ผลของยาโมโคลบีมายด์และอัลพราโซแลม
ต่ออาการพานิคในโรคพานิค

นายธรณินทร์ กองสุข

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาการพัฒนาสุขภาพ หลักสูตรการพัฒนาสุขภาพ
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2543

ISBN 974-347-163-4

EFFECT OF MOCLOBEMIDE AND ALPRAZOLAM ON PANIC ATTACKS IN PANIC DISORDER

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Health Development
Program of Health Development
Faculty of Medicine
Chulalongkorn University
Academic Year 2000

ISBN 974-347-163-4

Thesis Title : Effect of Moclobemind and Alprazolam on Panic Attack in Panic Disorder

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ธรณินทร์ กองสุข : ผลของโมโคลบีมายด์และอัลพราโซแลมต่ออาการพานิคในโรคพานิค (Effect of Moclobemide and Alprazolam on Panic Attack in Panic Disorder) คำสำคัญ : โมโคลบีมายด์, อัลพราโซแลม, โรคพานิค, อาการพานิค อาจารย์ที่ปรึกษา ศ.น.พ. จิตร สิทธิอมร,อาจารย์ที่ปรึกษาร่วม รศ.น.พ. สุมิตร สุตรา, 90 หน้า ISBN 974-347-163-4

วัตถุประสงค์ของการศึกษา : เพื่อเปรียบเทียบผลของโมโคลบีมายด์และอัลพราโซแลมในการรักษาโรคพานิค
วิธีการ : randomized double-blind controlled trial ศึกษาในผู้ป่วยโรคพานิคตามการวินิจฉัย DSM-IV 186 ราย โดยมีผู้ป่วย 93 ราย ได้รับการรักษาด้วยยาโมโคลบีมายด์และ 93 ราย ได้รับการรักษาด้วยยาอัลพราโซแลม มีระยะเวลาการศึกษา 8 อาทิตย์ ผู้ป่วยจะได้รับการสอนและแนะนำให้บันทึกอาการพานิคที่เกิดขึ้นทั้งหมดหลังจากที่ได้รับยาในสมุดบันทึกอาการพานิคแล้วจิตแพทย์จะประเมินและนับจำนวนตามเกณฑ์ DSM-IV ผลของยาในการลดการเกิดอาการพานิคจะวิเคราะห์ด้วย poisson regression and Generalized Estimating Equations (GEE)
ผลการศึกษา : โมโคลบีมายด์และอัลพราโซแลมสามารถลดอาการพานิคได้ตั้งแต่อาทิตย์แรกของการรักษาและอาการพานิคลดลงจนถึงอาทิตย์สุดท้ายของการรักษา ในอาทิตย์แรกอัลพราโซแลมสามารถลดการเกิดอาการพานิคได้มากกว่าโมโคลบีมายด์ Diff IR=0.96 (95%CI=0.36-1.55) แต่หลังจากอาทิตย์ที่3 โมโคลบีมายด์จะลดการเกิดอาการพานิคได้มากกว่า โดยมีผลต่างของอัตราการเกิดอาการพานิคตามลำดับจากอาทิตย์ที่ 4-6 ดังนี้ Diff IR= -0.42[95%CI=(-0.62)-(-0.24)], -0.27[95%CI=(-0.42)-(-0.13)], -0.44 [95%CI=(-0.61)-(-1.55)], -0.7[95%CI=(-0.29)-(-0.05)] , and –0.22[95%CI=(-0.34)-(-0.11)]. ผลการวิเคราะห์ด้วย GEE โดยนำจำนวนอาการพานิคก่อนการรักษา อายุ และเพศเข้ามาปรับด้วยจะได้ดังนี้ adjusted incidence rate ratio= 0.88 (95%CI=0.76-1.02) P=0.084
สรุปผลการศึกษา : โมโคลบีมายด์และอัลพราโซแลมเป็นยาที่ได้ผลในการรักษาผู้ป่วยโรคพานิค สามารถลดอาการพานิคได้ดี แต่ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติในการลดการเกิดอาการพานิค

ภาควิชา การพัฒนาสุขภาพ **ลายมือชื่อนิสิต**.....
สาขาวิชา การพัฒนาสุขภาพ **ลายมือชื่ออาจารย์ที่ปรึกษา**.....
ปีการศึกษา 2543 **ลายมือชื่ออาจารย์ที่ปรึกษาร่วม**.....

THORANIN KONGSUK : EFFECT OF MOCLOBEMIDE AND ALPRAZOLAM ON PANIC ATTACK IN PANIC DISORDER. KEY WORD: MOCLOBEMIDE, ALPRAZOLAM, PANIC DISORDER, PANIC ATTACK. THESIS ADVISOR: PROFESSOR CHITR SITTHI-AMORN, M.D., Ph.D. THESIS Co-ADVISOR: ASSOCIATE PROFESSOR SUMITRA SUTRA M.D., M.Sc. 90 PP. ISBN 974-347-163-4.

Objective: The purpose of this research is to evaluate the efficacy and tolerability of Moclobemide and Alprazolam in treatment of panic disorder.

Method: A randomized double-blind controlled trial was conducted and one instrument for collection data was developed. One hundred and eighty six panic disorder patients were enrolled for 8 week treatment period. Ninety three patients were given Alprazolam and Ninety three patients were given Moclobemide. The total panic attacks occurred in each week after intervention was recorded by patient in Panic Self-report Inventory (Diary record from). All of panic attacks were identified and counted by a psychiatrist according to DSM-IV criteria. The efficacy of Moclobemide and Alprazolam in reducing the panic attacks were analyzed by using poisson regression and Generalized Estimating Equations (GEE).

Result: The incidence of panic attacks was decreased by the first week of both treatment groups and this decrease was maintained until the end of study. At week1 Alprazolam showed efficacy in reducing panic attacks more than Moclobemide , the difference of incidence rate = 0.96 (95%CI=0.36-1.55) but After week 3 Moclobemide became more effective than Alprazolam , the difference of incidence rate at week4 to week 8 = -0.42[95%CI=(-0.62)-(-0.24)], -0.27[95%CI=(-0.42)-(-0.13)], -0.44[95%CI=(-0.61)-(-1.55)], -0.7[95%CI=(-0.29)-(-0.05)] , and –0.22[95%CI=(-0.34)-(-0.11)] respectively. Analysis by using GEE when adjusted baseline, age, and sex , the adjusted incidence rate ratio was 0.88 (95%CI=0.76-1.02) P-value =0.084.

Conclusion: Greater improvement in panic attacks in patients given Moclobemide and Alprazolam was shown by the end of the first week of treatment and sustained throughout the 8th week. There is no significant difference in the efficacy of Moclobemide and Alprazolam in reducing panic attacks.

Department……Student's signature……

Field of study……Advisor's signature……

Academic year……Co-advisor's signature……

ACKOWLEDGMENT

This study was completed with the support and assistance of many helpful people. I wish to express my sincere gratitude and appreciation to Professor Chitr Sitthi-Amorn, Associate Professor Sumitra Sutra, and Assistant Professor Bandit Thinkhamrop who guided and gave valuable comments throughout the process of this study.

I am most grateful to Dr. Tavee Tungseree, director of Nakornpanom Psychiatric Hospital, for his kindness in giving permission for this study.

The Mental Health Department of Ministry of Public Health gave me a great opportunity and all financial assistance to allow me to complete this Master degree study.

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CHAPTER 1

INTRODUCTION & BACKGROUND

1.1 INTRODUCTION & BACKGROUND

Panic disorder, is a psychiatric disorder, became an official diagnostic entity after it was codified in 1980 as a diagnosis in anxiety disorder's group in the third edition Diagnostic and Statistical Manual of Mental disorders (DSM III)[1]. Panic disorder is a common disease. Population-base studies in several countries have estimated the prevalence of about 1.5% to 2% in adult population [2,3], and the estimation from the National Comorbidity Study in USA about 15% of the survey respondent reported the occurrence of panic attack over their life time, and 1% met the DSM-III-R criteria for panic disorder in the month preceding interview[4].

Patients with panic disorder have recurrent, unexpected panic attack often more than one attack per week. The attacks are accompanied by concern or dread about having additional attack, so call anticipatory anxiety, when panic attack have occur in certain situation, patients begin to associate such situation with panic attack and become phobic and begin to avoid such situation [5]. This phobia limits or restricts activities. The severe phobia limits a person to his or her home.

Panic disorder is a disease of adults, primarily woman, that begins in early adulthood and often occurs concurrently with other anxiety-related disorder(e.g. GAD, Phobia, OCD)[4]. Because episodes of panic attack involve somatic symptoms, patient with panic disorder commonly present to a variety of general health care professionals who frequently misdiagnose causing increase rate of medication consumption [6], and high health care utilization [7,8]. Significant impairment in interpersonal work / leisure and health status domain about quality of life issue in treatment of panic disorder [6].

The appropriate diagnosis and treatment are necessary in panic disorder. Effective treatment can help to reduce the profound effects of panic disorder on

personal happiness, role functioning, quality of life and the costly and inappropriate use of health services.

The treatments of Panic disorder have ranged from psychotherapy [9] to pharmacotherapy. There are several groups of psychotropic drugs that have antipanic effect such as tricyclic antidepressants, monoamine oxidase inhibitors(MAOIs), selective serotonin reuptake inhibitors(SSRI) or high-potency benzodiazepines.

The antipanic effectiveness of tricyclic antidepressants such as imipramine, clomipramine, are well established [10-18]. Their disadvantages include a relatively delay onset of 4-8 weeks [19], produce many anticholinergic side effect, e.g. dry mouth and constipation, cause orthostatic hypotension, sexual effects, e.g. delayed ejaculation, impotence, and weight gain [20].

The selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, flavoxamine, paroxatine have strong evidence support the efficacy in the treatment of panic disorder [21]. The main problem observed clinically have Jitteriness, restlessness, insomnia, and sexual effect in long term treatment [22]. SSRIs are very expensive so they have limits their use in Thailand.

The large multicentre studies [23,24] clearly established alprazolam, a high potency benzodiazepine, is an effective antipanic agent. The disadvantages include their sedative effect, the risk of dependence and withdrawal symptoms, and their cognitive effects.

Monoamine oxidase inhibitors (MAOIs) such as phenelzine, isocarboxazid are potent antidepressant and antiphobic agent. The evidence strongly suggest the efficacy in treating panic related disorder [25-27] but the using of MAOIs have been diminished because of the drug and tyramine containing food interaction induce hypertensive crisis and the side effects, e.g. insomnia, orthostatic hypotension, sexual effects.

The new, type of MAOIs(selective, and reversible MAO-A inhibitor), moclobemide do not require dietary restrictions, and is better tolerated[28-30]. Moclobemide has already been shown in many controlled trial to be effective in major depressive disorder. Preliminary study of 18 patients has shown to be effective in blocking panic attacks [31].

Because all the currently antipanic drugs have disadvantages, the treatment of panic disorder still need effective, well-tolerated, less side effect profile agent. So if moclobemide demonstrates to be effective in treating panic disorder, it can represent a significant therapeutic advance because it appears to have a less unfavorable side effects e.g. no sedation, no impairment of psychomotor or cognition, no evidence of withdrawal symptoms and no evidence of drug dependency or drug abuse. Moclobemide is better in treating phobia and depression. Both phobia and depression are the important complication of panic disorder.

The purpose of this study is to investigate the comparative efficacy and tolerability of alprazolam and moclobemide in the treatment of panic disorder.

1.2 Research Objectives

1 To compare the efficacy in reducing panic attacks, between moclobemide, a reversible inhibitor monoamine oxidase and alprazolam, a high potency benzodiazepine.

2 To identify the adverse effect of moclobemide and alprazolam.

3 To identify the better alternative drug in the treatment of panic disorder.

1.3 Research Questions

1.3.1 Primary Research Question

- Can moclobemide reduce the panic attacks per person week more than 20% as compare to alprazolam in treating panic disorder patients?

1.3.2 Secondary Research Question

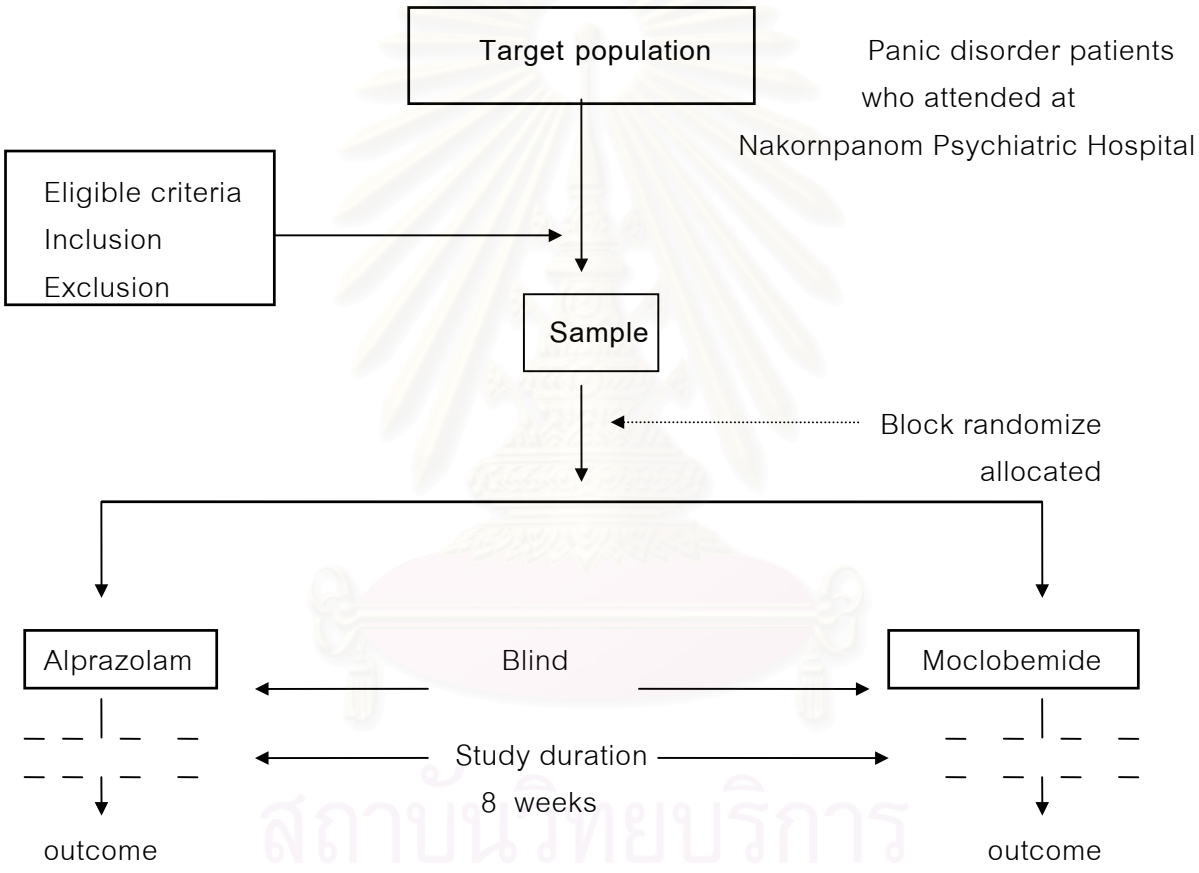
- What are the adverse effects of moclobemide and alprazolam?

1.4 Research Hypothesis

The panic disorder patients who were treated with moclobemide will have panic attacks per person week less than the patients who were treated with alprazolam.

1.5 Overall research design

Figure 1. Overall research design



1.6 Key words: Moclobemide, Alprazolam, panic attack, panic disorder.

1.7 Operational Definition

1.7.1 Panic disorder is a subtype of anxiety disorder. The anxiety in panic disorder manifests as recurrent unexpected panic attacks.

Table 1. Diagnostic criteria for panic disorder

Diagnostic Criteria for panic Disorder

A. Both (1) and (2):

(1) recurrent unexpected panic attacks

(2) at least one of the attacks has been followed by one month (or more) of one (or more) of the following:

(a) persistent concern about having additional attacks

(b) worry about the implications of the attack or its consequences(e.g. losing control. having a heart attack, “going crazy”)

(c) a significant change in behavior related to the attacks

B. Absence of agoraphobia (panic disorder without agoraphobia), presence of agoraphobia (panic disorder with agoraphobia).

C. The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medication) or a general medical condition (e.g., hyperthyroidism).

