THE ASSOCIATION OF ANXIETY AND MOOD SYMPTOMS IN PATIENTS WITH BIPOLAR DISORDERS ATTENDING FOLLOW-UP TREATMENT

DR. MOHAMMAD NABHAN KHALIL BIN AZIZAN

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (PSYCHIATRY)

MAY 2015

DECLARATION

I hereby testify that the work in this thesis is my own except for quotations and summaries which have been duly acknowledged.

Mohammad Nabhan Khalil bin Azizan, M.D.

PUM-0070/10

CERTIFICATION

I hereby certify that to the best of my knowledge, this research project is an original work of the candidate, Dr. Mohammad Nabhan Khalil bin Azizan.

Supervisor

Professor Dr. Hasanah Che Ismail, Lecturer and Consultant Psychiatrist

Department of Psychiatry, School of Medical Sciences

Universiti Sains Malaysia

ACKNOWLEDGMENTS

Words cannot express my gratitude to Professor Dr. Hasanah Che Ismail for her guidance, expert advice and encouragement throughout this difficult journey.

Special thanks to Drs. Faizul Islam, Lua Chong Teck, Norazhani Nordin and Rosliza Yahya for their constant support and companionship.

I am also grateful to the doctors in MICU II for without them, this voyage would have been lonely.

Thank you.

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATION

<	Less than
b	Regression Coefficient
BAI	Beck Anxiety Inventory
BD	Bipolar Disorders
BDI	Beck Depression Inventory
CI	Confidence Interval
DALY	Disability-Adjusted Life Year
DASS	Depression, Anxiety and Stress Scale
GAF	General Assessment of Functioning
HUSM	Hospital Universiti Sains Malaysia
IQR	Interquartile Range
r	Correlation Coefficient
SD	Standard Deviation
SNRI	Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)
SPSS	Statistical Package for the Social Sciences
SRRS	Social Readjustment Rating Scale
SSRI	Selective Serotonin Reuptake Inhibitors
WHO	World Health Organization
YMRS	Young Mania Rating Scale

LIST OF APPENDICES

ABSTRAK

HUBUNGAN ANTARA KERUNSINGAN DAN GEJALA AFEKTIF DALAM PENGHIDAP KECELARUAN BIPOLAR YANG MENGHADIRI RAWATAN ULANGAN

Latar Belakang: Gejala kerunsingan kerap berlaku pada pesakit Kecelaruan Bipolar. Ia dikaitkan dengan keadaan penyakit yang lebih serius, contohnya penyakit yang lebih kerap berulang, kemasukan ke hospital yang lebih kerap, penyalahgunaan dadah, serta simptom kemurungan dan mania yang lebih teruk. Setakat ini, kajian mengenai kerunsingan pada pesakit Bipolar di Malaysia masih berkurangan.

Tujuan kajian: Kajian ini bertujuan untuk menentukan kelaziman simptom kerunsingan dan pengesanannya pada pesakit rawatan ulangan yang menghidapi Kecelaruan Bipolar. Data sosiodemografi dan klinikal yang berkaitan dengan simptom keresahan dikenalpasti. Korelasi antara keresahan dan gejala afektif serta bebanan peristiwa hidup dalam setahun juga dikaji.

Kaedah kajian: Kajian keratan rentas ini dijalankan ke atas pesakit Kecelaruan Bipolar di Klinik Psikiatri Hospital Universiti Sains Malaysia. Peserta kajian memberikan maklumat sosiodemografi dan klinikal serta mengisi empat skala penilaian sendiri [Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Young Mania Rating Scale (YMRS) dan Social Readjustment Rating Scale (SRRS)] untuk mengenalpasti tahap kemurungan, mania dan keresahan, serta tahap peristiwa hidup dalam setahun. Analisis regresi dan korelasi dilakukan untuk mengenalpasti kaitan dan

korelasi antara simptoms keresahan dan simptom afektif serta data sosiodemografi dan klinikal.

Keputusan: 20.5% daripada kesemua 132 orang peserta kajian mempunyai gejala kerunsingan yang signifikan. Daripada peratusan tersebut, hanya 29.3% peserta telah dikenalpasti oleh pegawai perubatan yang merawat sebagai mengalami gejala kerunsingan. Tahap kerunsingan (BAI) mempunyai kaitan secara langsung yang positif dengan Kecelaruan Bipolar jenis II, jumlah penyakit berulang serta skala BDI. Terdapat korelasi positif yang baik antara BAI dan BDI ($r = 0.690$, $p < 0.001$), manakala terdapat korelasi positif yang lemah antara BAI dan SRRS ($r = 0.194$, $p = 0.026$).

