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Yuzhuo Wang

MSc Thesis

2004

**A study on the efficacy and tolerability of
Chinese traditional medicine using herbal
patches in smoking cessation**

University of Durham



21 JUN 2005

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Abstract

Cigarette smoking is a major public health issue in both developed and developing countries. There is estimated to be over a billion smokers in the world today, with almost one third of them living in China. In China, during the mid-1990s there were between 500,000 – 700,000 annual tobacco-related deaths. This predicted number of deaths could rise to nearly three million people a year by 2050. Many smokers in China want to quit, but Nicotine Replacement Therapy (NRT) is expensive in the East as the standard of living in China is a great deal lower than that in the West. The treatment costs more and the duration is about 4-6 weeks. Zhong Mai Yan Ke (Joymain Nicofree) – a Chinese herbal preparation for smoking cessation was produced in 1997 in China. It is claimed that Zhong Mai Yan Ke is effective but the claim has not been verified. In this study, the effectiveness of Zhong Mai Yan Ke was tested.

Research Design

Method: Open Randomised Controlled Trial (RCT). **Sample:** 64 volunteers were recruited based on a set of inclusion and exclusion criteria. 50 and 14 volunteers were allocated randomly to the treatment group and the control group. **Intervention:** Zhong Mai Yan Ke was given to the treatment group whereas the control group was given a placebo. **Location:** Dalian city in China. **Results:** 49 in the treatment group and 14 in the control group completed the study. The initial results at the end of the 9-day treatment were 51.0% (n=25) managed to stop smoking; 34.7% (n=17) managed to reduce smoking consumption and 14.3% (n=7) failed to quit smoking. None (100%) in the control group managed to stop or reduce smoking consumption. Only few people in the treatment group suffered from side effects, such as nausea and dizziness. The follow-up results 3 months after the treatment were 43% (21 out of the 25 quitters) managed to be ex-smokers; 38.8% (n=19) managed to reduce smoking consumption and 18.4% (n=9) failed to quit smoking. None (100%) in the control group managed to stop or reduce smoking consumption. No one suffered from any side effects 3 months after the trial.

Conclusion

Zhong Mai Yan Ke is an effective agent for smoking cessation. The findings of the present study suggest that Zhong Mai Yan Ke could be effective non-nicotine based herbal medicine for smoking cessation for worldwide use subject to further validation by other researchers.

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Chapter 1

Introduction

Many of my friends are smokers. Although they are young people, it has been shown that cigarette smoking is harmful to them, associated with cough, restlessness and insomnia. Their habits have affected other people too. For example, if they smoke in public places such as the classroom or the dormitory the air is contaminated. Many of them wanted to quit but found it is too difficult to give up smoking. That is why I have carried out research related to smoking cessation.

Epidemiologically, if there is an effective way of helping smokers to quit, especially in developing countries such as China, wider benefit for these countries could be achieved. For example, it has been shown that in smokers, health can improve after giving up the habit. It is hoped, therefore, in the longer term the mortality rate will reduce and people will live longer and healthier. As a result, poorer countries with large numbers of smokers will benefit economically from reduced health care costs and improvement in work productivity.

Health consequences of smoking

Cigarette smoking is a major public health issue in both developed and developing countries. Smoking causes more deaths than alcohol, microbial agents, toxic agents, firearms, high-risk sexual behaviour, and motor vehicle injuries combined (McGinnis & Foege, 1993). Smoking is a known detriment to health. The use of tobacco is

documented to increase the risk of heart disease, stroke, other vascular diseases, a variety of cancers and chronic obstructive pulmonary disease (USDHHS, 1990). Smoking during pregnancy substantially increases the risk of spontaneous abortion, prematurity, low birth weight, and perinatal mortality (Benowitz, 1991).

Tobacco is the single most important avoidable cause of chronic ill health and premature death in developed countries, where it now causes a quarter of all the deaths in middle age with maximum mortality among males and rising mortality among females. In developing countries many men now smoke, and mortality from tobacco is increasing. Worldwide, if current smoking patterns persist, it has been predicted that smoking related deaths will increase from three million in the early 1990s (which is 10% of all adult deaths) to ten million by the late 2020s (World Health Organization, 1996).

In China, lung cancer and other smoking related diseases are the most common causes of death. There were between 500,000 - 700,000 annual tobacco-related deaths during the mid-1990s (<http://www.cdc.gov/tobacco/who/china.htm>) which is equivalent to 10,000 people dying every week (<http://www.hhs.se/eijs/anomaly/CSsmoking.htm>). The mortality among males is higher than that in females in China. Dr. Yang of Chinese Academy of Preventive Medicine (<http://www.ctsu.ox.ac.uk/tobacco/chmed.htm>) said: "Men in China smoke far more cigarettes than they used to, but, surprisingly, women in the cities of China show the opposite pattern from men. Before 1950, 10% of young women became smokers, but for unknown reasons this plummeted: now only 1% do. However, there is still a danger of a large increase." In 1998, 12% of all adult male and 3% of all adult female deaths were caused by smoking. In the West, smoking causes a high number of heart-related deaths, but in China, the majority of deaths are due to respiratory diseases (<http://news.bbc.co.uk/1/hi/health/216998.stm>). Professor Liu from Chinese Academy of Medical Sciences (<http://www.ctsu.ox.ac.uk/tobacco/chmed.htm>) said: "about 45% of China's smoking deaths are from chronic lung disease, 15% from lung cancer and 5-8% from a combination of oesophagus cancer, stomach cancer, liver cancer, stroke, heart disease and surprisingly, tuberculosis." Although smoking causes more deaths from chronic lung diseases than from lung cancer, the reverse of what happens in the West, the death from lung cancer caused by smoking is still showing a rising trend.

For example, the rates of adult deaths per 100,000 from lung cancer were reported as 56.8 for males and 23.5 for females in 1995 compared to 49.3 and 20.6 in 1985-89 in China (<http://www.cdc.gov/tobacco/who/china.htm>). The contributory factor to the rising number of tobacco related deaths is thought to be caused by smokers not being convinced of the health risks associated with cigarette smoking. Surveys showed two-thirds of people in China think smoking does little or no harm, 60 % think it does not cause lung cancer and 96% do not know that it causes heart disease (<http://news.bbc.co.uk/1/hi/health/216998.stm>). If current smoking patterns persist, it is predicted there will be two million tobacco-related deaths by 2025 (<http://www.cdc.gov/tobacco/who/china.htm>). By 2050, researchers expect this number could rise to 8000 a day which is equivalent to some three million people a year (<http://news.bbc.co.uk/1/hi/health/216998.stm>).

Internationally, the increasing prevalence of smoking in third world countries and in Eastern Europe is expected to give rise to increasing numbers of deaths worldwide in the early decades of this century. It is difficult to give precise figures but, if current smoking patterns persist, the current estimate of three million deaths annually in the world as a whole is likely to rise to 10 million a year in about 30 years' time (Peto et al, 1994).

Smoking is the leading preventable cause of death in the United States (USDHHS, 1990). Nearly half a million Americans die annually as a result of smoking: 400,000 from the direct effects of smoking (Centres for Disease Control and Prevention, 1993) and 50,000 from second hand smoke (Houston et al, 1994). Smoking-related illnesses account for about 20% of all deaths in the United States. It has been estimated that on average, of one thousand 20 year olds in the United States who smoke cigarettes regularly, about six will die from homicide, about 12 from motor vehicle accidents, about 250 will be killed by smoking in middle age and another 250 in old age (Peto et al, 1994).

Smoking is the single greatest cause of preventable illness and premature death in the UK. Smoking kills over 120,000 people in the UK a year – more than 13 people an hour. Smoking causes 46,500 deaths from cancer a year in the UK – three out of ten cancer deaths. Smoking causes 84% of deaths from lung cancer, and 83% of deaths

from chronic obstructive lung disease, including bronchitis. Smoking causes one out of every seven deaths from heart disease – 40,300 deaths a year in the UK from all circulatory diseases (Callum, 1998). Cigarettes were responsible for about 1.2 million deaths in the European Region of the World Health Organisation in 1995, almost three quarters of a million of which occurred in middle age i.e. 35-69 years (Peto et al, 1994).

Passive smoking, or second-hand smoking, which can be defined as non-smokers breathing in other people's tobacco smoke, also kills. Exposure to environmental tobacco smoke is a cause of lung cancer. For example, several hundred people a year in the UK are estimated to die from lung cancer brought about by passive smoking (Hackshaw et al, 1997). It has been suggested that passive smoking almost certainly contributes to deaths from heart disease – an even bigger killer than lung cancer (Law et al, 1997). In the USA, about 50,000 die from second hand smoke annually (Houston et al, 1994). In China, there are now about 450 million passive smokers (<http://www.usembassy-china.org.cn/english/sandt/smoking.htm>).

In addition, smoking in the presence of infants and children is a cause of serious respiratory illness and asthmatic attacks. Sudden infant death syndrome, the main cause of post-neonatal death in the first year of life, has been claimed to be associated with exposure to environmental tobacco smoke. The association is judged to be one of cause and effect (The Stationary Office, 1998).

The problems of smoking worldwide

1. The prevalence of smoking in China

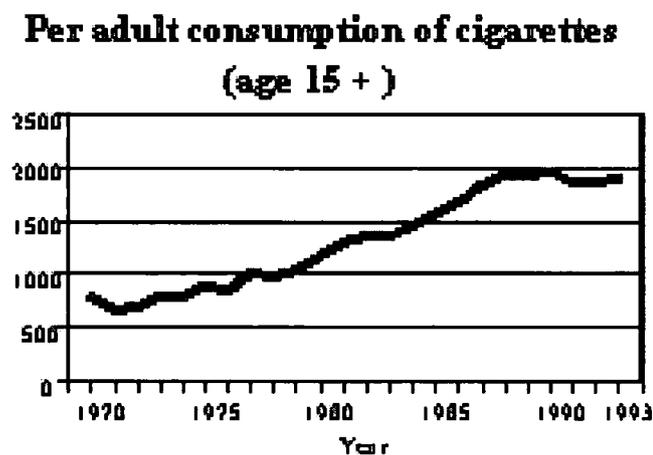
There is estimated to be over a billion smokers in the world today. There are 1,270,000,000 people in China in 2000 representing 20 % of the world's population and they consume 30% of the world's cigarettes

(<http://www.hcc.hawaii.edu/~pine/phil110/chinasmoking.htm>). In 1995, 61% of men but only 7% of women smoked

(<http://www.usembassy-china.org.cn/english/sandt/smoking.htm>). In the year 2000 there were 350,000,000 smokers in China which constitutes about 1/3 of the total Chinese population, accounting for about 1/4 of the total smoking population in the world (<http://www.chinatoday.com/data/data.htm#Hel>).

The incidence of smoking is on the increase as is the consumption of cigarettes. For example, the number of cigarettes consumed per adult each year in China rose from 700 in 1970 to 2000 in 1990/1992 (almost all of which are smoked by men) (Doll, 1996). Tobacco is increasingly consumed in the form of manufactured cigarettes (<http://www.cdc.gov/tobacco/who/china.htm>). This is shown in Figure 1.1.

Figure 1.1 Consumption of Manufactured Cigarettes in China



It was reported in 1984 that smokers in China smoke on average 16 cigarettes per day and that the average age of first smoking in China is 25 years old. A more recent report indicates that people start smoking three years younger than previously reported (<http://www.chinatoday.com/data/data.htm#Hel>).

2. The prevalence of smoking in other countries

Internationally, there are around 13 million adult smokers in the UK (The Stationary Office, 1998). Smoking peaked in the 1950s and 1960s, and fell steadily in the 1970s and 1980s (Wald et al, 1988). But the long downward trend in smoking may be levelling out. Adult smoking rates rose in 1996, the last full year for which figures are

available, for the first time since 1972. We may be seeing the beginning of a new upward trend in smoking. Among people aged 16 and over, the smoking rate of 28% in England was the same as in 1992 and was up on the 1994 rate of 26% (Thomas et al, 1998). The adult smoking rate is particularly high in Scotland and Wales at 32% (Thomas et al, 1998; Health in Wales Survey, 1996). In Northern Ireland it is 29% (Northern Ireland Statistics and Research Agency, 1997).

Smoking in third world countries is increasing. For example, the US Centres for Disease Control and Prevention show smoking has risen in sub-Saharan Africa where cheap brands are available and tobacco companies are using intensive advertising and marketing campaigns, sponsorship of events and cigarette price wars (The Stationary Office, 1998).

The picture for teenagers smoking is much worse. For example, in the UK, the percentage of regular smokers aged 11-15 was reported to be 13% in 1984. Between 1984 and 1994, the percentage reported dropped as low as 8%, but rose again in 1994 to 12% (HMSO, 1997; HMSO, 1992; HMSO, 1995; Health Education Board for Scotland, 1994). It was reported in 1996 that the prevalence of young people smoking had risen again to 13% (Jarvis, 1997; Barton & Jarvis, 1997). Recent records also show that 17,000,000 cigarettes are smoked every week in the UK by children of 11-15 years of age (Cheung & Woof, 2001). In the USA, there are 3,000 new smokers every day so the quantity of smokers increases by 1,000,000 every year. In France, the rate of smoking has reduced since 1977, but young people aged from 12 to 18 who smoke is still 35%. Although the rate of young people smoking remains 18%-19% in Australia and Canada, it has increased to 50% in some cities (Specialized Information, 1997). In China, in the year 2000, about 50 million smokers were teenagers (<http://www.chinatoday.com/data/data.htm#Hel>).

Economic costs of smoking

The cost of smoking is high in terms of people's health. But the cost of smoking is high in other ways too. The health consequences of cigarette smoking carry an enormous economic burden.

In China, a pack of 20 local cigarettes costs between US \$0.20 to US \$4.20, although most are cheaper than the imported cigarettes which cost about US\$ 2.00 in 1990. It was estimated that 20 cigarettes cost 25% of average daily income, up from 10-14% in 1987 (<http://www.cdc.gov/tobacco/who/china.htm>).

In the UK, treating illness and disease caused by smoking is estimated to cost the NHS up to £1.7 billion every year (Buck et al, 1997). It costs families, especially the poorest, a great deal too. It is estimated that, in 1996, there were approximately one million lone parents on Income Support, of whom 55% smoked an average of five packs of cigarettes a week at a cost of £2.50 per pack (Dorset & Marsh, 1998). That means lone parent families spent £375 million on cigarettes during that year (The Stationary Office, 1998)

In the USA, a conservative analysis estimated that the direct medical care costs attributable to smoking in 1993 reached nearly \$50 billion (Centre for Disease Control and Prevention, 1994b). These estimates do not include other direct medical costs, such as treatment for burns resulting from smoking-related fires, perinatal care for low-birth weight infants of mothers who smoke, and costs associated with diseases caused by exposure to environmental tobacco smoke. In addition to the direct medical costs, there are indirect non-medical costs resulting from smoking-related morbidity and premature mortality, such as lost productivity, missed work, and higher healthcare coverage costs for businesses (Lesmes, 1992). In 1990, the value of lost productivity resulting from premature deaths of smokers and former smokers was estimated to be \$40.3 billion. The indirect cost of morbidity (resulting from work loss and bed-disability days, for example) was estimated to be \$6.9 billion (Centre for Disease Control and Prevention, 1994b). Combined, the direct medical and indirect non-medical costs associated with smoking-related morbidity and mortality approach \$100 billion annually.

Evidence supports the assertion that cigarette smoking is a global public health problem. It affects both active and passive smokers. In spite of the increased attention given to health education warning people about the risks associated with cigarette smoking, the warnings are unheeded by smokers and intending smokers, particularly young people.

One of the problems of cigarette smoking is the effect on productivity in the developed countries and in the developing world. Cigarette smokers are absent from work about 6.5 days more per year than non-smokers. They average six more visits to healthcare facilities each year than non-smokers, and their dependents make about four more visits per year than non-smokers. Furthermore, smokers may be less productive on the job. In workplaces where people leave their stations to go to designated areas in order to smoke, smokers spend 8% or more of their time involved in smoking-related activities (Lesmes, 1992). Particularly, cigarette smoking will impact on the economic development of developing countries where many working adults who are smokers will die earlier than expected. It can be deduced demographically that countries where the population is denser will be more affected. China is the biggest developing country and the number of deaths caused by smoking will be greater than that in the UK, America and in other developed countries.

The other problem is that smokers find it difficult to give up the habit once the addiction has been established. Approximately 70% of cigarette smokers' report that they want to quit (Centre for Disease Control and Prevention, 1994a) and every year more than one third of smokers make at least one attempt to quit (Hatziandreu et al, 1990). Less than 10% of smokers who attempt to quit are successful each year (Centre for Disease Control and Prevention, 1994c). Although about half of all people who have ever smoked cigarettes have now stopped, (Centre for Disease Control and Prevention, 1994a), most attempted to quit several times before succeeding (Arnsten, 1996).

Currently, many approaches have been developed to help people stop smoking. Routine advice by family doctors, encouragement, and psychological approaches have been tried in developed countries. Nicotine replacement therapy, NRT products, combined pharmacological and psychological treatment has been introduced too. However, methods available to help smokers to quit are not completely effective. For example, nicotine replacement products are said to be effective but these products have shown to produce side effects and some side effects are serious. For example, 57 deaths are claimed in relation to Zyban, a centrally acting anti-smoking medication. (<http://uk.news.yahoo.com/020117/80/cpnrf.html>). New research should be

encouraged in smoking cessation using different approaches and other products which are not previously known through research and publications.

