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Passionflower in the treatment of opiates withdrawal: a double-blind randomized controlled trial

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SUMMARY

Objective: **Clonidine-based therapies have been utilized as the main protocol for opiate detoxification for several years. However, detoxification with clonidine has its limitations, including lack of efficacy for mental symptoms. Accumulating evidence shows the efficacy of *Passiflora incarnata* extract in the management of anxiety. In our continuing study of traditional medicines, which have neurotropic effects, this plant had an anxiolytic effect, which may be used as an adjuvant agent in the detoxification of opiates by clonidine. We present the results of a double-blind randomized controlled trial of clonidine plus passiflora extract vs. clonidine plus placebo in the outpatient detoxification of 65 opiates addicts.**

Methods: **A total of 65 opiates addicts were assigned randomly to treatment with passiflora extract plus clonidine tablet or clonidine tablet plus placebo drop during a 14-day double-blind clinical trial. All patients met the DSM IV criteria for opioid dependence. The fixed daily dose was 60 drops of passiflora extract and a maximum daily dose of 0·8 mg of clonidine administered in three divided doses. The severity of the opiate withdrawal syndrome was measured on days 0, 1, 2, 3, 4, 7 and 14 using the Short Opiate Withdrawal Scale (SOWS).**

Conclusion: **Both protocols were equally effective in treating the physical symptoms of withdrawal syndromes. However, the passiflora plus clonidine group showed a significant superiority over clonidine alone in the management of mental symptoms. These results suggested that passiflora extract may be an effective adjuvant agent in the management of opiate withdrawal. However, a larger study to confirm our results is warranted.**

Keywords: **clonidine, detoxification, methadone, opiate withdrawal, passionflower, randomized controlled trial, RCT**

INTRODUCTION

Opioids are a broad class of alkaloidal compounds, including all natural and synthetic opioid peptides, that have opium- or morphine-like activity. They may be categorized into natural, semi-synthetic or synthetic compounds. The term opiate applies only to drugs derived directly from opium, such as morphine and codeine (1, 2). Opioids exert their pharmacological effects by interacting with specific opioid receptors in the central nervous system (CNS) (3). The term dependence refers to the compulsion to continue the self-administration of a drug without medical need. A distinction is often made between psychological dependence, referring to the perceived need that some people feel for drugs to reduce anxiety or produce sleep, or for drugs that produce a sensation of euphoria, and physical dependence, in which withdrawal of the drug results in physical symptoms such as tremor, nausea and convulsion (4). If morphine is withdrawn from an opiate addict, a rather unpleasant set of physical and mental symptoms ensues, known as the withdrawal or abstinence syndrome. Therefore, one of the first obstacles facing the opiate addict who attempts to get off drugs is the opiate withdrawal syndrome (5). There are several goals for opioid detoxification: reducing the symptoms of opioid withdrawal, providing a

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setting in which the patient may enter recovery, identifying any current medical difficulties that have developed, and initiating the recovery process (4, 5). As with sedative detoxification, the process of detoxification serves only to eliminate the physical dependence upon the drug, as the withdrawal is terribly uncomfortable; detoxification procedures are generally completed in 75% of inpatients and only about 15% of outpatient cases (6, 7). Clonidine-based detoxification has been utilized as the main protocol for several years (8, 9). However, detoxification with clonidine ameliorates the symptoms of withdrawal but does not improve mental symptoms (8, 9). Clonidine simply ameliorates the physical symptoms of withdrawal. This non-addictive antihypertensive agent may be given in place of opioids and will markedly reduce symptoms other than insomnia, anxiety and muscular aches (8–12). It is important to note that the anxiety and insomnia preferably should not be treated with benzodiazepines or other addictive sedative agents. Passionflower is a woody, hairy, climbing vine, 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 extract tincture (13, 14). Accumulating evidence shows the efficacy of Passionflower (*Passi flora incarnata*) extract in the management of anxiety. 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 (15, 16). In our continuing study of traditional medicines that have neurotropic effects, this plant had an anxiolytic effect, suggesting that it may be a useful adjuvant agent in opiate detoxification. We report the results of a double-blind randomized controlled trial of clonidine plus passiflora extract vs. clonidine plus placebo drop in the outpatient detoxification of 65 opiates addicts.

METHODS

Patients

A total of 65 male opiates addicts who fulfilled DSM IV criteria for opioid dependence and who gave consent to randomization to detoxification with either clonidine tablet plus passiflora extract (group 1) or clonidine tablet plus placebo drop (group 2) were entered into the 14-day double-blind controlled clinical trial. The mean ± SD age for group 1 and 2 was 34·83 ± 7·6 and 35·92 ± 8·1, respectively (NS). Both groups were matched in terms of family history, education, economic status, marital status, years of dependence and interval since the last attempt at giving up opiates. All subjects were outpatients who were admitted to the drug-dependency treatment unit. Fifteen subjects dropped out from the passiflora group and 20 from the placebo group over the trial, leaving 30 subjects (15 in each group) who completed the trial.