Kesimpulan: Pengenalpastian gejala kerunsingan pada pesakit Bipolar oleh pegawai perubatan yang merawat adalah rendah. Kerunsingan dalam pesakit Bipolar adalah berkaitan dengan Kecelaruan Bipolar jenis II, jumlah penyakit yang lebih kerap berulang, simptom kemurungan yang lebih teruk serta bebanan peristiwa hidup yang lebih banyak dalam masa setahun. Pegawai perubatan yang merawat perlu sensitif dalam mengesan kerunsingan dalam pesakit Kecelaruan Bipolar. Lebih banyak kajian diperlukan untuk mencari rawatan yang berkesan untuk keresahan dalam pesakit Kecelaruan Bipolar.

Kata kunci: Kecelaruan Bipolar, kemurungan, keresahan, pengesanan, peristiwa kehidupan

ABSTRACT

THE ASSOCIATION OF ANXIETY AND MOOD SYMPTOMS IN PATIENTS WITH BIPOLAR DISORDERS ATTENDING FOLLOW-UP TREATMENT

Background: Anxiety is common in Bipolar Disorders (BD). It is associated with poorer outcome in BD, for example increased in relapse rate and hospitalization, suicidality, substance abuse and more severe symptoms of mania and depression. Malaysian study regarding anxiety in BD is still lacking.

Objective: The aim of this study was to determine prevalence of significant anxiety and its detection rate in psychiatric outpatient clinic. Sociodemographic and clinical characteristics associated with anxiety were also examined. Correlation between anxiety and mood symptoms and the burden of life events within one-year period were measured.

Method: This is a cross-sectional study done in psychiatric outpatient clinic in Hospital Universiti Sains Malaysia. Sociodemographic and clinical data were acquired from selected samples and four self-rated scales [Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Young Mania Rating Scale (YMRS) and Social Readjustment Rating Scale (SRRS)] were administered to measure mood symptoms, anxiety symptoms and the burden of life events within the previous one year. Regression and correlation analysis were done to examine relationship between anxiety symptoms and mood symptoms and sociodemographic and clinical data.

Results: 20.5% of the total 132 participants had significant level of anxiety. Among these, only 29.3% were detected by clinicians. Anxiety level (BAI) in BD was positively and independently associated with Bipolar II Disorder, number of relapse and BDI score. There was strong positive correlation between BAI and BDI ($r = 0.690$, $p < 0.001$). There was weak positive correlation between BAI and SRRS ($r = 0.194$, $p = 0.026$).

Conclusion: Anxiety in BD is poorly detected by clinicians and was associated with Bipolar II Disorder, higher frequency of relapse, more severe depression, and more burdens of life event within one-year period. Clinicians need to be sensitive in detecting anxiety in BD. More research is needed in finding effective treatment for anxiety in BD.

Keywords: anxiety, Bipolar Disorders, depression, detection, life events

CHAPTER 1: INTRODUCTION

Mental illness affects around 450 million of the world population (World Health Organization 2003). In Malaysia, it is estimated that 1.1 million adults are affected with mental illness (Malaysia Ministry of Health 2011). Mental illness causes major disabilities to the affected and causes distress and suffering to the sufferer and family members.

Bipolar Disorders are one of the major psychiatric disorders along with schizophrenia and Major Depressive Disorder. Its main feature is fluctuations of mood ranging from depression to mania or hypomania. The main aim of treatment of Bipolar Disorder is to stabilize the mood so that the person with the disease is free from extreme fluctuations of mood, leading to a state of euthymia. However clinicians frequently fail to address other important symptom of the illness, namely anxiety.

Studies show that anxiety comorbidity in Bipolar Disorder is very common. Lifetime prevalence of Anxiety Disorder was found to be up to 60% (Zutshi et al. 2006). Anxiety is associated with poorer course of illness in Bipolar Disorders such as increased in relapse and hospitalization, and increased in drug abuse and suicidality (Márcia Kauer-Sant'Anna et al. 2007). It is also associated with poorer quality of life (Simon et al. 2004).

