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REVIEW ARTICLE



Silexan in anxiety disorders: Clinical data and pharmacological background

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ABSTRACT

Objectives: Silexan is a lavender oil preparation available in 80-mg capsules. Here we review clinical trials investigating its anxiolytic efficacy, safety and tolerability in humans, as well as pre-clinical investigations supporting this therapeutic use.

Methods: Besides three selected publications reporting preclinical investigations, seven clinical trials are included, of which five had a treatment duration of 6 or 10 weeks. Primary outcome measure was the HAM-A total score reduction, while single items were assessed with regard to effects on concomitant depressive symptoms and on quality of sleep.

Results: In patients with subthreshold (subsyndromal) anxiety or generalised anxiety disorder (GAD), an anxiolytic effect of Silexan was evident after 2 weeks. HAM-A total score reductions between baseline and end of treatment were significantly superior to placebo in patients with subthreshold anxiety and comparable with those achieved under lorazepam or paroxetine in patients with GAD. In addition, Silexan had beneficial effects on typical concomitant symptoms of anxiety disorders, such as impaired sleep, somatic complaints, co-morbid depression or decreased quality of life. Except for mild gastrointestinal symptoms, Silexan did not induce any adverse effects and did not cause drug interactions, sedation or withdrawal symptoms at daily doses of 80 or 160 mg.

Conclusions: Silexan is a safe and effective treatment in anxiety disorders.

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Introduction

Subthreshold (subsyndromal) anxiety disorder is a serious, often unrecognised or unnoticed, and therefore undertreated condition that is associated with a high degree of co-morbidity and impairment of quality of life (Wittchen et al. 2000; Lewinsohn et al. 2004; Kessler et al. 2005). The development of a more severe form of anxiety such as generalised anxiety disorder (GAD) is more probable than spontaneous remission in case of missing or inadequate treatment, which includes the danger of interference of the disease with important activities of daily life (Rickels & Schweizer 1998; Wittchen et al. 2000; Lewinsohn et al. 2004). Untreated anxiety disorders also carry a considerable risk of secondary diseases due to the development of co-morbidities such as depression or the emergence of adverse health behaviour such as nicotine or alcohol abuse (Bonnet et al. 2005). With a 12-month

prevalence rate of 14%, anxiety disorders are the most prevalent psychiatric condition in Western Europe, accumulating to 61.5 million adults affected (Wittchen et al. 2011). Subthreshold presentations are estimated to occur twice as often as fully developed GAD (Haller et al. 2014).

In contrast to the ICD-10- and DSM 5-registered GAD, the features of subthreshold anxiety disorders are not yet strictly defined. Whereas GAD is categorically defined by a set of symptoms such as uncontrollable worries, somatisation, tension or disturbed sleep, that must have existed for at least 6 months, the subthreshold anxiety basically may include less symptoms while the time span of symptom persistence may last for less as 6 months (Volz et al. 2011). Due to the absence of binding diagnostic criteria, subthreshold anxiety disorders that fail to meet the required diagnostic standards are often not adequately dealt with in general practice and thus frequently remain

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inappropriately treated (Kroenke et al. 2007), even though the degree of functional impairment, distress and risk of chronification and co-morbidity associated with subthreshold presentations is similar to that appearing in syndromal anxiety conditions (Pincus et al. 1999; Andrews & Carter 2001; Lewinsohn et al. 2004; Kessler et al. 2005).