Study design

All study subjects were randomly assigned to receive detoxification using either clonidine 0·8 mg/day plus passiflora extract 60 drops/day or clonidine 0·8 mg/day plus placebo 60 drops/day on a double-blind basis. This trial medication was given three times per day in divided doses.

Drug schedule

The lowest daily dose of clonidine was 0·3 mg and was increased to 0·8 mg in four days. No other psychotropic medication was prescribed.

Inclusion and exclusion criteria

Those who fulfilled DSM IV criteria for opioid dependence and reported regular use of opioid on at least a daily basis were evaluated (17). All subjects were medically healthy, defined as having no current medical illness by history and a physical examination within normal limits. In view of concerns about possible postural hypertension, blood pressure was measured regularly before medication and any reading of less than 90 mmHg systolic or 60 mmHg diastolic prompted the temporary withholding of the next dose of clonidine. Potential subjects were excluded from participation if they had evidence of a current affective disorder, or had a history of psychosis or hospitalization for psychiatric reasons. All patients gave written, informed consent for participation in this 14-day, double-blind trial.

Assessment instrument

The severity of the opiate withdrawal syndromes was measured by a psychiatrist who was trained for this rating scale using Short Opiate Withdrawal Scale (SOWS). Measurements were made at baseline (day 0) and days 1, 2, 3, 4, 7 and 14 after medication started (Table 1) (18). The original SOWS contains 10 physical symptoms. We decided to add new items to cover mental symptoms (items 12–16) and an additional physical symptom (item 11), which was diarrhoea (19, 20). Symptom severity for each item was recorded on a four-point scale, with 0 = nil through to 3 = severe.

Statistical analysis

Repeated measures analysis of variance (RM-ANOVA) with a two-tailed posthoc Tukey mean comparison test was performed in the change from baseline for SOWS, mental symptoms and total scores. To compare the outcome of the two groups in the same week, an unpaired two-sided Student's *t*-test was used. Results are presented as mean ± SEM differences. The significance level was set at 5%. To compare the demographic data, Pearson Chi-square test was used.

Table 1. The modified Short Opiate Withdrawal Scale (SOWS) including 10 items of the SOWS, diarrhoea and five items of mental symptoms

	None	Mild	Moderate	Severe
Feeling sick				
Stomach cramps				
Muscle spasm/ twitching				
Feeling of coldness				
Heart pounding				
Muscle tension				
Aches and pains				
Yawning				
Runny eyes				
Insomnia/problems sleeping				
Diarrhoea				
Dysphoria				
Anxiety				
Agitation				
Irritability				
Craving for substances				

RESULTS

No significant differences were identified between patients assigned randomly to the two treatment groups with regard to basic demographic data, drug histories, including dose and route of opiate administration, and years of dependence.

Hereafter, the results are presented in three sections: firstly the data on the severity of the opiate withdrawal syndrome (SOWS) with either group 1 or 2. Secondly, the data on the severity of the mental symptoms induced by opiate withdrawal (items 12–16) and thirdly, the data on the severity of total symptoms including SOWS, mental symptoms and diarrhoea.

Short opiate withdrawal scale (physical symptoms)

The mean ± SEM scores of two groups of patients are shown in Fig. 1. There were no significant differences between two groups on day 0 (baseline) on the SOWS ($t = 0{\cdot}2366$, d.f. = 28, $P = 0{\cdot}8147$). A RM-ANOVA showed a significant effect for both treatments on the SOWS scores. In both groups, post-hoc comparisons of the baseline SOWS scores (day 0, when patients still took opiates) with the scores in day 14 by means of the Tukey procedure revealed significant differences from baseline. In other words, both protocols could alleviate the symptoms significantly by day 14.

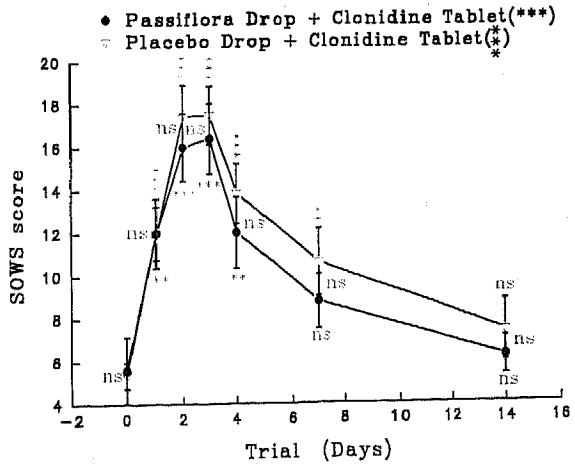

Fig. 1. Scores of two protocols on SOWS (mean ± SE). ns = non-significant.

