ABSTRAK

PENGGUNAAN UBAT PENENANG (BENZODIAZEPINES) UNTUK JANGKA MASA PANJANG DI KALANGAN PESAKIT KEMURUNGAN (DEPRESSION)

Pengenalan: Penggunaan ubat penenang untuk jangka masa panjang di kalangan pesakit kemurungan tidak digalakkan mengikut panduan yang sedia ada. Namun demikian, kadar penggunaan ubat tersebut masih tinggi pada masa kini. Untuk mencegah keadaan tersebut, adalah penting untuk kita mengetahui punca-puncanya supaya masalah ini dapat dikawal dengan berkesan.

Objective: Tujuan utama kajiaan ini adalah untuk mengkaji kadar kegunaan ubat penenang untuk jangka masa panjang di kalang pesakit yang menghidapi penyakit kemurungan serta faktor-faktor yang menyebabkan kegunaan ubat tersebut.

Kaedah: Penyelidikan ini merupakan kajian keratan rentas yang melibatkan 65 pesakit luar yang menghidapi penyakit kemurungan. Kajian ini dijalankan di hospital yang mempunyai kepakaran psikiatrik. Faktor-faktor yang menyebabkan kegunaan ubat penenang untuk jangka masa panjang dikaji.

Keputusan: Kadar kegunaan ubat penenang dalam jangka masa panjang di kalangan pesakit kemurungan adalah 70.2%. Faktor-faktor yang mempengaruhi kegunaan ubat penenang dalam jangka masa panjang adalah tahap kemurungan yang serious ($p=0.038$), tahap kerisauan yang serious ($p=0.004$), tahap kefungsian yang rendah ($p=0.047$), kekurangan sokongan social ($p=0.015$) dan kekurangan keagamaan ($p=0.010$).

Kesimpulan: Terdapatnya hubungan yang bermakna di antara jangka masa kegunaan ubat penenang dengan tahap kesedihan, tahap kerisauan, tahap kefungsian, tahap sokongan social dan tahap keagamaan. Penambahbaikan qualiti rawatan kemurungan yang sedia ada perlu dijalankan.

ABSTRACT

LONG-TERM USE OF BENZODIAZEPINE AMONG DEPRESSED PATIENTS

Introduction: Long-term benzodiazepine use in depression is not recommended by the treatment guidelines. Nevertheless, its prevalence is still remaining high. In order to prevent long-term use, it is important to know which determinant factors are associated with it. This may create awareness among the clinicians and take further measures regarding this issue.

Objective: The purpose of this study was to determine the prevalence of long-term benzodiazepines use among depressed patients in the specialty mental health setting and identify the socio-demographic, clinical and psychosocial factors that associated with the long-term use.

Methodology: This was a retrospective cross-sectional study involving 65 outpatients with major depressive disorder in specialty mental health setting. We investigate the socio-demographic, clinical and psychosocial factors which associated with long-term benzodiazepine use.

Results: The prevalence of long-term benzodiazepines use among depressed patient was 70.2%. Long-term use of benzodiazepines were significantly associated with more severe of depressive symptoms (p=0.038), more severe anxiety symptoms (p=0.004), poor functioning level (p=0.047), poor social support (p=0.015) and poor religiosity (p=0.010).

Conclusion: There was significant association between long-term use of benzodiazepines among depressed patient with severity of depressive and anxiety symptoms, level of functioning, social support and religiosity. This associations found point to possibilities to reduce long-term benzodiazepine use, for example if patient still having residual depressive and anxiety symptom, the medication and treatment plan should be further optimized.

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APA	: American Psychiatric Association
DSM	: Diagnostic and Statistic Manual
DUREL/DRI	: Duke Religious Index
GAD	: generalized anxiety disorder
HAM-D	: Hamilton Depression Rating Scale
HAM-A	: Hamilton Anxiety Rating Scale
MINI	: Mini International Neuropsychiatric Interview
MSPSS	: Multidimensional scale of perceived social support
NaSSA	: Noradrenergic and Specific Serotonergic Antidepressant
OCD	: Obsessive Compulsive Disorder
OR	: Odds ration
PTSD	: Post traumatic stress disorder
SD	: Standard deviation
SPSS	: Statistical package for social sciences
SNRI	: Serotonin Noradrenaline Reuptake Inhibitor
SSRI	: Selective Serotonin Reuptake Inhibitor
WHO	: World Health Organization

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CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 EPIDEMIOLOGY OF MAJOR DEPRESSIVE DISORDER

Depressive disorders are very common in nowadays. In the WHO World Mental Health (WMH) surveys representative community surveys in 28 countries throughout the world, the lifetime prevalence of major depressive disorder (MDD) has been estimated in the 4-10% range and 12-months prevalence estimates in the 3-6% range (Kessler et al., 2009)

Depressive illness can be happen at any age, but the average of onset age is between 30 to 40 years old. The depressive symptoms can develop either gradually over a period of times or it can be presented suddenly over a short duration. In many of the cases, the depressive symptoms always develop following a significant loss such as death of love one or episode of stress, although this is not necessary.

Community surveys frequently find that elderly people have much less clinical depression compare with younger people (Blazer & Hybels, 2005; Jorm, 2000). Several explanations have been suggested for this finding, most of it focusing on the possibility of underestimation of depression among the elderly. Others suggested explanations include age-related differentials in recall, mortality, selection out of the household population into nursing homes, willingness to participate in surveys, and willingness to admit psychiatric symptoms in the interviews (Schoevers et al., 2008; Snowdon, 1997).

Female gender was found to have higher risk of develop major depressive disorder in the community survey (Kessler et al., 2010). Elevated risk of Major Depressive Episode is related to being low income, unemployed and unmarried in the same community survey (Kessler et al., 2010). Lower education level was found to be associated with the development of major depressive disorder (Kessler et al., 2003).

Study done in Malaysia also found that those who were unmarried, without formal education, low total family income and urban residence were associated with depression (Sherina et al., 2003).

1.2 BURDEN OF MAJOR DEPRESSIVE DISORDER

A depressive episode can last up to six months or more if a depressed patient not received any treatment. In a prospective psychiatric epidemiological study, the mean time of a depressive episode to recovery was 8.4 months and about 20% of depressed patients had not recovered by 24 months (Spijker et al., 2002). A longitudinal studies result suggest that nearly 80% of individuals experiencing a major depressive episode will have at least one more episode during their lifetime and about 12% of patients who suffer from depression will have a chronic, unremitting course (Judd et al., 1997).

Due to the depressive disorders are commonly occurring in general population and its' chronic course of disease, depressive disorders has consumes a substantial amount of economic costs. In the US World Mental Health survey, for example, 6.4% of workers were found to have an episode of major depressive disorder (MDD) in the year of the survey, resulting in average of over five weeks of lost work productivity (Kessler & Akiskal et al., 2006). Given the salaries of these workers, the annualized human capital loss to employers in the US labor force associated with MDD was estimated to be in excess of $36 Billion. Besides, major depressive disorder is projected to be the second largest of the global burden of disease after heart disease at year 2020 (Murray et al., 1997).

In Malaysia, psychiatric disorders were responsible for 8.6% of the total Disability Adjusted Life Years and were ranked fourth as the leading cause of burden of disease by disease categories from 111 diseases (Malaysia Burden of Disease and

Injury Study, 2004). In the same study, unipolar major depression is the leading cause of non-fatal burden (54% is experienced among 30-59 years old). Apart from that, Malaysian Burden of Disease and Injury which done in 2000 reported that depression is the leading cause of disability among Malaysian females with about 12.7% affected compared with 7.2% in male (Malaysian Burden of Disease and Injury Study, 2000).

There are several complications arise due to major depressive disorder. The most serious and irreversible complication of major depressive disorder is suicide. The suicidal risk associated with major depressive disorder is 12 to 20 times more compare to the general population. The lifetime risk of major depressive disorder's patient for complete suicide is 10 – 15% (Guze et al., 1970).

Major depression in the elderly or in people with serious illness can leads to greater physical decline (Sherina et al., 2003). This may be due to decreased physical activity and social involvement. This condition may leads to greater risk of hospitalization (Huang et al., 2000) and inappropriate use of hospital bed (Ingold et al., 2000).

Depression is also an independent risk factor for other illnesses. It has been shown that it is associated with stroke, both in western (Jonas et al., 2000) and eastern cultures (Ohira et al., 2001). In older group of people, depression is linked with heart failure (Ariyo et al., 2000). In women over 50, being depressed is associated with a higher rate of hip fracture compare with general population (Forsen et al., 1999).

Despite the consequence of depression is severe as mentioned above, depressive illness is often under-recognized and under treated (Simon et al., 1995) (Gerber et al., 1989). It has been estimated that about 30-50% of cases of depression in primary care service are not detected (Ronalds et al., 1997).

There was a cross sectional study done among adult who attended the primary care service in Malaysia, and it reported that the prevalence of Major Depressive Disorder as 5.6% (Jammy et al., 2005).

1.3 SYMPTOMATOLOGY OF MAJOR DEPRESSIVE DISORDER

Since early Egyptian times, depression has been recognized as a distinct pathological entity. The term of "melancholia" was started to be used in Ancient Greek to describe a distinct disease with certain mental and physical symptoms (in the Ancient Greek, "*melas*" means black, and "*khole*" means bile). Melancholia was described by Hippocrates in his *Aphorisms* as "fears and despondencies, if they last a long time" as being symptomatic of the illness (Hippocrates, Aphorisms, Section 6.23). At that time melancholia was a far broader concept than today's depression; it characterized by the symptoms of sadness, dejection, and despondency, and often fear, anger, delusions and obsessions were included (Radden, 2003).

Influenced by Greek and Roman texts, physicians in the Persian and then the Muslim world developed ideas about melancholia during the Islamic Golden Age. The 11th century Persian physician Avicenna described melancholia as a depressive type of mood disorder in which the person may become suspicious and develop certain types of phobias (Haque, 2004).

In Ancient Greek, disease was thought to be due to an imbalance in the four basic bodily fluids, or known as *humors*. This humoral theory fell out of favor but was later revived in Rome by Galen. During the 18th century, the humoral theory of melancholia was increasingly challenged by mechanical and electrical explanations; references to dark and gloomy states gave way to ideas of slowed circulation and depleted energy (Jackson, 1983). German physician Johann Christian Heinroth,

however, argued melancholia was a disturbance of the soul due to moral conflict within the patient.

The term depression was derived from the Latin verb *deprimere*, "to press down". An early usage of this term to refer a psychiatric symptom was by French psychiatrist Louis Delasiauve in 1856, and by the 1860s it was appearing in medical dictionaries to refer to a physiological and metaphorical lowering of emotional function (Berrios, 1988).

Although melancholia remained the dominant diagnostic term, depression gained increasing currency in medical field and was a synonym to melancholia by the end of 19th century as psychiatrist Emil Kraepelin first to use it to refer the different kinds of melancholia as depressive state (Davison, 2006).

The influential system put forward by Kraepelin unified nearly all types of mood disorder into manic-depressive insanity. Kraepelin worked from an assumption of underlying brain pathology, but also promoted a distinction between endogenous (internally caused) and exogenous (externally caused) types (Davison, 2006).

German psychiatrist Kurt Schneider coined the term endogenous depression and reactive depression in 1920 (Schneider, 1920), the latter referring to reactivity in mood and not reaction to outside event, and therefore frequently misinterpreted. This division was challenged in 1926 by Edward Mapother who found no clear distinction between both types (Mapother, 1926).

The DSM-I (1952) contained depressive reaction and the DSM-II (1968) defined depressive neurosis as an excessive reaction to internal conflict or an identifiable event, and also included a depressive type of manic-depressive psychosis within Major affective disorders. At 1970s, diagnosed depression was either endogenous (melancholic) which considered a biological condition, or reactive (neurotic) which was a reaction to stressful events (Parker, 2000).

Debate has persisted for most of the 20th century over whether a unitary or binary model of depression in truer reflection of the syndrome (Parker, 2000); in the former, there is a continuum of the depression ranked only by severity, whereas the latter conceptualizes a distinction between biological (endogenous) and reactive depressive syndromes (exogenous). The publishing of DSM-III saw the unitary model gain a more universal acceptance (Parker, 2000).

Nowadays, DSM-IV-TR's criteria stated a major depressive episode must last at least for two weeks and without a history of manic, mixed or hypomanic episode prior to it. A major depressive episode was defined as experiencing at least four symptoms from a list that includes changes in appetite and weight, changes in sleep and activity, lack of energy, feelings of guilt, problems thinking and making decisions, and recurring thoughts of death or suicide (APA, 1994). Currently, the term "melancholia" indicates a major depressive disorder with changes in endogenous or vegetative function such as disturbance of sleep, appetite, and libido.

1.4 TREATMENT OF DEPRESSION

1.4.1 Pharmacological Treatment

Acute Phase Treatment

Antidepressants are effective in acute treatment of major depression. The greatest effects relative to placebo group are seen in patients' with major depression of at least moderate severity. In this group of patients, the short-term response rates are about 60% compare 30% for placebo group (number needed to treat [NNT] = 4-5) (Anderson et al.,2003). A meta-analysis done by de Lima et al. (1999) showed similar clinical response rate in dysthymia. In this study, the response rate in treatment group was 55% compare with 30% in placebo group (NNT = 4).

The value of antidepressant drugs in milder depression disorders such as minor depression and mixed anxiety-depression is not established. American Psychiatric Association (APA) gives antidepressant as an option rather than a mandatory measure in the initial primary treatment of mild major depressive disorder (APA, 2000).

NICE (2004) found that antidepressant are efficacious for reducing depressive symptoms in moderate to severe major depressive disorder. In the same study, it was found that the effectiveness among SSRIs, TCAs and MAOIs in both inpatients and psychiatric outpatients or primary care patients were similar. However, SSRIs are better tolerated compared to other antidepressant and therefore, make it appropriate as the drugs of first choice.

In a systematic review done by Hansen et al (2005) showed that the newer antidepressants such as mirtazapine, venlafaxine, escitalopram are generally did not differ substantially from each other in the efficacy.

If a patient does not show any response after 4 weeks of antidepressant treatment at adequate dosage, the likelihood of a later response on the same medication is low therefore switching of antidepressant was considered in this group of patient. If there is partial response by 4-6 weeks, there is a likelihood of further response after several more weeks of treatment (Bauer et al., 2002).

Continuation Phase Treatment

It is now well established that stopping antidepressants soon after treatment response is associated with a high risk of relapse. About one third of the patients withdrawn from medication having relapse over the next year with the majority of the relapses occurring in the first 6 months. Placebo-controlled studies of the role of continuation therapy have reached the following conclusions (Anderson et al., 2000):

- Continuing antidepressant treatment for 6-9 months after remission of the depressive episode
- Treatment should be at the originally effective dose of medication if possible
- In patients at low risk of further episodes, continuation of antidepressant treatment longer than 9 months confers little extra benefit except in the elderly where 12 months continuation therapy is more appropriate

Maintenance Phase Treatment

Controlled studies involving patients with recurrent depression (usually defined as at least three episodes over the last 5 years) have shown that maintenance antidepressant treatment can substantially reduce relapse rate. The effects of long-term maintenance treatment were confirmed in a systematic review (Geddes et al., 2003) where over one to two years of continued antidepressant treatment the relapse rate was lowered from 41% on placebo to 18% on active medication.

There is some variation in the literature regarding the duration of maintenance medication. Factors to be considered include the patient's absolute risk for recurrence (number and severity of previous episodes, the presence of residual depressive symptoms, ongoing psychosocial stressors) and patient preference. NICE (2004) considers that for patients who have had multiple recurrences, it is worthwhile to continue antidepressant medication for up to 2 years, but others have recommended maintenance treatment for up to 5 years, with possibility of life-long treatment (Anderson et al., 2000).

1.4.2 Psychological Treatment

There is some evidence that cognitive therapy given during an acute phase of depression leads to a more sustained improvement in depressive symptomatology and lessens the risk of subsequent relapse (Hollon et al., 2005). There is also growing interest in the use of continuation and maintenance treatment with cognitive therapy, particularly in patients who have residual depressive symptomatology and are thereby at increased risk of relapse. For example, Paykel et al. (1999) studied 158 patients who experienced significant residual symptoms after treatment of an episode of major depression. All patients received clinical management and continuation treatment with antidepressant medication and half also received 16 sessions of cognitive therapy. Over the next 16 months, the relapse rate in the patients receiving cognitive therapy was 29% compared with 47% in the group who received clinical management only.

1.5 ANXIETY IN MAJOR DEPRESSIVE DISORDER

Major Depressive Disorders are often accompanied by significant anxiety symptoms or full anxiety disorders. Therefore, anxiety symptoms are a common feature of major depressive episodes even in the absence of a discretely diagnosed anxiety disorder. When anxiety and depressive symptoms overlap and produce distress and impairment but fail to meet full diagnostic criteria for either class of disorder, the term "mixed anxiety-depressive states" has been proposed and incorporated into the ICD-10 (Boulenger et al., 1993). The present of anxiety symptoms may predict a poorer long-term outcome and a greater familial prevalence of MDD (Clayton et al., 1991, Coryell et al., 1992).

1.5.1 Prevalence of Co-morbid of Major Depressive Disorder and Anxiety Disorder in general population and Specialty Mental Health setting

In the general population, the frequency of develop co-morbid anxiety and mood disorders was 3.6% throughout their lifetime. For individuals in the community with mood disorders, 43% of them will develop a co-morbid anxiety disorder during their lifetime (Regier et al., 1990). In another community survey which involves general population, 64.2% of individuals in the community who was diagnosed to have mood disorder are associated with co-morbid anxiety disorder. These comorbid anxiety disorders included Panic disorder (14.6%), Generalized Anxiety Disorder (24.5%), Agoraphobia without panic (3.4%), Specific phobia (28.2%), Social phobia (27.9%) and Post-traumatic stress disorder (17.0%) (Kessler et al., 2010).

In a cross-sectional study was done in a Specialty Mental Health setting with the sample population of adult outpatient with major depression, the result showed that the present of co-morbid anxiety disorder among these patients was 50.6% and it include social phobia (27.0%), simple phobia (16.9%), panic disorder (14.5%), generalized anxiety disorder (10.6%), obsessive-compulsive disorder (6.3%), and agoraphobia (5.5%) (Maurizio et al., 2000).

1.5.2 The Relation between anxiety, MDD and substance use

A large scale of epidemiological study was done in US on the psychiatric disorder comorbidity revealed that half of the individuals who met criteria for any psychiatric disorder have met criteria for more than one disorder, and about 30% of them have more than two conditions (Kessler et al, 1994). Among these psychiatric diagnoses, affective disorders have been found to co-occur with other psychiatric conditions, especially with anxiety disorder and substance use disorder (Marks & Lader, 1973; Boyd et al., 1984; Maser & Cloninger, 1990). Affective disorders have

also been consistently associated with both alcoholism and drug misuse in clinical samples and in community surveys (Helzer & Pryzbeck, 1988; Ross et al., 1988; Merikangas & Gelernter, 1990; Reiger et al., 1990). The large epidemiological study to investigate comorbidity of substance misuse and psychiatric disorder reported that nearly a third of people with an affective disorder also report a history of some form of substance misuse (Reiger et al, 1990).

	Basel n=470	US: ECA n=12,688	Munich n=483	Puerto Rico n=1551	Zurich n=591
All anxiety disorder	3.0 (1.8-5.0)	6.7 (5.5-7.4)	5.5 (3.7-8.2)	14.9 (8.2-27.1)	2.7 (1.8-4.1)
GAD	7.4 (1.8-27.1)	-	-	-	4.1 (0.6-2.3)
Panic disorder	13.5 (4.5-40.4)	12.2 (9.0-14.9)	9.0 (4.5-18.2)	30.0 (13.5-81.5)	2.7 (1.3-5.0)
Agoraphobia	1.3 (0.6-3.3)	4.5 (4.1-5.5)	5.0 (3.0-8.2)	12.2 (7.4-20.0)	2.7 (1.5-5.0)
Simple Phobia	3.7 (1.3-9.0)	2.7 (2.5-3.3)	5.5 (3.3-9.0)	9.0 (5.0-16.4)	1.8 (1.1-3.3)
Social phobia	2.2 (1.3-4.0)	5.0 (4.1-6.7)	6.7 (3.3-13.5)	18.2 (6.7-44.7)	2.7 (1.3-6.0)
Alcohol misuse/ dependence	-	2.0 (1.6-2.5)	1.1 (0.6-1.8)	2.0 (1.0-3.7)	2.0 (0.8-5.5)
Drug misuse/ dependence	-	4.1 (3.3-5.0)	5.6 (2.5-12.2)	-	2.2 (1.3-3.7)
* Table above was adapted from "Comorbidity and Boundaries of Affective Disorders with Anxiety Disorders and Substance Misuse: Results of an International Task Force, 1996" by Merikangas et al.					

The above table presented the odds ratios (with 95% confidence intervals) measuring the associations of major depression with anxiety disorders and substance misuse across the study site. We noted that anxiety disorders were strongly associated

with major depression across all sites, with range of 2.7-14.9. Besides, the table also showed that substance misuse or dependence was also associated with major depression, but the magnitude was generally lower and findings were less consistent than those regarding anxiety disorder.

1.6 SOCIAL SUPPORT AND DEPRESSION

Social support is considered as one of the social determinants of health in the community (Wilkinson & Marmot 2003). The studies showed that people who get less social support from others are more likely to experience a poorer quality of life (Antonucci & Akiyama 1987, House et al., 1988). This result was found similar in the depressed patient group (George et al., 1989, Prince et al., 1997). Many people have tried to define and measure the social support in various ways. Most of the definitions were arising from Cobb (1976): "Social support is defined as information leading the subject to believe that he is cared for and loved, esteemed and a member of a network of mutual obligations".