Despite the high prevalence and a similar economic impact of subthreshold anxiety disorders, appropriate therapy is not available as the conventional treatment of these mild-to-moderate presentations by means of synthetic standard anxiolytics such as selective serotonin uptake inhibitors (SSRI) or benzodiazepines often implies an unfavourable benefit-to-side effect ratio, which subsequently leads to poor compliance among patients affected (Volz et al. 2011). Known side effects that accompany long-standing, first-line anxiolytics are, besides physiological alterations, sedation, impaired concentration, amnesia, depression, delirium, dependency and, not least, withdrawal syndrome (Lader 1999; Longo & Johnson 2000). Since withdrawal symptoms can appear in the shape of anxiety, insomnia, restlessness, poor attention and muscle aches (Baldwin et al. 2007), discontinuation of benzodiazepines or SSRIs requires great attentiveness and assisted off-tapering in order to prevent or minimise the degree of these symptoms (Tamam & Ozpoyraz 2002). Thus, administration and long-term use of synthetic standard anxiolytics always implies impairment of essential activities of daily life, which can place a negative impact on compliance and acceptance of these drugs by the patients. Therefore, there is an existing demand for efficacious, safe and therefore acceptable anxiolytics that are also applicable in subthreshold conditions (Carter et al. 2001; Rickels et al. 2008).

Silexan¹ (WS[®] 1265) is a special active substance with an essential oil produced from *Lavandula angustifolia* flowers by steam distillation. In Germany, the drug is registered as a medicinal product for the treatment of restlessness accompanying anxious mood. The product is available as immediate release soft capsules containing 80 mg of lavender oil. The German marketing authorisation recommends a daily dose of 80 mg/day Silexan.

The review at hand presents the results of nonclinical investigations as well as clinical trials and provides an overview of the findings with regard to efficacy and safety of Silexan in both subthreshold anxiety disorders and GAD. To this end, we review three selected publications on nonclinical investigations indicating the anxiolytic effect of Silexan, which are supplemented by results obtained in a clinical trial imaging the neural action of Silexan by positron emission

tomography. Furthermore, five randomised clinical efficacy trials are presented as well as two trials investigating drug interactions.

Pharmacological background

Kumar (2013) conducted a broad set of anxiety tests and a general screen on neuropharmacological properties of Silexan in rats and mice. This included an open-field test, an elevated plus-maze test, an elevated zero-maze test, a social interaction test, and a novelty-induced suppressed feeding latency test. Silexan (3, 10, and 30 mg/kg) was administered once daily for seven consecutive days and was compared with the standard anxiolytics lorazepam (5 mg/kg) and diazepam (3 mg/kg). All three doses of Silexan induced significant and dose-dependent anxiolytic effects which were comparable with that of lorazepam. Silexan increased pentobarbital-induced sleeping time, but in contrast to diazepam was devoid of any significant intrinsic sedating effect as shown by locomotor activity and muscle-grip performance.

Schuwald et al. (2013) confirmed the anxiolytic action of orally administered Silexan in an elevated plus-maze test with mice. The anxiolytic effect of Silexan (3 mg/kg) was comparable with that of the active controls diazepam (2.5 mg/kg) and pregabalin (100 mg/kg). Silexan also elevated the pentobarbital sleeping time at similar concentrations (3–30 mg/kg). However, this finding rather suggests sleep promoting activity following its anxiolytic effects as no sedative effect by itself was observed.

Furthermore, the authors were able to show that Silexan bears some similarities with the established anxiolytic pregabalin as it non-selectively inhibits voltage-operated calcium channels (VOCCs) already at nanomolar concentrations. Silexan, however, does not primarily interact with the $\alpha 2\delta$ subunit of P/Q-type calcium channels, which is the binding site of pregabalin. Instead, Silexan non-selectively reduces the calcium influx through several different types of VOCCs (e.g. N-type, P/Q-type and T-type VOCCs). It has been speculated that under pathological conditions, such as anxiety or stress disorders, an enhanced Ca^{2+} influx through N-type and P/Q-type VOCCs may increase the release of neurotransmitters such as glutamate and norepinephrine (Musazzi et al. 2011; Kalk et al. 2011), which are involved in the pathogenesis of these diseases. By inhibiting VOCCs, Silexan may have a normalising effect on hyperactive nerve cells and counteract the symptomatic expressions such as spinning thoughts and anxious moods.

