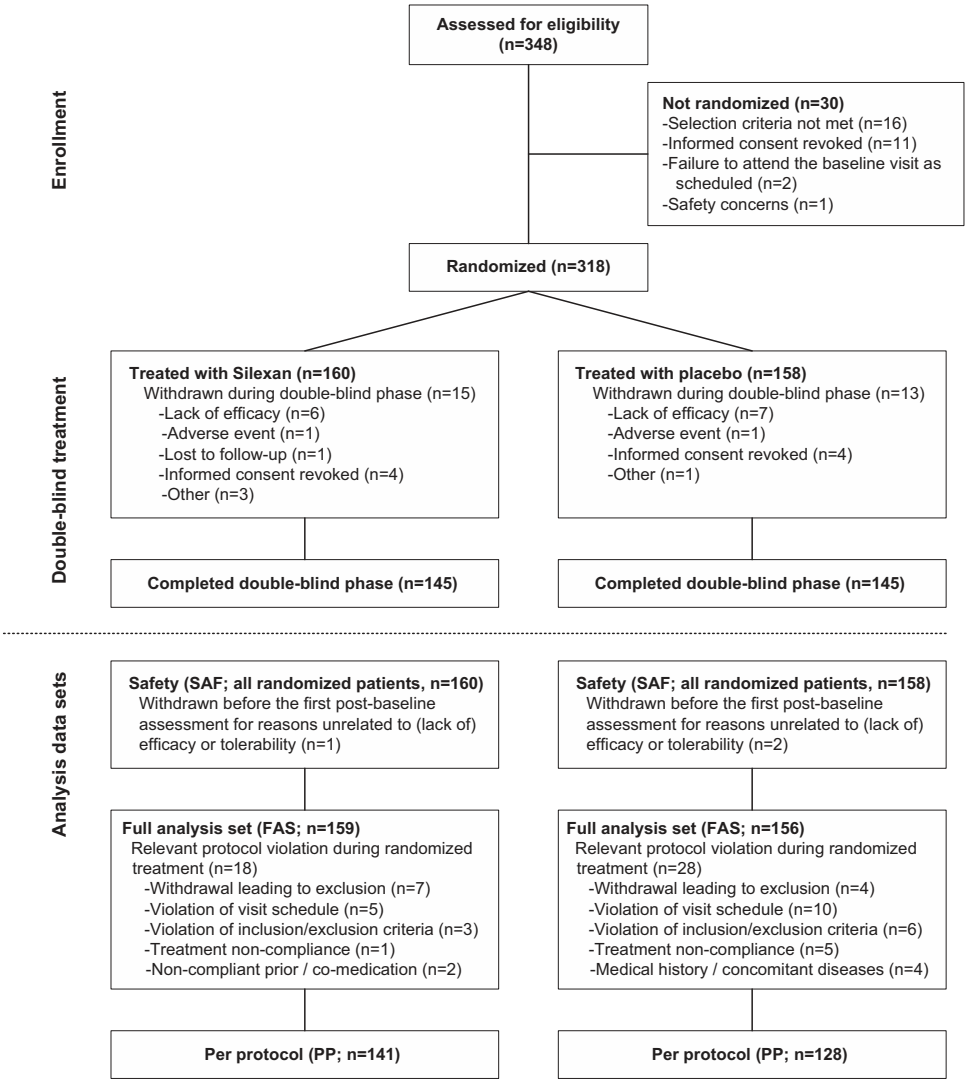

Figure 1 Disposition of patients, analysis data sets.

39.7% of the participants were current smokers or ex-smokers, and 6.3% and 7.1% drank alcohol more than twice a week, for Silexan ($n=159$) and placebo ($n=156$), respectively. At screening most frequent ongoing diseases were hypertension and hypercholesterolaemia with similar point prevalences in both treatment groups. No systematic treatment group differences were observed also for vital signs and physical status, and for previous and concomitant medication (data not shown). The duration of MADD was 31.5±25.1 weeks (mean±SD) in the Silexan group and 38.4±38.9 weeks in the placebo group.

Table 1 also shows that the treatment groups were well balanced with respect to the baseline values of the main efficacy outcome measures. According to CGI item 1 ('Severity of illness') half of the patients in both groups were assessed to be at least moderately ill (median of 4.0 in both treatment groups).

Table 1 Demographic data and efficacy outcome measures at baseline (full analysis set; absolute frequency and % or mean±SD, two-sided p-values).

