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Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam

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SUMMARY

Objective: **Passionflower (*Passiflora incarnata*) is a folk remedy for anxiety. A double-blind randomized trial compared the efficacy of *Passiflora incarnata* extract with oxazepam in the treatment of generalized anxiety disorder.**

Methods: **The study was performed on 36 outpatients diagnosed with GAD using DSM IV criteria. Patients were allocated in a random fashion: 18 to the *Passiflora* extract 45 drops/day plus placebo tablet group, and 18 to oxazepam 30 mg/day plus placebo drops for a 4-week trial.**

Results: ***Passiflora*** **extract and oxazepam were effective in the treatment of generalized anxiety disorder. No significant difference was observed between the two protocols at the end of trial. Oxazepam showed a rapid onset of action. On the other hand, significantly more problems relating to impairment of job performance were encountered with subjects on oxazepam.**

Conclusion: **The results suggest that *Passiflora* extract is an effective drug for the management of generalized anxiety disorder, and the low incidence of impairment of job performance with *Passiflora* extract compared to oxazepam is an advantage. A large-scale trial is justified.**

***Keywords*: herbal medicines, *Passiflora incarnata*, RCT, traditional medicine**

INTRODUCTION

Generalized Anxiety Disorder (GAD) is the most common anxiety disorder but is generally less severe than panic disorder. GAD is probably the disorder most often found with a coexisting mental disorder, usually another anxiety disorder or a mood disorder (1). The ratio of women to men is about 2 : 1. The cause of GAD is not known. The primary symptoms of GAD are anxiety, motor tension, autonomic hyperactivity and cognitive vigilance (1). DSM IV (2) employs the following criteria for GAD: excessive anxiety and worry, occurring more days than not for at least 6 months, about a number of events or activities that are difficult to control. Autonomic symptoms are no longer required for diagnosis. The principal neurotransmitter systems thought to modify anxiety are the gamma-aminobutyric acid (GABA) system, and the noradrenergic, serotonergic, dopaminergic and histaminergic system (3, 4). GABA is an important and abundant inhibitory transmitter in the mammalian nervous system. Three types of GABA receptor may be distinguished on the basis of their pharmacological properties and the physiological consequences of their activation: $GABA_A$, $GABA_B$ and $GABA_C$. $GABA_A$ receptors can be allosterically regulated by a diverse range of both naturally occurring and synthetic compounds (5–10). These substances include the barbiturates and benzodiazepines, which have important sedative, anxiolytic and anticonvulsant uses (11–16). The most effective treatment of patients with GAD is probably one that combines psychotherapeutic, pharmacotherapeutic and supportive approaches. Because of the long-term nature of the disorder, a treatment plan must be carefully thought out. The two major drugs to be considered for the treatment of GAD are buspirone and the benzodiazepines (3, 4). Benzodiazepines are the drugs most frequently prescribed for the treatment of anxiety disorders.

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They act through the benzodiazepines-GABA receptor, where they inhibit neuronal activity by increasing the chloride ion influx into neurones. This includes hyperpolarization of the nerve cell, a condition that leads to decreased responsiveness to incoming stimuli (17, 18).

Several problems are associated with the use of benzodiazepines (BZDs) in GAD. About 25–30% of all patients fail to respond, and tolerance and dependence may occur. Some patients also experience impaired alertness while taking the drugs. In addition, there are several reports that indicate cognitive impairment induced by benzodiazepines (19–25). The cessation of use of benzodiazepines can induce a withdrawal syndrome, characterized by psychological symptoms of anxiety, such as apprehension and irritability. Physiological symptoms of anxiety include tremor and palpitation, and perceptual disturbances include hypersensivity to light, sounds, touch or motion. Only one-third of patients who have GAD seek psychiatric treatment (19–25). Many patients go to general practitioners, internists and cardiologists but they also use herbal medicines like *Passiflora*.