A nonclinical trial on operantly conditioned rats was reported by Silenieks et al. (2013). In this trial rats that had been trained to discriminate diazepam (2 mg/kg) from saline were compared with animals pre-treated with Silexan (3–30 mg/kg) who did not show a diazepam-appropriate response in the test phase. These findings indicate that the interoceptive stimulus properties inherent in the benzodiazepine diazepam are absent in Silexan, thus suggesting the absence of a dependence-inducing potential as is known of benzodiazepines. Based on their findings, Silenieks et al. (2013) also conclude there is little likelihood of a benzodiazepine-like anxiolytic action of Silexan via interaction with GABA_A receptors, which supports the findings reported by Schuwald et al. (2013).

Baldinger et al. (2015) provided supportive information on the anxiolytic mode of action of Silexan by reporting data from a placebo-controlled clinical trial with a cross-over design. In order to elucidate the effect of Silexan on 5-HT_{1A} receptor binding, 17 healthy men underwent positron emission tomography measurements using the radioligand [carbonyl-¹¹C]WAY-100635 following a daily intake of 160 mg Silexan or placebo for a minimum of 8 weeks. It was shown that the serotonin-1A receptor binding potential was significantly reduced following the intake of Silexan in comparison with placebo in two large clusters encompassing the temporal gyrus, the fusiform gyrus and the hippocampus, as well as the insula and anterior cingulate cortex. These findings provide strong evidence that in humans, as in rodents (Chioca et al. 2013), the anxiolytic effect of Silexan is mediated via the serotonergic neurotransmitter system, particularly the 5-HT_{1A} receptor, and not through a GABAergic mechanism.

Summarizing the nonclinical findings and the results obtained from the human pharmacological study by Baldinger et al. (2015), it must be noted that, despite some similarities to the anxiolytic action of benzodiazepines, SSRIs or the gabapentinoid pregabalin, Silexan does not interact with typical targets of these standard anxiolytics (Schuwald et al. 2013). Instead, Silexan is reported to inhibit different types of VOCCs and to modulate serotonergic neurotransmitter systems. These findings are suggested to be at the basis of the non-sedative effect of Silexan, which established a fundamental difference in comparison with today's first-line anxiolytics (Müller et al. 2015).

Clinical trials

Our review includes all published clinical trials investigating the effects of Silexan administration in adults.

Five out of the seven clinical trials identified assess the anxiolytic efficacy of the drug employing the Hamilton Anxiety Rating Scale (HAM-A) as main outcome measurement, whereas two trials focus on interaction. Subjects investigated in the efficacy trials were included upon condition of existing anxiety disorder as predefined by the respective trial protocols, whereas subjects participating in the interaction trials were healthy volunteers. All clinical trials presented in this review were designed as controlled, double-blind, randomised trials. Placebo was chosen as control in all except one of the randomised trials, which was designed as reference-controlled (Woelk & Schläpke 2010), whereas one trial was designed both reference- and placebo-controlled (Kasper et al. 2014). Treatment duration in the efficacy trials presented was 6–10 weeks, study drug dosage was 80 or 160 mg/day. General safety and tolerability was assessed in all trials investigating Silexan, mainly observing and evaluating the occurrence of adverse events (AEs).

In a clinical trial of 10 weeks treatment duration, Kasper et al. (2010) investigated the efficacy of Silexan in comparison with placebo in patients suffering from subthreshold anxiety (not otherwise specified, NOS) according to ICD-10 F 41.9 and DSM-IV 300.00. This classification refers to anxiety disorders presenting with clinically relevant symptoms which, however, do not fully meet the formal criteria set by the current diagnostic standards for specific sub-categories such as GAD in terms of, e.g. duration, number and severity of symptoms. Main outcome measure was the reduction of the HAM-A total score under Silexan compared with placebo. The Pittsburgh Sleep Quality Index (PSQI) was employed in order to evaluate effects on anxiety-related sleep disturbances.

Woelk and Schläpke (2010) compared anxiolytic effects of Silexan and the standard benzodiazepine lorazepam in patients with GAD. The change of anxiety severity was assessed by the HAM-A total score over a treatment duration of 6 weeks.

