การศึกษาเปรียบเทียบประสิทธิภาพของการใช้ยานอร์ทริปทัยรินกับการให้คำแนะนำผู้ป่วยในการช่วยเลิกสูบบุหรี่

นายฉันชาย สิทธิพันธุ์

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A RANDOMIZED, CONTROLLED TRIAL TO COMPARE THE EFFECTIVENESS OF NORTRIPTYLINE PLUS BRIEF MOTIVATION COUNSELING AND MOTIVATION COUNSELING ALONE FOR SMOKING CESSATION IN THAI ACTIVE SMOKERS

Mr. Chanchai Sittipunt

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ฉันชาย สิทธิพันธุ์: การศึกษาเปรียบเทียบประสิทธิภาพของการใช้ยานอร์ทริปทัยรินกับการให้คำแนะนำผู้ป่วยในการช่วยเลิกสูบบุหรี่ (A RANDOMIZED, CONTROLLED TRIAL TO COMPARE THE EFFECTIVENESS OF NORTRIPTYLINE PLUS BRIEF MOTIVATION COUNSELING AND MOTIVATION COUNSELING ALONE FOR SMOKING CESSATION IN THAI ACTIVE SMOKERS) อ.ที่ปรึกษา: ศ.นพ.ธานินทร์ อินทรกำธรชัย, 53 หน้า ISBN: 974-14-2005-6

วัตถุประสงค์ : เพื่อศึกษาอัตราการเลิกสูบบุหรี่สำเร็จที่เวลา 3 เดือนภายหลังการช่วยให้ผู้ป่วยที่สูบบุหรี่หยุดสูบบุหรี่ด้วยการใช้ยานอร์ทริปทัยรินร่วมกับการให้คำปรึกษาอย่างสั้นเปรียบเทียบกับการให้คำปรึกษาอย่างสั้นอย่างเดียวในการรักษาภาวะสูบบุหรี่ในคนไทย

รูปแบบการทดลอง : การศึกษาเชิงทดลองแบบสุ่ม

สถานที่ทำการวิจัย: คลินิกอดบุหรี่ หน่วยโรคปอด ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

วิธีการศึกษา : ผู้ป่วยที่สูบบุหรี่ที่ต้องการได้รับการรักษาเพื่อเลิกสูบบุหรี่ ที่มารับการรักษาที่คลินิกอดบุหรี่ ที่อายุเกิน 18 ปีและสูบบุหรี่มากกว่า 10 มวนต่อวันและเข้าในเกณฑ์รับเข้าการวิจัยและยินยอมเข้าร่วมการวิจัย จะได้รับการสุ่มให้ได้รับรักษาด้วยการใช้ยานอร์ทริปทัยรินร่วมกับการให้คำปรึษาอย่างสั้นหรือยาหลอกร่วมกับการให้คำปรึกษาอย่างสั้น และติดตามการรักษาอย่างต่อเนื่อง ผู้ป่วยจะได้รับการประเมินการหยุดสูบบุหรี่หลังจากการรักษาเป็นเวลาสามเดือน เพื่อประเมินว่าผู้ป่วยสามารถหยุดสูบบุหรี่ได้ต่อเนื่องเกิน 2 สัปดาห์ติดต่อกัน

ผลการศึกษา: มีผู้เข้าร่วมการศึกษาทั้งสิ้น 137 ราย โดย 68 รายอยู่ในกลุ่มควบคุมและ 69 รายอยู่ในกลุ่มทดลอง พบว่าผู้ป่วยทั้งสองกลุ่มไม่มีความแตกต่างกันในด้านข้อมูลพื้นฐาน ภายหลังการทดลองพบว่าผู้ป่วยในกลุ่มทดลองมีอัตราการเลิกสูบบุหรี่ที่สูงกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (43.5% vs 26.5%, p=0.014, OR=2.5 95% CI 1.19-5.25) และพบว่าในกลุ่มทดลองมีอัตราการเกิดภาวะแทรกซ้อนที่ไม่รุนแรง คือ ปากแห้ง มากกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ

สรุป :การใช้ยานอร์ทริปทัยรินร่วมกับการให้คำปรึกษาอย่างสั้นเพื่อช่วยให้ผู้ป่วยเลิกสูบบุหรี่ ทำให้ผู้ป่วยสามารถเลิกสูบบุหรี่ได้สูงกว่าการให้คำปรึกษาอย่างสั้นเพียงอย่างเดียวภายหลังการรักษา 3 เดือน โดยมีผลข้างเคียงที่ไม่รุนแรงสูงกว่าเล็กน้อย

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่อนิสิต.....

ปีการศึกษา 2548 ลายมือชื่ออาจารย์ที่ปรึกษา.....

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KEY WORDS: SMOKING CESSATION NORTRIPTYLINE BRIEF MOTIVATION INTERVENTION ACTIVE SMOKERS

CHANCHAI SITTIPUNT: A RANDOMIZED CONTROLLED TRIAL TO COMPARE THE EFFECTIVENESS OF NORTRIPTYLINE PLUS BRIEF MOTIVATION COUNSELING AND MOTIVATION COUNSELING ALONE FOR SMOKING CESSATION IN THAI ACTIVE SMOKERS. THESIS ADVISER: PROF.THANIN INDRAGUMTHORNCHAI, 53 pp. ISBN 974-14-2005-6

Objective: To determine the smoking abstinence rate at 3 months in Thai active smokers who use nortriptyline combined with brief motivational counseling or brief motivational counseling alone for smoking cessation.

Design: Double blind randomized controlled trial

Setting: smoking cessation clinic, faculty of medicine, Chulalongkorn University

Method: Active smoking (more than 10 cigarettes per day) who was older than 18 years and are willing to quit smoking were randomized into control group and treatment group. Control group received brief motivation counseling and placebo. Treatment group received nortriptyline 50 mg/day and brief intervention counseling. Patients were followed up for 3 months. Success rate of smoking cessation and other secondary outcomes at 3 months were evaluated.

Result: There were 68 patients in control group and 69 patients in treatment group. There were no statistically significant difference in baseline demographic data and smoking history in 2 groups. Smoking cessation rate at 3 month rate was higher in treatment group than in control group 43.5% vs 26.5% respectively, p=0.014, OR=2.5 95% CI 1.19-5.25) . Patients received nortriptyline experienced more side effect of dry mouth than in control group.

Conclusion: Nortriptyline and brief motivational counseling was more effective in smoking cessation treatment than brief motivational counseling alone at 3 months after treatment and related with minor side effects from treatment.

Field of study…….. Health Development Student's signature……

Academic year 2005 Advisor's signature……

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CONTENTS

Page

CHAPTER

LIST OF TABLES

LIST OF FIGURES

Page

CHAPTER I

BACKGROUND AND RATIONALE

Tobacco is the agent most responsible for avoidable illness and death.worldwide [1]. Millions of world population consume this toxic product on a daily basis, its use brings premature death to millions of people each year and contributes to profound disability and morbidities in many others. Approximately one-third of all tobacco users will die prematurely because of their dependence on tobacco. Unlike so many epidemics in the past, there is a clear, contemporaneous understanding of the cause of this premature death and disability- the use of tobacco. It is a testament to the power of tobacco addiction that millions of tobacco users have been unable to overcome their dependence and save themselves from its consequences. Indeed, it is difficult to identify any other condition that presents such a mix of lethality, prevalence and neglect, despite effective and readily available interventions.[2]

In Thailand, cigarettes smoking are a major health problem. Approximately 10 millions of Thai population are active smokers and the number is increasing especially in teenagers and women.[3] Smoking cessation campaign has been introduced nationwide in our country in order to prevent future health consequences of smoking since 1974. Epidemiological data suggest that more than 70% of active smokers want to quit and have made at least one prior smoking cessation attempt. Approximately 47% of active smokers try to quit each year.[2] A study in Thai active smokers shows that 66.2 % of male smokers in Ayutthaya province wanted to quit smoking.[3] There are factors that lead an individual to want to quit such as beliefs about the benefits of quitting, medical advices, pressure from family or work related factors.[5] The first step in treating tobacco users and dependence is to identify active smokers who are willing to quit.[4,5] Willingness to quit is very crucial for smoking cessation and will lead to smoking cessation attempts and success. However smokers who were willing to quit and attempted quitting process, only 7% succeeded and remained smoking free at 1 year after quit attempt without any intervention. Success rates can be increased to 30-40% by using guideline-recommended treatment or participate in smoking cessation program.[4] However, despite extensive research, accurate and consistent predictors of successful smoking cessation attempt have not been identified.[6]

Smoking cessation program can be divided into 2 phases: the initial phase and the maintenance phase. The initial phase is the first 2 months after decision to quit smoking and the goal of treatment in this period is to assist smokers to start smoking cessation and deal with withdrawal symptoms and urge to smoke. The maintenance phase is to assist smokers who already quit in the initial phase in prevention of smoking relapse. The key components of clinical intervention for the initial phase of smoking cessation are counseling and pharmacotherapy.[5] Only brief clinical intervention (3 minutes or less) can significantly improve success rate of quitting attempt. The more intense clinical intervention can lead to higher success rate but may not be practical in routine practice for most practitioners because of time constraint. The recent guideline for treating tobacco use and dependence also recommend that all smokers attempt to quit should receive pharmacotherapy, except in cases in which pharmacotherapy uses requires special consideration (eg, those with contraindications, those who smoke fewer than 10 cigarettes per day, pregnant/breast feeding woman and adolescent smokers). There are several medications approved for smoking cessation in. First line pharmacotherapy approved by FDA are nicotine supplement medications and sustained released bupropion hydrochloride. These medications have been shown in clinical trials to increase success rate of smoking cessation.[7,8] But the cost of these medications is quite substantial. Both nicotine supplement and slow released bupropion cost approximately 120 bath/day in Thailand. The cost of treatment is one factor that can discourage smokers from quit smoking.

Nortriptyline is an antidepressant medication that has also been used in smoking cessation and has been shown to increase success rate significantly compared to placebo.[6,10,11,12,13] The present guideline from The United States has recommended nortriptyline as a second line therapy for smoking cessation because of concerns regarding side effects of nortriptyline. Nortriptyline is much cheaper than first-line smoking cessation medications and widely available in Thailand (cost of nortriptyline is 4 baht/day).

The ministry of health and Thai Thoracic Society have planned to develop a practical guideline for smoking cessation in Thailand. We really in need of smoking cessation guideline that is practical for primary health care providers. There is no sufficient data of pharmacotherapy agent for smoking cessation in Thai smokers. If we recommend first line medication approved by FDA, it can lead to a large medication costs and many Thai smokers would not be able to afford these relatively expensive medications. So we decided to conduct a clinical research to study effectiveness of nortriptyline and brief motivational intervention for smoking cessation in Thai active smokers.