Treatment of Bipolar Disorders with the presence anxiety is complicated. Usual medications to treat Bipolar Disorders might not be as affective as in Bipolar Disorders without anxiety (Gaudiano & Miller 2005). Usual medications to treat anxiety if used in the context of comorbidity with Bipolar Disorders might cause destabilization of mood (Ghaemi & Hsu 2003).

A lot of research is still needed to examine nature and treatment of anxiety in Bipolar Disorders.

CHAPTER 2: LITERATURE REVIEW

Mental illness is common. Its lifetime prevalence is more than 25% in developed and developing countries. Aggregate point prevalence for neuropsychiatric disorders is 10%, and it is estimated that 450 million people are affected by these disorders (World Health Organization 2003).

Mental disorders cause major disabilities to their sufferers. World Health Organization (WHO) estimated disability-adjusted life year (DALY) lost due to mental illness in 1990 to be 10.5%. The figure increased to 12.3% in the year 2000. It is estimated that DALYs for mental illness to increase to 15% in 2020 (WHO 2003).

Bipolar Disorders are the 9th contributor to the leading cause of DALYs in both sexes aged 14 – 44 years old. With total DALYs of 2.5%, it is only behind unipolar depression, alcohol use disorders, self inflicted injuries and Schizophrenia (WHO 2003).

In Malaysia, more than five percent of those 16 years and above have current mental illness (Malaysia Ministry of Health 2011; Krishnaswamy et al. 2012). It is estimated that 1.1 million Malaysian adults suffer from psychiatric illness (Malaysia Ministry of Health 2011).

2.1 Mood Disorder and Bipolar Disorders

Mood Disorder is a group of psychiatric disorders in which the clinical pictures show pathological moods and their related psychomotor features (Sadock et al. 2009). Major Mood Disorders include Bipolar Disorders and Major Depressive Disorder.

Bipolar Disorders are divided mainly into Bipolar I Disorder and Bipolar II Disorder, in which Bipolar I Disorder is the more severe form. To diagnose Bipolar I Disorder, a person needs to have at least one episode of mania with or without history of depression. As for Bipolar II Disorder, the person have at least one episode of hypomania and one episode of Major Depressive Disorder (American Psychiatric Association 2013).

Mania is characterized by elevated mood with talkativeness, increased activities and energy, reduced need for sleep, irritability, heightened sensorium, increased in libido and impulsivity. It could progress to psychosis, which is characterized by paranoid and grandiose delusion and hallucination (Gelder et al. 2003). Hypomania is the milder form of mania in which there is no psychosis and more or less no functional impairment.

Depression is a state in which the mood is low, bleak and pessimistic and the person is unable to experience pleasure. Thoughts as well as physical movement become slow. Neurovegetative activities such as sleep, appetite and libido also decreased. Psychosis may also occur in severe depression (Gelder et al. 2003).

The mainstay treatments for Bipolar Disorders are mood stabilizers and antipsychotics.

Since its discovery in 1960s, lithium has been widely used as a mood stabilizer. It has the most data on effectiveness for manic and depressive phase of illness (Malhi et al. 2013). It also fulfills all the proposed definition of mood stabilizer due to its effectiveness in acute manic and depressive state, as well as a prophylaxis against recurrence of mania and bipolar depression. Hence, it is still considered the 'gold standard' mood stabilizer (Ghaemi 2003).

Other mood stabilizers recommended for Bipolar Disorders include sodium valproate, lamotrigine and carbamazepine. Recommended antipsychotics include olanzapine, quetiapine, aripiprazole and typical antipsychotics such as haloperidol (Yatham et al. 2013).

Psychotherapy such as cognitive behavioral therapy and interpersonal and social rhythm therapy are also suitable for some patients, particularly in Bipolar II Disorder (Yatham et al. 2013).

2.2 Anxiety

Abnormal anxiety in an unpleasant emotional sensation due to 'fear for no adequate reason' (Casey & Kelly 2007). The individual frequently has physical symptoms such as palpitation, restlessness, shortness of breath and increased sweating. Cognitive symptoms of anxiety include worries or having a sense of something bad but unknown is going to happen. Anxiety could be mild to moderate and free-floating to severe, presenting with fear and panic.

There are various illnesses in which anxiety is the main features. This include Generalized Anxiety Disorder and Panic Disorder (American Psychiatric Association 2013).

Generalized Anxiety Disorder is a condition in which there is persistent worries occurring almost every day which is associated with symptoms such as fatigue, problems with concentration and irritability.