Another investigation on the efficacy of Silexan in patients suffering from GAD was conducted by Kasper et al. (2014). In this trial both placebo and an active comparator were employed, as were two different dosages of Silexan (80 and 160 mg/day). As active comparator the standard SSRI paroxetine was chosen as it currently belongs to the first-line treatment options in anxiety disorders. The change of the HAM-A total score between baseline and treatment end at week 10 was assessed as main outcome measure.

Kasper et al. (2015a) compared the effects of Silexan to placebo with regard to anxiety-related restlessness and agitation as the most common co-morbid

Table 1. Clinical trials investigating the anxiolytic efficacy of Silexan.

Trial	Inclusion diagnosis	Design	Intervention ^a	HAM-A Results (mean total score change/SD) ^b
Kasper et al. (2010)	Anxiety disorder not otherwise specified	Double-blind, randomised, placebo-controlled	80 mg/day Silexan (<i>n</i> = 104) or placebo (<i>n</i> = 108), 10 weeks	16.0 ± 8.3 (Silexan) 9.5 ± 9.1 (Placebo)
Woelk and Schläpke (2010)	Generalised anxiety disorder	Double-blind, double dummy, randomised, reference-controlled	80 mg/day Silexan (<i>n</i> = 40) or 0.5 mg/day Lorazepam (<i>n</i> = 37), 6 weeks	11.3 ± 6.7 (Silexan) 11.6 ± 6.6 (Lorazepam)
Kasper et al. (2014)	Generalised anxiety disorder	Double-blind, randomised, reference-controlled, placebo-controlled	160 mg/day Silexan (<i>n</i> = 121), 80 mg/day Silexan (<i>n</i> = 135), 20 mg/day Paroxetine (<i>n</i> = 132), or placebo (<i>n</i> = 135), 10 weeks	14.1 ± 9.3 (Silexan 160) 12.8 ± 8.7 (Silexan 80) 11.3 ± 8.0 (Paroxetine 20) 9.5 ± 9.0 (Placebo)
Kasper et al. (2015a)	Restlessness and agitation	Double-blind, randomised, placebo-controlled	80 mg/day Silexan (<i>n</i> = 86), or placebo (<i>n</i> = 84), 10 weeks	11.8 ± 7.7 (Silexan) 9.6 ± 8.7 (Placebo)
Kasper et al. (2016)	Mixed anxiety/depressive disorder	Double-blind, randomised, placebo-controlled	80 mg Silexan (<i>n</i> = 159) or placebo (<i>n</i> = 156), 10 weeks	10.8 ± 9.6 (Silexan) 8.4 ± 8.9 (Placebo)

^aSample size of the full analysis set.^bFull analysis set, last observation carried forward.

symptoms over a time span of 10 weeks. Besides the HAM-A total score, reduction measurements on restlessness were taken by means of the State Check Scale. The PSQI was employed in order to evaluate effects on anxiety-related sleep disturbances.

Due to the high prevalence of concomitant occurrence of symptoms of depression in anxiety disorders (Sartorius et al. 1996), all aforementioned efficacy trials assessed the effect of Silexan on co-morbid depression as a secondary efficacy outcome measure. Results indicate that Silexan may also have an antidepressant effect (Kasper & Dienel 2012), a finding that is also supported by the previously described results reported by Baldinger et al. (2015), who suggest a role of the serotonergic neurotransmitter system in the anxiolytic action of Silexan. Kasper et al. (2016) therefore investigated the effects of Silexan on concomitant anxiety and depression. Mixed anxiety and depressive disorder (MADD) is a condition characterised by subthreshold symptoms of both anxiety and depression, neither of which is clearly predominant. As indicated by the results of the clinical trials conducted earlier, this trial also aimed to look into the antidepressant effect of Silexan in patients suffering from co-morbid anxiety/depression. Thus, both HAM-A and the Montgomery-Åsberg Depression Rating Scale (MADRS) were employed as main outcome variables.

The main characteristics of the efficacy trials are shown in Table 1.

Results and discussion

In Kasper et al. (2010) patients treated with Silexan 80 mg/day showed a HAM-A total score decrease of 16.0 ± 8.3 points compared with 9.5 ± 9.1 points in the placebo group after 10 weeks of treatment. The HAM-A total score reduction was significant as of week 2.