The consequences of depression can be disabling and worsen until causing death. A several numbers of risk factors for depression have been studied and one of it was social support. The relationship between social support and depression has been studied well since mid-1970s (Broadhead et al., 1983).

The social support is a multidimensional construct such as instrumental support, emotional support, social network, quality of social support and reciprocal helping of other (Sarason et al., 1983). One of the scales designed to assess the social support was MSPSS. The MSPSS is a self-administered measure of social support and it assesses the adequacy of social support subjectively.

1.7 RELIGION AND DEPRESSION

Psychiatry continues to debate the appropriate of including religion issues into the clinical practice. These debates continue as there is increasing consensus among researchers and clinicians that religion is associated with improved mental and physical health (Kendler et al., 2003; Plante & Sherman, 2001; Powell, Shahabi, & Thoresen, 2003). Recently, a proposal for World Psychiatric Association consensus statement to include spirituality and religion in psychiatry practice was not passed due to controversy in two areas: First, the definition of religion and spirituality, and Second, the relationship between religion and spirituality (Verhagen et al., 2010).

Although the proposal has not been passed, but the authors did make this topic highlighted internationally and further encourage the topic to be discussed among the psychiatric field. This has created the awareness among the clinician and researchers the important of considering the spirituality and religion in the daily practice. The conflict in including the spiritual and religion into the daily practice was showed in a survey recently done in Quebec and Geneva, where over 90% of the psychiatrists felt comfortable discussing spirituality, but they still underestimated the importance of religion in the lives of their patients. The psychiatrist frequently did not know about the conflict between religion and psychiatric care, and this may subsequently affect the treatment adherence or therapeutic alliance (Borras et al., 2010). Study has showed that about one-fourth of patients with delusions of religious content were experienced conflict between belief and treatment, and in this population were actually less likely to adhere to the psychiatric treatment (Mohr et al., 2010).

Regarding the first controversy about the definitions of religion and spirituality brought up by World Psychiatric Association, Koenig offered some useful definitions after consulting with 60 experts and other written material. According to Koenig, religion can be defined as ‘an organized system of beliefs, practices, rituals, and

symbols' that facilitate closeness to the transcendent or a community. Spirituality refers to 'the personal quest for understanding answers to ultimate questions about life, about meaning, and about relationships to be sacred or transcendent' (Koenig et al., 2001). However, there is still lack of international consensus regarding the relationship between religion and spirituality.

In view of the impact of the religiosity to the psychiatry practice therefore we include religiosity as one of the assessment in order to determinant its effect on the duration of benzodiazepine use. We also examined the association between the religiosity and the severity of depressive and anxiety symptoms. The level of religiosity in our study sample was measure by using the Duke University Religion Index (DUREL)'s. It is a five-item scale assesses the three major dimensions of religious involvement which include organizational, non-organizational, and intrinsic religiosity.

1.8 PREVALENCE OF BENZODIAZEPINES USAGE

Benzodiazepines were first marketed in 1961 with the licensing of chlordiazepoxide, which was developed by Hoffmann La Roche. Several decades after their introduction to the market, benzodiazepines are still among the most widely prescribed drugs in the world (IMS America, 1998) and represent highly effective treatments for anxiety, panic disorder, bipolar illness, and sleep and seizure disorders (Shader et al., 1993, Woods et al., 1995, Ballenger et al., 1991, APA, 1994).

From the latest Netherlands Study of Depression and Anxiety (Leonie et al., 2011), an 8-year longitudinal cohort study, there were 2852 respondents involved which representative of individuals with depressive and/or anxiety disorders in the community, general practice and specialized mental health care institutions throughout the Netherlands. Of the 2852 subjects, 429 (15.0%) had used a benzodiazepine in the

past month. Among patient with major depression alone, 17.0% of them were benzodiazepines users. 18.1% of patient with anxiety disorder alone had used a benzodiazepine in the past month. Among patient with comorbid major depressive disorder and anxiety disorder, 27.3% of them use the benzodiazepines for the past month (Leonie et al., 2011).

Among the 429 benzodiazepines users, majority (84.8%) of them took benzodiazepines for a much longer period then recommend by international guidelines (NICE Clinical Guidelines, 2011). From the same study, benzodiazepines use was significant associated with older age, singleness, unemployment, treatment in secondary care, more severe anxiety and/or depressive symptoms, comorbid insomnia and antidepressant use (Leonie et al., 2011).

A cross-sectional study was carried out in family practices among users of benzodiazepines with regard to DSM-IV diagnosis. Long-term use of benzodiazepines was the dependent variable in the study. The study recruited 164 shor-term (< 90 days) and 158 long-term (>180 days) benzodiazepines users. From the study, long-term use of benzodiazepines was significantly associated with lower level of education, older age and loneliness. No statistically significant differences were found for the other independent variables such as gender and income (Zandstra et al., 2004).

A retrospective, population-based cross-sectional prescription survey with 520,000 patients was done in Swiss adult population. Participants were aged 15 years or older, and have a complete pharmacy record. This study showed that 45,309 out of 520,000 patients (9.1%) received at least one benzodiazepine prescription within a 6-month period. Most patients with benzodiazepine prescriptions were women (67.9% women versus 32.1% men), and half of the patients were aged 65 or older (50.7%) (Sylvie et al., 2007).

1.9 MECHANISM OF ACTION OF BENZODIAZEPINES

The clinical-pharmacologic effects of benzodiazepines can be explained by an increase of gamma-aminobutyric acid (GABA) inhibitory impulses in the central nervous system mediated via benzodiazepines receptors. Benzodiazepines act as allosteric modulators of the $GABA_A$ receptor. There are various subtypes of $GABA_A$ receptor and it was distributed in a different area in the brain (Haefely et al., 1990). In an experiment, benzodiazepine was significantly showed that it reduces the concentration of cortisol in the blood and also reduces the concentration of stress-induced catecholamine (File et al., 1987).

1.10 BASIC PHARMACOLOGY OF BENZODIAZEPINES

All benzodiazepines have 5 major actions, these include hypnotic, anxiolytic, anticonvulsant, muscular relaxant and amnesic. However, they exert these actions in slightly varying degree. There are large differences in potency among the benzodiazepines, possibly due to differences in affinity for various benzodiazepine-receptor subtypes. Thus, some benzodiazepines are more effective than others as anticonvulsant and some may differ in the ratio between anxiolytic and hypnotic actions.

Despite potency, the rate of penetration into the brain also differs significantly among the benzodiazepine. Polar benzodiazepines such as lorazepam and temazepam, which attached with a hydroxyl groups causing it enter the brain slower than the less polar benzodiazepines such as diazepam and alprazolam. Therefore polar benzodiazepines are less suitable to use as a hypnotic, but at the same time polar benzodiazepines has a lower abuse potential in view of their slower time of onset.

Apart from potency and rate of penetration into the brain, benzodiazepines also differ significantly in their elimination rate from the body (elimination half-lives vary

from 2 to 100 hours) and some of the benzodiazepines have pharmacological active metabolites which causing them to have longer elimination half-lives. Potent benzodiazepines with relatively short elimination half-lives (triazolam, alprazolam, lorazepam) have the highest risk of developing problems with dependence (Marriott et al., 1993). With respect to the elimination half-life, benzodiazepines can be divided into the short-acting benzodiazepines and long-acting benzodiazepines. The long-acting benzodiazepines have half-life values usually exceeding 24 hours (D.J. Greenblatt et al., 1981).

Clinical effects such as time of onset, duration of effect, and adverse effect of benzodiazepines are corresponding to the pharmacokinetic parameters of the drugs which include absorption, metabolism, and elimination half-life (Feely et al., 1990). Table below showed the pharmacologic properties and the relevant clinical anxiolytic effects, together with corresponding adverse effects that may occur (Laux et al., 1995):

Pharmacologic Properties	**Therapeutic Use**	**Adverse Experience**
Anticonvulsive	- Cerebral seizures - Epilepsy	
Centrally muscle-relaxing	- Central spasticity - Muscle tension - Tetanus	- Muscle asthenis, ataxia - Disturbance of gait - Respiratory depression
Sedative / hypnotic	- Sleep disturbances - Premedication in anesthesiology	- Diurnal sedation - Reduced attentiveness
Amnestic	- Various applications in anesthesiology	- Amnesia (anterograde) e.g. when used as a hypnotic
Anxiolytic, subduring excitement and aggression	- Tense, excited, and anxious states of various origins - Stress shielding	- Indifference - Retreat from reality - Flattening of affect
* All effects and side effects described here are caused by actions on central benzodiazepine receptors and can therefore be terminated with a benzodiazepine receptor antagonist (e.g. flumazenil). (Laux G. Aktueller stand der Berhandlung mit Benzodiazepinen. Nervenarzt 1995, 66: 311-22, Springer-Veriag).		

1.11 THE 'Z' DRUG AS NEWER BENZODIAZEPINES RECEPTOR AGONIST

The term Z-drugs refers to the three most recently developed hypnotic drugs, zolpidem, zopoclone and zaleplon. They have developed from a 20-year research effort to optimize both the pharmacokinetic and pharmacodynamic properties of hypnotic drug acting at the benzodiazepine receptor. The target of the development is to create a hypnotic drug that has a fast onset of hypnotic action, with a rapid clearance overnight in order to minimize and hopefully eliminate residual daytime sedation (hangover). This target has been achieved as the Z-drugs all have an elimination half-life of less than 6 hours, which is significantly shorter than any other currently available benzodiazepine hypnotic. Zaleplon has a very short elimination half-life, which make the Zaleplon can even be used to treat middle-of-the-night insomnia with little risk of develop daytime hangover.

Beside the pharmacokinetic properties, the Z drugs also have advantages in terms of their pharmacodynamic properties. In the aspect of receptor, both zolpidem and zaleplon were designed to be relatively selective for the subtype of the benzodiazepine receptor that was preferentially expressed in the cortex (originally called the benzodiazepine-1 receptor). It was predicted that this subtype would immediate the hypnotic action of the benzodiazepines (Rudolph and Mohler, 2004). "Z" drugs also have a better safety profile compare with less selective benzodiazepine receptor agonist such as clomethiazple and choral hydrate, (Nutt et al., 2005). However, both Z drugs and benzodiazepine group have equal efficacy in hypnotic effect. (Dundar et al., 2004)

Over the past few years, there was a gradual rising of Z drugs usage associated with reduction in prescribing of older benzodiazepine hypnotic (Dundar et al., 2004). This has been due to the fears over benzodiazepine use and abuse which causing the increase in prescribing of Z drugs (Holbrook et al., 2004). Nevertheless, withdrawal

reactions with rebound insomnia are still seen in some patients even with these newer hypnotic agents.

1.12 BENZODIAZEPINES IN TREATMENT OF INSOMNIA

Insomnia is extremely common in general population, especially in the elderly and in women. In the United Kingdom, nearly 40% of the elderly complain of sleeping difficultly in their daily life (Crook et al., 1987). Approximately 40% of all benzodiazepines hypnotic prescribed by family physicians were consumed by British women older than 65 years old (Taylor et al., 1987). In the adult population, 15% of them suffer from severe insomnia mainly happen in women, the elderly, and in persons with psychic distress, psychiatric disorder, or a history of drug and alcohol abuse (Gillin et al., 1991).

Benzodiazepines are probably the best hypnotic drugs available currently, but it is important to remember that the sleep induced by benzodiazepines differs from the natural sleep (Ashton, 1994). Generally, the benzodiazepine hasten sleep onset, decrease nocturnal awakenings, increase total sleeping time and often impart a sense of sleep, refreshing sleep. However, they alter the normal sleep pattern: Stage 2 (light sleep) is prolonged and mainly accounts for the increased sleeping time, while the duration of slow wave sleep (SWS) and rapid eye movement sleep (REMS) may be considerably reduced. The onset of the first REMS episode is delayed and dreaming is diminished. These effects of benzodiazepines have been well studied (Hartman et al., 1976, Kay et al., 1976, Wheatley et al., 1981).

The major disadvantages of benzodiazepines as hypnotic drugs were the rapid development of tolerance to their hypnotic effect and the occurrences of rebound insomnia which commonly happen on withdrawal of the drug. Benzodiazepines are initially very efficacious in inducing and prolonging sleep. However, tolerance to the

hypnotic effects develops rapidly, sometimes after only a few days of regular use (Petursson et al., 1984, Kales et al., 1978). Nevertheless, certain group of people may report continued efficacy without escalation of the benzodiazepine dosage and in these group of patients, the drugs are often used long term, possibly because of difficulties in withdrawal (Oswarld et al., 1982).

The other disadvantage of benzodiazepines as hypnotic agent was causing CNS depression. Due to the elderly have slower metabolism of benzodiazepines (which are oxidized by the liver) compared with younger persons, they are more susceptible to CNS depression. To minimize the adverse effect of benzodiazepine used as hypnotic agent, the UK Committee on Safety of Medicine recommended (Committee on Safety of Medicine, 1988) that benzodiazepines are prescribed for insomnia only when it is severe or disabling or it subjects the patient to extreme stress.

1.13 BENZODIAZEPINES IN TREATMENT OF ANXIETY

Benzodiazepines are potent anxiolytic drugs that are efficacious to the anxious patient and patient who undergoing psychological stress. The main advantage of benzodiazepines as an anxiolytic agent is the fast onset of action. This feature is contrast with the delayed anxiolytic effects of antidepressant and psychotherapy. Furthermore, benzodiazepines are relatively non-toxic and safer than most of the alternative drugs. Both the immediate efficacy and safety profile had made benzodiazepines the drugs of choice for rapid relief of anxiety that is unacceptably distressing.

Although benzodiazepines provide rapid symptomatic treatment for anxiety, but they do not cure the underlying disorder. The National Institute for Health and Clinical Excellence (NICE, 2011) guideline on the management of anxiety (panic disorder and generalized anxiety disorder) actually recommend selective serotonin reuptake

inhibitors (SSRIs) as the best choice for the treatment of these anxiety disorder, alongside cognitive-behavioral therapy (CBT) and self-help based on CBT principles.

According to NICE guidelines, benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder and, for GAD, they should not usually be used beyond 2-4 weeks.

Anxiolytic effects are exerted in doses that cause minimal sedation, although the hypnotic, muscular relaxant and perhaps amnesic actions may all contribute to relief of associated tensions and insomnia. The relatively selective effect on anxiety is probably related to the fact that benzodiazepines suppress activity in many limbic and other brain areas involved in anxiogenesis, including the septal area, amygdale, hippocampus, hypothalamus, locus coeruleus and raphe nuclei. They also decrease the turnover of acetylcholine, norepinephrine (noradrenaline), serotonin and dopamine in these areas (Haefley et al., 1981). Suppression of noradrenergic and/or serotonergic pathways appears to be of particular importance in relation to anxiolytic effects.

Tolerance to the anxiolytic effects of benzodiazepines is develops more slowly compare with the tolerance to the hypnotic effects (Rickels et al., 1985). The limitations of benzodiazepines as anxiolytic agents include long-term users of standard therapeutic doses show cognitive deficits (Lader et al., 1987), long-term use of benzodiazepines may cause or aggravate depression (Lader et al., 1981). Chronic user may carries a risk of become dependence (Marriott et al., 1993, Murphy et al., 1988, Tyrer et al., 1989).

1.14 OTHER USED OF BENZODIAZEPINES

Despite being hypnotic and anxiolytic agents, benzodiazepines such as diazepam are the drug of choice for the treatment of status epilepticus and for the control of seizures resulting from drug overdose. Clonazepam and clobazam (a 1,5-

benzodiazepine) are available in several countries as oral anticonvulsant agents. Limitations on the long-term use of these benzodiazepines for seizure control include the development of tolerance in many patients, sedation, and psychomotor impairment (Brodie et al., 1990, Trimble et al., 1990, Feely et al., 1989). Benzodiazepines such as midazolam are used in anesthesia due to their sedative and amnestic properties.

1.15 ROLE OF BENZODIAZEPINES IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

Antidepressant medications are the recommended pharmacological treatment for depression, and many antidepressant are effective for both the core symptoms of depression and for coexisting anxiety (Berk et al., 2000 ; Doraiswamy et al., 2001). However, antidepressants' beneficial effect often does not occur for several weeks, and physicians may prescribe benzodiazepines for more immediate relief.

According to Malaysia depression treatment guidelines, after weighing the potential risks and benefits, clinicians may consider prescribing benzodiazepines as an adjunct to antidepressant but avoid giving them for more than 2-4 weeks (Malaysia Psychiatry Association, 2007). However, not all the patient was tapered off the benzodiazepines once the antidepressant started to show the effect. And some of the patients may put on a duration longer than which is recommended by the guideline.

1.16 PREVALENCE OF BENZODIAZEPINE USE AMONG DEPRESSED PATIENT IN PRIMARY CARE SETTING AND SPECIALTY MENTAL HEALTH SETTING

A nationally representative survey of United State was done from 1987 to 2001 based on the data from National Disease and Therapeutic Index (NDTI). The study sample consists of patients treated by primary care office-based physicians in the

United State. In 1987, there was approximately 14.4 million primary care physician visited by patients with depression. This number has increased to 24.5 million in year 2001. 21% of the depression patient in 1987 was prescribed with benzodiazepine in their pharmacological treatment of depression and the number reduce steadily to 10% in 1994 and 7.5% in 2001 (Randall et al., 2001).

A latest study consist of 43,915 patients who diagnosed with depression was done in year 2007 in United State. The study was based on Veterans Health Administration data in United State. Results of the study showed that of the 43,915 Veterans Health Administration patients diagnosed with depression and started on an antidepressant, about 7.6% patients received a benzodiazepine on the same day as their initial antidepressant prescription (Paul et al., 2011). In the same study, 2.2% of the total study population received benzodiazepine prescription for 180 days or more (Paul et al., 2011).

A Veterans Affairs (VA) National Registry for Depression was used to identify patients treated for depression in specialty mental health settings in 129 VA facilities during the first 3 months of fiscal year 2001 in United State (N = 128,029). A total of 46,244 (36%) of the depressed patients received a benzodiazepines prescription during the year. The study also showed that almost all patients who received a benzodiazepines prescription were also taking antidepressant. Among the 46,244 benzodiazepine's users, 78% of them received more than 90 days' supply of benzodiazepines, and 61% received more than 180 days' supply (Marcia et al., 2004).

CHAPTER 2: RATIONALE AND OBJECTIVES

2.1 RATIONALE OF STUDY

Meta-analyses of randomized controlled trials have showed that coprescribing a benzodiazepine with an antidepressant reduces the likelihood of treatment dropout as the result of greater improvement in depression symptoms during the first 4 weeks (Furukawa et al., 2001).

However, benzodiazepine treatment carries risks of abuse, dependence, and withdrawal symptoms upon discontinuation, especially in long-term use (Ashton, 2005). Benzodiazepines also increase the risk of cognitive impairment, falls, and hip fractures in the elderly, although the impact of benzodiazepine use on these outcomes may be no worse than for many other psychotropic medications (Hanlon et al., 1998; Leipzig et al., 1999; Takkouche et al., 2007; Brooks et al., 2007). The above complications of benzodiazepines when used in conjunction with antidepressant to treat depression are not well established and therefore are important for clinicians to weigh the potential risks of this combination therapy.

Another controversial and relatively unstudied issue is the relationship between long-term therapeutic use of benzodiazepines and abuse. Although guidelines rarely recommended use of benzodiazepines for more than four months, long-term use may be warranted in some situations. For example, long-term use of benzodiazepines may improve outcomes among patient with comorbid anxiety disorder.

Therefore it is important for us to identify the prevalence of long-term benzodiazepines usage among depressed patients, and further determine the factors associated with it. This may create awareness among the clinicians and take further measures regarding this issue.

2.2 GENERAL OBJECTIVE

To study the prevalence of long-term benzodiazepines usage among depressed patients in Hospital Bahagia Ulu Kinta, and further determine the factors associated with it.

2.3 SPECIFIC OBJECTIVE

1. To determine the benzodiazepines prescribing rate among depressed patients
2. To determine the prevalence of long-term use of benzodiazepines among depressed patients
3. To determine the socio-demographic, clinical and psychosocial factors which associated with long-term use of benzodiazepines (>180 days) among depressed patients
4. To determine whether long-term benzodiazepine use is associated with dose escalation

2.4 RESEARCH HYPOTHESIS

1. There is a high prevalence of benzodiazepines prescribing rate among depressed patients in Hospital Bahagia Ulu Kinta compared with similar study at oversea.
2. Patients who on long-term benzodiazepine use will be elderly, low education level, low social economic status and single or divorve
3. Patients who on long-term benzodiazepines use are associated with poor functioning level, poor social support and lower level of religiosity

CHAPTER 3: METHODOLOGY

3.1 STUDY SETTING

This is a cross sectional study and it was conducted in the psychiatric outpatient clinic Hospital Bahagia Ulu Kinta (HBUK). HBUK is one of the largest mental hospitals which provide its service since 1911. Services included inpatient and outpatient services, community psychiatry and forensic psychiatry. Besides providing care for patients, Hospital Bahagia Ulu Kinta also functions as a training centre for candidates of Masters Programme in psychiatry and also functions as a research centre.

Psychiatric outpatient clinic Hospital Bahagia Ulu Kinta is a psychiatric specialty referral center. It receives referral from Klinik Kesihatan and District hospital in Perak state which does not have psychiatrist. Besides receiving referral, psychiatric outpatient clinic HBUK also provide walk-in service for all new cases, patient who needs services will be seen by walk-in doctor regardless of the patient place of origin.

After a new case has been seen in the walk-in clinic, patient will be allocated to follow-up clinic. Besides walk-in clinic, the follow-up clinic also provides services to the patient discharge from HBUK inpatient wards.