CHAPTER II

LITERATURE REVIEW

Interventions to aid smoking cessation are among the most important treatments that can be offered to smokers to improve their current and future health and reduce the risk of premature death. In the year 2000, an estimated 4.83 million premature deaths worldwide were a direct consequence of smoking. [26] Chronic obstructive pulmonary disease (COPD) accounted for one-fifth of these deaths. Smokers who are susceptible to developing COPD suffer a progressive decline in lung function, resulting in significant disability. For these people, smoking cessation is the only intervention that has been proven to modify the course of airways obstruction, and can result in improving pulmonary function, decreasing respiratory symptoms, and decreasing acute respiratory tract infections.[27] International COPD guidelines recommend that smokers be strongly advised to quit, and should be offered help in doing so.[28]

Most smokers say they want to stop, and about two-thirds will make an attempt each year. However, many will choose to make an unaided quit attempt; a method that has only a small chance of long-term success. [29] The primary reason why many smokers find it difficult to quit is because of their dependence on nicotine. Tobacco smoke provides rapid delivery of nicotine to the central nervous system, where it facilitates the release of a number of neurotransmitters, such as dopamine and noradrenaline .[30] In dependent smokers, nicotine deprivation precipitates a withdrawal syndrome, consisting of symptoms such as irritability, low mood, poor concentration, and urges to smoke that can undermine a smokers' attempt to quit. [31]

Nicotine is the substance in cigarettes smoke that is responsible for addictive effect of cigarettes. Nicotine from inhaled smoke is absorbed at alveolar into alveolar capillary and reaches central nervous system in seconds after inhalation. The dependence-producing effects of nicotine are believed to be mediated in part through its action as an agonist at neuronal nicotinic acetylcholine receptors (nAChRs).[53,54] Activation of this receptors increases the releases of dopamine and other neurotransmitters in the nucleus accumbens and prefrontal cortex, an effect shared by most substances of abuse.[54] (see figure 1)

Smokers who tried to quit by themselves without any intervention had low success rate and high rate of relapse .[1,4,5] Smoking cessation techniques consist of two main interventions, behavior modification and smoking cessation medications which have been demonstrated in a number of studies to increase success rate in smoking cessation. [1, 4, 5, 6]

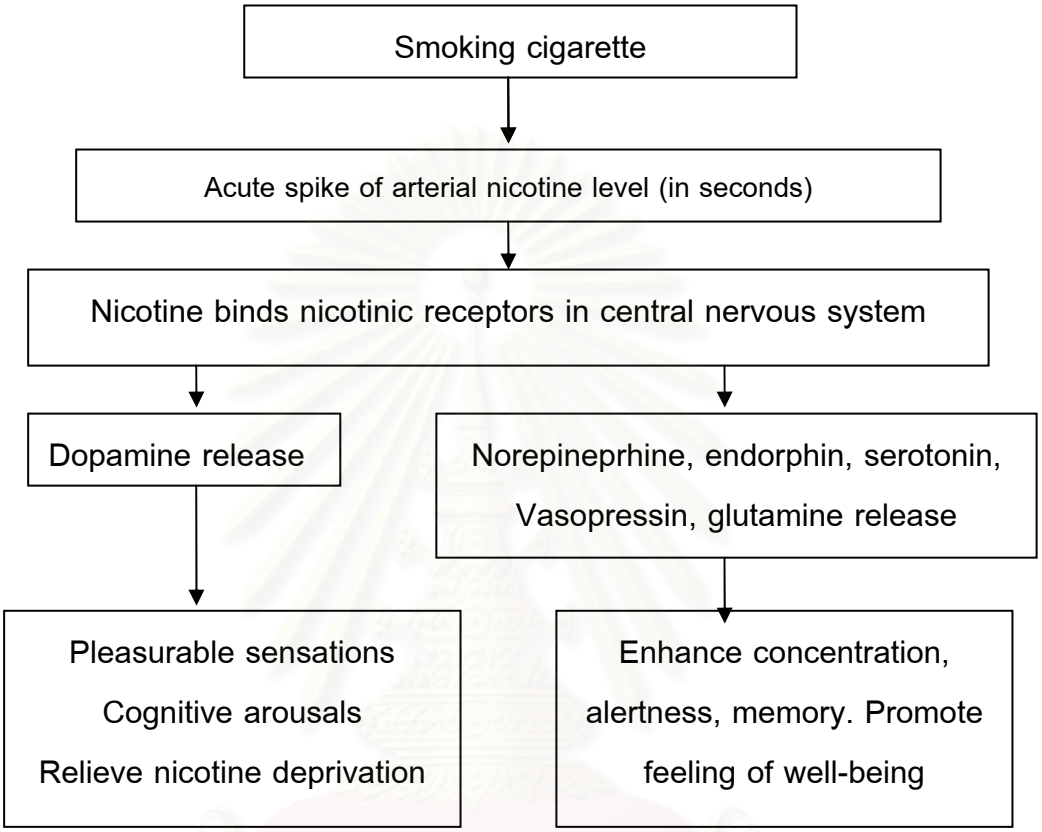


Figure 1: Psychopharmacologic effects of nicotine

Two first-line smoking-cessation medications approved by FDA are in common use: nicotine replacement therapy (NRT), of which there are six different products available, and bupropion slow released. NRT acts by replacing some of the nicotine smokers would have received from their cigarettes, and in doing so reduces the severity of withdrawal symptoms. NRT approximately doubles the chance of long-term abstinence (odds ratio [OR] 1.74; 95% CI: 1.64–1.86), [32] although the absolute success rate depends upon the intensity of the additional support provided and the type of smoker being treated.[33] Although effective, this medication is no magic cure, and at least 70% of smokers who try to quit using NRT relapse within a year.[34]

Review of non-nicotine medications for smoking cessation

Bupropion (slow released)

Bupropion, an atypical antidepressant, is the first, and, so far, the only non-nicotine treatment licensed for smoking cessation. There is good rationale for testing antidepressants for smoking cessation, as a strong association exists between smoking and depression. A higher prevalence of smoking exists among people who have, or have had a history of, depression. Smokers who are depressed find it more difficult to quit, some smokers become depressed when they stop smoking, and post-cessation depression is related to relapse. [37,38] However, not all antidepressants have been shown to be helpful for smoking cessation.[9,35] Bupropion is presumed to help smokers quit through its ability to inhibit the neuronal reuptake of dopamine and noradrenaline, both important in nicotine dependence and withdrawal. It may also help through its action as a non-competitive inhibitor of the nicotinic acetylcholine receptor, and perhaps by way of its effect on serotonin reuptake. [39] Although the precise mechanism by which this medication aids smoking cessation remains uncertain, bupropion has been proven to increase abstinence rates [35, 36, 39, 40] and reduce the severity of withdrawal symptoms experienced by smokers when they abstain.[41-44] Two pivotal outcome studies were published in the late 1990s. The first compared the effect of three different daily doses (100, 150, and 300 mg) with placebo.[41] Results showed a linear effect of an increasing dose on point-prevalence cessation, although no significant difference was found between 150 and 300 mg per day at 12 months follow-up. The second major study randomized smokers to receive either bupropion (300 mg/day), 21 mg/24 h nicotine patch, both bupropion and patch, or placebo.[43] The 1-year continuous abstinence rates were 18%, 10%, 23%, and 6%, respectively. All active treatments were significantly better than placebo, and bupropion was better than patch alone. There was no added advantage of using a combination regimen compared with bupropion alone. Since these studies, a number of other studies examining the efficacy of bupropion have been published. One Cochrane review [35] identified a total of 24 that met their inclusion criteria. Nineteen studies, which included more than 4000 smokers, looked exclusively at the efficacy of bupropion compared with placebo. All studies used adjunctive behavioral support. The meta-analysis showed that, compared with placebo, bupropion approximately doubled long-term abstinence rates (OR: 2.06; 95% CI: 1.77–2.40). The efficacy of bupropion has also been examined in smokers with smoking-related disease, a population typically more dependent and therefore

harder to treat. People with stable cardiovascular disease treated with bupropion, compared with placebo, achieved higher 1-year continuous abstinence rates (22% vs. 9%).[46] When used in smokers with mild to moderate COPD, bupropion was associated with significantly higher abstinence rates at 6 months (16% vs. 9%)[45] but not at 1 year (10% vs. 9%).[35] Its use in preventing smoking relapse has also been examined.[42,47] The results of one study investigating the use of bupropion, compared with placebo, for a year showed no difference in continuous abstinence rates between groups at 1 or 2 years after quitting.[42] Another study showed no advantage of using bupropion over placebo for preventing relapse in patients successfully quitting smoking using a nicotine patch.[47] Therefore, evidence currently available suggests there is little benefit for using bupropion long-term to prevent relapse.[35] Few studies have compared bupropion with other smoking-cessation medications. In one of the pivotal studies mentioned earlier, bupropion was more effective than the nicotine patch. [43] Combining NRT and bupropion significantly increased 1-year outcome compared with patch alone (23% vs. 10%). However, more recent studies have not confirmed these results. [35] Further data are needed on this issue. Bupropion is a safe treatment when used correctly. Contraindications should be checked when prescribing this medication. In addition, some precautions need to be considered. Smokers with a predisposition to seizures should not take bupropion unless the benefit of smoking cessation outweighs any risks associated with using the medication.[48] Bupropion, however, has been found safe to use in smokers with stable cardiovascular disease, without adverse effects on blood pressure or heart rate.[46] Bupropion undergoes hepatic metabolism, primarily by isoenzyme CYP2B6. Therefore, other drugs that affect this enzyme (e.g. cimetidine, sodium valproate and cyclophosphamide) may affect bupropion metabolism. Bupropion inhibits the activity of CYP2D6, and so there may be a reduced rate of metabolism of drugs such as betablockers and Type 1C antiarrhythmics. A dose reduction in these medications may be required. [49]

There were also some side effects related to bupropion therapy for smoking cessation. Tracey JA et al reported cases of bupropion overdose and toxicities in Ireland. [13] Common features included tachycardia, drowsiness, hallucinations and convulsions. Two patients developed severe cardiac arrhythmias, including one patient who was resuscitated following a cardiac arrest. All patients recovered without sequelae. There was also a report of acute myocardial ischemia associated with ingestion of bupropion and pseudoephedrine in a 21-year-old man. [18]

Jorenby DE et al conducted a controlled clinical trial comparing sustained-release bupropion, a nicotine patch, or both for smoking cessation.[20] This was a double-blind, placebo-controlled comparison of sustained-release bupropion (244 subjects), nicotine patch (244 subjects), bupropion and nicotine patch (245 subjects),and placebo (160 subjects) for smoking cessation. Smokers with clinical depression were excluded. The abstinence rates at 12 months were 15.6 percent in the placebo group, as compared with 16.4 percent in the nicotine-patch group, 30.3 percent in the bupropion group($P<0.001$), and 35.5 percent in the group given bupropion and the nicotine patch($P<0.001$).Seventy-nine subjects stopped treatment because of adverse events: 6 in the placebo group (3.8 percent), 16 in the nicotine-patch group (6.6 percent), 29 in the bupropion group (11.9 percent), and 28 in the combined-treatment group (11.4 percent). The most common adverse events were insomnia and headache.

Ahluwalia JS et al. conducted a clinical trial comparing a sustained-release form of bupropion hydrochloride (bupropion SR) with placebo for smoking cessation among African Americans.[15] Participants were randomly assigned to receive 150 mg of bupropion SR (n = 300) or placebo (n = 300) twice daily for 7 weeks. Brief motivational counseling was provided in-person at baseline, quit day, weeks 1 and 3, end of treatment (week 6), and by telephone at day 3 and weeks 5 and 7. The confirmed abstinence rates at the end of 7 weeks were 36.0% in the bupropion SR group and 19.0% in the placebo group (17.0 percentage point difference; 95% confidence interval, 9.7-24.4; P<..001).

Nortriptyline

Nortriptyline is one of tricyclic antidepressants which were discovered and has been used in clinical practice for management of depression since 1960's.[21] It has been shown to increase success rate of smoking cessation when used as an adjunctive therapy in patients regardless of a history of major depression.[6,7,9,11] Nortriptyline has an ability to inhibit neuronal uptake of norepinephrine[21] and therefore increases level of norepinephrine in central nervous system mimicking effect of nicotine. This is a possible mechanism of action of nortriptyline in smoking cessation. Another possible mechanism of efficacy for nortriptylineis that its noradrenergic actions substitute is that nortriptyline is a nicotine receptor antagonist. This possibility is raised because the other antidepressant found effective for smoking cessation—bupropion—is a nicotine

receptor antagonist. [55] However, nortriptyline appears to be a weak nicotine receptor antagonist [56] Nortriptyline may also prevent cessation related depression and therefore decrease chance of smoking relapse. [57]

Side effects of nortriptyline is less than other tri-cyclic antidepressant. Minimal night stimulation, low incidence of anticholinergic side effects, low incidence of orthostatic hypotension, low risk of seizure. Most common side effects are constipation and dry mouth. [21, 57] Nortriptyline should be used with caution in patients with cardiovascular diseases because risks of cardiac arrhythmia. In smoking cessation studies Hall et al studied nortriptyline for smoking cessation and found that there was higher incidence of minor side effects (dry mouth and lightheadedness) in nortriptyline treated group when compared to placebo but there was no significant difference in drop out rate because of medication side effects between 2 groups.[10] Da Costa et al conducted a clinical trial comparing nortriptyline and placebo for smoking cessation and found that there was no statistically significant in adverse reactions between the two groups and there was no serious side effects in nortriptyline treated group[14]

From Cochrane Database, Hughes JR et al reviewed clinical trials to assess the effectiveness of antidepressant medications in adding long term smoking cessation.[13,35] They stated that ”Some antidepressants (bupropion and nortriptyline) can aid smoking cessation. It is not clear whether these effects are specific for individual drugs, or would occur with any antidepressant.”

