THE UNIVERSITY OF CALGARY

# A Comparison of Two Depression Measures for People With Schizophrenia

by

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## ABSTRACT

Ninety-four outpatients with schizophrenia participated in a cross-sectional study of the association between depressive symptoms, as measured by both the Calgary Depression Scale for Schizophrenia (CDSS) and the Montgomery Asberg Depression Rating Scale (MADRS), and negative symptoms. Negative symptoms were measured using the Positive and Negative Syndrome Scale for Schizophrenia (PANSS).

Three items included in the CDSS were found to be significantly associated with total negative symptoms. The depression items: Depressed Mood, Hopelessness and Self-Depreciation were found to be positively related to negative symptoms. None of the items included in the MADRS was found to be associated with negative symptoms. An overall measurement of the association between total depressive symptoms and negative symptoms demonstrated a weak association between both scales and negative symptoms.

Results indicate that neither measurement of depression is significantly associated with negative symptoms. Further study on a depressed sample of patients with schizophrenia may provide more conclusive results.

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## LIST OF TABLES

## LIST OF FIGURES

# Chapter 1-Introduction

REVIEW OF THE LITERATURE:

## Depression in Schizophrenia

The presence of depressive symptoms among those with schizophrenia has been described since the times of Kraeplin. Bleuler, in his 1911 description of the dynamics of schizophrenia described a melancholic depressive syndrome as a frequent and acute complication of schizophrenia and proposed that it might be a separate condition released by the disease [1]. The prevalence of depressive symptoms among people with schizophrenia has been estimated as high as 81% [2-6]. It has been argued that symptoms of depression may in some cases be the result of chronic demoralization [7]. For these patients it appears that their depression and hopelessness may be more of a psychological reaction to severe illness [7]. Another term used to explain such a reaction is psychogenic postpsychotic depression [2]. This type of depression refers to the onset of depressive symptoms following the resolution of a psychotic experience [8]. The frequency of this disorder has been estimated between 25% and 29 % among those with schizophrenia [8, 9].

A study by Birchwood examined the hypothesis that depression in chronic schizophrenia is in part a psychological response to an apparently uncontrollable life-event [9]. In this study, patients receiving long-term maintenance therapy were randomly selected from an

outpatient clinic [9]. Out of this sample of 85 patients, 49 had schizophrenia [9]. The authors used the Beck Depression Inventory to measure depressive symptoms [9]. A new scale was developed to measure the patient's beliefs about their illness, the Personal Beliefs about Illness Questionnaire [9]. There are five dimensions to this measurement, one considers a patient's views about their control of the illness, one explores the extent to which the patient considers the illness a part of themselves, one considers the patient's beliefs about the future, another measures the stigma experienced by the patient with regards to their illness, and the final dimension measures the degree of separation the patient experiences from society [9]. A cutoff of 15 on the Beck Depression Inventory was used to determine the depression status of each patient [9]. A comparison of depressed and non-depressed patients with schizophrenia was conducted [9]. It was determined that patients who were depressed absorbed negative-social stereotypes significantly more than non-depressed patients [9]. Also, patients who were depressed assigned an external locus of control significantly more frequently than patients who were not depressed.

In a study by Liddle, 50 patients with schizophrenia were selected from a population of long-term mentally ill patients [10]. Among those patients who became depressed compared with those who remained depression free there was a significant association between the depressed group and higher scores on the scale for the assessment of Subjective Experience of Deficits in Schizophrenia ($P<0.01$)[10]. This scale measures a patient's awareness of deficits in thinking, feeling, drive, volition and perception associated with schizophrenia [10]. Evidence suggests that such awareness may confer

vulnerability of those with schizophrenia to becoming depressed [10]. In another study by Addington 1999, a significant association between negative attributional style and depression was observed in a group of 113 inpatients with schizophrenia [11]. It is theorized by Abramson that the tendency to attribute negative or bad events to internal, stable, and global causes plays a causal role predisposing people to depression [12]. Such evidence illustrates the importance of a patient's reaction to the mental illness in terms of depressive outcome.

It has also been demonstrated that when psychotic and depressive symptoms have been charted over time, in the majority of patients with chronic schizophrenia studied, they have run the same course [2]. In contrast, depression in first-episode schizophrenia has been demonstrated to follow a different course [13]. Addington followed 113 patients with schizophrenia after relapse and 13 patients experiencing their first psychotic episode for a period of 1 year [13]. First-episode patients had significantly higher depression scores at baseline and 3 months compared with patients experiencing a relapse [13].

Different theories have been proposed in order to explain depressive symptoms for patients with schizophrenia. A theory proposed by early researchers centers on the term pharmacogenic depression [2]. This theory proposed that depressive symptoms were actually the result of neuroleptic treatment for acute psychotic symptoms [2]. It was theorized that the blockage of dopamine by neuroleptics may interfere with 'reward' pathways in the brain [14]. Uncontrolled studies such as by Galdi 1981, seemed to demonstrate that patients with schizophrenia were significantly more likely to develop

depression after neuroleptic treatment than with placebo [15]. However, evidence from controlled studies refutes this proposition that neuroleptic medication is responsible for the development of depression in schizophrenia [16, 17]. Later, observation of the course of depressive symptoms in schizophrenia patients led to the development of a different theory, which included the term "revealed depression" [2]. This theory was based on the fact that although depressed symptoms are most prevalent in the acute phase of schizophrenia, they go often unnoticed by clinicians as a result of focusing on psychotic symptoms [2]. Depressive symptoms are then revealed to the clinician as psychotic symptoms become managed in the schizophrenia patient [2].

Certain studies have followed patients with schizophrenia from the time of discharge from hospitals and have monitored depressive symptoms [2]. In a 1981 study, Johnson found that 70% of the cohort which were followed for a 2 year period had a significant depressive syndrome at one point or another during that time [18]. Such studies provide evidence for the conception that depressive symptoms are an integral part of the disease process of schizophrenia [2].

Suicide in Schizophrenia

Persons with schizophrenia are at a significantly increased risk for premature death than those in the general population. In a 1978 study by Tsuang and Woolson, it has been estimated that the life expectancy as a group for individuals with schizophrenia is shortened by 9 to 10 years when compared with the general population [19]. It was also

determined in this study that the excess in mortality can be primarily attributed to instances of suicide and accidental death [19]. In a 1991 study it was determined that the leading cause of increased mortality among people with schizophrenia was suicide [20]. The lifetime incidence of suicide for patients with schizophrenia is 10-13% compared with a general population estimate of 1% [21].

As well as its magnitude, the incidence of suicide for people with schizophrenia has different characteristics than the general population. In general population studies on the incidence of suicide, it has been demonstrated that rates of suicide increase steadily with age. In contrast, similar studies on the incidence of suicide in a population of individuals with schizophrenia demonstrate that the risk of suicide decreases with advancing age [21]. In a study by Newman and Bland, it was reported that the magnitude of suicide risk peaked in the 10 to 29 age group in which people with schizophrenia were almost 33 times as likely to commit suicide as the general population [20]. This odds ratio decreased to roughly 18 in the 30 to 49 age group, and further declined to 7 times in the 50 to 69 age group [20].

A study by Modestin analyzed 149 psychiatric inpatient suicides, and developed a profile for the typical patient with schizophrenia who commits suicide [22]. The typical patient was young, unmarried and had never lived independently [22]. Social adjustment problems were evident very early on in the patient's life, often before the age of 25 [22]. Also, for most of the suicides, the age of onset was earlier than age 30, the course of illness was long and long hospitalizations were frequent [22].

Several risk factors for suicide in the population of those with schizophrenia have been proposed. Similar to the general population, gender is a risk factor for suicide in people with schizophrenia [21]. In both the general population and the population of those with schizophrenia, males are over represented among suicides [21]. It has been shown that the ratio of males to females among suicide victims with schizophrenia is 2:1, which is different from the 3:1 ratio in the general population [21]. This difference has been pointed to as evidence that schizophrenia diminishes the inhibition to commit suicide, which is a characteristic of women in suicide studies [21]. In general however, males are over-represented among suicide victims with schizophrenia. A study by Roy demonstrated that within a group of suicide victims with chronic schizophrenia 80% were male [23].

Depression as a Risk Factor for Suicide:

Similar to the general population, suicide victims with schizophrenia often have a clinical history of past and current depression, as well as a sense of hopelessness [21]. In a study which compared suicide victims with controls matched for sex, age and type of schizophrenia, significantly more of the suicides had in the past both been diagnosed by their psychiatrists as suffering from a depressive episode and had been treated in the past for depression [23]. Several studies have also demonstrated an association between depressive symptoms and both completed and attempted suicide among individuals with schizophrenia [2, 24]. Also, as in the general population, poor psychological functioning,

limited, unstable, or stressed social supports, social isolation, deteriorating health with a high level of premorbid functioning, and significant losses have been implicated as risk factors for suicide among individuals with schizophrenia [21].