D. The panic attacks are not better accounted for by another mental disorder, such as social situations. Specific phobia (e.g., on exposure to a specific phobic situation).Obsessive-compulsive disorder (e.g., on exposure to dirt in someone with an Obsession about contamination). Posttraumatic stress disorder (e.g., in response to stimuli associated with a severe stressor). or separation anxiety disorder (e.g. in response to being away from home or closed relatives).

1.7.2 Panic attack is a period of intense fear or discomfort, manifests as

a sudden rush of fearfulness accompanied by a number of physical and cognitive signs and symptoms, such as rapid heartbeat, trembling, feeling of unreality, and fear of dying.

(Diagnosis of panic attack will use criteria DSM-IV criteria for panic disorder) [32].

Table 2. Criteria for panic attack

Criteria for Panic Attack

A discrete period of intense fear or discomfort, in which four or more of the following symptoms developed abruptly and reached a peak within 10 minutes:

(1) palpitations, pounding heart, or accelerated heart rate

(2) sweating

(3) trembling or shaking

(4) sensation of shortness of breath or smothering

(5) feeling of choking

(6) chest pain of discomfort

(7) nausea or abdominal distress

(8) feeling dizzy, unsteady, light-headed, or faint

(9) derealization (feeling of unreality) or depersonalization (being detached from oneself)

(10) fear of losing control or going crazy

(11) fear of dying

(12) paresthesias(numbness or tingling sensations)

(13) chills or hot flushes

1.8 Ethical considerations

1. Alprazolam is a benzodiazepine widely used as antianxiety drug, general safety and high patient acceptability. Moclobemide, a RIMA available worldwide as an antidepressant, has no severe side effect.
2. Patients are completely free to refuse to participate or drop out at any time.
3. Informed consent for every patient.

CHAPTER 2

REVIEW OF THE RELATED LITERATURE

2.1 PANIC ATTACK

A panic attack is the cardinal feature of panic disorder. The essential feature of a panic attack is defined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [32] as a discrete period of intense fear or discomfort in which at least 4 of 10 possible cardiac, neurological, gastrointestinal, and/or respiratory symptoms develop abruptly and reach a peak within 10 minutes. As shown in Table 3, most of these symptoms are somatic and only 3—fear of losing control, fear of dying, and derealization—are psychological.

Table 3. DSM-IV Symptoms Used in the Diagnosis of Panic Attack*

Cardiac
Palpitations, pounding heart, or accelerated heart rate
Chest pain or discomfort
Sweating
Chills or hot flushes
Neurological
Dizziness, Faint, Unsteady, or light-headed
Paresthesia
Trembling or shaking
Gastrointestinal
Nausea, or Abdominal distress
Psychological
Fear of losing control, or going crazy
Fear of Dying
Derealization, or Depersonalization

Respiratory	
	Shortness of breath, Feeling of smothering
	Feeling of choking

***Data** from reference 32. An attack must include at least four of these symptoms, develop abruptly, and reach a peak within 10 minutes.

Panic attacks can occur in a variety of anxiety disorders (e.g., panic disorder, social phobia, specific phobia, posttraumatic stress disorder, and acute stress disorder). In determining the differential diagnostic significance of a panic attack, it is important to consider the context in which the panic attack occurs.

There are three characteristic types of panic attacks with different relationships between the onset of the attack and the presence or absence of situational triggers: **unexpected (uncued) panic attacks**, in which the onset of the panic attack is not associated with a situational trigger (i.e., occurring spontaneously "out of the blue"); **situationally bound (cued) panic attacks**, in which the panic attack almost invariably occurs immediately on exposure to, or in anticipation of, the situational cue or trigger (e.g., seeing a snake or dog always triggers an immediate panic attack); and **situationally predisposed panic attacks**, which are more likely to occur on exposure to the situational cue or trigger, but are not invariably associated with the cue and do not necessarily occur immediately after the exposure (e.g., attacks are more likely to occur while driving, but there are times when the individual drives and does not have a panic attack or times when the panic attack occurs after driving for a half hour).

The occurrence of unexpected panic attacks is required for a diagnosis of panic disorder (with or without agoraphobia). Situationally bound panic attacks are most characteristic of social and specific phobias. Situationally predisposed panic attacks are especially frequent in panic disorder but may at times occur in specific phobia or social phobia.

The differential diagnosis of panic attacks is complicated by the fact that an exclusive relationship does not always exist between the diagnosis and the type of panic attack. For instance, although panic disorder definitionally requires that at least some of the panic attacks be unexpected, individuals with panic disorder frequently report having situationally bound attacks, particularly later in the course of the disorder.

2.2 PANIC DISORDER

2.2.1 DIAGNOSIS

The typical presentation of panic disorder involves recurrent panic attacks, or discrete periods of intense fear or discomfort usually lasting minutes, with at least four associated symptoms (DSM-IV)[32].

Panic attacks most often occur unexpectedly in the initial phases of the disorder. To receive the diagnosis of panic disorder, the panic attacks must have occurred when not triggered by being the focus of other's attention (as in social phobia), by events or situations that normally trigger anxiety (as in simple phobia), or by organic factors.

The unexpected nature of the attacks is a central feature, although later in the course of the disorder various feared situations (e.g., driving a car) may trigger the attacks. To meet diagnostic criteria for the disorder, recurrent unexpected panic attacks must occur, with one or more attacks followed by at least one month of one or more of the following: (1) persistent concern over future attacks, (2) worry about implications or consequences of the attack, or (3) significant behavior change related to the attacks.

The onset of panic attack is typically marked by the sudden presence of intense fear, apprehension, or dread, frequently with the feeling of impending doom.

The DSM-IV requires the development of at least four of 13 symptoms, which must develop suddenly and reach a peak in intensity within 10 minutes of the first symptom perceived. The distinction of escalating symptom intensity within 10 minutes highlights the sudden and episodic nature of panic, differentiating it from the more diffuse anxiety symptoms present in an anxiety condition such as generalized anxiety disorder.

Panic symptoms include physiologic symptoms, such as palpitations, sweating, trembling, and shortness of breath; and cognitive symptoms, including derealization and fear of dying, going crazy, or losing control. (See Table 3.)

2.2.2 EPIDEMIOLOGY

Prevalence Rates

Table 4 shows prevalence rates for panic disorder from a cross-national collaborative study of 10 countries, using the Diagnostic Interview Schedule (DIS) and DSM-III criteria. These 10 community studies included over 40,000 subjects and were analyzed with appropriate standardization for age and sex differences among subjects from different countries. For comparison purpose, Table 4 also includes data from the National Comorbidity Study (NCS)[4] of a representative sample of 8098 persons living in the 48 contiguous United States conducted in 1990 to 1992 using the University of Michigan version of the Composite International Diagnostic Interview (UM-CIDI) and DSM-III-R criteria. The annual rate of DSM-III panic disorder ranged from 0.2 per 100 in Taiwan to 2.1 per 100 in Beirut, Lebanon [33]. The NCS reported an annual prevalence of 2.2 per 100 for DSM-III-R panic disorder [4].

Lifetime rates of DSM-III panic disorder showed excellent agreement, with the prevalence varying from 1.4 per 100 in Edmonton, Canada [34], to 2.9 per 100 in Florence, Italy [35]. The exception to this narrow range was Taiwan, where DSM-III panic disorder had a lifetime prevalence of 0.4 per 100. The lower rates of panic disorder in Taiwan are consistent with lower Taiwanese rates for most other disorders

studied. The reason for these lower rates is not clear. The only study that reported on lifetime DSM-III-R panic disorder was the NCS, which found a rate of 3.5 per 100, somewhat higher than the lifetime rates based upon DSM-III. The higher annual and lifetime rates reported in the NCS may reflect a period effect, with rates increasing between the ECA of the early 1980s [4] and the NCS of the early 1990s[36]. The higher rate in the NCS may also reflect the broader concept of panic disorder in DSM-III-R than in DSM-III or the differences in memory probes used in the NCS interview (the UM-CIDI) and the DIS used in the cross-national collaboration.

Table 4

Prevalence Rates for Panic Disorder Per 100 Subjects: Age 18-64 Years

		Lifetime			
Site	Annual	Total	Female	Male	F/M Ratio
United States (ECA)	1.0	1.7	2.3	1.0	2.3
Edmonton	0.9	1.4	1.9	1.9	2.1
Puerto Rico	1.1	1.7	1.8	1.4	1.3
Savigny, France	0.9	2.2	3.0	1.3	2.3
West Germany	1.7	2.6	3.8	1.4	2.7
Florence, Italy	1.3	2.9	3.9	1.2	3.2
Beirut, Lebanon	2.1	2.1	3.1	1.1	2.8
Taiwan	0.2	0.4	0.6	0.2	3.0
Korea	1.5	1.7	2.9	0.5	5.8
New Zealand	1.3	2.1	3.3	0.7	4.7
United States (NCS)	2.2	3.5	5.1	1.9	2.7

Age at Onset

The age at onset of panic disorder is usually in the early to middle 20s, with a late onset in West Germany and Korea (35.5 and 32.1, respectively). The NCS data showed a bimodal distribution of age of onset, with an early mode for panic disorder in the 15- to 24-year age range for both men and women and a later mode in the 45- to 54-year range.

Sex Differences

Comparing lifetime prevalence rates, all studies reporting on panic disorder showed higher rates for women than for men. An analysis of the NCS data found uniformly higher rates of panic attacks and panic disorder for women than in men within every age group. Another study analyzed incidence rates from the Epidemiologic Catchments Area (ECA) study [4] and found a twofold higher risk of incident panic disorder in women than in men. This finding is analogous to the higher incidence and prevalence rates of major depression in women than in men and suggests that for both panic disorder and major depression, the higher rates in women reflect a true increase in the risk for new-onset panic disorder and major depression rather than a greater tendency to seek treatment or have longer episodes of illness.

2.2.3 CLINICAL FEATURES

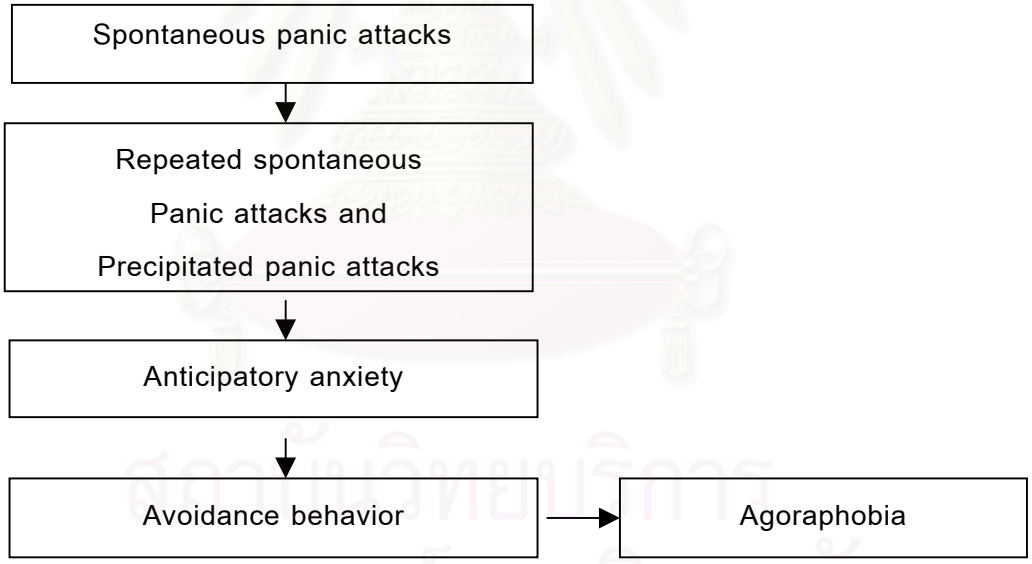
The first panic attack is often completely spontaneous, although panic attacks occasionally follow excitement, physical exertion, sexual activity, or emotional trauma. The major mental symptoms are extreme fear and sense of impending death and doom. Patients are usually not able to name the source of their fear.

The physical signs often include tachycardia, palpitation, dypsnea, and sweating. The patients often try to leave situation they are in to seek help. The attack generally lasts 20-30 minutes and rarely more than an hour. A formal mental status

examination during panic attack may reveal rumination, difficulty in speaking and impair memory.

The symptoms may disappear quickly or gradually. Between attack, patients may have anticipatory anxiety about having another attack. Somatic concerns of death from a cardiac or respiratory symptoms may be the major focus of patient's attention during panic attacks. They believe that the palpitation and the pain in chest indicate that they are about to die and may present to emergency room as young physical healthy persons who nevertheless insist they are about to die from a heart attack. When attacks are repeated, the patient may avoid situations believed to precipitate panic attacks or situations where getting help could be very difficult. Over time, this avoidance may evolve into frank agoraphobia (Figure 2)[5].

Figure 2. Development of panic Disorder



2.2.3 CLINICAL COURSE OF PANIC DISODER

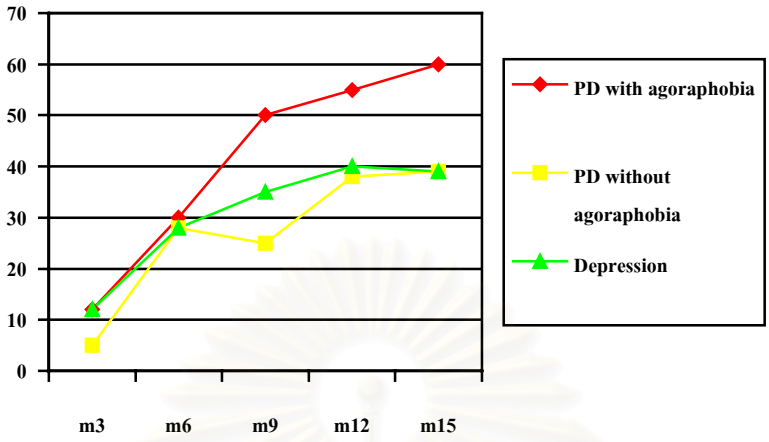
The panic disorder, in general, is a chronic disorder, although its course is variable both among patients and within a single patient. A prospective, naturalistic, and longitudinal study specifically charting the course and outcome of panic-related

disorders was initiated in 1988. Termed the Harvard/Brown Anxiety Disorders Research Program (HARP), this study of patients with DSM-III-R anxiety disorders includes an initial comprehensive evaluation assessing lifetime history and follow-up interviews conducted 6 and 12 months after the initial diagnosis to collect information on the course of illness, treatment, and psychosocial functioning[37]. Naturalistic data for the first 22 months after onset of an episode indicated that about 18% of patients with panic disorder with agoraphobia and about 43% of those with panic disorder with disorder without agoraphobia had recovered.[38-39]

The rate of relapse after recovery from episodes of panic disorder with agoraphobia was higher than that following recovery from a depressive episode. Naturalistic studies of the 18 months following recovery showed that the relapse rate increased steadily with time to about 60% among patients with panic disorder and agoraphobia (Figure 3) [38-39]. The rate of relapse was similar for patients who had recovered from episodes of depression and reached about 40%. These naturalistic data suggest that the element of agoraphobia in panic disorder influences the rates of recovery and relapse in these patients.

These trends are corraborated by the results of a placebo-controlled clinical trial of imipramine and alprazolam in which patients with panic disorder were followed for 4 years after treatment.[23] About one third of the patients recovered from their initial episodes of panic disorder and remained well at the end of the study. One in five patients continued to have a chronic course of repeated episodes, and the remaining patients, about half the population studied, had recurrent, but less severe, episodes of panic disorder.

Figure 3. Percent of relapse following recovery from episodes of panic disorder



2.3 PHAMACOLOGICAL TREATMENT IN PANIC DISORDER

Treatment of the panic disorder patient has traditionally focused on blocking panic attacks, diminishing anticipatory anxiety and reversing phobic avoidance while recognizing and treating comorbid conditions.

The current medical model of panic disorder emphasizes qualitative differences between a panic attack and other types of anxiety, According to this view, panic disorder is seen as reflecting a specific genetically influenced neurochemical dysregulation[41]. Thus, a rational pharmacological treatment intervention would target the neurobiological pathways associated with maladaptive and overreactive fear and alarm mechanisms. Putative sites of this dysregulation have included the locus ceruleus and the noradrenergic system [42], the serotonergic system [43], and the central GABA – benzodiazepine receptor complex [44]. Other studies suggest roles for various other factors in the neurobiology of panic disorder. Among them are cortisol – releasing factor, adenosine [45], and a variety of neuropeptides, including cholecystokinin [46].