Hall SM et al examined the effects of nortriptyline and cognitive-behavioral therapy on smokers with and without a history of major depression. 199 smokers who smoked more than 10 cigarettes/day received nortriptyline or placebo for 12 weeks. Patients also received cognitive-behavioral therapy or health education therapy. Counseling began at week 4 and patients selected quit date at week 5. Self reported abstinence rates, verified by cotinine concentrations and carbomonoxide level, were 31% for nortriptyline recipients and 21% for placebo recipients. The positive effect of nortriptyline was observed regardless of a history of major depression. The researchers also found that nortriptyline recipients experienced a greater reduction in depressive symptoms and fatigue during the first week after quitting than placebo recipients.[7] But all patients in this study received intensive counseling (either with small group session (ten 2-hour group session(with 5-11 members) for 8 weeks or five 90-minute sessions (with 5-11 members) for 8 weeks.). This type of counseling is not practical in our practice and probably has an additive effect on nortriptyline treatment. There was over-all 24% drop-out rate in this study.

Hall SM and colleagues conducted another clinical trial, comparing efficacy of bupropion, nortriptyline alone or combined with psychological intervention in the treatment of cigarette smoking.[12] They compared these 2 drugs with placebo. They enrolled 220 smokers and randomized into 6 groups (2 (medical management alone vs. combination with psychological intervention) x 3 (bupropion vs. nortriptyline vs. placebo). They found that both nortriptyline and bupropion were efficacious in producing abstinence in cigarette smokers. Similarly, psychological intervention produces better abstinence rates than simple medical management. Both drugs, and psychological intervention, have limited efficacy in producing sustained abstinence. The data also suggested that combined psychological intervention and antidepressant drug treatment may not be more effective than antidepressant drug treatment alone. Rate of abstinence at 12 weeks was 42%, 34% and 11% in Bupropion, nortriptyline and placebo group without psychological intervention, respectively.

Costa CL et al recently studied the efficacy of nortriptyline in smoking cessation. They enrolled 144 smokers and randomized to receive nortriptyline or placebo for smoking cessation.[14] All patients also had behavioral orientation group for 5 weeks. Most of the patients in this study were female. They found that at 6 weeks, patients receiving nortriptyline showed significantly higher cessation rate (55.9%) compared to the group receiving placebo (23.3%; $p < 0.001$). In a univariate analysis on prognosis factors influencing the rate of cessation in this study, the Fagerstrom test results ($p = 0.005$) and nortriptyline treatment ($p < 0.001$) were identified. Logistic regression showed that a Fagerstrom test score of < 7 (odds ratio [OR], 3.1; 95% confidence interval [CI], 1.47 to 6.7; $p = 0.003$) and nortriptyline use (OR, 4.1; 95% CI, 2 to 8.3;$p < 0.001$) were independent factors impacting the rate of success for smoking cessation. No significant complications were observed in the nortriptyline group.

Prochazka AV et al conducted a randomized, double blind, placebo-controlled trial comparing between adding nortriptyline or placebo to behavior smoking cessation program.[9] A total of 214 patients were randomized (108 to nortriptyline and 106 to placebo). There was a significant reduction in several withdrawal symptoms including anxious/tense, anger/irritability, difficulty concentrating, restlessness, and impatience by day 8 after quit day in the nortriptyline group. The cessation rate at 6 months for those who received nortriptyline was 14% compared with 3% among those who received placebo.

Summarization of randomized controlled trial and brief results are shown in table 1, odds ratios and 95% confidence intervals in table 2

Table 1 randomized controlled trial of nortriptyline for smoking cessation

study	Number of subjects	Follow up (months)	Odds ration(95%CI)	Dropouts due to adverse effects (%)
Hall et al. 1998[10]	199	16	2.4(1.1-5.0)	4
Prochazka et al. 1998[9]	214	6	5.5(1.6-19.7)	9
Da Costa et al. 2002[14]	144	3	4.7(1.5-15.0)	7
Hall et al. 2002[12]	220	12	1.2(0.4-3.7)	4

Table 2: Odds ratios and 95% confidence intervals across validated medication for smoking cessation treatments

medication	**Data from Cochrane [35]**
nortriptyline	2.1(1.5-3.1)
Bupropion	2.0(1.7-3.4)
clonidine	1.9(1.3-2.7)
Nicotine gum	1.7(1.5-1.8)
Nicotine patch	1.7(1.6-1.9)
Nicotine inhaler	2.1(1.7-3.0)
Nicotine nasal spray	2.3(1.6-3.2)

Brief intervention (physician advice) for smoking cessation

There are several studies comparing different methods of counseling for smoking cessation. In the recent review article to assess the effectiveness of advice from physicians in promoting smoking cessation,[50] the results of this review confirm that brief advice from physicians is effective in promoting smoking cessation. The pooled effect of a minimal intervention equates with a difference in the cessation rate of about 2.5% between those who received advice from a physician and those who did not. This means that, there would be one extra quitter as a result of minimal intervention from a physician for every 40 people who receive such advice. Absolute quit rates also depend on the period of follow up, the baseline rate, whether point prevalence or sustained abstinence is used, and whether reported abstinence is biochemically confirmed. Based on indirect comparisons, the effectiveness of physician advice appears to be greater in patients with established disease compared with smokers in an unselected population. Similarly, indirect comparisons indicate that use of various aids do not appear to enhance the effectiveness of physician advice. Direct comparison of differing intensities of physician advice suggested at best a small benefit from more intensive interventions in unselected smokers. The marginal benefit of intensive advice in smokers unselected for smoking-related disease translates into 50 smokers who would need to be treated to produce one extra quitter after 6 to12 months compared with smokers who receive minimal advice. Several strategies have been shown convincingly to enhance the effectiveness of advice from a medical practitioner, including provision of nicotine replacement therapy and/or bupropion[35,51] Addition of either of these forms of therapy appears to approximately double the odds of quitting, and is a potentially valuable adjunct to any advice provided. Both individual and group-based counselling are also effective at increasing cessation rates amongst patients prepared to accept more intensive intervention [52,53]

Predictor of success in smoking cessation

There are many factors that may have impact on smoking cessation success rate. Dale LC et al conducted a multicenter clinical trial to identify predictors for a successful outcome in smoking cessation with bupropion.[19] Logistic regression was used to identify predictors of abstinence at the end of the medication phase. Univariate predictors included the following:

bupropion dose ($p < 0.001$); older age ($p = 0.024$); lower number of cigarettes smoked per day (CPD) ($p < 0.001$); lower Fagerstrom Tolerance Questionnaire score ($p = 0.011$); longest time previously abstinent that was < 24 h or > 4 weeks ($p < 0.001$); absence of other smokers in the household ($p = 0.021$); greater number of previous stop attempts ($p = 0.019$). Multivariate predictors of abstinence at the end of the medication phase were the following: higher bupropion dose ($p < 0.001$); lower number of CPD ($p < 0.001$); longest time previously abstinent from smoking ($p = 0.002$); male gender ($p = 0.01$). However lower Fagerstrom tolerance questionnaire has not been shown to be predictive of long term success in others studies [26,28]

Other predictor of successful smoking cessation is a smoker's motivation. Saenghirunvattana [24] studied nicotine patch for smoking cessation in Thai smokers and found that smokers with strong motivation had a higher success rate compared with smokers who were referred to treatment because of pressure from relatives or spouses. Hurt and colleagues studied smokers who attended community smoking cessation clinic and found that current smoking related symptoms or illness was related to predicted outcomes for smokers trying to quit. [28]

Smoking cessation studies in Thai population

There are limited published studies about smoking cessation in Thai population. Saenghirunvattana examined the effect of transdermal nicotine patch in Thai active smokers. In treatment group, 37 Thai smokers received nicotine supplement for 4 weeks during smoking cessation. [24] In control non-medicinal group, 40 smokers were enrolled in an organized program which included physical rehabilitation, group therapy, psychotherapy, meeting with chest specialists and ex-smokers for discussion for 5 consecutive evenings. Quit smoking rates at 3 months was 42.5% in control group and only 21.6% in nicotine supplement group. [24]

Tansaringkarn K. and colleagues examined the effect of herbal sweet, Bimin 2, for smoking cessation in Thai active smokers. Patient with nicotine dependent (fagerstrom score >6) were randomized to receive Bimin 2 or placebo. There were 18 patients in treatment group and 15 patients in control group. No formal counseling was provided. 45.5% of patients in treatment group and 77.8% of patients in control group quitted smoking at 1 month. [25]

Summaries of review of literatures

1. Nortriptyline is an effective pharmocotherapy intervention in smoking cessation with success rate about 30% at 3 months after quit date.

2. There are minor side effects from nortriptyline used for smoking cessation but proportion of patients who stopped medication due to side effect was low and was not different from placebo in some studies.

3. Brief intervention (physician advice) is effective in smoking cessation.

4. There is no clinical trial comparing between brief motivation intervention alone or combination with nortriptyline for smoking cessation.

5. Smoking cessation data in Thai active smokers are limited. From the available data, Thai smokers may respond differently in smoking cessation treatment compared to other population. Thai smokers seem to have high success rate even without pharmacotherapy intervention.

CHAPTER III

RESEARCH METHODOLOGY

3.1 Research Questions

3.1 Primary research question

Is the smoking abstinence rate at 3 months in Thai smokers using nortriptyline combined with brief motivational counseling for smoking cessation different from smokers using brief motivational counseling alone?

3.1.2 Secondary research question

1. What is the side effects of nortriptyline administered to smokers for smoking cessation?

2. What is smoking abstinence rate at 3 months in Thai smokers using brief motivational counseling alone for smoking cessation?

3. What are the predictors of smoking cessation success in Thai active smokers who are willing to quit?

3.2 Research Objectives

3.2.1 To determine the smoking abstinence rate at 3 months in Thai active smokers who use nortriptyline combined with brief motivational counseling or brief motivational counseling alone for smoking cessation.