Passionflower (*Passiflora incarnata*) is a woody, hairy, climbing vine and is reputed to have sedative/anxiolytic properties and has been used widely as an ingredient of herbal remedies, chiefly in the form of a liquid tincture. The commission E approved the internal use of passionflower for nervous restlessness, and the British Herbal Compendium indicates its use for sleep disorders, restlessness, nervous stress and anxiety (26–29). In our continuing study of traditional medicines with neurotropic effects, we evaluated the use of this plant for its anxiolytic effect in a double-blind, randomized and parallel group trial, comparing it, at a fixed daily doses of 45 drops extract of *Passiflora incarnata* (Passipay™, Iran Darouk), with oxazepam 30 mg/day.

METHODS

Outpatients in group 1 received fixed daily doses of *Passiflora* extract 45 drops/day plus placebo tablet (group 1), whereas those in group 2 received oxazepam 30 mg/day plus *Passiflora* drop (group 2) for a period of 4 weeks. Thirty-six outpatients (20 women and 16 men) aged between 19 and 47 years of age, who satisfied the DSM IV (2) for a diagnosis of GAD (duration of illness of 6 months) and had a score of 14 or more on the Hamilton Anxiety Rating Scale (HAM-A) were recruited. Patients were excluded if screening showed a history of a serious suicide attempt or current acute suicidal ideation, an unexpected recent panic attack or full DSM IV panic disorder within the previous 6 months, a life-time diagnosis of DSM IV mania, psychosis, paranoia or dementia, or if there was a concurrent or recent diagnosis of substance abuse, drug psychosis, obsessive-compulsive disorder, hypomania or major depression. Pregnant and lactating women were also excluded. Prior to the study, the patients were free from all psychotropic medication for a minimum of 7 days. After giving informed consent, patients were randomly allocated to the two treatment groups. Four subjects dropped out of the trial due to non-compliance (two from each group), leaving 32 subjects who met the DSM IV criteria for GAD and completed the trial. Patients were assessed by a psychiatrist at baseline and 4, 7, 14, 21 and 28 days after the medication started. The principal measure of the outcome was the HAM-A score. The rater used standardized instructions in the use of HAM-A. The mean decrease in HAM-A score from baseline was used as the main outcome measure of response.

Statistical analysis

Repeated measures analysis of variance (ANOVA) with a two-tailed post-hoc Tukey mean comparison test was performed on the change in HAM-A scores from baseline. To compare the outcome of two groups in the same week, an unpaired two-sided Student's *t*-test was used. Results are presented as mean ± SEM Differences were considered significant when $P < 0{\cdot}05$. To compare the demographic data and the frequency of side-effects between the two groups, Pearson Chi square test was performed.

RESULTS

Efficacy

The mean ± SEM scores for the two groups of patients are shown in Fig. 1. There were no significant differences between the two groups on day 0

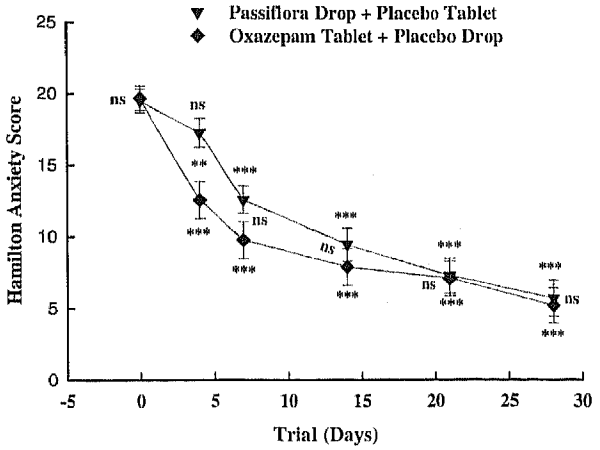

Fig. 1. Mean ± SEM scores of two protocols on Hamilton anxiety score. ns = non-significant.