Support for the neurobiological illness model also stems from experimental panic induction from biological challenges (e.g., CO_2 inhalation, lactate infusion, yohimbine), and the success of treatment with pharmacological agents.

Pharmacotherapy of panic disorder was initially shown to be effective with the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), with subsequent studies supporting the efficacy of benzodizepines, selective serotonin-reuptake inhibitors (SSRIs), and other agents.

The primary goals of pharmacological treatment are to prevent panic attacks, to address comorbid psychiatric conditions, and to extend treatment effects to achieve remission or recovery (i.e., the absence of impairment and other secondary symptoms). Drug treatment aims at re-regulating a dysregulated physiological system, addresses the underlying constitutional vulnerability, and reduces severe impairment.

2.3.1 BENZODIAZEPINES

Historically, benzodiazepines were considered ineffective in treating panic disorder. This perception changed when Sheehan, Uzogara, and Coleman [47] and Chouinard, Annable, Fontaine, and solyom [48] reported that alprazolam, a triazolobenzodiazepine, was effective in panic disorder. Since that observation, several other benzodiazepines have been shown to be effective antipanic drugs. Studies documenting antipanic efficacy have been reported for diazepam by Noyes and associates [49] and Dunner, Ishiki, Avery,et al [50], for clonazepam by Tesar and coworkers [51] ; and for lorazepam by Charney and Woods [52].

Choice of Benzodiazepine

A conservative approach would dictate that alprazolam be the initial choice in most cases, since it has been extensively studied, found consistently effective, has low

toxicity, and is the only drug approved by the Food and Drug Administration for panic disorder.

The most frequently prescribed benzodiazepines for panic disorder are alprazolam and clonazepam. In a double-blind, placebo-controlled study by Tesar and associates [51], both drugs were found equally effective. Patients who suffer from frequent acute panic attacks prefer benzodiazepines that are rapidly absorbed. Alprazolam, clonazepam, diazepam, and clorazepate are rapidly absorbed, while lorazepam is intermediate. Rapid onset of action is not always desirable, because it also may be accompanied by rapid onset of side effects.

Alprazolam is the most extensively studied of all benzodiazepine in panic disorder, having been proved effective in all of the major clinical trials[23,24]. The percentage of patients treated with alprazolam who achieved a panic free state at 8th week are 55%[23],and 61%[32]. Now alprazolam is the most widely used antipanic drug in Thailand. The efficacy of alprazolam in treating panic disorder was initially established in a large study utilizing doses averaging nearly 6 mg per day[23] but in clinical experience it appears that the optimal dose of alprazolam for many patients is in the range 2-4 mg per day. Alprazolam also has disadvantages including sedation, coordination disturbance, impairment of cognition, high potential for dependence and abuse, and withdrawal symptoms.

Dosage and Schedule

When starting with alprazolam, generally begin with 0.5 milligrams (mg) three times a day, then titrate the dose over time. If no side effects (drowsiness) or benefit occurs with medication, the dose will be increase to next level every two days. When coming off the medicine, do not reduce the dose for any reason at a rate faster than a 1/2 tablet every four days. The above directions are for 1 mg tablets of alprazolam. Doses should be reduced more cautiously in the elderly. There are no food or drug restrictions with benzodiazepines.

The dosage range is between 4 to 6 mg per day. Some patients will tolerate and need 9 mg, and others may require only 2 mg. The large phase I Cross National Collaborative study, which evaluated 540 patients with alprazolam vs. placebo in an eight-week trial, found that the mean effective and tolerated dose of alprazolam was approximately 5.5 mg (Ballenger et al.,1988)[23]. Although a wide dose range exists for alprazolam in the treatment of panic disorder, higher doses frequently are more effective than lower doses. Lydiard and associates [53] demonstrated in a fixed-dose, 6 mg, was significantly more effective in panic attack as well as on the other core symptoms of panic disorder—anticipatory anxiety and phobic avoidance.

Adverse Effects

In general, these medications are well tolerated, with minimal side effects and a wide margin of safety in case of overdose.

1. Sedation

Sedation is the commonest initial side effect.Schweizer et al [54] report rates as high as 88% percent for alprazolam. This drowsiness tends to disappear with time or reduction in dosage.

2. Intoxication

Intoxication is clinically manifested by ataxia and slurred speech. It is dose related and easily managed by dose adjustment.

3. Amnesia

Amnesia is now noted to occur even with oral dosing. It is anterograde in nature, due to disrupted consolidation and not impairment of memory retrieval. Larson, Kukull, Buchner, and Reifler [55] report that the elderly are at risk especially when using anxiolytics with long half-lives. Scharf, Saskin, and Fletcher[56] have found the highest risk to be with the use of high-potency benzodiazepines.

4. Psychomotor Impairment

Direct and indirect evidence document the potential of these drugs to cause psychomotor impairment. Oster, Russell, Huse, Adams, and Imbimbo [57] studied members of a health maintenance organization and found that benzodiazepines users were more likely to receive accident-related health care than nonusers. Skegg, Richards, and Doll [58] found benzodiazepines users were five times more likely to experience serious motor vehicle accidents than nonusers, and Smiley [59] observed that behavioral tolerance does not occur with chronic use. Therefore, patients should be warned about avoiding alcohol and being extra careful when performing skilled tasks.

5. Other Side Effects

Sexual side effects such as loss of libido, ejaculatory inhibition, erection failure, and inhibition of female orgasm have been reported but are infrequent. Unusual side effects such as reversible hepatitis and mania have been noted in the literature. Even with adequate control of panic, depression may emerge during the course of treatment. If depression persists even after drug reduction, it can be managed by adding an antidepressant. For alprazolam, rates of depression as low as 2.7 percent have been reported by Tesar and coworkers [51]and as high as 33 percent by Lydiard, Laraia, Ballenger, and Howell [60].

Other effects in Benzodiazepine Therapy

Prior to initiating or renewing a prescription for benzodiazepines, patients should be assessed for risk of abusing this class of drug. They should be informed of the potential for dependence and cautioned never to discontinue the medication abruptly.

1. Abuse

Despite popular perception of widespread benzodiazepine abuse, this is not supported by the literature. Ladewig and Grossenbacher [61], in a study of patients in Basle, found the prevalence of benzodiazepine abuse to be one in 10,000. In a prospective study of 71 patients with major depression or

anxiety disorder treated with benzodiazepines, Garvey and tollefson [62] did not find any cases of abuse; about 7 percent misused their medication, and all had a diagnosis of depression. In a study of 5426 randomly sampled physicians from the American Medical Association physician data base, Sheehan, Hughes, and Dtorr [63] found that while 11.9 percent of physicians have used benzodiazepines during the past year, only 0.6 percent of those users met criteria of the third revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) for benzodiazepine dependence during the past year.

2. Dependence

The consequence of dependence is the emergence of withdrawal symptoms when discontinuation. The longer the use of benzodiazepines, the greater the likelihood of physical dependence, although this phenomenon has been noted after only one week of treatment by Kales and associates [64]. As dependence often is confused with addiction, it is important to inform and discuss the consequences of long-term use with the patients and educate them never to discontinue these drugs abruptly.

3. Discontinuation

All benzodiazepines have anticonvulsant properties. Therefore, abrupt termination or rapid taper can lead to severe withdrawal symptoms, including seizures. In addition, during the discontinuation phase, patients may experience “rebound anxiety” (anxiety symptoms even worse than prior to treatment) usually peaking within the first week of discontinuation. A slow taper can minimize these withdrawal symptoms and help decipher rebound anxiety from relapse. To minimize the discomfort of withdrawal, Alprazolam should be tapered no faster than a half tablet every one to two weeks.

2.3.2 MONOAMINE OXIDASE INHIBITORS

Arnot (1960) was the first to describe the anxiolytic effect of a monoamine oxidase (MAO) inhibitor. Over the years, MAO inhibitors were branded as drugs of questionable efficacy by the Medical Research Council Study on Depression . When Sheehan, Ballenger, and Jacobson [65] showed that pheneizine was superior to impipramine on several panic disorder measures, including reduction of disability, renewed interest developed in this class of drug for panic disorder and agoraphobia.

Choice of Drug

The MAO inhibitors in psychiatric use in the United States are phenelzine and isocarboxazid (hydrazines) and tranylcypromine (a nonhydrazine). Controlled studies by Sheehan (Sheehan et al.,[65]; have shown phenelzine to be effective in panic disorder, while the evidence for isocarboxazid and tranylcypromine is anecdotal. Tranylcypromine may be the MAO inhibitor of choice in elderly patients, as it is less likely to decrease blood pressure and its MAO inhibition is more rapidly reversible.

Adverse Effects

Adverse effects are similar to those described for the cyclic agents. The MAO inhibitors are not particularly anticholinergic, but they do cause mild dry mouth, constipation, and even urinary retention. Unlike the tricyclics, they usually cause a slowing of the pulse and are even more hypotension. The onset of hypotension is sometimes a late event, occurring a few weeks into treatment. Weight gain and delayed or inhibited orgasm or ejaculation are even greater with phenelzine than the tricyclics. Several months into treatment, the patient may experience electric shock sensations or carpal tunnel syndrome. This is treated with 100 to 300 mg pyridoxine (Vitamin B_6) a day and a modest lowering of the dose. Nighttime insomnia is common and can be minimized by avoiding dosing after 5 P.M. Liver toxicity is more common

with phenelzine and isocarboxazid than with tranylcypromine, and liver enzymes should be checked every six to 12 months.

New MAO Inhibitors

Recently there has been interest in developing MAO inhibitors that are safer with less side effects. Moclobemide and brofaromine are examples of “reversible MAO inhibitors.” If enough dietary tyramine is present, tyramine will displace the MAO inhibitor from the MAO enzyme and be metabolized. This reversibility is associated with no reaction with cheese or hypertensive crisis. Currently these medications are being evaluated for panic disorder.

Moclobemide is a compound synthesized in 1972 in a program for antihyperlipidemia but it did not show the expected activity. In 1974 it was submitted for pharmacological testing for possible activity on central nervous system and found to increased the brain content monoamine and decreased acidic monoamine metabolites as typically seen with monoamine oxidase inhibitors(MAOIs). By the end of 1976 the pre-clinical pharmacological and toxicological studies were completed and moclobemide was accepted for clinical development [29].

Moclobemide has now been extensively investigated in depressive disorder in many studies and in many countries. The result showed the evidence of superiority to placebo and comparable efficacy to standard anti-depressants[67,68]. The average dose is 300 mg/day.

Moclobemide has proved its effective in treating phobia, 82% of Moclobemide treated patients were almost asymptomatic[69]. From the review article, Fulton et al [70], moclobemide is better tolerated at therapeutic doses, has less toxicity in over dose than trycyclic anti-depressants, and has few anticholinergic or sedative effect.

The recently study involving the administrative of moclobemide to 9,419 patients, there was no evidence of any serious events. [71]

A study of moclobemide showed no difference in sexual function between moclobemide and placebo in healthy volunteer at dose 300 mg [72] and may has sexually stimulating effect[73].

Panic disorder has been associated with abnormal function of noradrenergic, serotonergic and GABA ergic receptor as well as with abnormal sensitivity of brain stem chemoreceptors [74-76]. Moclobemide is a reversible inhibitor of MAO with a clear preference for the A type. It increased synaptic norepinephrine and serotonin by inhibiting the extraneuronal enzyme MAO from metabolizing monoamine [29,77,78]. So it should be effective in treating panic disorder.

But now, there is only one study of moclobemide in treating panic disorder, moclobemide has also been shown to be effective in an open dose finding study of 18 patients and found no different in efficacy between moclobemide 100 mg daily and 400 mg daily [31]. The percentage of patients with panic attack free state after treating with moclobemide was about 80 % at week 5/6.

2.4 EVALUATION OF DRUG TREATMENT OF PANIC DISORDER

2.4.1 Assessments Clinical Change

In the clinical trial of psychotropic drugs for panic disorder after an accurate diagnosis, the next critical step is the rigorous assessment of panic attacks, anticipatory anxiety, and phobic avoidance. This involves education of both patients and assessors because patients commonly confuse on episodes of anticipatory anxiety with panic attacks or believe their condition has not improved, even when panic attacks are blocked, because they continue to have phobic avoidance. Many studies evaluate the duration and intensity of attacks; others also distinguish type of attack. After the subject clearly understands the definition of a panic attack, the

number of daily attacks must be recorded. Ideally, daily diaries should include monitoring of the frequency, intensity, and duration of each attack.

The panic attack is the essential feature of panic disorder and other symptoms such as anticipatory anxiety and avoidance arise from concerns about the implication of the panic attacks and a desire to avoid situations in which panic attacks are likely to occur. Once the panic attacks are blocked by medication, the patient will gradual decrease in both avoidance and anticipatory anxiety [79]. Klein et al, suggest about outcome measurement, the major issue is targeting response measures to the panic attacks themselves rather than associated complication of panic disorder [8o]. So panic attack is the primary outcome in almost panic disorder treatment researches.

The minimum duration of clinical trial design for panic disorder, when monoamine oxidase inhibitors are included in the trial, is usually 8 weeks of active treatment because of pharmacology of the drug [80].

A critical assessment should include other substances that are self – administered during treatment. In addition to alcohol and other drugs, patients may surreptitiously use benzodiazepines during treatment trials, thus blurring the drug – placebo deferral points during a trial. Ideally, these samples should be collected randomly and without notice. If subjects use benzodiazepines during the trial they should be considered treatment failure [80].

2.4.2 Assessment of Adverse Experiences

There is disagreement over asking systematically about adverse side effects or simply asking the patient to volunteer symptoms. Some believe a volunteer format results in inadequate detection of important side effects so that a rigorous inquiry is generally advantageous, although supportive data are lacking. A useful instrument is the Systematic Assessment for Treatment Emergent Events (SAFTEE) (81) but it is very complex, too long, and too difficult to apply in Thai patients. Others (82)

found that it makes no difference for important medical evaluations whether a patient freely volunteers side effects or whether they are systematically probed. Although the report of Rabkin et al. (82) dealt with depressed patients, our impression is that the same would be found with panic patients.

2.4.3. Statistical Issues

An issue specific to panic is the analysis of the number of panic attacks during a clinical trial. The problem results from the distribution of attacks, given the erratic nature of panic occurrence and the frequent observation of outliers. Some patients have one attack per week, others 70. The data are rarely normally distributed, especially after treatment starts. Klein et al,[80] suggest two statistical methods should be considered for this special problem. First, a responder can be defined as a patient with no panic attacks per week; the frequency of such responders in the drug versus placebo group can then be compared by standard techniques. Second, the drug and placebo groups can be compared on the basis of their median rank scores using a nonparametric test on the distribution of panic attacks at any given week.

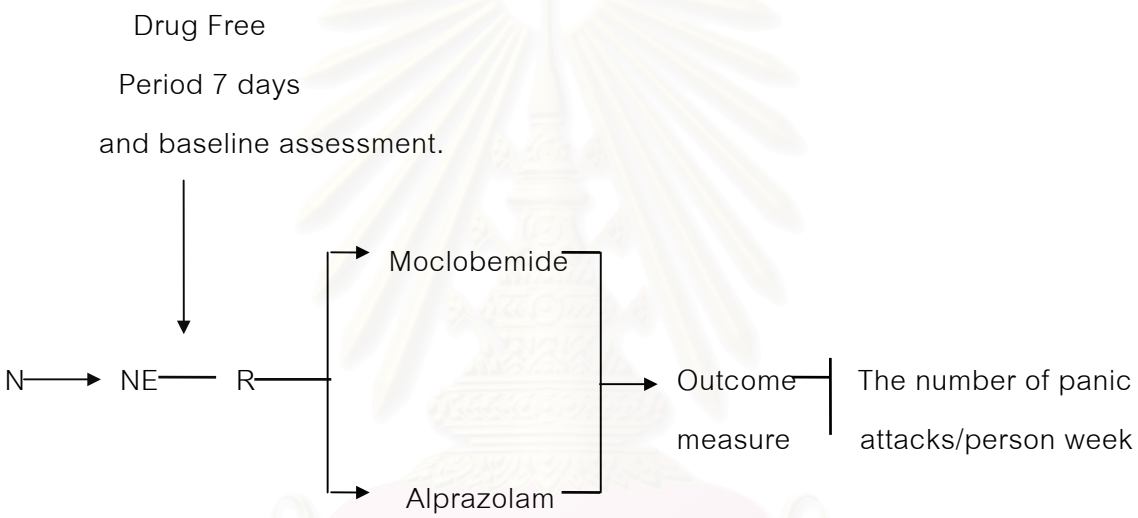
The number of panic attacks occurring during a specific time interval after receiving treatment, like number of epileptic seizure in each of time interval, are counted data with poisson distribution [83]. It should use a log-linear regression fitted by the Generalized estimating equation (GEE) method to estimate the overall treatment effect[83].

