Effect of Clonidine on Cigarette Cessation and in the Alleviation of Withdrawal Symptoms

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Summary
One hundred and eighteen cigarette smokers who wished to give up were randomly assigned to receive either clonidine (n=42), diazepam (n=38) or placebo (n=38) in a double-blind trial. All subjects also received at least three sessions of behavioural treatment. End of treatment abstinence rates for clonidine, diazepam and placebo groups were 69%, 40% and 40% respectively (p<0.01). At later follow-up, averaging 4.5 months from the end of treatment, abstinence rates were 57%, 37% and 37% respectively (NS). Compared with diazepam and placebo, clonidine received more positive ratings (p<0.005) and was more effective in relieving withdrawal symptoms (p<0.05). This report demonstrates that clonidine helps smokers to quit. The mechanism of action may involve decreased firing of α-2-noradrenergic cells in the locus coeruleus.

Introduction
National smoking statistics in China show an overall prevalence in adults of 33%. Smoking is much more common in males (68%) than in females (7%). There are not yet any reports on Chinese programs to stop smoking.

Many approaches have been tried in helping smokers to quit. They have targeted a multiplicity of different reasons for smoking but have met with only limited success. The conclusion has often been reached that, although treatment is better than no treatment, no single treatment has been shown to be more effective than simple support or attention placebo.

The reasons for failure to stop smoking include many factors. A major immediate obstacle facing treatments is believed to be withdrawal symptoms, which include craving for smoking, anxiety, irritability, restlessness, lack of concentration, tension, drowsiness, dizziness, drops in heart rate and blood pressure, gastrointestinal changes such as constipation, sleep disturbance, impaired performance, changes in the EEG and visual evoked potentials and an increase in aggressiveness. Glassman and co-workers reported that clonidine, an alpha-2-noradrenergic agonist, diminished withdrawal symptoms in a double-blind crossover study on the acute smoking withdrawal syndrome, and suggested that clonidine may have some clinical usefulness in helping heavy smokers to quit.

The present study was designed to test this possibility. Subjects wishing to give up smoking were offered clonidine, diazepam or placebo with randomized allocation to treatment. Three main aspects of smoking were targeted:

(i) Relieving or reducing the withdrawal syndrome after cessation in order to improve immediate results.

(ii) To help smokers cope with stressors experienced during the period of cessation in order to improve the long-term results.

(iii) To change the attitudes and cognitive style of smokers towards smoking in order to enhance motivation and quitting confidence.

The two drugs, clonidine and diazepam were used to resolve the first problem, while individual
treatment incorporating specific behavioural strategies was used to resolve the second and third problems.

Methods
Subjects
For inclusion in the study, subjects had to meet the following criteria:
(i) At least one pack (20 cigarettes) consumed per day.
(ii) Living in Changsha city (for convenience of treatment and follow-up).
(iii) No severe hypotension or heart, lung and kidney diseases.

One hundred and eighteen subjects (111 males and 7 females) were recruited between May and October 1986. They ranged in age from 18 to 80 years old with a mean of 45.5 years of age (SD = 13.7); the amount smoked was 20–60 cigarettes per day with a mean of 24.6 (SD = 7.9); the number of years smoked ranged from 2 to 65 years with a mean of 24.9 years (SD = 13.2). Eighty three subjects (78.5%) reported that they had at least once previously tried to quit smoking unsuccessfully, of whom 65 (58.9%) had tried twice, and 39 (36.4%) had tried three times or more. Most participants had some form of chronic disease related to smoking.

Drug Conditions
Clients were randomly assigned to one of three groups: clonidine (clonidine hydrochloride (Catapres) 0.075 mg/tablet), diazepam (Valium, 2.5 mg/tablet) and placebo. The trial design was double blind. The drugs were called ‘antismoking pills’ and participants were told that they had special effects on quitting smoking. The drug treatment lasted for 4 weeks, with a recommended dosage of one tablet three times a day. If participants felt a larger dose was needed, two tablets three times a day were also permitted (the exact dosage was not recorded, but most participants took one tablet three times a day). All the drugs were the same size, shape and colour. If there were severe hypotensive responses or other severe side effects, drug therapy was discontinued.

Procedures
Treatment lasted 2–3 weeks with every participant coming to the clinic at least three times (once a week) for individual treatment sessions with a psychiatrist lasting about 1 hour.