A recent study by Harkavy-Friedman, compared the demographic and clinical characteristics of 112 patients with schizophrenia who had and had not attempted suicide [25]. 57% of those who had both attempted suicide and who had a history of depression reported having made a suicide attempt during a major depressive episode [25]. Also, suicidal ideation during depression occurred twice as often for those who had attempted as for those who had not [25]. Researchers documented the reasons patients gave for having made a suicide attempt and the most frequent reason given was that the person was depressed [25]. Results from this study were consistent with a stress-diathesis model for suicide in patients with schizophrenia [25]. In this model, certain clinical syndromes may trigger suicidal behavior in those already at risk [25].

In a 1997 study by Rossau, researchers analyzed data from a cohort of 9156 Danish patients with schizophrenia admitted to hospital [26]. The incidence rate for suicide among the cohort was significantly higher for patients who had ever had a diagnosis of depression compared to those who had never been diagnosed as depressed [26]. It has been demonstrated that suicide is an important issue in the treatment of individuals with schizophrenia, and depression has been shown to be an important risk factor for attempted suicide [21, 26, 27].

Measurement of Depression in Schizophrenia

Despite the obvious importance of recognizing depressive symptoms in patients with schizophrenia, the study of this area of schizophrenia research has been hindered by confusion of depressive symptoms with symptoms of schizophrenia [28]. Becker conducted an examination of the relationships of items listed in the Hamilton Depression Scale with symptoms of depression in patients with schizophrenia [29]. Becker looked at 4 separate groups of patients, those with schizophrenia and no depression, those with schizophrenia and major-type depression, those with schizophrenia and dysthymic-type depression, and those with major depression [29]. Comparisons were made between patients in terms of the frequency and severity of each of the 24 Hamilton Depression Scale items [29]. The items retardation and insomnia were determined to be unreliable in differentiating between those with secondary depression and those without, among patients with schizophrenia [29]. The results suggest that some patients with schizophrenia diagnosed with a major depressive episode may meet accessory criteria because of a combination of symptoms that are part of the secondary depressive syndrome of schizophrenia with symptoms that are part of the syndrome of schizophrenia [29].

The most common depressive-like symptoms which have an organic etiology are extrapyramidal symptoms [7]. Extrapyramidal symptoms are frequent side-effects to first-generation antipsychotic medications, which were often prescribed to schizophrenia patients [7]. The two principal extrapyramidal side-effects which resemble depression

are akinesia and akathisia [7]. Akinesia is characterized by diminished spontaneity of movement and speech, apathy, and difficulty initiating usual activities [7]. Akathisia, on the other hand can mimic agitated depression [7]. Akathisia is characterized by a profound feeling of inner restlessness [7].

However, strategies have been developed by clinicians to diagnose these side-effects separate from depression in schizophrenia [7]. Akinesia should be suspected from the characteristic appearance of facial immobilization and diminished spontaneous motor activity [7]. Although patients suffering from akinesia may report a lack of energy, motivation and interest, such patients seldom report being sad or depressed [7]. Akathisia can be recognized in the observation of overt signs of motor restlessness or reports of an inner sense of agitation and anxiety, which are usually present in patients experiencing this side-effect [7].

The differentiation of depression from negative symptoms can also be difficult in assessing patients with schizophrenia [7]. Social withdrawal, apathy, and other negative symptoms common in schizophrenia can be confused with depression [30]. The term negative symptom, comes from the adaptation to schizophrenia, a model proposed by Jackson [31]. In this model, Jackson differentiated negative from positive symptoms in relation to presumed causes of each symptom type [31]. Negative symptoms were presumed to follow from tissue injury or loss, in contrast positive symptoms were presumed to result from an active state of neurological disinhibition [31]. This model has been adapted to describe two separate clusters of schizophrenic symptoms [7]. Positive

symptoms refer to florid psychosis such as delusions, hallucinations, and disorganized thinking [7]. Negative symptoms however refer to deficits of speech, affect, cognition, initiative, and social behavior [7].

In a 1993 study, Kibel attempted to clarify and determine which items belong to the negative syndrome [32]. In their analysis, researchers assessed patients with three separate negative symptom scales, the Scale for Assessment of Negative Symptoms, the Negative Symptoms Rating Scale, and the negative symptoms subscale of the Positive and Negative Symptoms Scale [32]. From analysis of the 45 items from the 3 scales, 18 items were highly correlated with the negative syndrome discriminant function [32]. These 18 items represented five classes of symptoms: poverty of thought and speech, blunted affect, decreased motor activity, apathy and avolition, and diminished interpersonal interaction [32].

Negative symptoms of schizophrenia, such as flat affect, psychomotor retardation, lack of gestures, social withdrawal, can be confounded by overlapping depressive symptoms [33]. Similarities between negative symptoms and depressive symptoms; difficulties in the differential diagnosis between schizophrenia patients with negative symptoms and patients with depressive symptoms have created considerable controversy in the literature pertaining to schizophrenia research [34].

Design and Testing of the CDSS:

The Calgary Depression Scale (CDSS) was developed in an attempt to address such problems in assessing depression for people with schizophrenia [35]. The CDSS was developed based on items selected from the Hamilton Depression Rating Scale and the Present State Examination [35]. This selection of items was based on a three-stage procedure involving factor analysis, followed by the measurement of internal consistency and finally a determination of face validity at two points in time [35]. The internal consistency of items selected for the scale was assessed using Cronbach's alpha calculations [35]. The items selected generated Cronbach's alpha scores of 0.84 and 0.89 at times 1 and 2 respectively [35]. The CDSS was found to have high inter-rater reliability with an intraclass correlation of 0.895 and a percentage agreement on specific items of 86% [36]. It was demonstrated that the items selected created a more parsimonious instrument for measuring depression in people with schizophrenia [35].

The CDSS is a 9 item scale, designed to measure depressive symptoms exclusive of other dimensions of psychopathology in people with schizophrenia [36]. These items refer to specific aspects of the patient's condition: Depressed Mood, Hopelessness, Self Depreciation, Guilty Ideas of Reference, Pathological Guilt, Morning Depression, Early Wakening, Suicide, and Observed Depression [36]. The measurement of each item is based on a four point scale: 0 refers to an absence of the item, 1 refers to a mild presence of the item, 2 refers to a moderate presence of the item, and 3 refers to the item being present in its most severe form [36]. The scores for each item can then be totaled

together and provide a measurement of the total depressive symptoms for the schizophrenia patient [36].

A comparison was made, subsequent to the 1990 study outlining the development of the CDSS, which provided evidence for the effectiveness of the CDSS in measuring depression across both acute and residual stages of schizophrenia [36]. The CDSS was also examined with regards to the measure's ability to distinguish symptoms of depression from negative and extrapyramidal symptoms [37] [38]. It was demonstrated that the CDSS provided a useful degree of separation between measures of depression and these other symptoms [37]. Correlation coefficients for each item compared with negative symptoms were all less than 0.34 [37]. The specificity of the CDSS as distinct from measures of negative and extrapyramidal symptoms was established using confirmatory factor analysis [37]. It was also shown that the CDSS was more effective in separating measures of depression from measures of positive and negative symptoms when compared with the Hamilton Depression Rating Scale first at a time of relapse and later at a time of relative remission of symptoms [38]. A principal components factor analysis was conducted to measure the divergence between the measurement of depressive symptoms with the CDSS and negative symptoms and to compare that divergence with depressive symptoms measured by the Hamilton Depression Rating Scale [38]. No significant correlations between the total CDSS score and positive or negative symptoms at either time were found [38]. In contrast, the Hamilton Depression Rating Scale total score was correlated with both positive and negative symptoms at the time of remission of symptoms [38]. Multiple regression analyses demonstrated that the

CDSS items did not significantly account for any of the variance in negative symptoms at either of the two time periods ($p=0.67$, $p=0.14$) [38]. In contrast Hamilton Depression Rating Scale items did significantly account for variance in negative symptoms at both time periods ($p<0.001$, $p<0.001$) [38]. A recent study demonstrated, using the CDSS, that depressive symptoms represent an independent dimension of psychopathology, separate from negative, parkinsonian and catatonic symptoms [39]. Pearson correlation coefficients were calculated between Negative Symptoms and Depressive Symptoms at three separate time periods [39]. Depressive symptoms did not correlate with negative, catatonic or extrapyramidal symptoms at admission, but did at the time of discharge [39]. However, the change in depressive symptoms across the three time periods was not associated with the change in other symptoms [39]. It was then concluded that depression, as measured by the CDSS, is relatively independent of the other symptoms [39].