A total of 76.9% of the patients in the Silexan group and 49.1% of the patients in the placebo group were responders according to the predefined margin of a ≥ 50% HAM-A or PSQI total score reduction by the end of treatment. Silexan was therefore superior to placebo regarding the rate of responders ($P < 0.001$), which also held true for that of remitters (60.6 vs 42.6%, $P = 0.009$) whose HAM-A total score had reduced to less than 10 points or whose PSQI total score had reduced to less than 6 points after 10 weeks of treatment. Patient-ratings by means of the Zung Self-Rating Anxiety Scale support these findings showing a total score reduction of 15.6 ± 11.4 points for Silexan vs 11.1 ± 12.2 points for placebo ($P = 0.003$). With 74.0 vs 40.7% being the percentage of patients with marked or moderate improvements compared with baseline according to Clinical Global Impressions, item 2 was greater in the Silexan group than in the placebo group. Both total scores 'physical health' and 'mental health' of the 36-item Short Form Health Survey (SF-36) improved more obviously in patients treated with Silexan compared with placebo-treated patients (physical health: improvement by 20.5 ± 22.6 points (Silexan) and 10.8 ± 19.8 points (placebo) $P < 0.001$; mental health: improvement by 32.5 ± 24.1 points (Silexan) and 19.7 ± 22.4 points (placebo), $P < 0.001$). The incidence of AEs in the Silexan group was comparable with that in the placebo group, with eructation and dyspepsia occurring more often under Silexan than under placebo.

Whereas Silexan also showed significant beneficial effects on sleep quality, sleep duration and daytime tiredness as assessed by the PSQI, no sedative or other unwanted major drug-specific effects were reported.

Kasper et al. (2015a) were able to confirm and elaborate these findings when conducting a further trial focussing on the anxiety-related inability to find a

resting state. With regard to restlessness, the percentage of patients who never felt, seldom felt, or sometimes felt restless increased from 14.0% at baseline to 69.8% in the Silexan group, and from 9.5 to 57.1% in the placebo group at treatment end, with a significant advantage for Silexan. Likewise, the HAM-A total score decreased by 11.8 ± 7.7 points in the Silexan group, and by 9.6 ± 8.7 points in the placebo group, from baseline till treatment end. After adjustment for baseline imbalances of the HAM-A total score, significant different treatment effects in favour of Silexan could be observed beginning in week 4 until week 10, which is in line with the findings described previously. By week 10 (end of trial), 53.5% of the patients treated with Silexan reported to never, seldom, or sometimes suffer from disturbed sleep compared with 44.0% in the placebo group.

Also the results obtained in the clinical trial by Kasper et al. (2014) investigating the anxiolytic efficacy of Silexan in patients with GAD indicate the superiority of the herbal drug over placebo. In addition to placebo, the anxiolytic efficacy of Silexan in GAD patients was compared with that of the active control paroxetine at a dose of 20 mg/day. Treatment duration was 10 weeks, and dosages of Silexan were either 80 or 160 mg/day. Results demonstrate that, in reducing major anxiety symptoms, the anxiolytic efficacy of Silexan 160 and 80 mg/day was significantly superior to placebo after 4 and 6 weeks of treatment, respectively, and remained so until treatment end. After 10 weeks of treatment, both Silexan doses investigated were found to be at least as effective as the standard anxiolytic paroxetine.

Secondary outcome assessments indicative of concomitant depression were performed by application of the Hamilton (HAM-D) rating scale for depression. After 10 weeks of treatment, total score changes of the HAM-D obtained for both Silexan and the paroxetine groups were superior to those found for placebo, and the total score of the Raskin depression scale had improved more clearly in patients treated with either Silexan 80 or 160 mg, or paroxetine, compared with patients treated with placebo, indicating a beneficial effect of Silexan and paroxetine on depression occurring concomitant to anxiety disorder.