Two questionnaires were given to all participants to complete before treatment.
(a) Smoking habits and attitudes: The items included smoking rate (cigarettes/day), the number of years smoked, health status, reasons for stopping smoking, self-expectations of the program results, and attitudes to participants’ smoking held by their family members. All items were semi-structured.

(b) Russell’s Reasons for Smoking Questionnaire. Following Russell’s procedure, this was analysed to yield scores on seven smoking factors: psychological image; hand-mouth activity; indulgent; sedative; stimulant; addictive; and automatic. Scores on the last two factors were combined with responses to three further items (‘I get a definite craving to smoke when I have to stop for a while’; ‘I find it difficult to go as long as an hour without smoking’; ‘I would find it difficult to go without smoking for as long as a week’) to yield a total dependence score.

In the second and third sessions participants were asked to fill out the following questionnaires.
(i) Cessation Diary: The items included the number of days they had not been smoking or smoking rate now, reasons for failure to stop smoking and subjective appraisal of drug and behavioural treatments. All items were semi-structured.

(ii) Withdrawal Questionnaire: We divided distress after cessation into two dimensions, one psychological and the other physical. There were 10 items including craving for smoking, anxiety, irritability, poor concentration, fatigue, nausea, increased salivary secretion, palpatations, tremor, sleep disturbance and discomfort in the abdomen. Items were scored on 4 point scales from ‘not at all’ (‘0’) to ‘severe’ (‘3’).

This questionnaire was designed by the authors, referring to diagnostic criteria for nicotine withdrawal in DSM-III, the results of a pilot study and some other research. At follow-up every participant was asked to fill out the Cessation Diary again.

Details of Behavioural Treatment
1. Cognitive Treatment and Discussion. The single most important reason that people have for quitting smoking is concern over their health. The known effects on human beings of toxic substances in cigarettes and the relationship of cigarette
smoking to health were presented to participants in several forms. Written materials included a smoking monograph 'Smoking, Health and Cessation' and a pamphlet called 'Guidance on Quitting Smoking'. In addition pathological specimens of lung cancer and bronchitis were demonstrated and there were oral presentations by the therapist. Participants were encouraged to discuss and question the health aspects. The therapist also gave instructions on how to cope with stress and personal difficulties when not smoking. He reassured participants that withdrawal symptoms were temporary and most intense during the first week or two after quitting.

Cautela's covert sensitization technique was employed for participants to build up vivid imagery to resist the craving for cigarettes through imagining aversive stimuli such as cough, nausea, vomiting and lung cancer when he or she wanted to smoke.

2. Cigarette Fading, Record Keeping, and Stimulus Control. At the first session participants were asked to contract for a deadline for quitting smoking completely within 2–3 weeks. Prior to this quit date cigarette consumption was reduced gradually, with the total number being reduced further each day by omitting cigarettes at random times. Abrupt cessation of all cigarettes was not recommended. A key procedure in this program was having the clients keep a daily log of all cigarettes smoked that included times of day, the environmental circumstances, accompanying emotional states, etc. This allowed the subjects, with the aid of the therapist, to understand the context of their smoking and to identify a variety of options to quit. In addition, participants were asked to keep cigarettes in inaccessible places in home or workshop.

Clients who quit smoking completely by the second or third session were told that they should maintain their no-smoking state and should not smoke at any time, in any environment or situation.

All participants in the three groups received the same behavioural treatment.

Statistical analyses are based on two-tailed analysis of variance or $\chi^2$ analysis unless otherwise stated.

Results
Pre-test Characteristics of Subjects
Table 1 gives pre-treatment characteristics. There were no significant differences among the groups in age, sex, educational level, daily cigarette consumption, or number of years of smoking. There was a significant difference in dependence scores ($F=3.38$, $p<0.05$), but pairwise comparisons showed no significant differences between the clonidine and placebo group or between the clonidine and the diazepam group.

Treatment Outcomes
Eleven subjects, all male, dropped out before the end of treatment. Four of these were allocated to clonidine, four to diazepam and three to placebo. All of these subjects received only one session of treatment. These subjects have been classified as treatment failures in the analysis. Table 2 shows abstinence rates at the end of treatment. 69% of subjects in the clonidine group and 40% of subjects in the diazepam and placebo groups reported abstinence ($\chi^2=9.46$, $p<0.01$). At a mean of 4.5 months after discontinuing medication, 57% of subjects in the clonidine group and 37% of subjects in the diazepam and placebo groups reported that they had remained abstinent. The differences among the three groups were no longer statistically significant ($\chi^2=4.53$, $p=0.12$), although the percentage of abstainers in the clonidine group was higher than those in the diazepam and placebo groups.

Subjective Appraisal of Drug and Behavioural Treatments
At the end of treatment participants were asked to
Table 2. Abstinence Rates

<table>
<thead>
<tr>
<th></th>
<th>End-of-treatment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Abstainer</td>
<td>Non-abstainer</td>
<td>Abstainer</td>
</tr>
<tr>
<td>Clonidine</td>
<td>29</td>
<td>69.0</td>
<td>13</td>
</tr>
<tr>
<td>Diazepam</td>
<td>15</td>
<td>39.5</td>
<td>23</td>
</tr>
<tr>
<td>Placebo</td>
<td>15</td>
<td>39.5</td>
<td>23</td>
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χ² = 9.46, p<0.01

<table>
<thead>
<tr>
<th></th>
<th>Follow-up</th>
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<tbody>
<tr>
<td></td>
<td>Abstainer</td>
<td>Non-abstainer</td>
<td>Abstainer</td>
</tr>
<tr>
<td>Clonidine</td>
<td>24</td>
<td>57.1</td>
<td>18</td>
</tr>
<tr>
<td>Diazepam</td>
<td>14</td>
<td>36.8</td>
<td>24</td>
</tr>
<tr>
<td>Placebo</td>
<td>14</td>
<td>36.8</td>
<td>24</td>
</tr>
</tbody>
</table>

χ² = 4.53, p = 0.12

Note: Abstinence assessed on a continuous basis. Treatment dropouts counted as failures.

Table 3. Subjective Appraisal of Drug and Behavioural Treatments—Number (%) Giving Each Rating

<table>
<thead>
<tr>
<th>Drug treatment</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>26</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diazepam</td>
<td>10</td>
<td>11</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Placebo</td>
<td>13</td>
<td>12</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

χ² = 15.26, d.f. = 6, p<0.005

<table>
<thead>
<tr>
<th>Behavioural treatment</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>24</td>
<td>10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diazepam</td>
<td>17</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Placebo</td>
<td>19</td>
<td>11</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

χ² = 6.42, d.f. = 6, NS

Base: All subjects completing treatment.

rate the effects of the drug and behavioural treatments that they received. Response options were ‘good’, ‘fair’, ‘poor’ and ‘no effect’. Sixty-eight per cent of subjects in the clonidine group, 29% of subjects in the diazepam group and 37% of subjects in the placebo group rated the drugs ‘good’ (see Table 3). χ² analysis showed that the differences were statistically significant (χ² = 15.26, d.f. = 6, p<0.005). 63% of subjects receiving clonidine, 50% of subjects receiving diazepam and 54% of subjects receiving placebo considered the behavioural treatment ‘good’. χ² analysis failed to reveal any significant differences (χ² = 6.42, d.f. = 6, p > 0.5).

Scores on Withdrawal Questionnaire

The results from the Withdrawal Questionnaire are shown in Table 4. Subjects in the clonidine group reported significantly less severe withdrawal than those allocated to the other groups (F = 3.50, p<0.05).

Table 4. Scores on Withdrawal Questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>2.18</td>
<td>2.22</td>
</tr>
<tr>
<td>Diazepam</td>
<td>3.48</td>
<td>3.78</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.57</td>
<td>5.35</td>
</tr>
</tbody>
</table>

F = 3.50, p<0.05.

Base: All subjects completing treatment.

Side effects of Drugs

Clonidine produced the most frequent side effects, especially dizziness, dry mouth and sleepiness (Table 5). Two participants discontinued the drug because of severe fatigue, blurring of vision and abdominal discomfort. Mean systolic and diastolic blood pressure in the clonidine group were reduced 9.1 mmHg and 6.9 mmHg respectively at the end of treatment compared with baseline (one-tailed p<0.005 and <0.001 respectively).
Effect of Clonidine on Cigarette Cessation

### Table 5. Side Effects of Drugs: number reporting specified effects

<table>
<thead>
<tr>
<th></th>
<th>Clonidine (n=38)</th>
<th>Diazepam (n=34)</th>
<th>Placebo (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleepiness</td>
<td>9</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Base: All subjects completing treatment*

The blood pressures of one client dropped from 130/80 to 100/60 mmHg. His dosage of clonidine was 0.675 mg/day. After stopping the drug his blood pressure was restored to baseline levels in 3 days. No participant's blood pressure was reduced below the normal range.

The main side effects of diazepam were sleepiness and dizziness, but only one participant (80 years old) had to discontinue the drug because of dizziness and incoordination. Diazepam had no effect on blood pressure.

Two clients who took placebo complained of dizziness and sleepiness that they attributed to their medication. One of them discontinued the placebo because he could not tolerate the side effects.

### Discussion

This study demonstrates three helpful effects of clonidine on smokers trying to quit smoking: (i) a higher end of treatment abstinence rate by comparison with the diazepam and placebo groups (ii) less severe withdrawal symptoms (iii) more favourable subjective appraisal than that given to diazepam and placebo.

Clonidine is a major central antihypertensive agent, and a demonstrated noradrenergic agonist. The use of clonidine as an anti-withdrawal drug resulted from the studies by Gold and his colleagues. These investigators hypothesized that clonidine would suppress opiate withdrawal by acting on brain regions such as the locus coeruleus. They reported that clonidine (5 μg/kg) given orally suppressed opioid withdrawal signs. In subsequent studies these investigators demonstrated the clinical utility of clonidine in opioid withdrawal. Extensive data have now accumulated from both experimental animals and man confirming the assertion that this diminished withdrawal behaviour is related to diminished noradrenergic activity. A double blind experiment done by Bjorkqvist showed that clonidine also seemed to suppress symptoms of alcohol withdrawal. A recent paper by Glassman et al. reporting similar research to the present concluded that clonidine is effective as an aid in short-term smoking cessation. Success rates at the end of treatment were 64% in the clonidine group and 29% in those allocated to placebo (p<0.01). Rather surprisingly they failed to demonstrate an effect of clonidine on male smokers. Our study, in which 95% of subjects were male, clearly shows a clonidine effect on male smokers.

Most of the participants were heavy, long-term smokers, with 78.5% of subjects quitting smoking previously, but failing to maintain non-smoking status although they had high motivation. One of the major reasons was that they could not tolerate the withdrawal syndrome. Clonidine helps smokers whose withdrawal symptoms are very severe, as shown by the results of this study. It may also have some value in studying the mechanisms of nicotine dependence.

Diazepam is used extensively as a major anti-anxiety agent. In the present study it was anticipated that it might reduce anxiety in the period of withdrawal from tobacco. This goal was not achieved and only 29% of subjects said diazepam was 'good'. Withdrawal scores and the abstinence rate in the diazepam group were similar to those in the placebo group, so there was no specific effect on relieving the withdrawal syndrome.

It is interesting that one-third of participants said that the placebo was 'good'. The mechanism is unclear, but may be related to behavioural treatment and to the placebo itself. Recently, an experiment showed that the effect of placebo in relieving pain was secondary to increasing the level of enkephalins in the brain. This suggests that any effect of the placebo on suppressing withdrawal symptoms may also be through increasing the level of enkephalins.

The role of behavioural treatment was important in this study as well as the effects of clonidine. Cognitive factors may be important in maintaining smoking behaviour. For example, smokers may not
personally believe in the danger of smoking, or they may view themselves as permanently addicted and incapable of change, or they may feel that they have no control over their health. Finally, smokers may conduct a cost-benefit analysis and conclude that the benefits obtained from smoking outweigh the costs. This study attempted to increase motivation for quitting through discussion, viewing specimens, communication, consultation and so on. However, since we included no behavioural controls, we cannot say whether the behavioural treatment had any specific effect on quitting or to what extent it may have helped prevent relapse.

Researchers agree that great attention needs to be devoted to maintenance of non-smoking following initial cessation. In our study we made arrangements for continued contact through phone calls, a visit or letter, which provided opportunities for timely reinforcement, additional counselling and support.

One limitation of this study was failure to obtain validation of the verbal reports of smoking status by use of biological measurement. Participants were told repeatedly that they should accurately report the amount smoked. Other ways were also employed to validate what participants had reported, for example, to phone a co-worker or to visit their families.

We conclude that clonidine given orally is effective both in reducing withdrawal symptoms and in promoting short-term smoking cessation.

References
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