CHAPTER 3

RESEARCH METHODOLOGY

3.1 RESEACH DESIGN

A randomized, double-blind, controlled trial comparing the efficacy of moclobemide versus alprazolam in reducing the frequency of panic attack in panic disorder patients.



N : Panic disorder patients who come to Nakornphanom Psychiatric Hospital

NE : Eligible patients

R : Random allocation

3.2 RESEARCH METHODOLOGY

3.2.1 POPULATION

3.2.1.1 Target Population ;

The target population is the panic disorder patients.

3.2.1.2 Sample Population ;

The sample population was the patients diagnosed with panic disorder at the out patient unit of Nakhonphanom Psychiatric Hospital who meeting the eligibility criteria.

3.2.1.3 Eligibility Criteria for the sample to study

Inclusion criteria

1. Patients aged between 18 and 65 years and either sex.
2. Fulfill DSM-IV criteria for panic disorder with and without agoraphobia.
3. Patients suffering at least one panic attack per week for the 2 weeks before baseline evaluation.

Exclusion criteria

1. Pregnancy or intention to become pregnant.
2. Patients who have a current or lifetime bipolar disorder, depressive disorder, obsessive compulsive disorder, psychosis, dementia, or substance abuse, personality disorders.
3. Patients with major medical disorders e.g. uncontrolled thyroid diseases, renal and hepatic function impairment, cardiac diseases, pulmonary diseases, endocrinologic or collagen disease.
4. Patients who take medication that will affect the study result e.g. propanolol, clonidine.

3.2.2 SAMPLE SIZE

The primary outcome was counted data but estimating sample size was calculated by using standard two independent groups formula because there is no available sample size calculation for counted data and repeated measure .

$$n/group = \frac{2(Z_\alpha+Z_\beta)^2\pi(1-\pi)}{(P_1- P_2)^2}$$

n/group = required sample size for each control and treated groups.

α = type I error probability

β = type II error probability

Z_α = the value of the standard normal distribution cutting off probability for α = 0.05 (two-tailed) is 1.96

Z_β = the value of the standard normal distribution cutting off probability β in the upper tail = 0.84 for 80% power

P_1 = success rate of alprazolam in treatment for panic disorder. = 0.6 [32]

P_2 = success rate of moclobemide in treatment for panic disorder = 0.8 .

$$\pi = \frac{P_1+P_2}{2}$$

$$n/group = \frac{2(1.96+0.84)^2(0.7)(0.3)}{(0.6-0.8)^2}$$

= 82.32 cases/group

If dropout rate = 10% n/gr $\frac{n}{1-r} = \frac{82.32}{0.9} = 92.2$

The required sample size = 93 cases / group

Block randomization

The patients were divided into 2 groups.

1. Group A treated by alprazolam
2. Group B treated by moclobemide

The subjects were randomly assigned with equal probability to group A or B, using the block size of four. One half of the subjects was assigned to group A and the other half to group B. The order, in which the interventions are assigned in each block, is randomized, and this process was repeated for consecutive blocks of subjects until all subjects were allocated to either group.

3.2.3 INTERVENTION

- The study patients underwent a 7 days drug-free washout period, during which they were screened for benzodiazepines and other psychotropic medication and laboratoryscreening test (If these results are normal, patients will be randomly assigned on double-blind basis to 8 weeks of treatment).
- Baseline assessment was done after complete drug free period. The assessment included demographic data.
- Then, followed by random allocation to either moclobemide and alprazolam treatment groups.
- In the first three weeks of study, alprazolam dose was gradually increased to 6 mg./day (2 mg in the 1st week, 4 mg in the 2nd week, and 6 mg in the 3rd week) and moclobemide dose was also gradually increased to 300 mg./day (75 mg in the 1st week, 150 mg in the 2nd week, and 300 mg in the 3rd week), unless there were adverse events or the patients can not tolerate.

- The patients were assessed weekly during the first 3 weeks and biweekly thereafter, (including outcome measure, adverse event measure).
- To prevent the bias, the masking method were applied, following: After the subjects were randomly allocated with equal probability to Alprazolam group and Moclobemide group, a psychiatric nurse at panic disorder care unit who had responsibility in the process will keep secret the list of allocated patient name. All patients was given three physically identical tablets each day and the psychiatric nurse who given the package of this three physically identical tablets did not know what kind of drugs because the package of drugs were prepared by pharmacy unit. A psychiatrist in panic disorder care unit reviewed the daily record form with patient and assessed the symptoms whether they met the criteria of panic attack and completed case report form. He did not know what group the patient had being and what drug patient taken. If the patient had severe side effect he taken responsibility to consider to reduced the dosage of drug to the previous dosage or stop medication.
- The Patients compliance were assessed at each visit by tablet counts.

3.2.4 COINTERVENTION

Psychotropic drugs were not available in the drugstore because they were classified in special control substance in this country. Patients were instructed not to take any other drugs during the study, if they do, all the drugs consumed by the patients were recorded during each visit and were included during analysis.

3.2.5 CONTAMINATION

Contamination should be negligible because both drugs are physically similar and both drugs are also not available in drugstore. However the patients may get it from private clinic. Urine test for benzodiazepines was done in all of patients. If contamination occurs, these patients are recorded and applied subgroup analysis during data analysis.

CHAPTER 4

DATA COLLECTION & INSTRUMENT

4.1 OUTCOME MEASUREMENT

The primary outcome

The number of panic attacks in each patient were measured by psychiatrist who assessed the panic attack according to DSM-IV criteria.

The secondary outcomes

1. Adverse side effects assessment.

   Open question "Do you feel different in any way since starting the treatment or the last visit?

2. Safety assessment
   - vital signs e.g. blood pressure, pulse rate, body weight
   - laboratory tests of the hematology (at 1^{st},8^{th} week)
   - clinical chemistry variables (at 1^{st},8^{th} week)
   - liver function(SGOT, SGPT)
   - kidney function(BUN, Cr,)

4.2 DATA COLLECTION PROCEDURE

- Baseline assessment was done before randomly allocated the patients to either moclobemide group or alprazolam group. Baseline assessment include demographic data, total number of panic attack within a week.

- All of panic disorder patients who meet eligible criteria were instructed to identify the panic attack, detect the symptoms that appear in a panic attack, and how to record the daily record form (Panic Self-report Inventory).

- At each study visit, the psychiatrist reviewed the daily record form (Panic Self-report Inventory) with the patients and completed a frequency count of the number of panic attack. The psychiatrist assessed the symptoms in the Panic Self-report Inventory whether they meet the criteria panic attack.

The number of panic attacks, symptoms of each attack, and severity of each attack was recorded by the patients in daily record form (Panic Self-report Inventory).The treating clinician collected the number of panic attacks after carefully reassessed according to standard criteria (DSM-IV criteria) at consecutive 2-week interval. Adverse events and the results of safety measurement were recorded by the attended physician.

4.3 INSTRUMENT DEVELOPMENT

4.3.1 Instrumental Design

Panic Self-report Inventory

Panic Self-report Inventory is the symptom checklist used to define the panic attack and it also can apply as daily diary for collecting the number of panic attack.

Step to developed instrument

1. Literature review of studies which have been done in this area.
   - DSM-IV criteria for panic attack is a fruitful source of items[32]. There are 13 characteristic symptoms and the four-symptom threshold is optimal for defining a panic attack.
2. Expert opinion
   - Experienced psychiatrists were interviewed to determine what the most important symptoms of panic attack in panic disorder patients.
3. Group discussion.
   - Five of the panic disorder patients were discussed about panic attack symptoms that they were experienced.

Then, the Panic Self-report inventory was formulated by using the data from all of three steps. There are 2 main items and with 13 sub-items.

a. Physical symptoms

Divide into 6 neuromuscular symptoms, 2 respiratory symptom,1 cardiovascular symptom, 1 gastrointestinal symptom.

b. Psychological symptoms

- fear of losing control
- fear of going crazy
- fear of dying and depersonalization, derealization.

The level of measurement is nominal scale as a present-absent response.

4. Pre-test the item in small group of panic disorder patients (about 10 patients).
   - To ensure that they are unambiguous by asking the patients whether they had the symptoms, but rather what they think the term means.

After pre-test the items, the psychological symptoms such as depersonalization and derealization were eliminated because the subjects felt it was too difficult understand or they could not understand the meaning of the questionnaire. Finally the number of sub-items was reduced to 12. (see Table 5.)

Table 5. แบบบันทึกอาการพานิค(Panic Self-report Inventory)

ชื่อ..... วันที่.....เดือน.....พ.ศ.....

ครั้งที่ Time of attack	1	2	3	4	5	6	7
อาการที่เกิดขึ้นในแต่ละครั้ง **Symptoms** (ให้ใส่เครื่องหมาย ✓ ถ้ามีอาการ)							
ใจสั่น ใจเต้นแรง ใจเต้นเร็ว Palpitation, pounding heart, accelerated heart rate							
เหงื่อออก Sweating							
ตัวสั่น Trembling or shaking							
รู้สึกหายใจไม่อิ่ม หายใจไม่ออก Sensation of shortness of breath or smothering							
รู้สึกจุกแน่นหายใจขัด Dyspnea							
เจ็บหน้าอก ไม่สบายในหน้าอก Chest pain or discomfort							
คลื่นไส้ ไม่สบายท้อง Nausea or abdominal distress							
วิงเวียนศีรษะ รู้สึกโคลงเคลง หน้ามืด เป็นลม Feeling dizzy, unsteady, light-headed or faint							
กลัวจะควบคุมตัวเองไม่ได้ หรือ กลัวจะเป็นบ้า Fear of losing control or going crazy							
กลัวตนเองจะตาย Fear of dying							
รู้สึกเหน็บชา หรือ รู้สึกเสียวๆเจ็บๆคล้ายเข็มแทง Numbness or tingling sensation							
รู้สึกหนาวสั่น หรือ ร้อนวูบวาบ Chills or Hot flushes							

- Present = 1 , absent = 0
- The score ≥ 4 is optimal for defining panic attack

CHAPTER 5

RESULTS OF INSTRUMENT DEVELOPMENT

5.1 VALIDITY STUDY

5.1.1 Content validity

Panic Self-report Inventory is tested for content validity by asking 3 experts in department of psychiatry to evaluate the content and give score for each item. Item correlation is calculated, and the results are shown in table 6.

Table 6 Content validity of Panic Self-report Inventory

	Item No	Expert I	Expert II	Expert III	Total	IC
ใจสั่น ใจเต้นแรง ใจเต้นเร็ว Palpitation, pounding heart, accelerated heart rate	1	+1	+1	+1	3	1
เหงื่อออก Sweating	2	+1	+1	0	2	0.6
ตัวสั่น Trembling or shaking	3	+1	0	+1	2	0.6
รู้สึกหายใจไม่อิ่ม หายใจไม่ออก Sensation of shortness of breath or smothering	4	+1	+1	+1	3	1
รู้สึกจุกแน่นหายใจขัด Dyspnea	5	+1	+1	+1	3	1
เจ็บหน้าอก ไม่สบายในหน้าอก Chest pain or discomfort	6	+1	+1	+1	3	1
คลื่นไส้ ไม่สบายท้อง Nausea or abdominal distress	7	+1	+1	0	2	0.6
วิงเวียนศีรษะ รู้สึกโคลงเคลง หน้ามืด เป็นลม Feeling dizzy, unsteady, light-headed or faint	8	+1	+1	+1	3	1
กลัวจะควบคุมตัวเองไม่ได้ หรือ กลัวจะเป็นบ้า Fear of losing control or going crazy	9	+1	+1	+1	3	1
กลัวตนเองจะตาย Fear of dying	10	+1	+1	+1	3	1
รู้สึกเหน็บชา หรือ รู้สึกเสียวๆเจ็บๆคล้ายเข็มแทง Numbness or tingling sensation	11	0	+1	+1	2	0.6
รู้สึกหนาวสั่น หรือ ร้อนวูบวาบ Chills or Hot flushes	12	+1	+1	+1	3	1

+1 for relatively valid item

0 not sure

-1 for relative irrelevant

5.1.2 Criterion validity

Compare the diagnosis outcome (panic attack) between clinical diagnosis by mental status examination (by experienced psychiatrist), according to DSM-IV criteria for define panic attack and Panic Self-report Inventory.

The subject were the twenty cases of panic disorder patients who had been treating at department of Psychiatry. After they completed the Panic Self-report Inventory and then mental status examination by the psychiatrist. If the patient has 4 or more symptoms as recorded in Panic Self-report Inventory, the panic attack will be diagnosed.

Table 7. Criterion validation of Panic Self-report Inventory

		Mental status exam by psychiatrist		Total
Panic		+	-	
Self-report	+	8	1	9
Inventory	-	1	10	11
		9	11	20

$$\text{Sensitivity} = \frac{8}{8+1} = 88.9\%$$

$$\text{Specificity} = \frac{10}{10+1} = 90.9\%$$

$$\text{Accuracy} = \frac{8+10}{20} = 90\%$$

$$\text{Phi coefficient} = \frac{|BC - AD|}{\sqrt{(A+B)(C+D)(A+C)(B+D)}} = 0.80$$

$$Z = r_\phi \sqrt{n}\ , = 0.8\sqrt{19}\ , = 3.48 \quad (P < 0.5)\ \text{reject}\ H_0\ r_\phi = 0$$

5.2 RELIABILITY STUDY

5.2.1 Test-retest reliability

After the panic disorder patients completed the Panic Self-report Inventory, the test was repeated again for those who had one panic attack within a week one week later.

Calculation of test-retest reliability by was done using Peason product moment correlation.

Table 8. Test-retest reliability

No of patient	1st time	2nd time	X^2	Y^2	XY
1	4	4	16	16	16
2	5	5	25	25	25
3	8	6	64	36	48
4	4	4	16	16	16
5	6	6	36	36	36
6	7	6	49	36	42
7	5	5	25	25	25
8	5	5	25	25	25
9	4	4	16	16	16
10	7	6	49	36	42
SUM	55	51	321	280	291

$$r = \frac{n\Sigma XY - (\Sigma X)(\Sigma Y)}{\sqrt{[n\Sigma X^2-(\Sigma X)^2]\,[n\Sigma Y^2-(\Sigma Y)^2]}}$$

$$= \frac{12(291)-2805}{\sqrt{[12(321)-3025]\,[12(280)-2601]}}$$

$$= 0.87$$

5.3 INTERPRETATION

Panic Self-report Inventory is recorded in nominal scale. It can be used as diagnostic instrument for defining of panic attack.

By using the categorical approach [84], the panic attack in Panic Self-report Inventory requires that the patient exhibit at least four of twelve symptoms.

Content validity was evaluated by 3 experts and item correlation score in each item is 0.66 to 1.00. The perfect agreement is reached 8 of 12 item and the scores are above 0.5 in all items.

Criterion validity is evaluated by comparing with the mental status examination (by psychiatrist) according to DSM IV criteria for defining of panic attack and sensitivity is 88.9% specificity is 90.9% accuracy is 90% and phi coefficient is 0.80 which mean, that Panic Self-report Inventory has high relationship with DSM IV.