The effect of Silexan on anxiety-related lack of sleep quality was investigated as another secondary outcome in this trial by application of HAM-A item 4 ('Insomnia'). By treatment end, insomnia values had decreased by 48.3% (Silexan 160 mg), and 46.2% (Silexan 80 mg), both of which exceeded the reductions achieved under paroxetine 20 mg/day (37.4%) and placebo (24.4%) (Kasper et al. 2015b). The

reduction of anxiety levels by Silexan administration is therefore likely to be associated with an improvement of sleep quality in patients with GAD. Compared with placebo, Silexan administration over 10 weeks led to a clearly greater improvement of health-related quality of life (HRQL), as assessed by the patient-rated Sheehan Disability Scale and the SF-36 questionnaire. Whereas there was an overall significant superiority of Silexan 160 mg/day over placebo with regard to the HRQL-related items assessed, administration of Silexan 80 mg/day led to results comparable with those found for paroxetine, both of which, however, were much better than those of placebo. AE rates for Silexan were lower than for the active control paroxetine and comparable with those of placebo, except of gastrointestinal disorders with a 4.5% greater incidence in the Silexan groups as compared with placebo.

The clinical trials referred to provide results indicative of an anxiolytic efficacy of Silexan doses of 80 or 160 mg/day that is significantly superior to that of placebo as of treatment weeks 2–4. Furthermore, antidepressant effects in patients suffering from anxiety disorders were reported, as was the absence of major unwanted effects. An improvement of anxiety-induced poor sleep quality could be demonstrated with a statistically significant superiority of Silexan over placebo and the absence of sedating side effects. This sleep-improving, although non-sedating, effect of Silexan suggests a normalisation of underlying anxiety-related conditions such as restlessness and worrying to be at the basis of the favourable findings on the calming and anxiolytic efficacy of Silexan.

Woelk and Schläpke (2010) compared the anxiolytic effect of Silexan 80 mg/day with the standard benzodiazepine lorazepam 0.5 mg/day in patients with GAD. After the end of the 6-week active treatment phase, the HAM-A total score had decreased by 11.3 ± 6.7 points in the Silexan group and by 11.6 ± 6.6 points in the lorazepam group. The results suggest that the ameliorating effects of Silexan 80 mg/day in GAD are comparable with the starting dose of lorazepam. In the trial, an improving effect on sleep quality could be demonstrated for both drugs with Silexan showing neither sedative effects nor any potential for drug addiction.

Basing on the results of previous trials indicating a beneficial effect of Silexan on concomitant depressive symptoms in patients suffering from anxiety disorders, a clinical trial on the efficacy of Silexan in MADD patients was conducted recently (Kasper et al. 2016). With regard to anxiolytic effects Silexan 80 mg/day showed a statistically significant advantage over

Table 2. Clinical trials investigating whether or not there is an interaction and withdrawal behaviour of Silexan.

Trial	Assessment criteria	Design	Participants	Intervention	Main outcome measures
Doroshenko et al. (2013)	Drug interactions	Double-blind, randomised, placebo-controlled, two-fold cross-over	Healthy male or female volunteers	160 mg/day Silexan or placebo for 11 days ($n = 16$) ^a	Probe substrates: CYP1A2 caffeine (150 mg), CYP2C9 tolbutamide (125 mg), CYP2C19 omeprazole (20 mg), CYP2D6 dextrometorphan (30 mg), CYP3A4 midazolam (2 mg) AUC _{0-t} in plasma
Heger-Mahn et al. (2014)	Interaction with oral contraception	Double-blind, randomised, placebo-controlled, two-fold cross-over	Healthy female volunteers	160 mg/day Silexan or placebo for 28 days ($n = 22$) ^b Oral contraception: 0.15 mg levonorgestrel 0.03 mg ethinylestradiol/day	Ethinylestradiol and levonorgestrel pharmacokinetics (Days 1 and 28), follicle size (Days 7, 14, 21 and 28), plasma concentration of progesterone, oestradiol (Days 7, 14, 21 and 28) and sex hormone-binding globulin (Day 21); Hoogland score
Kasper et al. (2011)	Withdrawal symptoms	Double-blind, randomised, reference-controlled, placebo-controlled, parallel groups	Patients with generalised anxiety disorder	Discontinuation of 160 mg/day Silexan ($n = 97$), 80 mg/day Silexan ($n = 115$), 20 mg/day Paroxetine ($n = 101$) or placebo ($n = 105$), 1 week	Physician Withdrawal Checklist (PWC-20)