3.2.2 To determine side effects of nortriptyline in smoking cessation treatment.

3.3 Hypothesis

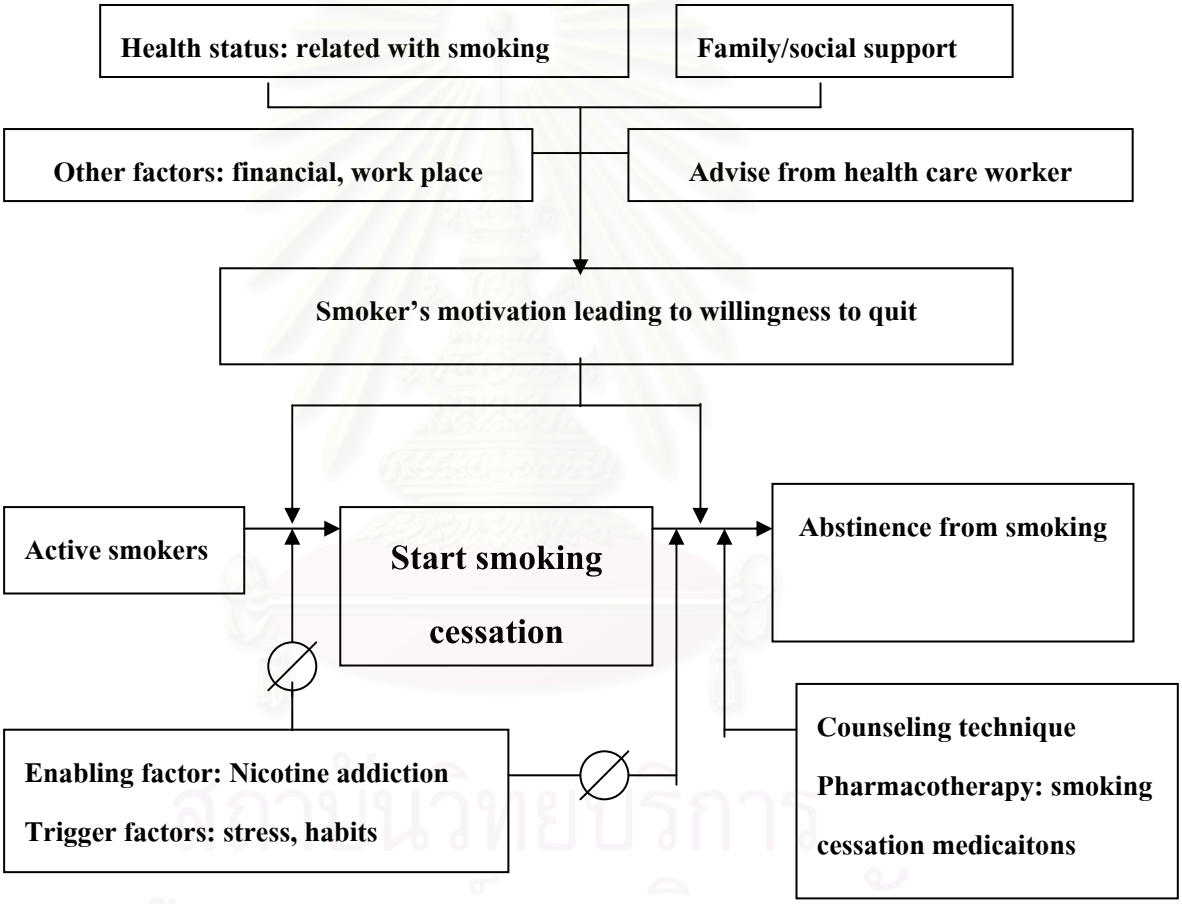
Research hypothesis

There are differences between the smoking abstinence rate at 3 months in patients receiving nortriptyline plus brief motivational counseling and patients receiving brief motivational counseling alone for smoking cessation.

3.4 Statistical hypothesis

There is no significant difference between the smoking abstinence rate at 3 months in patients receiving nortriptyline plus brief motivational counseling and patients receiving brief motivational counseling alone.

Conceptual framework



3.5 Keywords

Smoking cessation, nortriptyline, brief motivational intervention, active smokers

3.6 Operation definition

3.6.1 Smoking: Using tobacco related product by lighting and inhale smoke

3.6.2 Active smoker: An individual who regularly smokes tobacco related products at least 5 days/week in the past 4 weeks

3.6.3 Smoking cessation: A process for active smoker in order to refrain from tobacco use permanently

3.6.4 Success of smoking cessation from medication: smoker who refrain from smoking for at lease 2 consecutive weeks at the end of medication treatment period. In this study the patient has to meet all of the following criterion

1) Self report total abstinence of tobacco smoking in the last 2 weeks of medications

2) Urine for nicotine test is negative

3) Exhaled carbon monoxide lower than 10 ppm

4) Report from closed friends or relative of total abstinence of tobacco smoking in the last 2 weeks of medications.

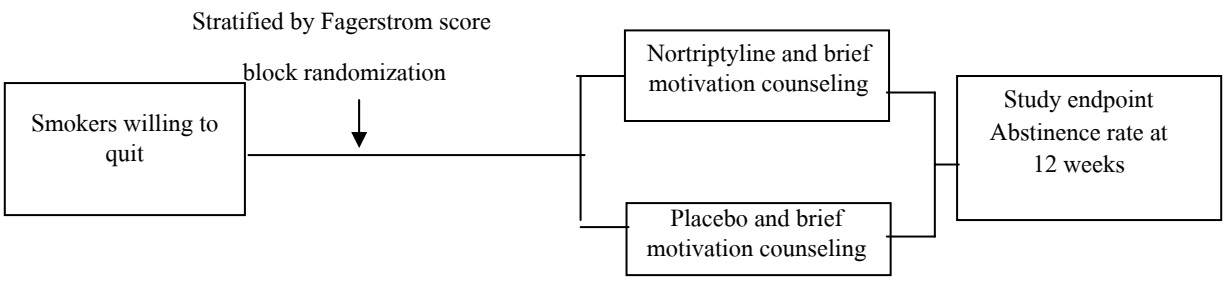
3.6.5 Brief motivational counseling: Counseling given to smoker during clinic visit for smoking cessation. This counseling is brief (between 5-10 minutes) and is given by primary health care provider and general nurse trained for smoking cessation counseling.

3.6.6 Past experience: Personal experience regarding previous quitting attempts in term of success or failure, any obstacles during previous quit attempts.

3.6.7 Quit date: A Date that patient has chosen to give up smoking completely. Quit date should be within 2 weeks after enrollment into the study.

3.6.8 Willingness to quit: Active smoker who want to quit smoking and is willing to start quitting attempt on the pre-specified quit date.

3.7 Research design: Double blind randomized controlled trial



3.8 Research methodology

3.8.1 Study location: Study will be conducted at King Chulalongkorn Memorial hospital, Bangkok, Thailand

3.8.2 Target population: The target population in this study are all active Thai smokers aged more than 18 years, who smoke > 10 cigarettes per day and have willing to quit smoking.

3.8.3 Sample population: Adults (age >18 years) who are active smokers and smoke more than 10 cigarettes per day and have willing to quit smoking and attend smoking cessation clinic at department of Medicine, King Chulalongkorn Memorial hospital.

3.8.3.1 Inclusion criteria

3.8.3.1.1 Age>18-year and < 65-year old

3.8.3.1.2 Active smoking, smoking habit of an average >= 10 cigarettes per day in the last 2 months

3.8.3.1.3 Good general health, as evaluated by a clinician

3.8.3.1.4 Had not taken any antidepressant during the past the last month

3.8.3.1.5 Had not taken any antipsychotic drugs

3.8.3.1.6 Has willingness and want to enroll in smoking cessation treatment program

3.8.3.1.7 Given informed consent to participate in the study

3.8.4 Exclusion criteria

3.8.4.1 Patient who is pregnant or lactation

3.8.4.2 Patient who has mental deficiency or demential syndrome

3.8.4.3 Patient with underlying cardiovascular disease: hypertension,

3.8.4.4 Coronary heart disease or history of cardiac arrhythmia

3.8.4.5 Patient known to have allergy reaction to nortriptyline

3.8.4.6 Patient with major psychiatric disorders, major depression

3.8.4.7 Patient uses thyroid or anticonvulsant medication

3.8.4.8 Patient who use other therapy for smoking cessation

3.8.4.9 Patient who use other medication that might have drug interaction with nortriptyline

3.8.5 Sampling of the population

The subjects will be screened for history of tobacco use and eligible subjects will be approached by researcher. All subjects who are eligible and agree to participate will be enrolled to the study.

3.8.6 Sample size

Sample size calculation on the basis of α=0.05, power of 80% with estimated rate of abstinence in nortriptyline group of 35% and in control group 15% (two-tailed test)

(estimated abstinence rate from reference 9)

Ho: $\pi_1 - \pi_2 = 0$

Ha: $\pi_1 - \pi_2 \neq 0$

π_1 =Abstinence rate at 12 weeks of patients receiving placebo and brief motivational counseling

π_2= Abstinence rate at 12 weeks of patients receiving nortriptyline and brief motivational counseling

Estimate abstinence rate in placebo group=15% and in treatment group= 35%

N/group= $\left(Z_\alpha \sqrt{2P(1-P)} + Z_\beta \sqrt{P1(1-P1)+P2(1-P2)} \right)^2 / (P1-P2)^2$

Total cases required= 50/group with estimated drop out 20% :N in each group= 60

3.8.7 Randomization and allocation technique

Stratified randomization will be used. The patients will be stratified into two groups by Fagerstorm score (< 6 and $\geq$ 6), then block (restricted) randomization will be performed by drawing a card from a sealed envelope. The separate block of 4 randomization list will be used for each subgroup. Both patient and the physician who is taking care of the patient do not know the treatment for the patient. Placebo and treatment medications will be pre-packed in the sealed containers. Both placebo and treatment medications have the same appearance.

3.9 Intervention

Baseline measurements

Questionnaires to assess smoking history, previous quitting attempts, baseline characteristics, history of medical illness, smoking related illness and symptoms and estimated degree of nicotine dependence with the Fagerstrom Nicotine Dependence Questionnaire.[19] **(Appendix A)** Following clinical evaluation, all patient will receive full information on the protocol and sign the consent form. **(Appendix B)** Then they will be stratified by Fagerstrom score in to two group and randomized to receive nortriptyline or placebo. Patient will pick quit date within 2 weeks of randomization. **(see patient CRF in Appendix C)**

Brief motivation counseling

Brief motivational counseling will be provide by research nurse at baseline, weeks 2 and 4, and at end of treatment. The counseling will include identification of trigger factors, simple coping skills. The nurse will also identify and review problems quitting and help to develop strategies for abstinence from smoking. Patients will be contact by telephone on quit date and research nurse or research physician will be available for telephone counseling during working hours.

In each visit, patient will be assessed for nicotine withdrawal symptoms, side effects from medication and detail of cigarettes use in that period.

Drug therapy

Medication will be placebo controlled and double blind. Patient will meet with study physician at first visit and begin administration of medication. In nortriptyline group, patient will take one 25 mg tablet before bed time and increase to 2 tablets after 7 days if there were no side effects. Placebo group will be instructed to take pills with the same regimen. All patients will continue on 2 tablets before bedtime until 2 weeks and return for follow up visit. After 8 weeks, medication will be titrated and discontinue at week 12.

All possible side effects will be recorded at each visit. Patients will be allowed to stop treatment at any time if they feel that they have side effects from the treatment.

Study endpoint

All patients will be followed until 12 weeks. At 12 weeks, the success of treatment will be assessed individually. It will be considered to successful if patient stopped smoking for at least 2 consecutive weeks at the end of treatment.

Monitoring of cigarette uses

At the end of study (week 12 visit), expired carbon monoxide will be determine by expired carbon monoxide analyzer. Urine cotinine level will be measured using Urine cotinine test strip (Craig Medical, USA with cut off point of 200 ng/ml) Patients closed friend or family member will be interviewed randomly and at the end of treatment for patient history of smoking. Patient will keep log book to record cigarette smoking during study period.

Patients will be considered to succeed in smoking cessation if they met all the following criterion

1) self report total abstinence of tobacco smoking in the last 2 weeks of medications

2) urine for nicotine test is negative

3) exhaled carbon monoxide lower than 10 ppm

4) report from closed friends or relative of total abstinence of tobacco smoking in the last 2 weeks of medications.

3.10 Data collection

The following data will be recorded

Demographics: age, sex, education, marital status, employment status

Nicotine dependency: Fagerstrom score

Motivation for smoking cessation: smoking related symptoms/diseases (self or relatives), family related factors (new born baby, family member's illness)

Smoking history: number of cigarettes per day, Pack-year smoking, previous quitting attempts, longest previous abstinence periods, previous quitting techniques

Tobacco withdrawal symptoms: craving, irritable/angry, anxious/tense, restless, insomnia, impatient, drowsiness, headache, increased eating

Side effects from medications: dry mouth, constipation, dizziness, postural hypotension, cardiac arrhythmia

Exhaled carbon monoxide : by portable CO analyzer at smoking cessation clinic

Urine cotinine level at the end of treatment: by using urine test for cotinine kit (Craig Medical, USA) detecting cotinine in urine at cut off level of 200 ng/ml

Proportion of patients succeed in smoking cessation at the end of treatment

3.11 Statistical analysis

3.11.1 Basic and demographic variables

Baseline demographic data: sex, age, educational level, underlying medical illnesses and symptoms will be described.