(baseline) on the HAM-A ($t = 0{\cdot}1563$, d.f. = 30, $P = 0{\cdot}8769$). A repeated measures ANOVA showed a significant effect of treatment on the GAD scores. In both groups post-hoc comparisons of the baseline GAD scores with the scores at week 4 by means of the Tukey procedure revealed a significant reduction from baseline ($P < 0{\cdot}001$). However, post-hoc testing revealed a significant reduction from baseline from day 4 in oxazepam group and from day 7 in the *Passiflora* group. At days 4, 7 and 14 the mean HAM-A scores for the *Passiflora* placebo group were higher than the oxazepam group. The differences between the two treatments were significant at day 4 ($t = 2{\cdot}842$, d.f. = 30, $P = 0{\cdot}008$). However, after day 4 the differences were no longer significant.

Clinical complications and side-effects

A number of probable side-effects were studied (Table 1). Although impairment of job performance was observed more often in the oxazepam group, there were no significant differences between the two treatments in terms of total side-effects profile ($P = 0{\cdot}831$, NS; Table 1).

DISCUSSION

Anxiety is a common reaction to a significant life stress. It is characterized by fear and apprehension that may or may not be associated with a clearly identifiable stimulus (30–32). BZDs are considered as first line in the pharmacotherapy of anxiety (33). They were hailed as a breakthrough because they have fewer of the drawbacks of prior sedative-hypnotics and are effective in a range of disorders (20). However, BZDs have been the subject of debate that tends to centre on issues related to overuse, misuse and abuse (15). The realization that BZDs have a narrow safety margin between

Table 1. Clinical complication and side-effects

	Passiflora drop + placebo tablet					Placebo drop + oxazepam tablet					
Complications	None	Mild	Moderate	Severe	Severe, Disabling	None	Mild	Moderate	Severe	Severe, Disabling	*P*
Dizziness	9	3	4	0	0	8	3	4	1	0	0·787
Drowsiness	10	6	0	0	0	9	5	2	0	0	0·342
Confusion	12	4	0	0	0	12	3	1	0	0	0·565
Slurred speech	16	0	0	0	0	16	0	0	0	0	None
Ataxia	14	1	1	0	0	12	3	1	0	0	0·562
Hyporeflexia	16	0	0	0	0	15	0	1	0	0	0·310
Respiratory depression	16	0	0	0	0	13	1	2	0	0	0·191
Dyspenea	16	0	0	0	0	14	0	2	0	0	0·144
Allergic reaction	14	1	1	0	0	13	2	1	0	0	0·831
Aggression	16	0	0	0	0	16	0	0	0	0	None
Disinhibition	16	0	0	0	0	16	0	0	0	0	None
Impairment of job performance	8	5	3	0	0	4	3	2	6	1	0·049*

*Significantly more problems relating to impairment of job performance were encountered with patients on oxazepam.

the anxiolytic effect and the untoward side-effects has prompted many researchers to evaluate new compounds in the hope that safer alternative drugs will be discovered (20). Among these alternative drugs, medicinal plants such as *Passiflora* have a special place. To the best of our knowledge, the present study is the first double-blind controlled trial of *Passiflora* in the treatment of GAD (27–29). Our main overall finding was that *Passiflora* extract and oxazepam are effective in the treatment of GAD. No significant difference in efficacy was observed between the two treatments. Nevertheless, in the oxazepam group, but not the *Passiflora* group, significant effects were observed by day 4. This indicates a rapid onset of action for BZDs. On the other hand, the substantially lower incidence of impairment of job performance could be an important advantage of *Passiflora* extract. However, it should be emphasized that there was no significant difference between the two treatments in terms of the overall frequency of side-effects. We conclude that *Passiflora* extract is potentially a significant improvement over benzodiazepines in the management of GAD, particularly when drug-induced impairment of job performance is to be avoided. A large-scale trial is justified.

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