Chapter 1

Introduction

Background and Rationale

Schizophrenia is a complex illness characterized by disruptions of chemical messengers and nerve pathways in the brain, which cause disturbances to thinking, emotions, and behavior. Those manifestations combine in various ways, creating considerable diversity among patients, but cumulative effect of the illness is always severe and usually long lasting.

World wide, there are currently an estimated 45 million people suffering from schizophrenia.[1] It affects about 1 percent of the world population. One in ten of schizophrenic patients will develop a severe, chronic form of illness that requires substantial health and social care for the rest of their lives. Also, up to 2/3 of schizophrenic patient will develop a recurring pattern of relapses and remission of illness.[2] There are estimated to be 15 to 30 new cases of schizophrenia per 100,000 people each year.[3]

Since the incidence usually peaks during ages of 15 to 35 years old [4] which means, schizophrenia begins early in life. Therefore, it causes significant and long lasting impairments which make the patients and their family suffered. The burden on the patient's family is heavy and both the patient and his or her relatives are often exposed to the stigma associated with the illness, sometimes over generations.

In Thailand, schizophrenia are most common among all mental disorder. In 1997, there are 80.9 percent of inpatient diagnosed as schizophrenia at Somdet Chaophraya Hospital, one of the famous mental hospital in Thailand. As for King Chulalongkorn Memorial Hospital, schizophrenic patient were admitted more than any other mental disorder for the past 10 years.[5]

Schizophrenia has a heavy demand for hospital care, and requires an ongoing clinical care, and rehabilitation. Since 30 percent to 40 percent of schizophrenic patient may have an inadequate or poor response to treatment,[6] leading to repeated hospital admissions and poor social and occupational function. Therefore, the financial cost of schizophrenia constitute a significant percentage of the total direct health care costs. The cost for all mental illness in 1988 was an estimated $129.3 billion, of which almost $40 billion was spent on schizophrenia. It currently estimated at $1605 per person per year which are 9 percent of the gross national product.[7]

From the overall explanation, schizophrenia is the greatest loss financially and also the greatest waste of human resources. To reduce the financial cost and help the patients improve their social skills, the appropriate treatment strategies must be develop.

Clinical treatment of the schizophrenic patient may include hospitalization and antipsychotic medication (neuroleptic), as well as psychosocial treatments, such as behavioral, family, group, individual, and social skills and rehabilitation therapies.[8] There are variety treatments of schizophrenia, in which, have been developed gradually by researches and experiences.

In the early 1930s, inducing a coma with large dosages of insulin was introduced by Sakel, but later findings by others were less encouraging. In 1935 Moniz, a Portuguese psychiatrist, introduced the prefrontal lobotomy, a surgical procedure that destroys the tracts connecting the frontal lobes to lower centers of the patient's brain. Moniz claimed high rates of success. And for twenty years thereafter thousands of mental patients underwent variations of psychosurgery, especially if their behavior was violent. But during the 1950s this intervention, too, fell into disrepute for several reasons.[9]

Without question, the most important development in the treatment of the schizophrenia disorders was the advent in the 1950s of several drugs collectively referred

to as antipsychotic medications. They are also called neuroleptics because, in addition to their beneficial effects, they have side effects similar to the behavioral manifestations of neurological diseases. Neuroleptic medications are significantly more powerful in controlling the symptoms of psychosis than are antianxiety, antidepressant, and antimanic agents. There are two indications for neuroleptic agents in the treatment of schizophrenia. The first is to control the active symptoms of the illness, and the second is to provide a prophylactic effect in preventing relapse. The first is aimed at controlling the acute episode, whereas the second is aimed at maintenance management. In a significant number of patients, however, the control of symptoms is only partial, and therefore the treatments are often combined.[10]

Neuroleptics have numerous side effects. These are important because they have a major impact on the patient's compliance with neuroleptic medications. The extrapyramidal systems are involved in the nonconscious control of all voluntary musculature. Neuroleptics have complex effects on the extrapyramidal systems that are exacerbated by anxiety disappear during sleep and can be consciously controlled for a limited time with effort.[10] Also, tardive dyskinesia is a late complication of neuroleptic treatment and has been described as a syndrome consisting of abnormal stereotyped involuntary movements usually of choreoathetoid type principally affecting the mouth, face, limbs, and trunk, which occurs relatively late in the course of drug treatment and the etiology of which the drug treatment is a necessary factor. Continued treatment with neuroleptics results in potential worsening of the symptoms of tardive dyskinesia and make them more likely to be irreversible.[11]