Baseline smoking history including cigarette per day, nicotine addiction score, past quitting attempts and detailed. Factor related quitting attempt such as motivation will be described.

3.11.2 Outcome variables

The primary outcome is sustained smoking abstinence at 12 weeks. Analysis will be performed with the statistical software (SPSS version 11.5). χ^2 test will be used to compare abstinence rate between two groups 95% CI will be calculated using Z statistics.

Tobacco withdrawal symptoms and adverse reaction in each group will be compared by using Fisher exact test.

If there was a different in motivational factors between 2 groups, multiple logistic regression will be used to identify adjusted odds ratio of each variable.

Outcomes of the patient will be calculated on the intention to treat basis

3.12 Ethical consideration

Although the recent guideline for treating tobacco use and dependence recommend that all smokers attempt to quit should receive pharmacotherapy, this statement is not supported by data available in Thailand. Patients in placebo group will also receive brief motivational counseling which is one of the standard treatments for smoking cessation.

3.13 Limitation

Patients who are enrolled in this study may not represent Thai population. We may have subgroup of urban population with specific characteristics other than patients participate in this study.

There might be other factors which may have effect on smoking cessation such as religious or personality of each patient etc. These factors may have an impact on the outcome of the study. However we have tried to identify all known important confounding factors such as nicotine dependency and use multiple logistic model to analyze the data.

3.14 Benefit of this study

The result of the study will give an important data about smoking cessation in Thai population. We will have our own data to make suggestion for smoking cessation guideline in Thailand. The result of this study will help us to understand more about smoking cessation in Thai smokers, effectiveness of nortriptyline, which may be a drug of choice for our smoking cessation guideline due to availability, cost

3.15 Obstacles

Patients who fail smoking cessation attempt has a tendency to loss to follow up. This may result in high drop out rate in this study. We will have access to contact every patient directly by phone or mail and will try to re

CHAPTER IV

RESULT OF THE STUDY

After being recruited and randomized in accordance to the protocol, there were 68 patients in control group and 69 patients in treatment group. Demographic data of these patients were shown in Table 3. Among the patients enrolled in the study there were 3 women in control group and 4 women in treatment group. Average ages were 38.0 years and 40.1 years in control group and treatment group respectively.

Table 3: demographic data

	Control (n=68)	**Treatment(n=69)**
Male (%)	64 (96%)	63 (96%)
Age (mean, ange,SD)	39.9 (19-62,10.5)	38.6 (19-66,11.7)
Primary school	8 (11.8%)	9 (13.0%)
Secondary school	36 (52.9%)	31 (44.9%)
College	22 (32.4%)	25 (36.2%)
Master degree	2 (2.9%)	4 (5.9%)

Mean age of both groups were 39.9 and 38.6 yr-old in control and treatment group respectively. Age distribution of all subjects is shown in figure 1. Most of the patients aged between 30-50 yrs old. Both control and treatment groups have the same age distribution. Most of the patients graduated from secondary school or high school. Small proportion had master degree or higher. The oldest patient in treatment group is 66 yrs old and in control group is 66 yrs old.

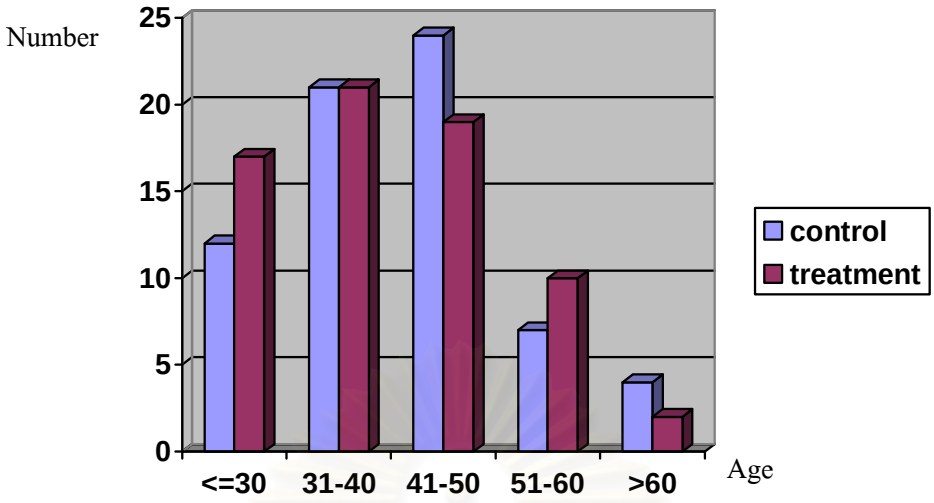


Figure 2: Age distribution

Underlying diseases and patients' symptoms are shown in table 4. Most common underlying disease in both control and treatment group is chronic obstructive pulmonary disease (COPD)(19.1% and 14.5%, respectively. Some patients had either diabetes or dyslipidemia. Pulmonary tuberculosis is the most common lung infection in both groups of the patients and most of them is treated and inactive tuberculosis. Small proportion of both groups are HIV positive.

Table 4: Underlying diseases of the patients

	Control (n=68)	**Treatment(n=69)**
COPD	13 (19.1%)	10 (14.5%)
NIDDM	6 (8.8%)	4 (5.8%)
Tuberculosis	7(10.3%)	5 (7.2%)
Asthma	5(7.4%)	2(2.9%)
HIV infection	3 (4.4%)	2(2.9%)
Hyper-cholesterol	9 (13.2%)	8(11.6%)
Chronic cough	29(42.6%)	23 (37.7%)
Shortness of breath	21 (30.9%)	27 (39.1%)
Relation with health	23 (32.4%)	27 (39.1%)

Most common symptoms of the patients in both groups are chronic cough and shortness of breath (Table 4). In control group, 23.5% reported having chronic cough, 11.7% having shortness of breath and 19.1% having both symptoms. There were 31 patients (45.6%) in control group that were asymptomatic. (Figure 2) 6 patients (37.5%) who had only chronic cough and 4 patients (50%) who had only shortness of breath related their symptoms with cigarette smoking but all 13 patients with both symptoms felt that their symptoms had relation with cigarette smoking.

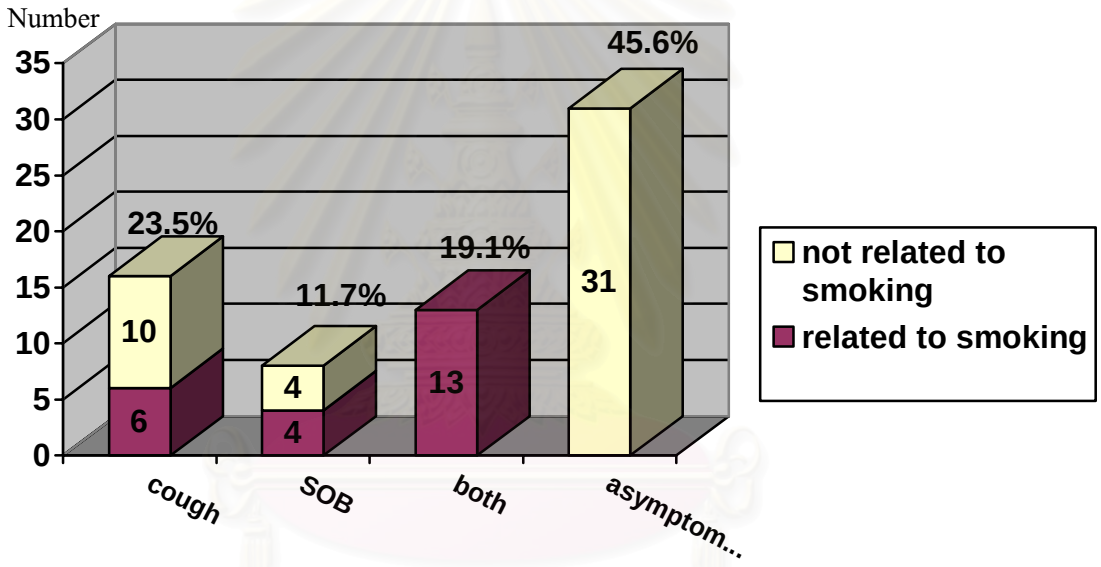


Figure 3: Symptoms of the patients in control group

In treatment group, 13.0% reported having chronic cough, 21.7% having shortness of breath and 18.8% having both symptoms. There were 32 patients (46.4%) in treatment group that were asymptomatic. (Figure 3) 4 patients (44.4%) who had only chronic cough and 10 patients (66.7%) who had only shortness of breath related their symptoms with cigarette smoking but 12 patients (92.7%) with both symptoms felt that their symptoms had relation with cigarette smoking.

From figure 2 and 3, patients in both groups with more symptoms (both shortness of breath and cough) related their symptoms with cigarette smoking more frequent that patients with either symptoms only.

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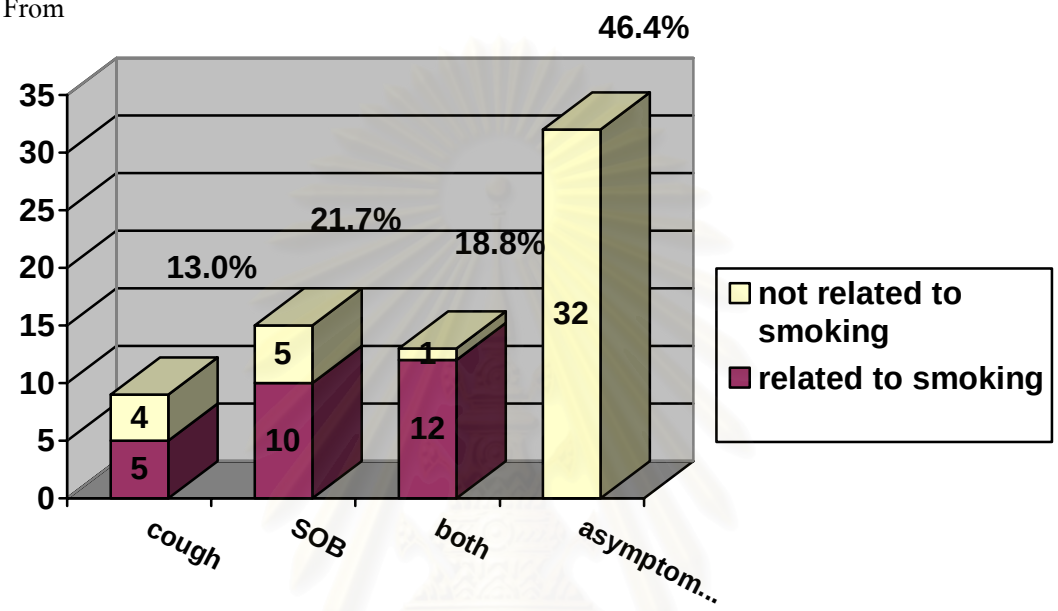

Figure 4: Symptoms of the patients in treatment group

Average fagerstrom score in control group was 4.2 and in treatment group was 4.5. Fagerstrom scores distributions in both groups are shown in Table 5. Patients were classified by fagerstrom scores into 3 groups (figure 4) ,with score 1-4 (mild nicotine dependent), 5(moderate nicotine dependent) and more than 5 (severe nicotine dependent). 57.2% of patients in control group and 59.4% of patients in treatment group were classified by fagerstrom scores in mild nicotine dependent. 12 patients in both groups (17.7% and 20.2 % in control and treatment group, respectively) were in severe nicotine dependent group.