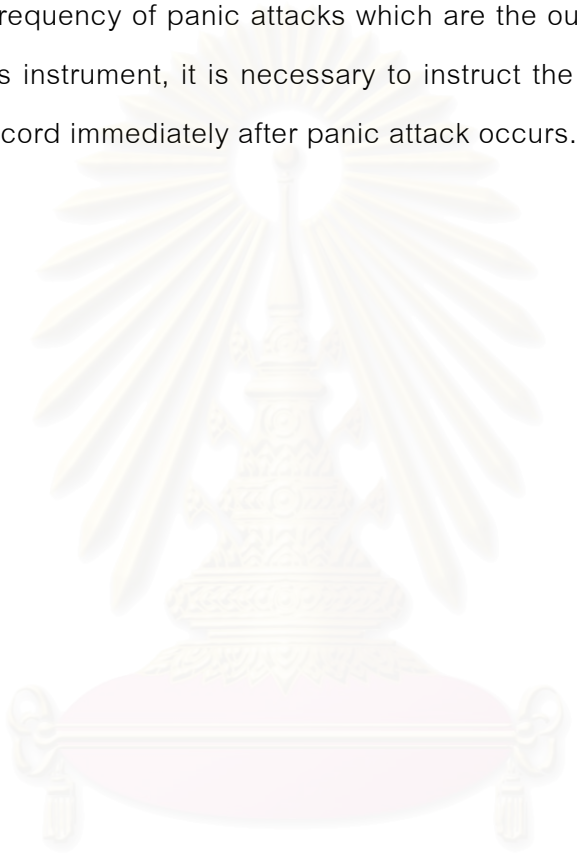
Because Panic Self-report Inventory is the self-rated test and there is no observer, thus the test-retest method was used to test reliability and analyzed by using pearson product moment correlation. Its result is r = 0.87 which is considered high reliability.

5.4 CONCLUSION

1. Panic Self-report Inventory has item correlation score range from 0.66 to 1.00 and the score of all items are above 0.5, that are acceptable.
2. The Panic Self-report Inventory has high sensitivity, high specificity, and high accuracy for detection of panic attack and there is also high correlation between this self-rated test and DSM IV criteria by phi coefficient = 0.80
3. The result from test-retest method show that the Panic Self-report has high reliability.

The Panic Self-report Inventory can be the instrument both for collecting the data and the diagnostic test for defining of panic attack. It gives satisfactory sensitivity, specificity and accuracy. In the content validity, item correlation score of all item are acceptable. The Panic Self-report Inventory has high test-retest reliability.

It is suitable to use as instrument for measure the outcome of this study. It give the actual data of frequency of panic attacks which are the outcome of this study. But before applying this instrument, it is necessary to instruct the patients how to identify panic attack and record immediately after panic attack occurs.



CHAPTER 6

DATA ANALYSIS & INTERPRETATION

6.1 DATA ANALYSIS

Intention-to-treat analysis was applied in analyzing the outcome variable. For the drop out patients, we tried our best to contact family or patients to find out the reasons and outcome.

Outcome analysis

Primary outcome

The number of panic attacks in each group was analyzed by using Generalized Estimating Equation(GEE) link function poisson and the incidence rate of panic attacks per person-week was analyzed by using poisson regression because this outcome is counted data which follow poisson distribution[47,48].

Secondary outcome

Adverse event

The numbers of patients who experience in each adverse event and in each group of treatment were categorized and were calculated by percent.

CHAPTER 7

RESULT

The sample consisted of 186 cases of panic disorder who met the eligibility criteria. The studies patients were 93 cases in each group of treatment. There was 8 cases (4.3%) drop out from the study with the following reasons: - 2 cases move to another place, 6 cases loss of follow up because no symptom and belief disease was cured. Drop out cases were 4 cases for Alprazolam-treatment group and 4 cases for Moclobemide-treatment group.

There were only 11(11.8%) patients who could take full dose 6 mg of Alprazolam in Alprazolam-treatment group and eighty two (88.2%) cases got 4 mg of Alprazolam. Because of sedative effect prevented patients in Alprazolam-treatment group reach highest dose of treatment.

7.1GENERAL CHARACTERISTICS OF THE SAMPLE

The general characteristics of patients in both groups are summarized in table 9 The mean age of studies patients was 29 years (S.D.=7.9) for Alprazolam -treatment group and 31 years(S.D.=8.9) for Moclobemide- treatment group. There were women 53.8%(N=93) in Alprazolam-treatment group and 60.2%(N=93) in Moclobemide-treatment group.

Table 9 Baseline Demographic characteristics of the patients

Demographic characteristic	Group A (Alprazolam)		Group B (Moclobemide)	
	N=93	%	N=93	%
Age				
18-28	49	52.7	43	46.2
29-39	32	34.4	35	37.6
40-50	11	11.8	13	14.0
51-61	1	1.1	2	2.2
Mean	29.3	-	30.8	-
S.D.	7.9	-	8.9	-
Sex				
Male	43	46.2	37	39.8
Female	50	53.8	56	60.2

7.2BASELINE CLINICAL DATA

The number of panic attacks at baseline assessed before allocation was shown in Table 10. At baseline, assessed frequency of panic attacks was 7.8 attacks per week (S.D.=4.3)(range=4-28) and 8.1 attacks per week (S.D.=4.9)(range=4-28) for the Alprazolam-treatment group and the Moclobemide-treatment group, respectively.

Table 10 The number of panic attacks at baseline

No. of panic attacks Per week	No. of cases Gr.A (Alpazolam-treatment group)	No. of cases Gr.B (Moclobemide-treatment group)	Total
4	23	23	46
5	7	9	16
6	14	12	26
7	5	8	13
8	15	11	26
9	9	4	13
10	5	10	15
11	2	1	3
12	1	1	2
13	-	1	1
14	8	6	14
15	1	4	5
20	1	-	1
24	1	-	1
28	1	3	4
Total	93	93	186
Mean	**7.8**	**8.1**	
S.D.	**4.3**	**4.9**	

7.3THE CHANGE OF THE EPISODE OF PANIC ATTACKS FROM BASELINE TO END POINT AFTER 8 WEEKS OF TREATMENT

The total panic attacks occurred in each week after intervention was counted by all patients and assessed by psychiatrist from baseline to end point (week8) were presented by graph for each group separately (figure 4, and 5).

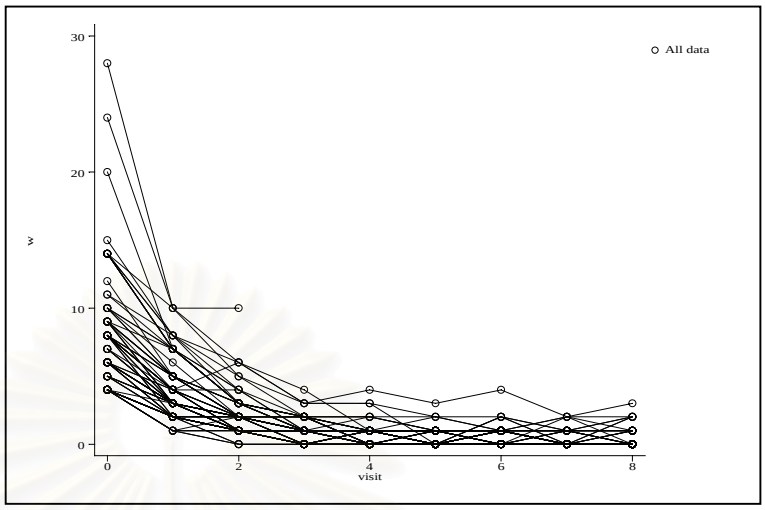
The incidence of panic attacks was decreased by the first week of Alprazolam treatment and this decrease was maintained until the end of study. Especially, in the first two weeks which decreased faster than latter week.

In moclobemide-treatment group, the incidence of panic attacks was decreased by first week and maintained until week8 like alprazolam-treatment group but the decrease was slow or in first two week. After week4 moclobemide reduced the incidence of panic attacks more than Alprazolam.

Figure 4

Graph present the change of the number of panic attacks of Alprazolam-treatment group (weak1-weak8)

No. of panic attacks

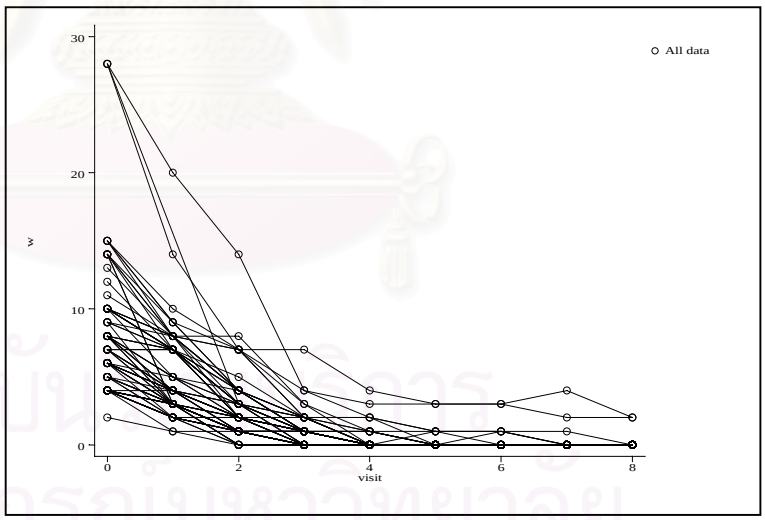


week

Figure 5

Graph present the change of the number of panic attacks of Moclobemide-treatment group (weak1-weak8)

No. of panic attacks



week

7.4 COMPARISON OF THE INCIDENCE RATE OF PANIC ATTACKS IN EACH WEEK

The incidence rate of panic attacks per one person-week was analyzed by poisson regression to compare between Alprazolam-treatment group (group A) and Moclobemide-treatment group(group B) from week1 to week8 (table 11).

We found that in the first week Alprazolam significantly reduced the panic attack more than Moclobemide, the difference of incidence rates was 0.96 (95%CI= [0.36-1.55]) and the incidence rate ratio was 1.25 (95%CI=[1.08-1.44]). From week4 to the end of study week8, Moclobemide showed the efficacy in reducing the panic attack significantly more than alprazolam, the difference of incidence rate from week4 to week8 were –0.42, -0.27, -0.44, -0.17, and-0.22, consecutively. The incidence rat ratio from week4 to week8 were 0.33, 0.28, 0.20, 0.32, and 0.17, consecutively.

Table 11 The incidence rate of panic attacks per one person-week and Incidence rate ratio of Alprazolam-treatment group and Moclobemide-treatment group in each week

Weak	Group A (n=93 person-weak)	Group B (n=93 person-weak)	Diff (95% CI)	Incidence rate ratio (95% CI)	P-value
Weak1	3.83	4.79	**0.96** [(0.36) – (1.55)]	**1.25** [1.08-1.44]	0.0017
Weak2	2.02	2.35	**0.33** [(-0.09) – (0.76)]	**1.16** [0.95-1.42]	0.1247
Weak3	0.97	0.88	**-0.09** [(-0.38) – (0.18)]	**0.90** [0.66-1.23]	0.4994
Weak4*	0.64	0.22	**-0.42** [(-0.62) – (-0.24)]	**0.33** [0.19-0.57]	0.0001
Weak5*	0.38	0.11	**-0.27** [(-0.42) – (-0.13)]	**0.28** [0.13-0.59]	0.0002
Weak6*	0.55	0.11	**-0.44** [(-0.61) – (-0.27)]	**0.20** [0.09-0.40]	0.0001
Weak7*	0.25	0.08	**-0.17** [(-0.29) – (-0.05)]	**0.32** [0.11-0.77]	0.0052
Weak8*	0.26	0.04	**-0.22** [(-0.34) – (-0.11)]	**0.17** [0.04-0.49]	0.0001

* Moclobemide reduce panic attack per person-week more than 20% as compare to Alprazolam

7.5 COMPARISON OF THE EFFICACY OF ALPRAZOLAM AND MOCLOBEMIDE IN REDUCING PANIC ATTACK BY USING GENERALIZED ESTIMATING EQUATION (GEE)

For more accurate estimating the efficacy of both drugs in reducing the panic attack in treatment period, I included all associated factors that influenced the effect of treatment in process of analyzing. Those factors were the number of panic attacks at baseline, age, and sex. Because the outcome of this study was counted data which follow poisson distribution and repeated measure, so analysis by using GEE was suitable. The complete analysis was presented in table 12

We found that crude incidence rate ratio was 0.94 [(95%CI=(0.77-1.14)] and adjusted incidence rate ratio was 0.88 [(95%CI=(0.76-1.02)].(From the 95% CI of the adjusted incidence rate ratio, it means that Moclobemide reduced panic attacks 24% more than Alprazolam to Alprazolam reduced panic attacks 2% more than Moclobemide, so the result is inconclusive.

Table 12 Crude incidence rate ratio and Adjusted incidence rate ratio (adjust for baseline, age, sex)

Treatment	Crude IRR (95% CI)	Adjusted IRR (95% CI)	P-value
Alprazolam	1	1	0.084
Moclobemide	0.94 (0.77-1.14)	0.88 (0.76-1.02)	

7.6 THE ADVERSE EFFECTS

The adverse effects per treatment group are shown in table 13. We found that somnolence or sleepiness was the most common adverse effect of Alprazolam, particularly in the first week. There were 31 cases (33.3%) had severe somnolence at week3 after they were increased dose to 6 mg. The severity of this symptom decreased after decreasing dose of Alprazolam to 4 mg and the tolerance to sedation rapidly developed. In the last week there was only 5 cases (5.4%) complained somnolence or daytime sleepiness. Dizziness, vertigo, tremor and muscle twisting, and ataxia are reported in 10 cases (10.7%), 4 cases (4.3%), and 2 cases (2.2%), respectively. These symptoms developed at week 3 and disappeared after decreased dose of Alprazolam.

Insomnia is the most common adverse effect of Moclobemide. Ten (10.7%) of patients in moclobemide-treatment group reported insomnia at week 1,2, and3 and subside in the later week. Vertigo, dizziness, orthostatic hypotension, and palpitation occurred at week 3 after increased dose of Moclobemide to 300 mg and found in 5 cases (5.4%), 5 case (5.4%), 4 cases (4.3%), and 3 cases (3.2%), respectively. These symptoms were not severe and subsided in the later week. Dry mouth, constipation were the anticholenergic side effect of moclobemide was reported in 9 cases (7.5%), and 4 case (4.3%), consecutively. There were nine patients (9.7%) complaint of headache in the first week of treatment. Five patients (5.4%) had somnolence in week1 and improved week after.

Table 13 Adverse effects in Alprazolam and Moclobemide

Adverse effect	Alprazolam N=93	Moclobemide N=93
Headache	5.4%	9.7%
Somnolence/sleepiness	33.3%	5.4%
Dizziness	10.7%	5.4%
Vertigo	4.3%	5.4%
Ataxia	4.3%	-
Insomnia	-	10.7%
Dry mouth	-	7.5%
Constipation	-	4.3%
Orthostatic hypotention	-	4.3%
Palpitation	-	3.2%
Tremor/muscle twisting	2.2%	5.4%
Heart burn/gastitis	-	4.3%

7.7THE RESULT OF SAFETY ASSESSMENT

The change of vital signs, laboratory tests of hematology, and clinical chemistry variable (e.g. liver function, kidney function) were monitor and record for safety assessment in all patients.

Four cases (4.3%) in each group had orthostatic hypotension (table 13). Mean weight of patients in both groups did not change between baseline and treatment end point. None of laboratory parameter tested was shift from normal to pathological values.

CHAPTER 8

SUMMARY, DISCUSSION, RECOMMENDATION

8.1 SUMMARY OF THE STUDY

This study aim to investigate the comparative efficacy and tolerability of Alprazolam, a conventional drug, and Moclobemide, a new type of monoamine amine oxidase inhibito, in treatment of panic disorder. In panic disorder, panic attack is the essential feature. Once the panic attack are blocked, the patient will gradual decrease in other symptoms and clinical will improve. A randomized double-blind controlled trial was conducted to compare the efficacy of Alprazolam versus Moclobemide in reducing panic attack in panic disorder patients. One hundred and eighty six eligible cases undergo 7 days drug free washout period before being randomly assigned with equal probability to Alprazolam-treatment group or Moclobemide-treatment group and are assessed by a psychiatrist weekly during the first three weeks then biweekly thereafter until at the end of eight weeks study.

There was 8 cases (4.3%) drop out from the study with the following reasons: move to another place (2 cases), loss of follow up because no symptom and belief disease was cured (6 cases). Drop out were 4 cases for Alprazolam-treatment group and 4 for Moclobemide-treatment group.

The total panic attacks occurred in each week after intervention were recorded by patients in Panic self-report Inventory (Diary record form). All of panic attack were identified and counted by psychiatrist from baseline to the end point .

The result of the study reveals that, the incidence of panic attacks was decreased by the first week in both treatment groups and this decrease was maintained until at the end of the study. Generalized Estimating Equation (GEE) was applied for comparing the efficacy of Alprazolam versus Moclobemide in reducing the

panic attack. The result is inconclusive. The adjusted incidence rate ratio was 0.88 [(95%CI=(0.76-1.02)] and P value=0.084.