Traditional Chinese Medicine (TCM), including acupuncture and Chinese herbal preparations, have been used in the Far East and are claimed to have been successful in helping smokers to quit. Herbal preparations have been used in China for thousands of years. Recently, a Chinese herbal patch "Zhong Mai Yan Ke" based on the theories of herbs and meridians and collaterals was introduced for smoking cessation. The product has been readily commercially available in herbal shops in China and is commonly used. It has been judged safe for public use. It has been claimed that it has helped one million smokers to give up the habit after one (9 days) or two (18 days) courses of treatment. However, such claims cannot be substantiated as there has been no systematic investigation.

The purpose of this open label therapeutic trial is to establish the extent of the effect of Zhong Mai Yan Ke as an effective smoking cessation agent and to ascertain any side effects from the product. In addition, this study is to confirm the acceptability of the use of placebo in a commercial and specific culture setting in China. The following hypotheses will be tested:

- (1) Zhong Mai Yan Ke is an effective agent achieving a 30% quitting rate at the end of a 9-day treatment
- (2) Zhong Mai Yan Ke is effective in the long term achieving a 20% quitting rate three months after the trial
- (3) There are no serious side effects associated with the use of Zhong Mai Yan Ke
- (4) It is feasible to organise an open label randomised controlled trial in a commercial, and specific cultural setting in China.

This thesis is organised into five chapters. Chapter two is the literature review. It presents the main reasons for difficulty in quitting smoking – nicotine addiction. It also evaluates the effectiveness of smoking cessation approaches; especially Nicotine Replacement Treatment (NRT) products. The role of Traditional Chinese Medicine (TCM) including acupuncture and an approved herbal preparation Zhong Mai Yan Ke in particular is introduced.

Chapter three provides a background description of the area in which the trial took place and presents the aims pursued and the methodology used in this project. The reasons why the method was selected and explanation of the advantages and disadvantages are given.

Chapter four presents the findings of the trial.

Chapter five discusses the possibility of integrating allopathic medicine with Traditional Chinese Medicine (TCM) for smoking cessation and presents a critical analysis of the methodology, a summary of the results and their interpretation and suggestions for further research in this field.

Chapter 2

A Review of the Literature

2.1. Introduction

Many smokers want to kick the habit but it is very difficult for them to give up unaided because of the pharmacological effects of the nicotine. One of the problems often experienced by smokers while trying to give up cigarettes is the desire to smoke on a regular basis caused by fluctuating plasma nicotine level and the associated symptoms of craving (Cheung & Childs, 1996). Ex-smokers have found that craving can be overcome by various distractions or goals, direct activities such as exercise and hobbies (CHS, 1996). Self determination or will power is considered more important than anything else.

Other researchers recognised that giving up smoking is a process and not a simple decision to give up suddenly. There are various stages of behaviour change associated with smoking cessation (Prochaska & Di Clement, 1992). Prochaska's theory postulates that smokers go through various stages of behaviour change, i.e. from pre-contemplation to contemplation, preparation, action and maintenance. Researchers in this field of work appear to apply Prochaska's theory in their work, but, the theory appears to contradict practical experience of many ex-smokers (CHS, 1996)

This thesis focuses on active interventions which are claimed to have helped smokers to successfully relinquish their habit. This chapter will begin with a brief review of

the hazards associated with cigarette smoking, and then proceed to review the following topics:

- The methods used in countries where smoking cessation has been integrated in primary health care, in particular, where pharmaceutical products have been prescribed for smokers.
- Other non-nicotine based products
- The methods used by Traditional Chinese Medicine practitioners

2.2. Hazards of cigarette smoking

Cigarette smoke contains in excess of 4000 substances. The components most often linked to adverse effects are nicotine, tar and carbon monoxide (Table 2.1) (Quit, 1994).

Table 2.1 The contents of tobacco smoke

Tar
A mixture of over 1,000 chemicals, including a variety of irritants and at least 60 known carcinogens
Nicotine
It is an addictive element. It is absorbed very rapidly from the lungs into the bloodstream, and reaches the brain after about seven seconds. Through its actions on the autonomic nerves, nicotine raises heart rate and blood pressure.
Carbon monoxide
Also found in car exhaust fumes, it displaces oxygen from haemoglobin, causing a reduction in the oxygen carrying capacity of the blood. This is particularly important in pregnant women and those with vascular disease.
Other chemicals
Hydrogen cyanide, benzene, ammonia and formaldehyde are all present in small quantities.

2.2.1 The effects of smoking

The use of tobacco is documented to increase the risk of heart disease, stroke, other vascular diseases, a variety of cancers, and chronic obstructive pulmonary disease (USDHHS, 1990). According to the US Surgeon General, the younger children start smoking, the younger they are likely to die from cancer (USDHHS, 1982).

Smoking in pregnancy causes adverse outcomes, notably miscarriage, reduced birth weight for gestation and perinatal death. Where parents continue to smoke after pregnancy there is an increased rate of sudden infant death syndrome (The Stationary Office, 1998). Of particular concern is the effect on children of smokers, either smoking mothers or non-smoking mothers with smoking partners. Smoking can cause problems, such as increased foetal and neonatal mortality, low birth weight, delayed physical and mental development of children and respiratory illness in infants and young children (Taylor, 1992).

Smoking in the presence of infants and children is a cause of serious respiratory illness and asthmatic attacks. Sudden infant death syndrome, the main cause of post-neonatal death in the first year of life, is associated with exposure to environmental tobacco smoke. The association is judged to be one of cause and effect (Quit, 1994).

Particularly, studies of teenagers have shown that pharmacological factors become important very early in the smoking career. By the time daily smoking is established, within only a few months of starting, children take in as much nicotine per cigarette as do dependent adult smokers (McNeil & Jarvis, 1989). Children as young as 14-15 years report experiencing nicotine withdrawal effects, and perceive that stopping smoking will be hard to achieve successfully (McNeil, 1991). These observations confirm the US Food and Drug Administration's view of cigarette smoking as a "paediatric disease" (Kersler et al, 1997).

Non-smokers can be harmed by smoking as well. Non-smokers involuntarily inhale tobacco smoke when in the presence of people who are smoking. The smoke breathed

in by non-smokers is 85% side stream and 15% exhaled mainstream smoke. This smoke contains more than 4000 chemicals and at least 40 known carcinogens as well as nicotine. Many toxic constituents are found in higher concentrations in side stream than in mainstream smoke. Non-smokers continue to inhale smoke even when the cigarette is extinguished because smoke can persist in internal environments for many hours, depending on ventilation and mixing of room air with uncontaminated air. Smoking affects the smoker's family, friends and work colleagues, plus people encountered in public places. These people are at risk of the same diseases as the smoker. For example, risk of death from heart disease is about 30% higher amongst non-smokers exposed to smoke in the home. This figure is probably higher for people exposed in the workplace (Taylor, 1992).

2.2.2 The benefit of quitting smoking

The main benefit of quitting smoking is improved smokers' health. Quitting smoking can reduce or even put an end to long-time diseases, such as heart disease, stroke and lung cancer (Specialized Information, 1997).

Short and long term effects of ceasing to smoke:

- 20 minutes: Blood pressure and pulse rate return to normal. Circulation improves in hands and feet, making them warm.
- 8 hours: Oxygen level in the blood returns to normal. Chances of a heart attack start to fall
- 24 hours: Carbon monoxide is eliminated from the body. The lungs start to clear out mucous and other debris.
- 48 hours: Nicotine is no longer detectable in the body. The ability to taste and smell is improved.
- 72 hours: Breathing becomes easier as the bronchial tubes relax. Energy levels increase.
- 2-12 weeks: Circulation improves throughout the body, making walking easier.
- 3-9 months: Breathing problems such as cough, shortness of breath, and wheezing improve. Overall, lung function is increased by 5-10%.

- 5 years: Risk of a heart attack falls to about half that of a smoker.
- 10 years: Risk of lung cancer falls to about half of that found in a smoker. Risk of a heart attack falls to about the same as someone who has never smoked.

2.2.3 Problems of quitting

Although approximately 70% of cigarette smokers report that they want to quit (Centre for Disease Control and Prevention, 1994a), it is very difficult to give up the habit due to the pharmacological effects of nicotine on the central nervous system.

1. Long-term side effects

Although the long-term side effects have been confirmed, it is difficult for smokers to appreciate that they are in danger of the possibility of chronic diseases which have not yet appeared. When a person is smoking, some physiological changes occur, such as increasing heart rate, rising blood pressure and other problems such as oral ulcers, cough in the morning, increase in the reflux of gastric acid, periodontal disease, increasing levels of nervous mood or worry, impotence and sterility, aggravation of asthma and skin conditions (Zhang, 2000). However these changes happen gradually so that smokers do not pay attention to them and cannot make a decision to quit at once.

2. Addiction to nicotine – the main reason of quitting unsuccessfully

The Surgeon General of the Department of Health and Human Sciences of the US Government claim that the central element amongst all forms of drug addiction is that the user's behaviour is largely controlled by a substance that produces transient mood changes where the brain acts as the mediator. Secondly, the drug is sufficiently rewarding to warrant repeated administration; for example, smokers recognise the relief from stress that can be gained from continuing smoking. Thirdly, once the tolerance to the drug is established, a given dose of drug produces less effect, so that increased doses or increased frequency of usage are required to maintain the intensity of effect. Finally, there is impulsive use: those smokers feel the urge to smoke, despite

the potential risk of damage to themselves or society (USDHHS, 1988).

Nicotine is the drug in tobacco that causes addiction, and the pharmacological and behavioural processes that determine tobacco addiction are similar to those that determine addiction to heroin and other addictive drugs. For example, once the smoking habit is established, the need to smoke to maintain a required level of physical and mental alertness is controlled by the half-life (the speed at which a chemical becomes disintegrated) of nicotine. Nicotine has a half-life between two and four hours, depending on the metabolic rates of individuals. The need to smoke is completely dependent on the level of plasma nicotine present in the circulation. This dependency can be explained by the effects of the nicotine regulatory model (Knapp et al, 1963; Lucchesi et al, 1967). Initially, nicotine produces the desired pharmacological effects such as alertness, muscular relaxation, and so forth, which are effectively termed the initial affective reaction. At the same time, these “positive” effects bring about the “slave-type” negative effects, the hedonic effects, in the sense that the body needs the cigarette to produce the positive effects. Both the positive and negative effects are constantly reinforcing each other. As the smoking experience continues, the negative effects take on a more dominant role, in that the habit of smoking is driven by internal and external cues such as fluctuating plasma nicotine levels and hostile environments, for example environments or tasks that smokers see as being burdensome or unpleasant, which further reinforce the negative effects. Consequently, there is an urge to smoke regularly (Cheung & Woof, 2001).

Further research conducted during the past decade shows that the mesolimbic dopamine system, which is involved though the neurobiology of nicotine addiction is not completely understood (Nisell et al, 1995). Dopamine appears to play an important role in the physiologic mechanism for the experience of “pleasure”. This system is commonly described as the "reward pathway." All known drugs of abuse, including nicotine, stimulate increases in dopamine along this pathway (Leshner, 1996).

The withdrawal pathway is believed to arise from the locus ceruleus and to involve norepinephrine (Leshner, 1996). This pathway presumably mediates pathophysiologic symptoms such as the cravings, irritability, and difficulty concentrating that characterizes withdrawal from an addictive substance.

Normally, dopamine-containing vesicles release dopamine into the synapses. Dopamine then is either quickly absorbed or broken down by the enzyme monoamine oxidase B (MAO-B). Nicotine increases the amount of dopamine within the synapses by stimulating the release of dopamine, while another substance in cigarette smoke (which remains to be identified) blocks the action of MAO-B (Leshner, 1996).

According to the latest research in the biology of addiction, the drug-addicted brain is qualitatively different from the non-addicted brain. First, the long-term effects of nicotine and other addictive drugs on the brain include a persistent decrease in glucose metabolism and intraneuronal changes in gene expression. There also appear to be persistent alterations in the brain's responsiveness to environmental cues, which can induce drug craving and drug-seeking behaviour (Leshner, 1996).

Even though nicotine alters the brain's systems, it is important to keep in mind that nicotine addiction is more than just a neurological disease. Addiction occurs in a particular set of environmental, historical, and physiologic contexts that affect the way drug use interacts with the brain (Leshner, 1997). Therefore, effective treatment of nicotine addiction requires simultaneous targeting of biological and behavioural aspects of the disorder (Leshner, 1996; Leshner, 1997).

2.3 Effective smoking cessation approaches in the world

Although most smokers want to quit, they experience well-recognised barriers and withdrawal symptoms during their attempts to quit, and they are largely unsuccessful in quitting. Social movement and all kinds of medicine or therapies for quitting smoking, i.e. Nicotine Replacement Therapy (NRT), non-nicotine drugs, acupuncture and herbal medicine, were tried to help smokers to quit in Western and Eastern countries.

2.3.1 Social and health education

There have been anti-tobacco laws in the majority of Western countries for at least 20 years. These laws have been introduced gradually and include restrictions on direct advertising, minimum age requirements for purchase, and explicit warning labelling requirements. It is generally believed that these laws are responsible for the decline in smoking in the West (<http://www.hhs.se/eijs/anomaly/CSmoking.htm>).

In the United Kingdom, smoking cessation has tended to focus on brief interventions which can be delivered by mass media or by non-specialists to a large number of smokers, e.g. National No Smoking Day, quit lines, nicotine replacement products available from pharmacists and brief advice from health professionals. Though these may encourage large numbers to quit, most smokers (97%) do not succeed in quitting long-term after an unaided quit attempt. The relapse rate is very high (Foulds & Ghodse, 1995).

Norway, Finland and Iceland all introduced advertising bans back in the 1970s which were followed by large reductions in smoking rates or tobacco consumption (Joosens, 1997). The Canadian government handed out manuals between 1992 and 1995 to help adolescents quit smoking (Zhang & Ma, 1999).

Cambodia produced 10,000 anti-tobacco stickers and broadcast anti-tobacco messages on television On World No-Tobacco Day in 1993. The Minister and Vice-Minister of Health made personal commitments to the *Tobacco or Health* message. During the celebration of World No-Tobacco Day 1994, amidst extensive media coverage, the Minister of Health requested the Council of Ministers to ban tobacco advertising in public places (<http://www.cdc.gov/tobacco/who/china.htm>).

China introduced its first anti-tobacco law at the beginning of 1992. The law contains four health clauses which include: reduction of tar and printing of tar levels and a health warning on cigarette packs; bans/control of smoking on public transport and in public places; bans on smoking by elementary and high school students; bans on tobacco advertising on TV, radio, and in newspapers and magazines. Increased health

education on the dangers of smoking is also required by law. Subsequently, China has banned advertising in other media, such as billboards, television 'infomercials', and sponsorship of sports, arts, and music. In 1995, a national Advertisement Law extended the advertising ban to waiting rooms, cinemas and theatres, meeting rooms, sports stadium, etc. (<http://www.cdc.gov/tobacco/who/china.htm>). Even more recently, in 1996, further regulations were introduced banning smoking in hospitals, schools, museums, shops, and other public places. It can be seen that China is approximately 15-20 years behind the West in regards to widespread awareness and official smoking regulations (<http://www.hhs.se/eijs/anomaly/CSmoking.htm>).

The Chinese government strengthened the protection for non-smokers. Smoking was banned in many public places, and in some workplaces (usually because of fire hazard). Since 1949, the government has carried out a policy that smoking was asked being banned on public transport vehicles in all big cities from the start of the communist regime. Anyone who smokes on public transport vehicles would be fined. Smoking was asked being banned on subways, and in 1986, no-smoking sections were introduced on trains. All domestic flights have been totally smoke-free since 1983 and since 1995, all flights became smoke-free. Smoking is banned in Ministry of Public Health premises, and is partially banned in hospitals and health facilities (<http://www.cdc.gov/tobacco/who/china.htm>).

Health education is improved constantly. The first recommendation by doctors for action against tobacco was in 1979, and health information campaigns commenced in the 1980s. The first "No-smoking Day" was held in 1987, and since 1988 WHO's World No-Tobacco Day has been celebrated nationally every year; it is reported that cigarettes are not sold throughout China on that day. The Rural Farmers Quitting Project organized by the National Health Education Institute, is a smoking cessation program targeting illiterate, rural farmers (<http://www.cdc.gov/tobacco/who/china.htm>). Other developments indicating a move away from cigarette acceptance include Chinese participation in international 'Quit and Win' contests - In 1996 China had the largest number of contestants in this contest (15,000 out of 66,000) (<http://www.hhs.se/eijs/anomaly/CSmoking.htm>).

2.3.2 Advantages and disadvantages of smoking cessation approaches used in Western countries

1. Advice and encouragement

The results of the review (Law & Tang, 1995) show that simple, brief, unsolicited advice from a general practitioner (GP) is effective in increasing rates of smoking cessation. An estimated 2% of smokers, given advice by their GPs, stopped smoking and did not relapse up to one year as a direct consequence of such advice. The Cochran Collaboration review confirmed the effectiveness of GP smoking cessation advice (Silagy et al, 1997). This form of intervention is extremely cost effective. Additional interventions, supplementary to simple advice, such as follow up letters and visits, show mixed results.

Advice and encouragement to stop smoking are known to be more effective in some groups, particularly high risk groups such as pregnant women and patients who have ischaemic heart disease or who have recently had a heart attack. There is no available evidence on interventions in sufferers from asthma or in others at times of stress, such as prospective fathers or people awaiting elective surgery under general anaesthesia (The Stationary Office, 1998).