^aSample size of the per protocol set for PK analysis.^bSample size of the PK/PD population for analysis of the pharmacokinetics and pharmacodynamics.

placebo from week 2 until treatment end (week 10). The mean HAM-A total score decrease between baseline and week 10 was 10.8 ± 9.6 and 8.4 ± 8.9 points for Silexan and placebo, respectively. The antidepressant effect of Silexan as assessed by MADRS became statistically significant at week 2 and remained so until week 10. The rate of favourable antidepressant response was 40.3% in the Silexan group and 32.1% in the placebo group, with 46.5% of the Silexan group being in remission by trial end compared with 34.0% of those participants randomised to placebo.

In a pooled analysis reviewing the antidepressant effect of Silexan 80 mg/day on depressive symptoms associated with subthreshold anxiety, Kasper and Dienel (2012) could demonstrate a significant improvement of HAM-A item 6 ('depressive moods') under Silexan 80 mg/day after 10 weeks of treatment, with an even more pronounced effect in those patients that were more severely affected at baseline.

Two additional trials were included into our review for further insight into the safety and tolerability of Silexan (Table 2).

Doroshenko et al. (2013) and Heger-Mahn et al. (2014) studied the interaction potential of Silexan in healthy volunteers. In the double-blind, randomised, placebo-controlled trials a potential influence of the herbal drug on human cytochrome P450 activity (Doroshenko et al. 2013) and on the contraceptive efficacy of a combined oral contraceptive whose active

compounds are ethinylestradiol and levonorgestrel (Heger-Mahn et al. 2014) were investigated.

In the course of their efficacy trial Kasper et al. (2014) investigated the dependence potential of Silexan during a 1-week follow-up. The trial included patients suffering from GAD who had been administered either Silexan 80 mg/day, Silexan 160 mg/day, placebo, or paroxetine 20 mg/day, and assessed values of the 20-item Physician Withdrawal (PWC-20) (Rickels et al. 2008) in all groups at the beginning and end of a 1-week down-titration phase. Silexan was discontinued abruptly.

Doroshenko et al. (2013) performed a cocktail trial in healthy subjects investigating the interaction potential of Silexan with the cytochrome P450 enzymes system that is important for metabolising most of the currently available drugs. In this double-blind, randomised, placebo-controlled cross-over trial possible effects of Silexan on the activity of CYP1A2, 2C9, 2C19, 2D6 and 3A4 enzymes were tested. Silexan 160 mg/day or placebo were administered over 11 days. On the last day of the treatment period, Silexan or placebo were administered orally together with the five-probe phenotyping cocktail. Absence of a clinically relevant interaction could be concluded if the 90% confidence interval (CI) for estimated ratio $\mu_{\text{test}}/\mu_{\text{reference}}$ did not exceed a range of 0.70–1.43 for a phenotyping metric. A clinically relevant interaction of Silexan administration on CYP1A2, CYP2C9, CYP2D6 and

CYP3A4 could be excluded since the 90% CIs for the ratios (AUC (0– t_z) Silexan/AUC (0– t_z) placebo) were within the predefined range of (0.70–1.43). Due to the high variability of measurements as to CYP2C19 the upper limit of the 90% CI of the ratio for the enzyme exceeded the predefined threshold of 1.43 slightly. The ratio of the point estimator was close to unity and heterogeneity of measurements was unexpectedly large. The deviation as to the upper bound of the CI is thus clinically irrelevant.