	Silexan ($n=159$)	Placebo ($n=156$)	p
Sex Female/Male	105 (66.0%) 54 (34.0%)	113 (72.4%) 43 (27.6%)	0.22[a]
Age (years)	47.7±12.6	47.9±12.6	0.77[b]
Body mass index (kg/m^2)	25.8±3.0	25.5±3.0	0.26[b]
HAMA total score	25.7±5.6	25.7±5.2	0.99[*]
MADRS total score	22.0±6.4	22.1±6.1	0.99[*]
CGI Item 1 (severity of illness)	4.4±0.7	4.4±0.7	0.95[b]
SDS, global impairment	17.9±6.9	17.2±7.7	0.38[*]
SF-36, total score physical health	48.2±23.5	49.3±22.7	0.68[*]
SF-36, total score mental health	30.0±19.5	33.4±21.3	0.15[*]

CGI - Clinical Global Impressions scale; SDS - Sheehan Disability Scale; SF-36 - Health Status Inventory.
[*] t-test.
[a] Pearson χ^2-test.
[b] Mann-Whitney U-test.

3.3. Treatment compliance

Compliance was assessed by counting of return medication. The actual amount of study medication intake across the entire treatment period ranged between 88% and 104% of the amount assuming full protocol compliance (mean: 99.6% ±2.3%) in the Silexan group and between 80% and 111% (mean: 99.4±3.2%) in the placebo group. Compliance was considered acceptable in case of an intake of 80-120% of the amount for every period between 2 adjacent visits. One patient in the Silexan group (0.6%) and 5 (3.2%) in the placebo group were excluded from the PP analysis due to unacceptable compliance (Figure 1).

3.4. Efficacy

3.4.1. Anxiolytic effect

In the FAS the HAMA total score decreased monotonically from a baseline average of 25.7±5.6 points to 14.9±9.3 points at treatment end in the Silexan group and from 25.7±5.2 to 17.3±9.7 points in the placebo group (Figure 2). Silexan showed a statistically significant advantage over placebo from week 4 until treatment end. The average intraindividual HAMA total score decrease between baseline and week 10 was 10.8±9.6 and 8.4±8.9 points for Silexan and placebo, respectively. In the confirmatory ANCOVA model the difference between the adjusted (marginal) treatment group mean values was 2.47 points favouring Silexan (95% confidence interval [CI]: 0.48-4.47 points; $p=0.008$, one-sided). In the PP analysis an adjusted mean value difference of 2.68 points (95% CI: 0.51-4.85 points) was observed ($p=0.008$, one-sided). The MMRM analysis performed in the FAS as a sensitivity analysis regarding missing data imputation resulted in a marginal means difference of 2.71 points (95% CI: 0.71-4.71 points; $p=0.0008$, one-sided) favouring Silexan and was thus slightly larger than the difference observed in the primary analysis using missing data imputation through LOCF. According to the HAMA subscores Silexan had a comparably pronounced anxiolytic effect on psychic and somatic symptoms of anxiety (Table 2).

The numbers of patients who were considered responders (i.e. those with a HAMA total score decrease ≥50% compared to baseline) were 66 (41.5%) and 54 (34.6%) for Silexan and placebo, respectively ($p=0.21$), and 55 (34.6%) and 45 (28.8%) patients were in remission at treatment end (HAMA total score <10 points; $p=0.27$). Moreover, the patients in the Silexan group showed a more pronounced reduction of state and trait anxiety according to the STAI and of self-rated anxiety according to the HADS than those who received placebo (data not shown).

3.4.2. Antidepressant effect

The antidepressant effect of Silexan was obvious after 2 weeks of randomized treatment, became statistically significant at week 4 and remained significant until week 10 (Figure 3). The MADRS total score decreased from a baseline average of 22.0±6.4 points to 12.8±8.7 points and from 22.1±6.1 points to 16.0±9.8 points for Silexan and placebo, respectively. The treatment group difference between the adjusted (marginal) mean values in the confirmatory ANCOVA model was 3.25 points (95% CI: 1.36-5.14 points; $p<0.001$, one-sided) favouring Silexan (MMRM analysis: difference 3.53 points; 95% CI: 1.61-5.44 points; $p=0.0003$, one-sided). The result was confirmed in the PP analysis where a treatment group difference of 3.41 points (95% CI: 1.34-5.48 points) was observed ($p<0.001$, one-sided).