Mental symptoms

The mean ± SEM scores for the two groups are shown in Fig. 2. There were no significant differences in baseline mental symptoms between the two treatment groups ($t = 0{\cdot}131$, d.f. = 28, $P = 0{\cdot}896$). A RM-ANOVA showed a significant effect with both treatments on the mental symptoms scores. Post-hoc testing revealed a significant reduction from baseline in the passiflora group from day 2, but not in the clonidine group. The mean mental scores for the clonidine group were significantly higher than for the passiflora group on days 2, 3, 4, 7 and 14.

Total scores

The mean ± SEM scores of two groups are shown in Fig. 3. No significant difference was observed in baseline total score ($t = 0{\cdot}212$, d.f. = 28, $P = 0{\cdot}833$). A RM-ANOVA showed a significant effect for both treatments on the total scores. The passiflora treatment alleviated the symptoms significantly from day 4. The means total score for the clonidine group was significantly higher than for the passiflora group on day 14 ($t = 2{\cdot}716$, d.f. = 28, $P = 0{\cdot}011$).

DISCUSSION

Non-opiate alternatives to opiate detoxification have been tried in an attempt to overcome some of the limitations of methadone-based detoxification regimens (20, 21). Clonidine is an α_2-adrenergic agonist, which ameliorates those withdrawal symptoms caused by noradrenergic overactivity (8, 9). The main disadvantage of clonidine-based detoxification, in addition to a hypotensive effect, is lack of efficacy for mental symptoms. As the mental symptoms of withdrawal can be very severe, the clonidine detoxification procedure is generally completed in approximately only 15% of outpatient cases (22–25). Benzodiazepines are not recommended, as they may induce dependence. There is increasing evidence that extracts of *Passiflora incarnata* have sedative-hypnotic and anxiolytic properties without inducing dependence (13–16). Therefore, we undertook a randomized controlled trial of this extract as a potential adjuvant agent to compensate for the lack of effect of clonidine on mental symptoms of opiate withdrawal.

The main overall findings from this study are (i) that both treatments reduce physical symptoms of acute opiate withdrawal syndrome but the passiflora-clonidine combination may have a more rapid onset of action, and (ii) that passiflora extract may be of therapeutic benefit in the management of mental symptoms of opiate withdrawal.

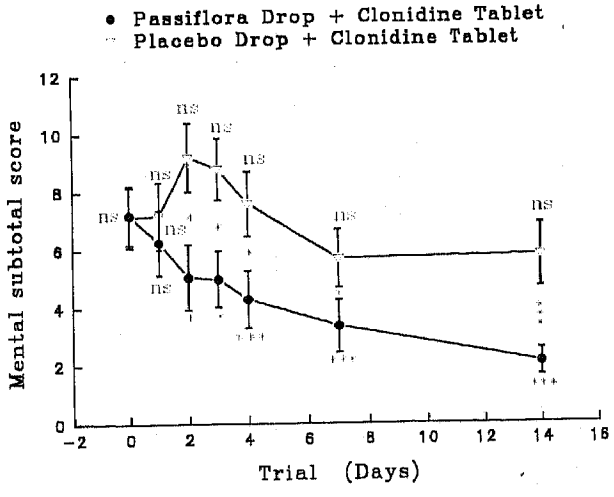

Fig. 2. Scores of two protocols on mental score (mean ± SE). ns = non-significant.

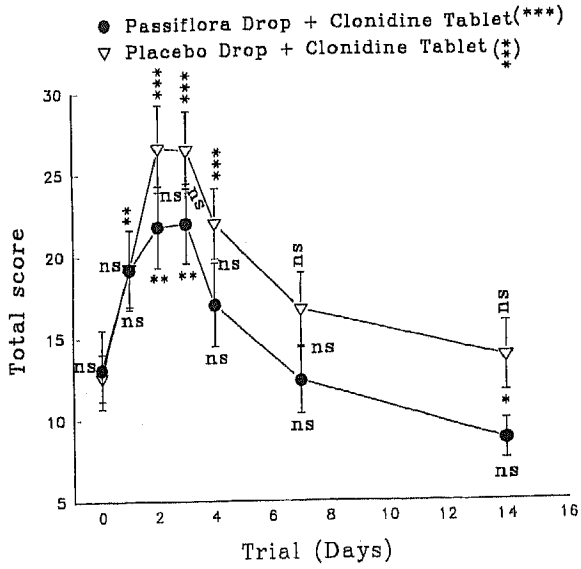

Fig. 3. Scores of two protocols on total score (mean ± SE). ns = non-significant.

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