When analyzed for each week, it shown that in the first week Alprazolam is significantly reduced the panic attack more than Moclobemide, the difference of incidence rates was 0.96 and the incidence rate ratio was 1.25 but from week4 to the end of study week8, Moclobemide shown the effect of reducing the panic attack significantly more than alprazolam, the difference of incidence rate week4 to week8 were –0.42, -0.27, -0.44, -0.17, and-0.22, consecutively. The incidence rate ratio week4 to week8 were 0.33, 0.28, 0.20, 0.32, and 0.17, consecutively.

Moclobemide was generally well tolerated. Insomnia and Headache were most often adverse effects, they are reported 10.7% and 9.7%, respectively. The sedative effect was major problem in Alprazolam-treatment group. The patients more than 80% could not reach highest dose of 6 mg Alprazolam because of daytime sleepiness/somnolence and dizziness. There were 31 cases (33.3%) had severe somnolence at week3 while increase dose to 6 mg.

8.2 DISCUSSION

This double-blind study found that the treatment with Moclobemide is well tolerated and there was no serious adverse effect but almost patient treatment with Alprazolam developed somnolence or daytime sleepiness. These symptoms were dose-related if dose of Alprazolam is decreased, the severity it will also decreased. The increasing Alprazolam to full therapeutic dose is limited by this sedative effect.

Although, the result of comparative efficacy analysis by GEE is inconclusive, greater improvement in panic attacks in patients given Moclobemide and Alprazolam were shown by the end of the first week of treatment and sustained throughout the 8th week. Alprazolam and Moclobemide was difference in duration of action. Alprazolam reduced the incidence of panic attacks significantly more than Moclobemide at the first week but moclobemide in long term (more than 3 weeks) reduced incidence of panic attacks significantly more than Alprazolam (see table 12). The rapid action of Alprazolam in panic attacks was reported in other Alprazolam research such as clinical trial for compare efficacy of Alprazolam, Imipramine, and Trazadone by Chaney DS [85] and The study of sustained-release preparation of Alprazolam by Schweizer E [54] . High efficacy in reducing panic attacks of long term moclobemide treatment was reported by Berger p, at al [31], 80% of patients who was treated with

moclobemide had no panic attack at week 5/6. From the result of this study maybe useful in panic disorder treatment if we combine Alprazolam with moclobemide at the first three weeks of treatment course and taper off Alprazolam after that. The incidence of panic attacks in severe cases (>10 panic attacks per week) were reduced in Alprazolam group more than Moclobemide group especially in the first week (in figure4,5). Alprazolam may be more advantage than Moclobemide in treating the severe cases of panic disorder.

In this study, the highest mean dose of Alprazolam at the end of week 8 was 4.2 mg/day which was slightly lower than the highest dose used in the Cross-National Collaborative Panic Study [24] (4.9 mg/day, at week4, which was increased to 5.7 mg/day by week 8). This study was not designed to formally address dose-response question, so it is uncertain what might be the minimally adequate dose of alprazolam for the majority of Thai patients with panic disorder.

In this study, insomnia and headache were the most often adverse effect of Moclobemide similar to what report in long-term treatment by Moll E, at al [86] but the rates were low as compare to the other study [69] (Insomnia 19.2%, and headache 11.5%) so, Moclobemide should not use at bedtime. It should be good if panic patients was given in the morning.

The symptoms of dizziness, vertigo, orthostatic hypotension, and palpitation occurred at week 3 while increasing dose of Moclobemide from 150 mg to 300 mg. So, in clinical practice , increasing dose of Moclobemide should slower than this.

Most patients in Alprazolam-treatment group had somnolence, particularly in the first week and when high dose was used. The rate in this study was similar to what reported in the Cross-National Collaborative Panic Study [24] and Schweizer E, et al reported somnolence 88%[54]. In clinical practice it very difficult to deal with sedative effect of Alprazolam although the tolerance to sedation in many patients rapidly developed. We could not apply Alprazolam only at bedtime for decrease its sedative effect because alprazolam is a short half-life benzodiazepines, interdose rebound anxiety may complicate treatment. Alprazolam should be given by divided into t.i.d. or q.i.d. dose. If patients have severe somnolence when increase to high dose and cannot tolerate, the dose should be reduced or change to another antipanic drug.

8.3 RECOMMENDATIONS

1. The currently effective antipanic drugs have been identified through trial and error. Most, but not all, antidepressants are also antipanic agents. Hence, new antidepressants should be tested for antipanic efficacy such as Moclobemide, a new type of antidepressant, was proved in this study has high efficacy in reducing panic attacks in panic disorder patients.
2. Current psychopharmacologic issue focus on choice among agents, minimization of side effects, hastening response, and examining long-term results including the effects of medication discontinuance. So, The using Moclobemide in panic disorder should be observed and follow up in long-term for side effects, discontinual symptoms and relapse rate after discontinue medication.
3. The psychopharmacological treatment of panic disorder has become one of the most successful in clinical psychiatry. Nevertheless, there is clear need for additional medications that have more rapid onset of action and fewer adverse effects. Alprazolam was proved for rapid onset in reducing the panic attacks but it has more sedative effect, risk of dependence, and withdrawal symptoms. It will be useful for using in short term at initial phase of treatment combine with another antipanic drug such as Moclobemide or SSRIs. It may be decrease the risk of dependence and withdrawal symptoms of Alprazolam. The Efficacy and tolerability of combination of both drugs may be the interested issue for further research.
4. From the result of this study, the therapeutic dose of Alprazolam in thai patients may not necessary to reach high dose. Mean of Alprazolam dose was 4.2 mg/day.
5. Alprazolam had advantage in severe cases of panic disorder. It reduced the number of panic attacks more than Moclobemide in severe cases at first week.
6. In clinical trial of panic disorder, the major issue is targeting response measure to the panic attacks but it is very difficult to assess, identify or count the incidence of panic attacks because of the problem in recall symptoms of patients and the complex of diagnostic criteria. This study, Self-reporting Inventory was applied as daily diary and symptom checklist. Patients could take it anywhere and record suddenly after a panic attack occurred. The patients was included in the study should be literate and should be trained how to record before used. Psychiatrist should reevaluate and reassess before record the number of panic attack.

7. All of enrolled patients should be recorded address clearly in detail and telephone number if available. It is very useful for follow up drop out cases.

8.4 LIMITATION

1. Although the prevalence of panic disorder was not uncommon but patients with panic disorder commonly present to general health care professional such as cardiologist, neurologist, or general practitioner so, collecting cases in psychiatric hospital was take long time to reach 186 case.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental disorder.Third edition. Washington, DC: American Psychiatric Press, 1980.
2. Weissman MM. The Epidemiology of panic disorder and agoraphobia. In : Hales RE, Frances AJ, editors. Review of Psychiatry. Washington, DC: American Psychiatric Press, 1988; 7: 54-66.
3. Canino Gi, Bird HR, Shrout PE et al. The prevalence of specific psychiatric disorders in Pueto Rico. Arch Gen Psychiatry, 1987 ; 44 : 727-735.
4. Eaton WW, Kessler RC, Wittchen Hu, et al. Panic and panic disorder in the United State. Am J Psychiatry, 1994; 151 : 413-420.
5. Hirschfeld RM. Panic disorder: Diagnosis, Epidemiology, and Clinical course. J Clin Psychiatry,1996;57 suppl 10:3-8.
6. Markowitz JS, Weismann MM, Quellette R, et al. Quality of life in panic disorder. Arch Gen Psychiatry, 1989; 46:984-992.
7. Katon WJ, Vonkorff M, Lin E, et al. Panic disorder: relationship to high medical utilization. Am J Psychiatry, 1992 ; 92 Suppl 1A : 75-115.
8. Katon WJ, Vonkorff M, Lin E, et al. Distressed high utilizes of medical care: DSM IV diagnosis and treatment need. Gen Hosp Psychiatry, 1990 ; 12 : 355-362.
9. Sokol L, Beck AT, Grensberg RL, Wright FD, Berchick RJ. Cognitive therapy of panic disorder: a nonpharmacological alternative. J Nerv Ment Dis, 1989; 177:711-716.
10. Jobson K, Linnoila M, Gillam J, Sullivan JL. Successful treatment of severe anxiety attack with antidepressants: a potential mechanism of action. Am J Psychiatry, 1978; 135:863-864.
11. Nurnberg HG, Coccaro EF. Response of panic disorder and resistance of depression to imipramine. AM J Psychiatry, 1982; 139: 1060-1062.

12. Aronson TA. A naturalistic study of imipramine in panic disorder and agoraphobia. Am J Psychiatry, 1987; 144: 1014-1019.

13. Mavissakalian MR, Perel JM. Imipramine dose-response relationship in panic disorder with agoraphobia. Arch Gen Psychiatry, 1986; 46: 127-131.

14. Uhlenhuth EH, Matuzas W, Glass RM, Eaton C. Response of panic disorder to fix dose of alprazolam or imipramine. J affect Disord, 1989; 17: 261-270.

15. Mavissakalian MR, Perel JM. Imipramine treatment of panic disorder with agoraphobia: dose ranging and plasma level-response relationship. AM J Psychiatry, 1995; 152: 673-682.

16. Fahy TJ, O'Rourke D, Brophy J et al. The galway study of panic disorder I: clomipramine and lofepramine in DSM-II-R panic disorder: a placebo control trial. J Affect Disorder, 1992; 25: 63-76.

17. Gentil V, Lotufo-Neto F, Andrede L. Clomipramine, a better reference drug for panic and agoraphobia I: effectiveness comparison with imipramine. J Psychopharmacol, 1993; 7: 316-324.

18. Mordigh K, Westberg P, Eriksson E. Superiority of clomipramine over imipramine in the treatment of panic disorder: a placebo controlled trial. J Clin Psychophamcol, 1992;12: 251-261.

19. Ballenger JC. Long-term pharmacological treatment of panic disorder. J Clin Psychiatry, 1991; 52(2 suppl): 18-23.

20. Noyes R Jr, Garvey MJ, Cook BL. Problem with tricyclic antidepressant use in patients with panic disorder or agoraphobia: result from a naturalistic follow up study. J Clin Psychiatry, 1989; 50: 163-169.

21. Boyer W. Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attack: a meta-analysis. Int Clin Psychopharmacol, 1995; 10: 45-49.

22. Gorman JM, LiebowitzMR, Fyer AJ, et al. An open trial of fluoxetine in the treatment of panic attack. J Clin Psychopharmacol, 1987; 7: 329-332.

23. Ballenger JC, Burrows G, DuPont RL, et al. Alprazolam in panic disorder and agora phobia: results from multicenter study. Arch Gen Psychiatry, 1988; 45: 413-422.

24. Cross-national collaborative study, second phase investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine, and placebo. Br J Psychiatry, 1992; 160: 191-201.

25. Buigues J, Vallejo J, Therapeutic response to phenelzine in patients with panic disorder and agoraphobia with panic attacks. J Clin Psychiatry, 1987; 48: 55-59.

26. van Vliet IM, Westenberg HGM, den Boer JA. MAO inhibitors in treatment panic disorder: clinical effect of brofaromine. Psychopharmacology, 1993; 112: 483-489.

27. Bakish D, Saxena BM, Bowen R, et al. Reversible monoamine oxidase A inhibitor in panic disorder. Clin Neuropharmacol, 1993;16 (2suppl): s77-s82.

28. Korn A, Da Prada M, Raffesberg M, Allen S, Casic S. Tyramine pressor effect in man: study with moclobemide a novel reversible monoamine oxidase inhibitor. J Neural Transm, 1988; 26suppl: 57-72.

29. Haefely W, Burkard WP, Cesura A, et al. Pharmacology of moclobemide. Clin Neuropharmacol, 1993; 16suppl2: s8-s18.

30. Callingham BA. Drug interactions with monoamine oxidase inhibitors. Clin Neuropharmacol, 1993; 16suppl2: s42-s50.

31. Berger P, Amering M, Dantendorfer K, et al. Moclobemide in panic disorder-an open dose finding study. Poster presented at the IV Congress of biological Psychiatry, Florence, Italy 1991.

32. American Psychiatric Association. Diagnostic and Statistical Manual of Mental disorder. Fourth edition. Washington, DC: American Psychiatric Press, 1994.

33. Weissman MM, Bland RC, Canino GL, et al. The cross-national Epidemiology of panic disorder. Arch Gen Psychiatry, 1997; 54: 305-320.

34. Bland RC, Newman SC, Orn H: Period Prevalence of Psychiatric disorder in Edmonton. Acta Psychiatr Scand, 1988; suppl 338: 33-35.

35. Faravelli C, Degl'Innocenti BG, Giardinelli L, et al. Epidemiology of anxiety disorder in Florence. Acta Psychiatr Scand, 1989; 79: 308-310.

36. Kendler KS: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Study. Arch Gen Psychiatry, 1994; 51:8-15.

37. Keller MB, Hanks DL. Course and outcome in panic disorder. Prog Neuropsychopharmacol Biol Psychiatry, 1993; 17: 551-570.

38. Keller MB, Baker LA. The clinical course of panic disorder and depression. J Clin Psychiatry, 1992; 53suppl3: 5-8.

39. Keller MB, Lavori PW, Mueller TI, et al. Time to recovery, chronicity and levels of psychopathology in major depression: a 5-year prospective for-low-up of 431 subjects. Arch Gen Psychiatry, 1992; 49: 809-816.

40. Rosenbaum JF, Pollack MH, Fredman SJ. The pharmacotherapy of panic disorder. In Rosenbaum JF, Pollack MH, editors. Panic disorder and its treatment. New York. Marcel Dekker, Inc. 1998; 153-180.

41. Sheehan DV. Panic attacks and Phobias. New Engl J Med, 1982; 307: 156-158.

42. Gray JA. The neuropsychology of anxiety: An enquiry into the function of the Septo-hippocampal system. New York. Oxford University Press, 1982.

43. Lesch KP, Weissman MM, Hoh A, et al. 5-HT1A recepter-effector system responsibility in panic disorder research. Psychopharmacology, 1992; 106: 111-117.

44. Roy-Byrn pp, Dager SR, Cowley PS, et al. Relapse of panic attacks: Alprazolam versus Diazepam. Am J Psychiatry, 1989; 146: 860-865.

45. Uhde TW. Caffeine provocation of panic: a focus on biological mechanism. In Ballenger JC, editor. Nuerobiology of panic disorder. New York. Wiley-Liss, 1990; 219-242.

46. Bradwejn J, Koszycki D, Couetoux du Tertre A, et al. The cholecystokynin hypothesis of panic and anxiety disorder: A review. J Psychopharmacol, 1992; 6: 345-351.

47. Sheehan DV, Uzogara E, Coleman JH. The treatment of panic attacks with agoraphobia with alprazolam and ibuprofen: A controlled study. Paper presented at the annual meeting of the American Psychiatric Association. Toronto. 1982, May.

48. Chouinard G, Annable L, Fontaine R, et al. Alprazolam and the treatment of generalized anxiety and panic disorders: A double-blind placebo-controlled study. Psychopharmacology, 1982; 77(3): 229-223.

49. Noyes R., Anderson DJ, Clancy J, et al. Diazepam and propanolol in panic disorder and agoraphobia. Archives of General Psychiatry,1984; 41(3): 287-292.

50. Dunner DL, Ishiki D, Avery DH, et al. Effect of alprazolam and diazepam on anxiety and panic attacks in panic disorder: A controlled study. Journal of Clinical Psychiatry, 1986; 47: 458-460.

51. Tesar G E, Rosenbaum J F, Pollack MH, et al. Double-blind placebo controlled comparison of clonazepam and alprazolam for panic disorder. Journal of Clinical Psychiatry, 1991; 52(2): 69-76.

52. Charney DS,Woods SW. Benzodiazepine treatment of panic disorder: A comparison of alprazolam and lorazepam. Journal of Clinical Psychiatry, 1989; 50: 418-423.

53. Lydiard RB, Lesses IM, Ballenger JC, et al. A fixed-dose study of alprazolam of 2 mg, 6 mg and placebo in panic disorder. Journal of clinical Psychopharmacology, 1992; 12(2): 96-103.