The high prevalence of anxiety and restlessness in younger women (Bekker & van Mens-Verhulst 2007) increases the likelihood of co-administration of contraceptives and anxiolytic drugs. Thus, the interaction potential of Silexan with oral contraceptives was investigated by Heger-Mahn et al. (2014) in a double-blind, randomised cross-over trial testing possible effects of Silexan on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive containing ethinylestradiol (EE) 0.03 mg and levonorgestrel (LNG) 0.15 mg in healthy, fertile, adult females. During two consecutive 28-day cycles, the oral contraceptive was administered for 21 days in combination with Silexan 160 mg/day or placebo. Plasma concentration–time profiles of EE and LNG were obtained on day 18 ± 1. The primary outcome measure was the area under the concentration–time curve over a dosing interval of 24 h (AUCs) for EE and LNG plasma levels. This trial showed that Silexan did not affect the pharmacokinetic properties of the combination oral contraceptive containing EE and LNG to a relevant degree. Similarly, pharmacodynamic parameters such as progesterone, oestradiol, or sex hormone-binding protein levels, mean endometrial thickness, follicle size, and ovarian activity remained unaffected by the administration of Silexan.

Given the anxiolytic activity of Silexan as shown in the previously described trials, dependency potential is an important matter to look into, as all standard synthetic anxiolytics are to some degree associated with habituation and drug dependence and require careful down-tapering in order to avoid or control unwanted withdrawal symptoms (Lader 1999; Longo & Johnson 2000). In the follow-up of an above referred-to efficacy trial on Silexan in patients suffering from GAD (Kasper et al. 2014), dependency potentials of Silexan after prolonged (10 weeks) administration were investigated (Kasper et al. 2011). In the course of this follow-up period, medication of patients who had been randomised to Silexan 80 mg/day, Silexan 160 mg/day, placebo, or paroxetine 20 mg/day was discontinued over 1 week. Whereas paroxetine was tapered down according to instructions, Silexan was discontinued

abruptly. Patients were asked to complete the PWC-20 at the beginning and end of the 1-week withdrawal phase. PWC-20 total scores had reduced by 0.19 ± 4.20 in the placebo group, 0.23 ± 3.81 in the Silexan 80 mg/day group, 0.65 ± 4.93 in the Silexan 160 mg/day group, and 0.51 ± 4.47 in the paroxetine group, which indicates no withdrawal effects in all four randomisation groups after discontinuation. There is no hint for a dependency potential of Silexan.

Conclusions

Subthreshold anxiety disorders are often undertreated conditions as they fail to meet diagnostic criteria of syndromal presentations such as GAD. In both conditions, ongoing worries are accompanied by somatic symptoms such as restlessness or disturbed sleep. Daily life is massively affected by anxiety disorders and concomitant diseases such as depression. Thus, in order to avoid the development of more severe or chronic disorders or increasing co-morbidity, an early appropriate treatment is inevitable.

Nonclinical studies have shown the unique mode of anxiolytic action of Silexan which allows for anxiolytic efficacy superior to placebo and comparable with that of standard synthetic anxiolytics as shown in the clinical trials reviewed. Concomitant anxiety-related symptoms such as restlessness and agitation could be significantly reduced under Silexan compared with placebo. Also, Silexan had a positive effect on sleep disturbances, somatic symptoms and depressed mood, and proved to have a beneficial impact on the trial participants' overall quality of life.

Except for mild gastrointestinal symptoms and allergic skin reactions, Silexan is devoid of adverse effects and does not cause drug interactions or withdrawal symptoms at daily doses of 80 or 160 mg. The clinical trials included in this review confirm the findings from preclinical studies that there are no sedative effects caused by Silexan, other than in synthetic anxiolytics.

The interaction studies included into our review demonstrated that Silexan neither inhibits nor induces the activity of cytochrome P450 enzymes, and thus does not interfere with the expected metabolism of major marketed drugs. Furthermore, Silexan also does not modify the plasma levels of oral contraceptives based on ethinylestradiol or levonorgestrel, and does not affect relevant pharmacodynamic parameters. Silexan can thus be safely administered concomitantly with the majority of other therapeutic agents and oral hormonal contraceptives. Reviewed data did not suggest the occurrence of any withdrawal symptoms after

the Silexan administration was terminated, which allows for a safe abrupt discontinuation.

Note

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

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