Table 5: Fagerstrom score

	Control (n=68)	Treatment(n=69)
Fargerstorm score	4.2	4.5
2 or less	2 (2.9%)	2(2.9%)
3	15 (22%)	13 (18.8%)
4	22 (32.3%)	26 (37.7%)
5	17 (25.0%)	16 (23.2%)
6	4 (5.9%)	4 (5.8%)
7	7(10.3%)	7 (10.1%)
8	1 (1.5%)	3 (4.3%)

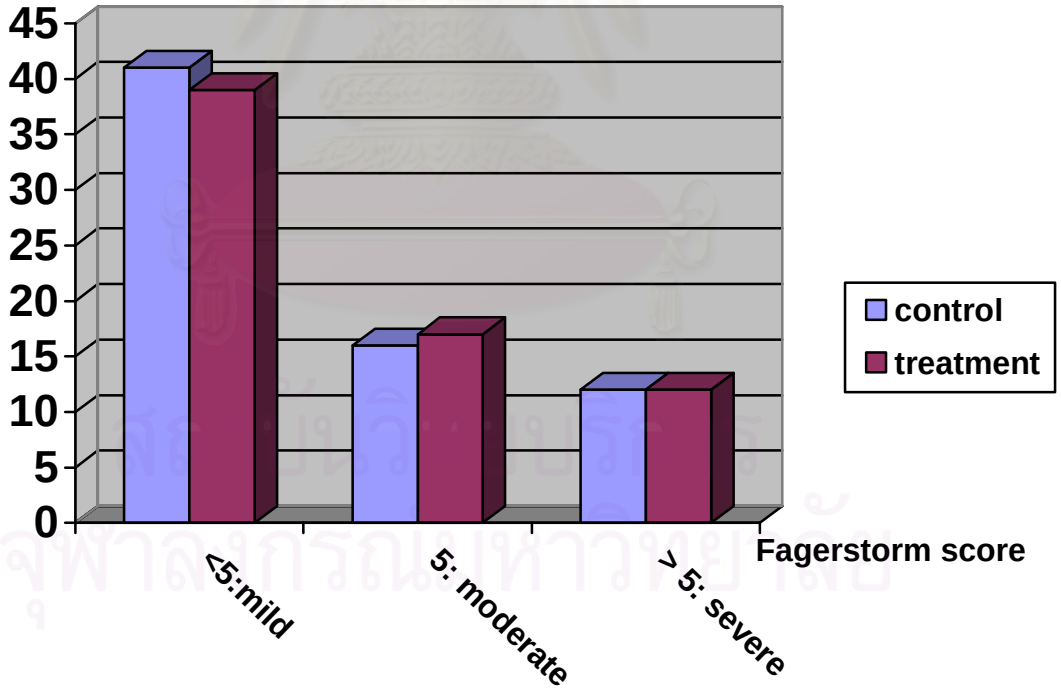

Figure 5 Classification of severity of nicotine dependent

Table 6: History of cigarette smoking and quit attempts

	Control (n=68)	Treatment(n=69)	P value
cigarette/day (Mean±SD)	14.3 (±5.9)	13.9 (±7.05)	0.43
Previous quit attempts • Never • 1 • 2 • 3 or more	 22 (32.4%) 21 (30.8%) 14 (20.6%) 11 (16.2%)	 25 (36.2%) 24 (34.8%) 12 (17.4%) 8 (11.6%)	0.64
previous smoking cessation treatment	12 (17.6%)	8 (11.6%)	0.63
Household active smokers	14 (20.6%)	9 (13%)	0.24

History of cigarettes smoking and previous quit attempts are shown in table 6. Mean cigarettes smoked per day was not different in both group with average of 14.3 cigarettes per day in control group and 13.9 cigarettes per day in treatment group. Both groups had the same rate of previous quit attempt with 67.6% in control group and 63.8% in treatment group had previous quit attempts which had failed or relapse prior to this current attempt. Most of previous quit attempts were unassisted and only 17.6% in control group and 11.6% in treatment group had received smoking cessation treatment before. 20.6% of patients in control group reported another active smoker(s) in the same house compared to 13% of patients in treatment group (no statistically different).

Table 7: reasons to quit smoking

	Control (n=68)	Treatment(n=69)
medical reasons	21(30.8%)	27 (39.1%)
Advise from doctor/healthcare worker	19(27.9%)	16 (23.2%)
Family/ social	9 (8.8%)	10 (14.5%)
Working pressure	5 (7.4%)	7 (10.1%)
others	14 (20.6%)	9 (13.0%)

Motivations for patients to start quitting process are shown in table. 4 most common motivations were medical reasons, advise from healthcare workers, family (social) or work place pressure. Common family and social motivations were newly born baby in family, planning to get marry or strictly non-smoking work-place. Other reported motivations were economic concern (cigarettes are expensive), self improvement plan or motivated by anti-smoking campaign especially around world anti-smoking day (May, 31st).

There were 7 patients in control group and 8 patients in treatment group who stopped taking medications before completed one month of treatment. The common reasons for discontinuing medications were reported side effects and did not feel that the medication was helpful. There is no statistically different in patients who stopped medication in control and treatment group. There was no other medications related side effects reported during the period of the study. There was no mortality or any hospital admission in both groups of patients during study period of 3 months.

Table 8: outcome of treatment

	Control (n=68)	Treatment(n=69)	P value
Stopped medications	7 (10.3%)	8 (8.6%)	0.8
Side effects	2 (2.9%)	4 (5.8%)	0.8
Does not work	5 (4.4%)	4 (5.8%)	0.8

Patients reported side effects in both groups which include constipation, dry mouth and drowsiness. (Table 9) There was statistically significant higher incidence of dry mouth (p=0.032) but not for drowsiness (p=0.177) in treatment group when compared to control group but most patients still tolerated treatment medication and continue using the treatment medication.

Table 9: side effects of medications

	Control (n=68)	Treatment(n=69)	P value
Constipation	9 (13.2%)	7 (10.1%)	0.971
Dry mouth	11 (16.2%)	22 (31.9%)	0.032
drowsiness	13 (19.1%)	20 (29.0%)	0.177

During the study period, there was no other significant adverse event occurring in both control and treatment group. One patient with COPD received treatment at emergency room due to mild acute exacerbation and there was no mortality occurring during this study.

Table 10: withdrawal symptoms

	Control (n=68)	Treatment(n=69)	P value
Agitation/ frustration	23 (33.8%)	16 (23.2%)	0.168
Anxiety	18 (26.5%)	13 (18.8%)	0.199
Insomnia	14 (20.65)	9 (13.0%)	0.237

In both group, patients reported withdrawal symptoms when they tried to stop smoking (Table 10). Most common symptom was agitation/ frustration. Some patients also reported increase anxiety level and insomnia. There was no statistically significant different in rate of withdrawal symptoms in both group. However, there were trends toward fewer patients in all withdrawal symptoms in treatment group when compared with control group but did not reach statistical significant.

Table 11: Success rate at 3 months

	Control (n=68)	Treatment(n=69)	P value
Stopped medications	7 (10.3%)	8 (8.6%)	0.8
Loss to follow up	2 (2.9%)	3 (4.3 %)	0.9
Quitted at 3 months	16 (26.5%)	30 (43.5%)	0.014

The primary outcomes of the study were shown in Table 11. There were 7 patients in control group and 8 patients in treatment group stopped medications before 1 month but they were still followed as scheduled by protocol and received brief intervention and suggestion during clinic visit. One in each group can quit at 3 months after follow up despite stopped using medication. Although the patients did not complete 1 month of treatment, we still included them in statistical analysis as an intention to treat basis. 3 patients in control group and 2 patients from treatment group could not be contacted after follow up for more than 1 month and were considered loss to follow up.

At 3-month follow up, 16 patients in control group (26.5%) and 30 patients in treatment group (43.5%) reported cigarettes abstinence for more than 2 weeks, confirmed by exhaled CO level and urine cotinine test. All but 2 patients used study medications at least until quit date. There is a statistically significant different in quit rate at 3 month between treatment and control group (p=0.14, OR=2.5 95% CI 1.19-5.25).

Worst case scenario for loss to follow up cases was analyzed. If all patients in control group could quit and all in treatment group failed, quit rate in treatment group is still significantly higher than in control group (p=0.038, OR 2.13 95%CI 1.04-4.38) (Table 12)

Table 12 Worst case scenario analysis for loss to follow up

	success	failure	P value
control	18* (16)	48 (50)	P=0.038
treatment	30 (30)	39 (39)	

* 2 case loss to follow up in control group were considered as success

Other factors that might have effect in quit rate are shown in table 13. Chi-square test was used to identify factors that might have association with quit rate. Of all the factors analyzed, patients with shortness of breath, patients related their symptoms with cigarette smoking, motivation factors were factors with $p<0.2$. These factors were entered into logistic regression analysis and factors that have significant correlation with quit rate are medications used (placebo vs. nortriptyline) (OR 2.7 95% CI 1.23-5.96), shortness of breath (OR 2.9. 95%CI 1.31-6.45), related symptoms with smoking (OR 2.9. 95%CI 1.31-6.45). There was no statistical significant difference between reasons for quit smoking and success rate.

Table 13 Factors that might have effect on quit rate

	Failure	Success	P value
Treatment			
Control	52	16	0.014
Nortryiptyline	39	30	
Fagerstorm			
1-3	17	15	P=0.69
4-8	74	31	
Other Smokers			
no house hold	75	39	P=0.727
house hold smoke	16	7	
SOB			
No	67	21	P=0.001
Yes	24	25	
Previous quit			
No	37	10	P=0.28
Yes	54	36	
Related with health problem			
No	66	21	P=0.02
Yes	25	25	

	Failure	Success	P value
Motivation			
• Health	30	18	P=0.105
• Family	25	10	
• Doctor	17	2	
• Working	8	6	
• Others	21	12	
Cough			
No	62	24	P=0.92
Yes	29	21	

CHAPTER V

DISCUSSION

In this study, we found that in active smokers willing to quit smoking, treatment with nortriptyline combined with brief motivational counseling resulted in higher abstinence rate at 3-month than brief motivational counseling and placebo with odd ratio of 2.7 (95% CI 1.23-5.96). This is similar with result from Cochrane review which Hugh et al reviewed available data of nortriptyline compared with placebo for smoking cessation[13] and found that pooled results from 4 studies resulted in odd ratio of 2.79 (95% CI 1.70-4.59).

Wagena et al recently reported a randomized controlled trial comparing nortriptyline, bupropion and placebo in active smoker with COPD[65], all of which also received cessation counseling. The prolonged abstinence rate (defined as no smoking from week 4 to week 26 after quit date) in nortriptyline group was 10.2% (95% CI -1.7- 22.2) and there was not statistically different from placebo. In bupropion SR study, Tonessen reported an abstinence rate of 46% for bupropion during week 4-7 after smoking cessation (OR 2.82 95% CI 1.89-4.28).[74] These results are comparable with the result form our study.

Patients received nortriptyline in our study had a considerably high abstinence rate at 3 month (43.5%) when compared with previous studies which reported abstinence rate about 15-30%.[9,10,12] Given the same odds ratio with previous study, one explanation is the high success rate of patients received only motivational counseling only (26.5%) in this study. Physician advice for smoking cessation alone has been shown to increase success rate when compared with no treatment (odd ratio of 1.74 95%CI 1.48-2.05) [53] although a percent success rate increase was low (2.5%). Previous studies showed a success rate in counseling alone between 3-15% [61,62,63]. The factor associated with increase success rate of brief counseling is follow-up appointment [53]. From available evidence, the intensity of counseling or other method of counseling such as counseling aids did not seem to have significant impact on success rate. In our study we scheduled patients for follow up with brief intervention in every visit which can explain the high success rate of our control group. However there are other factors need to be considered that might responsible for this high success rate. First, patients in our study did not receive only counseling, but they also received placebo. This can result in placebo effect and increased likelihood of success if the patients thought they received medications. Second, patients in our study had considerably low fagerstrom score which might reflect low nicotine dependency and

possibly high success rate of quitting with or without treatment. We did not have a control group without any counseling to answer this question but from our analysis, fagerstrom did not have any significant effect on success rate of studied patients so the fagerstrom itself might not solely explain this finding. Third, our physician and nurses are specialized in smoking cessation and have previous training and expertise in giving patients a brief and effective counseling. Lastly, our patients might be highly motivated patient to attend to our smoking cessation clinic because our clinic was a separate unit and patients needed to walk and tried to find clinic location. This can be like a screening tool for selection of highly motivated patients.