3.2 STUDY DESIGN

This is a cross sectional study looking at the prevalence of benzodiazepines use among depressed patients attending outpatient service in Hospital Bahagia Ulu Kinta from November 2011 to January 2012. This study also aim to study the associated socio-demographic and clinical factors, and it also examine the determinant of long-term benzodiazepine use (>180 days) among depressed patients.

3.3 SAMPLE SIZE AND CALCULATION

The sample size is calculated with the following formula (Naing, 2006)

$$n = \frac{Z^2 P(1-P)}{d^2}$$

n = sample size

Z = 1.96 (level of confidence: 95%)

P = Expected prevalence of benzodiazepine use among depressed patients in specialty mental health setting: 36% (Marcia et al., 2004)

d = Precision (0.12)

$$n = \frac{1.96 \times 1.96 \times 0.36 \times 0.64}{0.12 \times 0.12}$$

= 61

The sample size required through calculation is 61.

3.4 STUDY POPULATION

Subjects were recruited from patients who were attending follow-up clinic at outpatient department Hospital Bahagia Ulu Kinta between November 2011 and January 2012. Written informed consent was obtained from each subject before proceeding to the study (Appendix 1, 2). Explanation regarding the study will be given to all patients prior to consent.

Recruitment was done at pharmacy department HBUK. After patients finish clinic session with treating doctor, patient will approach the pharmacy department for their medication, patient with clinical diagnosis of major depressive disorder stated in their prescription slip would be invited for the study. For those who agree to participate in the study, they would be administered with Mini International

Neuropsychiatric Interview (M.I.N.I) (Appendix 4) to confirm the diagnosis. Patients were screened for inclusion and exclusion criteria.

Demographic data and clinical data were obtained in the interview using questionnaire (Appendix 3). Demographic data on age, gender, ethnicity, level of education, employment status and marital status were obtained. Clinical data on age of onset, duration of illness, the current medication and co-morbid physical illness was obtained. For those who were prescribed benzodiazepines during their treatment of major depressive episode, they are further selected for clinical assessment below:

- Hamilton Depression Rating Scale (HAM-D) (Appendix 5) was administered to access the severity of depression
- Hamilton Anxiety Rating Scale (HAM-A) (Appendix 6) was administered to access the severity of anxiety
- Global Assessment of Functioning (GAF) (Appendix 7) was administered to assess the level of functioning
- Multidimensional Scale of Perceived Social Support (Appendix 8) was administered to assess the level of social support
- Duke Religious Index (Appendix 9) was administered to rate the level of religiosity

3.5 INCLUSION CRITERIA

1. Patients diagnosed with major depressive disorder using Mini International Neuropsychiatric Interview (M.I.N.I)
2. Patients who are treated with antidepressant for at least 6 months or more
3. Patients aged 18 years old and above in the period of study
4. Patients who are able to understand, communicate and able to give consent

3.6 EXCLUSION CRITERIA

1. Patients who were unable to give consent
2. Patients who were too depress to be interviewed or unable to cooperate

3.7 STUDY INSTRUMENTS

3.7.1 SOCIO-DEMOGRAPHIC CLINICAL DATA SHEET (APPENDIX 3)

The identification data sheet was used to document demographic data and clinical variables of the patients. Demographic variables collected included age, gender, ethnic group, marital status and employment status. Clinical variables included duration of illness, age of presentation, current medication and co-morbid physical illness.

3.7.2 MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW V6.0.0 (M.I.N.I) (APPENDIX 4)

M.I.N.I is a short structured diagnostic interview designed to diagnose both current and lifetime DSM-IV and ICD-10 psychiatric disorders. It is a relatively brief instrument and consists of different modules corresponding to different diagnostic categories. In this study, module A is used to confirm diagnosis of major depressive disorder while modules E, F, G, H, I, O are used to diagnose anxiety disorders (panic disorder, agoraphobia, social phobia, obsessive compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder). Module I, J was used to screen for substance related disorder. The M.I.N.I has good validity and reliability and it had been used extensively in local studies in the field of psychiatry. M.I.N.I English version 6.0.0 was used in this study.

3.7.3 HAMILTON DEPRESSION RATING SCALE (HAM-D) (APPENDIX 5)

The Hamilton Depression Rating Scale has been the gold standard for the assessment of depression for more than 40 years by the Food and Drug Administration (FDA) (Healy, 1997). Although HAM-D was developed in the late 1950s and was originally published in 1960, but until now it still retained its function and is the most commonly used measure of depression (Williams, 2001).

HAM-D is an interviewer-rated, 17-item rating scale for depressive illness. It is not a diagnostic instrument because it measures the severity of the depressive syndrome rather than the symptom of depression. 17 items were scored based on the severity of depressive symptoms and summing up the score of all 17-item will produce a total score.

A good clinician-rated instrument should demonstrate three types of reliability: 1) internal reliability, 2) retest reliability, and 3) interrater reliability. Many of the psychometric properties of the Hamilton depression scale are adequate and the overall internal, interrater, and retest reliability are mostly good. Similarly, established criteria are met for convergent, discriminant, and predictive validity (Michael et al, 2004). The scale has been translated into a number of languages including French, German, Italian, Thai, and Turkish.

3.7.4 HAMILTON ANXIETY RATING SCALE (HAM-A) (APPENDIX 6)

The Hamilton anxiety rating scale was one of the first rating scales developed to measure the severity of anxiety symptoms, and is still widely used today in both clinical and research settings. HAM-A is a 14 items and rated by an interviewer on 5-point scales. The scale is useful to assess both psychic anxiety and somatic anxiety. Psychic anxiety refers to psychological agitation and distress while somatic anxiety refers to physical manifestation due to anxiety. Some depressive symptoms are

included so that the scale is in fact a measure of the severity of the anxiety syndrome and not the symptom of anxiety. The total score of HAM-A ranged from 0-56 with score of < 17 refers to mild anxiety, 18-24 indicates mild to moderate severity, 25-30 indicates moderate to severe anxiety and >30 refers to severe anxiety.

The Hamilton anxiety scale has been validated in patient with anxiety and depressive disorders. In this study, the reliability and the concurrent validity of the HAM-A is proved to be sufficient (Wolfgang et al., 1988). The reported levels of interrater reliability for the scale were good, score distribution and known groups validity with satisfactory discriminative properties with moderate to good specificity (0.74-0.79) and fair sensitivity (0.67-0.72) at optimal cut-off points (11/12 and 12/13) (Leentjens et al., 2011) (Hamilton, 1959). The HAM-A also had a satisfactory inter-item correlation, convergent validity and factorial structure (Leentjens et al., 2011). This scale has been translated into Cantonese for China, French and Spanish.

3.7.5 GLOBAL ASSESSMENT OF FUNCTIONING (GAF) (APPENDIX 7)

Global Assessment Functioning (GAF) was introduced in Axis V in DSM-IV, and is a revised version of the Global Assessment Scale (Endicott et al., 1976). This Axis is used to report a clinician's judgment of a patient's overall level of functioning. The GAF is a 100-point scale on which the clinician rates the overall functioning of the patient. Each decile has a brief description of psychological, social and occupational performance.

3.7.6 MULTIDIMENSIONAL SCALE OF PERCEIVED SOCIAL SUPPORT (APPENDIX 8)

The MSPSS was originally developed on university students (Zimet, Dahlem, Zimet, & Farley, 1988) and was later validated in a wide range of samples, including pregnant

women, adolescents, older adults, doctor-trainees and psychiatric patients (Kazarian & McCabe, 1991; Stanley, Beck, & Zebb, 1998; Zimet, Powell, Farley, Werkman, & Berkoff, 1990). Even though all the items are worded in the positive, the MSPSS has been shown to be relatively free of social desirability bias (Dahlem, Zimet, & Walker, 1991; Kazarian & McCabe, 1991). The reliability, concurrent validity and construct validity of the Malay version of MSPSS were established on a group of medical students in Faculty of Medicine, University Malaya (C.G. Ng et al., 2010). This version of MSPSS was used in this study.

MSPSS is a scale that assesses three sources of support which are family (FA), friends (FR), and significant other (SO). Zimet and his colleagure have mentioned a several superiority of this scale compare with other assessment tools of social support (Canty-Mitchell & Zimet, 2000; Zimet et al., 1988). Firstly, it is a short (12 items) scale, therefore is suitable for a research requires assessment of multiple variables and population which cannot tolerate a long questionnaire. This is especially important for us as our study involve several rating scale that may consume a large amount of time. A 7-poin Likert-type 1 scale that consisted of 12 items ranging from "Definitely No" to "Definite Yes" was used. This scale consists of 4 main items with 3 subscales that determine family, friend, and a special person support. The lowest point to be received from the whole MSPSS survey is 12 and the highest point is 84. Higher points mean that the perceived social support will be higher.

Secondly, the point rating system using in MSPSS rating scale are easy to understand (requiring just fourth grade reading level). In view of our sample consisted of 37.0% patient who received education until primary school or below, therefore this feature of the MSPSS scale is important for our study. Thirdly, despite being a brief instrument, MSPSS are reliable as it measure the social support multi-dimensionally which include support from three source which include family (FA), friends (FR), and

significant other (SO). In addition, the SO subscale is unique compare with other assessment tools of social support whereby it allow the "significant other(s)" to the defined by the respondent in the study.

3.7.7 DUKE RELIGIOUS INDEX (APPENDIX 9)

Duke Religion Index (DRI) is a brief and comprehensive assessment tool that assesses multiple dimensions of religiosity created by Koenig, Parkerson, and Meador (1997a). DRI is a five-item self-report scale that assesses the organizational, non-organizational, and intrinsic dimensions of religiousness. Organizational religiosity is measured by one-item and defined as the frequency with which one attends formal religious services. Non-organizational religiosity is measured by one-item and defined in terms of the amount of time spent in private religious activities such as prayer or meditation. Intrinsic religiosity is measured by three-items and conceptualized as the degree to which one integrates their religiousness into their life. The DRI has been used in over 100 published studies and is available in 10 languages (Koenig et al., 2010). A validated Malay version of Duke University Religion Index (DUREL-M) was used in this study (Nurasikin et al., 2010).

3.8 DEFINITION OF VARIABLES

3.8.1 CO-MORBID ANXIETY DISORDER IN MAJOR DEPRESSIVE DISORDER

Co-morbid anxiety disorder refers to patients with anxiety symptoms which are adequate to diagnose any of the anxiety disorders (generalized anxiety disorder, panic disorder, agoraphobia, phobias, social anxiety disorder, obsessive compulsive disorder, post traumatic stress disorder) according to M.I.N.I. module E, F, G, H, I, O which included current diagnosis

3.8.2 CO-MORBID SUBSTANCE RELATED DISORDER IN MAJOR DEPRESSIVE DISORDER

Co-morbid substance related disorder refers to alcohol dependence, alcohol abuse, substance dependence and substance abuse, diagnosed using M.I.N.I. module I, J which included current diagnosis.

3.8.3 LONG-TERM USE OF BENZODIAZEPINES

Long term use of benzodiazepines was defined according to WHO criteria as 180 days or more (Committee on the Safety of Medicine, 1988; Salzman, 1991). Long-term continuous of benzodiazepines was defined as use for 75% or more of the time during the 180 days following the first date diagnosis of major depressive disorder. This definition was considered both a clinically relevant definition of long-term continuous use and a definition that would ensure the inclusion of the majority of long term users (Egan et al., 2000).

For patients treated with benzodiazepines for more than one treatment episode, the longest treatment episode was analyzed (John et al., 2005).

3.8.4 DIAZEPAM MILIGRAM EQUIVALENTS (DMEs)

We defined DME dosage for each benzodiazepine generic entity, which allowed us to convert dosages for all benzodiazepines prescribed to therapeutically equivalent DME dosages. We used the equivalencies proposed by Shader and colleagues (Shader et al., 1994), which already validated by Havard Medical School and Harvard Pilgrim Health Care (Stephen et al., 2003). The relative potencies of equivalent dosages of various benzodiazepines are diazepam, 1.00; Alprazolam, 10.00; Clonazepam, 20.00; Lorazepam, 6.67 (Stephen et al., 2003) and Bromazepam, 1.67; Zolpidem, 0.20 (Ashton H, 2002).

3.8.5 AVERAGE DAILY DOSAGE OF BENZODIAZEPINES

Average benzodiazepine daily dosage for a specific clinic visit was determined by the total benzodiazepine dose prescribed over the duration divided by the number of days of the prescription (John et al., 2005).

3.8.6 DOSE ESCALAION OF BENZODIAZEPINES USAGE

To determine the dose escalation, we take the average benzodiazepine daily dosage of a clinic visit after a 3 months initiation period (Stephen et al., 2003). The dosage was then converted to DMEs dosage. This figure was use to compare with the average benzodiazepine daily dosage of the last clinic visit of the same patient (in DMEs dosage).

3.9 STATISTICAL ANALYSIS

The data obtained from the study will be assessed using Statistical Package for Social Study (SPSS). Descriptive analysis was done for socio-demographic and clinical variables by expressing frequencies, means or medians and range.

Prevalence of long-term benzodiazepines use was calculated. The associations of socio-demographic, clinical and psychosocial variables with long-term benzodiazepines use were analyzed using chi square test (for categorical variables), Mann-Whitney U test (for non-normally distributed, continuous variables) and independent t-test (for normally distributed, continuous variables).

Correlation between HAM-D, HAM-A, GAF, Multidimensional Scale of Perceived Social Support and Duke Religious Index were done using Pearson (for normally distributed, continuous variables) and Spearman correlation (for non-normally distributed, continuous variables).

3.10 ETHICAL CONSIDERATIONS

This study was registered in National Medical Research Register (NMRR) of Ministry of Health, Malaysia. Ethical approval was obtained from Ministry of Health Research and Ethic Committee (MREC). Further ethical approval was obtained from ethical committee, Hospital Bahagia Ulu Kinta. A written informed consent was obtained from each subject prior to recruitment into the study.

CHAPTER 4: RESULTS

4.1 SOCIO-DEMOGRAPHIC CHARACTERISTICS

Socio-demographic of 65 patients was as below:

Table 4.1: Socio-demographic characteristics of study participants

Characteristic	Range	Mean	SD
Age	21 - 72	49.86	12.995

Characteristic		No	%
Gender	Male	21	32.3
	Female	44	67.7
Ethnic	Malay	11	16.9
	Chinese	51	78.5
	India	2	3.1
	Others	1	1.5
Educational level	No formal education	4	6.2
	Primary school	20	30.8
	Secondary school	36	55.4
	Tertiary	5	7.7
Marital status	Single	6	9.2
	Married	51	78.5
	Divorce/ widow	8	12.3
Employment	Unemployed	33	50.8
	Employed	32	49.2
Monthly income	no income	33	50.8
	< RM 500	5	7.7
	RM 501 – RM 1000	7	10.8
	RM 1001 – RM 3000	20	30.8
Usage of benzodiazepines	Yes	57	87.7
	No	8	12.3

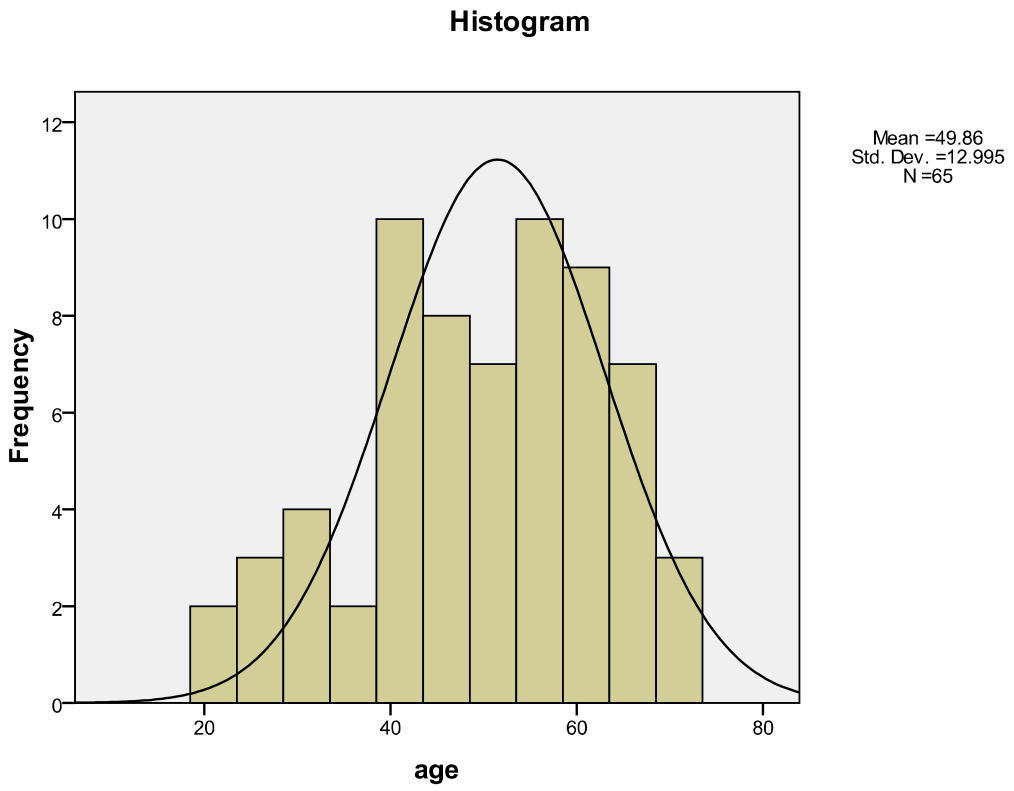

Figure 4.1: Distribution of age of the study sample

A total of a 65 patients were recruited into this study. The mean age of the patients was 49.86 years old with standard deviation of 12.995 (Table 4.1 and Figure 4.1). 78.5% of the patients were Chinese, while Malay patients constitute 16.9%, Indian patients constitute 3.1% and other race constitutes 1.5%. 6.2% of the patients of the patients not received any formal education. Majority of patients (55.4%) received education until secondary. 30.8% of the patients received education until primary and 7.7% patients studied until tertiary level (Table 4.1).

9.2% of the patients were single and 12.3% of them were divorce or widow. Majority of them (78.5%) were married. There were 49.2% of the patients still working at the time of recruitment. However, most of them (50.8%) were unemployed

at the time of recruitment. 87.7% of the patients were prescribed with benzodiazepines during their treatment with antidepressant. Only 12.3% of patients not received benzodiazepine during their treatment course of major depressive disorder (Table 4.1).

4.2 CLINICAL CHARACTERISTIC

Total of 57 patients were prescribed benzodiazepines during their major depressive episode and they were further analyzed about their clinical and psychosocial characteristic as below:

Table 4.2: Clinical characteristics of BDZ's user

Characteristic	Range	Mean	SD
Duration of illness (years)	0.5-13.77	3.67	3.492
Age of onset of MDD (years)	24-70	47.72	11.866
HAM-D score	0-27	9.93	7.973
HAM-A score	0-31	10.75	8.586
GAF score	40-95	77.49	11.972
MSPSS score	21-78	54.88	13.561
DRI score	5-27	17.51	6.009
DRI subscale 1	1-6	3.39	1.360
DRI subscale 2	1-6	4.40	1.801
DRI subscale 3	3-15	9.68	3.883

The mean duration of MDD was 3.67 years (SD 3.492). The mean age of onset of MDD was 47.72 years old (SD 11.866) and it range from 24 years old to 70 years old. Regarding the severity of depression, the mean score of HAM-D was 9.93 (SD 7.973). Mean score of HAM-A was 10.75 (SD 8.586) showed that most of the patients were mild severity of anxiety (Table 4.2).

GAF had mean score of 77.49 (SD 11.972), while MSPSS had mean score of 54.88 (SD 13.561). Mean score of DRI, DRI subscale 1, DRI subscale 2 and DRI subscale 3 showed 17.51 (SD 6.009), 3.39 (SD 1.360), 4.40 (SD 1.801), 9.68 (SD 3.883) respectively (Table 4.2).

4.3 TYPE OF ANTIDEPRESSANT USE

Table 4.3: Type of antidepressant use among depressed patient prescribed with benzodiazepines

Type of antidepressant	No	%
Tricyclic Antidepressant (TCA)	5	8.8
SSRI	39	68.4
SNRI	6	10.5
NaSSA	7	12.3

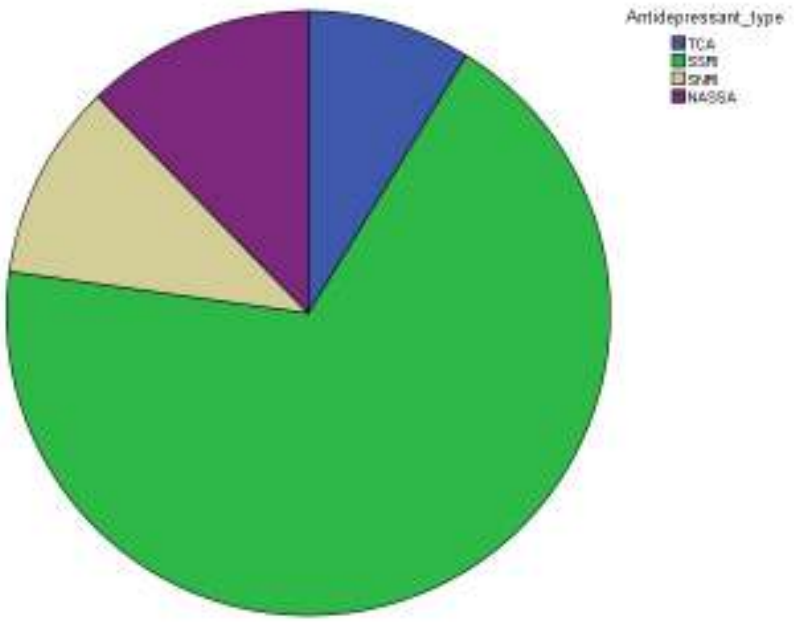

Figure 4.2: Type of antidepressant using by the patients

Among depressed patients who were prescribed with benzodiazepine, majority of them (68.4%) using SSRI as the treatment of MDD. 12.3% were administered with NaSSa while SNRI and Tricyclic antidepressant constitute 10.5% and 8.8% of the treatment respectively (Table 4.3) (Figure 4.2).

