

Phyto-anxiolytic effects of a fixed herbal drug combination for the relief of stress and its potential to reduce benzodiazepine use

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ABSTRACT

Stress affects already young healthy people and many elderly or patients with psychiatric disorders receive benzodiazepines. A recent study has shown that the phyto-anxiolytic herbal extract combination Ze 185 (Relaxane[®]) significantly reduced the subjective stress reaction in healthy men in an acute stress setting. Further, in a retrospective data analysis from stationary patients in a psychiatric hospital in Switzerland it was concluded that the use of benzodiazepines could be reduced under the treatment with Ze 185. As an example in evidence-based phytotherapy Ze 185 is discussed in the context of stress and anxiety-related disorders.

Key words: stress, anxiety, Relaxane[®], Ze 185, evidence-based phytotherapy

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INTRODUCTION

Psychological distress in terms of symptoms of depression and anxiety is dose-dependently associated with an elevated risk of mortality from different pathological causes. Even at low levels of psychological distress the risk of mortality is increased (1). People with chronic stress or recurring stressful situations more often visit their physicians or use drugs for the treatment of stress-related symptoms than people with a low level of stress (2). Besides psychological trainings to handle stressful situations few options exist for the treatment of stress-related reactions without negatively affecting cognitive functions (e.g. by benzodiazepines). Among herbal medicinal products, several medicinal plants are traditionally used for the relief of symptoms of mental stress such as valerian (*Valeriana officinalis* L.), passion flower (*Passiflora incarnata* L.) or lemon balm (*Melissa officinalis* L.) which hold high acceptability among patients and increasing levels of scientific evidence (3-5). In combination with butterbur (*Petasites hybridus* L.) these herbal drugs are part of the fixed herbal drug combination Ze 185 (Relaxane[®]) which has been shown to be comparably efficient in the reduction of anxiety as oxazepam in patients with psychosomatic disorders (6). Further it could be shown that Ze 185 significantly reduced exam nerves in healthy volunteers (7) and significantly improved symptoms of anxiety and depression in patients with somatoform disorders (F45.0 and F45.1 ICD-10)(8). Recently, in a randomised, placebo-controlled, double-blind study the effect of Ze 185 was further investigated in healthy volunteers in a psychosocial stress paradigm (9).

SIGNIFICANT REDUCTION OF SUBJECTIVE ANXIETY IN A SITUATION OF ACUTE PSYCHOSOCIAL STRESS

In this study, 72 healthy men between 18 and 45 years were randomised in three groups (Ze 185, placebo and no treatment) and underwent a standardised psychological stress test (Trier Social Stress Test, TSST) (10) to investigate the effects of the herbal drug combination Ze 185 on acute physiological and emotional stress reactions (9). The participants were treated for 4 days with Ze 185 or Placebo (tid) or received no treatment. On day 4 all participants were exposed to the TSST which resulted in an acute stress reaction which was confirmed by an increase of salivary cortisol, increased heart rate and a reduction in heart rate variability over time. The TSST is a well described, validated tool to assess acute stress situations which provokes physiological stress responses combined with high levels of psychosocial-evaluative threat and uncontrollability (11). As a result of the TSST, groups did not differ significantly in physiological stress reactions. However, as a measure of stress perception the participants reported their subjective level of anxiety before and after the TSST using the state-trait anxiety inventory (STAI)(12, 13). Ze 185 showed a significantly decreased stress-induced elevation of subjective anxiety response in comparison to placebo and no treatment ($p \leq 0.05$) and a faster return to baseline (Fig 1.) (9). In this study it could be shown that Ze 185 attenuates the subjective emotional stress response during an acute stress situation without affecting physiological reactions. Cortisol as the main stress hormone remains unaffected, sustaining one of the most important physiological adaptive mechanisms – inevitable to overcome stressful situations.

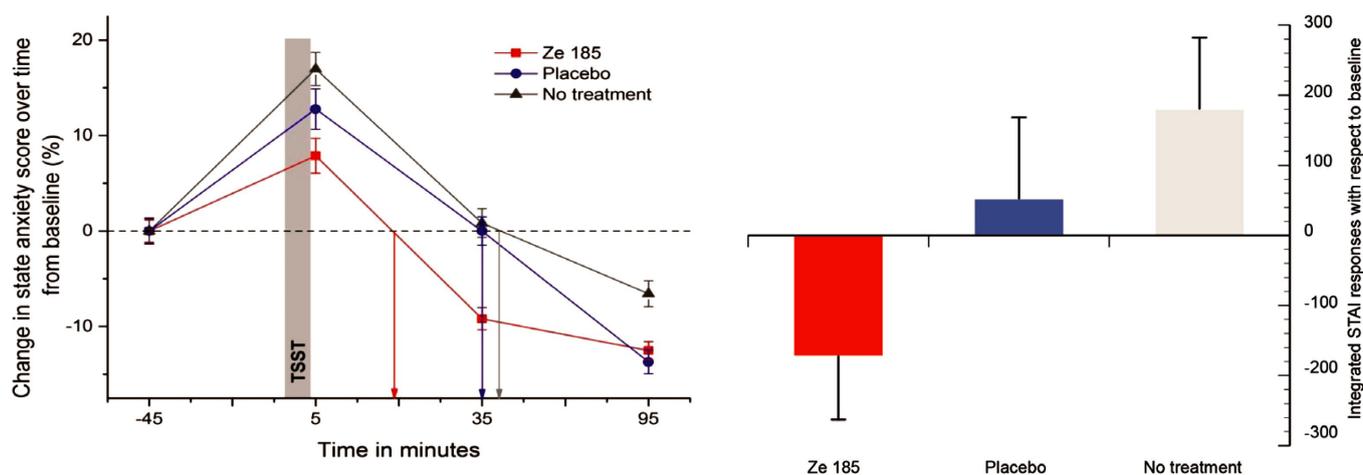


Figure 1.

Relative and integrated state anxiety of the STAI-state response (mean values \pm SEM) of the three study groups in the Trier social stress test (TSST). Ze 185 significantly reduced the state anxiety score and AUCi compared to placebo and no treatment ($p \leq 0.05$).

LESS BENZODIAZEPINES DUE TO PHYTOTHERAPY ?

In an early exploratory study the acute sedating effect of the herbal tranquilizer Ze 185 was compared to placebo and bromazepam (14). A test battery of objective performance tests, reaction time, vigilance and mental state after the intake of a single dose of 2 tablets of Ze 185 did not show any sedation or reduction of vigilance which would lead to an impairment of cognitive performance. Although only a single administration was investigated at this time, the safety and tolerability of Ze 185 could be confirmed in further clinical trials (6-9). In comparison to benzodiazepines, which are generally known for adverse drug reactions such as somnolence, impairment of cognitive functions and memory and the risk of addiction the fixed herbal drug combination Ze 185 appeared to provide a viable alternative. As a consequence, in a single-centre retrospective data analysis the prescriptions and outcomes of 3252 patients of a psychiatric hospital in Switzerland were investigated (15). Patients with diverse psychiatric (F-) diagnoses of mental and behavioural disorders (ICD-10) were separated into comparable groups of Relaxane[®]-treated patients (n=1548) and a control group (n=1704) to analyse matched pairs selected for age, gender, treatment duration and primary diagnosis. Most patients had a primary F3-diagnosis such as F32 "Depressive episodes" and F33 "Recurrent depressive disorders". Depression is often associated with anxiety and somatoform disorders. This was also reflected in the study population as the second most diagnosis belonged to the category F4 "Neurotic, stress-related and somatoform disorders". In both groups, the patient's treatments were effective as the Clinical Global Impression (CGI) and Global Assessment of Functioning (GAF) scores and selected items of the AMDP system (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie) were significantly improved. Importantly, in the Relaxane[®]-group significantly less patients were treated with benzodiazepines than in the control group (n = 661 vs.

n = 809 patients, $p = 0.006$), postulating that Relaxane[®] might provide a safe and well-tolerated alternative to benzodiazepines.

CONCLUSION

Evidence-based phytotherapy is an emerging treatment option not only for mild to moderate psychiatric diseases like anxiety-related disorders or depression. The very high acceptance of phytotherapy as a natural option offers great potential for successful first-line treatments in various diagnoses. With the example of the fixed herbal drug combination Ze 185 (Relaxane[®]) as a phyto-anxiolytic drug, a meaningful alternative to synthetic drugs such as benzodiazepines was suggested. In Switzerland, Ze 185 is a registered herbal medicinal product since over 45 years with demonstrated efficacy and safety. It is authorised for the treatment of nervousness, tension, restlessness and exam nerves with concomitant symptoms of spasmodic gastrointestinal complaints, increased irritability and occasional sleeping disorders. In four clinical studies Ze 185 was significantly more effective than placebo in the reduction of anxiety-related symptoms (6-9). For people suffering from acute stressful situations Ze 185 (Relaxane[®]) offers now a novel option for relief.

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