Patients in this study were predominantly male patients with very few female participants. This finding reflected the normal pattern of smokers in Thailand. From the latest data of Thai smokers which 37% of male and only 2.2% of female are active smokers. Because of this, result of the study might not be applicable for female patient. Furthermore, one clinical study showed that male gender was one predictor of success in smoking cessation[73] According to this, a high proportion of male patients in our study might partly responsible for high success rate of both control and treatment groups. However there is a study of nortriptyline in smoking cessation which 70% of participants were female and still reported a good efficacy of nortriptyline when compared with placebo [9]. So we believe that female patients should also benefit from nortriptyline during smoking cessation.

Some other psychological factor may have an effect on outcome of smoking cessation [66, 67]Humfleet et al. found that patients with history of childhood attention-deficit/hyperactivity disorder had higher incidence of smoking cessation failure than patients without this particular problem.[66] Patients with depression are likely to be addictive to cigarette and may have beneficial effect from antidepressant during cessation period. Although recent report from Killen et al demonstrated that major depression was not uncommon among adult and adolescent seeking smoking cessation but abstinence and relapse rate after treatment was not different between patients with or without major depression.[71] Study from Catley el al also underscored these findings.[75] We excluded patients with history of major depression or obvious psychological problem form our study. But we did not screen for minor depression or other psychological problems so we can not definitely rule out possibilities that nortriptyline's effectiveness may partly due to anti-depressant effect. However, not all antidepressant medications are effective in smoking cessation. Saules KK et al reported a clinical trial compared fluoxetine with nicotine supplement and showed that fluoxetine did not improve cessation rate even patients with major or elevated depression [68]. Lerman C et al showed that efficacy of

bupropion in smoking cessation did not mediate by depressive symptoms at any time point during cessation period[69] So this implies that the action of antidepressant in smoking cessation mediated via other mechanisms, not only anti-depressant effect alone. Given all of these evidences, we believed that underlying depression did not have any significant impact on the outcome of our study.

There were 4 major reasons for patients to start quitting process in our study. There was no different in abstinence rate between smokers with different motivation. Patients still motivated by health problems, family and social concern, doctor advice and pressure from work place. Other important factor was economical concern. This emphasized roles of family members and physicians in motivating patients to start quitting process. In our study also showed that patients with shortness of breath or had symptoms that they thought related to smoking had a higher abstinence rate at 3 months. This is a strong evidence to suggest that when patients seek medical advice for smoking related disease, physician should advise patients to quit smoking and educate patients about relationship of the current illnesses and cigarette exposure.

The primary concern of using nortriptyline is a serious cardiovascular side effect. In this study, we excluded patients with underlying cardiac problems or hypertension. Our patients did not report any cardiovascular side effects and to our knowledge, there was no significant cardiac complication in our patients. Blood pressure and heart rate and rhythm were recorded during follow up and every patient was specifically asked for any symptoms suggested of cardiovascular complications such as palpitation, syncope or chest pain. The other side effects found in our study were similar with literature. The most common side effects found in our study were dry mouth and drowsiness. Patients received nortriptyline had significantly higher incidence of dry mouth when compared with placebo (31.9% and 16.2%, respectively) (OR 2.43 95% CI 1.07-5.51). Although there were more patients with drowsiness in nortriptyline group than placebo this did not reach statistically significant (29.0% and 19.1% respectively, p=0.177). These symptoms, although frequent, were well tolerated and only 5.8% stopped nortriptyline due to side effect which was not different from placebo. Haggstram FM et al .[64] reported incidence of dry mouth and drowsiness were 67.3% and 19.2% respectively in patients received nortriptyline for smoking cessation and very few patients needed to stop medications because of side effects. Prochazka et al reported 38% and 20% incidence of dry mouth and drowsiness respectively. [70] Our study confirmed that patients who received nortriptyline tolerated this medication well.

Prochazka et al reported a randomized trial compared between placebo and nortiptyline to nicotine supplement. [70] The abstinence rate at 6-month were 23% in nortriptyline and 10% for placebo (absolute difference 13% 95%CI 1.3-24.5% ,p=.052) Although the abstinence rate was lower than using nortriptyline alone in our study, this possible due to longer period of follow up (6 months period instead of 3 months in our study). But this study emphasized that combination of nortriptyline with other smoking cessation medication can improve efficacy and increase rate of abstinence.

In our study, there was no significant different in all withdraw symptoms in both groups. This finding was quite surprising that despite the same rates of withdrawal symptoms, patients treated with nortriptyline still had higher rate of success. This is similar to findings from some other study, Haggstram et al. reported the same withdrawal score in patients received bupropion, nortriptyline or placebo despite a higher quit rate in bupropion group. [64] This emphasize the possibility that the method to estimate withdrawal symptoms may not be sensitive enough for the accurate measurement of the withdrawal symptoms. There is another composite score that has been used in assessing withdrawal symptoms such as Wisconsin Smoking Withdrawal Scale (WSWS). This composite score had been demonstrated in one study to change slightly in treatment with bupropion compared with placebo [74]. However, this score has not been validated and test in Thailand yet. The other possibility is that in our patients; mean fagerstrom was relatively low, suggesting possible low level of nicotine dependent. These might explain low incidence of withdrawal symptoms during smoking cessation. This also emphasized that there may be other factor not only nicotine addiction that can have influence on smoking cessation.

We used self-report, data from friends and family members, urine cotinine level and exhaled CO to verify the true abstinence in our study. Exhaled CO is very convenient but has limitation due to short half life of CO and only detects someone who has abstained for many hours [72] and urine cotinine can detect nicotine exposure in the past 96 hours. This raised a concern whether the primary end point recorded (2 weeks abstinence at 3 months) were reliable or not. From our study, we have good reasons to believe that these end point measurements were reliable. First, patients were informed that urine and exhaled test will be performed to confirm abstinence but they did not know how long nicotine persisted in the body and can be detected by the tests. So if they still smoked, we believed they would report cigarette consumption. Second, self reported abstinence rates had perfect concordance with friends and family members and urine and exhalation test. We did not have any patients who reported 2 weeks of abstinence with positive urine cotinine or exhaled CO.

Some study had identified predictors of success in smoking cessation. Aubin et al. studied in French patients comparing bupropion and placebo for smoking cessation. The six months' point prevalence abstinence rate was 31% in bupropion group (OR 2.3 95%CI 1.4-3.7) compared with placebo. In this particular study, the factors that associated with success were low level of nicotine dependent, high motivation, male gender, absence of smoking related disease and living with couple [73] In our study the most important predictors are symptoms of patients (especially shortness of breath), and patient's perception that cigarette caused related health problems.

Fagerstrom addiction score did not predict success rate in our patients. But most of our patients were in low to moderate fagerstrom score. The fagerstrom score has not been widely used in Thai active smokers and we have found that some questions in the scoring system may not appropriate with Thai smoker (such as" do you have any problem stopping smoking while staying in the hospital" which we almost got all negative response (No)). We have found that questions regarding number of cigarette smoke and when smokers started their first cigarette seem to have some correlation with perception of patient's addiction by the treating physician. However, fagerstrom score needs to be verified in Thai population before recommended as a tool for patient's assessment.

There are some weakness and limitations of this study. First, we only follow up patients for 3 months. We anticipate that the abstinence rate at 1 year probably will be significantly lower than at 3 months and should be an important question regarding effectiveness of nortriptyline in long-term abstinence (more than 1 year). But we believe that quit rate at 3 month is also very crucial for smokers before they can proceed with longer period of abstinence. We need a longer follow up time to answer this important question. Second, in this study, high proportion of the patients had low nicotine addiction score. We probably will need to study effectiveness of nortriptyline in patients with more severe nicotine addiction which can be a difficult smoking cessation case in clinical practice. Third, we did not compare nortriptyline with available first-line smoking cessation medications such as bupropion or nicotine supplement. But when compared with previous study, effectiveness of nortriptyline in our study is comparable to other first-line medications in previously published articles. The last, our study enrolled very few female smokers, so the result of this study might not be applicable to Thai woman. We will need to plan a study on female smokers who might have different response to smoking cessation.

CHAPTER VI

CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

1. Nortriptyline is an effective smoking cessation when combined with brief counseling intervention in Thai active smokers.

2. There are significant minor side effects from nortriptyline such as dry mouth and drowsiness which are usually tolerable.

3. Brief intervention alone in Thai active smokers is also effective in assisting smokers to quit.

4. Concerning about health status, advice from physician, family concern and pressure from work place were major motivation factor for the patients.

5. Patients with shortness of breath or health problems related to smoking had a higher abstinence rate at 3 months.

6.2 Recommendations

1. Nortriptyline can be used in smoking cessation process to help smokers quit smoking.

2. Patients also should receive counseling from health care providers.

3. From this study, we can not recommend nortriptyline as first line anti-smoking medications because there we did not compare nortriptyline with already available first-line medications such as bupropion or nicotine replacement. But physicians should consider nortriptyline for smoking cessations in appropriate smokers especially when there is a concern regarding cost of treatment.

4. Physician has a major role in motivating and assisting smokers to quit smoking effectively.

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APPENDICES

APPENDIX A

แบบทดสอบวัดระดับการติดนิโคติน (Fagerstrom score)

1. โดยปกติคุณสูบบุหรี่กี่มวนต่อวัน
   - ☐ 10 มวน หรือน้อยกว่า
   - ☐ 11-20 มวน
   - ☐ 21-30 มวน
   - ☐ 31 มวนขึ้นไป
2. หลังตื่นนอนตอนเช้า คุณสูบบุหรี่มวนแรกเมื่อไหร่
   - ☐ ภายใน 5 นาทีหลังตื่นนอน
   - ☐ 6-30 นาที หลังตื่นนอน
   - ☐ 31-60 นาที หลังตื่นนอน
   - ☐ มากกว่า 60 นาทีหลังตื่นนอน
3. คุณสูบบุหรี่จัดในชั่วโมงแรกหลังตื่นนอน
   - ☐ ใช่
   - ☐ ไม่ใช่
4. บุหรี่มวนไหนที่คุณไม่อยากเลิกมากที่สุด
   - ☐ มวนแรกในตอนเช้า
   - ☐ มวนอื่น ๆ
5. คุณรู้สึกลำบากหรือยุ่งยากไหมที่ต้องอยู่ในเขตปลอดบุหรี่ เช่น โรงภาพยนตร์ รถโดยสาร
   - ☐ รู้สึกลำบาก
   - ☐ ไม่รู้สึกลำบาก
6. คุณยังต้องสูบบุหรี่ แม้จะเจ็บป่วยนอนพักตลอดในโรงพยาบาล
   - ☐ ใช่
   - ☐ ไม่ใช่

APPENDIX B

ใบแสดงความยินยอมในการเข้าร่วมโครงการวิจัย
เรื่อง การศึกษาประสิทธิภาพของยานอร์ทริปทัยรินในการช่วยเลิกสูบบุหรี่

1. **คำชี้แจงเกี่ยวกับการใช้ยานอร์ทริปทัยรินในการช่วยเลิกบุหรี่**

แนวทางในการช่วยให้ผู้ป่วยเลิกบุหรี่ในปัจจุบันนี้มีแนวทางที่ได้ประโยชน์และสามารถช่วยให้ผู้ป่วยประสบความสำเร็จมากขึ้นในการเลิกบุหรี่ 2 วิธีหลัก คือการให้คำแนะนำที่เหมาะสมกับผู้ป่วยที่เริ่มหยุดบุหรี่และการใช้ยาช่วยในการเลิกบุหรี่ การได้รับคำแนะนำที่เหมาะสมจากบุคลากรทางการแพทย์เพื่อแนะนำวิธีการปฏิบัติตัวที่เหมาะสมจะสามารถช่วยให้ผู้สูบบุหรี่หยุดบุหรี่ได้มากขึ้น ส่วนยาที่ใช้ในการช่วยหยุดบุหรี่ในปัจจุบันมีหลายชนิดและได้ผลแตกต่างกัน ไม่มีการศึกษาในประเทศไทยที่จะสามารถบอกได้ว่ายาชนิดใดได้ผลดีกว่ากัน