4.4 COMORBIDITY

Table 4.4: Co-morbidity of anxiety disorder, substance related disorder and physical illness

Co-morbidity	No	%
Co-morbid anxiety disorder		
• Yes	10	17.5
➢ Panic disorder	4	7.0
➢ Agoraphobia without panic attack	1	1.8
➢ Post traumatic stress disorder	4	7.0
➢ Generalized anxiety disorder	1	1.8
• No	47	82.5
Co-morbid substance related disorder (other than benzodiazepine)		
• Yes	0	0.0
• No	100	100.0
Physical illness		
• Yes	22	38.6
• No	35	61.4

Among the benzodiazepines users, up to 38.6% of the patients suffer from physical illness which may consist of diabetes mellitus, hypertension, hyperlipidemia or other common medical disorders (Table 4.4).

Among all the anxiety disorder, both panic disorder without agoraphobia and post traumatic stress disorder constitute of 7.0% of the patients each. While agoraphobia without panic attacks and generalized anxiety disorder were appear in 1.8% of patients each. 82.5% of patients did not suffer from any anxiety disorder (Table 4.4).

None of the benzodiazepines users have reported any substance related disorder other than benzodiazepine (Table 4.4).

4.5 CLINICAL CHARACTERISTICS OF BENZODIAZEPINES USER

For those who receiving benzodiazepine prescription during their treatment course of major depressive episode, 17.5% of the patient consumes benzodiazepine in short-term duration, while12.3% in intermediate duration and 70.2% in long-term nature (Table 4.5) (Figure 4.3).

About 82.5% of the BDZ user receive benzodiazepine prescriptions consume short-acting benzodiazepines at the time of recruitment of this study. 17.5% of patients receive a long-acting benzodiazepine (Table 4.5) (Figure 4.4).

21.1% of the patients who receiving benzodiazepines prescription complaint of adverse effect including sleepiness, poor memory, tremor and increase of body temperature while 78.9% of the patients did not complain of adverse effect of benzodiazepines (Table 4.5) (Figure 4.5).

There are total of 40 patients consumes the benzodiazepines in long-term duration. Among them, 40.0% show decreasing in dosage, 35.0% show no changed in dosing and 25.0% show increasing in dosage (Table 4.5) (Figure 4.6)

Table 4.5: Clinical characteristics of benzodiazepines use

Characteristics	No	%
Duration of benzodiazepines use		
• Short-term	10	17.5
• Intermediate	7	12.3
• Long-term	40	70.2
Type of benzodiazepines		
• Short-acting benzodiazepines	47	82.5
• Long-acting benzodiazepines	10	17.5
Adverse effects of benzodiazepines use		
• Yes	12	21.1
➢ Sleepiness	8	14.1
➢ Poor memory	2	3.5
➢ Tremor	1	1.8
➢ Increase of body temperature	1	1.8
• No	45	78.9
Benzodiazepines dosage trends among long-term users		
• Decreasing	16	40.0
• Remained unchanged	14	35.0
• Increasing	10	25.0

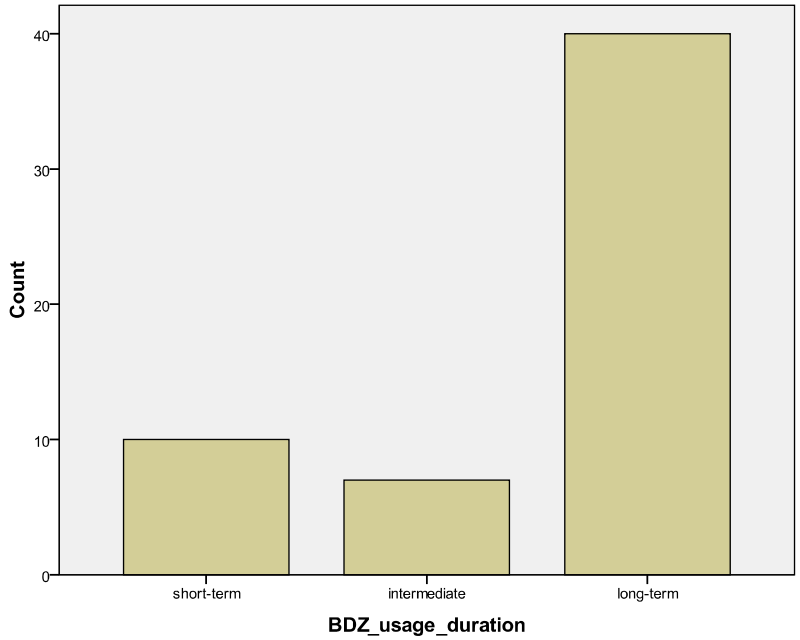

Figure 4.3: Benzodiazepines usage duration

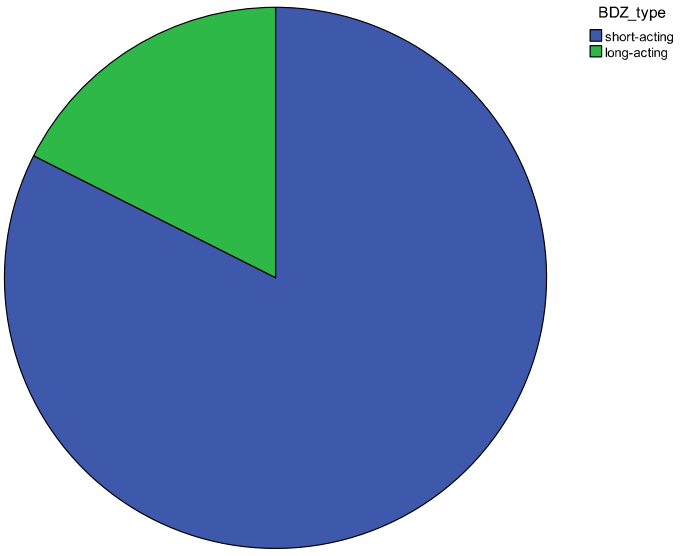

Figure 4.4: Type of BDZ using by the patients

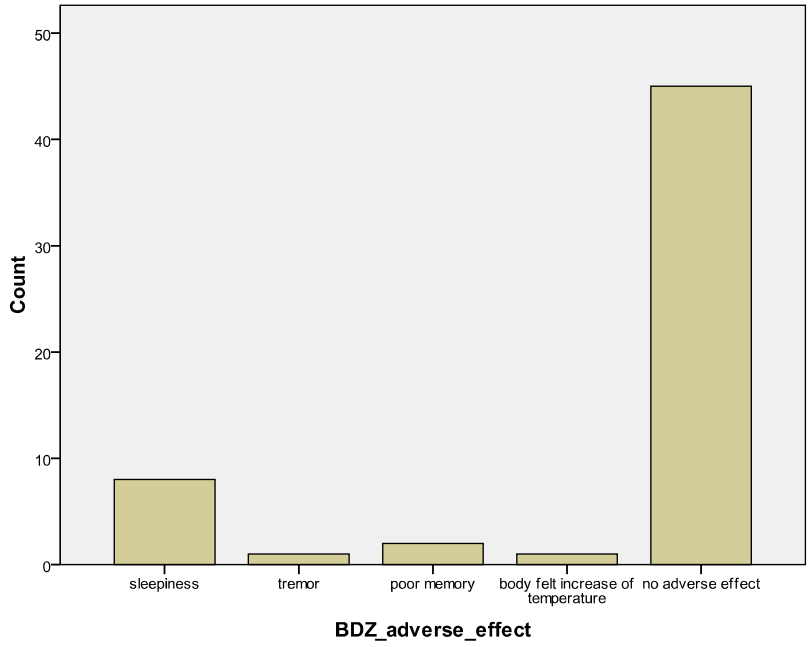

Figure 4.5: Benzodiazepines usage adverse effect

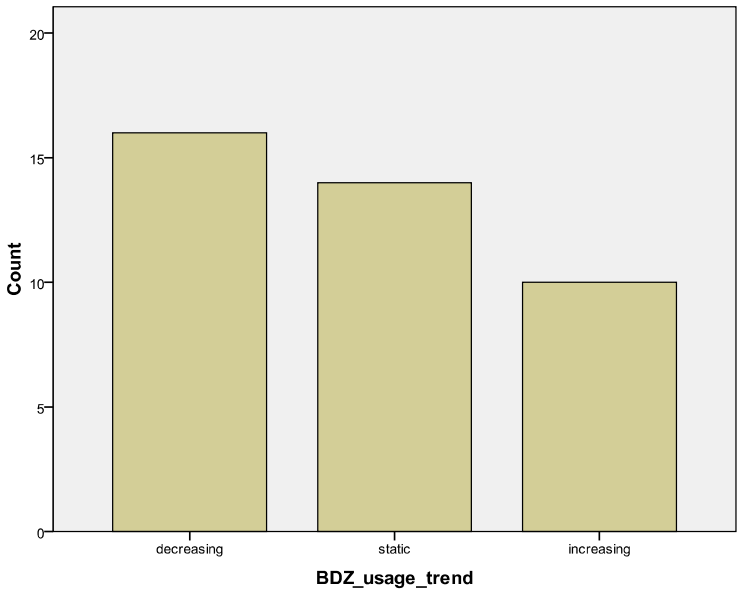

Figure 4.6: Dose escalation of benzodiazepines usage

4.6 ASSOCIATION BETWEEN SOCIODEMOGRAPHIC AND CLINICAL VARIABLES WITH LONG-TERM USE OF BENZODIAZEPINES

Table 4.6: Univariate analysis of association between sociodemographic, clinical characteristic with long-term use of benzodiazepines

Variables	Duration of BDZ use(n)		OR	95% CI	P-value
	Long-term	Not long-term			
Age					
• Below 65 years old	33	15	0.629	0.116-3.390	0.710
• Age 65 and above	7	2			
Gender					
• Male	16	4	2.165	0.598-7.874	0.233
• Female	24	13			
Ethinicity					
• Malay	6	2	1.323	0.239-7.353	1.000
• Non-Malay	34	15			
Education level					
• Primary and below	18	5	1.965	0.582-6.623	0.272
• Secondary, tertiary	22	12			
Marriage					
• Single/Divorce/Widowed	11	1	6.061	0.717-52.632	0.085
• Married	29	16			
Employment					
• Unemployed	20	9	0.889	0.285-2.770	1.000
• Employed	20	8			
Co-morbid physical illness					
• Yes	16	6	1.222	0.376-3.968	0.738
• No	24	11			
Co-morbid anxiety disorder					
• Yes	8	2	1.876	0.354-9.901	0.706
• No	32	15			
Type of antidepressant					
• Older antidepressant	5	0			0.308
• Newer antidepressant	35	17			
Type of benzodiazepines					
• Short-acting	2	15	0.533	0.101-2.823	0.706
• Long-acting	8	2			
Adverse effect of benzodiazepines					
• Yes	5	7	0.204	0.053-0.784	0.029*
• No	35	10			

*Significance level: $p<0.05$

Univariate analysis was done between socio-demographic and clinical variables with the long-term use of benzodiazepines using Chi square test and Fisher's extract test (Table 4.6). Variables such as age, ethnicity, educational level, marriage, duration of illness were re-categorized.

For socio-demographic variables, elderly (age 65 years old and above), being male, Malay, lower education, single or divorce or widow, being employed appeared to be associated with longer duration of benzodiazepines use but the associations were not statistically significant.

For clinical variables, the only statistical significant finding was that those who experience side effect of benzodiazepines appeared to have lower odd of using benzodiazepines in long-term, with odd ration of 0.204, p=0.029. Patient with comorbid medical illness, comorbid anxiety disorder and on long-acting benzodiazepines appeared to be associated with longer duration of benzodiazepines use. However, the associations were not statistically significant.

4.7 TO DETERMINE THE DISTRIBUTION OF HAM-D, HAM-A, GAF, MSPSS, DRI, DRI SUBSCALE 1, DRI SUBSCALE 2 AND DRI SUBSCALE 3

Before we perform statistic analysis, we need to determine the distribution nature of the data in order to select appropriate statistical method. Using SPSS, we conduct Kolmogrov-Smirnov test with the quantitative variable which include HAM-D, HAM-A, GAF, MSPSS, DRI, DRI SUBSCALE 1, DRI SUBSCALE 2 AND DRI SUBSCALE 3. If the Kolmogrov-Smirnov test is significant, it indicates the distribution is significantly different from the normal distribution.

Table 4.7: Tests of Normality of the continuous variables

	Kolmogorov-Smirnov		
	Statistic	**df**	**Sig**
HAM-D	0.131	57	0.016
HAM-A	0.105	57	0.180
GAF	0.212	57	0.000
MSPSS	0.090	57	0.200
DRI	0.071	57	0.200
DRI subscale one	0.173	57	0.000
DRI subscale two	0.244	57	0.000
DRI subscale three	0.130	57	0.018

Below are the nature of the continuous data and the corresponding statistic method:

Continuous data	**Nature of distribution**	**Corresponding statistical method**
HAM-D	Non-normal distribution	Mann Whitney U test
HAM-A	Normal distribution	Independent t-test
GAF	Non-normal distribution	Mann Whitney U test
MSPSS	Normal distribution	Independent t-test
DRI	Normal distribution	Independent t-test
DRI subscale one	Non-normal distribution	Mann Whitney U test
DRI subscale two	Non-normal distribution	Mann Whitney U test
DRI subscale three	Non-normal distribution	Mann Whitney U test

4.8 ASSOCIATIONA OF PSYCHOSOCIAL FACTORS WITH LONG-TERM BENZODIAZEPINES USE

Table 4.8: Association of Psychosocial Factors with Long-term Benzodiazepines use using Mann Whitney U test

	Mean rank		**P value**
	Long-term	**Not long-term**	
HAM-D score	31.98	22.00	0.038*
GAF score	26.20	35.59	0.047*
DRI#1	28.55	30.06	0.747
DRI#2	29.20	28.53	0.884
DRI#3	25.35	37.59	0.010*

*Significance level: $p<0.05$

Table 4.9: Association of Psychosocial Factors with Long-term Benzodiazepines use using t test

Independent t-test	Mean score	Mean difference	95% CI	P value
HAM-A				
• **Not long-term**	6.41			
• **Long-term**	12.60	-6.188	-10.309 - -2.068	0.004*
MSPSS				
• **Not long-term**	61.47			
• **Long-term**	52.08	9.396	1.873-16.918	0.015*
DRI				
• **Not long-term**	19.53			
• **Long-term**	16.65	2.879	-0.552-6.311	0.098

*Significance level: p< 0.05

HAM-D score was significantly higher in long-term benzodiazepine user's group. This means long-term benzodiazepine user's group is associated with more severe depressive symptoms (Table 4.8).

HAM-A score was also significantly higher in long-term benzodiazepine user's group. This means long-term benzodiazepine user's group is associated with more severe anxiety symptoms (Table 4.9).

Functioning level also impaired significantly in long-term benzodiazepine user's group compare with not long-term user (Table 4.8).

Religiosity of long-term benzodiazepine depressed patients was significantly poorer compared with not long-term user. This was evidenced by DRI subscale three score with p value less than 0.05. DRI total score and DRI subscale one were showed poorer score in long-term group but there were statistically not significant (Table 4.8).

Social support was significantly poorer in long-term benzodiazepine user's group compare with not long-term user (Table 4.9).

Table 4.10: Correlation between MSPSS, DRI, DRI_1, DRI_2, DRI_3 with HAM-D, HAM-A and GAF

		Correlation	P value
MSPSS			
▪ **HAM-D**	Spearman Correlation	- 0.405	0.002*
▪ **HAM-A**	Pearson Correlation	- 0.267	0.045*
▪ **GAF**	Spearman Correlation	0.514	< 0.001*
DRI			
▪ **HAM-D**	Spearman Correlation	- 0.286	0.031*
▪ **HAM-A**	Pearson Correlation	- 0.358	0.006*
▪ **GAF**	Spearman Correlation	0.492	< 0.001*
DRI_1			
▪ **HAM-D**	Spearman Correlation	- 0.105	0.435
▪ **HAM-A**	Spearman Correlation	- 0.137	0.310
▪ **GAF**	Spearman Correlation	0.180	0.180
DRI_2			
▪ **HAM-D**	Spearman Correlation	0.042	0.765
▪ **HAM-A**	Spearman Correlation	- 0.082	0.544
▪ **GAF**	Spearman Correlation	0.205	0.126
DRI_3			
▪ **HAM-D**	Spearman Correlation	- 0.0414	p < 0.001*
▪ **HAM-A**	Spearman Correlation	- 0.512	p < 0.001*
▪ **GAF**	Spearman Correlation	0.587	p < 0.001*

*Significance level: p<0.05

Poorer social support was significantly associated with more severe depressive and anxiety symptoms. While better social support was significantly associated with good functioning level (Table 4.10)

Poorer religiosity associated with more depressive and anxiety symptoms while better religiosity associated with good functioning level. DRI subscale one and DRI subscale two produced non-significant result. However DRI subscale 3 produce similar conclusions with DRI total score (Table 4.10)

CHAPTER 5: DISSCUSSION

5.1 Concept of research

This was a cross sectional study with the purpose of determines the prevalence of long-term benzodiazepines use among depressed patients in the specialty mental health setting. This study also attempted to identify the socio-demographic, clinical and psychosocial factors that associated with the long-term use of benzodiazepines.

5.2 Socio-demographic and clinical characteristic of study patients

Psychiatric outpatient clinic HBUK is a specialist referral center for psychiatric cases. Patient was referred from primary care clinic in Ipoh which include Klinik Kesihatan Tanjung Rambutan, Klinik Kesihatn Kampung Simee, Klinik Kesihatan Jelapang, Klinik Kesihatan Manjoi, Klinik Kesihatan Pasir Pinji, Klinik Kesihatan Kampar, Klinik Kesihatan Karai, Klinik Kesihatan Gopeng. The clinic also received referral from district hospital which does not have psychiatric specialty service include Hospital Sungai Siput, Hospital Grik, Hospital Batu Gajah, Hospital Tapah, Hospital Changkat Melintang, and Hospital Kampar.

Outpatient clinic HBUK have total of 10,960 patient's visits in year 2010 compare with 9,400 visits in year 2009 (HBUK, 2011). Among 10,960 patient's visits in year 2010, there were 593 new cases which constitute 5.4% of 2010 total clinic visit (HBUK, 2011).

In our study population, the Chinese patients consisted of 78.5%, Malay patients consisted of 16.9% and Indian patients were made up of 3.1%. This is different from a cross sectional study done for major depressive disorder among psychiatric outpatient in Malaysia, whereby the percentage of Malay, Chinese and Indian were 34.7%, 51.4% and 13.9% respectively (Hat NH et al., 2011). This

discrepancy was due to different patient's ethnicity distribution of psychiatric outpatient HBUK where Chinese community is in proximity. The ethnicity distributions of psychiatric outpatient HBUK were 24.4% for Malay, 63.0% for Chinese, 11.3% for Indian and 1.3% for other race (HBUK, 2003).

67.7% of participants in this study were female while the remaining were male patients. This is comparable to a cross sectional study done in Malaysia among psychiatric outpatients with major depressive disorder, whereby the percentage of female patients was 66.7% (Hat NH et al., 2011).

The mean age of our study samples was 49.9 comparable to 46.0 in the study done in Malaysia (Hat NH et al., 2011). In this study, the patients who studied until secondary school and above was 63.1% compare with 84.7% in the similar study in Malaysia (Hat NH et al., 2011). The difference in education level probably reflects that patients from Hospital Bahagia Ulu Kinta outpatient clinic came from semi-urban areas while patients attending the University Kebangsaan Malaysia Medical Centre psychiatric outpatient clinic came from urban area (Hat NH et al., 2011). About 78.5% of our study samples married which was similar to the 73.6% in the study done in UKM (Hat NH et al., 2011).

The unemployment rate of study sample was 50.8% compare with the study done in Mukim Sepang is about 83.4% (M. S. Sherina et al., 2004). This may be due to age of patients from Mukim Sepang was older than study sample which was reflected by the older mean age.

In this study, there was 21.1% of the patient complaint of having adverse effect secondary to benzodiazepine use. This figure is comparable with the similar study done at in U.K. which shows 16% of respondents experience undesirable effect from their benzodiazepines (Michael et al., 1990). Our study showed that patient who had history of experiencing side effect of benzodiazepine was significantly associated with

shorter duration of benzodiazepine use. This can be understood as patients were reluctant to put on medication that brought uncomfortable effect such as tremor, poor memory and sleepiness.

5.3 Prevalence of Benzodiazepines Use in HBUK among Depressed Patient

87.7% of our study sample was prescribed with benzodiazepines during their treatment course of depression. Compare with 36% depressed patients at specialty mental health settings in United State (Marcia et al., 2004), our study sample appear to have higher percentage of benzodiazepine use.

This discrepancy may be related to strict government regulation in United State. The United State government regulation of benzodiazepines use was started at New York State in year 1989. This regulation has emphasize that the benzodiazepine can only be prescribed with the filling on the State's triplicate-copy prescription forms, whereby one of the copy must forwarded to the State Department of Health for the purpose of computerized monitoring (Eadie et al., 1990). The effect of this regulation was seen whereby the benzodiazepine prescribing rate in the New York State had declined by about half in the year following its implementation. However at the same time, there was increased of non-benzodiazepine drugs prescription which apparently prescribed by physicians to substitute the benzodiazepine included meprobamate, barbiturates, and other sedative-hypnotics that we known as "older, less effective, and more hazardous" (Shader et al., 1991) than benzodiazepines.