According to pre-defined criteria 64 patients in the Silexan group (40.3%) and 50 (32.1%) in the placebo group showed a favourable antidepressant response (MADRS total score reduction >50% of the baseline value; $p=0.13$) and 74 (46.5%) and 53 (34.0%) were in remission (MADRS total score ≤10 points at treatment end; $p=0.02$). In the self-rated

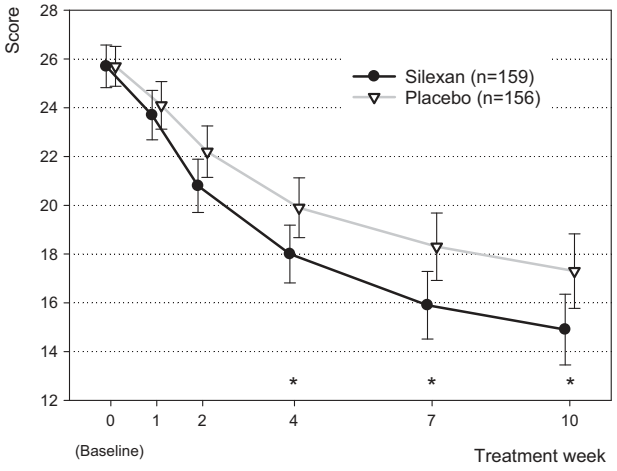

Figure 2 Hamilton Anxiety Scale total score time course (means and 95% confidence intervals, full analysis set, last observation carried forward. *t*-test for treatment group difference regarding change from baseline: * - $p \leq 0.05$, two-sided).

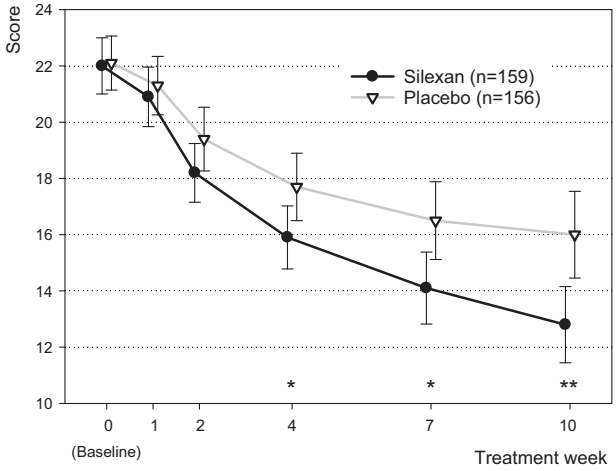

Figure 3 Montgomery-Åsberg Depression Rating Scale total score time course (means and 95% confidence intervals, full analysis set, last observation carried forward. *t*-test for treatment group difference regarding change from baseline: * - $p \leq 0.05$; ** - $p \leq 0.01$, two-sided).

Table 2 Efficacy outcome measures - change between baseline and week 10 (full analysis set; mean ± SD, and two-sided *p*-values).

	Silexan	Placebo	*p*
HAMA Total score[a]	−10.8±9.6	−8.4±8.9	0.02*
Somatic anxiety[a]	−4.2±4.4	−3.1±4.4	0.03*
Psychic anxiety[a]	−6.6±5.7	−5.3±5.1	0.03*
MADRS total score[a]	−9.2±9.9	−6.1±7.6	<0.01*
CGI Item 1 (severity of illness)[a]	−1.1±1.5	−0.7±1.2	0.01[b]
Item 2 (global improvement, week 10)[c]	2.7±1.3	3.1±1.2	<0.01[b]
Item 3.1 (therapeutic effect, week 10)[a]	2.4±1.2	2.9±1.1	<0.01[b]
SDS, global impairment[a]	−5.1±8.5	−2.3±6.6	<0.01*
SF-36Total score physical health[c]	12.9±25.0	6.3±16.7	0.01*
Total score mental health[c]	20.6±29.5	11.3±20.3	<0.01*

HAMA - Hamilton Anxiety Rating Scale; MADRS - Montgomery-Åsberg Depression Rating Scale; CGI - Clinical Global Impressions scale; SDS - Sheehan Disability Scale; SF-36 - Health Status Inventory Number of patients evaluated, Silexan/placebo: HAMA, MADRS 159/156 (last observation carried forward); all other scales 155/154 (observed cases).

[a]Negative/smaller values denote improvement.

[b]Mann-Whitney *U*-test.

[c]Positive/larger values denote improvement.

*t-test.