ยานอร์ทริปทัยริน (nortriptyline) เป็นยาที่มีฤทธิ์ช่วยลดอาการซึมเศร้าที่มีการใช้กันอย่างแพร่หลายในทางการแพทย์ พบว่ายาชนิดนี้สามารถมีฤทธิ์ช่วยให้ผู้ป่วยบางกลุ่มมีอาการอยากสูบบุหรี่น้อยลงและสามารถเลิกสูบบุหรี่ได้ จากการศึกษาในต่างประเทศพบว่ายาชนิดนี้เพิ่มโอกาสให้ผู้ป่วยส่วนหนึ่งประสบความสำเร็จมากขึ้นในการหยุดบุหรี่ ปัจจุบันไม่มีข้อมูลเกี่ยวกับการใช้ยานี้เพื่อในการเลิกสูบบุหรี่ในผู้สูบบุหรี่ชาวไทยที่มีความต้องการเลิกบุหรี่ว่าจะได้ผลต่างจากการศึกษาในต่างประเทศหรือไม่

โครงการวิจัยนี้มีจุดประสงค์เพื่อศึกษาว่าการใช้ยานอร์ทริปทัยรินร่วมกับการให้คำแนะนำกับผู้สูบบุหรี่ที่ต้องการเลิกสูบบุหรี่ว่าจะมีประสิทธิภาพในการช่วยให้ผู้ป่วยเลิกสูบบุหรี่ได้มากกว่าการให้คำแนะนำอย่างเดียวหรือไม่ เพื่อนำผลที่ได้มาใช้ในการวางแนวทางการรักษาผู้ที่สูบบุหรี่ในประเทศไทยต่อไป

2. คำชี้แจงเกี่ยวกับการปฏิบัติตนระหว่างการเข้าร่วมโครงการวิจัย

เมื่อตกลงเข้าร่วมโครงการ แพทย์จะทำการตรวจร่างกายของผู้เข้าร่วมโครงการวิจัยอย่างละเอียด จะมีการเก็บข้อมูลรายละเอียดส่วนบุคคล ประวัติการสูบบุหรี่ในอดีต ประเมินความรุนแรงในการติดนิโคติน และเจ้าหน้าที่จะให้คำแนะนำเกี่ยวกับการปฏิบัติตนระหว่างการพยายามเลิกสูบบุหรี่ ผู้เข้าร่วมโครงการจะกำหนดวันที่ต้องการหยุดบุหรี่ภายในเวลา 30 วัน หลังจากนั้นผู้เข้าร่วมโครงการจะได้รับยาตามการเลือกแบบสุ่มให้ได้รับนอร์ทริปทัยรินหรือยาเม็ดหลอก แพทย์และเจ้าหน้าที่จะไม่ทราบว่าผู้เข้าร่วมโครงการจะได้ยาชนิดใด ผู้เข้าร่วมโครงการต้องรับประทานยาตามที่ได้กำหนดไว้ หลังจากนั้นแพทย์จะนัดผู้ป่วยมาติดตามในอาทิตย์ที่ 2, 4, 8 และ 12 เจ้าหน้าที่วิจัยและแพทย์จะทำการติดต่อผู้ป่วยในกรณีที่ผู้ป่วยไม่มาตามนัด

3. คำชี้แจงเกี่ยวกับผลข้างเคียงจากการใช้ยานอร์ทริปทัยริน

ผลข้างเคียงที่พบได้ไม่บ่อยนักจากยาคือ ปากแห้ง ง่วงนอน ซึ่งอาการส่วนมากไม่เป็นมาก อาการที่เกิดรุนแรงจะเกิดในผู้ป่วยที่รับยาในขนาดสูงมากๆ

4. คำชี้แจงเกี่ยวกับการเจาะเลือดและตรวจปัสสาวะระหว่างการวิจัย

ในการพบแพทย์ในสัปดาห์ที่ 12 ผู้ร่วมโครงการจะได้รับการตรวจปัสสาวะหา cotinine และวัดปริมาณคาร์บอนมอนนอกไซด์ในลมหายใจเพื่อเป็นการประเมินว่าผู้เข้าร่วมโครงการยังสูบบุหรี่อยู่หรือไม่

5. ประโยชน์ที่คาดว่าจะได้รับจากโครงการนี้

ผู้ที่เข้าร่วมโครงการจะได้รับการรักษาที่เป็นมาตรฐานในการรักษาผู้ที่ต้องการเลิกบุหรี่และได้รับการดูแลและตรวจร่างกายอย่างใกล้ชิดจากแพทย์ ผลของการวิจัยนี้สามารถนำไปช่วยวางแผนการรักษาผู้สูบบุหรี่ในระดับชาติต่อไป

6. คำชี้แจงเกี่ยวกับสิทธิของผู้ถูกวิจัย

ข้อมูลและผลการตรวจในโครงการวิจัยนี้ จะนำไปใช้เฉพาะในโครงการวิจัยเพื่อวัตถุประสงค์ทางวิชาการ โดยที่ข้อมูลส่วนตัวของผู้เข้าร่วมโครงการจะถูกเก็บไว้เป็นความลับ ผู้วิจัยไม่สามารถนำไปใช้เพื่อวัตถุประสงค์อื่นนอกจากจะได้รับอนุญาตเป็นลายลักษณ์อักษรจากผู้ร่วมโครงการวิจัย

ผู้เข้าร่วมโครงการไม่จำเป็นต้องเสียค่าใช้จ่ายในด้านการตรวจทางห้องปฏิบัติการณ์หรือการตรวจร่างกายระหว่างเข้าร่วมโครงการวิจัย

การเข้าร่วมโครงการนี้เป็นไปโดยสมัครใจ ผู้เข้าร่วมโครงการอาจจะปฏิเสธที่จะเข้าร่วมหรือถอนตัวออกจากโครงการวิจัย หรือหยุดใช้ยาที่ได้รับได้ทุกเมื่อ

หากท่านมีปัญหาหรือข้อสงสัยประการใด กรุณาติดต่อผู้วิจัยหลัก ผศ นพ ฉันชาย สิทธิพันธุ์ ที่หน่วยโรคปอด ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทรศัพท์ 02-256-4252

คณะผู้วิจัยขอขอบคุณในความร่วมมือของท่านมา ณ ที่นี้ด้วย

ข้าพเจ้า_____ ได้รับการอธิบายเกี่ยวกับรายละเอียดของการวิจัยนี้อย่างครบถ้วน และผู้ทำการวิจัยได้ตอบคำถามของข้าพเจ้า

ลายมือชื่อ_____ วันที่_____

(_____)

แพทย์ผู้ทำการวิจัย_____วันที่_____

(_____)

พยาน_____ วันที่_____

(_____)

APPENDIX C

Case Record Form

Case No._____

A Randomized, controlled trial to compare the effectiveness of nortriptyline plus brief motivation counseling and motivation counseling alone for the treatment of smoking cessation in Thai active smokers.

Name_____ HN_____/_____ DOB___/___/___

Address_____phone_____

Contact person (family or closed friend)_____

Address_____phone_____

Visit 1 Date of enrollment___/___/___

Part 1 Demographic data

1. Gender ☐ 1. Male ☐ 2. Female 1☐
2. Age ……years 2☐☐
3. Marital status 3☐
   - ☐ 1) single ☐ 2) married
   - ☐ 3) divorced ☐ 4) widow/widower
4. Occupation 4☐
   - ☐ 1) student ☐ 2) government officer
   - ☐ 3) Employee ☐ 4) private business
   - ☐ 5) unemployed ☐ 6) others……
5. Education 5☐
   - ☐ 1) primary school ☐ 2) secondary school
   - ☐ 3) college/bachelor degree ☐ 4) master degree or higher

Part 2 smoking data

6. Age when start smoking:……year 6☐
7. Other family member who is an active smokers ☐ 1) yes ☐2) no 7☐
8. Number of cigarettes you smoke per day (average in the past month) 8☐
   - ☐ 1) 10-20 ☐ 2) more than 20
9. previous attempts to quit smoking ☐ 1) yes ☐ 2)no 9.1☐

   How many times have you tried to quit before? _____ times 9.2☐

What of the following techniques have you tried for smoking cessation?

☐ 1) attempt to quit by yourself ☐ 2) consult physician

☐ 3) smoking cessation medication ☐ 4) herbal medications

☐ 5) group therapy 9.3☐☐☐☐☐

longest period that you refrained from smoking in previous attempt _____ days9.4☐☐

Part 3 medical history

10. Underlying medical illness 10 ☐☐☐☐☐.....

☐ 1) COPD/emphysema/chronic bronchitis ☐ 2) asthma ☐ 3) cancer

☐ 4) Cerebrovascular disease (stroke) ☐ 5) Cancer ☐ 6) อื่นๆ.....

11. Do you experience any of the following symptoms? 11☐☐☐☐

☐ 1) chronic cough ☐ 2) productive sputum ☐ 3) shortness of breath with exertion

☐ 4) chest pain/chest discomfort

12. Do you think that any of you current illness or symptoms related to smoking?

☐ 1) yes ☐ 2) no ☐ 3) not sure 12☐

Part 4 physical examination

13. vital sign BP_____mmHg HR_____/min RR_____/min BW _____Kg

general appearance_____ HEENT_____

Heart/lung_____

Abdomen_____ Extremities_____

EKG result_____

Patient has bee allocated to the treatment number _____

Patient has chosen the quit smoking date on _____/_____/_____

Investigator name_____ signature_____date___/___/___

Next follow clinic visit date _____/_____/_____

Follow up record Case No._____

Visit 2 Date ___/___/___

vital sign BP_____mmHg HR_____/min RR_____/min BW _____Kg

general appearance_____ HEENT_____

Heart/lung_____

Abdomen_____ Extremities_____

1) Smoking ☐ none for_____days ☐still smoking

2) Study medication ☐ still using regularly ☐stop using

reasons for stop using medication

☐ does not work ☐side effects ☐others_____

3) Withdrawal symptoms ☐craving, ☐irritable/angry ☐anxious/tense,

☐restless ☐ insomnia ☐ impatient ☐drowsiness ☐others_____

4) Side effects from medication

☐dry mouth ☐constipation ☐ dizziness ☐urinary retention ☐ other_____

Investigator name_____ signature_____date___/___/___

Next follow clinic visit date _____/_____/_____

Visit 3 Date ___/___/___

vital sign BP_____mmHg HR_____/min RR_____/min BW _____Kg

general appearance_____ HEENT_____

Heart/lung_____

Abdomen_____ Extremities_____

1) Smoking ☐ none for_____days ☐still smoking

2) Study medication ☐ still using regularly ☐stop using

reasons for stop using medication

☐ does not work ☐side effects ☐others_____

3) Withdrawal symptoms☐craving, ☐irritable/angry ☐anxious/tense,

☐restless ☐ insomnia ☐ impatient ☐drowsiness ☐others_____

4) Side effects from medication

☐dry mouth ☐constipation ☐ dizziness ☐urinary retention ☐ other_____

Investigator name_____ signature_____date___/___/___

Next follow clinic visit date _____/_____/_____

VITAE

Mr. Chanchai sittipunt was born on May, 24th, 1966 in Bangkok, Thailand. He graduated from faculty of medicine, Chulalongkorn University in 1989 with second class honor. After graduated, he worked in General Police hospital during 1889-1992 as an internist. He completed residency training in internal medicine from faculty of medicine, Chulalongkorn University in 1995. He received further training at Mayo Clinic, Rochester, Minnesota USA during 1995-1996 and received certificate in critical care medicine. He was working as clinical fellowship in pulmonary and critical care at university of Washington, Seattle, USA during 1996-1998 and received certificate in pulmonary and critical care medicine. He is now working as a pulmonoligist/intensivist at faculty of medicine, Chulalongkorn University, Bangkok Thailand.