54. Schweizer E, Patterson W, Rickels K, et al. Double-blind, placebo-controlled Study of a once-a day Sustain-release preparation of Alprazolam for the treatment of panic disorder. Am J Psychiatry, 1993; 150: 1210-1215.

55. Larson IB, Kukull WA, Buchner D, et al. Adverse drug reactions associated with global cognitive impairment in elderly persons. Annals of Internal Medicine, 1987; 107: 169-173.

56. Scharf MB, Saskin P, Fletcher K. Benzodiazepine induced amnesia: Clinical and laboratory findings. Journal of Clinical Psychiatry Monograph,1987; 5(1):14-17.

57. Oster G. Russell MW, Huse DM, Adams SF, et al. Accident – and injury – related health care utilization among benzodiazepine users and nonusers. Journal of Clinical Psychiatry, 1987; 48(12): 17-21.

58. Skegg DCG, Richards SM, Doll R. Minor tranquilizers and road accidents. British Medical Journal, 1979; 1: 917-919.

59. Smiley A. Effects of minor tranquilizers and antidepressants on psychomotor performance. Journal of Clinical Psychiatry, 1987; 48 Suppl12: 22-28.

60. Lydiard RB, Laraia MT, Ballenger JC, et al. Emergence of depressive symptoms in patients receiving alprazolam for panic disorder. Am J Psychiatry, 1987; 144: 664-665.

61. Ladewig D, Grossenbacher H. Benzodiazepine abuse in patients of doctors in domicilary practice in the Baslle area. Pharmacopsychiatry,1988; 21(2): 104-108.

62. Garvey MJ, Tollefson GD. Prevalence of misuse of prescribed benzodiazepines in patients with primary anxiety disorder or major depression. Am J Psychiatry, 1986; 143(12): 1601-1603.

63. Sheehan DV, Hughes P, Storr C. Benzodiazepine use by physicians. Paper presented at the annual meeting of the American Psychiatric Association. New Orleans. 1991, May.

64. Kales A, Bixler EO, Vela-Bueno A, et al. Comparison of short and long half–life benzodiazepine hypnotics: Triazolam and quazepam. Clinical Pharmacological Theragy,1986; 40: 378-386.

65. Sheehan DV, Ballenger J, Jacobson G. (1980). Treatment of endogenous anxiety with phobic, hysterical and hypochondriacal symptoms. Archives of General Psychiatry, 1980; 37: 51-59.

66. Sheehan DV, Claycomb JB, Surman OS. The relative efficacy of alprazolam, phenelzine and imipramine in treating panic attacks and phobias. Abstracts of 137th Annual Meeting of the American Psychiatric Association, 1984

67. Versiani M, Oggero U, Alterwain P, et al. A double-blind comparative trial of moclobemide VS. Imipramine and placebo in major depressive episodes. Br J Psychiatry, 1989; 155suppl6: 72-77.

68. Bakish D, Bradwejn J, Nair N, et al. A comparison of moclobemide, amitryptiline, and placebo in depression: a Canadian multicentre study. Psychophamacology, 1992; 106: 98-101.

69. Versiani M, Nardi AE, MundimFD, et al. Pharmacotherapy of Social Phobia, a controlled study with moclobemide and phenelzine. Br J psychiatry, 1992; 161: 353-360.

70. Fulton B, Benfield P. Moclobemide. An update of its phamacological properties and therapeutic use. Drug, 1996; 52(3): 450-474.

71. Loux G, Baier D. Qualitity-mornitoring of psychotropic drug therapy in post marketing surveillance. Results of a drug utilization observation(DUO) study on moclobemide. Pharmacopsychiatry, 1997; 30: 1suppl: 21-27.

72. Kenedy SH, Ralovski T, Davis C. The effect of moclobemide on sexual desire and function in health volunteers. Eur-Neuropsychophar, 1992;6(3):177-181.

73. Phillipp M, Rohnen R, Benkert O. A comparison study of moclobemide and doxepine in major depression with special reference to effects on sexual dysfunction. Int Clin Psychopharmacol, 1993; 7(3-4): 149-153.

74. Johnson MR, Lydriard BR. The Neurobiology of anxiety disorders. Phychiatr Clin North Am, 1995; 18: 681-725.

75. Krystal JH, Dentsch DN, Charney DS. The biological basis of panic disorder. J clin Psychiatry, 1996; 57 suppl 10: 23-31.

76. Goddard AW, Charney DS. Toward an integrated neurobiology of panic disorder. J clin Psychiatry, 1997; 58 suppl 2: 4-12.

77. Finberg JPM. Pharmacology of reversible and selective inhibitors of monoamine oxidase type A Acta Phychiatr Scand, 1995;19 suppl 386:8-13.

78. Hartmann D, Cesura AM, Schmid-Burgk W,Amrein R. Relevance of reversible inhibitors of monoamine oxidase type A and of reuptake Inhibition of noradrenaline turnover. Acta Phychiatr Scand,1995;19 suppl 386:14-21.

79. Fyer AJ, Mannuzza S, Coplan JD. Panic disorder and agoraphobia. In; Kaplan HI, Sadock BJ, editors. Comprehensive Textbook of Psychiatry. 5th ed. Baltimore: William & Wilkins, 1995:1191-1204.

80. Klein DF, Leibowitz MR, Gorman JM, Lewis CP. Evaluation of Psychotropic Drug Treatment of Panic-related disorder and Social phobia. In: Prien RF, Robinson DS,editors. Clinical evaluation of psychotropic drug principle and guideline. New York : Raven Press, 1994:411-429.

81. US Department of health and human service. Systematic assessment for treatment emergent events (SAFTEE-SI). Rockville Maryland: National Institute of Mental Health. ADAMHA,1983.

82. Rapkin J, Markovitz J, Occepek-welikson, et al. General versus Systematic inquiry about medication side effect with SAFTEE: implication for clinical research. J Clin Psychopharmacol, 1992;12(1):3-10.

83. Diggle PJ, Liang K, Zeger SL. Analysis of longitudinal data. Oxford: Clarendon Press, 1994.

84. Striner DI, Norman GR. Health Measurement Scale 2nd edition. Oxford. Oxford university press, 1994.

85. Charney DS, Woods SW, Goodman WK, et al. Drug treatment of panic disorder: the comparative efficacy of Imipramine, Alprazolam, and Trazadone. J Clin Psychiatry, 1986; 47: 580-586.

86. Moll E, Newmann N, Schmid-Buryk W, et al. Safety and efficacy during long-term treatment with moclobemide. Clinical Nueropharmacology, 1994;17(1): S74-87.

APPENDICES

APPENDIX 1

แบบฟอร์มใบยินยอมให้ทำการศึกษา
โครงการวิจัยโรคพานิก

ข้าพเจ้า (นาย,นางสาว) .....นามสกุล.....อายุ.....ปี

อยู่บ้านเลขที่.....หมู่ที่.....ถนน.....หมู่บ้าน.....

ตำบล.....อำเภอ.....จังหวัด.....

ได้รับฟังการอธิบายจาก(นาย, นาง, นางสาว)..... เกี่ยวกับ

[ ] ยา (ระบุ).....**โมโคลบีมายด์ และ อัลพราโซแลม**

[ ] วิธีการตรวจ/รักษา (ระบุ).....

[ ] อื่น ๆ (ระบุ).....

ได้ทราบถึงผลข้างเคียงอันอาจจะเกิดขึ้น ข้อดี ข้อเสียของยา/วิธีการตรวจ/รักษาเท่าที่ได้มีการศึกษาทดลองในต่างประเทศแล้ว โดยข้อความที่อธิบายประกอบด้วย

- วัตถุประสงค์และระยะเวลาที่ทำการศึกษา
- ขั้นตอนและการปฏิบัติตัวที่ข้าพเจ้าต้องปฏิบัติ
- ผลข้างเคียงหรืออันตรายที่อาจเกิดขึ้นจากการใช้ยา/วิธีการตรวจ/รักษา นี้

และข้าพเจ้าสามารถถอนตัวจากการศึกษาการใช้ยา/วิธีการตรวจ/รักษานี้ เมื่อใดก็ได้ ถ้าข้าพเจ้าปราถนา และหากเกิดมีอาการข้างเคียงขึ้น ข้าพเจ้าจะรายงานให้แพทย์หรือเจ้าหน้าที่ ที่กำลังปฏิบัติงานอยู่ในขณะนั้นทราบทันที

ข้าพเจ้าได้อ่านและเข้าใจตามคำอธิบายข้างต้นแล้ว จึงได้ลงนามยินยอมให้ทำการศึกษา

ลายมือชื่อ.....

(.....)

พยาน.....(ไม่ใช่ผู้อธิบาย)

(.....)

APPENDIX2

สมุดบันทึกอาการพานิก

โครงการวิจัยการรักษาโรคพานิก
โรงพยาบาลจิตเวชนครพนม
กรมสุขภาพจิต

APPENDIX 2

สมุดบันทึกอาการพานิก

สมุดบันทึกอาการพานิก เป็นสมุดบันทึกประจำวัน จัดทำขึ้นเพื่ออำนวยความสะดวกในการประเมินอาการพานิก ซึ่งจะเกิดประโยชน์ทั้งกับผู้ที่มีอาการและผู้รักษา คือ ผู้ที่มีอาการจะตระหนักรู้ เข้าใจอาการตนเองและสามารถสังเกตอาการได้ด้วยตัวเอง ส่วนผู้รักษาก็จะง่ายในการติดตามอาการหลังให้การรักษา มีความเที่ยงตรงและเชื่อถือได้ในการวัดอาการพานิก

สมุดบันทึกเล่มนี้จะมี ใบบันทึกอาการ 31 แผ่น แต่ละแผ่นสำหรับบันทึกอาการที่เกิดขึ้นใน 1 วัน

ให้ท่านบันทึกอาการและความรุนแรงในแผ่นใหม่ทุกเช้าของวันใหม่และให้ตรงกับวันที่ที่กำหนดไว้ในแต่ละแผ่น

คำแนะนำในการบันทึก

1. มื่อท่านมีอาการพานิกเกิดขึ้น (อาการพานิกที่เกิดขึ้นแต่ละครั้งจะมีอาการย่อยๆหลายอาการ)ให้ท่านสังเกตว่ามีอาการอะไรเกิดขึ้นบ้าง แล้วบันทึกทันทีขณะมีอาการหรือหลังจากอาการสงบลง โดยให้ท่านใส่เครื่องหมาย √ ลงในช่องที่ตรงกับอาการที่เกิดขึ้น
2. ในวันหนึ่งอาจจะมีอาการพานิกเกิดขึ้นหลายครั้ง ขอให้ท่านบันทึกอาการย่อยๆเหล่านั้น เรียงลำดับตามครั้งที่เกิดอาการพานิก
3. การบันทึกความรุนแรงของอาการพานิกที่เกิดขึ้นแต่ละครั้ง ขอให้ท่านบันทึกตามความรู้สึกของท่านว่ามีความรุนแรงระดับใด ตั้งแต่

(1) คือ แทบไม่รู้สึกเลย จนถึง (7) คือ รุนแรงมาก โดยใส่หมายเลขระดับความรุนแรงนั้น ลงในช่องที่กำหนดให้

ระดับความรุนแรงของอาการพานิก

1 = แทบไม่รู้สึกเลย

2 = น้อยมาก

3 = น้อย

4 = ปานกลาง

5 = ปานกลาง ถึง รุนแรง

6 = รุนแรง

7 = รุนแรงมาก

อาการพานิก : ขณะที่เกิดอาการพานิกจะรู้สึกว่ามีความอึดอัด มีความกลัว หรือวิตกกังวลอย่างรุนแรง พร้อมกับเกิดอาการทางกายหลายๆอย่าง เช่น ใจสั่น ใจเต้นเร็ว เหงื่อออกมาก จุกแน่นหายใจขัด แน่นหน้าอก หน้ามืด วิงเวียน และเกิดความกลัวตนเองจะตาย หรือกลัวตนเองจะเป็นบ้า อาการเหล่านี้จะเกิดขึ้นอย่างรวดเร็วภายในเวลา 10-20 นาที และต่อมาอาการจะหายไป กลับสู่ภาวะปกติ

อาการพานิกอาจเกิดขึ้นเองโดยไม่มีสิ่งกระตุ้น บางครั้งอาจเกิดขณะนอนหลับจนทำให้ต้องตื่นกลางดึก

ใบบันทึกอาการพานิก ประจำวันที่.....เดือน.....พ.ศ.....

ชื่อ.....

อาการที่เกิดขึ้นในแต่ละครั้ง	ครั้งที่ 1	2	3	4	5	6	7	8	9	10	11	12
ใจสั่น ใจเต้นแรง ใจเต้นเร็ว												
เหงื่อออกมาก												
ตัวสั่น												
รู้สึกหายใจไม่อิ่ม												
รู้สึกจุกแน่นหายใจขัด												
เจ็บหน้าอก ไม่สบายในหน้าอก												
คลื่นไส้ ไม่สบายท้อง												
วิงเวียนศีรษะ รู้สึกโคลงเคลง หน้ามืด หรือ เป็นลม												
กลัวจะควบคุมตัวเองไม่ได้ หรือ กลัวจะเป็นบ้า												
กลัวตนเองจะตาย												
รู้สึกหนาวสั่น หรือ ร้อนวูบวาบ												
รู้สึกชา หรือ เสียวๆ เจ็บๆคล้ายเข็มแทงตามร่างกาย												
ความรุนแรงของอาการที่เกิดขึ้น (ให้ใส่หมายเลข)												

APPENDIX 3

CASE REPORT FORM

In the treatment of panic disorder (DSM-IV)

1998-1999

Investigator

Dr. Thoranin Kongsuk M.D.

Nakornphanom Psychiatric Hospital

210 Muang Nakornphanom

Thailand,48000

PATIENT NUMBER

แบบบันทึกข้อมูลงานวิจัยโรคพานิก

ประวัติผู้ป่วย

วันที่สัมภาษณ์ day. month. Year ☐☐ ☐☐ ☐☐

ชื่อผู้ป่วย…… ☐☐☐☐

Patients No…….. ☐☐☐☐

เพศ ชาย (1) ☐
หญิง (2)

วันเดือนปีเกิด day. month. Year (วัน.เดือน.ปี) ☐☐ ☐☐ ☐☐

สถานภาพสมรส โสด (1) คู่ (2)
แยก/หย่า (3) ม่าย (4) ☐

การศึกษา ประถมหรือต่ำกว่า (1) มัธยม (2)
ปวช, ปวส (3) ปริญญาตรีหรือสูงกว่า (4) ☐

Consent of the patient : written (1)
Oral (2) ☐

If oral, complete below :

_____ _____ _____ _____
(Date) (Signature of witness) (Date) (Investigator's signature)

Baseline examination

Date of assessment day ☐☐

month ☐☐

year ☐☐

Degree of global psychopathology

How ill is this subject now, compared to your

Experience with other panic patients?

1 Not
2 Very mild
3 Mild
4 Moderate
5 Moderate to severe
6 Severe
7 Extremely severe ☐

Vital signs

Pulse rate supine _____ beats/min ☐☐☐

standing _____ beats/min ☐☐☐

Blood supine systolic _____ mm Hg ☐☐☐

diastolic_____ mm Hg ☐☐☐

standing systolic _____ mm Hg ☐☐☐

diastolic_____ mm Hg ☐☐☐

Bodyweight _____ Kg ☐☐☐

ลักษณะของ Panic attack

วัน เดือน ปี

- เริ่มมีอาการครั้งแรก ____ ____ ____

- จำนวน panic attack ใน 2 อาทิตย์ที่ผ่านมา ____

- ลักษณะการเกิด panic attack ในครั้งแรก ____

  1. ไม่มีสิ่งกระตุ้น
  2. มีสิ่งกระตุ้น ระบุ 1.....
     2.....
     3.....

- เคยได้รับการรักษาด้วยยา 0 ไม่เคย 1 เคย ____

  ระบุชื่อยา 1.....ปริมาณยา mg ____

  2.....ปริมาณยา mg ____

  3.....ปริมาณยา mg ____

  4.....ปริมาณยา mg ____

- มีโรคประจำตัวอื่น ๆ ที่ยังได้รับการรักษาหรือไม่ 0 ไม่มี 1 มี ____

  ถ้ามีระบุโรคและยาที่รับประทาน

  โรค 1..... ยา 1.....

  2..... 2.....

  3..... 3.....

