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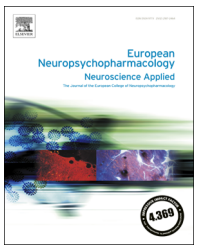

Efficacy of Silexan in mixed anxiety-depression – A randomized, placebo-controlled trial

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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).