5.4 Long-term Benzodiazepines Use and unresolved depressive symptom and anxiety symptoms

70.2% of BDZ user in our sample consumed benzodiazepine in long-term duration (> 180 days). This finding was found higher compare to the study done at specialty mental health settings in United State that percentage of depressed patient who received benzodiazepine prescription for 180 days or more was 61% (Marcia et al., 2004).

There are several reasons related to the higher rate of long-term benzodiazepine use among depressed patient in our study samples. One of the possible reasons was due to the unresolved depressive symptom and anxiety symptoms. These facts were evidenced by the patient with higher score of HAM-D and HAM-A score were associated with longer duration of benzodiazepines usage. These associations were statistically significant. These may be due to depressed patients need to take longer duration of benzodiazepine in order to overcome their depressive and anxiety symptoms. As a tertiary referral center, HBUK more likely to receive referral of treatment resistant depression from primary and secondary center such as Klinik Kesihatan and District hospital, these groups of patient tend to have more severe depressive and anxiety symptoms which may need longer duration of benzodiazepines to control their symptom in addition of antidepressant treatment.

5.5 Long-term benzodiazepines use and Social support

In our study, there was association between perceived social support and duration of benzodiazepines use. The independent t-test showed that poor social support was significantly associated with long-term use of benzodiazepines among depressed patient. The Spearman correlation of MSPSS and HAM-D was statistically significant. This concluded that poor social support was associated with more severe

depressive symptoms. This probably suggested that poor social support is a risk factor to the persistent of depressive symptoms. Beside HAM-D score, the Pearson correlation of MSPSS and HAM-A was statistically significant too. As the present of anxiety symptoms may predict a poorer long-term outcome (Clayton et al., 1991, Coryell et al., 1992), the poor social support may be a risk factor to the worsening of depression. Apart from that, the functioning level of patient was correlated with the social support and it was statistically significant. This means better social support will bring a better functioning level.

5.6 Long-term benzodiazepines use and Religiosity

In our study, we noted that the poor religiosity was significantly associated with longer duration of benzodiazepines use among the depressed patient. The Mann-Whitney U test showed that poor religiosity was significantly associated with long-term use of benzodiazepines among depressed patient.

The Spearman correlation of DRI subscale 3 and HAM-D was statistically significant. This concluded that poor religiosity was associated with more severe depressive symptoms. This probably suggested that poor religiosity is a risk factor for the persistent of depressive symptoms. Beside HAM-D score, the Spearman correlation of DRI subscale 3 and HAM-A was statistically significant too. Apart from that, the functioning level of patient was correlated with the level of religiosity and it was statistically significant, which means better religiosity will bring a better functioning level.

We noted the phenomenon of DRI total score is not statistically significant despite the DRI subscale 3 showed significant results. This phenomenon is due to the three subscale in the DUREL assess the different component. DUREL actually was designed to measure three dimensions of religiosity therefore it consists of three

"subscale". Each subscale assesses a particular aspect of religious practices or religious devotions (spirituality) which are ORA, NORA and IR. The first subscale is assess the organizational religious activity (ORA) involves public religious activities such as attending religious services or participating in other group-related religious activity (prayer groups, Scripture study groups, etc.). The second subscale is assess the non-organizational religious activity (NORA) consists of religious activities performed in private, such as prayer, Scripture study, watching religious TV or listening to religious radio. Both the ORA and NORA also termed as extrinsic religiosity (ER). The third subscale is assess the intrinsic religiosity (IR) which determined by the degree of personal religious commitment or motivation.

Extrinsic religiosity (ER) was a form of religiosity that is used as a means to some more important gain such as financial success, social status, comfort, a congenial social activity inherit from parent, rather than for religion's sake alone. Intrinsic religiosity (IR), in the contrary, it involves pursuing religion as an ultimate end in itself. Allport and Ross had defined IR as "Persons with this orientation find their master motive in religion. Other needs, strong as they may be, are regarded as of less ultimate significance, and they are, so far as possible, brought into harmony with the religious beliefs and prescriptions. Having embraced a creed, the individual endeavors to internalize it and follow it fully. It is in this sense that he lives his religion." (Allport et al., 1967).

Literature review has showed that summing all three 'subscale' of DUREL into a total overall religiosity score is not recommended (Harold et al., 2010). This is because of combining all three subscales in a single analysis could result in subscale scores canceling out the effects of each other.

Based on the study done by Koenig and his colleague, the first 'subscale' assessing religious attendance (ORA) has been related to less depression, more social

support, better physical health, lower health service use, and lower mortality (Koenig et al., 2008). The second 'subscale' assessing prayer, meditation and Scripture reading (NORA), on the other hand, has been related to poorer physical health, greater social support, and has been associated with both less and more depression, depending on population (Koenig et al., 1997).

In view of the reasons above, we agree that the intrinsic religiosity (subscale 3) is a better measurement of religiosity than the subscale 1, subscale 2 or total score. It is more reliable to use subscale 3 as assessment tool to assess the religiosity in our study sample.

5.7 Long-term benzodiazepines use and Dosage escalation

Some of the articles have argued that the high prevalence of long-term benzodiazepines use among depressed patient must have reflected the over-use of these drugs and they related this phenomenon to the liability of benzodiazepines to abuse and dependence. However, in other study including our study have attributed this phenomenon to the present of unresolved depressive and anxiety symptom for which the benzodiazepines are prescribed. Wood and colleague have proposed that the divergent views of benzodiazepines use as "abuse model" and "therapeutic use model" (Woods et al., 1987, 1988).

Although clinical research had showed that prolonged use of therapeutic doses of benzodiazepine can lead to physiological dependence; however this dependence is not usually accompanied by a tendency of dose escalation which is a characteristic of "psychological dependence" or "addiction" (Stephen et al., 2003). However, this condition did not happen in our study. Among the long-term benzodiazepines users in our study sample, 40.0% of them showed decreasing of benzodiazepines dosage (mean for HAM-D score was 8.50 with SD of 6.55) (mean for HAM-A score was 9.94 with

SD of 6.94), only 25.0% of them show increasing in dosage (mean for HAM-D score was 13.40 with SD of 9.77) (mean for HAM-A score was 16.30 with SD of 11.19). While 35.0% of them showed no change in dosage of benzodiazepines. This findings were similar to a study done in United State which also did not support the hypothesis that long-term benzodiazepines use are frequently results in notable dose escalation (Stephen et al., 2003). Therefore, we associated the use of benzodiazepines in HBUK is better explained by "therapeutic use model" than "abuse model".

In the New York State, the evidence to support that the benzodiazepine are used to control the anxiety symptom is that in the three months time after the government regulation enforce, quite a number of the presentations at a New York City emergency room for problems associated with benzodiazepine use was associated with the re-emergence of anxiety disorders that had previously under controlled by the benzodiazepines treatment (Schwartz and Blank, 1991).

CHAPTER 6: LIMITATION

1. The sample size of this study was limited, leading to a relatively limited precision. Ideally a larger sample size was preferred with higher precision.
2. The cross-sectional study design does not allow us to make causal interferences on whether determinants preceded BDZ use or vice versa. Therefore, the cause-effect relationship could not be ascertained between the long-term BDZ use and the severity of depression, severity of anxiety, level of functioning, level of social support or level of religiosity. We only able to showed the significant association between them in this study.
3. Patients may have tendency to give 'acceptable' answers, especially to the question concerning any substance misuse and dependence such as alcohol, amphetamine, morphine, ecstasy and other types of illicit drug. They may worry about the legal consequences of their substance misuse behavior and termination of benzodiazepines prescription by treating doctor. But we have try to minimize this bias by making clear that the interviewer had no direct connection with the patient's treating doctor and that all information would be used solely for the purpose of research only. Urine test should be used in determined the substance use behavior.
4. There were limited socio-demographic factors captured. Other factors which may be relevant were financial status, amount of debt, social class, type of job and available of caretakers.
5. There were also limited clinical factors captured. Although our patients were relatively stable (as patient recruit 6 months or more after diagnosis of major depressive disorder), however it still a heterogenous group of sample whereby phase of illness, medication dosage, genetic loading data should be captured for more accurate analysis.

6. The internal, interrater, and retest reliability for the overall Hamilton depression scale are mostly good. However, at the individual item level, interrater reliability is poor for many items. Cicchetti and Prusoff assessed reliability before treatment initiation and 16 weeks later at trial end. Only early insomnia was adequately reliable before treatment, and only depressed mood was adequately reliable after treatment (Cicchetti et al., 1983). Beside interrater reliability, the retest coefficients are also weak for many items at the individual item level (Michael et al, 2004).
7. Another limitation of Hamilton depression scale is that atypical symptoms of depression (e.g., hypersomnia, hyperphagia) are not assessed.
8. The internal validity of Hamilton anxiety scale was insufficient (Wolfgang et al., 1988).
9. The applicability of the Hamilton anxiety scale in anxiolytic treatment studies is limited due to its subscale of somatic anxiety is strongly related to somatic side effect (Wolfgang et al., 1988).
10. There was limitation of generalization of the study in view of this study is convenience sampling and non-randomization (Non-probability sampling). This is due to all the individuals in the psychiatric outpatient clinic do not gave equal chance of being selected to participate in this study. Patients who defaulted follow-up or those who admitted to inpatient ward were not captured in this study. Only stable outpatient who willing to come for follow-up in HBUK was selected.

CHAPTER 7: CONCLUSION AND RECOMMENDATIONS

Prevalence of benzodiazepines use among depressed patients in HBUK (87.7%) was higher compare with specialty mental health setting in United State (36%). 70.2% of the benzodiazepine user in HBUK consumes 180 days or more, this figure is higher compare with similar setting in United State (61%).

Despite government regulation, the persistent of depressive and anxiety symptoms appeared to be another risk factor associated with longer duration of benzodiazepines use. In our study, patients with higher score of HAM-D and HAM-A were significantly associated with long-term use of benzodiazepines. This phenomenon most likely due to depressed patients need to take longer duration of benzodiazepine in order to overcome their depressive and anxiety symptoms.

Patient who has better social support was significantly shortened the duration of benzodiazepine use and this was consistent with other similar studies done in oversea. Patients who have better social support were also significantly associated with lower HAM-D and HAM-A score. Therefore social supports have become a determinant of mental health in our study samples.

It was demonstrated that poor religiosity was significantly associated with longer duration of benzodiazepine use. Patients who have poorer religiosity were significantly associated with higher HAM-D and HAM-A score as well. Therefore, good religiosity able to contribute for a better outcome in depressed patient. We noted that the DRI subscale 3 is more reliable in determine the religiosity of the patients compare with DRI total score. This is due to the DRI subscale 3 is measuring the intrinsic religiosity rather extrinsic religiosity. Besides, our study showed that better social support and good religiosity were significantly associated with better functioning level.

After considering above facts, we can conclude that longer duration of benzodiazepines use among depressed are closely related to the severity of the depression, the severity of anxiety, the level of functioning, social support and religiosity. These associations found point to possibilities to reduce long-term benzodiazepine use, for example we can improve these factors in order to reduce the dependence of the patient to benzodiazepines rather than taper off benzodiazepines directly without further examine the factor associated with long-term benzodiazepine use.

Besides, 40% of long-term benzodiazepines user in our study showed decreasing dosage of benzodiazepines use, only 25.0% of them show increasing in dosage. While 35.0% of them showed no change in dosage of benzodiazepines. Therefore we would suggest that our study population is better explained by the "therapeutic use model" than by the "abuse model" as majority of them did not show the tendency of dose escalation, a characteristic feature of "psychological dependence" or "addiction".

In future, it is recommended that a different study design to be use to determine the determinant of long-term use of benzodiazepines among depressed patients. Prospective study design would a better option in order to determine the causal relationship of longer duration benzodiazepine use and social support or religiosity. Apart from that, more extensive studies could be done to study other related socio-demographic and clinical factors involved.

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APPENDICES

APPENDIX 1

LEMBARAN INFORMASI PESAKIT

Sila baca maklumat berikut dengan teliti, jangan ragu untuk membincangkan soalan yang mungkin anda hadapi dengan doktor anda.

Tajuk Penyelidikan

PENGGUNAAN UBAT PENENANG (BENZODIAZEPINES) SECARA JANGKA MASA PANJANG DI KALANGAN PESAKIT KEMURUNGAN (DEPRESSION) / *LONG TERM USE OF BENZODIAZEPINES AMONG DEPRESSED PATIENTS*

Pendahuluan

Penyakit kemurungan (depression) merupakan penyakit mental yang sering dialami oleh masyarakat hari ini. Adalah dijangkakan seramai 17% daripada masyarakat mempunyai risiko menghidapi penyakit kemurungan dalam masa seumur hidup mereka. Pesakit kemurungan pada masa yang sama juga sering kali mengalami tanda kerisauan (anxiety symptoms) ataupun penyakit kerisauan (anxiety disorder). Kewujudan tanda kerisauan di kalangan pesakit kemurungan akan menyusahkan kesembuhan pesakit daripada penyakit kemurungan.

Ubatan kemurungan (antidepressant) adalah berkesan dalam mengubati tanda kesedihan dan tanda kerisauan. Namun demikian, ubat kemurungan mengambil masa beberapa minggu untuk menunjukkan kesannya, oleh itu doktor juga akan memberikan ubat penenang (benzodiazepine) pada waktu permulaan rawatan supaya emosi pesakit dapat dikawal dengan lebih cepat. Tetapi ubat penenang hanya berkesan dari segi pengawalan emosi dan menyenangkan pertiduran, tetapi ia tidak berkesan dalam mengubati penyakit kemurungan.

Kebanyakkan ubat penenang membawa kesan sampingan terutamanya pada pesakit yang menggunakkannya untuk jangka masa panjang. Kesan sampingan yang sering dihadapi oleh pesakit adalah ketagihan kepada ubat tersebut, kekurangan daya ingatan dan mengurangan kecerdasan pemikiran. Memandangkan ubat penenang membawa kesan sampingan yang tidak diingini, maka adalah penting untuk kita mengenalpasti betapa ramai pesakit menggunakan ubat tersebut dalam jangka masa panjang. Maklumat ini akan membolehkan kami menambahbaikan perkhidmatan yang disediakan oleh kami.

Apakah tujuan kajian ini?

Untuk mengenalpasti betapa ramai pesakit kemurungan menggunakan ubat penenang dalam jangka masa panjang serta faktor-faktor yang berkaitan dengan kewujudan keadaan tersebut.

Apa prosedur yang harus diikuti?

Anda akan diminta mengisikan boring kebenaran untuk mengikuti penyelidikan ini. Anda kemudian akan diminta untuk menjawab soalan-soalan dalam set soal selidik. Soalan akan mengambil kira-kira 45 minit. Sebarang pertanyaan anda akan dijelaskan dengan terang oleh doktor.

Tiada sebarang perubahan terhadap rawatan yang sedang anda terima.

Siapakah yang tidak harus menyertai kajian ini?

Mereka yang berumur di bawah 18 tahun atau melebihi umur 65 tahun atau mereka yang tidak dapat berkomunikasi.

Apakah manfaat yang diperolehi dari kajian ini?

(a) Kepada anda?
Anda akan membantu kami dengan menyediakan maklumat yang penting untuk kami dalam proses penambahbaikan kualiti perkhidmatan kami.

(b) Kepada penyelidik?
Anda akan membantu kami untuk menyediakan data yang sangat penting dalam bidang perubatan. Segala maklumat yang diberikan oleh anda adalah sulit.

Apakah kekurangan yang mungkin dihadapi oleh anda?

Anda akan diminta untuk menjawab soal selidik yang mungkin memerlukan 45 minit daripada masa anda.

Bolehkan anda menarik diri dari mengambil bahagian dalam kajian ini?

Ya, anda boleh. Kajian ini adalah bersifat sukarela dan anda boleh menarik diri tanpa menjejaskan kualiti rawatan yang anda sedang terima.

Siapakah yang boleh anda hubungi sekiranya anda mempunyai pertanyaan mengenai kajian ini?

Nama doktor: Dr. Tan Chea Loon Tel : 05-5332333

KEIZINAN OLEH PESAKIT UNTUK PENYELIDIKAN KLINIKAL

Saya,..... **No. Kad Pengenalan** .....
(Nama Pesakit)

beralamat.....
(Alamat)

dengan ini bersetuju menyertai dalam penyelidikan klinikal (pengajian klinikal/pengajian soal-selidik/percubaan ubat-ubatan) disebut berikut:

Tajuk Penyelidikan:

LONG TERM USE OF BENZODIAZEPINES AMONG DEPRESSED PATIENTS

yang mana sifat dan tujuannya telah diterangkan kepada saya oleh Dr......
(Nama & Jawatan Doktor)

mengikut terjemahan .....
(Nama & Jawatan Penterjemah)

yang telah menterjemahkan kepada saya dengan sepenuh kemampuan dan kebolehannya di dalam

Bahasa / loghat.....

Saya telah diberitahu bahawa dasar penyelidikan klinikal dalam keadaan methodologi, risiko dan komplikasi (mengikut kertas maklumat pesakit). Selepas mengetahui dan memahami semua kemungkinan kebaikan dan keburukan penyelidikan klinikal ini, saya merelakan/mengizinkan sendiri menyertai penyelidikan klinikal tersebut di atas.

Saya faham bahawa saya boleh menarik diri dari penyelidikan klinikal ini pada bila-bila masa tanpa memberi sebarang alasan dalam situasi ini dan tidak akan dikecualikan dari kemudahan rawatan dari doktor yang merawat.

Tarikh: ..... **Tandatangan/Cap Jari** .....
(Pesakit)

DI HADAPAN

Nama .....)

No. K/P.....) **Tandatangan** .....
(Saksi untuk Tandatangan Pesakit)

Jawatan .....)

Saya sahkan bahawa saya telah menerangkan kepada pesakit sifat dan tujuan penyelidikan klinikal tersebut di atas.

Tarikh: ..... **Tandatangan** .....
(Doktor yang merawat)

KEIZINAN OLEH WARIS YANG BERTANGGUNGJAWAB UNTUK PENYELIDIKAN KLINIKAL

Saya,..... Kad Pengenalan .....
(Nama Waris yang bertanggungjawab)

beralamat.....
(Alamat)

dengan ini bersetuju supaya saudara saya..... menyertai
(Nama Pesakit)

dalam penyelidikan klinikal (pengajian klinikal/pengajian soal-selidik/percubaan ubat-ubatan) disebut berikut:

Tajuk Penyelidikan:

LONG TERM USE OF BENZODIAZEPINES AMONG DEPRESSED PATIENTS

yang mana sifat dan tujuannya telah diterangkan kepada saya oleh Dr.....
(Nama & Jawatan Doktor)

..... mengikut terjemahan .....
(Nama & Jawatan Penterjemah)

yang telah menterjemahkan kepada saya dengan sepenuh kemampuan dan kebolehannya di dalam Bahasa / loghat.....

Saya telah diberitahu bahawa dasar penyelidikan klinikal dalam keadaan metodologi, risiko dan komplikasi (mengikut kertas maklumat pesakit). Saya mengetahui dan memahami semua kemungkinan kebaikan dan keburukan penyelidikan klinikal ini. Saya merelakan/mengizinkan saudara saya menyertai penyelidikan klinikal tersebut di atas.

Saya faham bahawa saya boleh menarik balik penyertaan saudara saya dalam penyelidikan klinikal ini pada bila-bila masa tanpa memberi sebarang alasan dalam situasi ini dan tidak akan dikecualikan dari kemudahan rawatan dari doktor yang merawat. Sekiranya saudara saya kembali berupaya untuk memberi keizinan, beliau mempunyai hak untuk terus menyertai kajian ini atau memilih untuk menarik diri.

Tarikh: ..... Pertalian dengan Pesakit ..... Tandatangan/Cap Jari Waris yang bertanggungjawab .....

DI HADAPAN

Nama .....)

No. K/P.....) Tandatangan .....
(Tandatangan Saksi)

Jawatan.....)

Saya sahkan bahawa saya telah menerangkan kepada waris yang bertanggungjawab sifat dan tujuan penyelidikan klinikal tersebut di atas.

Tarikh: ..... Tandatangan .....
(Doktor yang merawat)

APPENDIX 2

PATIENT INFORMATION SHEET

Please read the following information carefully, do not hesitate to discuss any questions you may have with your doctor.

Study title

LONG TERM USE OF BENZODIAZEPINES AMONG DEPRESSED PATIENTS

Introduction

Depressive disorders are extremely common, and it has been estimated that approximately 17% of community residents experience a major depressive episode during their lifetime. Depressive disorders are often accompanied by significant anxiety symptoms or full anxiety disorders. The present of anxiety symptoms may predict a poorer long-term outcome and a greater familial prevalence of MDD.

Antidepressant medications are the recommended pharmacological treatment for depression, and many antidepressant are effective for both the core symptoms of depression and for coexisting anxiety. However, antidepressants' beneficial effect often does not occur for several weeks, and physicians may prescribe benzodiazepines for more immediate relief. However, benzodiazepines are less effective than antidepressant, as they address sleeplessness and restlessness but not the other core depressive symptoms.

Most benzodiazepine problem arises with long-term use of these drugs. Impairment of memory, decreased psychomotor performance and dependence are commonly reported adverse effect. In view of the side effect of benzodiazepines, it is important for us to identify the prevalence of long-term use of benzodiazepines among depressed patients in Hospital Bahagia Ulu Kinta. This may create awareness among the clinicians and population.

What is the purpose of this study?

To assess the prevalence of long-term use of benzodiazepines among depressed patients in Hospital Bahagia Ulu Kinta and the possible associated factors

What are the procedures to be followed?

You will be asked by the researcher to fill out an informed consent form. You will then be asked to answer a set of questionnaire; the questions will roughly take 45 minutes. There will be no intervention. You can asked any questions if you are interested.

Who should not enter the study?