- ตรวจร่างกายปกติหรือไม่ 0 ไม่ปกติ 1 ปกติ ____

  ถ้าไม่ปกติ ระบุ

  1.....

  2.....

  3.....

Inclusion criteria

☐ อายุ 18 – 65 ปี

☐ มีอาการ พานิก (Panic attack) อย่างน้อย 1 ครั้ง/อาทิตย์ ใน 2 อาทิตย์ที่ผ่านมา

☐ ครบเกณฑ์ชี้วัดของ DSM – IV

เกณฑ์ชี้วัดของ DSM – IV

ต้องมีครบ 3 ข้อหลัก A, B, C จึงถือว่าครบเกณฑ์ชี้วัดของ DSM – IV

ใช่	ไม่ใช่	
◯	◯	A. มีอาการทั้ง (1) และ (2)
☐	☐	(1) มี Panic attack เกิดขึ้นซ้ำ ๆ (โดยไม่สามารถคาดการณ์ได้)
		(2) อย่างน้อยหนึ่งครั้ง หลังจากมี Panic attack แล้วจะต้องมีอย่างน้อย 1 ข้อ ดังต่อไปนี้ติดตามมาเป็นเวลา 1 เดือน
☐	☐	a. กังวลตลอดเวลาจะเกิด Panic attack ขึ้นอีก
☐	☐	b. กังวลว่าจะเป็นโรคร้ายแรง หรือมีผลร้ายเกิดขึ้นตามมา เช่น กังวลว่าจะคุมตนเองไม่ได้ กังวลว่าจะเป็นบ้า, กังวลว่าจะหัวใจวาย
☐	☐	c. พฤติกรรมเปลี่ยนไปอย่างชัดเจนเนื่องจากการเกิดอาการ
◯	◯	B. Panic attack ไม่ได้เกิดจากผลด้านสรีรวิทยาโดยตรง ของสารเสพติด หรือยาอื่น ๆ หรือไม่ได้เกิดจากภาวะความเจ็บป่วยทางกาย เช่น โรคไทรอยด์
◯	◯	C. Panic attack นี้ไม่ได้เข้ากับโรคทางจิตเวชอื่น ๆ เช่น Social phobia, obsessive compulsive disorder, Post – traumatic stress disorder, separation anxiety disorder
☐	☐	มีอาการ agoraphobia

Exclusion criteria

ใช่	ไม่ใช่	
☐	☐	1. ตั้งครรภ์หรือมีแผนจะตั้งครรภ์เร็ว ๆ นี้
☐	☐	2. เคยเจ็บป่วยด้วยโรคจิตเวชเหล่านี้ Bipolar disorder, depressive disorder Obsessive compulsive disorder, psychosis. Dementia, substance abuse disorder.
☐	☐	3. มีโรคทางกายเหล่านี้ โรคไทรอยด์เป็นพิษ โรคหลอดเลือดหัวใจ โรคหัวใจเต้นผิดจังหวะ โรคถุงลมปอดโป่งพอง โรคหอบหืด โรคต่อมหมวกไตทำงานผิดปกติ มีความผิดปกติในการทำงานของไตและตับ(จากผล Lab)
☐	☐	4. ได้รับยาดังต่อไปนี้ และไม่สามารถหยุดได้ ขณะเข้าโครงการวิจัย Alpha, Beta – blocker เช่น propanolol, metropolol , clonidine.

Laboratory Parameters at baseline

Date of blood sampling …. ….. …..

	Normal range	Unit	
Hematology			
Hemoglobin	_____ – _____	_____	☐☐☐
Platelets	_____ – _____	_____	☐☐☐
Leucocyte	_____ – _____	_____	☐☐☐
Blood chemistry			
Alkaline phosphatase	_____ – _____	_____	☐☐☐
AST (SGOT)	_____ – _____	_____	☐☐☐
ALT (SGPT)	_____ – _____	_____	☐☐☐
Total bilirubin	_____ – _____	_____	☐☐☐
BUN	_____ – _____	_____	☐☐☐
Creatinine	_____ – _____	_____	☐☐☐

Follow - up examination, 1st week

Date of assessment

day ☐☐

month ☐☐

year ☐☐

Degree of global psychopathology

How ill is this subject now, compared to your Experience with other panic patients ?

1 Not
2 Very mild
3 Mild
4 Moderate
5 Moderate to severe
6 Severe
7 Extremely severe ☐

How much has subject changed since study onset ?

1. Very much better
2. Much better
3. A little better
4. No change
5. A little worse
6. Much worse
7. Very much worse

In doctor's option ☐

In patient's option ☐

Vital signs

Pulse rate supine ____ beats/min

Standing ____ beats/min

Blood Pressure supine systolic _____ mm Hg

diastolic_____ mm Hg

standing systolic _____ mm Hg

diastolic_____ mm Hg

Bodyweight _____ Kg

Adverse events 1 not present, 2 present

If present, please complete forms for

Adverse events

Concurrent therapy 1 none, 2 yes

Intercurrent disease 1 none, 2 yes

If yes, please complete forms for

Concurrent therapy / intercurrent disease

Follow - up examination, 2nd week

Date of assessment

day ☐☐

month ☐☐

year ☐☐

Degree of global psychopathology

How ill is this subject now, compared to your experience with other panic patients ?

1 Not
2 Very mild
3 Mild
4 Moderate
5 Moderate to severe
6 Severe
7 Extremely severe

☐

How much has subject changed since study onset ?

1. Very much better
2. Much better
3. A little better
4. No change
5. A little worse
6. Much worse
7. Very much worse

In doctor's option ☐

In patient's option ☐

Vital signs

Pulse rate supine _____ beats/min ☐☐☐

Standing ____ beats/min ☐☐☐

Blood Pressure supine systolic _____ mm Hg ☐☐☐

diastolic_____ mm Hg ☐☐☐

standing systolic _____ mm Hg ☐☐☐

diastolic_____ mm Hg ☐☐☐

Bodyweight _____ Kg ☐☐☐

Adverse events 1 not present, 2 present ☐

If present, please complete forms for

Adverse events

Concurrent therapy 1 none, 2 yes ☐

Intercurrent disease 1 none, 2 yes ☐

If yes, please complete forms for

Concurrent therapy / intercurrent disease

Follow - up examination, 4th week

Date of assessment

day ☐☐

month ☐☐

year ☐☐

Degree of global psychopathology

How ill is this subject now, compared to your experience with other panic patients ?

1. Not
2. Very mild
3. Mild
4. Moderate
5. Moderate to severe
6. Severe
7. Extremely severe ☐

How much has subject changed since study onset ?

1. Very much better
2. Much better — In doctor's option ☐
3. A little better
4. No change
5. A little worse — In patient's option ☐
6. Much worse
7. Very much worse

Vital signs

Pulse rate	supine	_____ beats/min	___
	Standing	____ beats/min	___
Blood Pressure	supine	systolic _____ mm Hg	___
		diastolic_____ mm Hg	___
	standing	systolic _____ mm Hg	___
		diastolic_____ mm Hg	___
Bodyweight		_____ Kg	___

Adverse events 1 not present, 2 present ___

If present, please complete forms for

Adverse events

Concurrent therapy 1 none, 2 yes ___

Intercurrent disease 1 none, 2 yes ___

If yes, please complete forms for

Concurrent therapy / intercurrent disease

Follow - up examination, 6th week

Date of assessment day ☐☐

month ☐☐

year ☐☐

Degree of global psychopathology

How ill is this subject now, compared to your Experience with other panic patients ?

1. Not
2. Very mild
3. Mild
4. Moderate
5. Moderate to severe
6. Severe
7. Extremely severe ☐

How much has subject changed since study onset ?

1. Very much better
2. Much better — In doctor's option ☐
3. A little better
4. No change
5. A little worse — In patient's option ☐
6. Much worse
7. Very much worse

Vital signs

Pulse rate	supine	_____ beats/min	☐☐☐
	Standing	____ beats/min	☐☐☐
Blood Pressure	supine	systolic _____ mm Hg	☐☐☐
		diastolic_____ mm Hg	☐☐☐
	standing	systolic _____ mm Hg	☐☐☐
		diastolic_____ mm Hg	☐☐☐
Bodyweight		_____ Kg	☐☐☐

Adverse events 1 not present, 2 present ☐

If present, please complete forms for

Adverse events

Concurrent therapy 1 none, 2 yes ☐

Intercurrent disease 1 none, 2 yes ☐

If yes, please complete forms for

Concurrent therapy / intercurrent disease

Follow - up examination, 8th week

Date of assessment day ☐☐

month ☐☐

year ☐☐

Degree of global psychopathology

How ill is this subject now, compared to your Experience with other panic patients ?

1. Not
2. Very mild
3. Mild
4. Moderate
5. Moderate to severe
6. Severe
7. Extremely severe ☐

How much has subject changed since study onset ?

1. Very much better
2. Much better — In doctor's option ☐
3. A little better
4. No change
5. A little worse — In patient's option ☐
6. Much worse
7. Very much worse

Vital signs

Pulse rate	supine	_____ beats/min	___
	Standing	____ beats/min	___
Blood Pressure	supine	systolic _____ mm Hg	___
		diastolic_____ mm Hg	___
	standing	systolic _____ mm Hg	___
		diastolic_____ mm Hg	___
Bodyweight		_____ Kg	___

Adverse events 1 not present, 2 present ___

If present, please complete forms for

Adverse events

Concurrent therapy 1 none, 2 yes ___

Intercurrent disease 1 none, 2 yes ___

If yes, please complete forms for

Concurrent therapy / intercurrent disease

End of Treatment visit

วัน เดือน ปี ☐☐ ☐☐ ☐☐

1. การตรวจร่างกาย วันสุดท้าย 1 ปกติ 0 ไม่ปกติ ☐

   ถ้าไม่ปกติ ระบุ 1.....

   2.....

   3.....

2. ผู้ป่วยติดตามรักษาทุกครั้งจนครบกำหนด 1 ครบ 0 ไม่ครบ ☐

3. สาเหตุการขาดนัด

   (1) เกิดผลข้างเคียง หรือ เกิดพิษของยา

   (2) รู้สึกอาการแย่ลง หรือ อาการไม่ดี

   (3) รู้สึกอาการดีขึ้น

   (4) มีโรคทางกาย

   (5) ขาดนัดเนื่องจากสาเหตุอื่น ระบุ.....

   (6) ไม่ทราบเหตุผลหรือไม่สามารถติดต่อได้

Laboratory Parameters at the end of treatment

Date of blood sampling ....

	Normal range	Unit	
Hematology			
Hemoglobin	____–____	_____	☐☐☐
Platelets	____–____	_____	☐☐☐
Leucocyte	____–____	_____	☐☐☐
Blood chemistry			
Alkaline phosphatase	____–____	_____	☐☐☐
AST (SGOT)	____–____	_____	☐☐☐
ALT (SGPT)	____–____	_____	☐☐☐
Total bilirubin	____–____	_____	☐☐☐
BUN	____–____	_____	☐☐☐
Creatinine	____–____	_____	☐☐☐

AE Report Form

		1 st adverse event	2nd adverse event
Adverse event (AE*)		----------	----------
		----------	----------
Data of onset	day. month.year	☐☐. ☐☐. ☐☐	☐☐. ☐☐. ☐☐
Duration	days	☐☐☐	☐☐☐
Severity	mild (1)		
	Moderate (2)	☐	☐
	Severe (3)		
Course	continous (1)		
	Intermittent (2)	☐	☐
Relationship			
	Unrelated (0)		
	remote (1)		
	possible (2)		
	probable (3)	☐	☐
Action taken			
	None (0)		
	increased surveillance (1)		
	symptomatic treatment (2)		
	suspend test drug (3)		
	discontinue test drug (4)	☐	☐
Outcome of event			
	Alive with sequeale (1)		
	Recovered (2)	☐	☐
	Died (3)		
Hospitalisation " required "		☐ 1= no, 2= yes	☐ 1= no, 2= yes

AE Report Form

		3 rd adverse event	4th adverse event
Adverse event (AE*)		---------- ----------	---------- ----------
Data of onset	day. month.year	☐☐. ☐☐. ☐☐	☐☐. ☐☐. ☐☐
Duration	days	☐☐☐	☐☐☐
Severity	mild (1)		
	Moderate (2)	☐	☐
	Severe (3)		
Course	continuous (1)		
	Intermittent (2)	☐	☐
Relationship			
	Unrelated (0)		
	remote (1)		
	possible (2)		
	probable (3)	☐	☐
Action taken			
	None (0)		
	increased surveillance (1)		
	symptomatic treatment (2)		
	suspend test drug (3)		
	discontinue test drug (4)	☐	☐
Outcome of event			
	Alive with sequale (1)		
	Recovered (2)	☐	☐
	Died (3)		
Hospitalisation " required "		☐ 1= no, 2= yes	☐ 1= no, 2= yes

AE Report Form

		5 th adverse event	6th adverse event
Adverse event (AE*)		----------	----------
		----------	----------
Data of onset	day. month. year	☐☐. ☐☐. ☐☐	☐☐. ☐☐. ☐☐
Duration	days	☐☐☐	☐☐☐
Severity	mild (1)		
	Moderate (2)	☐	☐
	Severe (3)		
Course	continuous (1)		
	Intermittent (2)	☐	☐
Relationship			
	Unrelated (0)		
	remote (1)		
	possible (2)		
	probable (3)	☐	☐
Action taken			
	None (0)		
	increased surveillance (1)		
	symptomatic treatment (2)		
	suspend test drug (3)		
	discontinue test drug (4)	☐	☐
Outcome of event			
	Alive with sequeale (1)		
	Recovered (2)	☐	☐
	Died (3)		
Hospitalisation " required "		☐ 1= no, 2= yes	☐ 1= no, 2= yes

AE Report Form

		7 th adverse event	8 th adverse event
Adverse event (AE*)		----------	----------
		----------	----------
Data of onset	day. month.year	☐☐. ☐☐. ☐☐	☐☐. ☐☐. ☐☐
Duration	days	☐☐☐	☐☐☐
Severity	mild (1)		
	Moderate (2)	☐	☐
	Severe (3)		
Course	continuous (1)		
	Intermittent (2)	☐	☐
Relationship			
	Unrelated (0)		
	remote (1)		
	possible (2)		
	probable (3)	☐	☐
Action taken			
	None (0)		
	increased surveillance (1)		
	symptomatic treatment (2)		
	suspend test drug (3)		
	discontinue test drug (4)	☐	☐
Outcome of event			
	Alive with sequeale (1)		
	Recovered (2)		☐
	Died (3)	☐	
Hospitalisation " required "		☐ 1= no, 2= yes	☐ 1= no, 2= yes

Intercurrent diseases

Disease	Date began day. month. year	Date ended day. month. year	
____________	__ . __ . __	__ . __ . __	____
____________	__ . __ . __	__ . __ . __	____
____________	__ . __ . __	__ . __ . __	____
____________	__ . __ . __	__ . __ . __	____
____________	__ . __ . __	__ . __ . __	____
____________	__ . __ . __	__ . __ . __	____

Concurrent Medications

Medications of intercurrent disease

Generic name (in case of combinations, trade name)	Date began day. month. year	Date ended day. month. year	Maximal daily dose (mg)	
____________	__ . __ . __	__ . __ . __	____	____
____________	__ . __ . __	__ . __ . __	____	____
____________	__ . __ . __	__ . __ . __	____	____
____________	__ . __ . __	__ . __ . __	____	____
____________	__ . __ . __	__ . __ . __	____	____

Other concurrent medications

Generic name (in case of combinations, trade name)	Date began day. month. year	Date ended day. month. year	Maximal daily dose (mg)
_____	__.__.__	__.__.__	____ ‘‘‘‘
_____	__.__.__	__.__.__	____ ‘‘‘‘
_____	__.__.__	__.__.__	____ ‘‘‘‘
_____	__.__.__	__.__.__	____ ‘‘‘‘
_____	__.__.__	__.__.__	____ ‘‘‘‘

VITAE

Mr.Thoranin Kongsuk was born on 16 September 1964 in Roi-et, Thailand. He graduated Medical Doctor from Khonkaen University, in 1988. He got Board of Psychiatry from Royal College of Psychiatrist of Thailand. He has been enrolled in the Master Degree of Science in Health Development at Faculty of Medicine, Chulalongkorn University since 1997. The present position is Director of Loei Psychiatric Hospital, Department of Mental Health, Ministry of Public Health, Thailand.