Panic Disorder is a condition in which there are panic attacks associated with persistent worry about getting another attacks and change in behaviors associated with the worry. Panic attacks are sudden unexpected extreme anxiety that are accompanied by palpitations, sweating, trembling, nausea and other symptoms.

Recommended first line treatment for anxiety disorders are Selective Serotonin Reuptake Inhibitors (SSRI) such as escitalopram and sertraline; and Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) such as venlafaxine and duloxetine (Bandelow et al. 2012).

2.3 Anxiety and Bipolar Disorders

Bipolar Disorders are highly comorbid with other mental illness. Comorbidities of Bipolar Disorders include substance abuse and various anxiety disorders (Merikangas & Jin 2011).

It is widely thought that between the intervals of depression and mania or hypomania, patients with Bipolar Disorders return to the normal state of wellbeing with mood being euthymic and functioning returning to normal. However, the fact that a number of bipolar patients still have ongoing symptoms between the affective episodes is increasingly recognized. For example, Macqueen et al. (2003) followed 138 patients for 3 years and found that around 26% of them had subsyndromal symptoms between the episodes, and had some difficulties in functioning with Global Assessment of Functioning scores averaging 69. This means that around one-third of these patients are at least mildly symptomatic and experiences some difficulties in functioning in daily life.

The affective phenomenon of mania, hypomania and depression are regarded as the main conditions that characterize the Bipolar Disorders that the other important facets of it, the anxiety symptoms, are often overlooked.

In the 19th century, Kraepelin (1921) already recognized the symptoms of anxiety in Bipolar Disorders, formerly known as Manic Depressive Insanity. He described "depressive or anxious mania" as *"morbid state arises, which is composed of flight of ideas, excitement and anxiety ... mood is anxiously despairing, it gives itself vent in great restlessness"*. In the phase of "excited depression", he stated that *"mood is anxious, despondent, lachrymose, irritable…"*

Research found that current Anxiety Disorder comorbidity in Bipolar Disorders to be ranging from 19 to 56 percent (Márcia Kauer-Sant'Anna et al., 2007; Mantere et al.,

2010; Simon et al., 2004). Lifetime comorbidity of Anxiety and Bipolar Disorders is slightly higher, ranging from 51 to 61 percent (Simon et al. 2004; Zutshi et al. 2006).

Data from Singapore showed that Generalized Anxiety Disorder comorbidity of Bipolar Disorders was 18.1% (Subramaniam et al. 2013). Other anxiety disorders are not stated. So far, there is no data on Anxiety Disorder comorbidity in Malaysian setting.

Anxiety Disorder brings a challenge in managing Bipolar Disorders as it alters the course, functioning and treatment of Bipolar Disorders patients.

The onset of Bipolar Disorders is significantly earlier in the presence of Anxiety Disorder comorbidity. Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) participants with comorbid Anxiety Disorder had significantly lower mean age of onset of Bipolar Disorders, which is 15 years old, as compared to 19 years old in Bipolar Disorders without comorbidity (Simon et al. 2004). Other study also showed significant age difference, which is 19 years old in Bipolar Disorders comorbid with Anxiety Disorder, and 23 years old in patients without an Anxiety Disorder (Zutshi et al. 2006).

The presence of Anxiety Disorder is associated with higher level of depressive and manic symptoms (Gaudiano & Miller 2005), rapid cycling, and psychosis (Márcia Kauer-Sant'Anna et al. 2007) as compared to Bipolar Disorders without anxiety comorbidity. Anxiety symptom level is also found to be positively correlated with the level of depression (Mantere et al., 2010). With treatment, anxiety level reduced along with the level of depression.

Patients with comorbid Mood Disorders and Anxiety Disorders also show high degree of impulsivity. However Anxiety Disorder-Bipolar Disorders comorbidity shows higher impulsivity than Anxiety Disorder-Major Depressive Disorder comorbidity (Bellani et al. 2012).

There is a higher risk of alcohol and drug abuse (Márcia Kauer-Sant'Anna et al. 2007) in Bipolar Disorders patients who have Anxiety Disorder. It is also associated with more suicide attempts (Márcia Kauer-Sant'Anna et al. 2007; Simon et al. 2004).