Those who are below 18 years old or above 65 years old or those who are too ill to communicate will be excluded from the study.

What will the benefits of the study?

(a) To you as the subject?
You will be helping us by providing information in this area of management which we hopefully can use in providing better services later.

(b) To the investigator?
You will be helping us to provide much needed data in this area of medicine under researched. All information is strictly confidential

What are the possible drawbacks?

You will be required to answer a set of questionnaires which may take up 45 minutes of your time.

Can I refuse to take part in the study?

Yes, you can. This survey is voluntary in nature and you may refuse to participate without any affect to your current care.

Who should I contact if I have additional question during the course of the study?

Doctor's name: Dr. Tan Chea Loon Tel: 05-5332333

CONSENT BY PATIENT FOR CLINICAL RESEARCH

I, ...Identity Card No.....
(Name of Patient)

of.....
(Address)

hereby agree to take part in the clinical research (clinical study/questionnaire study/drug trial) specified below:

Title of Study:

LONG TERM USE OF BENZODIAZEPINES AMONG DEPRESSED PATIENTS

the nature and purpose of which has been explained to me by Dr.....
(Name & Designation of Doctor)

.....and interpreted by .....
(Name & Designation of Interpreter)

.....to the best of his/her ability in ..... language/dialect.

I have been told about the nature of the clinical research in terms of methodology, possible adverse effects and complications (as per patient information sheet). After knowing and understanding all the possible advantages and disadvantages of this clinical research, I voluntarily consent of my own free will to participate in the clinical research specified above.

I understand that I can withdraw from this clinical research at any time without assigning any reason whatsoever and in such a situation shall not be denied the benefits of usual treatment by the attending doctors.

Date: ..... Signature or Thumbprint .....
(Patient)

IN THE PRESENCE OF

Name .....)

Identity Card No. .....) Signature .....
(Witness for Signature of Patient)

Designation .....)

I confirm that I have explained to the patient the nature and purpose of the above-mentioned clinical research.

Date ..... Signature.....
(Attending Doctor)

CONSENT BY RESPONSIBLE RELATIVE FOR CLINICAL RESEARCH

I, ... Identity Card No.....
(Name)

of .....
(Address)

hereby agree that my relative ..... I.C. No.....
(Name)

participate in the clinical research (clinical study/questionnaire study/drug trial) specified below:-

Title of Study:

LONG TERM USE OF BENZODIAZEPINES AMONG DEPRESSED PATIENTS

the nature and purpose of which has been explained to me by Dr. .....
(Name & Designation of Doctor)

..... and interpreted by .....
(Name & Designation of Interpreter)

.....to the best of his/her ability in ..... language/dialect.

I have been informed of the nature of this clinical research in terms of procedure, possible adverse effects and complications (as per patient information sheet). I understand the possible advantages and disadvantages of participating in this research. I voluntarily give my consent for my relative to participate in this research specified above.

I understand that I can withdraw my relative from this clinical research at any time without assigning any reason whatsoever and in such situation, my relative shall not be denied the benefits of usual treatment by the attending doctors. Should my relative regains his/her ability to consent, he/she will have the right to remain in this research or may choose to withdraw.

Date: ..... Relationship to Patient ..... Signature or Thumbprint .....

IN THE PRESENCE OF

Name .....)

Identity Card No. .....) Signature .....
(Witness)

Designation .....)

I confirm that I have explained to the patient's relative the nature and purpose of the above-mentioned clinical research.

Date ..... Signature .....
(Attending Doctor)

APPENDIX 3: SOCIO-DEMOGRAPHIC AND CLINICAL DATA SHEET

Patient Data (no)

Socio-demographic Variables

Patient initials	:	
RN	:	
Age	:	
Gender	□male	□female
Ethnicity	□ Malay	□ Chinese
	□ Indians	□ others
Education level	□ no formal education	□ primary and below
	□ Secondary	□ tertiary
Marriage status	□ single	□ married
	□ Divorce	□ widow/widower
Employment	□ unemployed	□ employed

Clinical variables

Duration of illness	:
Age of onset	:
Antidepressant	:
Benzodiazepine	:
Co-morbid medical illness	:

APPENDIX 4

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 6.0.0

DSM-IV

USA: D. Sheehan[1], J. Janavs, K. Harnett-Sheehan, M. Sheehan, C. Gray.
[1]University of South Florida College of Medicine- Tampa, USA

EU: Y. Lecrubier[2], E. Weiller, T. Hergueta, C. Allgulander, N. Kadri, D. Baldwin, C. Even.
[2]Centre Hospitalier Sainte-Anne – Paris, France

DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

M.I.N.I. 6.0.0 (January 1, 2009)

Patient Name:		*Patient Number:*				
Date of Birth:		*Time Interview Began:*				
Interviewer's Name:		*Time Interview Ended:*				
Date of Interview:		*Total Time:*				

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV-TR	ICD-10	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	☐	296.20-296.26 Single	F32.x	☐
		Past	☐	296.20-296.26 Single	F32.x	☐
		Recurrent	☐	296.30-296.36 Recurrent	F33.x	☐
B	SUICIDALITY	Current (Past Month) ☐ Low ☐ Moderate ☐ High	☐			
C	MANIC EPISODE	Current	☐	296.00-296.06	F30.x-F31.9	☐
		Past	☐			
	HYPOMANIC EPISODE	Current	☐	296.80-296.89	F31.8-F31.9/F34.0	☐
		Past	☐			
	BIPOLAR I DISORDER	Current	☐	296.0x-296.6x	F30.x-F31.9	☐
		Past	☐	296.0x-296.6x	F30.x-F31.9	☐
	BIPOLAR II DISORDER	Current	☐	296.89	F31.8	☐
		Past	☐	296.89	F31.8	☐
	BIPOLAR DISORDER NOS	Current	☐	296.80	F31.9	☐
		Past	☐	296.80	F31.9	☐
D	PANIC DISORDER	Current (Past Month)	☐	300.01/300.21	F40.01-F41.0	☐
		Lifetime	☐			
E	AGORAPHOBIA	Current	☐	300.22	F40.00	☐
F	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)				
		Generalized	☐	300.23	F40.1	☐
		Non-Generalized	☐	300.23	F40.1	☐
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	300.3	F42.8	☐
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	309.81	F43.1	☐
I	ALCOHOL DEPENDENCE	Past 12 Months	☐	303.9	F10.2x	☐
	ALCOHOL ABUSE	Past 12 Months	☐	305.00	F10.1	☐
J	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	☐
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	☐
K	PSYCHOTIC DISORDERS	Lifetime	☐	295.10-295.90/297.1/	F20.xx-F29	☐
		Current	☐	297.3/293.81/293.82/ 293.89/298.8/298.9		
	MOOD DISORDER WITH	Lifetime	☐	296.24/296.34/296.44	F32.3/F33.3/	☐
	PSYCHOTIC FEATURES	Current	☐	296.24/296.34/296.44	F30.2/F31.2/F31.5 F31.8/F31.9/F39	☐
L	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	307.1	F50.0	☐
M	BULIMIA NERVOSA	Current (Past 3 Months)	☐	307.51	F50.2	☐
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	☐	307.1	F50.0	☐
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	300.02	F41.1	☐
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT		☐ No	☐ Yes ☐Uncertain		
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	☐	301.7	F60.2	☐

IDENTIFY THE PRIMARY DIAGNOSIS BY CHECKING THE APPROPRIATE CHECK BOX.
(Which problem troubles you the most or dominates the others or came first in the natural history?)

The translation from DSM-IV-TR to ICD-10 coding is not always exact. For more information on this topic see Schulte-Markwort. Crosswalks ICD-10/DSM-IV-TR. Hogrefe & Huber Publishers 2006.

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

- At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.
- At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question G6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. Interviewers need to be sensitive to the diversity of cultural beliefs in their administration of questions and rating of responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.
The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).
Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session or information about updates of the M.I.N.I., please contact:
David V Sheehan, M.D., M.B.A.
University of South Florida College of Medicine
3515 East Fletcher Ave, Tampa, FL USA 33613-4706
tel : +1 813 974 4544; fax : +1 813 974 4575
e-mail : dsheehan@health.usf.edu

Yves Lecrubier, M.D. / Christian Even, M.D.
Centre Hospitalier Sainte-Anne
Clinique des Maladies Mentales de l'Encéphale
100 rue de la Santé, 75674 Paris Cedex 14, France
tel : +33 (0) 1 53 80 49 41; fax : +33 (0) 1 45 65 88 54
e-mail: ylecrubier@noos.fr or even-sainteanne@orange.fr

A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	a	Were you ever depressed or down, most of the day, nearly every day, for two weeks?	NO	YES
		IF NO, CODE NO TO **A1b**: IF YES ASK:		
	b	For the past two weeks, were you depressed or down, most of the day, nearly every day?	NO	YES
A2	a	Were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks?	NO	YES
		IF NO, CODE NO TO **A2b**: IF YES ASK:		
	b	In the past two weeks, were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time?	NO	YES
			➡	
		IS **A1a** OR **A2a** CODED YES?	NO	YES

A3 IF **A1b** OR **A2b** = YES: EXPLORE THE CURRENT AND THE MOST SYMPTOMATIC PAST EPISODE, OTHERWISE
IF **A1b** AND **A2b** = NO: EXPLORE ONLY THE MOST SYMPTOMATIC PAST EPISODE

Over that two week period, when you felt depressed or uninterested:

		Past 2 Weeks		Past Episode	
a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lbs. or ±3.5 kgs., for a 160 lb./70 kg. person in a month)? IF YES TO EITHER, CODE YES.	NO	YES	NO	YES
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES	NO	YES
d	Did you feel tired or without energy almost every day?	NO	YES	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES	NO	YES
	IF YES, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes; Past Episode ☐ No ☐ Yes				
f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead? Did you attempt suicide or plan a suicide? IF YES TO EITHER, CODE YES.	NO	YES	NO	YES
A4	Did these symptoms cause significant problems at home, at work, socially, at school or in some other important way?	NO	YES	NO	YES

A5 In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any significant depression or any significant loss of interest? NO YES

ARE 5 OR MORE ANSWERS (A1-A3) CODED YES AND IS A4 CODED YES FOR THAT TIME FRAME?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF A5 IS CODED YES, CODE YES FOR RECURRENT.

NO	YES
MAJOR DEPRESSIVE EPISODE	
CURRENT	❐
PAST	❐
RECURRENT	❐

A6 a How many episodes of depression did you have in your lifetime? ____

Between each episode there must be at least 2 months without any significant depression.

B. SUICIDALITY

				Points
	In the past month did you:			
B1	Suffer any accident? IF NO TO B1, SKIP TO B2; IF YES, ASK B1a:	NO	YES	0
B1a	Plan or intend to hurt yourself in that accident either actively or passively (e.g. not avoiding a risk)? IF NO TO B1a, SKIP TO B2: IF YES, ASK B1b:	NO	YES	0
B1b	Intend to die as a result of this accident?	NO	YES	0
B2	Feel hopeless?	NO	YES	1
B3	Think that you would be better off dead or wish you were dead?	NO	YES	1
B4	Want to harm yourself or to hurt or to injure yourself or have mental images of harming yourself?	NO	YES	2
B5	Think about suicide? IF NO TO B5, SKIP TO B7. OTHERWISE ASK:	NO	YES	6

Frequency		Intensity	
Occasionally	❐	Mild	❐
Often	❐	Moderate	❐
Very often	❐	Severe	❐

	Can you state that you will not act on these impulses during this treatment program?	NO	YES	
B6	Feel unable to control these impulses?	NO	YES	8
B7	Have a suicide plan?	NO	YES	8
B8	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die?	NO	YES	9
B9	Deliberately injure yourself without intending to kill yourself?	NO	YES	4
B10	Attempt suicide? IF NO SKIP TO B11: Hope to be rescued / survive ❐ Expected / intended to die ❐	NO	YES	9
	In your lifetime:			
B11	Did you ever make a suicide attempt?	NO	YES	4

IS AT LEAST 1 OF THE ABOVE (EXCEPT B1) CODED YES?

IF YES, ADD THE TOTAL POINTS FOR THE ANSWERS (B1-B11) CHECKED 'YES' AND SPECIFY THE SUICIDALITY SCORE AS INDICATED IN THE DIAGNOSTIC BOX:

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDALITY IN THE SPACE BELOW:

NO YES

SUICIDALITY CURRENT

1-8 points	Low	❒
9-16 points	Moderate	❒
≥ 17 points	High	❒

C. MANIC AND HYPOMANIC EPISODES

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN MANIC AND HYPOMANIC DIAGNOSTIC BOXES, AND MOVE TO NEXT MODULE)

Do you have any family history of manic depressive illness or bipolar disorder, or any family member who had mood swings treated with a medication like lithium, sodium valproate (Depakote) or lamotrigine (Lamictal)? NO YES

THIS QUESTION IS NOT A CRITERION FOR BIPOLAR DISORDER, BUT IS ASKED TO INCREASE THE CLINICIAN'S VIGILANCE ABOUT THE RISK FOR BIPOLAR DISORDER.

IF YES, PLEASE SPECIFY WHO:_____

C1 a Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, - or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) NO YES

IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior; phoning or working excessively or spending more money.

IF NO, CODE NO TO **C1b**: IF YES ASK:

b Are you currently feeling 'up' or 'high' or 'hyper' or full of energy? NO YES

C2 a Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? NO YES

IF NO, CODE NO TO **C2b**: IF YES ASK:

b Are you currently feeling persistently irritable? NO YES

➡

IS **C1a** OR **C2a** CODED YES? NO YES

C3 IF **C1b** OR **C2b** = YES: EXPLORE THE CURRENT AND THE MOST SYMPTOMATIC PAST EPISODE, OTHERWISE
IF **C1b** AND **C2b** = NO: EXPLORE ONLY THE MOST SYMPTOMATIC PAST EPISODE

During the times when you felt high, full of energy, or irritable did you:

	Current Episode		Past Episode	
a Feel that you could do things others couldn't do, or that you were an especially important person? IF YES, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes Past Episode ☐ No ☐ Yes	NO	YES	NO	YES
b Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
c Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d Have racing thoughts?	NO	YES	NO	YES

		Current Episode		Past Episode	
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Have a significant increase in your activity or drive, at work, at school, socially or sexually or did you become physically or mentally restless?	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES
C3	SUMMARY: WHEN RATING CURRENT EPISODE: IF C1b IS NO, ARE 4 OR MORE C3 ANSWERS CODED YES? IF C1b IS YES, ARE 3 OR MORE C3 ANSWERS CODED YES?	NO	YES	NO	YES
	WHEN RATING PAST EPISODE: IF C1a IS NO, ARE 4 OR MORE C3 ANSWERS CODED YES? IF C1a IS YES, ARE 3 OR MORE C3 ANSWERS CODED YES?				
	CODE YES ONLY IF THE ABOVE 3 OR 4 SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.				
	RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE C3 SYMPTOMS, WHILE IRRITABLE MOOD ALONE REQUIRES 4 OF THE C3 SYMPTOMS.				
C4	What is the longest time these symptoms lasted?				
	a) 3 days or less		❑		❑
	b) 4 to 6 days		❑		❑
	c) 7 days or more		❑		❑
C5	Were you hospitalized for these problems?	NO	YES	NO	YES
	IF YES, STOP HERE AND CIRCLE YES IN MANIC EPISODE FOR THAT TIME FRAME.				
C6	Did these symptoms cause significant problems at home, at work, socially in your relationships with others, at school or in some other important way?	NO	YES	NO	YES

ARE C3 SUMMARY AND C5 AND C6 CODED YES AND EITHER C4a or b or c CODED YES?

OR

ARE C3 SUMMARY AND C4c AND C6 CODED YES AND IS C5 CODED NO?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

NO YES

MANIC EPISODE

CURRENT ❑
PAST ❑

ARE C3 SUMMARY AND C5 AND C6 CODED NO AND EITHER C4b OR C4C CODED YES?

OR

ARE C3 SUMMARY AND C4b AND C6 CODED YES AND IS C5 CODED NO?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

NO YES

HYPOMANIC EPISODE

CURRENT ❑
PAST ❑

ARE C3 SUMMARY AND **C4a** CODED YES AND IS C5 CODED NO? NO YES

HYPOMANIC SYMPTOMS

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

CURRENT ❒
PAST ❒

C7 a) IF MANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more manic episodes (**C4c**) in your lifetime (including the current episode if present)? NO YES

b) IF HYPOMANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more hypomanic EPISODES (**C4b**) in your lifetime (including the current episode)? NO YES

c) IF PAST "HYPOMANIC SYMPTOMS" IS CODED POSITIVE ASK:
Did you have 2 or more episodes of hypomanic SYMPTOMS (**C4a**) in your lifetime (including the current episode if present)? NO YES

D. PANIC DISORDER

(➡ MEANS : CIRCLE NO IN D5, D6 AND D7 AND SKIP TO E1)

D1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO	YES
D2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
D3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack - or did you make a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms)?	NO	YES
D4		**During the worst attack that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
D5		ARE BOTH **D3**, AND **4** OR MORE **D4** ANSWERS, CODED YES? IF YES TO D5, SKIP TO D7.	NO	YES *PANIC DISORDER LIFETIME*
D6		IF **D5 = NO**, ARE ANY D4 ANSWERS CODED YES? THEN SKIP TO **E1.**	NO	YES *LIMITED SYMPTOM ATTACKS LIFETIME*

D7	In the past month, did you have such attacks repeatedly (2 or more), and did you have persistent concern about having another attack, or worry about the consequences of the attacks, or did you change your behavior in any way because of the attacks?	NO	YES *PANIC DISORDER CURRENT*

E. AGORAPHOBIA

E1	Do you feel anxious or uneasy in places or situations where help might not be available or escape might be difficult, like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, or traveling in a bus, train or car or where you might have a panic attack or the panic-like symptoms we just spoke about?	NO	YES

IF **E1 = NO**, CIRCLE **NO** IN **E2**.

E2	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	NO	YES *AGORAPHOBIA CURRENT*

IS **E2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **D7** (CURRENT PANIC DISORDER) CODED **YES**?

NO YES

PANIC DISORDER with Agoraphobia CURRENT

IS **E2** (CURRENT AGORAPHOBIA) CODED **NO**

and

IS **D7** (CURRENT PANIC DISORDER) CODED **YES**?

NO YES

PANIC DISORDER without Agoraphobia CURRENT

IS **E2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **D5** (PANIC DISORDER LIFETIME) CODED **NO**?

NO YES

AGORAPHOBIA, CURRENT without history of Panic Disorder

F. SOCIAL PHOBIA (Social Anxiety Disorder)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

F1	In the past month, did you have persistent fear and significant anxiety at being watched, being the focus of attention, or of being humiliated or embarrassed? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➡ NO	YES
F2	Is this social fear excessive or unreasonable and does it almost always make you anxious?	➡ NO	YES
F3	Do you fear these social situations so much that you avoid them or suffer through them most of the time?	➡ NO	YES
F4	Do these social fears disrupt your normal work, school or social functioning or cause you significant distress?	NO	YES

SUBTYPES

Do you fear and avoid 4 or more social situations?

If YES Generalized social phobia (social anxiety disorder)

If NO Non-generalized social phobia (social anxiety disorder)

EXAMPLES OF SUCH SOCIAL SITUATIONS TYPICALLY INCLUDE

- INITIATING OR MAINTAINING A CONVERSATION,
- PARTICIPATING IN SMALL GROUPS,
- DATING,
- SPEAKING TO AUTHORITY FIGURES,
- ATTENDING PARTIES,
- PUBLIC SPEAKING,
- EATING IN FRONT OF OTHERS,
- URINATING IN A PUBLIC WASHROOM, ETC.

NOTE TO INTERVIEWER: PLEASE ASSESS WHETHER THE SUBJECT'S FEARS ARE RESTRICTED TO NON-GENERALIZED ("ONLY 1 OR SEVERAL") SOCIAL SITUATIONS OR EXTEND TO GENERALIZED ("MOST") SOCIAL SITUATIONS. "MOST" SOCIAL SITUATIONS IS USUALLY OPERATIONALIZED TO MEAN 4 OR MORE SOCIAL SITUATIONS, ALTHOUGH THE DSM-IV DOES NOT EXPLICITLY STATE THIS.