Although these neuroleptic medications were effective for many patients in reducing the intensity and frequency of the *positive* symptoms of schizophrenia (for example: hallucinations, delusions), a troubling phenomenon emerged. *Negative* symptoms of schizophrenia, consisting of blunted affect, emotional and social withdrawal, and lack of motivation, developed. These became formidable obstacles to efforts at

psychiatric rehabilitation. In addition, which have been mentioned before there were many schizophrenic patients who did not respond to typical neuroleptic.[12]

In 1990, a new neuroleptic medication, clozapine, was introduced in United States. It represented the first significant advance in the pharmacotherapy of schizophrenia since the introduction of typical neuroleptic in the 1950s. This new neuroleptic medication often referred to as *atypical* agents, as opposed to the *typical* agents such as haloperidol and chlorpromazine. Atypical neuroleptic generally cause few or no extrapyramidal side effects. They reduce the negative symptoms of schizophrenia, and effective for treating refractory schizophrenia, and are less likely to cause tardive dyskinesia.

However, clozapine has not been used on widespread basis or as a first-line treatment due to its potential for agranulocytosis. The mechanism of action of atypical neuroleptic has been the target of intensive research efforts by the pharmaceutical industry and the psychopharmacology research community, which led to development of numerous putative atypical compounds with novel pharmacological profiles. These compounds include selective DA (dopamine antagonist) receptor subtype antagonist (D1, D2, D3, D4), predominantly DA and serotonin receptor antagonists, mixed neuroreceptor antagonists, and pure serotonin antagonists.[13] Now, we have a new therapeutic standard set by clozapine and many compounds that aspire to be clozapine without agranulocytosis.

Olanzapine is one of candidate compound, it is a thienobenzodiazepine derivative which displays efficacy in patients with schizophrenia and related psychoses. It has structural and pharmacological properties resembling those of the atypical neuroleptic clozapine and an improved tolerability profile compared with the typical neuroleptic haloperidol. The efficacy of olanzapine has a rapid onset (within 1-2 weeks), also there have been no report of agranulocytosis as occurs with clozapine.[14] Olanzapine was associated with significantly fewer extrapyramidal side effects because it targets primarily

mesolimbic and mesocortical areas, and receptors for other transmitters such as serotonin. Unlike typical neuroleptic which also block dopamine receptors in the striatum causing extrapyramidal side effects.[15]

ECT (electroconvulsive therapy) is a safe and effective treatment of patients with mental disorder. It has been used to treat schizophrenia since the 1930s, until it was replaced by typical neuroleptic drug. ECT was reintroduced in the 1970s as the treatment of treatment-resistant schizophrenia.[16] Despite over 50 years of continuous use of ECT, many clinicians believe that ECT is grossly underused as a treatment. In medical record collected by the National Institute of Mental Health (NIMH) estimated that in 1980, 16.6 percent of the patients who received ECT in public and private inpatient facilities in the United States carried the diagnosis of schizophrenia. These patients constituted only 2.1 percent of admitted schizophrenic patients.[17] In Great Britain 13 percent of patient treated with ECT were schizophrenic patient, in Ireland 17 percent,[18] and in Canada 28.8 percent were schizophrenic patients.[19]

There are many studies trying to improve standard treatment of schizophrenia. Both ECT and neuroleptic are effective treatment of schizophrenia, therefore, topic of combining ECT with neuroleptic have been studied world wide. There were evidences that treatment with typical neuroleptic in combination with ECT was more effective than treatment with typical neuroleptic alone. For example, in findings reported by Smith and his colleague,[20] a reduced rate of relapse in patients treated acutely with a combination treatment of typical neuroleptics and ECT compared with typical neuroleptics alone.

The researcher suggest that a combination between ECT and atypical neuroleptic should be emphasize, since atypical neuroleptics clinically is a gold standard treatment of schizophrenia. In which, it can improve positive and negative symptoms and have fewer extrapyramidal side effects unlike typical neuroleptics.[21] However, a substantial proportion of schizophrenic patients do not respond to atypical neuroleptic. There are some cases report on the use of ECT in clozapine-resistant patients.[22] In combining ECT

with atypical neuroleptics, there may be a way to lower financial cost, from relapse, and rehospitalization, also establish better outcome for resistant-schizophrenic patients. So far, there have not been any study, only some case reports. Therefore, the researcher decided to do this research, on the comparison of ECT combined with atypical neuroleptic versus atypical neuroleptic in schizophrenic patients. In which, researcher believe that this study can be valuable in finding a better gold standard treatment to help schizophrenic patients or at least, can guide the way for even better treatment strategies.

Objectives

1. To compare the effectiveness between combination treatment of ECT with atypical neuroleptic and treatment of atypical neuroleptic alone.

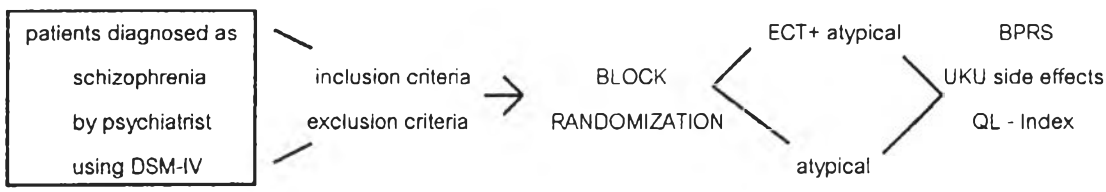
2. To compare the side effects between combination treatment of ECT with atypical neuroleptic and treatment of atypical neuroleptic alone.

Hypothesis

1. Combination treatment of ECT and atypical neuroleptic are more effective than atypical neuroleptic treatment alone.

2. Combination treatment of ECT and atypical neuroleptic have less side effect than atypical neuroleptic treatment alone.

Conceptual Framework



Assumptions

1. Schizophrenic patients are psychiatric patients at King Chulalongkorn Memorial Hospital and were diagnosed as schizophrenia by psychiatrist using reference of Diagnostic and Statistic Manual of Mental Disorder, fourth edition(DSM-IV) who have passed the inclusion and exclusion criteria, which will be mention later. Researcher then categorized the patient into control and experimental group by using block randomization.

2. Schizophrenic patient who were chosen to be in experimental group received modified electroconvulsive therapy (ECT) for at least 12 times during the period of observation as part of their intervention.

3. For both control and experimental group, took Olanzapine (Zyprexa) as their atypical neuroleptic at therapeutic dose of 10-20 mg. per day during the whole period of observation.

4. Measuring instruments that used to assess both group of control and experimental were Brief Psychiatric Rating Scale (BPRS),[23] Quality of Life Index (QL-Index),[24] and The UKU Side Effects Rating Scale.[25]

Operational Definition

electroconvulsive therapy (ECT) : treatment of electrical induced seizure with limited currents. Modified ECT are electroconvulsive therapy which additionally included brief anesthetic, adequate muscle relaxants, monitored brain and heart rhythms, and appropriate oxygen supplementation.

atypical neuroleptic : a group of drugs which block dopamine and serotonin receptors, which appear to treat both negative and positive symptoms without inducing movement disorders. In this case, Olanzapine (Zyprexa) were being used for every schizophrenic patient participated in this study.

schizophrenic patient : person who have signs and symptoms that fit diagnostic criteria of schizophrenia from Diagnostic and Statistic-Manual of Mental Disorder, fourth edition (DSM-IV)[26] as stated below :

A. Characteristic symptoms : Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

1) delusions

2) hallucinations

3) disorganized speech (e.g., frequent derailment or incoherence)

4) grossly disorganized or catatonic behavior

5) negative symptoms, i.e., affective flattening, alogia, or avolition

B. Social / occupational dysfunction : For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration : Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by one negative symptoms or two or more symptoms listed in criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective and mood disorder exclusion : Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either: 1) no major depressive, manic, or mixed episodes have occurred concurrently with the active phase symptoms; or 2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance / general medical condition exclusion : The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. Relationship to a pervasive developmental disorder : If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Expected Benefit and Application

1. To search for a safe and effective treatment with most beneficial for the patients.
2. To help lower the cost of treatment for patients and hospital.
3. To increase compliance from patients and their family.
4. Lead to another research topic.

Ethical Considerations

There are some ethical issues that need to be considered. But with the appropriate methodology, the patients can be safely treated. The whole research procedure are under supervision of professional psychiatrist, also every patients need to passed inclusion and exclusion criteria. Every patient must signed research consent form to confirmed their approval of participation in this research study. During the observational period, every patient received treatments appropriated with their individual's conditions.