The presence of anxiety in bipolar patients showed poorer quality of life, more impairment in functioning, and lower General Assessment of Functioning (GAF) score. These patients also experiences significantly less time being in euthymia, and increased severity and chronicity of illness (Márcia Kauer-Sant'Anna et al. 2007; Simon et al. 2004; Gaudiano & Miller 2005).

Treatment for comorbidity of anxiety in Bipolar Disorders is not as straight forward as treating these disorders separately. Antidepressants, which are the medication of choice for Anxiety Disorders, may destabilize the mood and cause manic switch and rapid-cycling Bipolar Disorders (Ghaemi & Hsu 2003). Treatment for Anxiety Disorders in the setting of Bipolar Disorders that is recommended by Canadian Network for Mood and Anxiety Treatments (CANMAT) include first line treatment with gabapentin and quetiapine, and also sodium valproate, lamotrigine and SSRI as the second line treatment (Schaffer et al. 2012).

Bipolar Disorders with comorbid anxiety also showed poorer response to both treatment of pharmacotherapy and psychotherapy (Gaudiano & Miller 2005). It responds less to mood stabilizing agents which were lithium and anticonvulsants (Boylan et al. 2004; Henry et al. 2003), and showed less antimanic response of olanzapine (Joshi et al. 2010; Henry et al. 2003).

Overall, the presence of Anxiety Disorder comorbidity indicates poorer prognosis of this already chronic and debilitating illness.

2.4 Life Events

Effects of life events on medical illness have been observed in research. Rahe et al. (1964) found that a number of life events requiring certain adjustment within two-year period are associated with the onset of tuberculosis, heart disease, inguinal hernia and skin diseases.

This is also true for psychiatric illness. A community survey was done to observe relationship between life events over the past 12 months and 1-year prevalence of psychiatric disorders (Newman & Bland 1994). It was found that increased scoring of life event over the previous 12 months was correlated with Generalized Anxiety Disorder and Major Depressive Episode, with Major Depressive Episodes having greater burden of life event than Generalized Anxiety Disorder alone, and mixed Major Depressive Episode and Generalized Anxiety Disorder having the greatest burden of life events.

Simhandl et al. (2015) found that 62.2% of Bipolar Disorders patients had at least one life event within 6 months prior to a relapse of mood episode. Risk of depressive relapse in Bipolar I Disorder also increase with the number of life events after the index episode.

Life events also affect remission of psychiatric illness. Positive life events increase remission rates of depression, anxiety and ill-defined emotional distress 2.9-fold. This effect is irrespective of the diagnosis and severity of the illness (Neeleman 2003).

2.5 Gap in the Literature and Rationale of the Study

In literature search, there is no Malaysian study examining Anxiety Disorder comorbidity in Bipolar Disorders. There is also no local or international study about relationship between life events and anxiety in Bipolar Disorders. Because of the high comorbidity of Anxiety Disorder and its associated poorer outcome in bipolar patients, it is important for clinicians to detect it in clinical settings.

Thus, this study will demonstrate the relationship of clinical and demographic parameters, depression and life events with anxiety in Bipolar Disorders.

This study will also look into the detection rate of anxiety by the treating clinicians.

It is important for us to have local data on anxiety in Bipolar Disorders. As anxiety symptoms is a poor prognostic factor for Bipolar Disorders, there in a need to know detection rate of anxiety in bipolar patients in order to improve the detection and treatment of Bipolar Disorders as a whole.

CHAPTER 3: OBJECTIVE AND RESEARCH QUESTIONS

3.1 General Objective

To determine the extent of anxiety symptoms in patients with Bipolar Disorders under psychiatric clinic follow-up.

3.2 Specific Objectives

1. To examine the presence of anxiety symptoms in Bipolar Disorders outpatients.
2. To ascertain physician's detection rate of anxiety symptoms in outpatients with Bipolar Disorders.
3. To study the sociodemographic and clinical factors that are significantly associated with anxiety symptoms.
4. To determine the correlation of anxiety symptoms with manic and depressive symptoms and life events.

3.3 Research Questions

1. Do anxiety symptoms frequently occur in Bipolar Disorders outpatients?
2. Do clinicians frequently detect anxiety symptoms in Bipolar Disorders patients in clinical setting?
3. What are sociodemographic and clinical parameters that are associated with anxiety symptoms in Bipolar Disorders?

4. Do anxiety symptoms correlate with depressive and manic symptoms and life events in Bipolar Disorders during follow-up?

3.4 Hypotheses

1. Anxiety symptoms frequently occur in Bipolar Disorders outpatients.
2. Physician detection rate of anxiety symptoms in bipolar patients is low.
3. Anxiety symptoms are associated with low sociodemographic and poor clinical parameters.
4. Anxiety symptoms are positively correlated with depressive but not manic symptoms, and positively correlated with more burden of life events.

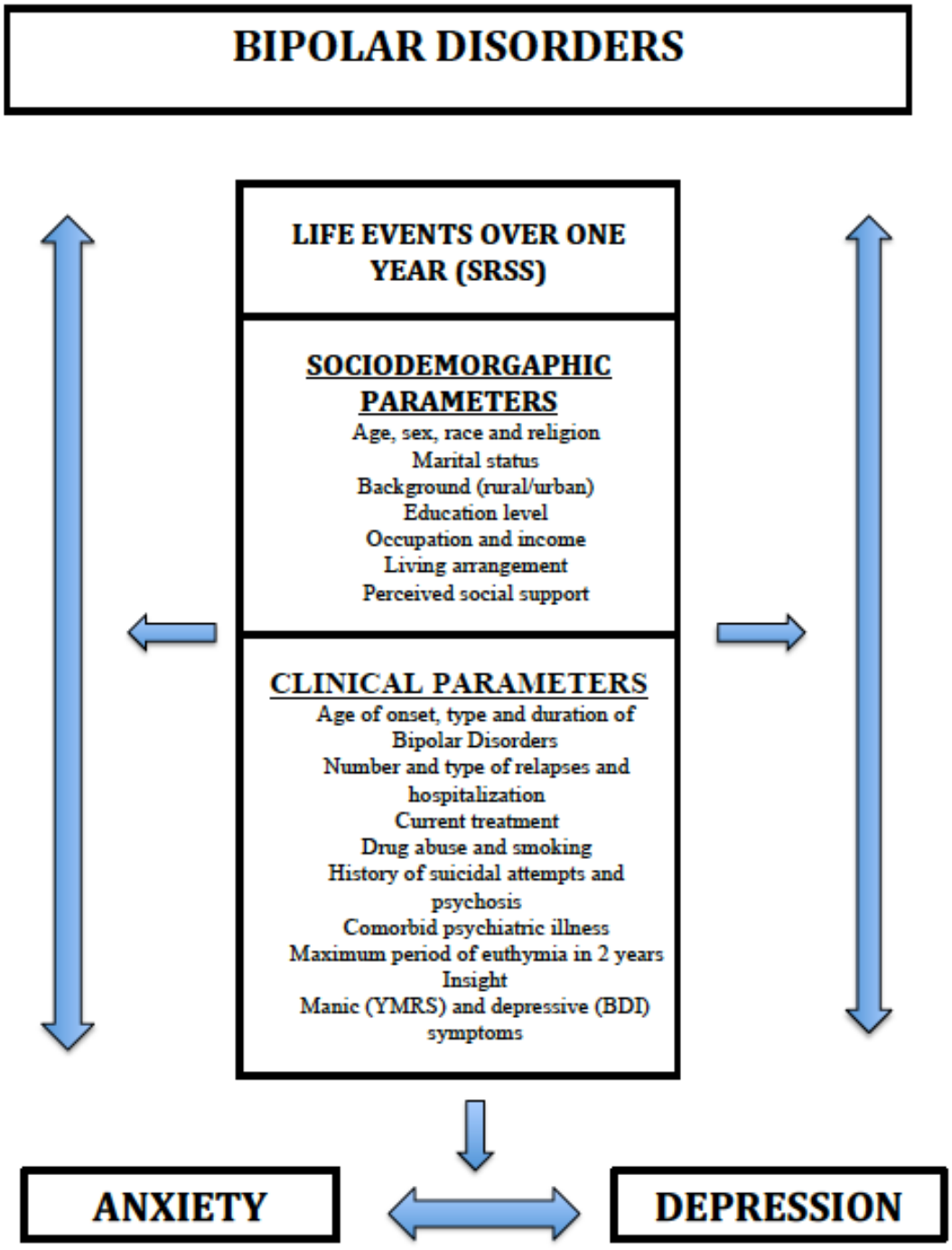

Figure 3.1 Conceptual Frameworks

CHAPTER 4: METHODOLOGY

4.1 Study Setting

This study was conducted at the Psychiatric Clinic of Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian. It is situated at Kota Bharu, the state capital of Kelantan. HUSM is one of the two government tertiary center hospitals in Kelantan.

4.2 Study Design and Study Period

This was an observational cross-sectional study conducted between March 2013 and December 2014.

4.3 Study Population and Sample

a) Reference population: Reference population was all Bipolar Disorders patients in Kelantan.
b) Source population: The source population was all Bipolar Disorders patients attending psychiatric clinic in HUSM, Kota Bharu during the study period that fulfilled the criteria for the study.
c) Study Population: Study populations were patients fulfilling the selection criteria as below.

4.4 Selection Criteria.

4.4.1 Inclusion criteria.

a) Diagnosed to have Bipolar I or Bipolar II Disorders by the treating clinicians
b) Age 18 years old and above
c) At least six months since last admission for mood disorder. This period was taken on the basis that a cycle of Bipolar Disorder relapse would usually arrive to recovery phase after six months. After this period, the likelihood for the patients to relapse reduced (Calabrese et al. 2006; Grunze et al. 2013) and the patients would most likely be in a stable clinical condition.
d) Literate and understands Malay language

4.4.2 Exclusion criteria

a) Learning disability or mental retardation
b) Severe communication problem e.g. deafness and mute
c) Unable to read and understand Malay

4.5 Determination of sample size

a) Prevalence of current Anxiety Disorder in Bipolar Disorders patients in STEP-BD samples is 30.5% (Simon et al. 2004).

Using single proportion formula: Sample size = $(1.96/\Delta)^2$ p(1-p)

Whereas,

p = prevalence from previous study

Δ = between 0.03-0.08

Sample size = 127.24

b) From Simon et al. (2004), drug abuse in bipolar patients with anxiety is 57.93%. Using PS software (Dupont & Plummer 2013), for sample size for 2 proportions, sample size calculated is 51 for each proportion.

Sample size = 51.

c) From Zutshi et al. (2006), mean age of onset of Bipolar Disorders in subjects with Anxiety Disorder is 19.83 (SD 7.9) whereas in subjects without Anxiety Disorder, mean age of onset was 23.2 (SD 6.59).

Using PS software, sample size calculated is 76.

d) From Mantere et al. (2010), BDI and BAI correlate with correlation coefficient of 0.44. Using Stata version 11 software (Gould 2013):

Estimated sample size for Pearson Correlation

Assumptions:

Alpha = 0.0500 (two-sided)

Power = 0.8000

Null Rho = 0.0000

Alt Rho = 0.4400

Estimated required sample size = 38

Based on the above calculations, sample size of this study,

N = 127 + 20%

= 153

4.6 Sampling method

Because of limited study duration, samples were chosen by convenience sampling.

4.7 Method of data collection

The study was conducted after obtaining approval from Universiti Sains Malaysia Ethical Committee.

Patients' case notes were reviewed for diagnosis of Bipolar Disorders and suitability. Suitable patients were approached and explained briefly about the study without informing them about depression and anxiety. Patients were able to refuse to participate in the study without any reason and they were informed that their quality of treatment would be the same even if they refused to participate.

Patients who agreed to participate in the study were met again after seeing the treating doctors. They were informed about the study in more detail and were assured of their anonymity and the confidentiality of the data obtained. If agreeable, inform consent was obtained and questionnaires would be administered.

While interviewing the patients, their behaviors and responses were observed and assessed using Young Mania Rating Scale (YMRS) form.

They were asked to fill in Becks Depression Inventory (BDI-Malay) and Beck Anxiety Inventory (BAI-Malay). The researcher was available to help the patients to fill in the questionnaires.

After filling in the questionnaires, they would be asked regarding subjective symptoms of mania that were not observed during the interview and their response were rated in YMRS.

Finally, the case notes were reviewed again to see whether the treating physician detected anxiety symptoms as evidenced by explicit documentation of anxiety such as complaints of worry, palpitations, inability to relax and evidence of anxiety during mental state examination such as looking tense and fidgety; and prescription of antidepressants or benzodiazepine.

All data were collected and analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 22 for Macintosh (IBM Corp. 2013).

4.8 Measures Taken to Minimize Study Errors

These are steps taken to reduce errors during the study:

a) Subject was selected using the inclusion and exclusion criteria
b) The same instruments were used for assessment of the participants
c) The participants were not being treated by the researcher
d) The subjects were not informed that this study would assess anxiety symptoms prior to them seeing the treating clinicians to avoid bias in reporting symptoms
e) The subjects are not allowed to bring the questionnaires home to avoid being influenced by other people in answering the questions

4.9 Research Tools

Four rating scales will be used in this study:

a) Beck Anxiety Inventory (BAI)
b) Beck Depression Inventory (BDI)
c) Young Mania Rating Scale (YMRS)
d) Social Readjustment Rating Scale (SRRS)

4.9.1 Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI)

BAI and BDI are self-rated scales to measure anxiety and depression respectively in clinical and research settings. Both were created by Aaron T. Beck (Beck et al. 1961; Beck et al. 1988).

BAI has 21 items and evaluates key anxiety symptoms, which are psychological and somatic symptoms of anxiety such as inability to relax, fear, shortness of breath and sweating. Malay version of BAI was validated in local context by Firdaus & Sheereen (2011) and showed excellent reliability and validity to be used in Malaysia with Cronbach alpha of 0.91 and acceptable concurrent validity ($r = 0.22$ to 0.67).

BDI also has 21 items and evaluates main symptoms of depression such as mood, pessimism and suicidal ideas. BDI-Malay was validated by Mukhtar & Oei (2008) and showed good reliability and validity with Cronbach alpha of 0.91 and good concurrent validity.

The questionnaires were used with the translators' permission. Cut-off scores for BAI and BDI are as follow:

1. **Beck Anxiety Inventory (BAI)**

   0 – 7 : minimal level of anxiety

   8 – 15 : mild anxiety

   16 – 25 : moderate anxiety

   26 – 63 : severe anxiety

2. **Beck Depression Inventory (BDI)**

   0 – 9 : minimal depression

   10 – 18 : mild depression

   19 – 29 : moderate depression

   30 – 63 : severe depression

4.9.2 Young Mania Rating Scale (YMRS)

YMRS was developed by Young et al. to measure severity of mania. This scale has eleven items and measures objective and subjective symptoms of mania (Young et al. 1978). The items include, among others, elevated mood, sexual interest and irritability. The authors reported interrater reliability of 0.93 with inter-rater coefficient for each individuals items ranging from 0.67 to 0.95.

No validation study in the context of Malaysia was found. YMRS is widely used in local and international researches done in Malaysia (Osman et al. 2009; Chan et al. 2010; Normala et al. 2010).

The scores of YMRS could be classified as euthymia, and mild to severe hypomania/mania or mixed symptoms, as below.

0-4 : euthymia

5-10 : mild hypomania/mania/mixed symptoms

11-25 : moderate hypomania/mania/mixed symptoms

26-60 : severe mania/mixed symptoms

4.9.3 Social Readjustment Rating Scale (SRRS)

As stated earlier, Rahe et al. (1964) found that life events were associated with disease onset. SRRS was created in which the samples were asked to give scoring of life events according to the most need for psychosocial adjustment and the least. The result was a list of life event and their severity scoring, which they called SRRS (Woon et al. 1971).

Lauer examined 778 English and American sample and found positive relationship between SRRS score and generalized state of anxiety (Lauer 1973). Woon et al. (1971) compared SRRS between Malaysian and American and they found similarity between their attitudes towards life events with remarkable concordance, Spearman's rho of 0.97 to 0.91. SRRS is widely used in Malaysia. For example Chan et al. (2010), Zamzam et al. (2011) and Fong et al. (2012).

4.10 Data Entry

Data entry and analyses were done using IBM Statistical Package for the Social Sciences (SPSS) version 22 for Macintosh (IBM Corp. 2013). Both univariate and multivariate analyses were performed. Independent variables that have p-value of < 0.25 in single linear regression or those judged to be clinically important would be entered in multivariate analysis (Bachok 2011).

4.11 Statistical Analysis

4.11.1 Specific Objective 3: To study the sociodemographic and clinical factors that are significantly associated with anxiety symptoms.

1. Statistical analysis: multiple linear regression (MLR)
2. Dependent variable: severity of anxiety symptoms (BAI score)
3. Independent variables: Sociodemographic and clinical variables

Sociodemographic variables:

1. Age
2. Sex
3. Race
4. Religion
5. Marital status
6. Background (rural/urban)
7. Education level
8. Occupation
9. Income
10. Living arrangement
11. Perceived social support
12. Recent life events