SOCIAL PHOBIA
(Social Anxiety Disorder)
CURRENT

GENERALIZED ❒

NON-GENERALIZED ❒

G. OBSESSIVE-COMPULSIVE DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? - (For example, the idea that you were dirty, contaminated or had germs, or fear of contaminating others, or fear of harming someone even though it disturbs or distresses you, or fear you would act on some impulse, or fear or superstitions that you would be responsible for things going wrong, or obsessions with sexual thoughts, images or impulses, or hoarding, collecting, or religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO YES ↓ SKIP TO G4
G2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES ↓ SKIP TO G4
G3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	NO YES obsessions
G4	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?	NO YES compulsions
	IS G3 OR G4 CODED YES?	➡ NO YES
G5	At any point, did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?	➡ NO YES
G6	In the past month, did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?	NO YES *O.C.D. CURRENT*

H. POSTTRAUMATIC STRESS DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

H1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, WAR, OR NATURAL DISASTER, WITNESSING THE VIOLENT OR SUDDEN DEATH OF SOMEONE CLOSE TO YOU, OR A LIFE THREATENING ILLNESS.	➡ NO	YES
H2	Did you respond with intense fear, helplessness or horror?	➡ NO	YES
H3	During the past month, have you re-experienced the event in a distressing way (such as in dreams, intense recollections, flashbacks or physical reactions) or did you have intense distress when you were reminded about the event or exposed to a similar event?	➡ NO	YES

H4	In the past month:			
	a	Have you avoided thinking about or talking about the event ?	NO	YES
	b	Have you avoided activities, places or people that remind you of the event?	NO	YES
	c	Have you had trouble recalling some important part of what happened?	NO	YES
	d	Have you become much less interested in hobbies or social activities?	NO	YES
	e	Have you felt detached or estranged from others?	NO	YES
	f	Have you noticed that your feelings are numbed?	NO	YES
	g	Have you felt that your life will be shortened or that you will die sooner than other people?	NO	YES
		ARE 3 OR MORE **H4** ANSWERS CODED YES?	➡ NO	YES
H5	In the past month:			
	a	Have you had difficulty sleeping?	NO	YES
	b	Were you especially irritable or did you have outbursts of anger?	NO	YES
	c	Have you had difficulty concentrating?	NO	YES
	d	Were you nervous or constantly on your guard?	NO	YES
	e	Were you easily startled?	NO	YES
		ARE 2 OR MORE **H5** ANSWERS CODED YES?	➡ NO	YES

H6	During the past month, have these problems significantly interfered with your work, school or social activities, or caused significant distress?	NO	YES
			POSTTRAUMATIC STRESS DISORDER CURRENT

I. ALCOHOL DEPENDENCE / ABUSE

(➡ MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE NO IN BOTH AND MOVE TO THE NEXT MODULE)

			➡	
I1		**In the past 12 months**, have you had 3 or more alcoholic drinks, - within a 3 hour period, - on 3 or more occasions?	NO	YES
I2		**In the past 12 months**:		
	a	Did you need to drink a lot more in order to get the same effect that you got when you first started drinking or did you get much less effect with continued use of the same amount?	NO	YES
	b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms (for example, "the shakes", sweating or agitation) or to avoid being hungover? IF YES TO ANY, CODE YES.	NO	YES
	c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
	d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
	e	On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES
	f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
	g	If your drinking caused you health or mental problems, did you still keep on drinking?	NO	YES

ARE 3 OR MORE I2 ANSWERS CODED YES?

NO YES*

* IF YES, SKIP I3 QUESTIONS AND GO TO NEXT MODULE. "DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

ALCOHOL DEPENDENCE
CURRENT

I3		**In the past 12 months**:		
	a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE YES ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
	b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
	c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
	d	If your drinking caused problems with your family or other people, did you still keep on drinking?	NO	YES

ARE 1 OR MORE I3 ANSWERS CODED YES?

NO	YES
	ALCOHOL ABUSE CURRENT

J. SUBSTANCE DEPENDENCE / ABUSE (NON-ALCOHOL)

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

			➡	
J1	a	**In the past 12 months, did you take any of these drugs more than once, to get high, to feel elated, to get "a buzz" or to change your mood?**	NO	YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, Darvon, codeine, Percodan, Vicoden, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA.

Phencyclidine: PCP ("Angel Dust", "PeaCe Pill", "Tranq", "Hog"), or ketamine ("special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Cannabis: marijuana, hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Cough Medicine? Any others?

SPECIFY THE MOST USED DRUG(S): _____

WHICH DRUG(S) CAUSE THE BIGGEST PROBLEMS?: _____

FIRST EXPLORE THE DRUG CAUSING THE BIGGEST PROBLEMS AND MOST LIKELY TO MEET DEPENDENCE / ABUSE CRITERIA.

IF MEETS CRITERIA FOR ABUSE OR DEPENDENCE, SKIP TO THE NEXT MODULE. OTHERWISE, EXPLORE THE NEXT MOST PROBLEMATIC DRUG.

J2 **Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:**

	a	Have you found that you needed to use much more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	NO	YES
	b	When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?	NO	YES
		IF YES TO EITHER, CODE YES.		
	c	Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?	NO	YES
	d	Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?	NO	YES
	e	On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or in recovering from the drug, or thinking about the drug?	NO	YES
	f	Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use?	NO	YES
	g	If (NAME OF DRUG / DRUG CLASS SELECTED) caused you health or mental problems, did you still keep on using it?	NO	YES

ARE 3 OR MORE J2 ANSWERS CODED YES?

SPECIFY DRUG(S): _____

* IF YES, SKIP J3 QUESTIONS, MOVE TO NEXT DISORDER.
"DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

NO YES *

SUBSTANCE DEPENDENCE
CURRENT

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

J3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem?

(CODE YES ONLY IF THIS CAUSED PROBLEMS.) NO YES

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct? NO YES

d If (NAME OF DRUG / DRUG CLASS SELECTED) caused problems with your family or other people, did you still keep on using it? NO YES

ARE 1 OR MORE J3 ANSWERS CODED YES?

SPECIFY DRUG(S): _____

NO YES

SUBSTANCE ABUSE
CURRENT

K. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE YES ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.
HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.
THE PURPOSE OF THIS MODULE IS TO EXCLUDE PATIENTS WITH PSYCHOTIC DISORDERS. THIS MODULE NEEDS EXPERIENCE.

		Now I am going to ask you about unusual experiences that some people have.			BIZARRE
K1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? NOTE: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES └K6
K2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES └K6
K3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES └K6
K4	a	Have you ever believed that you were being sent special messages through the TV, radio, newspapers, books or magazines or that a person you did not personally know was particularly interested in you?	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES └K6
K5	a	Have your relatives or friends ever considered any of your beliefs odd or unusual? INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS K1 TO K4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITUTION, ETC.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do they currently consider your beliefs strange?	NO	YES	YES
K6	a	Have you ever heard things other people couldn't hear, such as voices?	NO	YES	
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO		YES
	b	**IF YES OR YES BIZARRE TO K6a:** have you heard sounds / voices in the past month?	NO	YES	
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO		YES └K8b

K7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES

CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b IF YES: have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

K8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

K9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

K10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

K11 a ARE 1 OR MORE « a » QUESTIONS FROM K1a TO K7a CODED YES OR YES BIZARRE AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT, RECURRENT OR PAST)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED YES? NO YES
└ K13

IF NO TO K11 a, CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO K13.

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED YES FROM **K1a** TO **K7a**) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

IF THE ANSWER IS NO TO THIS DISORDER, ALSO CIRCLE NO TO K12 AND MOVE TO K13

NO YES

MOOD DISORDER WITH
PSYCHOTIC FEATURES

LIFETIME

K12 a ARE 1 OR MORE « b » QUESTIONS FROM K1b TO K7b CODED YES OR YES BIZARRE AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT) CODED YES?

IF THE ANSWER IS YES TO THIS DISORDER (LIFETIME OR CURRENT), CIRCLE NO TO K13 AND K14 AND MOVE TO THE NEXT MODULE.

NO YES

MOOD DISORDER WITH
PSYCHOTIC FEATURES

CURRENT

K13 ARE 1 OR MORE « b » QUESTIONS FROM K1b TO K6b, CODED YES BIZARRE?

OR

ARE 2 OR MORE « b » QUESTIONS FROM K1b TO K10b, CODED YES (RATHER THAN YES BIZARRE)?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO YES

PSYCHOTIC DISORDER
CURRENT

K14 IS K13 CODED YES

OR

ARE 1 OR MORE « a » QUESTIONS FROM K1a TO K6a, CODED YES BIZARRE?

OR

ARE 2 OR MORE « a » QUESTIONS FROM K1a TO K7a, CODED YES (RATHER THAN YES BIZARRE)

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO YES

PSYCHOTIC DISORDER
LIFETIME

L. ANOREXIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

L1	a	How tall are you?	❑ft ❑❑in. ❑ ❑ ❑cm.	
	b.	What was your lowest weight in the past 3 months?	❑ ❑ ❑lbs. ❑ ❑ ❑kgs.	
	c	IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)	➡ NO	YES
		In the past 3 months:		
L2		In spite of this low weight, have you tried not to gain weight?	➡ NO	YES
L3		Have you intensely feared gaining weight or becoming fat, even though you were underweight?	➡ NO	YES
L4	a	Have you considered yourself too big / fat or that part of your body was too big / fat?	NO	YES
	b	Has your body weight or shape greatly influenced how you felt about yourself?	NO	YES
	c	Have you thought that your current low body weight was normal or excessive?	NO	YES
L5		ARE 1 OR MORE ITEMS FROM L4 CODED YES?	➡ NO	YES
L6		FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?	➡ NO	YES

FOR WOMEN: ARE L5 AND L6 CODED YES?

FOR MEN: IS L5 CODED YES?

NO YES

ANOREXIA NERVOSA
CURRENT

HEIGHT / WEIGHT TABLE CORRESPONDING TO A **BMI THRESHOLD** OF **17.5** KG/M²

Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lbs.	81	84	87	89	92	96	99	102	105	108	112	115	118	122
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs	37	38	39	41	42	43	45	46	48	49	51	52	54	55

Height/Weight					
ft/in	5'11	6'0	6'1	6'2	6'3
lbs.	125	129	132	136	140
cm	180	183	185	188	191
kgs	57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m² for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.

M. BULIMIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

M1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➡ NO	YES
M2	In the last 3 months, did you have eating binges as often as twice a week?	➡ NO	YES
M3	During these binges, did you feel that your eating was out of control?	➡ NO	YES
M4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	➡ NO	YES
M5	Does your body weight or shape greatly influence how you feel about yourself?	➡ NO	YES
M6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO	YES ↓ Skip to M8
M7	Do these binges occur only when you are under (____lbs./kgs.)? INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO	YES

M8 IS **M5** CODED YES AND IS EITHER **M6** OR **M7** CODED NO?

NO YES

BULIMIA NERVOSA
CURRENT

IS **M7** CODED YES?

NO YES

ANOREXIA NERVOSA
Binge Eating/Purging Type
CURRENT

N. GENERALIZED ANXIETY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

N1	a	Were you excessively anxious or worried about several routine things, over the past 6 months? IN ENGLISH, IF THE PATIENT IS UNCLEAR ABOUT WHAT YOU MEAN, PROBE BY ASKING (Do others think that you are a "worry wart") AND GET EXAMPLES.	➡ NO	YES
	b	Are these anxieties and worries present most days?	➡ NO	YES
		ARE THE PATIENT'S ANXIETY AND WORRIES RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	➡ YES
N2		Do you find it difficult to control the worries?	➡ NO	YES
N3		FOR THE FOLLOWING, CODE NO IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT.		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Have muscle tension?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
		ARE 3 OR MORE N3 ANSWERS CODED YES?	➡ NO	YES
N4		Do these anxieties and worries disrupt your normal work, school or social functioning or cause you significant distress?	NO	YES

GENERALIZED ANXIETY DISORDER CURRENT

O. RULE OUT MEDICAL, ORGANIC OR DRUG CAUSES FOR ALL DISORDERS

IF THE PATIENT CODES POSITIVE FOR ANY CURRENT DISORDER ASK:

Just before these symptoms began:

O1a	Were you taking any drugs or medicines?	❒ No	❒ Yes	❒ Uncertain
O1b	Did you have any medical illness?	❒ No	❒ Yes	❒ Uncertain
	IN THE CLINICIAN'S JUDGMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S DISORDER? IF NECESSARY ASK ADDITIONAL OPEN-ENDED QUESTIONS.			
O2	SUMMARY: HAS AN ORGANIC CAUSE BEEN RULED OUT?	❒ No	❒ Yes	❒ Uncertain

P. ANTISOCIAL PERSONALITY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO)

P1 **Before you were 15 years old, did you:**

a	repeatedly skip school or run away from home overnight?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone to have sex with you?	NO	YES
	ARE 2 OR MORE P1 ANSWERS CODED YES?	NO ➡	YES

DO NOT CODE YES TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.

P2 **Since you were 15 years old, have you:**

a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
e	exposed others to danger without caring?	NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

ARE 3 OR MORE P2 QUESTIONS CODED YES?

NO	YES
ANTISOCIAL PERSONALITY DISORDER **LIFETIME**	

THIS CONCLUDES THE INTERVIEW

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Scientific committee for the MINI 6.0.0:

A. Carlo Altamura, Milano, Italy
Cyril Hoschl, Praha, Czech Republic
George Papadimitriou, Athens, Greece
Hans Ågren, Göteborg, Sweden
Hans-Jürgen Möller, München, Germany
Hans-Ulrich Wittchen, Dresden, Germany
István Bitter, Budapest, Hungary
Jean-Pierre Lépine, Paris, France
Jules Angst, Zurich, Switzerland
Julio Bobes, Oviedo, Spain
Luciano Conti, Pisa, Italy
Marelli Colon-Soto MD, Puerto Rico, United States
Michael Van Ameringen MD, Toronto, Canada
Rosario Hidalgo MD, Tampa, United States
Siegfried Kasper, Vienna, Austria
Thomas Schlaepfer, Bonn, Germany

Translations	M.I.N.I. 4.4 or earlier versions	M.I.N.I. 4.6/5.0, M.I.N.I. Plus 4.6/5.0 and M.I.N.I. Screen 5.0:
Afrikaans	R. Emsley, W. Maartens	
Arabic		O. Osman, E. Al-Radi
Bengali		H. Banerjee, A. Banerjee
Braille (English)		
Brazilian Portuguese	P. Amorim	P. Amorim
Bulgarian	L.G. Hranov	
Chinese		L. Carroll, Y-J. Lee, Y-S. Chen, C-C. Chen, C-Y. Liu, C-K. Wu, H-S. Tang, K-D. Juang, Yan-Ping Zheng, P. Svlosky
Czech		
Danish	P. Bech	P. Bech, T. Schütze
Dutch/Flemish	E. Griez, K. Shruers, T. Overbeek, K. Demyttenaere	I. Van Vliet, H. Leroy, H. van Megen
English	D. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan, E. Knapp, M. Sheehan	D. Sheehan, R. Baker, J. Janavs, K. Harnett-Sheehan, M. Sheehan
Estonian		J. Shlik, A. Aluoja, E. Khil
Farsi/Persian		K. Khooshabi, A. Zomorodi
Finnish	M. Heikkinen, M. Lijeström, O. Tuominen	M. Heikkinen, M. Lijeström, O. Tuominen
French	Y. Lecrubier, E. Weiller, I. Bonora, P. Amorim, J.P. Lepine	Y. Lecrubier, E. Weiller, P. Amorim, T. Hergueta
German	I. v. Denffer, M. Ackenheil, R. Dietz-Bauer	G. Stotz, R. Dietz-Bauer, M. Ackenheil
Greek	S. Beratis	T. Calligas, S. Beratis, GN Papidimitriou, T Matsoukas CR Soldatos
Gujarati		M. Patel, B. Patel, Organon
Hebrew	J. Zohar, Y. Sasson	R. Barda, I. Levinson, A. Aviv
Hindi		C. Mittal, K. Batra, S. Gambhir, Organon
Hungarian	I. Bitter, J. Balazs	I. Bitter, J. Balazs
Icelandic		J.G. Stefansson
Italian	I. Bonora, L. Conti, M. Piccinelli, M. Tansella, G. Cassano, Y. Lecrubier, P. Donda, E. Weiller	L. Conti, A. Rossi, P. Donda
Japanese		T. Otsubo, H. Watanabe, H. Miyaoka, K. Kamijima, J.Shinoda, K.Tanaka, Y. Okajima

Kannada		Organon
Korean		K.S. Oh and Korean Academy of Anxiety Disorders
Latvian	V. Janavs, J. Janavs, I. Nagobads	V. Janavs, J. Janavs
Lithuanian		A. Bacevicius
Luganda		WW. Muhweziosal, H. Agren
Malayalam		Organon
Marathi		Organon
Norwegian	G. Pedersen, S. Blomhoff	K.A. Leiknes , U. Malt, E. Malt, S. Leganger
Polish	M. Masiak, E. Jasiak	M. Masiak, E. Jasiak
Portuguese	P. Amorim	P. Amorim, T. Guterres
Punjabi		A. Gahunia, S. Gambhir
Romanian		O. Driga
Russian		A. Bystritsky, E. Selivra, M. Bystritsky, L. Shumyak, M. Klisinska.
Serbian	I. Timotijevic	I. Timotijevic
Setswana	K. Ketlogetswe	
Slovenian	M. Kocmur	
Spanish	L. Ferrando, J. Bobes-Garcia, J. Gilbert-Rahola, Y. Lecrubier	L. Ferrando, L. Franco-Alfonso, M. Soto, J. Bobes-Garcia, O. Soto, L. Franco, G. Heinze, C. Santana, R. Hidalgo
Swedish	M. Waern, S. Andersch, M. Humble	C. Allgulander, H. Agren M. Waern, A. Brimse, M. Humble.
Tamil		Organon
Telugu		Organon
Thai		P. Kittirattanapaiboon, S. Mahatnirunkul, P. Udomrat, P. Silpakit,, M. Khamwongpin, S. Srikosai.
Turkish	T. Örnek, A. Keskiner, I. Vahip	T. Örnek, A. Keskiner, A.Engeler
Urdu		S. Gambhir
Yiddish		J. Goldman, Chana Pollack, Myrna Mniewski

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MOOD DISORDERS: DIAGNOSTIC ALGORITHM

Consult Modules:

A	Major Depressive Episode
C	(Hypo) manic Episode
K	Psychotic Disorders

MODULE K:

1a	IS **K11b** CODED YES?	NO	YES
1b	IS **K12a** CODED YES?	NO	YES

MODULES A and C:		Current	Past
2 a	CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **A3e**?	YES	YES
b	CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **C3a**?	YES	YES

c Is a Major Depressive Episode coded YES (current or past)?
and
is Manic Episode coded NO (current and past)?
and
is Hypomanic Episode coded NO (current and past)?
and
is "Hypomanic Symptoms" coded NO (current and past)?

Specify:

- if the depressive episode is current or past or both
- **With Psychotic Features** Current: If 1b or 2a (current) = YES
  With Psychotic Features Past: If 1a or 2a (past) = YES

MAJOR DEPRESSIVE DISORDER

	current	past
MDD	❑	❑

With Psychotic Features

Current	❑
Past	❑

d Is a Manic Episode coded YES (current or past)?

Specify:

- If the Bipolar I Disorder is **current or past** or both
- With **Single Manic Episode**: If Manic episode (current or past) = YES
  and MDE (current and past) = NO
- **With Psychotic Features** Current: If 1b or 2a (current) or 2b (current) = YES
  With Psychotic Features Past: If 1a or 2a (past) or 2b (past) = YES
- If the **most recent episode** is manic, depressed,
  mixed or hypomanic or unspecified (all mutually exclusive)
- **Unspecified** if the Past Manic Episode is coded YES AND
  Current (C3 Summary AND C4a AND C6 AND O2) are coded YES

BIPOLAR I DISORDER

	current	past
Bipolar I Disorder	❑	❑
Single Manic Episode	❑	❑

With Psychotic Features

Current	❑
Past	❑

Most Recent Episode

Manic	❑
Depressed	❑
Mixed	❑
Hypomanic	❑
Unspecified	❑

---

e Is Major Depressive Episode coded YES (current or past)?
and
Is Hypomanic Episode coded YES (current or past)?
and
Is Manic Episode coded NO (current and past)?

Specify:

- If the Bipolar Disorder is **current** or **past** or both
- If the most recent mood episode is **hypomanic** or **depressed** (mutually exclusive)

BIPOLAR II DISORDER

	current	past
Bipolar II Disorder	❑	❑

Most Recent Episode

Hypomanic	❑
Depressed	❑

f Is MDE coded NO (current and past)
and
Is Manic Episode coded NO (current and past)?
and is either:

1) C7b coded YES for the appropriate time frame?

or

2) C3 Summary coded YES for the appropriate time frame?
and
C4a coded YES for the appropriate time frame?
and
C7c coded YES for the appropriate time frame?

Specify if the Bipolar Disorder NOS is **current** or **past** or both

BIPOLAR DISORDER NOS

	current	past
Bipolar Disorder NOS	❑	❑

M.I.N.I. PLUS

The shaded modules below are additional modules available in the MINI PLUS beyond what is available in the standard MINI. The un-shaded modules below are in the standard MINI.

These MINI PLUS modules can be inserted into or used in place of the standard MINI modules, as dictated by the specific needs of any study.