2. Nicotine Replacement Therapy (NRT)

It is claimed that Nicotine Replacement Therapy (NRT) approximately doubles the rate of smoking cessation from simple advice from GPs or more intensive clinic interventions (Silagy et al, 1997). These products replace some of the nicotine that smokers used to get from smoking. Nicotine replacement is used to wean smokers off nicotine by replacing the very high concentrations of nicotine obtained from cigarette smoking with much lower doses delivered more slowly. It is a means of delivering nicotine without the harmful tar, gases and other elements of smoking. NRT reduces the cravings for cigarettes and the withdrawal symptoms associated with quitting.

NRT is the most thoroughly researched method and tests have shown that, used correctly, it will double the chance of success. Nicotine replacement therapy appears to benefit those smokers who tend to light up within 30 minutes of waking (<http://www.quit.org.uk>).

Some authorities advocate a harm reduction approach and suggest that nicotine replacement products could be given to heavily dependent smokers on a long term basis to reduce exposure to toxins and reduce morbidity and mortality (Russell, 1991; Warner et al, 1997). The justification for this approach is not that nicotine itself is harm free, but that in a pure form it is much less harmful than smoking (Russell, 1974). There is a persuasive analogy which likens the cigarette to a dirty drug syringe and points to the potential benefits of a clean delivery system. Since smoking related diseases show clear evidence of dose and duration response, even partial and temporary reductions in total smoke exposure are likely to lower risk. On present evidence, nicotine from currently available pharmaceutical preparations does not pose a major threat to health (Benowitz & Gourlay, 1997). Nevertheless, there is an obvious need to study the effects of the long term use of NRT by persistent smokers and to establish the relationship between smoking reduction and reduced incidence of disease.

Because the adverse effects of smoking in pregnancy are well known, many women stop smoking before or during pregnancy and active programmes to encourage and assist smoking cessation can achieve further cessation. Unfortunately some of the heaviest smokers continue to smoke. Nicotine replacement therapy has not been evaluated in pregnancy because nicotine probably contributes to the deficit in birth weight in the babies of cigarette smokers (Olsen, 1992). However a review of the pharmacology of cigarette smoking and NRT has concluded that NRT results in lower plasma cotinine levels than heavy cigarette smoking, except during sleep (Benowitz, 1991). The American Agency for health care Policy and Research (AHCPR) has suggested that NRT should be offered in pregnancy to heavy smokers. This is currently not advocated in the UK, but a research evaluation of such a programme should be undertaken (USDHHS, 1996).

Nicotine replacement products that are FDA-approved include nicotine gum,

transdermal nicotine patches (TNPs), nicotine nasal spray, and nicotine inhaler (<http://www.musc.edu/psychiatry/slater/smoke1.htm>). However, NRT is best viewed as a treatment adjunct rather than as a complete treatment in itself. It will not help smokers who lack motivation to stop (<http://www.quit.org>).

2.1 Nicotine Gum

In 1984 nicotine gum, Nicorette, became available in the United States as a prescription only medication. A box of 48 pieces costs approximately \$30.00. In order to benefit from the gum, patients must use at least ten pieces of the gum per day. Patients who smoke fewer than 15 cigarettes per day should use the 2 mg dose while the 4 mg dose should be reserved for those who smoke more. The gum should be chewed slowly until a "peppery" taste appears in the mouth, and then "parked" between the gum and the cheek until the taste fades. Intermittent chewing and "parking" should continue for 30 minutes (<http://www.musc.edu/psychiatry/slater/smoke1.htm>).

One of the disadvantages of the gum includes the special chewing techniques required as smokers might inadvertently forget. Smokers will also need to use the gum frequently. Adverse effects from the gum include jaw fatigue and soreness as well as gastrointestinal upset such as gaseous distension, hiccups, and nausea (Henningfield, 1995). The gum is contraindicated for patients with gastric ulcers and is difficult for patients with dentures to use. Perhaps secondary to its demanding use requirements, nicotine gum has been shown to be more effective when used in specialised clinics than when used in general medicine practices. In a meta-analysis of randomized controlled trials, the success rates in specialised cessation clinics were significantly higher with nicotine gum than with placebo gum at 6 months (27% vs 18%) and 12 months (23% vs 13%) (Capeda, 1993). In contrast, success rates in general medical practices were no different with the gum and placebo (12%) at 6 months (Lam et al, 1987). Higher quit rates in specialised smoking cessation clinics may be a result of more in-depth counselling, better trained counsellors, and possibly smokers with higher motivation to quit (<http://www.musc.edu/psychiatry/slater/smoke1.htm>).

2.2 Transdermal Nicotine Patches (TNPs)

Three major brands of TNPs are Habitrol, Nicoderm CQ and Nicotrol. Patch brands differ in the rate control mechanisms, starting dose and weaning regimen. Patches are sold in 1-2 week boxes at a cost of approximately \$30 per week, and initial therapy of some of the products include a cassette tape and a self-help booklet. The Habitrol and Nicoderm CQ patches are available as 21 mg, 14 mg and 7 mg for 6-8 week, 2-4 week duration. The overall regimen for using these two patch brands is consistent: after approximately 1-2 months; patients switch to progressively lower dose patches until they are effectively weaned off the patch. Patients who smoke at least ten cigarettes per day can begin with the highest dose patch. The Nicotrol patch is a single dose patch of 15 mg and is intended for daytime use only as a 16-hour patch (i.e. it should be removed before going to sleep). Treatment is recommended for 6 weeks (<http://www.musc.edu/psychiatry/slater/smoke1.htm>).

Continuous controlled release of nicotine through a TNP resolves some of the problems associated with nicotine gum such as difficulty with use and side effects. Also, the potential for addiction to the medication is much lower by daily self-administration of nicotine replacement with the patch than hourly replacement with the gum (Benowitz, 1988). A number of studies have shown the success of the TNP under controlled and real-world settings (Ahluwalia et al, 1998; Orleans et al, 1994; Silagy et al, 1994). The efficiency of the nicotine patch is reported to be about 20-30% at six months.

It is claimed that the main side effects of nicotine patches are itching or redness of the skin and this can be lessened by varying the position of the patch when users put a new one on. Some people who use the patch develop a mild skin rash on their body where the patch is placed.

2.3 Nicotine Nasal Sprays

Nicotine nasal spray (Nicotrol nasal spray) is a relatively new product approved by FDA in 1996 for nicotine replacement delivery system. The spray is available only by prescription. It is designed to deliver nicotine more rapidly than the gum or patch, but less rapidly than smoking cigarettes (Schneider et al, 1996a). Users tend to self-administer in order to produce plasma nicotine concentrations that are approximately 50% of those achieved by smoking (Sutherland et al, 1992). The rapid delivery and relatively high plasma concentrations make the nasal spray more suitable for treating withdrawal symptoms and especially beneficial to highly dependent smokers.

In a randomized controlled study, 32% of patients using the spray as prescribed were able to abstain from smoking 6 months after treatment, compared to 12% on the placebo. The rates at one year after quit dates were 26% and 10% for active and placebo sprays respectively. These findings suggest that the nicotine nasal spray is helpful in aiding smoking cessation.

The spray frequently irritates smokers' nose and throat for the first few days. The nasal spray may cause sneezing and a running nose (Quit, 1994).

2.4 Nicotine Inhaler

In 1998, the nicotine inhaler (Nicotrol Inhaler) became available as a prescription drug for smoking cessation. It consists of a mouthpiece and a plastic cartridge designed to deliver 4 mg nicotine from a porous plug containing 10 mg nicotine. Most of the nicotine released from the inhaler is absorbed in the mouth, with less than 5% reaching the lower respiratory tract (Bergstorm et al, 1995). The nicotine inhaler also mimics the hand-to-mouth routine similar to cigarette smoking. It may therefore reduce the problems associated with abrupt cessation of the hand-to-mouth ritual.

In a randomized controlled trial, individuals on active inhalers had continuous abstinence rates of 29% and 24% compared to 14% and 10% on placebo at 6 weeks and 3 months post-quit date respectively (Schneider et al, 1996b). Other studies have reported similar findings (Leischow et al, 1996). The side effect is irritation of throat and mouth when people first start to use the inhaler. It might make the user cough.

In summary, the patch gives smokers a continual supply of nicotine at a low dose while smokers are wearing it - so smokers can't respond quickly to a craving or a stressful moment. The gum and the spray deliver a higher dose quickly so smokers can respond to a craving with a "quick fix", as with cigarettes. If smokers smoke steadily through the day, the patch may suit them better. If smokers smoke mainly in response to cravings or stress, the gum or spray might be more flexible for them. One study has compared the effectiveness of gum, patch, spray and inhalator and found that they were similarly effective (Quit, 1994).

3 Non-nicotine drugs

3.1 ZYBAN (bupropion hydrochloride SR)

A number of non-nicotine products have been tested for smoking cessation, but only one has been approved by the FDA. Initially developed and marketed as an antidepressant under the trade name Wellbutrin, the sustained-release form was approved in 1997 as an aid for smoking cessation under a new trade name, Zyban. Bupropion is an alternative for smokers who either cannot tolerate nicotine replacement therapy or prefer non-nicotine treatment. In a randomized controlled trial (Hurt et al, 1997), 27% of patients who received the active drug were able to abstain from smoking 6 months after treatment compared to 16% of patients on placebo. Two months are needed to complete the treatment.

Zyban is a non-nicotine treatment to help smokers who are motivated to quit. Zyban works in the brain to help break the addiction to nicotine and differs from nicotine replacement therapies in that it does not substitute one source of nicotine with another. Zyban reduces the cravings for cigarettes and the withdrawal symptoms associated with quitting. Zyban comes in tablet form; it is taken as a two month treatment course. The most common side effects are difficulty sleeping, dry mouth

and headache. These are usually mild and generally disappear within the first few weeks (<http://www.quit.org>). However, fifty-seven people have died after taking the anti-smoking drug Zyban (<http://uk.news.yahoo.com/020117/80/cpnrf.html>).

3.2 Other non-nicotine drugs

There are many other non-nicotine drugs. There is not enough good scientific evidence to say how effective they are. One has to be wary of claims of very high success rates (<http://www.quit.org>).

a) Name of Capsules

Contains menthyl valerate, quinine, camphor and eucalyptus oil aimed at improving breathing and controlling withdrawal symptoms. The manufacturers recommend 1-2 per day for 28 days. There is no evidence of their long-term efficacy, but they are not thought to be harmful. Because of the herbal contents, pregnant women should not use them.

b) Dummy cigarettes

A plastic look-a-like that lasts between 1-3 months provides the hand-to-mouth stimulation of smoking. They do not help with the physical withdrawal symptoms. They are of no proven benefit, but they are not shown to be harmful. It has been reported by ex-smokers as a means of working off symptoms of cigarettes (CHS, 1996).

c) Herbal cigarettes

Again these provide the activity of smoking without the nicotine, so they do not help with withdrawal symptoms. They still contain tar and poisonous carbon monoxide gas which are found in ordinary cigarettes and which cause considerable damage to health. The idea is that they claim to eliminate nicotine from the body whilst not challenging the behaviour of smoking. There is no proven evidence that these herbal cigarettes are effective.

d) Filters

Filters are designed to remove some of the tar and nicotine before the smoke is inhaled. Filters are attached to the end of an ordinary cigarette. Smokers tend

to compensate for the drop in nicotine by puffing longer and drawing harder or even covering up the filter to stop it working. They are meant to help smokers to adjust to less nicotine - but as with cutting down they have not been shown to work.

e) Mouthwash

Mouthwash is supposed to work by making cigarettes taste unpleasant. The product recommends you gargle with it for about 15 seconds whenever smokers feel a strong desire to smoke. It affects the taste of cigarettes for three to four hours, but it also adversely affects the taste of food for about half an hour. The product is not clinically proven.

4. Combination drug therapy

Although all the pharmaceutical products discussed above have been recommended for use as stand alone as single treatment, combination of treatments may be appropriate for smokers who are unable to quit with monotherapy.

4.1 Combined use of Nicotine Replacement Products

Given its acute delivery and, therefore, usefulness for acute cravings, some physicians began prescribing gum in conjunction with the TNPs. A review of four studies which documented statistical significance (Fagerstrom, 1994), concluded that for heavy smokers, combined use of 5-7 pieces per day of gum with the 16 or 24 hour TNP significantly reduced withdrawal symptoms and increases initial cessation rates more than use of either produce alone. Side effects were not significantly increased by combined use of nicotine patch and gum. A recent study (Blondal et al, 1999) also reported higher quit rates when the patch was combined with the nasal spray than with the patch alone (15% vs 35% at 6 weeks, 37% vs 25% at 3 months for the combination and patch only respectively). Combined treatments should be considered for smokers with significant craving or withdrawal symptoms despite adequate doses of single agents.

4.2 Combined use of Transdermal Nicotine Patch and Bupropion

A recent randomized controlled study compared bupropion and nicotine patch against treatment using both agents. The study concluded that abstinence rates were significantly higher in the subjects using bupropion and nicotine patch than the subjects using the patch alone. However, the difference in abstinence rates between the combined treatment and bupropion alone was not statistically significant (Jorenby et al, 1999).

5. Diet and exercises therapy

Both diet and exercise have an important effect on the smokers' body. Stopping smoking is a major change for the body to adapt to, and a healthy diet and regular exercise suitable to level of fitness, may help the body to cope with withdrawal and boost sense of self-confidence and well-being. There is now some evidence that regular light exercise can help people to stop smoking. For example, keeping busy to help take the mind off cigarettes, drinking plenty of fluids, getting more active – walking instead of using the bus or car, changing routines. There is also a tendency for smokers either during the process of quitting or immediately after quitting, to compensate smoking by nibbling. Therefore, there is a danger for them to put on weight. Diet and exercises are also important to counteract adverse effects of giving up smoking (Quit, 1994).

2.3.3 Traditional Chinese Medicine (TCM) to smoking cessation

Traditional Chinese Medicine (TCM) has been used since the 8th century B.C. TCM can be used for promoting health as well as preventing and curing diseases. The theory behind TCM is that the body is a dynamic energy system. There are two types of energy – Yin and Yang. Yin represents the earth, cold, and femininity and Yang represents the sky, heat and masculinity. The interaction between Yin and Yang gives

rise to energy called “qi” which is transported throughout the body via meridians and collaterals. It is thought if there is an imbalance in Yin and Yang then symptoms occur. TCM uses a number of treatment methods to restore the balance of Yin and Yang; these include herbal medicine, acupuncture, moxibustion, manual therapies, exercise, breathing techniques and diets. Surgery is rarely used. TCM, particularly the theory of meridians and collaterals is the most widely used traditional medicine.

The meridians and collaterals are the pathways that carry qi, blood and body fluid and they can connect all parts of the human body. All the internal organs, apertures, skin, tendons, muscles, bones, hair and other tissues in the body are connected through the meridians and collaterals. Most meridians and collaterals have certain running routes. In physiology, the meridians and collaterals, qi, blood and body fluid are distributed around the body to play the roles of nourishing all parts of the human body. The functional activities of the meridians and collaterals are presented as the reactions and transmissions of them. In pathology, the external pathogens invade the human body from the body surface to the internal organs through the meridians and collaterals; while the dysfunction of the internal organs can affect the relative parts of the body through the meridians and collaterals. For example, in the case of cardiac pain, the pain may radiate to the ulnar side of the arm. Furthermore, diseases of the internal organs may also be reflected on certain parts of the body surface with tenderness, nodules, prominences, depression, congestion, etc. The reactions are often helpful in the diagnosis of the internal organ diseases. The therapies of acupuncture, moxibustion, massage, Qigong and some herbal medicine are all based on the theory of meridians and collaterals. They are practised in every region in the world.

Additionally, there are certain acupoints along the meridians and collaterals. Acupoints are the specific sites in the skin where qi comes in and goes out from the body surface. They are related to the internal organs closely through meridians and collaterals. Acupoints can not only reflect the physical and pathological changes of the internal organs, but also receive various stimulations, such as herbal medicine, acupuncture, moxibustion massage, etc. It can regulate the functions of the internal organs and make Yin and Yang balanced in the human body for preventing and treating diseases when stimulating acupoints.

TCM has been used for thousands of years in the Far East, including acupuncture and herbal medicine (Cheung & Woof, 1994). Tobacco use has developed gradually in the past, one hundred years ago. There is relatively little evidence to demonstrate the effectiveness of TCM on smoking cessation. However, anecdotally, many people report that they found these treatments helpful. Up to now, it has been the most common method used to treat nicotine addiction, based on the theories of meridians and collaterals and herbal medicine.

In 1981, a new acupoint for smoking cessation “Tim Mee” (Appendix A) was discovered by American Doctor James S. Olms, and was used to stop cessation successfully (Tan, 1996). Where is it exactly? Tim Mee acupoint is located in the wrists of both hands. Along a horizontal line along the edge of the styloid process of radius and the side of short extensor muscle tendon of thumb close to the palm, as a vertical line. The intersection point of the two lines is Tim Mee acupoint (<http://www.zhongmai.com>).

James S. Olms reported he treated 5000 nicotine addicts by giving Tim Mee acupoints an acupuncture therapeutic method in 1981. He inserted the filiform needles into the Tim Mee acupoints of both hands accurately, leaving the needles in the acupoints for 15 minutes. The general rate of effectiveness was 80%. In 1984, he reported he treated 2282 nicotine addicts by stimulating Tim Mee acupoint using a laser. The total rate of success was more than 90% (Tan, 1996).

Ren X. (Ren, 1993) treated 61 nicotine addicts through needling Tim Mee acupoint with filiform needles. Firstly, he needled Tim Mee acupoints, and then the needles were connected with electric-needle apparatus. Thirdly, the needles remained in the acupoint for 30 minutes. The treatment was carried out once a day or every other day, a course of treatment 3 times. 55.74% of smokers quit smoking 6 months after the treatment. 18.03% of smokers managed to reduce smoking per day to less than 2/3 of the previous amount, 6 months after the treatment.

Yang H.O. (Zhou, 1997) treated 51 smokers by needling the Tim Mee acupoints. He needled the Tim Mee acupoints of both hands, the needles remained in the acupoints for 10 minutes per day, a course of treatment from 2 to 4 times. The rate of quitting

smoking was 98.04% at the end of the treatment.

Xia M. (Zhou, 1997) treated 51 smokers by needling the Tim Mee acupoints. Tim Mee acupoints of both hands were stimulated strongly with filiform needles. 16 (31.4%) smokers quit smoking completely; 20 (39.2%) managed to reduce their smoking to less than the previous amount and 15 (29.4%) failed to quit at the end of the treatment.

Xu J. (Xu, 1997) worked in the Department of the Orient Medicine in Bastyr Medicine Institute and Freedom Acupuncture Clinic from July 1994 to May 1997. He treated 51 nicotine addicts by needling the Tim Mee acupoints, mainly. The treatment achieved “satisfied” therapeutic effectiveness. 17 males and 34 females aged from 19 to 55 joined the study. Their years of smoking experiences were 1-40 years and the average smoking experience was 8.3 years. The Tim Mee acupoints of both hands were needled first, and then the needles remained in the acupoints for 25 minutes. The treatment was carried out every other day, a course of six treatments. 66.67% of smokers quit smoking and 17.65% managed to reduce smoking per day less than 2/3 of the previous amount 6 months after the treatment.

Peng X. (Peng, 1984) treated 126 nicotine addicts using “skin applied plaster instead of acupuncture”. There were two herbal ingredients - Clovers and Cassis - in the plaster. He applied the plasters on the skin where Tim Mee acupoints of both hands were located. The plasters were applied for 24 hours. Patients smoked one cigarette after applying the plasters for 15 minutes. It was found that 65.1% of smokers at the taste of smoking became pale, dizzy and nauseous. The rate of total effectiveness was 88.9%.

Tim Mee (Zhou, 1997) is an effective acupoint for smoking cessation. It is the most sensitive point of human body when someone is addicted to smoking, and is the effective acupoint to be stimulated to stop smoking. Many doctors found the taste sensation of smokers changed when they smoked again after the Tim Mee acupoints were stimulated. They thought this kind of change was based on some substance in the human body which had changed. Many scholars thought the reason for smoking addiction was that “internal opium” was restrained to excrete, a lack of this after

“external opium” was absorbed by the body, caused dependency for “external opium” substances, such as nicotine. The production of “internal opium” in the brain after stimulating Tim Mee acupoints, reduced the dependency for “external opium” substances.

More recently, a number of prepared herbal medicines for smoking cessation were launched, based on the theories of TCM on meridians and collaterals and herbal medicine, such as Zhong Mai Yan Ke. This herbal preparation conquered the disadvantages of acupuncture treatment. It utilizes various Chinese herbs and biological magneto-therapy, acts on Tim Mee acupoint on the wrists of both hands, reportedly stimulates taste, sense and nerve system of the human body and changes the smell of cigarette smoking, so as to encourage smoking cessation. Zhong Mai Yan Ke contains the following main active ingredients:

- (1) **Cloves:** It contains clove oil whose primary material is clove-phenol. This is a fragrant pharmaceutical which can be used particularly for alleviating abdominal discomfort and vomiting, regulating digestion and promoting appetite. Clove-phenol in Zhong Mai Yan Ke can reportedly influence the function of stomach and intestines and improve constipation often caused by long-term smoking. Additionally, clove-phenol can influence to inhibit cramps caused by tobacco-alkali during the course of quitting smoking.
- (2) **Cassia:** Cassia contains cassia bark oil and cassia bark aldehyde which is found in fragrant elements in them. Cassia bark aldehyde can stimulate natural endorphins within the brain to relieve irritation and reduce cramps caused by strong tobacco-alkali. It has been commented that the absorption for cassia bark aldehyde can prolong the time of patches’ adherence. Cassia bark aldehyde in Zhong Mai Yan Ke ensures that the active ingredients reach meridians and collaterals completely through Tim Mee acupoint where Zhong Mai Yan Ke applies. Cassia in Zhong Mai Yan Ke can improve the harmful effects caused by tobacco-related toxins and plays a role to substitute acupuncture treatment.

(3) **Areca:** Areca contains areca alkali, nutmeg and areca oil. Areca can regulate the function of central nervous system through improving the functions of stomach, intestines, lungs and bronchus, expanding blood vessels and stimulating N-choline receptors, skeletal muscle and neuromere. It can stimulate the brain to produce endorphins to reduce pain and irritability caused by nicotine withdrawal during the course of quitting smoking. Present research indicates that smokers' tobacco cravings are interrelated to the stimulation for endorphin central nervous system. Thus Areca in Zhong Mai Yan Ke can influence the brain to produce endorphin to adapt the physiological uncomfortable feeling caused by quitting smoking. Furthermore, it also stimulates the central nervous system to promote easier relief from symptoms caused by tobacco withdrawal. Reports indicate that areca-alkali and areca-tannin can suppress the desire for tobacco and restore appetite at the same time.

(4) **Magnetic disc:** From the perspective of biological polarity, the human body is a charged entity and capable of electric conduction. Different organs and tissues have different electrical activity. The functions of organs and tissues can be affected when an external magnetic field acts upon the human body continuously. The theory behind the use of magnetic discs is that magnetism produced by a low magnetic field is sufficient to adjust people's desire. The magnetic disc (approx. 400 gauss) in Zhong Mai Yan Ke is combined with herbal ointments which act upon Tim Mee acupoint simultaneously to strengthen the transmission function of meridians and collaterals so that drug ions within the herbal ointment are absorbed easier and pass through the skin more rapidly, thus the active ingredients in the medicine are more effective.

It is claimed that the rate of effectiveness (quitting completely and reducing cigarettes per day) of Zhong Mai Yan Ke for smoking cessation is 85% and has no serious side effects. However, there is no feasibility study to prove that herbal preparations are efficacious. It is necessary to ascertain the extent of the effect of Zhong Mai Yan Ke (<http://zhongmai.com>).

2.4 Summary

Nicotine addiction is the main problem preventing smokers from quitting successfully. Many smoking cessation approaches have been tried in the world. Social and health education, advice and encouragement and some products, especially Nicotine Replacement Therapy (NRT), are used widely in the West. Traditional Chinese Medicine, particularly acupuncture has been used to treat smoking cessation in China and other countries because a new acupoint - Tim Mee - for smoking cessation was found in recent years. The therapeutic effect of needling Tim Mee acupoint is effective, but it is not stable because it is limited by the acupuncture techniques. Moreover, it is not a hugely convenient approach. In the last few years, it has been claimed that Zhong Mai Yan Ke, a Chinese herbal preparation for smoking cessation has achieved good therapeutic effect in China. However, it is necessary to ascertain the true extent of the effect of Zhong Mai Yan Ke through research.

Chapter 3

Aims and Methodology

3.1 Introduction

New research should be encouraged in smoking cessation using different approaches and other products which are not previously known through research and publications. A herbal preparation “Zhong Mai Yan Ke (Joymain Nicofree)” which was invented according to the theories of Traditional Chinese Medicine (TCM) was introduced for smoking cessation and it has been claimed by the manufacturer that the effective rate of Zhong Mai Yan Ke on smoking cessation is 85% after 9 days or 18 days of treatment (<http://zhongmai.com>). However, such a claim cannot be substantiated as there has been no systematic investigation of the substance used.

My chief aspiration was to attempt to determine the extent of the effect of nine days application of Zhong Mai Yan Ke and the effect at three months. Zhong Mai Yan Ke is a commonly used, commercially easily available product in China and over one million smokers in China have purchased the product. Like many other herbal remedies in China, its effect has never been formally evaluated, even though it has been available widely in public for a long time. If the product is shown to be effective to help smokers to quit, it could help many smokers throughout the world. As a preliminary it is necessary to do a therapeutic trial for detailed research on Zhong Mai Yan Ke.

The study had the following objectives:

(1) To ascertain the effect of Zhong Mai Yan Ke through an open randomised trial in a pragmatic setting in China at the end of a 9 day trial, based on whether at least 30% of the smokers in the treatment group would be able to reduce the number of cigarettes smoked per day, (b) at least 20% will be able to give up the habit completely and if at the 9-day trial (c) 3 months, at least 20% of the smokers in the treatment group would be able to reduce the number of cigarettes smoked per day and at least 10% would be able to give up the habit completely.

(2) If smokers in the treatment group experienced effects as indicated by the manufacturer of Zhong Mai Yan Ke.

(3) To ascertain the feasibility of organising an open label randomised controlled trial and confirming the acceptability of the use of placebo in the cultural and commercial setting of China.

3.2 Research approach: Randomised controlled trials

The most appropriate approach for evaluating pharmacological intervention is the application of methodology used for experimental studies. Most experimental studies use randomised controlled design because the intention of the research is to influence events and ascertain the effects of the treatment. Randomised controlled trials are widely used in medical research. The aim of the randomised control design is to ensure that differences between individuals, other than the method of treatment, being evaluated are distributed evenly by chance between two groups. Such an application was considered suitable to evaluate the treatment effects produced by Zhong Mai Yan Ke as a smoking cessation agent, but there were a number of constraints to this.

Randomisation also serves the important purpose of allocating treatments to patients free from the researcher's biases. It also provides a basis for the application of

significant tests likely to be used to assure treatment effects.

(<http://www.bmjpg.com/rct/chapter1.html>)

Typically, RCTs seek to measure and compare events (outcomes) that are present or absent after the participants receive the interventions. As the outcomes are quantified (or measured), RCTs are regarded as quantitative studies. RCTs are referred to as randomised controlled trials because one of the interventions is regarded as a standard of comparison or control. The control can be conventional practice, a placebo, or no intervention at all. RCTs are experiments because the investigators can influence the number and the type of interventions, as well as the regimen (amount, route and frequency) with which the interventions are applied to the participants.

(<http://www.bmjpg.com/rct/chapter1.html>).

In summary, RCTs are quantitative, comparative, controlled experiments in which a group of investigators who design the study, administer the interventions, assess the results and analyse them. The studies involve two or more interventions in a series of individuals who receive them in random order.

(<http://www.bmjpg.com/rct/chapter1.html>).

3.3 Open randomised controlled trial

Randomised clinical trials (RCTs) can be used to evaluate different types of interventions in different populations of participants, in different settings, and for different purposes. Once investigators ensure that allocation of participants to the study groups is random, they can design the study using strategies to match the characteristics of the interventions they want to study, the resources they have available, and their academic, political, marketing, or clinical motivations.

(<http://www.bmjpg.com/rct/chapter1.html>).

“There is empirical evidence confirming that the effects of new interventions can be exaggerated if the randomisation sequence is not concealed from the investigators at the time of obtaining consent from prospective trial participants (Chalmers et al, 1983;

Schulz, 1995). One study showed that trials with inadequate allocation concealment can exaggerate the effects of interventions by as much as 40% on average (Schulz, 1995).” (<http://www.bmj.com/rct/chapter3.html>). That means allocation concealment helps to prevent selection bias and protects the randomisation sequence before and until the interventions are given to study participants.

In a RCT, random allocation is an important part that could influence the outcome of the experiment. Random allocation means that all participants have the same chance of being assigned to each of the study groups (Altman, 1991). Random allocation of the participants to different study groups increases the potential of a study to be free of bias (<http://www.bmj.com/rct/chapter3.html>). Therefore, allocation is not determined by the investigators, the clinicians, or the study participants.

By allocating the participants randomly, the characteristics of the participants are likely to be similar across groups at the start of the comparison (also called the baseline). By keeping the groups as similar as possible at the start of the study, the investigators will be more able to isolate and quantify the impact of the interventions that they are studying, with minimal effects from other factors that could influence the course of the study participants. The factors that could influence the outcomes of a study, which are not related directly to the interventions, could be known or unknown. (<http://www.bmj.com/rct/chapter1.html>).

The generation of random sequences of allocation can be achieved using one of a variety of procedures, such as flipping a coin or rolling a dice, using number tables or a computer. The trial used the method of drawing out randomly.

Sometimes investigators feel it is not necessary to make the number of participants in each of the study groups the same and can decide to allocate unequal numbers to each group, when they are preserving the homogeneity of the distribution of the characteristics of the participants across the study groups. This is called unequal randomisation (<http://www.bmj.com/rct/chapter1.html>) or “weighted randomisation”. The trial in this study used unequal randomisation. The investigator

took one month to recruit the volunteers. The poster had been posted up to the window of the medicine shop for one month. The investigator screened 75 volunteers recruited through advertisements. At the deadline of the recruitment, 64 smokers were selected to participate in the trial according to their healthy condition and smoking status (see 3.4.2). Nutralife Company has provided 50 boxes of Zhong Mai Yan Ke, so the investigator decided to allocate 50 volunteers in the treatment group to receive Zhong Mai Yan Ke – Chinese herbal patches, whereas the other 14 volunteers in the other group received placebo patches, Band-aid super-elastic adhesive bandage, which resembles the appearance of Zhong Mai Yan Ke. Applying the Fisher exact test, the findings of the trial is found to be of statistical significance. It is explained in chapter 4 one by one.

The investigator in charge of recruiting volunteers for this trial recruited the volunteers based strictly on the inclusion and exclusion criteria. That is to say the volunteers who did not meet the inclusion criteria or meet exclusion criteria were excluded from the trial. Of the 75 volunteers, 64 of them were selected to participate in the trial. The randomisation sequence was concealed at the time of obtaining consent from prospective trial volunteers and until the interventions were given to them. The volunteers did not know which intervention, Zhong Mai Yan Ke or placebo, would be provided to them until they had actually received it.

Depending on the extent to which the participants are exposed to the study interventions, RCTs can have parallel, crossover, or factorial designs. Most RCTs have a parallel design. In these studies, each group of participants is exposed to only one of the study interventions (<http://www.bmj.com/rct/chapter2.htm1>). In the trial, the researcher used a parallel design to evaluate the effects of Zhong Mai Yan Ke compared with those of a placebo in participants.

Depending on the extent of blinding, RCTs can be classified as open, single-blind, double-blind, triple-blind, and quadruple-blind. The trial was designed as an open randomised controlled trial (RCT). An open RCT is a randomised trial in which those involved in the trial know which intervention is given to each participant (<http://www.bmj.com/rct/chapter2.htm1>). In the trial, the volunteers in the

treatment and control groups knew the identity of the interventions, Zhong Mai Yan Ke or placebo when they applied them because Zhong Mai Yan Ke is an approved medicine in China and they were given to the volunteers in the treatment group in sealed boxes designed by the manufacturer. The employed medicine shop keeper who administered the interventions and the researcher, who assessed the outcomes of the interventions, analysed the data and wrote the results of the trial, also knew the identity of the interventions.

3.4 Study design

3.4.1 Background

The trial investigated the extent of the effect of Zhong Mai Yan Ke as compared with placebo. The trial was completed in China because Zhong Mai Yan Ke and the placebo are legally licensed medicine only in China. Zhong Mai Yan Ke (No.126006) was registered in official trade documents by Jiangsu Province Medicine and Medical Apparatus Controlling Station in 1998 in China and was available for purchase in 1998 in China. The placebo - Band-aid super-elastic adhesive bandage are products of the Johnson Company. There is no medication in the bandages.

Although the placebo - Band-aid super-elastic adhesive bandage has a very similar appearance and size, it was impossible to design the trial as a blinded one. The study had to be designed on a feasibility basis for the following reasons:

(1) ZYMK, legally licensed, is commonly known and available in China. It was not possible to alter the packaging or its presentation to make it appear completely similar to a placebo. It was inevitable thus that the participants would know which item they had been given.

(2) ZMYK was extensively advertised on TV, radio, newspaper, etc and was a well-known smoking cessation product. It's TV advertisement showed detailed instruction of how the product was applied. Many people, including smokers, knew there was a magnetic disc in the patch of ZMYK. However, Band-aid adhesive bandage included

no such magnetic discs in its patch. That meant that the volunteers always knew if the product they used was ZMYK by checking if a disc was in it.

Nutralife Company agreed to provide 50 boxes of Zhong Mai Yan Ke for the study. The “placebo” was purchased by the researcher and the researcher paid £200 to employ a medicine shop keeper to recruit the volunteers, administer the interventions and to collect data.

3.4.2 Recruitment

Healthy adult volunteers who were smokers were recruited from the city of Dalian in China. The investigator had put up a poster recruiting volunteers in the window of the shop for one month (Appendix B₁). During one month’s recruiting, the investigator screened 75 volunteers recruited through these advertisements. They were asked to come to the medicine shop. The volunteers were given a health screening questionnaire (Appendix B₂) and their smoking status was recorded (Appendix B₃). Sixty four volunteers were recruited based on the inclusion and exclusion criteria as mentioned below. Informed consent (Appendix B₃) and volunteer instruction leaflets (Appendix C) were used. Volunteers could withdraw from the study at any time. The proportion of male and female volunteers in this study is representative of the proportion of males and females in the smoking population.

Current cigarette smokers have been further sub-divided by the reported number of cigarettes smoked per day. Smokers are grouped into three categories. Light smokers are those who reported smoking under 10 a day, moderate smokers are those who reported smoking 10 to less than 20 a day, and heavy smokers are those reported smoking 20 or more a day (<http://www.official-documents.co.uk/document/deps/doh/survey01/fvc/fvc-08.htm>).

The volunteers were selected based on the following criteria:

- 18 years of age or older
- moderate and heavy smokers who smoke more than 10 cigarettes a day
- Motivation to quit was high

- Dextrous in applying Zhong Mai Yan Ke patches and placebo plasters
- Could follow instructions carefully

The volunteers were not selected based on the following criteria:

- pregnant women
- anyone with hypersensitivity to patches
- anyone with serious illness and receiving medication or herbal treatment

3.4.3 Random allocation

The generation of random sequences of allocation can be achieved using one of a variety of procedures. The trial uses the method of drawing out to generate random sequences of allocation. Firstly, the investigator numbered the 64 selected volunteers randomly. These scripts were folded and the numbers concealed. Thirdly, the 64 scripts were mixed. Fourthly, 14 scripts were drawn out. These 14 scripts were allocated to placebo and the other 50 scripts to Zhong Mai Yan Ke.

3.4.4 Intervention

As discussed in section 3.3, an open randomisation approach was used. Therefore, the subjects in both groups knew the substance they were given. The smokers in treatment groups were given one box of Zhong Mai Yan Ke and those in control groups were given placebo. Similar written instructions on the application of patches were given to both groups.

- The treatment group:
50 participants were given a supply of one box of Zhong Mai Yan Ke – 18 patches, sufficient for the 9 day trial. They were asked to apply a patch once a day to each wrist at the acupoint of Tim Mee (Appendix A & Appendix C) and left in place for 22 hours, then remove the patches and apply a new patch to each wrist after 2 hours. The course of treatment was for 9 days.

- The control group:
14 participants were given placebo – 18 pieces of Band-aid super-elastic adhesive bandage which has a similar appearance to Zhong Mai Yan Ke. This kind of bandage can be bought in any medicine shop in China. The participants were asked to apply the placebo once a day to each wrist at the acupoint of Tim Mee and left in place for 22 hours then remove them and reapply a new patch to each wrist after 2 hours. The course of treatment was for 9 days.

3.4.5 Data Collection

The trial was conducted in Dalian City, China and the researcher was responsible for the selection of a medicine shop for the research. An investigator was also appointed by the researcher to oversee the conduct of the research, responsible particularly for the initial data collection and for the three month follow-up data collection. The health screening (Appendix B₂) and smoking status questionnaire (Appendix B₃) were collected immediately when the volunteers agreed to join the trial in the medicine shop. The smoking status questionnaire was repeated to both treatment and control groups at the end of the 9 day trial. The data sheet was designed by the researcher and was translated into Chinese by the researcher herself. All data were recorded in Chinese by the appointed investigator, and then translated into English by the researcher. The data sets in English are presented in the appendix (Appendix D).

All subjects were followed up three months after the trial using a telephone interview technique. The telephone interviews were conducted using some of the questions in the smoking status questionnaire, e.g.

Are you still a smoker?

If yes, how many cigarettes do you smoke a day?

Did you have any unpleasant reactions while wearing the patches?

If yes, please give the details.

3.4.6 Data Analysis

The data analysis was performed with the help of a professional statistician from the department of mathematical sciences at the University of Durham. Chi-square test or Fisher's exact test was used in analysis.

3.4.7 Ethics

In China there is no conventional ethics committee structure as in the UK. However, all the steps required for such a study were adhered to – i.e. recruitment of volunteers, informed consent and the ability of the participants to withdraw at any stage.

Furthermore the following factors were considered:

(1) Zhong Mai Yan Ke and the placebo Band-aid adhesive bandages are all legally licensed products and have been available widely for a long time and are relatively well known to the public.

(2) They are readily available without a prescription.

(3) It has attained acceptance as a well known product; Zhong Mai Yan Ke is known to contain a herbal remedy.

(4) Zhong Mai Yan Ke and placebo are not associated with any known or worrying side effects.

(5) The researcher sought advice and received a letter from the Institute of Pharmacology at the School of Medicine, Dalian University, in which Professor Xie, Director of the Institute of Pharmacology, confirmed that the methodology used in this therapeutic trial was appropriate, without ethical concerns in China (Appendix E).

3.5 Limitations

It has been argued by researchers and manufacturers of herbal products in the UK that the acceptability of research findings is partly dependent on the location where the study was conducted. For example, studies conducted outside the UK, EU or the USA may be regarded with some suspicion. The researcher is aware of this argument. This

study was an attempt to apply recognised western research methods to ascertain the effects of a potential treatment for smoking cessation. The researcher does not believe that the pharmacological effects of nicotine differ greatly, if at all, amongst the human race irrespective of the country of origin. Therefore, the findings in the East, provided that the protocols used could be replicated, could be applied to the West.

The researcher could have employed a double-blind trial as an additional safeguard. However, only an open randomised trial was possible in a commercial setting in China within that very specific cultural setting. In fact, one could prolong the discussions on the relative merits of various research methodologies used in medical investigation. Randomised controlled trials advocated by the west are not without problems. RCTs are vulnerable to multiple types of bias at all stages of their lifespan. In health care research, bias is defined as any factor or process that tends to deviate the results or conclusions of a trial systematically away from the truth. This deviation from the truth can result in underestimation or exaggeration of the effects of an intervention. The main reason to anticipate, detect, quantify, and control bias is that the true effects of any health care intervention are unknown. The purpose of RCTs, as well as any other study or research enquiry, is to produce results from a sample of participants that could be generalised to the target population at large. It is impossible ever to know for sure whether the results of a study are biased, simply because it is impossible to establish whether such results depart systematically from a truth that is unknown. Despite this major limitation, many possible sources of biases have been recognised over the years. The existence of most of these biases is supported mainly by common sense. Some biases can occur at any point during the course of a trial. Other biases can occur during the dissemination of a trial from the investigators to potential users, or during the uptake of trial information by potential users of the trial (<http://www.bmj.com/rct/chapter3.htm>).

For example, one bias occurs when the results or conclusions of a trial are systematically distorted by knowledge of which intervention each participant is receiving. The best way to protect a trial against this kind of bias is by keeping the people involved in the trial unaware of the identity of the interventions for as long as possible (<http://www.bmj.com/rct/chapter3.htm>). However, the trial was designed

as an open trial. All participants in the study knew the identity of the interventions. So this bias may occur under this circumstance.

The other bias was introduced by drop outs. Ideally, all participants in a trial should complete the study, follow the protocol, and provide data on all the outcomes of interest at all time-points. In reality, however, most trials have missing data. Data can be missing because some of the participants drop out before the end of the trial, because participants do not follow the protocol either deliberately or accidentally, or because some outcomes are not measured correctly or cannot be measured at all at one or more time-points. Regardless of the cause, inappropriate handling of the missing information can lead to bias (<http://www.bmj.com/rct/chapter3.html>). In the trial, only one participant who was allocated to Zhong Mai Yan Ke did not complete the study due to business, when he missed the first 9-day treatment course.

3.6 Summary

An open randomised controlled trial was considered appropriate to evaluate the effectiveness of Zhong Mai Yan Ke in a commercial setting in China within that very special cultural environment. When designing the study, the researcher has considered about the bias that can occur in the trial. As a fully blinded randomised controlled trial was not possible it was considered that this open trial would provide data on the feasibility of a study in this setting and pilot data on the possible effectiveness of the product. This has been accomplished within this limited project.

Chapter 4

Clinical Trial of Zhong Mai Yan Ke (ZMYK)

4.1 Introduction

The study consisted of three phases: a screen/baseline phase, a 9 day treatment phase, and a three month follow-up phase. This chapter presents the main findings of the clinical trial in China using Zhong Mai Yan Ke herbal patches involving 50 volunteers in the treatment group and 14 volunteers in the control group. These 64 volunteers were declared in their self-administered health screening questionnaire to be healthy. The smokers in the treatment groups were given a course of Chinese herbal Zhong Mai Yan Ke treatment for 9 days, whereas the smokers in the control group were given placebo for 9 days.

4.2 Findings

4.2.1 Demographic Data and Baseline Characteristics

1. Gender, age, length of smoking experience, the level of addiction and the No. of unsuccessful attempts at quitting distribution

50 smokers of the 64 volunteers recruited were randomly allocated to the treatment group and the remaining 14 to the control group. All the smokers in the treatment group were men whereas in the control group 13 were men and 1 was a woman. All smokers conformed to the inclusion and exclusion criteria as discussed in chapter 3. All except one in the treatment group successfully completed the trial. 1 person in the treatment group was excluded from the analysis as he failed to apply the patches correctly; therefore, he was excluded from the trial. Smokers' personal data and smoking characteristics are presented in table 4.1.

Table 4.1 personal data and characteristics of smokers

		N	gender		Minimum	Maximum	Mean	Std. Deviation
			Male (No.)	female (No.)				
treatment group	Age (years)	49	49	0	21	72	36.41	13.53
	Number of years smoked	49			2	40	14.27	11.38
	Number of cigarettes	49			12	40	24.41	8.64
control group	Age (years)	14	13	1	25	76	42.29	13.26
	Number of years smoked	14			7	34	17.43	8.47
	Number of cigarettes	14			12	38	23.21	8.13

As shown in table 4.1, a total of 63 cigarette smokers were enrolled in the trial. Just 98.4% (n=62) were male. There are large variations in the age, length of smoking experience and the level of addiction, i.e. no. of cigarettes smoked per day, amongst the volunteers in both groups. However, there are no significant differences seen in these variables between the treatment and control group. For example, the mean age was 36.41 (SD±13.53) years (range, 21 to 72 years) in the treatment group and 42.29 (SD±13.26) years (range, 25 to 76 years). Volunteers enrolled in this trial had smoked an average of 24.41 (SD± 8.64) cigarettes per day at present (range, 12 to 40) in the treatment groups and 23.21 (SD±8.123) cigarettes (range, 12 to 38) in the control group. They had smoked for an average of 14.27 (SD±11.38) years (range, 2 to 40) in the treatment group and 17.43 (SD±8.47) years (range, 7 to 34) in the control group.

It is also noted that, 83.7% (n=41) of the smokers in the treatment group had not tried stopping smoking before the trial and 16.3% (n=8) of them had tried to stop smoking unsuccessfully one or more times. All the smokers in the control group had not tried stopping stop smoking before the trial.

2. The relationship between age, years of smoking and degree of addiction, i.e. No. of cigarettes smoked per day.

It is found that there are certain relationships between the smokers' age, length of smoking experience and the level of addiction in both groups. The relationship of their variables can be observed from tables 4.2, 4.3, and 4.4 and figures 4.1, 4.2 and 4.3. It is found there is no difference in status of smokers between treatment group and control group at the beginning of the trial. It also shows whether the placebo is effective or not, it was not due to other differences in critical determinants of the likelihood of success for smoking cessation. Those smokers in both groups who were older had smoked for many more years than the younger smokers and tended to smoke more heavily. However, this observation really reflects the natural path of nicotine addiction, in that, the older the smoker is, the more years he/she would have spent smoking and the degree of addiction would correlate with age (Cheung & Woof, 2001).

Table 4.2 Relation between age and years of smoking

		groups of years of smoking				total
		10 years or less	11 to 20 years	21 to 30 years	over 30 years	
age groups	20 to 30 years old	<u>22</u>				<u>22</u>
	31 to 40 years old	<u>3</u>	<u>8</u>			<u>11</u>
<u>treatment group</u>	41 to 50 years old	<u>0</u>	<u>2</u>	<u>6</u>		<u>8</u>
	51 to 60 years old		<u>3</u>	<u>4</u>		<u>7</u>
control group	Over 60 years old	<u>0</u>		<u>1</u>	<u>4</u>	<u>5</u>
		<u>1</u>			<u>3</u>	<u>3</u>
Total		<u>25</u>	<u>10</u>	<u>7</u>	<u>7</u>	<u>49</u>
		<u>4</u>	<u>5</u>	<u>4</u>	<u>1</u>	<u>14</u>

Figure 4.1 Relation between age and years of smoking

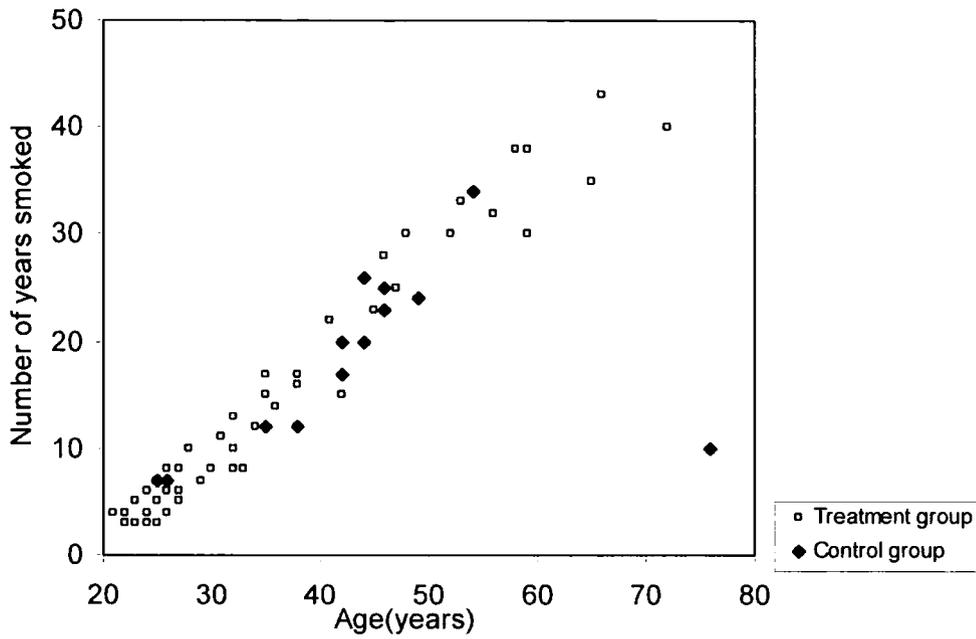


Table 4.3 Relation between age and degree of addiction

		groups of degree of smoking			total
		10 to 20 cigarettes	21 to 30 cigarettes	over 31 cigarettes	
age groups treatment group <u>(underlined)</u> control group (bold)	20 to 30 years old	<u>20</u> 3	<u>2</u> 0		<u>22</u> 3
	31 to 40 years old	<u>4</u> 1	<u>7</u> 1		<u>11</u> 2
	41 to 50 years old	<u>0</u> 1	<u>3</u> 5	<u>5</u> 1	<u>8</u> 7
	51 to 60 years old		<u>2</u> 0	<u>3</u> 1	<u>5</u> 1
	over 60 years old	<u>0</u> 1		<u>3</u> 0	<u>3</u> 1
total		<u>24</u> 6	<u>14</u> 6	<u>11</u> 2	<u>49</u> 14

Figure 4.2 Relation between age and degree of addiction

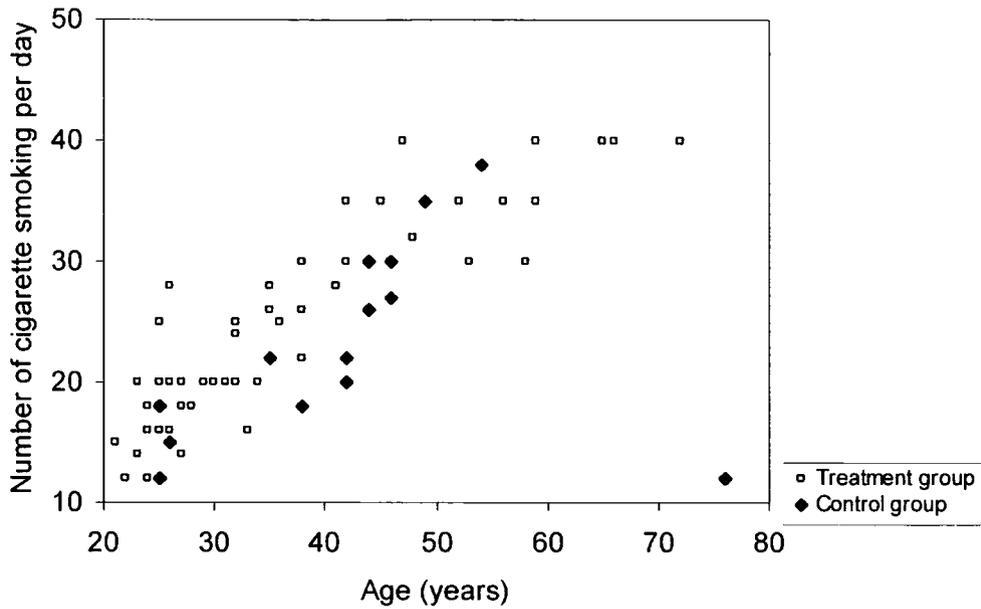
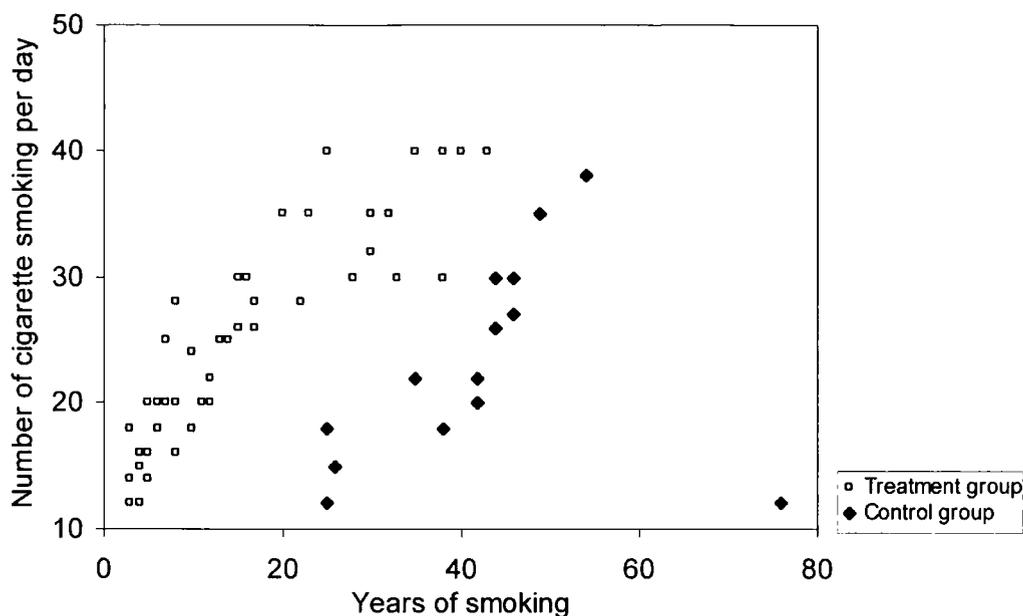


Table 4.4 Relation between years of smoking and degree of addiction

		groups of degree of smoking			total
		10 to 20 cigarettes	21 to 30 cigarettes	over 31 cigarettes	
years of smoking treatment group (underlined) control group (bold)	10 years or less	<u>22</u> 4	<u>3</u> 0		<u>25</u> 4
	11 to 20 years	<u>2</u> 2	<u>7</u> 3	<u>1</u> 0	<u>10</u> 5
	21 to 30 years		<u>2</u> 3	<u>5</u> 1	<u>7</u> 4
	over 30 years		<u>2</u> 0	<u>5</u> 1	<u>7</u> 1
total		<u>24</u> 6	<u>14</u> 6	<u>11</u> 2	<u>49</u> 14

Figure 4.3 Relation between years of smoking and degree of addiction



4.2.2 Effectiveness of Zhong Mai Yan Ke

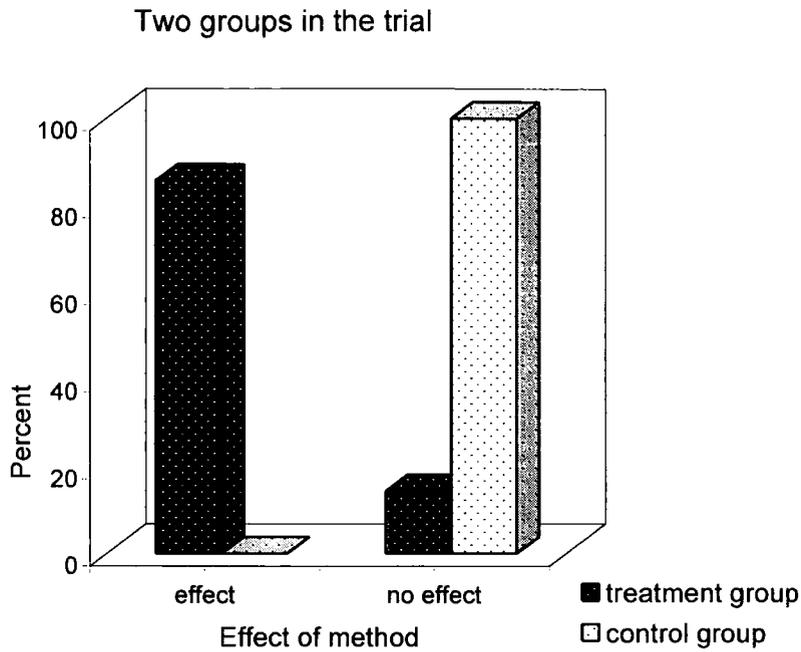
1. At the end of the 9-day trial

The smokers in the treatment group were given a supply of herbal Zhong Mai Yan Ke patches for 9 days together with an instruction leaflet (Appendix B) giving details of the trial and where the 2 patches should be applied every day for 9 days. The smokers in the control group received 2 placebo patches per day each for 9 days.

It is found that all 14 smokers (100%) in the control group have failed to quit.

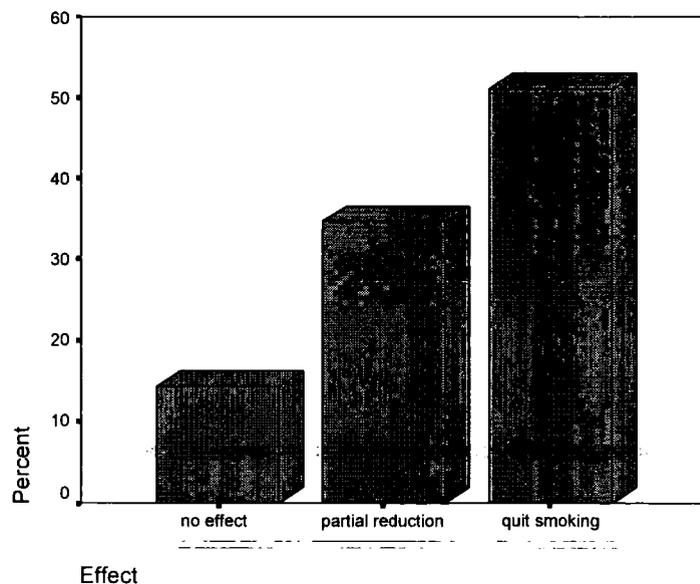
However, amongst the 49 smokers in the treatment group, 7 smokers have failed to quit; however, 42 smokers have managed, either to give up their habit completely or reduce their daily smoking consumption. The overall effective rate is therefore 85.7% as shown in figure 4.4. Applying the Fisher exact test, the overall effectiveness of Zhong Mai Yan Ke is found to be of statistical highly significance with a *p-value* < 0.001.

Figure 4.4 Percentage of people in the treatment and control group managed to change their smoking habit at the end of the 9-day trial



When the overall effectiveness rate is to be broken down into those who have managed to quit successfully and those who have not but nonetheless have reduced their daily consumption, then the effectiveness of Zhong Mai Yan Ke as a smoking cessation agent is shown to be highly significant. .

Figure 4.5 Treatment effect at the end of the 9-day trial



As shown in Figure 4.5, at the end of the 9-day trial, 51% (n=25) in the treatment group managed to stop smoking completely while 35% (n=17) were able to reduce the number of cigarettes daily. However there was no effect at all in 14.3% (n=7) of the subjects of treated group. Among those who reduced the number of cigarettes smoked per day, 5 cases (10.2%) smoked less than 1/3 of previous, 7 cases (14.3%) smoked between 1/3 and 1/2 of the number at Day 9, 5 cases (10.2%) smoked more than 1/2 of the number at Day 9 and 7 cases (14.3%) had no effect after the trial. In the control group, all cases who applied placebo had no effect on smoking cessation (table 4.5).

Table 4.5 Pattern of degree of addiction on Day 9 of trial in active ingredient and control group

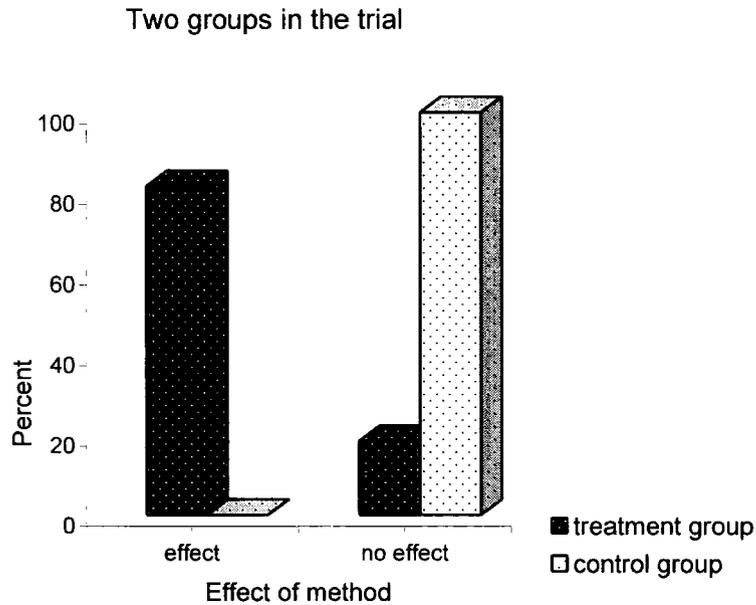
		treatment groups		total
		active ingredient group	control group	
effect groups	no change in smoking habit	7 (14.3%)	14 (100.0%)	21 (33.3%)
	smokes more than 1/2 of the number at Day 9	5 (10.2%)	0 (0%)	2 (3.2%)
	smokes between 1/3 and 1/2 of the number at Day 9	7 (14.3%)	0 (0%)	4 (6.3%)
	smokes but less than 1/3 of the number at Day 9	5 (10.2%)	0 (0%)	11 (17.5%)
	quit smoking	25 (51.0%)	0 (0%)	25 (39.7%)
total		49 (100.0%)	14 (100.0%)	63 (100.0%)

2. Three months after the trial

The smokers in both the treatment and control group were followed-up three months after the trial using the same questionnaire applied prior to the trial. All 14 smokers in the control group are reported to be smokers, therefore, the failing rate in the control group is 100%. However, amongst the 49 smokers in the treatment group, 2 smokers who had managed to reduce smoking consumption at the end of the 9-day trial smoked daily cigarettes at the same level as before the trial began, therefore 18.4% (n=9) of smokers failed to quit smoking 3 months after the trial. 40 smokers have managed, either to give up their habit completely or reduce their daily smoking consumption. The overall effective rate is therefore 81.6% (n=40) as shown in Figure

4.6. The overall effectiveness of Zhong Mai Yan Ke is shown to be statistical significant (Fisher's exact test, P -value < 0.001).

Figure 4.6 Treatment Effect at 3 months after the trial



In the light of the results 3 months after the trial, it can be said Zhong Mai Yan ke is an effective agent for smoking cessation as 42.9% (n=21) of those who initially quit managed to refrain from smoking, 19 smokers (38.8%) managed to reduce the smoking consumption and 9 smokers (18.4%) had not changed in smoking habit 3 months after the trial (table 4.6 and figure 4.7). Compared with the results at the end of the 9-day trial, it is shown that the effectiveness of Zhong Mai Yan Ke 3 months after the trial is not as good as that at the end of the 9-day trial (table 4.6 and figure 4.8) but is still considered highly effective. It would be useful to follow up the smokers for another 12 months in order to ascertain the permanent effect of Zhong Mai Yan Ke.

Table 4.6 Percentage of success at the end of the 9-day trial and 3 months after the trial

	smoking status	at the end of the 9-day trial	3 months after the trial
treatment group	complete success (quit smoking)	25 (51.0%)	21 (42.9%)
	partial success (manage to reduce smoking consumption)	17 34.7%	19 (38.8%)
	Failure (no change in smoking habit)	7 (14.3%)	9 (18.4%)
total		49 (100%)	49 (100%)
control group	complete success(quit smoking)	0 (0%)	0 (0%)
	partial success (manage to reduce smoking consumption)	0 (0%)	0 (0%)
	Failure (no change in smoking habit)	14 (100%)	14 (100%)
total		14 (100%)	14 (100%)

Figure 4.7 Percentage of quitting smoking, partial smoking and having no change in smoking habit (no effect) 3 months after the trial

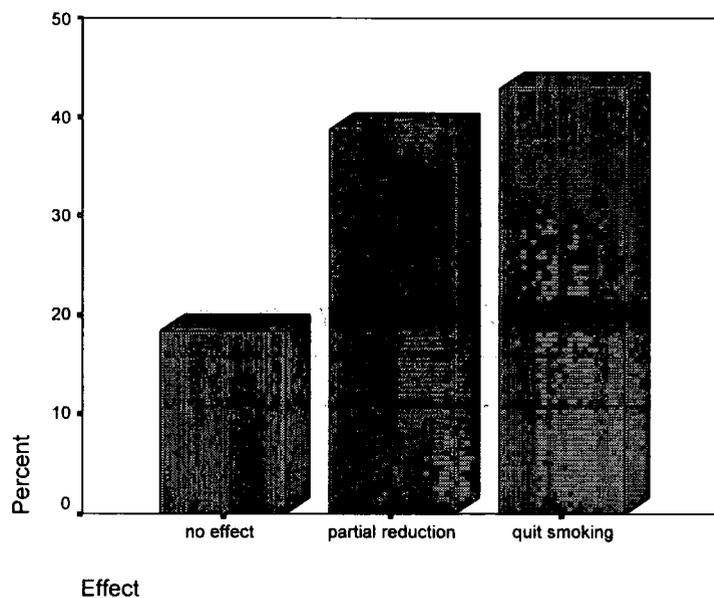
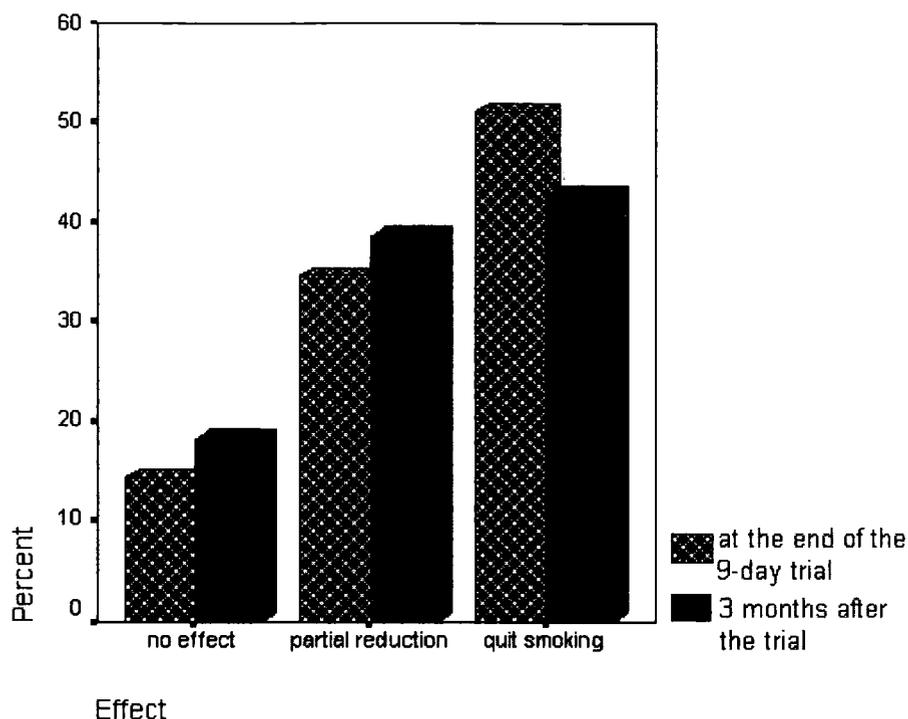


Figure 4.8 Smoking status in the treatment group at the end of the 9-day trial and 3 months after the trial

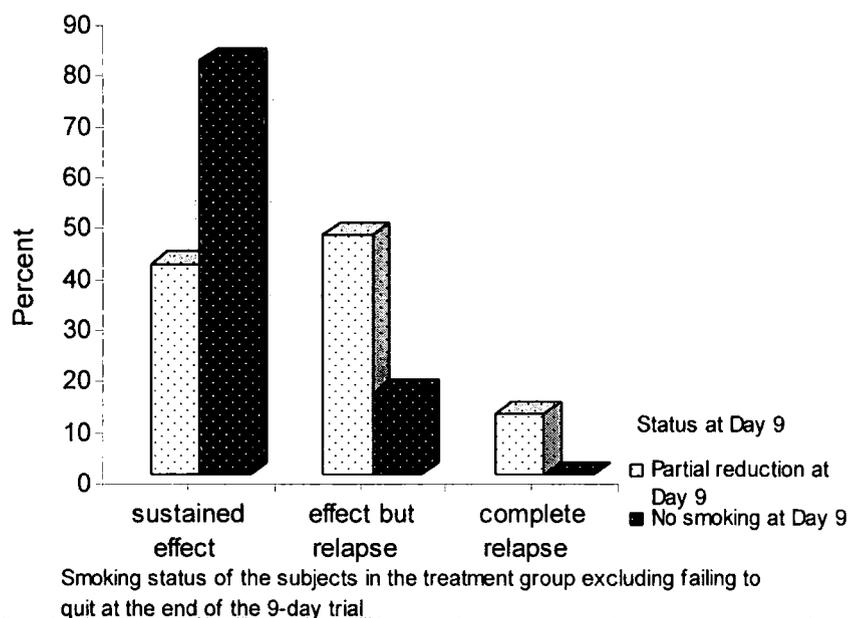


The results also showed that a small proportion of those treated, who were initially able to quit completely, 4 had relapsed and had taken up smoking again to quit smoking completely at the end of the 9 day trial. So the sustained quitting rate was 81.4% (21/25). The relapse rate was 16% (4/25) from the initial quitters; however, it was reported they smoked fewer than before the trial. In the partially successful group, it was reported that 10 out of the 17 had increased their smoking consumption including 8 (47.1%) who were smoking more cigarettes per day than at the end of the 9-day trial but less than that before the trial began and 2 (11.8%) who were smoking the same amount of cigarettes as before the trial began. So the sustained reducing smoking consumption was 41.2% (7/17) (table 4.7 and figure 4.9).

Table 4.7 Smoking status at the end of the 9-day trial and 3 months after the trial

	at the end of the 9-day trial		3 months after the trial	
	smoking status	N	smoking status	N
treatment group	quit smoking	25	quit smoking	21
			relapse but smoking less than before the trial began	4
	manage to reduce smoking consumption	17	smoke the consumption as same as that at the end of the 9-day trial	7
			smoke consumption more than that at the end of the 9-day trial	8
			smoke consumption as same as that before the trial	2
no change in smoking habit	7	no change in smoking habit	7	
total		49		49
control group	quit smoking	0	quit smoking	0
	manage to reduce smoking	0	manage to reduce smoking consumption	0
	no change in smoking habit	14	no change in smoking habit	14
total		14		14

Figure 4.9 Smoking status of initially successfully treated smokers at 3 months



At the end of 3 months, of those who were treated with ZMYK, 21 cases (42.9%) quitted smoking successfully, 5 cases (10.2%) smoked less than 1/3 of the number at

Day 9, 7 cases (14.3%) smoked between 1/3 and 1/2 of the number at Day 9, 7 cases (14.3%) smoked more than 1/2 of the number at Day 9 and 9 cases (18.4%) smoked the same number 3 months after the trial. In the control group, all the subjects who applied placebo patches, no effect on smoking cessation was seen at the end of 3 months (table 4.8).

Table 4.8 effect groups * treatment group degree of addiction obtained 3 months after the trial

		group		total
		treatment group	control group	
effect groups	no change in smoking habit	9 (18.4%)	14 (100.0%)	23 (36.5%)
	smokes more than 1/2 of the number at Day 9	7 (14.3%)	0 (0%)	7 (11.1%)
	smokes between 1/3 and 1/2 of the number at Day 9	7 (14.3%)	0 (0%)	7 (11.1%)
	smokes but less than 1/3 of the number at Day 9	5 (10.2%)	0 (0%)	5 (7.9%)
	quit smoking	21 (42.9%)	0 (0%)	21 (33.3%)
total		49 (100.0%)	14 (100.0%)	63 (100.0%)

At the end of 3 months, 2 people who smoked more than 1/2 of their pretreatment level at Day 9, had increased their consumption of cigarettes back to their baseline number. 4 people who smoked between 1/3 and 1/2 of the number at the end of 9-day trial had increased their consumption of cigarettes to more than 1/2 of the number at Day 9 dependence level after three months. 4 people who smoked less than 1/3 of the number at Day 9 had increased their consumption of cigarettes to between 1/3 and 1/2 of the number at Day 9 after three months. 4 people who quitted smoking at the end of 9-day trial had taken up smoking again and their consumption of cigarettes had less than 1/3 of the the number at Day 9 after three months (table 4.9).

Table 4.9 treatment groups three months after the trial * treatment group at the end of the 9-day trial degree of addiction

treatment group		at the end of the 9-day trial					Total
		no change in smoking habit	smokes more than 1/2 of the number at Day 9	smokes between 1/3 and 1/2 of the number at Day 9	smokes less than 1/3 of the number at Day 9	quit smoking	
3 months after the trial	no change in smoking habit	7 100.0%	2 40.0%				9 18.4%
	smokes more than 1/2 of the number at Day 9		3 60.0%	4 57.1%			7 14.3%
	smokes between 1/3 and 1/2 of the number at Day 9			3 42.9%	4 80.0%		7 14.3%
	smokes less than 1/3 of the number at Day 9				1 20.0%	4 16.0%	5 10.2%
	quit smoking					21 84.0%	21 42.9%
total		7 100.0%	5 100.0%	7 100.0%	5 100.0%	25 100.0%	49 100.0%

Further analysis of the successful quitters at the end of the 9-day treatment and at 3 months after the trials reveals that 3 of the 21 were heavy smokers, e.g. smoking over 21 cigarettes per day, and have smoked for more than 10 years. The remaining 4 smokers who have successfully given up smoking were moderate smokers, e.g. smoking 11-20 cigarettes per day, and have smoked for less than 10 years. However, there is no strong relationship between age, length of smoking experience and degree of addiction amongst those 4 smokers who took up smoking again 3 months after the trial. Amongst those 17 smokers who managed to reduce their daily consumption, 10 of them had increased their daily intake 3 months after the trial. Taking all these factors into consideration it can be said Zhong Mai Yan Ke is equally effective for a range of smokers.

3. Currently treatment effects on different age groups, years of smoking groups and degree of addiction groups

a) Relationship between effectiveness of Zhong Mai Yan Ke and Age

It is found that the rate of quitting smoking is highest (90.9% at the end of 9-day trial and 77.3% obtained 3 months after the trial) in the age group between 21 and 30 years old. Those who were aged over 60 were not at all responsive to Zhong Mai Yan Ke. Although the sample is too small to be conclusive, in general it appears that the success rate is higher among younger people than it is among the older people (table 4.10).

Table 4.10 Relationship between effectiveness of Zhong Mai Yan Ke and age

effect group		age groups					Total
		20 to 30 years old	31 to 40 years old	41 to 50 years old	51 to 60 years old	over 60 years old	
at the end of the 9-day trial (<u>underlined</u>) 3 months after the trial (bold)	no change in smoking habit	<u>0</u>	<u>1</u>	0	3	3	7
		(0%)	(9.1%)	(0%)	(50.0%)	(100.0%)	(14.3%)
		0	2	0	4	3	9
		(0%)	(18.2%)	(0%)	(66.7%)	(100.0%)	(18.7%)
	smokes more than 1/2 of the number at Day 9	<u>0</u>	1	1	3	0	5
		(0%)	(9.1%)	(14.3%)	(50%)	(0%)	(10.2%)
		0	2	3	2	0	7
		(0%)	(18.2%)	(42.9%)	(33.3%)	(0%)	(14.3%)
	smokes between 1/3 and 1/2 of the number at Day 9	<u>1</u>	3	3	0	0	7
		(4.5%)	(27.3%)	(42.9%)	(0%)	(0%)	(14.3%)
	3	2	2	0	0	7	
	(13.6%)	(18.2%)	(28.6%)	(0%)	(0%)	(14.3%)	
smokes less than 1/3 of the number at Day 9	<u>1</u>	2	2	0	0	5	
	(4.5%)	(18.2%)	(28.6%)	(0%)	(0%)	(10.2%)	
	2	2	1	0	0	5	
	(9.0%)	(18.2%)	(14.3%)	(0%)	(0%)	(10.2%)	
quit smoking	20	4	1	0	0	25	
	(90.9%)	(36.4%)	(14.3%)	(0%)	(0%)	(51.0%)	
	17	3	1	0	0	21	
	(77.3%)	(27.3%)	(14.3%)	(0%)	(0%)	(42.9%)	
total	22	11	7	6	3	49	
	(100.0%)	(100.0%)	(100.0%)	(100.0%)	(100.0%)	(100.0%)	
	22	11	7	6	3	49	
	(100.0%)	(100.0%)	(100.0%)	(100.0%)	(100.0%)	(100.0%)	

b) Relationship between effectiveness of Zhong Mai Yan Ke and duration of smoking in years

It is found that the rate of quitting smoking is highest (88.0% at the end of 9-day trial and 76.0% obtained 3 months after the trial) in the group where the number of years smoked is 10 years or less. Those whose number of years smoked were over 30 had the highest rate (57.1% at the end of 9-day trial and 71.4% obtained 3 months after the trial) of no change in their smoking habit. Although the sample is too small to be conclusive, in general it appears that the success rate was higher among smokers who had smoked for fewer years (see table 4.11).

Table 4.11 Relationship between effectiveness of Zhong Mai Yan Ke and duration of smoking in years

effect group		number of years smoked				Total
		10 years or less	1 to 20 ars	21 to 30 years	over 31 years	
at the end of the 9-day trial (<u>underlined</u>) 3 months after the trial (bold)	no change in smoking habit	<u>0</u> (0%)	<u>1</u> (10.0%)	<u>2</u> (28.6%)	<u>4</u> (57.1%)	<u>7</u> (14.3%)
		1 (4.0%)	1 (11.1%)	2 (25.0%)	5 (71.4%)	9 (18.7%)
	smokes more than 1/2 of the number at Day 9	<u>1</u> (4.0%)	<u>1</u> (10.0%)	<u>0</u> (0%)	<u>3</u> (42.9%)	<u>5</u> (10.2%)
		0 (0%)	2 (22.2%)	3 (37.5%)	2 (28.6%)	7 (14.3%)
	smokes between 1/3 and 1/2 of the number at Day 9	<u>1</u> (4.0%)	<u>3</u> (30.0%)	<u>3</u> (42.9%)	<u>0</u> (0%)	<u>7</u> (14.3%)
		3 (12.0%)	2 (22.2%)	2 (25.0%)	0 (0%)	7 (14.3%)
	smokes less than 1/3 of the number at Day 9	<u>1</u> (4.0%)	<u>2</u> (20.0%)	<u>2</u> (28.6%)	<u>0</u> (0%)	<u>5</u> (10.2%)
		2 (8.0%)	2 (22.2%)	1 (12.5%)	0 (0%)	5 (10.2%)
	quit smoking	<u>22</u> (88.0%)	<u>3</u> (30.0%)	<u>0</u> (0%)	<u>0</u> (0%)	<u>25</u> (51.0%)
		19 (76.0%)	2 (22.2%)	0 (0%)	0 (0%)	21 (42.9%)
total	<u>25</u> (100.0%)	<u>10</u> (100.0%)	<u>7</u> (100.0%)	<u>7</u> (100.0%)	<u>49</u> (100.0%)	
	25 (100.0%)	9 (100.0%)	8 (100.0%)	7 (100.0%)	49 (100.0%)	

c) Relationship between effectiveness of Zhong Mai Yan Ke and the degree of smoking addiction

It is shown in table 4.12, that those smokers in the treatment group who smoked between 10 to 20 cigarettes per day achieved the highest rate (91.7% at the end of 9-day trial and 79.2% obtained 3 months after the trial) of quitting smoking. Those smokers who smoked over 31 cigarettes per day achieved the highest rate (54.5% at the end of 9-day trial and 3 months after the trial) of no change in their smoking habit.

It is found the percentage of smokers that stopped completely differs significantly for the different groups of degree of smoking addiction (X^2 -test, P value<0.001); the percentage of smokers that managed to reduce their smoking differs significantly for different groups of degree of smoking addiction (X^2 -test, P value<0.05).

Table 4.12 Relationship between effectiveness of Zhong Mai Yan Ke and degree of smoking addiction

effect group		number of cigarettes smoked			Total
		10 to 20 cigarettes	21 to 30 cigarettes	over 31 cigarettes	
at the end of the 9-day trial (<u>underlined</u>) 3 months after the trial (bold)	no change in smoking habit	<u>0</u> <u>(0%)</u>	<u>1</u> <u>(7.1%)</u>	<u>6</u> <u>(54.5%)</u>	<u>7</u> <u>(14.3%)</u>
		0 (0%)	3 (21.4%)	6 (54.5%)	9 (18.7%)
	smokes more than 1/2 of the number at Day 9	<u>0</u> <u>(0%)</u>	<u>3</u> <u>(21.4%)</u>	<u>2</u> <u>(18.2%)</u>	<u>5</u> <u>(10.2%)</u>
		0 (0%)	4 (28.6%)	3 (27.3%)	7 (14.3%)
	smokes between 1/3 and 1/2 of the number at Day 9	<u>1</u> <u>(4.2%)</u>	<u>5</u> <u>(35.7%)</u>	<u>1</u> <u>(9.1%)</u>	<u>7</u> <u>(14.3%)</u>
		3 (12.5%)	3 (21.4%)	1 (9.1%)	7 (14.3%)
	smokes less than 1/3 of the number at Day 9	<u>1</u> <u>(4.2%)</u>	<u>2</u> <u>(14.3%)</u>	<u>2</u> <u>(18.2%)</u>	<u>5</u> <u>(10.2%)</u>
		2 (8.3%)	2 (14.3%)	1 (9.1%)	5 (10.2%)
quit smoking	<u>22</u> <u>(91.7%)</u>	<u>3</u> <u>(21.4%)</u>	<u>0</u> <u>(0%)</u>	<u>25</u> <u>(51.0%)</u>	
	19 (79.2%)	2 (14.3%)	0 (0%)	21 (42.9%)	
total	<u>24</u> <u>(100.0%)</u>	<u>14</u> <u>(100.0%)</u>	<u>11</u> <u>(100.0%)</u>	<u>49</u> <u>(100.0%)</u>	
	24 (100.0%)	14 (100.0%)	11 (100.0%)	49 (100.0%)	

It was found that 51.0% (n=25) of smokers in the treatment group achieved complete success, i.e. gave up smoking completely, and 85.7% (n=42) managed to reduce their smoking at the end of the 9-day treatment period; the sustained quitting rate in the treatment group, i.e. 3 months after the trial, was 42.9% (n=21) and the rate of managing to reduce the smoking was 81.6% (n=40). In the light of the findings, a conclusion may therefore be drawn that Zhong Mai Yan Ke is an effective agent for smoking cessation and has achieved more than the predicted level of success specified in the hypothesis, i.e. at least 30% of the smokers in the treatment group will be able to reduce the number of cigarettes smoked per day and at least 20% will be able to give up the habit completely at the end of the 9-day trial; at least 20% of the smokers in the treatment group will be able to reduce the number of cigarettes smoked per day and at least 10% will be able to give up the habit completely 3 months after the trial.

Whilst 51% of treated subjects managed to quit smoking completely at day 9, many (42.9%) still managed to maintain their success at the end of 3 months. Even more encouraging, those who were smoking for less than 10 years, 22 (88%) of them successfully stop smoking at day 9 and 19 (76%) managed sustain that at 3 months.

Within the treatment group, there were 7 smokers at the end of the 9-day trial and 9 smokers obtained 3 months after the trial had no change in smoking habit. 7 smokers at the end of the 9-day trial and 8 of 9 smokers obtained 3 months after the trial smoked 30 cigarettes or more per day; 6 of these 7 smokers at the end of the 9-day trial and 7 of these 9 smokers obtained 3 months after the trial had smoked for 20 years or more. One can argue therefore, Zhong Mai Yan Ke is not effective for heavy smokers and those who have been addicted for a long period of time (table 4.7 and 4.8)

4.2.3 Side effects

Some systemic side effects occurred at the end of the 9-day trial, such as nausea and dizziness when applying Zhong Mai Yan Ke. 41 smokers (83.7%) experienced no side effects; 3 smokers (6.1%) felt nausea, 2 smokers (4.1%) felt dizziness and 3 smokers (6.1%) felt dizziness and nausea (table 4.13).

Table 4.13 side effects when applying Zhong Mai Yan Ke, i.e. during the course of the 9-day trial

		Frequency	Valid Percent
Valid	no side effects	41	83.7
	nausea	3	6.1
	dizziness	2	4.1
	dizziness and nausea	3	6.1
	Total	49	100.0

We asked the smokers who had suffered from side effects to explain the uncomfortable feelings in detail by telephone.

Smoker 1

“I feel a little nausea and suffer from poor appetite during the treatment course of 9 days. I feel better when I withdraw the patches.”

Smoker 2

“Nausea, mainly nausea, is not only for cigarettes, but also for other foods.”

Smoker 3

“I do not feel good, dizziness bothers me and I do not want to eat food and I feel nausea when I try to smoke.”

Smoker 4

“I feel dizziness and this feeling disappears when I withdraw the patches.”

Only one smoker who applied ZMYK and another one who applied placebo plaster suffered from slight red rashes on the skin during the 9-day trial. People who have sensitive skin can suffer from an allergic reaction when he applies the patches. So this event could be a barrier against use of these patches just as with nicotine patch. Also this side effects from placebo plaster as future studies may be limited by this event.

No one suffered from any side effects at three months after the trial. That means some side effects such as nausea and dizziness will disappear when people stop applying Zhong Mai Yan Ke. In the light of the findings, it can be said Zhong Mai Yan Ke is an effective agent for smoking cessation and that the hypothesis is proven, i.e. smokers in

the treatment group experience minor side effects as indicated by the manufacturer of Zhong Mai Yan Ke.

4.3 Summary

64 smokers were recruited in the clinical trial, 50 in treatment group and 14 in control group. The initial results and the 3 months follow-up data suggest that Zhong Mai Yan Ke is an effective smoking cessation agent for young people and those who have smoked for less than 10 years. It is not effective for those who are older than 50 years of age and have smoked for more than 30 years or more.

The rates of quitting smoking completely in the active treatment group were 51.0% at the Day 9 and 42.9% at 3 months after the trial. 85.7% of the subjects at Day 9 and 81.6% at 3 months of the study, managed to reduce their smoking (i.e either stopping completely or reducing the number of cigarettes smoked per day. At 3 months of the study 2 smokers smoked the same number of cigarettes as before. 12 smokers smoked more cigarettes per day at 3 months after the trial than that at the end of the 9-day trial, ranging from 3 to 9. 14 smokers in the control group who applied the placebo bandages were unsuccessful in smoking cessation. 100% of them did not quit smoking at all nor managed to reduce the number of cigarettes smoked per day.

Chapter 5

Integrating Allopathic Medicine and Traditional Chinese Medicine (TCM)

5.1 The present situation of smoking and smoking cessation in the world

It is well known that smoking is harmful to people's health. It has a bad effect on families and on national economies. During the past decade, people and governments have campaigned against smoking. Most smokers want to quit, but they find it difficult to do successfully because they experience the well-characterised barriers, and withdrawal symptoms during their attempts to quit. In Western countries, many kinds of methods to stop smoking have been carried out, such as social movements, health education, advice and encouragement.

The basic premise of Western medicine or allopathic medicine is founded on the principle of diagnosis and intervention. The study of anatomy, physiology, biochemistry and other related subjects provides the basic understanding of how the human body functions and how to deal with disease processes. The management of diseases in this branch of medicine relies by-and-large on the use of pharmaceutical products to control or minimise symptoms. Surgery is one example of an intervention where doing therapies cannot succeed. In recent years, many kinds of medicines,

health products and therapies for quitting smoking, such as Nicotine Replacement Therapy (NRT), and non-nicotine drugs have been tried to help smokers to quit in both Western and Eastern countries. However, the effectiveness of these products is not high and they can not help all smokers to cease successfully. At the same time practitioners of Traditional Chinese Medicine (TCM) have been seeking effective treatment method for smoking cessation, such as acupuncture.

TCM has a long history and dates back to the ancient times. As early as the late period of the New Stone Age, around 2700 B.C., Chinese Ancestors in the Yellow River valley primarily summed up their primitive experiences in herbs, acupuncture, massage etc. which had gradually been accumulated by their forefathers in their struggle for life and fight against nature. This turned spontaneous reactive medical behaviour that originated from a self-defence instinct, into a medical mode for the early human race. In the past 5000 years, social changes promoted the development of such ancient medicines. Sui and Tang Dynasties were a flourishing age for TCM. Thanks to the rapid development of China's politics, economy, culture, transportation and the excellent situation of cultural exchange with foreign countries during that period, TCM was also introduced into Korea, Japan, Arabian countries, etc. and it promoted the development of this branch of medical science in those countries. For example, "Law and Decrees of Tai Bao" issued during the Tai Bao years (701-703) of Japan's Civil and Military Dynasty, stipulated massage as one of the compulsory courses for medical students. This laid a solid foundation for "the three manipulating skills" that remain current now in Japan.

Over the last century, TCM has co-existed with allopathic medicine in China. There are 350,000 staff working in more than 2,500 hospitals of traditional medicine in China. In addition, 95% of general hospitals have units for TCM and 50% of rural doctors are able to provide both traditional and allopathic medicine.

In China, there are 800 manufacturers of herbal products. There are 170 research institutions across the country with perhaps the most prestigious being the Academy of TCM in Beijing. Chinese people believe the effectiveness of TCM and would like to be treated by using TCM. So TCM might be more appropriate and useful in China. Unfortunately, the channels for communication in this field between the West and

East are poor. Consequently, some good examples of practice and research evidence have not been disseminated. One of the reasons may also be that since TCM, particularly herbal medicines have been used for many centuries - providing evidence is not seen to be important.

Nonetheless, TCM, including acupuncture, herbs and massage, etc. is gradually introduced to the outside world because it can produce unexpectedly positive effects with fewer side effects for many diseases. Acupuncture especially is accepted in Western countries, partly due to its fast therapeutic effect. For example, there are more than 3,000 TCM clinics registered in England now, according to yellow pages.

The main TCM approach for smoking cessation is the acupuncture-needling Tim Mee acupoint. Practitioners of Traditional Chinese Medicine seek to regulate the balance of two different types of energy - ying and yang with acupuncture therapy through the meridians and collaterals, which are the roads that serve as transporting energy within the human body. Acupuncture therapy is to treat diseases through stimulating certain acupoints on the body surface. Acupoints are the specific sites where the energy within the human body through the meridians and collaterals is transported to the skin and are located on the meridians and collaterals. In recent years, acupuncturists attempted to promote smoking cessation by stimulating Tim Mee acupoints on both hands. However, the effectiveness is different depending on various acupuncture techniques. In recent years, a new herbal patch for smoking cessation, Zhong Mai Yan Ke, which conquers these disadvantages, has been used to substitute acupuncture treatment completely. It contains Cloves, Cassia, Areca and biological magneto-therapy, acts on Tim Mee acupoint on the wrists of both hands, stimulates taste, sense and nerve system of the human body and changes the smell of cigarette smoking to stop smoking. It is claimed that the rate of effectiveness (quitting completely and reducing cigarettes per day) of Zhong Mai Yan Ke for smoking cessation is 85% and has no serious side effects.

5.2 Some comparisons between allopathic interventions and Traditional Chinese Medicine (TCM)

The effectiveness and side effects of allopathic interventions and Traditional Chinese medicine (TCM) can be compared (See table 5.1).

Table 5.1 Compare among different smoking cessation products

Product		Function	Therapeutic Regimen	Advantages	Side effects	Efficacy
Form of prepared drugs	Brand					
Nicotine Patches	Habitrol	absorption through skin	21mg/day (4 wks), 14mg/day (2 wks), 7mg/day (2 wks)	easy to use	itching or redness of the skin	about 20-30% at 6 months
	Nicotine Transderma					
	Nicoderm CQ		14mg/day (6 wks), 7mg/day (2 wks)			
	Nicotrol		15 mg/day for 6 wks			
Nicotine Gum	Nicorette (2mg/piece)	absorption through the lining of the mouth	9 pcs/day (6 wks), 6 pcs/day (3 wks), 3 pcs/day (3 wks)	far safer than cigarette smoking	jaw fatigue and soreness, gaseous distension, hiccups and nausea	27% at 6 months and 23% at 12 months
Nicotine Nasal Sprays	Nicotrol	absorption through the lining of the nose	64 squirts/day for 12 wks	rapid delivery and relatively high plasma concentrations	irritation of nose and throat	32% at 6 months and 26% at one year
Nicotine Inhaler	Nicotrol Inhaler	absorption through the mouth	24mg/day for 12 wks	reduce fears associated with abrupt cessation of the hand-to-mouth ritual	irritation of throat and mouth	29% at 6 wks and 24% at 3 months
Non-nicotine products	Zyban	absorption through the stomach and intestines	300mg/day for 7-12 wks (150mg/day for first 3days)	be suitable for the smokers who either cannot tolerate NRT or prefer non-nicotine treatment	dry mouth and insomnia	27% at 6 months after the treatment
Traditional Chinese Medicine (TCM)	Zhong Mai Yan Ke (ZMYK)	absorption through skin	2 pics/day for 18 days	natural herbs	nausea and dizziness when applying	42.9% at 3 months after the treatment

It shows that Traditional Chinese Medicine is more effective for stopping smoking and lack of side effects. The cost of ZMYK is cheaper than that of allopathic interventions which are used in England because ZMYK is made of herbs and made in China where there are plenty of herbs and ZMYK is purchased according to the expense level of Chinese people. So it must be cheaper for English people if it is allowed to be sold in England.

In China, people believe the effectiveness of Traditional Chinese Medicine because it has been developed for about 5000 years. And herbs are planted everywhere. So Traditional Chinese Medicine might be more appropriate in China now.

5.3 A critical analysis of the study

In order to test the claim, this therapeutic trial to ascertain the extent of the effect of Zhong Mai Yan Ke was designed. Blind controlled studies are able to measure “genuine” quantitative differences between placebo and the active ingredient. However, only an open randomised controlled trial was possible for this project, here in this commercial and culture setting in China as discussed in chapter 3. It was inevitable the study was carried out as an open randomised trial.

The trial was only completed in China because Zhong Mai Yan Ke and the placebo Band-aid super-elastic adhesive are legally licensed medicines and commonly known in China. It was impossible to alter the packaging or their presentation to make them appear completely similar. Moreover, many people, including smokers, knew there was a magnetic disc in the patch of ZMYK whilst the Band-aid adhesive bandage did not include any magnetic discs. That meant that the volunteers always knew if the product they used was ZMYK by checking if a disc was in it. This was then an open trial.

In the trial 64 volunteers were recruited, based on the inclusion and exclusion criteria. 50 in the treatment group applied Zhong Mai Yan Ke for 9 days and 14 in the control

group used placebo for 9 days. In the treatment group, the rates of quitting smoking completely in the treatment group were 51.0% at the end of the 9 day trial and 42.9% at three months after the trial. Results in those managing to reduce smoking (quitting smoking completely and reducing cigarettes smoked per day) were 85.7% at the end of the 9 day trial and 81.6% three months after the trial. Smokers in the control group who applied the placebo bandages were unsuccessful in smoking cessation or reduction.

Zhong Mai Yan Ke was more effective for younger people and those who had smoked for less than 10 years. It was not effective for those who were older than 50 years and had smoked for 30 years or more.

Overall the results showed that ZMYK was effective in helping smokers to quit and to reduce their rate of smoking. No one reported side effects at three months. The initial side effects such as nausea and dizziness disappeared when people stopped applying Zhong Mai Yan Ke.

5.4 The future research directions

In this study, the application of herbal medicine in the treatment of nicotine addiction was shown to be of benefit to a small sample of smokers. A blinded randomised controlled trial would need to be carried out in the West to confirm that these results are reproducible.

This acupuncture based herbal patch might have a role in the UK if it were marketed because it contains natural herbs and not nicotine and because it can conquer the disadvantages of traditional acupuncture. For example, some people are afraid that needles would cause pain. It takes 20 to 30 minutes to complete one session of acupuncture treatment. The greatest advantage of patches is that they are convenient to apply and saving time. People can apply the patch themselves. If truly successful in the Western setting such patches would be welcomed.

5.5 Summary

This therapeutic trial ascertained the extent of the effect of Zhong Mai Yan Ke using an open randomised controlled trial. The results showed that ZMYK was effective in stopping smoking and that there are no lasting side effects. More research using a double blind trial, in a Western setting is needed before the results can be generalised.

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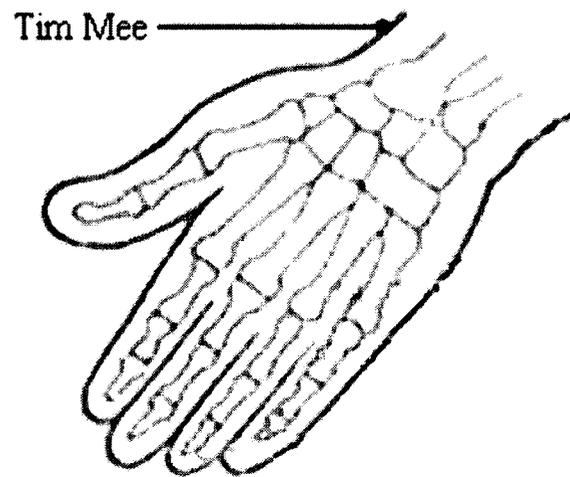
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Appendix A

Body Acupoint



Appendix B₁

Poster

Dear.....

We are carrying out research into helping smokers to give up smoking using Zhong Mai Yan Ke and placebo patches. Volunteers will be randomly allocated to Zhong Mai Yan Ke and placebo.

Zhong Mai Yan Ke which is composed of various kinds of Chinese herbs and a biological magnet flake needs to be applied on the acupoint of Timmei on the wrist. The patches are not very noticeable. Only a few users may have experienced any unpleasant effects, which will disappeared upon removal of the patches.

Band-aid super-elastic adhesive bandage are used as placebo patches. There is no any medication in it. So there is no any side effect when applying them.

The trial lasts for 9 days. You will be requested to complete some questionnaires at the outset of the trial and at the end of the 9-day trial. The follow-up data 3 months after the trial need to be collected using a telephone interview technique.

If you are interested in taking part please contact:

Shujuan Yao on 2466496 (help line)
Northeast Centre for selling Zhong Mai Yan Ke
188 Taiyuan Street
Northeast Road
Xigang District
116012

You can discontinue with the treatment at any time if you wish and it does not affect the treatment or service you will be provided in the further.

Appendix B₂

HEALTH SCREENING QUESTIONNAIRE

Name.....Date of birth.....

Please answer all of the following questions. If you answer yes, please give further details, continuing on a separate piece of paper if necessary.

	Yes	No	Details
Have you ever been treated in hospital? If yes, please give reason(s) and dates.			
Have you seen a doctor in the last year for any kind of health problem? If so please give reason(s).			
Are you having any treatment or investigations of any kind at the moment?			
Are you waiting for any treatment, operation or investigation?			
Have you ever had any illness or health related problem that may have been caused or made worse by your work?			
Have you ever been medically retired from any job, or left any job because of ill health?			
Have you had any days off sick in the last 3 years? If yes, please give number of days and reasons to the best of your recollection.			
Do you have any eyesight problems not corrected with glasses?			
Do you have any hearing problems?			
Do you have any difficulties standing, bending, lifting or with any other movements?			
Have you ever had any back problem?			
Have you ever had any problem with your joints including pain, swelling or stiffness?			
Have you ever suffered from any mental illness, psychological or psychiatric problem, including depression, anxiety, nervous debility, nervous breakdown, schizophrenia or eating disorder (anorexia or bulimia)?			

Have you ever had a drug or alcohol problem?			
Have you ever had fits, blackouts or epilepsy?			
Have you ever had any skin problems?			
Have you ever had any heart or blood pressure problems?			
Have you ever suffered from asthma, bronchitis or chest problems?			
Have you ever had treatment for tuberculosis (TB)?			
Have you ever had hepatitis or jaundice?			
Do you have any other medical conditions?			
At present, are you on any medication or Traditional Chinese Medicine (TCM), such as acupuncture and herbal treatment?			
Do you feel well at present?			
If applicable, please state whether you are pregnant or not.			

Appendix B₃

SURVEY OF SMOKING STATUS

Please enter the following information:

Name _____ Age _____ Sex: M F

1. How old were you when you started smoking? _____
2. How many cigarettes do you smoke a day now? _____
3. Have you tried giving up smoking? _____
4. If the answer to Question 3 is yes, how many times have you tried? _____
5. If the answer to Question 3 is yes, which method did you use? _____
6. Do you want to quit smoking very much now? _____

Consent for smoking cessation trial

I, (Full name) _____, having been fully informed of the trial and any associated complications with the application of the patches, agree to undertake the trial. I will also consent to give personal information about my smoking habits and a contact telephone number and address for progress monitoring.

I understand I can withdraw from the trial at any time.

I have been assured any information given will be kept in the strictest confidence and will only be used for anti-smoking research purposes solely by Dr. Cheung's team.

Signed _____

Date _____

Tel _____

Address _____

Thank you for completing this questionnaire. Please return the questionnaire immediately to Shujuan Yao.

Appendix C

Volunteer instruction leaflet

Dear.....

You will be given a supply of one box of Zhong Mai Yan Ke or 18 pieces placebo patches for 9 days. The application of these patches is very simple. Just remove the wrapper, and then apply the patches on both wrists at the acupoint of Tim Mee shown in the diagram.

Firstly, massage the acupoint of Tim Mee shown in the diagram 10 minutes before application. Secondly, apply a patch once a day to each wrist at the acupoint and left in place for 22 hours and then remove the patch. A new patch should be applied to each wrist after 2 hours.

Time for application: any time during the day

Precaution:

- Not edible
- KEEP AWAY FROM CHILDREN
- After each application, wash wrists with soap and water, and leave to air for 2 hours, then apply new patches.
- The effect of patches may make cigarettes taste insipid or bitter if you apply Zhong Mai Yan Ke. It is a normal reaction.
- Those who are extremely sensitive to Zhong Mai Yan Ke may occasionally feel slight dizzy, nauseated.
- If you want to discontinue the trial, please contact the “help line – 2466496 (China)” immediately.

Appendix D

Data from the Treatment Group

No.	Sex (M/F)	Age (years)	years of smoking	the number of cigarette smoking per day	history of quitting smoking		the effectiveness of using Zhong Mai Yan Ke at the end of the 9-day trial				the effectiveness of using Zhong Mai Yan Ke 3 months after the trial						
					times quitting smoking	methods or medicine	apply correctly (Y/N)	no effects (N)	the number of cigarette smoking per day	quitting smoking (Y)	side effect	no effect (N)	the number of cigarette smoking per day	quitting smoking (Y)	side effects		
1	M	22	3	12			Y									Y	
2	M	45	22-23	35	2	Nothing	Y	8						12			
3	M	21	4	15			Y									Y	
4	M	72	40	40			Y		N								
5	M	28	10	18			Y									Y	
6	M	34	12	20	1	Nothing	Y										
7	M	25	7	25			Y										
8	M	25	5	16			Y	3									
9	M	56	32	35	4	Nothing	Y	20									
10	M	26	8	28			Y									Y	
11	M	42	15	30			Y									Y	
12	M	24	4	12			Y									Y	
13	M	27	8	20			Y	10									10

Appendix D

Data from the Control Group

No.	sex (M/F)	Age (years)	years of smoking	number of cigarette smoking per day	history of quitting smoking		apply correctly (Y/N)	the effectiveness of using placebo at the end of the 9-day trial				the effectiveness of using placebo 3 months after the trial			
					times of quitting smoking	methods or medicine		no effect (N)	number of cigarette smoking per day	quitting smoking	side effect	no effect (N)	number of cigarette smoking per day	quitting smoking (Y)	side effect
1	M	35	12	22			Y	N			N				N
2	M	54	34	38			Y	N			N				N
3	M	42	17	20			Y	N			N				N
4	M	49	24	35			Y	N			N				N
5	M	44	26	30			Y	N			N				N
6	M	46	23	27			Y	N			N				N
7	M	42	20	22			Y	N			N				N
8	M	38	12	18			Y	N			N				N
9	F	76	10	12			Y	N			N				N
10	M	44	20	26			Y	N			N				N
11	M	26	7	15			Y	N			N				N
12	M	25	7	12			Y	N			N				N
13	M	25	7	18			Y	N			N				N
14	M	46	25	30			Y	N			N				N

Appendix E

The letter from dalian university in china

大连大学

Institute of Pharmacology
School of Medicine
Dalian University
Dalian, Liaoning, 116622
CHINA
10 January 2004

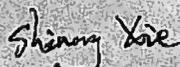
Professor Pali Hungin
Wolfson Research Institute
University of Durham, Queen's Campus
Thornaby
Stockton on Tees, TS17 6BH
U.K.

Dear Professor Pali Hungin,

In regard to Zhong Mai Yan Ke (ZMYK) trial conducted by Ms. Yuzhuo Wang in China, the trial is considered as an appropriate trial without ethical concerns in China. ZMYK is a licensed and non-prescription product in China. It has been on the Chinese market for many years and is considered as a safe product by Chinese authority.

I wish you find that this information is helpful.

Yours sincerely,



Professor Shirong Xie
Director of Institute of Pharmacology