Subsequent studies have further validated the CDSS with regards to other instruments traditionally used to measure depression in schizophrenia. In a study conducted by Collins, the CDSS was compared to both the Hamilton Depression Rating Scale and the depression subscale of the Positive and Negative Syndrome scale [40]. The relationship between negative symptoms, extrapyramidal symptoms and depression was evaluated using Pearson product moment calculations [40]. Results indicated that negative symptoms were not significantly associated with depressive symptoms as measured by the CDSS ($r=0.228$, $p>0.05$) [40]. However, negative symptoms were significantly associated with depressive symptoms as measured by the Hamilton Depression Rating

Scale ($r=0.453$, $p<0.005$) [40]. It was determined that the CDSS was unique in its ability to differentiate between depressive symptoms, negative symptoms and extrapyramidal symptoms [40]. Furthermore, a French version of the CDSS was validated for a stabilized group of schizophrenia patients [41]. This validation was conducted through the analysis of receiver operating characteristic curves for various cut-off values for the CDSS in terms of the identification of minor and major depression [41]. Also, correlational analyses were conducted between CDSS scores and negative symptom and extrapyramidal scores [41]. All correlational coefficient scores were less than 0.50 [41]. Internal consistency of the French version of the CDSS was established through the measurement of Cronbach's alpha (0.80) [41]. The validity of the CDSS has also been established for several other translations of the scale [42, 43].

Design of the MADRS:

In contrast to the CDSS, the MADRS was developed for use in the study of treatment effects in response to the pharmacotherapy of depressive symptoms for individuals with depression, not for people with schizophrenia [44]. Items from the Comprehensive Psychopathological Rating Scale were used in the development of the MADRS [44]. Items were selected based on their sensitivity towards change produced by various antidepressants [44]. This resulted in the development of a scale consisting of ten items which demonstrated the largest changes with treatment [44].

The items which compose the MADRS include: Apparent Sadness, Reported Sadness, Inner Tension, Reduced Sleep, Reduced Appetite, Concentration Difficulties, Lassitude, Inability to Feel, Pessimistic Thoughts, and Suicidal Thought [44]. The measurement of each item is based on a 6 point scale, ranging from 0, referring to the relative absence of the item, to 6 referring to the item being present in its most severe form [44]. These items can be then totaled to give an overall depressive symptom measurement [44].

It was shown that this newly developed scale had a high inter-rater reliability [44]. Measurement of inter-rater reliability was accomplished using Pearson correlation coefficients and values were greater than 0.88 [44]. Point biserial correlations were used to measure the abilities of the MADRS and the Hamilton Depression Rating Scale to differentiate between responders and non-responders to antidepressant therapy [44]. A higher correlation was observed for the MADRS ($r=0.70$) than for the Hamilton Depression Rating Scale ($r=0.59$). It was therefore demonstrated that the MADRS was more sensitive to changes in response to antidepressant treatment in patients with depression [44]. Subsequently, the reliability and validity of the MADRS has been further tested [45]. Inter-rater reliability was found to be 0.76 for the total MADRS score [45]. Concurrent validity relative to the Hamilton Depression Rating Scale was measured as well, ($r=0.44$). It was shown that the MADRS is more internally cohesive when compared with the Hamilton Rating Scale for Depression [45]. Seven of the 10 items correlated significantly with the subtotal scores for the MADRS [45]. In contrast, only 58% of the items for the Hamilton Depression Rating Scale were so correlated [45].

Despite the validity of the MADRS having been determined through previous studies for depressive populations, its effectiveness for use in a population of patients with schizophrenia has not been clearly shown. The MADRS has been used as a depressive measure in several recent studies of patients with schizophrenia [46-52]. It was cautioned by Montgomery, that when items are being selected for inclusion in a scale it is important that those items included are relevant to the illness [44]. It has been shown that certain MADRS items were associated with the negative syndrome of schizophrenia, and as a result may be unreliable measures of depression in the presence of negative symptoms [32]. Kibel attempted to clarify the composition of the negative syndrome in chronic schizophrenia [32]. Researchers administered 3 separate negative symptom measurement scales, a positive symptom scale, and a depression scale to 73 inpatients [32]. The items: observed sadness, lassitude, and inability to feel, included in the MADRS, significantly correlated with negative symptoms.

Discussion of Psychometrics:

In general, measurement scales are designed to measure a construct through the use of specific items in the scale. These items are used to measure the construct because many constructs cannot be measured directly [53]. In the measurement of depression in schizophrenia for example, scale items are used in combination to measure the construct of depression. Another term which helps to explain the concept of a construct is latent variable [53]. A latent variable has two primary qualities, the first is that it is latent and not manifest [53]. Latency refers to the fact that the variable cannot be observed directly.

With regards to depression in schizophrenia, it is the depressive symptoms which can be measured to assess the latent depression. The second quality is that the latent variable is not constant and has varying amounts of strength or magnitude [53]. A measurement scale is intended to estimate the actual magnitude of the latent variable at the time and place of measurement [53]. A scale measures the latent variable indirectly through the measurement of items contained in the scale. Items are related to the latent variable in a causal fashion [53]. The latent variable is regarded as a cause of the strength and the quantity of the item score [53]. With regards to depression in schizophrenia therefore, the underlying depression causes depressive symptoms which can be measured by a scale.

The quality of a measurement scale is determined through analysis of validity and reliability. Validity can be defined as the extent to which a test measures what it is intended to measure [54]. The reliability of a measurement is defined as the proportion of observed variation in scores that reflects the actual variation in health levels, while unreliability is the proportion of variation due to random error in the measurement [54]. In more general terms, it is the degree to which the measurement scale scores can be replicated [54].

In analyzing validity, there are two primary aspects which must be assessed. The first is content validity, which addresses the extent to which the items of a scale are representative of all of the potential questions which could be asked to measure a particular construct [54]. In the measurement of depression in schizophrenia, items

included in a measurement scale must be representative of all of the symptoms of depression in schizophrenia. It is important to question whether all items chosen for inclusion in the scale appear relevant to depression in schizophrenia and that all aspects of the disorder are satisfactorily covered by the scale. A common procedure to assess content validity is to ask experts to comment on the clarity and completeness of the measurement scale [54]. Another aspect of validity which should be addressed is factorial validity [54]. This form of validity concerns the correlation, or association, of individual items within the scale to the construct being measured. One statistical method frequently used to assess factorial validity is factor analysis [54]. Factor analysis involves the measurement of the patterns of inter-correlations between potential scale items and the construct of interest [54]. Potential scale items can then be grouped together based on these measures of association [54]. In the construction of a scale for people with schizophrenia to measure depression for example, only items which correlate strongly with a diagnosis of depression will be included. Another important aspect in the analysis of the validity of a scale is the lack of correlation between the scale and measurement tools designed to measure different themes [54]. A term used to describe this lack of association is discriminant validity In the measurement of depressive symptoms in schizophrenia for example, it is important that the measurement scale used does not correlate with measures of negative symptoms.

Once validity is established, researchers can then assess the reliability of a measurement scale. Reliability is concerned with the degree of influence random errors have on the scale [54]. Random errors have certain characteristics: 1) Being randomly distributed,

they are as likely to increase or decrease the score of the scale. 2) The magnitude of the random error is not related to the magnitude of the true score. 3) The observed score is the sum of the true score and the error. There are two types of reliability, inter-rater reliability and test-retest reliability. Inter-rater reliability refers to the situation where two different raters obtain the same result while using the same instrument to assess the same respondent [54]. Levels of agreement greater than 80% are generally satisfactory when determining whether a scale should be considered reliable or not [54]. Test-retest reliability involves the assessment of whether a scale administered at different points in time on the same respondent generates the same result, when the underlying true score remains unchanged [54]. In assessing the test-retest reliability of a scale, short periods between test administration are maintained in order to reduce the actual variation in the construct being measured [54].

Measurement scales are of two main types, observer-report scales and self-report scales. Each type has its own limitations and strengths associated with its methodology. One type of self-report scale is a questionnaire. The primary advantage of using self-report scales is that they are less expensive to administer [55]. They are also less time-consuming to administer than observer-report scales and allow for many respondents to be assessed at one time [55]. Another advantage of self-report scales is that they avoid potential interviewer bias [55]. For example, the way particular questions are asked by the interviewer may lead to different responses from the person being interviewed, in an observer-report setting [55]. However, problems can arise with an individual's interpretation of the questions contained in the questionnaire [55]. Respondents may

become confused about what a question is asking and record their answer based on this misunderstanding. An observer-report interview, in contrast to a self-report scale, allows for the clarification of questions being asked by the interviewer [55]. An interview is also more appropriate for revealing information that is both complex and emotionally laden [55]. In the measurement of depression in schizophrenia, items being measured are frequently complex and have an emotional quality to them. Due to these aspects, the measurement of depression in schizophrenia is accomplished through the use of observer-report scales as opposed to self-report scales.

## PURPOSE OF STUDY:

The purpose of this study was to compare two depression rating scales applied to a sample of people with schizophrenia in terms of their ability to differentiate negative symptoms from depressive symptoms. A comparison was made between the Montgomery-Asberg Depression Rating Scale (MADRS) and the Calgary Depression Scale for Schizophrenia (CDSS) [35, 44].

## STUDY RATIONALE:

The objective comparison of the CDSS and the MADRS provides an accurate assessment of the abilities of each scale with regard to the measurement of depressive symptoms separate from negative symptoms. This comparison is based on the understanding that depressive and negative symptoms are separate aspects which may be part of the

condition of a patient with schizophrenia. Studies have shown that negative and depressive syndromes follow a different course in time and demonstrate different responses to treatment [56]. There are a number of reasons for making such a comparison between measures of depression. Despite the fact that the MADRS has not been validated for use as a measure of depression for people with schizophrenia it has been used in several instances to measure depression. Also, the face validity of MADRS items, such as lassitude and concentration difficulties may be questionable when applied in schizophrenia. Finally, research has demonstrated an association between MADRS items and negative symptoms [32]. Such a comparison had not been made before. This study may provide additional support and evidence for the use of a newly developed measurement tool.

HYPOTHESIS:

It is anticipated that:

A greater number of MADRS items will be significantly related to negative symptoms when compared with CDSS. This will demonstrate that the CDSS is more effective at measuring depressive symptoms in schizophrenia separate from negative symptoms.

## Chapter 2 - Design of the Study

PARTICIPANTS:

The participants for this study are 94 individuals who met DSM-IV criteria for schizophrenia. Individuals were recruited into the study from the Schizophrenia Disorders Clinic and the Early Psychosis Program at the Foothills Hospital, from a patient population of approximately 400 individuals with schizophrenia. Recruitment took place after appropriate informed consent from each participant had been obtained.

The size of this sample, 94 people, allows for the detection of a statistically significant correlation coefficient of 0.4 with 95% power at the 1% level of significance [57]. Therefore, a sample size of 94 is sufficient in order to answer this research question.

To be included in the study, individuals met DSM-IV criteria for schizophrenia. A clinical diagnosis from the patient's chart was accepted for the purposes of this study. The DSM-IV criteria for schizophrenia are as follows: (i) The presence of two or more of the following characteristic symptoms present for a significant portion of time during a one month period: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (ii) evidence of social/occupational dysfunction. (ii) That continuous signs of the disturbance must persist for at least 6 months. (iii) A diagnosis of either schizoaffective or mood disorder must be excluded. (iv) The attribution of symptoms to a substance/general medical condition must also be

excluded. (v) For a diagnosis of schizophrenia to be made, the relationship of symptoms to a pervasive developmental disorder must also be addressed. An additional diagnosis of schizophrenia is only made if prominent delusions or hallucinations are also present for at least a month. [58].

MEASURES:

1. Demographic Measures:

   The following demographic measures were collected from the individuals with schizophrenia for descriptive purposes: age and gender.

2. The Calgary Depression Scale for Schizophrenia [35] was one of the scales used to measure depressive symptoms for each study participant. The scale was administered by one investigator who had established sufficient inter-rater reliability prior to the start of the study. A copy of the interview guide for the CDSS is included in appendix A.

3. The Montgomery-Asberg Depression Rating Scale [44] is the comparison scale which was also used to measure depressive symptoms for each study participant. The scale was administered by another investigator who had established sufficient inter-rater reliability prior to the start of the study. A copy of the interview guide for the MADRS is included in appendix B.

4. The Positive and Negative Syndrome Scale for Schizophrenia [59] was used to measure negative symptoms for each study participant. The scale was administered by the investigator who also used the CDSS who had established sufficient inter-rater reliability prior to the start of the study.

PROCEDURES:

The schizophrenia subjects (SS) were recruited through the Schizophrenia Disorders Clinic and the Early Psychosis Program at the Foothills Hospital. The attending psychiatrist or case manager asked potential subjects whom he or she considers competent, if they would agree to discuss a research project with the investigator. Careful research has demonstrated that the majority of patients with schizophrenia, who are admitted to an acute admission ward meet three out of three standards of competence [60]. It was made clear that participation in the project would be voluntary and not related to treatment. Subjects then were approached by myself and invited to participate in the screening part of the study. Those who agreed to discuss the research project with the investigator had their charts reviewed to ensure that they met inclusion criteria. SS who agreed to participate were asked to complete a consent form (See appendix C). A clinical diagnosis of schizophrenia, obtained from the patient's chart was accepted for the purposes of this study.

The researcher then met with the SS at which time measurement of depressive symptoms with each scale took place, as well as the measurement of negative symptoms. The

research assistant and myself were present at different times during this interview. I was blinded to the results of the negative symptom measurement and the results of the CDSS score. By using two interviewers in this process we were able to protect against interviewer bias. At this time demographic information was also collected for descriptive purposes.

## ESTABLISHMENT OF RELIABILITY:

In order for myself to become able to perform reliable semi-structured interviews for the measurement of depression in schizophrenia a significant amount of training was conducted. Several interview sessions were observed where the CDSS was administered by a trained and reliable interviewer. I successfully completed a course on the psychopathology of schizophrenia. As well, I practiced rating taped interviews performed by a trained and reliable interviewer administering the CDSS. A cut-off of 80% agreement on the MADRS over 5 separate interviews between myself and a trained and reliable interviewer was used to determine reliability before the study was conducted.

## ETHICAL CONSIDERATIONS:

### (i) Recruitment and Consent Procedures

Individuals with schizophrenia in this study were outpatients. A subject was judged to be competent to give informed consent if he or she demonstrated the following three

elements of consent: (1) the ability to communicate a choice. (2) Had the ability to understand relevant information. This includes the nature of the study, the risks and benefits and the voluntary nature of their involvement. In addition they understood that they had the right to withdraw from the study at any time without prejudice to their treatment. (3) And had the ability to appreciate the situation and its likely consequences. It was made clear to them that their participation in this study was voluntary and was not related to their treatment. Patients had to agree to give their names to the researcher. A consent form was signed prior to any procedures being conducted (appendix C). All subjects were informed of their right to withdraw their participation at any time. Any questions asked by subjects were answered in full at the time of obtaining consent or prior to each assessment.

(ii) Potential Risks

There were no immediate or long-term risks to the subjects. However, if they experienced distress during the interview, it would have been terminated and a clinician notified. Subjects were given the opportunity to withdraw from the research or to complete the testing at a later date.

(iii) Confidentiality

Confidentiality was assured by assigning a code number to each subject at the time of his/her assessment. All forms were identified only by these code numbers. Only one list

containing the names and code numbers of participants was maintained; it was kept in a locked file separate from the numbered data files. The data files were also stored in a locked filing cabinet. No identifiable records were used for teaching or any other scientific purpose.

## DATA ANALYSIS

Demographic data are reported using descriptive statistics.

### Proposed data analysis

A regression analysis of each measurement item was to have been used to determine the degree with which each item predicts negative symptoms. The dependent variables was to have been each individual item for both depression measurement scales. The independent variable was to have been the total score of negative symptoms. Each scale item was first analyzed as a categorical variable to determine whether there was any evidence for violation of the assumption of linearity for linear regression. Other residual diagnostic procedures were used to assess other assumptions for linear regression. However, analysis of residuals demonstrated violations of the assumptions of linearity, homogeneity of variance, and normality of residuals. Also, relatively low $R^2$ values were observed for the univariate models. For models examining CDSS items an $R^2$ range of .0007 to .08 was observed. For models examining MADRS items an $R^2$ range of .0008 to .05 was observed. Therefore the analysis of the association between depression items

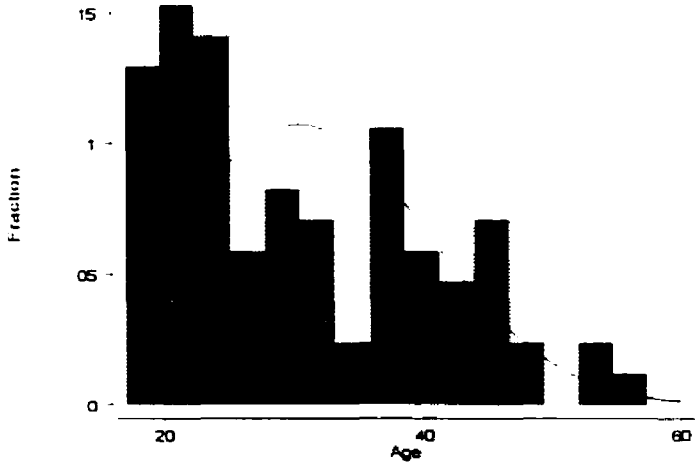
and total negative symptoms was not conducted using simple linear regression. In order to test the hypothesis of this study a different method of analysis was used which is discussed in the results section.

# Chapter 3 – Results

DEMOGRAPHIC DATA:

A total of 94 outpatients with schizophrenia were sampled. The mean age of the sample was 30 years. The age of the sample was positively skewed, as can be observed in figure 4. This skewness would be expected because the majority of patients sampled were from the Early Psychosis Program at the Foothills Hospital Calgary. The average age of onset of psychotic symptoms for patients with schizophrenia is between 21 and 27 years [61]. Also, the development of symptoms in childhood is rare and less than 1% of patients with schizophrenia become ill before the age of 12 [61]. By sampling from the Early Psychosis Program, a program designed to identify and treat individuals with first episode psychosis, it would be expected that the sample would tend to have a young average age with some individuals older and very few individuals younger than the mean.

**Figure 1. Age distribution of the sample**



The ratio of males to females in the sample was roughly 3 to 1, with 74 % of the sample being male and 26 % female. Figure 5 graphically illustrates the distribution of gender in this sample.

**Figure 2. Gender distribution of the sample**

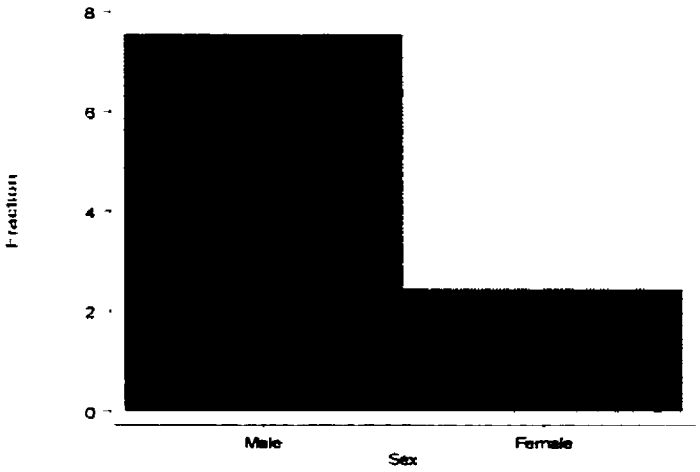
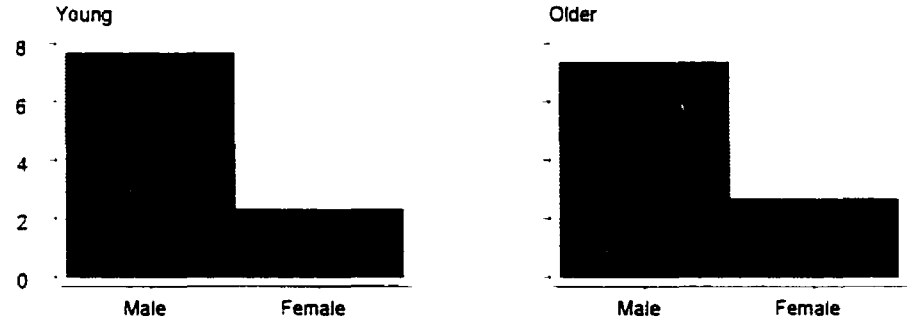



Figure 5 demonstrates the large proportion of males in the sample compared to females. This is consistent with the literature on the ratio of males to females in studies of individuals with schizophrenia. In a 1995 article, Swaab and Hofman reviewed several studies relating gender ratios observed in various mental diseases [62]. An average ratio of 73 males to 27 females was observed from 8 studies reviewed [62]. The gender ratio for the sample obtained in this study appears to be consistent with other studies. In analyzing the age distribution, as presented in Figure 1, it appears that age may be bimodally distributed. The sample was split into two groups, those 35 years old and younger and those older than 35 years. To determine if there was a difference in the

proportion of males to females between age groups a comparison was made between the two proportions. Figure 6 graphically represents the proportions in the two age groups.

**Figure 3. Gender distribution in age groups**




A Fisher's exact test was conducted to determine if there was a statistically significant difference in the proportion of males to females between the two age groups. No significant difference ($p=0.46$) was found between the two age groups.

In conclusion, it appears that the sample taken for this study is representative of other studies of patients with schizophrenia, in terms of age and gender.

Internal consistency of each scale was assessed with Cronbach's alpha coefficients. For the CDSS measurement an alpha coefficient of .81 was obtained. For the MADRS measurement an alpha coefficient of .83 was determined. Both depression measurements demonstrated high internal consistency. The MADRS appears to demonstrate a slightly higher internal consistency than the CDSS. However, this value may have been inflated

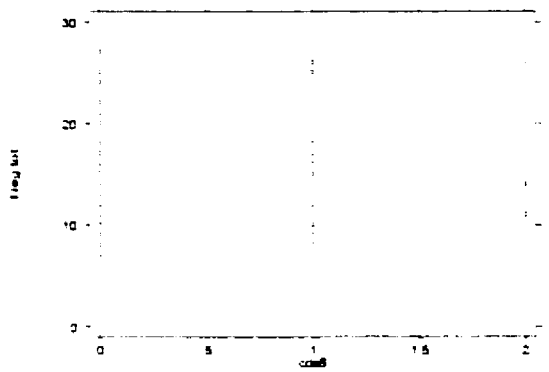
due to the fact that the MADRS has 10 items compared to the 9 items included in the CDSS. Alpha coefficients tend to increase when scale items are added [63]. An alpha coefficient of .83 for the MADRS has implications with regard to how the scale was administered in this study. The high internal consistency demonstrated by the application of the MADRS in this study implies that scale items were measured appropriately. If for example MADRS item 7, lassitude, was measured less as a form of sluggishness but more as sleepiness, this would have reduced the internal consistency of the scale as a whole. Therefore, it appears that the MADRS, as well as the CDSS, were used appropriately.

In this sample the mean total CDSS score was 3.4 (SD=3.6) and the mean total MADRS score was 7.4 (SD=8.7). A mean total negative symptom score of 14.8 (SD=5.5), as measured by the PANSS, was also observed.

DATA ANALYSIS CONDUCTED:

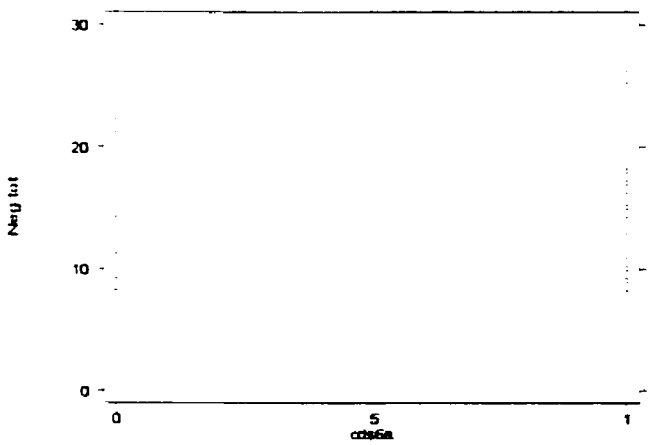
Analysis of the individual CDSS item plots comparing depressive symptoms as measured by the CDSS and negative symptoms demonstrated a clustering of points around scores of 0 and 1. 90 % of points were clustered around scores of either 0 or 1 for CDSS depression items. An example of this clustering is presented in Figure 1, which compares total negative symptoms with CDSS depression item 6, morning depression.

**Figure 4. Negative symptoms vs. CDSS item 6 scores**



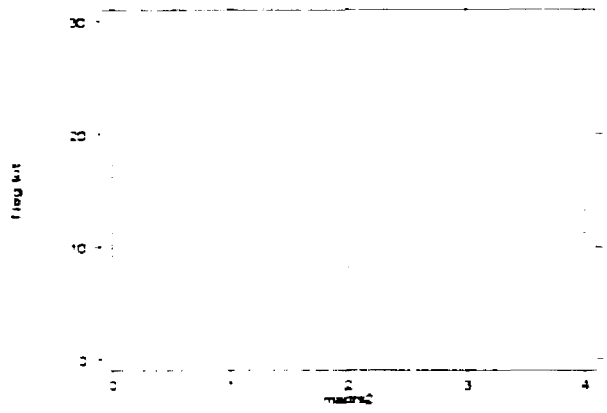

It was decided that the mean negative symptoms could be compared between individuals with a CDSS item score of 0 and individuals with a CDSS item score of 1 using t-tests. If there was a significant difference between the mean total negative symptoms it could be inferred that the depressive item was significantly associated with total negative symptoms. Depression scores were then collapsed to either 0 or 1 to allow for this comparison of means within each item. CDSS item scores greater than 1 were collapsed into a score of 1. Figure 2 demonstrates this collapsing of the data.

**Figure 5. Negative symptoms vs. collapsed CDSS item 6 scores**



Analysis of the individual MADRS item plots comparing depressive symptoms as measured by the MADRS and negative symptoms demonstrated a clustering of points around scores of 0, 2, and 4. 90 % of points were clustered around scores of either 0, 2, or 4 for MADRS depression items. For MADRS items, scores were collapsed to either 0, 2 or 4. MADRS scores of 1 or 2 were clustered into a score of 2. MADRS scores of 3 or greater were collapsed into a score of 4. An example of the clustering is presented in Figure 3, which compares total negative symptoms with MADRS depression item 2, reported sadness.

**Figure 6. Negative symptoms vs. MADRS item 2 scores**



Similar to the analysis of the CDSS, it was decided that the mean negative symptoms could be compared between individuals with MADRS item scores of 0 and individuals with a MADRS item scores of 2. The mean negative symptoms could also be compared between individuals with MADRS item scores of 2 and individuals with MADRS item scores of 4. These comparisons were made by conducting an ANOVA comparison. If

there were significant differences between the mean total negative symptoms it could be inferred that the depressive item was significantly associated with total negative symptoms.

Thus, the analysis of the levels of association between individual item scores and total negative symptoms will be conducted through various t-test comparisons. A p-value cutoff of 5 % will be used to determine significance.

In addition to this analysis, an overall measure of the association between total negative symptoms and total depressive symptoms as measured by either the CDSS or the MADRS can be represented by simple regression. By combining the depressive items together as opposed to analyzing items individually, the problems with the linear regression assumptions were corrected. It was determined that the assumptions of linearity, homogeneity of variance, and normality of residuals were valid for regression analysis on this data. As a result, a comparison of two regression models measuring the association of total negative symptoms and depressive symptoms, as measured by the CDSS and the MADRS, can be made. Also, the effects of the demographic variables age and gender on the relationships between total depressive symptom measurements and total negative symptoms will be examined in the regression analysis.

TESTING OF HYPOTHESIS:

The measurement of the levels of association between total negative symptoms and the score of individual CDSS items was conducted using t-tests. The t-tests compared the mean negative symptoms for individuals with a collapsed depression item score of 1 with individuals with a collapsed score of 0. Justification of this collapsing of scores was presented in the methods section. The results of the comparisons between negative symptoms are presented in Table 1.

**Table1. Comparisons of negative symptoms between depression item groups ***

| Scale Item | Difference in Negative Symptoms between Score=1 and Score=0 | Sample Sizes (N) | P-value | Association (yes/no) |
|---|---|---|---|---|
| 1. Depressed Mood | 2.88 | (44, 50) | .010 | **Yes** |
| 2. Hopelessness | 3.51 | (32, 62) | 003 | **Yes** |
| 3. Self Depreciation | 2.92 | (28, 66) | .017 | **Yes** |
| 4. Guilty Ideas of Reference | 1.59 | (17,77) | .277 | No |
| 5. Pathological Guilt | -0.34 | (38, 56) | .768 | No |
| 6. Morning Depression | 1.88 | (36, 58) | 104 | No |
| 7. Early Wakening | 1.78 | (10, 84) | .333 | No |
| 8. Suicide | 1.16 | (21, 73) | .392 | No |
| 9. Observed Depression | 1.95 | (17, 77) | 183 | No |

* Comparison of individuals with CDSS item scores of 0 or 1.

As can be observed from Table 1, CDSS items 1, 2 and 3 demonstrated a significant positive difference between the mean negative symptoms for individuals with a score of 0 compared to individuals with a score of 1. Therefore, it could be inferred that these three items are significantly related to total negative symptoms.

The measurement of the levels of association between total negative symptoms and the score of individual MADRS items was conducted using an ANOVA procedure. T-tests compared the mean negative symptoms for individuals with a collapsed depression item score of 2 with individuals with a collapsed score of 0. A second t-test compared the mean negative symptoms for individuals with a collapsed depression item score of 4 with individuals with a collapsed score of 2. Justification of this collapsing of scores was presented in the methods section. The results of the comparisons between negative symptoms are presented in Table 2.

**Table2. Comparisons of negative symptoms between depression item groups ***

| Scale Item | Difference in Negative Symptoms | | | | | | Assoc. |
|---|---|---|---|---|---|---|---|
| | Score=2 vs. Score=0 | Sample Sizes (N) | P-value | Score=4 vs. Score=2 | Sample Sizes (N) | P-value | (yes/no) |
| 1. Apparent Sadness | 3.09 | (23, 60) | .021 | -0.78 | (11, 23) | .333 | No |
| 2. Reported Sadness | 2.39 | (14, 64) | .136 | 0.46 | (16, 14) | .333 | No |
| 3. Inner Tension | 1.12 | (18, 51) | .333 | 2.21 | (25, 18) | .184 | No |
| 4. Reduced Sleep | 7.15 | (5, 79) | .004 | -9.20 | (10, 5) | .002 | No |
| 5. Reduced Appetite | 1.17 | (13, 78) | .333 | 2.64 | (3, 13) | .333 | No |
| 6. Concentration Difficulties | 0.02 | (14, 59) | .333 | 3.36 | (21, 14) | .072 | No |
| 7. Lassitude | -0.61 | (23, 63) | .333 | 2.15 | (8, 23) | .333 | No |
| 8. Inability to Feel | 1.97 | (5, 83) | .333 | -0.77 | (6, 5) | .333 | No |
| 9. Pessimistic Thoughts | 2.72 | (15, 71) | .078 | 0.70 | (8, 15) | .333 | No |
| 10. Suicidal Thoughts | 3.14 | (16, 75) | .037 | -2.04 | (3, 16) | .333 | No |

* Comparison of individuals with MADRS item scores of 0 or 2 and between individuals with scores of 2 or 4.

Table 2 presents two separate comparisons for each depression scale item. One type of comparison is made between the mean negative symptoms for individuals with a score of 2 on the MADRS depression items and individuals with a score of 0. A second

comparison type is made between the mean negative symptoms for individuals with a score of 4 on the MADRS depression item and a score of 2. An association was determined to exist if results demonstrated two outcomes. An association would be concluded if the differences between negative symptoms for both comparisons were significant and in the same direction. For example, item 4, reduced sleep, was not shown to associate significantly with negative symptoms because despite the differences in both comparisons being significant they were in different directions. There was a positive difference between individuals with a score of 2 compared to individuals with a score of 0. But, there was a negative difference between individuals with a score of 4 compared to individuals with a score of 2. Therefore, it was concluded that no association was observed between this depression item score and negative symptoms. A second outcome which would have resulted in the conclusion that an association was observed between a depression item score and negative symptoms would be if the difference in mean negative symptoms was not significant in the first comparison but was significant in the second comparison. However, no such observation was made for any MADRS items. In summary, no items in the MADRS were determined to be significantly related to negative symptoms.

A comparison of the relationships between total negative symptoms and total depressive symptoms as measured by the CDSS and the MADRS was conducted using simple regression analysis. The slope coefficients for both the MADRS and CDSS depression scores were positive and significantly different from 0. The F-test provided a p-value of .008 for the CDSS model, and a p-value of .018 for the MADRS model. The slope

coefficient for the CDSS model was .412. This coefficient can be interpreted that for two individuals, one of which has a total depression score one unit higher than the other, this individual would have a .412 times higher total negative symptom score than the other individual. The slope coefficient for the MADRS model was .166. This coefficient can be interpreted that for two individuals, one of which has a total depression score one unit higher than the other, this individual would have a .166 times higher total negative symptom score than the other individual.

The residual error, represented by the residual sum of squares, was higher for the MADRS model than for the CDSS model. A residual sum of squares value of 2569 was observed for the CDSS model. The residual sum of squares value for the MADRS model was 2610. The variance explained by each model is represented by the model sum of squares value. The MADRS model has a model sum of squares value equal to 166 which is lower than the CDSS model, which had a value equal to 208. These differences in model and residual sum of squares values can be interpreted such that the CDSS model accounts for more of the explained variance than the MADRS model.

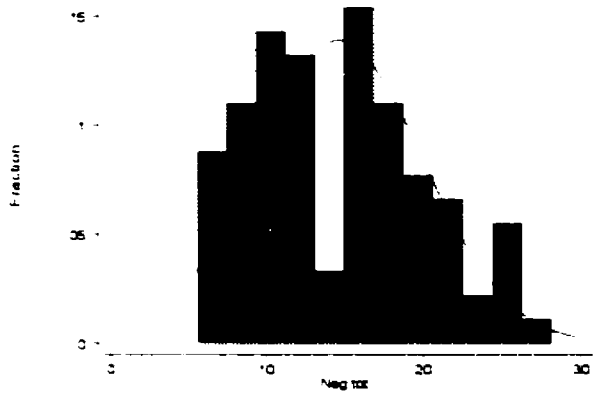
When the demographic variables age and gender were controlled for in either of the regression equations it was determined that there was no influence on the level of association between total depressive symptoms and negative symptoms for either demographic variable. Therefore the level of association, as measured by linear regression, between total depressive symptoms from either the CDSS or the MADRS and negative symptoms appears to be independent of age and gender.

## SUPPLEMENTARY ANALYSIS

A supplementary analysis was conducted which further compared the relationship between negative symptoms and depressive symptoms measured by the CDSS or the MADRS. Clinical cut-points for depression are frequently used with the administration of both scales in order to characterize patients as either depressed or not depressed. A cutoff of 6 or higher for the CDSS was suggested by Addington as a criterion for a major depressive episode in patients with schizophrenia [64]. A cutoff of 20 or higher for the MADRS was suggested by Snaith as indicative of a moderate level of depression for depressed patients [65]. For the sample collected in this study, patients were classified as either depressed or not depressed according to a cutoff of 6 for the CDSS measurement. This gave rise to two groups, a high depressive symptom group with a mean CDSS total score of 8.8 (SD=2.4) and a low depressive symptom group with a mean CDSS total score of 1.6 (SD=1.7). Secondly, patients were classified as either depressed or not depressed according to a cutoff of 20 for the MADRS measurement. This gave rise to two other groups, a high depressive symptom group with a mean MADRS total score of 28.3 (SD=4.8) and a low depressive symptom group with a mean MADRS total score of 5.68 (SD=5.5).

Negative symptoms were observed to be distributed in somewhat of a bimodal fashion, as illustrated in figure 7.

**Figure 7. Distribution of total negative symptoms**



In this sample it appears as though there are two clusters of individuals, those who have relatively high negative symptoms and those who have relatively low negative symptoms. It was determined that two groups could be created by dividing the sample into those who have total negative symptoms scores of 14 or less and those who have total negative symptoms scores greater than 14. The mean total negative symptom score in the high negative symptom group was 19.2 (SD=3.7), in the low negative symptom group the mean was 10.21 (SD=2.2).

A comparison was then made between the proportion of people who have high negative symptoms compared to low negative symptoms for individuals who are diagnosed as depressed with the CDSS measurement. A similar comparison was made for individuals grouped as depressed by the MADRS measurement. A summary of these results is presented in Table 3.

**Table 3. Comparison of the proportion of individuals with high vs. low negative symptoms in different depression categories for CDSS and MADRS**

| MADRS | | | CDSS | | |
|---|---|---|---|---|---|
| Negative Symptoms | Depressed | Not-Depressed | Negative Symptoms | Depressed | Not-Depressed |
| High | 6 (86%) | 42 (48%) | High | 14 (61%) | 34 (48%) |
| Low | 1 (14%) | 45 (52%) | Low | 9 (39%) | 37 (52%) |
| | p-value | .111 | | p-value | .341 |

As can be observed in Table 3, there is a higher proportion of individuals with relatively high negative symptoms compared with low negative symptoms among those considered depressed by either depression measurement. It appears that this difference in proportions appears to be greater for those who are depressed as determined by the MADRS than for those who are depressed as determined by the CDSS. Of those MADRS-determined depressed individuals 86% had high total negative symptoms. Of those CDSS-determined depressed individuals only 61% had high total negative symptoms. However, in both cases this difference in proportions was not significant. For the difference in proportion for MADRS-determined depressed individuals a p-value of .111 was observed. For the difference in proportion for CDSS-determined depressed individuals a p-value of .341 was observed.

The relationship between the two depression scales, in terms of depression status was assessed by a cross-table comparison presented in Table 4.

**Table 4. Comparison of depression status as measured by the CDSS and the MADRS**

| | MADRS | | |
|---|---|---|---|
| **CDSS** | Depressed | Not-Depressed | Total |
| Depressed | 7 | 16 | 23 |
| Not-Depressed | 0 | 71 | 71 |
| Total | 7 | 87 | 94 |

Among the 23 individuals who are depressed according to the CDSS measurement, only 7 are depressed according to the MADRS measurement. Among the 68 individuals who are not depressed according to the CDSS, none are depressed according to the MADRS. Therefore, it appears that the CDSS measurement is more sensitive at measuring depression in schizophrenia than the MADRS.

It was also questioned whether the proportion of individuals with high negative symptoms compared with negative symptoms was different within the depressed patient subgroup, as determined by the CDSS.

**Table 5. Comparison of the proportion of individuals with high vs. low negative symptoms in different depression categories of the MADRS within the CDSS depressed subgroup**

| MADRS | | | CDSS | |
|---|---|---|---|---|
| Negative Symptoms | Depressed | Not-Depressed | Negative Symptoms | Depressed |
| High | 6 (86%) | 8 (50%) | High | 14 (61%) |
| Low | 1 (14%) | 8 (50%) | Low | 9 (39%) |
| | p-value | .176 | Total | 23 |

As can be observed from the comparison of Table 5 with Table 3, there is no difference in the proportion of individuals with high versus low negative symptoms among those who are depressed using the MADRS between the total sample and the CDSS-depressed subgroup. The proportion of 86% versus 14% is the same as that in the total sample. The difference in proportions is also not significant (p-value .176).

## Chapter 4 - Discussion

The results obtained in this study contradict the hypothesis stated. It was predicted that the CDSS scale would have fewer items which are significantly associated with negative symptoms than the MADRS scale. The results demonstrate that 3 items in the CDSS, depressed mood, hopelessness and self-depreciation are significantly associated with negative symptoms. In contrast, no MADRS items were significantly associated with negative symptoms.

However, the significance of a t-test, as used in this study, is related to the size of the samples being compared. For each CDSS item analyzed a comparison was made between the mean total negative symptoms between two groups of individuals, those with a clustered score of 0 or a clustered score of 1. The total sample then was divided into two groups. For each MADRS item analyzed a comparison was made between the mean total negative symptoms between 3 groups of individuals, those with clustered scores of 0, 2 or 4. In this case the sample was divided into 3 groups. As a result, it could be inferred that in the MADRS/negative symptom comparison there was in effect a lower sample size than in the CDSS/negative symptom comparison. This could have reduced the number of MADRS items which were significantly associated with negative symptoms. The positive differences observed for MADRS items such as, reported sadness, inner tension, reduced appetite, and concentration difficulties may have been significant if the sample size was larger. For example, if 10 additional patients were

measured, who had a score of either 2 or 4 on MADRS item 6 (concentration difficulties), a significant association would have been observed for that item.

Also, the clinical significance of a score of either 0 or 1 on a CDSS item is questionable. Inferences based on such a grouping may not be clinically relevant, because individuals with such item scores would not be considered depressed.

The association of negative symptoms with total depression scores as measured by either the CDSS or the MADRS was assessed using simple linear regression. In both cases, the models demonstrated a very weak association between total depression scores and negative symptoms. The residual sum of squares values were large for both models. The results indicate that the association between negative symptoms and the total depression score, as measured by either the CDSS or the MADRS, is not substantial.

In answer to the question of which measurement scale is more associated with negative symptoms, the results obtained in this study are inconclusive. Neither measurement scale appears to be associated with negative symptoms to any large degree.

The supplementary analysis conducted provided some interesting results. It appears as though the CDSS measurement is more sensitive towards depression in outpatients with schizophrenia. Of the 23 individuals who are depressed according to the CDSS measurement, only 7 are depressed according to the MADRS measurement. Among the 68 individuals who are not depressed according to the CDSS, none are depressed

according to the MADRS. However, without a gold-standard diagnosis of a major depressive episode a clear assessment of the sensitivity of each depression measurement scale cannot be clearly obtained. This difference in depression classification between scales could have been due to the cutoff values used for either depression scale. The MADRS cutoff suggested by Snaith, for moderate depression, was based on assessing mood in patients with depression, not with schizophrenia [77]. Perhaps a more objective comparison of depression classification could have been made if the MADRS cut-off selected was one which was standardized for patients with schizophrenia.

It also appears that there may be a relationship between negative symptoms and depression status for the MADRS. According to the MADRS, individuals with depression tend to have high negative symptoms. However, a significant relationship was not observed ($p=0.059$). The individuals sampled for this study were predominantly not depressed (mean CDSS total score of 3.4) which reduced the statistical power of this supplementary analysis.

LIMITATIONS OF THE RESEARCH:

In conducting this study, there may be concern for a potential lack of objectivity of the investigators. The CDSS was developed by persons who were involved in this study which may introduce some bias into the comparison of the CDSS with the MADRS. However, I was blinded to the results of the negative symptom measurement and the results of the other depression measurement. Also, a sample of convenience was

collected for this study. Patients were recruited who were attending their clinic appointments. If patients attending clinic tended to respond differently to questions about depressive symptoms than patients who did not attend clinic this could have influenced the results obtained and as a result limit the generalizability of the findings of this study. In conclusion, the study design as presented limited the introduction of bias and minimized concerns about objectivity.

## FUTURE RESEARCH:

Future research could look more closely at patients who are depressed, as determined by a gold-standard measurement, and clearly measure the sensitivity of the MADRS compared to the CDSS. It would also be interesting to investigate the relationship between negative symptoms and depressive symptoms for each scale in this depressed subgroup. The results from such study could be more clinically useful than the results obtained in this study.

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# APPENDIX A

## Interview Guide For The Calgary Depression Scale For Schizophrenia

*Interviewer:*

Ask the first question as written. Use follow up probes or qualifiers at your discretion. Time frame refers to last 2 weeks unless stipulated. Item 9 is based on observations of the entire interview.

(1) *Depressed Mood*

- How would you describe your mood over the last 2 weeks: Do you keep reasonably cheerful or have you been very depressed or low spirited recently? In the last 2 weeks how often have you (own words) every day? All day?

0 Absent

1. Mild, expresses some sadness or discouragement on questioning

2. Moderate, distinct depressed mood over last 2 weeks; present daily.

3. Severe, markedly depressed mood persisting daily over half the time interfering with normal motor and social functioning.

(2) *Hopelessness*

- How do you see the future for yourself? Can you see any future? Or has life seemed quite hopeless? Have you given up or does there still seem some reason for trying?

0 Absent

1. Mild, has at times felt hopeless over the last week but still has some degree of hope for the future.

2. Moderate, persistent, moderate sense of hopelessness over last week. Can be persuaded to acknowledge possibility of things being better.

3. Severe, persisting and distressing sense of hopelessness.

(3) *Self depreciation*

- What is you opinion of yourself compared to other people? Do you feel better or not as good or about the same as most? Do you feel inferior or even worthless?

0 Absent

1. Mild, some inferiority; not amounting to feeling of worthlessness.

2. Moderate, subject feels worthless, but less than 50% of the time.

3. Severe, subject feels worthless more than 50% of the time. May be challenged to acknowledge otherwise.

(4) *Guilty ideas of reference*

- Do you have the feeling that you are being blamed for something or even wrongly accused? What about? (Do not include justifiable blame or accusation. Exclude delusions of guilt.)

0. Absent

*1.* Mild, subject feels blamed but not accused less than 50% of the time.

*2.* Moderate, persisting sense of being blamed, and/or occasional sense of being accused.

*3.* Severe, persistent sense of being accused. When challenged acknowledges that this is not so.

*(5) Pathological guilt*

- Do you tend to blame yourself for little things you may have done in the past? Do you think you deserve to be so concerned about this?

0 Absent

*1.* Mild, subject sometimes feels over guilty about some minor peccadillo, but less than 50% of the time.

*2.* Moderate, subject usually (over 50% of the time) feels guilty about past actions, the significance of which he exaggerates.

*3.* Severe, subject usually feels he/she is to blame for everything that has gone wrong, even when not his/her fault.

(6) *Morning depression*

- When you have felt depressed over the last 2 weeks have you noticed the depression being worse at any particular time of day?

0. Absent, no depression

1. Mild, depression present but no diurnal variation

2. Moderate, depression spontaneously mentioned to be worse in a.m.

3. Severe, depression markedly worse in a.m., with impaired functioning which improves in p.m.

(7) *Early Wakening*

- Do you wake earlier in the morning than is normal for you? How many times a week does this happen?

0 Absent, no early wakening.

1. Mild, occasionally wakes (up to twice weekly) 1 hr or more before than normal time to wake or alarm time.

2. Moderate, often wakes early (up to five times weekly) 1 hr or more before normal time to wake or alarm.

3. Severe, daily wakes 1hr or more before normal time.

*(8) Suicide*

- have you ever felt that life wasn't worth living? Did you ever feel like ending it all? What did you think you might do? Did you actually try?

0. Absent

1. Mild, frequent thought of being better off dead, or occasional thoughts of suicide.

2. Moderate, deliberately considered suicide with a plan, but made no attempt.

3. Severe, suicidal attempt apparently designed to end in death (ie. accidental discovery or inefficient means).

*(9) Observed depression*

- *Based on interviewer's observations during the entire interview.* The question ' Do you feel like crying' used at appropriate points in the interview may elicit information useful to this observation.

0. Absent

1. Mild, subject appears sad and mournful even during parts of the interview involving affectively neutral discussion.

2. Moderate, subject appears sad and mournful throughout interview, with gloomy monotonous voice and is tearful or close to tears at times.

3. Severe, subject chokes on distressing topics, frequently sighs deeply and cries openly, or is persistently in a state of frozen misery.

# APPENDIX B

## Interview Guide For The Montgomery-Asberg Depression Rating Scale

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0,2,4,6) or between them (1,3,5).

(1) *Apparent Sadness*

- Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0. No sadness
1.
2. Looks dispirited but does brighten up without difficulty.
3.
4. Appears sad and unhappy most of the time.
5.
6 Looks miserable all the time. Extremely despondent.

(2) *Reported Sadness*

- Representing reports of depressed mood, regardless of whether there it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0. Occasional sadness in keeping with the circumstances
1.
2. Sad or low but brightens up without difficulty.
3.
4. Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5.
6. Continuous or unvarying sadness, misery or despondency.

(3) *Inner tension*

- Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for

0 Placid, only fleeting inner tension.
1.
2 Occasional feelings of edginess and ill defined discomfort.
3.
4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5.
6 Unrelenting dread or anguish, overwhelming panic.

(4) *Reduced sleep*

- Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0. Sleeps as usual.
1.
2. Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
3.
4. Sleep reduced or broken by at least two hours.
5.
6. Less than two to three hours sleep.

(5) *Reduced appetite*

- Representing the feeling of a loss of appetite compared when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite.
1.
2. Slightly reduced appetite.
3.
4. No appetite, food is tasteless.
5.
6. Needs persuasion to eat at all.

(6) *Concentration difficulties*

- Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentrating
1.
2. Occasional difficulties in collecting one's thoughts.
3.
4. Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5.
6. Unable to read or converse without great difficulty.

(7) *Lassitude*

- Representing a difficulty getting started or slowness initiating and performing everyday activities.

0. Hardly any difficulty in getting started, no sluggishness.
1.
2. Difficulties in starting activities.
3.
4. Difficulties in starting simple routine activities which are carried out with effort.
5.
6. Complete lassitude. Unable to do anything without help.

(8) *Inability to feel*

- Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0. Normal interest in the surroundings and in other people.
1.
2. Reduced ability to enjoy usual interests.
3.
4. Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
5.
6. The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

(9) *Pessimistic thoughts*

- Representing thought of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0. No pessimistic thoughts.
1.
2. Fluctuating ideas of failure, self-reproach, or self-depreciation.
3.
4. Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5.
6. Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

(10) *Suicidal thoughts*

- Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

0. Enjoys life or takes it as it comes.
1.
2. Weary of life. Only fleeting suicidal thoughts.
3.
4. Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5.
6. Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

# APPENDIX C

A Comparison of two Depression Measures for People with Schizophrenia.

INDIVIDUAL SUBJECT CONSENT FORM

RESEARCH PROJECT: A Comparison of Two Depression Measures for People With Schizophrenia.

INVESTIGATORS: Dr. Donald Addington, Michael Fisher

This consent form, a copy of which has been given to you, is only part of the process of informed consent. It should give you a basic understanding of what the research project is about and what your participation will involve. If you would like more details about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

1. PURPOSE: The purpose of this research project is to make an objective comparison between two depression rating scales for patients with schizophrenia.

2. PROCEDURES: There will be 100 individuals invited to participate in this study. Participation in this study will involve one interview which will cover:

1. Providing the researcher with some general information about myself.
2. Answering questions related to the measurement scales, which will be administered.

3. DESIGN OF THE STUDY: This study has a cross-sectional design to determine significant predictors of negative symptoms within each depression rating scale and to measure the sensitivity of each scale in the measurement of major depression.

4. RISKS: There are no known risks to these procedures beyond those encountered in daily life. Should you feel fatigued or stressed by the demands of the questions you may take a break, postpone the interview time, or refuse to continue.

5. PARTICIPANTS INVOLVEMENT:

1) The researcher will contact you by phone

2) A meeting at the hospital will be set up at a time suitable to you for an interview that will take a maximum of one hour.

3) The interview will involve you answering questions about your age and length of illness. You will also be interviewed by 2 individuals both of whom will ask you questions regarding symptoms you are or may not be experiencing.

6. BENEFITS: There are no direct benefits to you from participating in this research.

7. ALTERNATIVES: You may choose not to participate in this research. Just as there are no risks or benefits to participating, there are no risks or benefits to not participating.

Neither participating or refusing will affect any decisions about your treatment or your involvement in your treatment program.

8. ACCESS TO INFORMATION: Your name and the information obtained from the research will be kept confidential. This will be ensured by a number of safeguards.

(i) You will be interviewed in a private office.

(ii) Your records will be identified only by a number and not by your name.

(iii) Your records will be kept in a locked file cupboard in a locked office.

(iv) No information concerning your identity will be used in any published reports.

9. COSTS: There are no costs associated with participation in this study.

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and that you agree to participate as a subject. In no way does this waive your legal rights or release the investigators, sponsors or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time without jeopardizing your health care. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation. If you have any further questions please contact:

Dr. Donald Addington 670-4836

If you have any questions concerning your rights as a possible participant in this research, please contact the Office of Bioethics, Faculty of Medicine, The University of Calgary at 220-7990.

| | |
|---|---|
| (Name of Subject) | (Name of Witness) |
| (Signature of Subject) | (Signature of Witness) |
| (Investigator) | (Signature of Investigator) |
| (DATE) | |

A copy of this consent form will be given to you. Please keep it for your records and future reference.