HADS the depression subscore decreased in both treatment groups (data not shown).

3.4.3. Confirmatory proof of efficacy in MADD

Since the one-sided *p*-values of the confirmatory hypothesis tests referring to HAMA ($p=0.008$) and MADRS total score reduction ($p<0.001$) both fell below the local type I error level of $\alpha_1=0.0152$ pre-specified for the interim analysis, both associated null hypotheses could be rejected and the anxiolytic and antidepressant efficacy of Silexan in patients with MADD was confirmed. The trial was therefore stopped after the interim analysis in accordance with the adaptive test model.

3.4.4. Subgroup analyses based on baseline severity of symptoms

Pre-specified subgroup analyses revealed that the treatment group differences regarding HAMA and MADRS total score improvements and favouring Silexan were larger in patients with more severe symptoms at baseline than in those with milder baseline impairment (data not shown).

3.4.5. General clinical outcome

General clinical outcome was assessed using the CGI. Compared to the placebo group, the patients treated with Silexan showed a more pronounced decrease in severity of mental illness as well as greater improvement from their condition at baseline (Table 2). The number of patients whose severity of mental illness decreased by at least 2 categories during randomized treatment was 55 (35.5%) for Silexan and 27 (17.5%) for placebo ($p<0.01$), and the number of participants who were assessed to be much or very much improved at treatment end was 74 (47.7%) for Silexan and 48 (31.2%) for placebo ($p<0.01$). Moreover, according to the investigators' rating Silexan had a more pronounced therapeutic effect. The treatment group

differences for all CGI items were statistically significant (Table 2).

3.4.6. Daily living skills and quality of life

According to the SDS the patients in the Silexan group showed more pronounced improvements of their daily living skills that were reflected by a decrease of the global impairment score of the scale with a significant difference to placebo (Table 2) as well as by equally significant treatment group differences regarding all subscores and assessing impairment at work, school, or university, of social life, and of family life and home responsibilities ($p<0.05$; data not shown). The patients treated with Silexan also exhibited a more pronounced decrease in the number of days missed at work, school or university as well as in the number of days with reduced productivity.

Significant advantages for Silexan were also observed for improvement of the SF-36 physical and mental health total scores (Table 2). Among the subscores of the scale the treatment group differences regarding change from baseline were most pronounced for general health, vitality, role emotional, mental health social functioning and bodily pain (Figure 4).

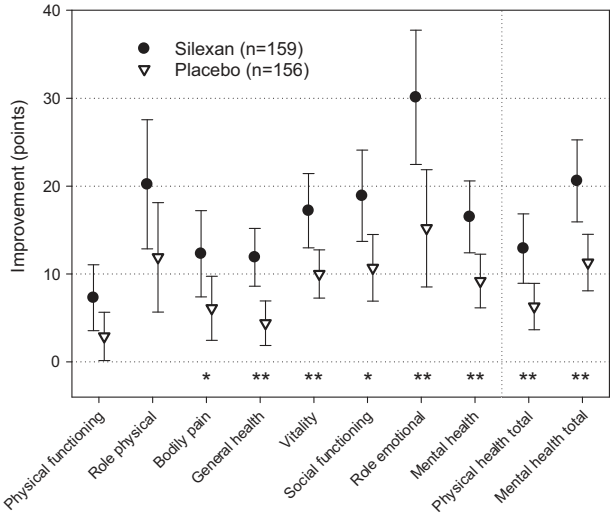

Figure 4 SF-36 individual item and total scores – change between baseline and treatment week 10 (means and 95% confidence intervals, full analysis set, last observation carried forward. *t*-test for treatment group difference regarding change from baseline: * – $p \leq 0.05$; ** – $p \leq 0.01$, two-sided).

3.5. Safety/tolerability

During and up to 2 days after the end of randomized treatment 56 AEs were reported by 40 out of the 160 patients exposed to Silexan (25.0%) compared to 57 events reported by 36 out of the 158 patients (22.8%) in the placebo group, corresponding to one AE in 205 patient days of exposure to Silexan and to one event in 199 patient days of placebo treatment.

Table 3 shows all AEs that were reported by totals of at least 3 (all events) or 2 (potentially related events) patients. Eructation was the only event for which a marked difference between the treatment groups was observed.

A total of 4 serious AEs were reported (Silexan: invasive duct breast carcinoma, hypertension [reported more than 2 days after the end of treatment]; placebo: diverticular perforation, syncope) all of which were assessed to be not related to the investigational treatments.

Table 3 Most frequently reported adverse events (safety analysis set; number (%) of patients with at least 1 event). Table shows events with any causal relationship that were observed in at least 3 patients, and potentially related events observed in at least 2 patients in total.

		Silexan ($n=160$)	Placebo ($n=158$)
Any causal relationship	Eructation	16 (10.0%)	0 (0.0%)
	Headache	4 (2.5%)	9 (5.7%)
	Nasopharyngitis	3 (1.9%)	8 (5.1%)
	Diarrhoea	2 (1.3%)	4 (2.5%)
	Nausea	3 (1.9%)	1 (0.6%)
Potentially related events[a]	Eructation	16 (10.0%)	0 (0.0%)
	Diarrhoea	1 (0.6%)	3 (1.9%)
	Nausea	3 (1.9%)	1 (0.6%)
	Headache	1 (0.6%)	2 (1.3%)

[a]Causal relationship was not entirely excluded.

4. Discussion

Silexan has previously been investigated in patients with syndromal and subsyndromal anxiety disorders as well as in other conditions with predominantly anxiety related symptoms (Kasper et al., 2015; Kasper et al., 2014; Kasper et al., 2010; Uehleke et al., 2012; Woelk and Schläfke, 2010). Results from these trials suggest that, in addition to its anxiolytic efficacy, the herbal medicinal product has a beneficial effect on co-morbid depression (Kasper and Dienel, 2013). This study now demonstrates that Silexan, at the marketed dose of 1×80 mg/day given for 10 weeks, is also efficacious in MADD, in which symptoms of anxiety and depression are of similar importance. In this patient population Silexan exerted comparably pronounced anxiolytic and antidepressant effects.

According to the WHO collaborative study on 'Psychological Problems in General Health Care' up to 25% of the patients seen in general practice suffer from comorbid symptoms of anxiety and depression (Sartorius et al., 1996). In a study published by Stein et al., (1995) 12.8% of primary care clinic attendees without known psychiatric illness had a combination of subsyndromal anxiety and depressive features that fulfilled the criteria for MADD. Although there is some variation in the estimated prevalence rates, probably due to differences between clinical definitions (Spijker et al., 2010), researchers widely agree that MADD is a very common disorder, particularly in primary care (Barkow et al., 2004; Das-Munshi et al., 2008).

Patients suffering from subsyndromal psychiatric conditions, including MADD, have been shown to suffer from similarly pronounced distress, co-morbidity, and impairment of daily living skills as those with fully syndromal disorders (e.g. Das-Munshi et al., 2008; Lewinsohn et al., 2004). This

is consistent with the global assessment of the psychiatrists participating in this trial according to which the majority of the patients were at least moderately mentally ill before starting the investigational treatment. It is therefore important to note that Silexan not only improved the specific symptoms of anxiety and depression, but also had a beneficial effect on global clinical impression as well as on patient relevant outcomes like daily living skills and health related quality of life.

Patients suffering from subsyndromal anxiety or depressive symptoms frequently do not receive appropriate treatment (Culpepper et al., 2008; Dunlop et al., 2013). Besides frequent underrecognition of the clinical significance and implications of subsyndromal anxiety and MADD, this may also be attributable to the reluctance of the patient or the treating physician to accept the possible adverse effects of antidepressant or anxiolytic drugs. SSRIs, that are currently recommended as first-line drugs for both anxiety and depression (Bandelow et al., 2012; Bauer et al., 2013), have a more favourable safety profile than older drugs but are still associated with bothersome and partly disabling side effects such as anticholinergic reactions, headache, sedation, gastrointestinal complaints, somnolence, weight gain or sexual dysfunction (Ferguson, 2001). Moreover, they may even aggravate the symptoms of anxiety and co-morbid insomnia that they were prescribed to treat, and their intake has been associated with increased suicidal risk (Breggin, 2003–2004). The safety data of this trial indicate that there were no specific adverse reactions to Silexan other than eructation, which has been described as side effect earlier (Kasper, 2013). In contrast to many other anxiolytic or antidepressant drugs, sedative effects or withdrawal symptoms have not been described to date, and the drug has also been found to be devoid of interactions with the cytochrome P450 enzyme system (Doroshyenko et al., 2013) and with oral contraceptives (Heger-Mahn et al., 2014), the latter of which is important because the majority of patients with anxiety or MADD are female.

Unfortunately the ICD-10 criteria for MADD (World Health Organization, 1992) include only a rather vague description of the condition (Das-Munshi et al., 2008). This may lead to substantial heterogeneity between different studies in MADD and restrict the comparability of the results (Spijker et al., 2010). A helpful operationalization and more detailed definition of the existing ICD-10 criteria is, however, included in the Diagnostic and Management Guidelines for Mental Disorders in Primary Care issued by the World Health Organization (WHO), (1996) which were applied in case of our study to characterize the patient population. In this context it is regrettable that MADD, a clinically meaningful diagnosis that could help to assure that patients receive adequate treatment, has not been included into DSM-5 (American Psychiatric Association, 2013).

This trial was planned with an adaptive interim analysis that involved unblinding, hypothesis testing, and options for sample size re-estimation and early stopping, either with rejection of the pre-defined null hypotheses, or for futility (Bauer and Köhne, 1994). In such a design the decision rules to be followed at the interim look, depending on the *p*-values obtained from the data of the first part of the trial, must be (and actually were) prespecified in order to assure that the studywise type I error level is controlled in the strong sense. Since the null hypotheses corresponding to both primary outcome measures could be rejected and superiority of Silexan over placebo could be demonstrated already at the interim stage, the early stopping of the trial was a mandatory, pre-planned consequence of the study design, not a premature abortion, and the interim results are to be considered the definitive results of the trial. The trial was stopped for preparing the interim analysis. All randomized patients are included in the interim analysis. By specifying a local type I error of $\alpha_1 = 0.0152$ for significance at the interim stage, the adaptive design assures that the study would also have been significant at a type I error level of $\alpha = 0.025$, had it been performed in a 'conventional', fixed sample size design without an interim analysis.

Another methodological issue is that a study with an adaptive interim analysis and two primary outcome measures constitutes a multiple testing problem that requires control of the pre-specified, studywise type I error level (Kieser et al., 1999). In this trial multiplicity, caused by testing two primary outcome measures, was controlled by a-priori ordering of the hypotheses referring to HAMA and MADRS total score change versus baseline (Maurer et al., 1995). Multiplicity, caused by confirmatory hypothesis testing both at the interim analysis and then at the final analysis, would have been controlled by the features of the adaptive design (Bauer and Köhne, 1994; Kieser et al., 1999), had the study been continued into its second stage. Since all other *p*-values presented in this paper are intended to be purely descriptive, further multiplicity adjustment was neither required nor performed.

It is a limitation of our trial that, beyond the WHO Diagnostic and Management Guidelines, no structured clinical interview was used to further confirm the diagnosis of MADD. Uniform diagnostic and rating standards were, however, assured by a mandatory investigator training performed before the start of patient inclusion.

In conclusion, in patients suffering from MADD according to ICD-10 criteria, Silexan has an anxiolytic and antidepressant effect that leads to an improvement of impaired daily living skills and health related quality of life and it was very well tolerated.

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Contributors

Dr. Kasper was involved in the design of the original randomized clinical trial and contributed to the interpretation of the current analysis. Dr. Dienel helped to develop the design of the study. Dr. Kasper, Dr. Volz, Dr. Dienel and Mrs. Schläfke helped to draft the analysis plan of the current study and assisted in the creation of the initial draft of the manuscript. All authors contributed revisions to subsequent drafts of the manuscript, and have contributed to and approved the final manuscript.

Conflict of interest

Siegfried Kasper has received grant/research support from Eli Lilly, Lundbeck, Bristol-Myers Squibb, GlaxoSmithKline, Organon, Sepracor and Servier; has served as a consultant or on advisory boards for Angelini, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Lundbeck, Pfizer, Organon, Schwabe, Sepracor, Servier, Janssen, and Novartis; and has served on speakers' bureaus for AstraZeneca, Eli Lily, Krka Pharma, Lundbeck, Schwabe (Spitzner), Sepracor, Servier, Pierre Fabre, and Janssen.

Hans-Peter Volz has served as a consultant or on advisory boards for Astra/Zeneca, Eli Lilly, Lundbeck, Pfizer, Schwabe, Janssen, Otsuka, Merz, Wyeth, neuraxpharm and has served on speakers' bureaus for Astra/Zeneca, Eli Lilly, Lundbeck, Schwabe, Janssen, Merz, Wyeth, Lichtwer, Steigerwald, Hormosan, neuraxpharm and Bristol-Myers Squibb.

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