	MODULES	TIME FRAME
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks) Past Recurrent
	MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current Past
	SUBSTANCE INDUCED MOOD DISORDER	Current Past
	MDE WITH MELANCHOLIC FEATURES	Current (2 weeks)
	MDE WITH ATYPICAL FEATURES	Current (2 weeks)
	MDE WITH CATATONIC FEATURES	Current (2 weeks)
B	DYSTHYMIA	Current (Past 2 years) Past
C	SUICIDALITY	Current (Past Month) Risk: ❑ Low ❑ Medium ❑ High
D	MANIC EPISODE	Current Past
	HYPOMANIC EPISODE	Current Past
	BIPOLAR I DISORDER	Current Past
	BIPOLAR II DISORDER	Current Past
	BIPOLAR DISORDER NOS	Current Past
	MANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current Past
	HYPOMANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current Past
	SUBSTANCE INDUCED MANIC EPISODE	Current Past
	SUBSTANCE INDUCED HYPOMANIC EPISODE	Current Past
E	PANIC DISORDER	Current (Past Month) Lifetime
	ANXIETY DISORDER WITH PANIC ATTACKS DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED ANXIETY DISORDER WITH PANIC ATTACKS	Current
F	AGORAPHOBIA	Current
G	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)
H	SPECIFIC PHOBIA	Current
I	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)
	OCD DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED OCD	Current
J	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)
K	ALCOHOL DEPENDENCE	Past 12 Months
	ALCOHOL DEPENDENCE	Lifetime
	ALCOHOL ABUSE	Past 12 Months
	ALCOHOL ABUSE	Lifetime
L	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months
	SUBSTANCE DEPENDENCE (Non-alcohol)	Lifetime
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months

M	PSYCHOTIC DISORDERS	Lifetime
		Current
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Current
	SCHIZOPHRENIA	Current
		Lifetime
	SCHIZOAFFECTIVE DISORDER	Current
		Lifetime
	SCHIZOPHRENIFORM DISORDER	Current
		Lifetime
	BRIEF PSYCHOTIC DISORDER	Current
		Lifetime
	DELUSIONAL DISORDER	Current
		Lifetime
	PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current
		Lifetime
	SUBSTANCE INDUCED PSYCHOTIC DISORDER	Current
		Lifetime
	PSYCHOTIC DISORDER NOS	Current
		Lifetime
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime
	MOOD DISORDER NOS	Lifetime
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current
		Past
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current
		Past
N	ANOREXIA NERVOSA	Current (Past 3 Months)
O	BULIMIA NERVOSA	Current (Past 3 Months)
	BULIMIA NERVOSA PURGING TYPE	Current
	BULIMIA NERVOSA NONPURGING TYPE	Current
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current
	ANOREXIA NERVOSA, RESTRICTING TYPE	Current
P	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)
	GENERALIZED ANXIETY DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED GAD	Current
Q	ANTISOCIAL PERSONALITY DISORDER	Lifetime
R	SOMATIZATION DISORDER	Lifetime
		Current
S	HYPOCHONDRIASIS	Current
T	BODY DYSMORPHIC DISORDER	Current
U	PAIN DISORDER	Current
V	CONDUCT DISORDER	Past 12 Months
W	ATTENTION DEFICIT/HYPERACTIVITY DISORDER (Children/Adolescents)	Past 6 Months
	ATTENTION DEFICIT/HYPERACTIVITY DISORDER (Adults)	Lifetime
		Current
X	ADJUSTMENT DISORDERS	Current
Y	PREMENSTRUAL DYSPHORIC DISORDER	Current
Z	MIXED ANXIETY-DEPRESSIVE DISORDER	Current

APPENDIX 5

THE HAMILTON RATING SCALE FOR DEPRESSION

(to be administered by a health care professional)

Patient's Name _____

Date of Assessment _____

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

1. **DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)

_____
- **0**= Absent
- **1**= These feeling states indicated only on questioning
- **2**= These feeling states spontaneously reported verbally
- **3**= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
- **4**= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. **FEELINGS OF GUILT**

_____
- **0**= Absent
- **1**= Self reproach, feels he has let people down
- **2**= Ideas of guilt or rumination over past errors or sinful deeds
- **3**= Present illness is a punishment. Delusions of guilt
- **4**= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **SUICIDE**

_____
- **0**= Absent
- **1**= Feels life is not worth living
- **2**= Wishes he were dead or any thoughts of possible death to self
- **3**= Suicidal ideas or gesture
- **4**= Attempts at suicide (any serious attempt rates 4)

4. **INSOMNIA EARLY**

_____
- **0**= No difficulty falling asleep
- **1**= Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
- **2**= Complains of nightly difficulty falling asleep

5. **INSOMNIA MIDDLE**

_____
- **0**= No difficulty
- **1**= Patient complains of being restless and disturbed during the night
- **2**= Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

Adapted from Hedlung and Viewog, The Hamilton rating scale for depression, *Journal of Operational Psychiatry*, 1979;10(2):149-165.

6. **INSOMNIA LATE**

_____
0= No difficulty
1= Waking in early hours of the morning but goes back to sleep
2= Unable to fall asleep again if he gets out of bed

7. **WORK AND ACTIVITIES**

_____
0= No difficulty
1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2= Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3= Decrease in actual time spent in activities or decrease in productivity
4= Stopped working because of present illness

8. **RETARDATION: PSYCHOMOTOR** (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

_____
0= Normal speech and thought
1= Slight retardation at interview
2= Obvious retardation at interview
3= Interview difficult
4= Complete stupor

9. **AGITATION**

_____
0= None
1= Fidgetiness
2= Playing with hands, hair, etc.
3= Moving about, can't sit still
4= Hand wringing, nail biting, hair-pulling, biting of lips

10. **ANXIETY (PSYCHOLOGICAL)**

_____
0= No difficulty
1= Subjective tension and irritability
2= Worrying about minor matters
3= Apprehensive attitude apparent in face or speech
4= Fears expressed without questioning

11. **ANXIETY SOMATIC:** Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

_____
0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

_____
- **0=** None
- **1=** Loss of appetite but eating without encouragement from others. Food intake about normal
- **2=** Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

_____
- **0=** None
- **1=** Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
- **2=** Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

_____
- **0=** Absent
- **1=** Mild
- **2=** Severe

15. HYPOCHONDRIASIS

_____
- **0=** Not present
- **1=** Self-absorption (bodily)
- **2=** Preoccupation with health
- **3=** Frequent complaints, requests for help, etc.
- **4=** Hypochondriacal delusions

16. LOSS OF WEIGHT

_____ **A.** When rating by history:
- **0=** No weight loss
- **1=** Probably weight loss associated with present illness
- **2=** Definite (according to patient) weight loss
- **3=** Not assessed

17. INSIGHT

_____
- **0=** Acknowledges being depressed and ill
- **1=** Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
- **2=** Denies being ill at all

18. DIURNAL VARIATION

_____ **A.** Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none
- **0=** No variation
- **1=** Worse in A.M.
- **2=** Worse in P.M.

_____ **B.** When present, mark the severity of the variation. Mark "None" if NO variation
- **0=** None
- **1=** Mild
- **2=** Severe

19. DEPERSONALIZATION AND DEREALIZATION (Such as: Feelings of unreality; Nihilistic ideas)

_____ **0**= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

20. PARANOID SYMPTOMS

_____ **0**= None
1= Suspicious
2= Ideas of reference
3= Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

_____ **0**= Absent
1= Mild
2= Severe

Total Score _____

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 Printed in USA. WEL056R0 February 1997

APPENDIX 6

Hamilton Anxiety Rating Scale (HAM-A)

Reference: **Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50–55.**

Rating Clinician-rated

Administration time 10–15 minutes

Main purpose To assess the severity of symptoms of anxiety

Population Adults, adolescents and children

Commentary

The HAM-A was one of the first rating scales developed to measure the severity of anxiety symptoms, and is still widely used today in both clinical and research settings. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Although the HAM-A remains widely used as an outcome measure in clinical trials, it has been criticized for its sometimes poor ability to discriminate between anxiolytic and antidepressant effects, and somatic anxiety versus somatic side effects. The HAM-A does not provide any standardized probe questions. Despite this, the reported levels of inter-rater reliability for the scale appear to be acceptable.

Scoring

Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe.

Versions

The scale has been translated into: Cantonese for China, French and Spanish. An IVR version of the scale is available from Healthcare Technology Systems.

Additional references

Maier W, Buller R, Philipp M, Heuser I. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. J Affect Disord 1988;14(1):61–8.

Borkovec T and Costello E. Efficacy of applied relaxation and cognitive behavioral therapy in the treatment of generalized anxiety disorder. J Clin Consult Psychol 1993; 61(4):611–19

Address for correspondence

The HAM-A is in the public domain.

Hamilton Anxiety Rating Scale (HAM-A)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe.

1 Anxious mood [0] [1] [2] [3] [4]

Worries, anticipation of the worst, fearful anticipation, irritability.

2 Tension [0] [1] [2] [3] [4]

Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.

3 Fears [0] [1] [2] [3] [4]

Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.

4 Insomnia [0] [1] [2] [3] [4]

Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.

5 Intellectual [0] [1] [2] [3] [4]

Difficulty in concentration, poor memory.

6 Depressed mood [0] [1] [2] [3] [4]

Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.

7 Somatic (muscular) [0] [1] [2] [3] [4]

Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.

8 Somatic (sensory) [0] [1] [2] [3] [4]

Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.

9 Cardiovascular symptoms [0] [1] [2] [3] [4]

Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.

10 Respiratory symptoms [0] [1] [2] [3] [4]

Pressure or constriction in chest, choking feelings, sighing, dyspnea.

11 Gastrointestinal symptoms [0] [1] [2] [3] [4]

Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.

12 Genitourinary symptoms [0] [1] [2] [3] [4]

Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.

13 Autonomic symptoms [0] [1] [2] [3] [4]

Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.

14 Behavior at interview [0] [1] [2] [3] [4]

Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.

APPENDIX 7

Global Assessment of Functioning (GAF) Scale

(From DSM-IV-TR, p. 34.)

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical (or environmental) limitations.

Code	(Note: Use intermediate codes when appropriate, e.g., 45, 68, 72.)
100 | 91	**Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.**
90 | 81	**Absent or minimal symptoms** (e.g., mild anxiety before an exam), **good functioning in all areas, interested and involved in a wide range of activities. socially effective, generally satisfied with life, no more than everyday problems or concerns** (e.g. an occasional argument with family members).
80 | 71	**If symptoms are present, they are transient and expectable reactions to psychosocial stressors** (e.g., difficulty concentrating after family argument); **no more than slight impairment in social, occupational or school functioning** (e.g., temporarily failing behind in schoolwork).
70 | 61	**Some mild symptoms** (e.g. depressed mood and mild insomnia) **OR some difficulty in social, occupational, or school functioning** (e.g., occasional truancy, or theft within the household), **but generally functioning pretty well, has some meaningful interpersonal relationships.**
60 | 51	**Moderate symptoms** (e.g., flat affect and circumstantial speech, occasional panic attacks) **OR moderate difficulty in social, occupational, or school functioning** (e.g.. few friends, conflicts with peers or co-workers).
50 | 41	**Serious symptoms** (e.g.. suicidal ideation, severe obsessional rituals, frequent shoplifting) **OR any serious impairment in social, occupational, or school functioning** (e.g., no friends, unable to keep a job).
40 | 31	**Some impairment in reality testing or communication** (e.g., speech is at times illogical, obscure, or irrelevant) **OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood** (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).
30 | 21	**Behavior is considerably influenced by delusions or hallucinations** **OR serious impairment in communication or judgment** (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) **OR inability to function in almost all areas** (e.g., stays in bed all day; no job, home, or friends).
20 | 11	**Some danger of hurting self or others** (e.g., suicide attempts without clear expectation of death; frequently violent; manic excitement) **OR occasionally fails to maintain minimal personal hygiene** (e.g., smears feces) **OR gross impairment in communication** (e.g., largely incoherent or mute).
10 | 1	**Persistent danger of severely hurting self or others** (e.g., recurrent violence) **OR persistent inability to maintain minimal personal hygiene** **OR serious suicidal act with clear expectation of death.**
0	Inadequate information.

APPENDIX 8

SKALA MULTIDIMENTIONAL UNTUK SOKONGAN SOCIAL

(The Malay version of the Multidimensional Scale of Perceived Social Support, MSPSS-M)

Sila baca kenyataan-kenyataan berikut. Bulatkan nombor mengikut skala di bawah

1	2	3	4	5	6	7
Tersangat tidak setuju	Sangat tidak setuju	Tidak setuju	Berkecuali	Setuju	Sangat setuju	Tersangat setuju

1.	Ada seseorang yang istimewa bersama saya bila saya dalam keadaan yang memerlukan.	1	2	3	4	5	6	7
2.	Ada seseorang yang istimewa untuk saya berkongsi kegembiraan dan kesedihan.	1	2	3	4	5	6	7
3.	Keluarga saya cuba sedaya-upaya untuk menolong saya.	1	2	3	4	5	6	7
4.	Saya mendapat pertolongan dan sokongan emosi yang saya perlukan daripada keluarga.	1	2	3	4	5	6	7
5.	Saya mempunyai seseorang yang istimewa yang benar-benar membuat saya selesa.	1	2	3	4	5	6	7
6.	Kawan-kawan saya cuba sedaya-upaya untuk menolong saya.	1	2	3	4	5	6	7
7.	Saya boleh berharap kepada kawan-kawan saya apabila sesuatu hal yang tidak baik berlaku.	1	2	3	4	5	6	7
8.	Saya boleh bercerita tentang masalah saya dengan keluarga.	1	2	3	4	5	6	7
9.	Saya mempunyai kawan-kawan yang saya boleh berkongsi kegembiraan dan kesedihan.	1	2	3	4	5	6	7
10.	Ada seseorang yang istimewa dalam hidup saya yang mengambil berat tentang perasaan saya.	1	2	3	4	5	6	7
11.	Keluarga saya bersedia untuk menolong saya membuat keputusan.	1	2	3	4	5	6	7
12.	Saya boleh bercerita tentang masalah saya dengan kawan-kawan saya.	1	2	3	4	5	6	7

[1]*Ng, C.G., Amer Siddiq, A.N., Aida, S.A.,Zainal, N.Z., Koh, O.H., 2010. Validation of the Malay version of the Multidimensional Scale of Perceived Social Support (MSPSS-M) among a group of medical students in Faculty of Medicine, University Malaya. Asian Journal of Psychiatry 3, 3-6.*

[2]*Zimet, G.D., Dahlem, N.W., Zimet, S.G., Farley, G.K., 1988. The Multidimensional Scale of Perceived Social Support. Journal of Personality Assessment 52, 30-41.*

APPENDIX 9

The Malay Version of Duke Religious Index (DUREL-M)

Indeks Agama Duke

1. Berapa kerapkah anda menghadiri aktiviti keagamaan di masjid, gereja, kuil, tokong atau perjumpaan agama?

1. Tidak pernah	2. Sekali setahun atau kurang dari itu	3. Beberapa kali setahun	4. Beberapa kali sebulan	5. Seminggu sekali	6. Lebih dari sekali dalam seminggu

2. Berapa kerapkah anda meluangkan masa untuk aktiviti keagamaan secara bersendirian seperti sembahyang, bermeditasi atau membaca kitab seperti A-Quran atau Bible?

1. Jarang atau tidak pernah	2. Beberapa kali sebulan	3. Sekali seminggu	4. Dua kali atau lebih dalam seminggu	5. Setiap hari	6. Lebih dari sekali dalam sehari

Bahagian berikutnya mengandungi 3 kenyataan tentang kepercayaan agama atau amalan.
Sila tandakan jawapan bagi kenyataan yang tepat bagi anda.

3. Saya dapat merasakan kehadiran Maha Pencipta (Tuhan) dalam hidup saya.

1. Tidak benar sama sekali	2. Lebih cenderung kepada tidak benar	3. Tidak pasti	4. Lebih cenderung kepada benar	5. Amat benar sekali

4. Kepercayaan terhadap agama saya menjadi pedoman kepada kehidupan saya secara menyeluruh.

1. Tidak benar sama sekali	2. Lebih cenderung kepada tidak benar	3. Tidak pasti	4. Lebih cenderung kepada benar	5. Amat benar sekali

5. Saya telah sedaya upaya menerapkan elemen keagamaan saya dalam menangani segala urusan kehidupan saya.

1. Tidak benar sama sekali	2. Lebih cenderung kepada tidak benar	3. Tidak pasti	4. Lebih cenderung kepada benar	5. Amat benar sekali

Nurasikin MS, Aini A, Aida Syarinaz AA, Ng CG. Validity and Reliability of the Malay Version of Duke University Religion Index (DUREL-M) Among A Group of Nursing Student. Vol 19, No 2 (2010): Malaysian Journal of Psychiatry.

APPENDIX 10

INVESTIGATOR'S AGREEMENT, HEAD OF DEPARTMENT'S AND INSTITUTIONAL APPROVAL

PERSETUJUAN PENYELIDIK, PENGESAHAN KETUA JABATAN DAN INSTITUSI

This document is intended for online submission for purpose of formal research review and approval. It is to be used in lieu of other equivalent manually printed document such as Borang JTP/KKM 1-2 and Borang JTP/KKM 3. After completing the form below and obtaining the required signatures, please scan this document and submit online.
Dokumen ini adalah untuk penghantaraan atas talian (online) mengikut prosedur rasmi semakan dan persetujuan penyelidikkan. Borang ini dikeluarkan sebagai gantian dokumen kebenaran manual yang serupa seperti Borang JTP/KKM 1-2 dan Borang JTP/KKM 3. Selepas melengkapkan borang di bawah dan mendapatkan tanda tangan yang diperlukan sila imbaskan dokumen ini dan hantar atas talian.

Unique Research ID : *[Nombor Pendaftaran]*	9585
Research Title : *[Tajuk]*	Long Term Use of Benzodiazepines among Depressed Patients
Protocol Number if available *[Nombor Protokol jika ada]*	

Investigator agreement ***[Persetujuan penyelidik]***
I have understood the above titled proposed research and I agree to participate in the research as an investigator.
Saya faham cadangan penyelidikan yang bertajuk di atas dan saya bersetuju mengambil bahagian dalam projek tersebut sebagai penyelidik.

Name of Investigator : *[Nama Penyelidik]*	TAN CHEA LOON
IC number : *[Nombor KP]*	780124086505
Site Institution : *[Institusi]*	Hospital Bahagia Ulu Kinta
Signature & Official stamp : *[Tandatangan dan Cop*	DR. TAN CHEA LOON (MMC : 41468) Pegawai Perubatan UD48 Hospital Bahagia Ulu Kinta Perak Darul Ridzuan
Date : *[Tarikh]*	25 NOVEMBER 2011

Head of Department Agreement ***[Persetujuan Ketua Jabatan]***
I agree to allow the above named investigator to conduct or to participate in the above titled research.
Saya membenarkan pegawai yang bernama di atas untuk menjadi penyelidik dalam projek penyelidikan tersebut di atas.

Name of Head : *[Nama Ketua]*	Dr Cheah Yee Chuang
Name of Department and Institution *[Jabatan dan Institusi]*	Hospital Bahagia Ulu Kinta
Signature & Official stamp : *[Tandatangan dan Cop*	DR. CHEAH YEE CHUANG (MMC : 27572) Pakar Perunding Psikiatri Gred Khas C Hospital Bahagia Ulu Kinta Perak Darul Ridzuan
Date : *[Tarikh]*	30/11/11

Institutional approval ***[Pengesahan Institusi]***
This section maybe omitted if one of the NIH institute is authorized to approve on behalf of institution. Refer NIH for
(Bahagian ini tidak perlu jika salah satu daripada institusi NIH diberi kuasa pengesahan bagi pihak institusi tersebut. Rujuk NIH untuk maklumat lanjut)
I agree to allow the investigator(s) named above to conduct or to participate in the above titled research. Where applicable, I further agree to allow my institution to be one of the sites participating in the research.
Saya membenarkan pegawai yang bernama di atas menjalankan penyelidikan selaku penyelidik dalam projek penyelidikan tersebut. Jika berkenaan, saya juga membenarkan institusi ini mengambil bahagian dalam projek tersebut.

Name of Director : *[Nama Pengarah]*	
Name of Institution *[Institusi]*	DR. HJH RABAIAH BT. MOHD SALLEH, KMN., AMP (MMC: 25876) Pengarah & Pakar Perunding Psikiatri (Forensik) Gred Khas 'C' Hospital Bahagia Ulu Kinta Perak Darul Ridzuan
Signature & Official stamp : *[Tandatangan dan Cop*	
Date : *[Tarikh]*	30 Nov 2011

APPENDIX 11

NATIONAL INSTITUTES OF HEALTH APPROVAL FOR CONDUCTING RESEARCH IN THE MINISTRY OF HEALTH MALAYSIA

PENGESAHAN INSTITUSI PENYELIDIKAN NEGARA UNTUK MENJALANKAN PENYELIDIKAN DI KEMENTERIAN KESIHATAN

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Research Title : [Tajuk]	Long Term Use of Benzodiazepines among Depressed Patients
Protocol Number if available : [Nombor Protokol jika ada]	

#	**Investigator Name** [Name Penyelidik]	**Institution Name** [Nama Institusi]
1	TAN CHEA LOON	Hospital Bahagia Ulu Kinta

I have reviewed the above titled research, and approve of its design and conduct.

Saya telah menyemak kajian yang bertajuk seperti di atas dan meluluskan rekabentuk dan perlaksanaannya.

Name of Director : *[Nama Pengarah]*	Dr. Goh Pik Pin
NIH Institute (IMR, CRC, IPH, IHM, IHSR and IHBR) *[Nama Institusi di bawah NIH]*	Clinical Research Centre (CRC)
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APPENDIX 12

PEJABAT TIMBALAN KETUA PENGARAH KESIHATAN
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(RESEARCH & TECHNICAL SUPPORT)
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA
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Federal Government Administrative Centre
62590 PUTRAJAYA

Tel : 03-88832543
Faks : 03-88895184

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur

Ruj. Kami : (2) dlm.KKM/NIHSEC/08/0804/P11-743
Tarikh : 23 Februari 2012

Dr Tan Chea Loon
Hospital Bahagia Ulu Kinta

Puan,

NMRR-11-805-9585
Long Term Use of Benzodiazepines among Depressed Patients

Lokasi Projek : Hospital Bahagia Ulu Kinta

Dengan hormatnya perkara di atas adalah dirujuk.

2. Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) mengambil maklum bahawa projek tersebut adalah untuk memenuhi keperluan akademik Program Sarjana Perubatan Psikologi , Universiti Malaya (UM).

3. Sehubungan dengan ini, dimaklumkan bahawa pihak JEPP KKM tiada halangan, dari segi etika, ke atas pelaksanaan projek tersebut. JEPP mengambil maklum bahawa kajian ini tidak mempunyai intervensi klinikal ke atas subjek dan hanya melibatkan rekod perubatan, temuramah dan borang soal selidik untuk mengumpul data kajian. Segala rekod dan data pegawai adalah SULIT dan hanya digunakan untuk tujuan kajian dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi. Kebenaran daripada Pengarah Hospital di mana kajian akan dijalankan mesti diperolehi terlebih dahulu sebelum kajian dijalankan. Puan perlu akur dan mematuhi keputusan tersebut.

4. Laporan tamat kajian dan sebarang penerbitan dari kajian ini hendaklah dikemukakan kepada Jawatankuasa Etika & Penyelidikan Perubatan selepas tamatnya projek ini.

Sekian terima kasih.

BERKHIDMAT UNTUK NEGARA

Saya yang menurut perintah,

(DATO' DR CHANG KIAN MENG)
Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia