DEPRESSIVE SYMPTOMS IN SOUTH AFRICAN BLACK PATIENTS WITH RHEUMATOID ARTHRITIS

Anersha Pillay

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of

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DECLARATION

I, Anersha Pillay, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Psychiatry in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

……..

Signed

This 05th day of August 2012

DEDICATION

This work is dedicated to my husband, Ajay - for all your encouragement and true inspiration.

Life, this sea of storms, has only been easier to navigate with you by my side

ABSTRACT

Background:

Rheumatoid Arthritis (RA) is a chronic auto-immune musculoskeletal disorder of unknown aetiology that can result in physical disability, chronic pain and impaired quality of life. RA is associated with an increased prevalence of depression. The presence of depression in RA is reported to be associated with pain, functional disability, high disease activity and mortality.

This study aims to determine the prevalence of depressive symptoms in a cohort of Black South African patients attending a Rheumatology outpatient clinic at a public health center. It also aims to determine the association and correlation between the presence of depressive symptoms and the sociodemographic profile and RA clinical characteristics of the study population.

Methodology:

The study was conducted in a Rheumatology out patient clinic. The study sample consisted of 100 systematically selected participants of Black race. The participants completed the disability questionnaire (HAQ-DI), Visual Analogue Scales (VAS) for pain, fatigue and disease activity; and the depression and tension subscales of the Arthritis Impact Measurement Scale (AIMS). The MADRS was then administered to assess depressive symptoms.

Study participants were clinically assessed for disability, joint status and disease activity. Data was analyzed using the SAS version 9.1 statistical program.

Results:

The majority of the sample was female (85%) and unmarried (66%). The prevalence of current depression was 13.2%, although a further 22.2% of the sample was already stable on antidepressant treatment. The mean RA disease duration was 12.5 ± 9.2 years.

No significant associations were found between the presence of depression and the sociodemographic variables. MADRS scores were significantly associated and correlated with disability ($p = 0.002$, $r = 0.30$); fatigue ($p = <0.001$, $r = 0.43$); disease activity ($p = 0.001$, $r = 0.32$); AIMS-D ($p < 0.001$, $r = 0.40$) and AIMS-T ($p < 0.001$, $r = 0.35$). Upon adjusting for age and clinical status, significant associations remained with MADRS scores and all five above-mentioned RA variables although correlations weakened slightly.

Conclusions:

Co morbid depression is prevalent in South African Black patients with RA. In order to improve clinical outcomes in RA, depression must be actively sought and effectively managed.

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NOMENCLATURE

1. RA – Rheumatoid Arthritis
2. South Africans of African Descent – South African Black Population
3. HREC – Human Research Ethics Committee
4. CEO – Chief Executive Officer
5. OA – Osteoarthritis
6. BDI – Beck Depression Inventory
7. HDRS – Hamilton Depression Rating Scale
8. MADRS – Montgomery – Asberg Depression Rating Scale
9. AIMS – Arthritis Impact Measurement Scale [for Depression (AIMS-D) and Tension (AIMS-T)]
10. SLE – Systemic Lupus Erythematosus
11. CRP – C – Reactive Protein
12. VAS – Visual Analogue Scale [for Pain (VAS-P, for Fatigue (VAS-F) and for Disease Activity (VAS-DA)]
13. VA – Veterans Affairs
14. HAQ-DI – Health Assessment Questionnaire- Disability Index
15. DMARDS – Disease Modifying Anti-Rheumatoid Drugs
16. DAS28 – Disease Activity Score using 28-Joint Score
17. NHLS – National Health Laboratory Services
18. AD – Antidepressants
19. SSRI – Selective Serotonin Reuptake Inhibitor

CHAPTER ONE: INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic auto-immune musculoskeletal disorder of unknown aetiology. It affects approximately one percent of the population (range 0.3 to 2.1 percent) with women being three times more likely to be affected than men.[1] The disorder is characterized by joint destruction and extra-articular manifestations; that can result in physical disability, chronic pain and impaired quality of life.

Sprangers et al compared the results of eight studies looking at the quality of life in a wide range of chronic disorders, affecting various organ systems. The study found that musculoskeletal conditions like RA were associated with the most adverse sequelae and the poorest quality of life.[2]

In view of its clinical manifestations, chronicity and impact on quality of life, RA is expected to be associated with an increased prevalence of depression.

Indeed, various studies have reported that between 13-20% of patients with RA have co-morbid depression, reflecting at least a two-fold increase in depression as compared to the general population.[3, 4, 5] One of these studies noted that the effect size of depression in those study patients was not reduced when controlling for age, sex and socioeconomic status; suggesting that the depression was due to RA and not sociodemographic factors.[3]

Depression in RA is also associated with other disease manifestations. The most robust findings being, in its association with pain, functional disability, disease activity and mortality.[3, 4]

1.1 Rationale:

There is a paucity of published data on the psychological aspects, including prevalence of depressive symptoms and its associations with other disease characteristics in South African RA patients.[6]

Evidence was reported that South African patients of African (Black) descent experience more sociodemographic disadvantage and higher degrees of functional disability than non-African patients. The occurrence and burden of depressive symptoms is therefore expected to be high in this patient population.[7]

1.2 Research Aims:

1) To determine the prevalence of depressive symptoms in a cohort of Black African patients with RA, attending a public health centre in South Africa.
2) To determine the association between the presence of these depressive symptoms with patient sociodemographic and other RA disease manifestations.

1.3 Hypothesis:

There is a high prevalence of depressive symptoms in Black South African patients with RA, attending the Rheumatology outpatient clinic at the Charlotte Maxeke Johannesburg Academic Hospital.

The presence of depressive symptoms is associated with increased pain, greater functional disability and increased disease activity.

1.4 Study Approval:

This study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand [Appendix A]. Permission to conduct the study was also granted by the Chief Executive Officer (CEO) of the Charlotte Maxeke Johannesburg Academic Hospital.

CHAPTER TWO: LITERATURE REVIEW

2.1 RA and Depression

2.1.1 Prevalence

Assessing prevalence rates of depression in RA, as with most chronic medical disorders, has been fraught with difficulties. These include variable patient populations, type of screening tool used (self-report questionnaire versus clinical interview) and overlap in RA disease and depression symptomatology (termed 'criterion contamination'). Despite this, and the varying prevalence rates detected, the literature generally supports a positive relationship between depression and RA.[3, 5, 6] Very early prevalence studies like that of Rimon and Laakso , as cited by Creed et al quote prevalence rates of between 22 and 80%, with more recent studies narrowing the rate to between 15- 21%.[8, 9, 10]

Pincus et al attempted to obtain a more accurate prevalence rate of depression in RA patients, by removing symptoms in the screening tools that may contribute to criterion contamination. Although the prevalence rates for depression detected were found to be lower (15%), RA patients were still found to be significantly more depressed than controls.[10]

A 2002 meta analysis of the literature, found 12 studies which compared RA sufferers with healthy controls. The findings indicated that subjects with RA were more likely to be depressed, with a small to moderate effect size noted. Additionally, the authors concluded that

the excess of depression as compared to healthy controls was due to the presence of RA and not sociodemographic factors.[3]

More recent studies looking at the prevalence rates of depression in RA do not seem to differ much in their findings either with rates of 41.5% and 56.7% respectively, being reported.[11, 12] The study by Isik et al included an age- and sex-matched control group and not only found a higher prevalence rate of depression but also positively correlated depression with a longer RA disease duration.[11] Mella et al compared RA patients with Osteoarthritis (OA) patients in a study looking at the prevalence rates of depression in a Brazilian population. In addition to finding a higher prevalence of depression in the RA patients, the authors also found that the RA patients with depression had a lower education level, higher disease activity and greater functional disability than non-depressed RA patients.[12]

Despite the challenges faced in detecting and confirming prevalence rates of depression in the RA patient population, studies consistently point not only to a positive relationship between these two disorders; but also to a negative impact on health outcomes when they coexist.

2.1.2 Impact of Depression on RA

Dickens and Creed in an editorial on the burden of depression in patients with RA reflected not only on the negative impact of the presence of depression on pain and functional disability, but also on the reaction of these patients to their illness. Negative illness beliefs, increased health-seeking behaviour, increased reports of physical symptoms and high service

utilization seem to be characteristic of this patient group. In addition and concerning for patient health outcomes, was the observation that these patients displayed reduced medication compliance and a lack of confidence in their treating doctors.[13]

Regarding the role of psychosocial factors in RA, two factors emerge as important: stressful life events (particularly of an interpersonal nature) and the presence of depression. In a study comparing the impact of depression, on RA sufferers with a group of Osteoarthritis (OA) patients; the RA group was found to have greater reactivity to perceived stress and arthritis pain.[14]

The ultimate consequence of the impact of depression in patients with RA seems to be poorer health outcomes and greater healthcare costs.

2.1.3 Detecting Depression in RA

Obtaining an accurate indication of the presence of co morbid depressive symptoms or a depressive disorder within the context of a medical disorder like RA can be challenging.
This is, firstly, due to the difficulty of differentiating the neurovegetative symptoms of depression (fatigue, appetite and weight changes, and sleep difficulties) from the similar somatic manifestations of RA; termed 'criterion contamination'.[15] Secondly, there does not appear to be an ideal measurement instrument or process to accurately determine the presence of depression within this cohort of patients. Even structured clinical interviews are thought to be susceptible to criterion contamination.[16]

In an attempt to reduce or, at best, modify this phenomenon numerous studies have looked at different measurement scales that can be used to best assess the presence of depression within the RA and more generally, medical populations.[17, 18, 19. 20]

At the core of this discussion is the use of self-report versus observer rating scales. In terms of rating scales developed for use within the general population, the Beck Depression Inventory (BDI) is reported to be the most widely used. The disadvantage of this scale, as with other self-report measurement scales, is its tendency to overestimate the severity of depressive symptomatology in patients who present with somatic complaints.[18] The use of the BDI in RA subjects would for this reason probably be limited.

The Hamilton Depression Rating Scale (HDRS) and Montgomery- Asberg Depression Rating Scale (MADRS) are probably two of the most well known observer rating scales for depression. With regard to their use in medically ill populations, the MADRS is considered a better alternative as it includes fewer somatic items, thereby reducing the possibility of falsely elevated depression score as a result of criterion contamination.[19, 21, 22]

Demyttenaere and De Fruyt recommend that the choice of measurement scale for depression must include an awareness of the limitations of the commonly used scales; consideration of the combined use of self-report and observer rating scales on a study population and the use of subscales where indicated.[18]

In literature looking specifically at detecting depression in patients with RA, numerous self-report and observer rating scales have been used and reported on.[10, 17] There is general consensus that variability exists when using the different scales to detect the presence of depression. As such, Covic et al, suggests that some self report scales may require modification and possible removal of somatic items; and higher cut–off points for the detection of depressive symptoms.[17]

The Arthritis Impact Measurement Scale for depression (AIMS-D) was developed specifically to assess mood in arthritis patients.[23] This six-item subscale is part of the broader AIMS, which is used to assess the overall impact of RA. While this subscale has the ability to measure the degree of the patient's mood, it does not presume to be able to make a clinical diagnosis of depression.[16]

Despite advances in the understanding of the difficulties detecting and diagnosing depression; and extensive literature on the use of a variety of measurement scales, the task of accurately determining the presence of depression within this complex medical disorder, remains a difficult one.

2.1.4 Treatment of Depression in RA

The treatment of depression with antidepressant therapy in patients with RA appears to be effective. Parker et al in a study looking at the management of depression in RA randomized 54 subjects to 3 treatment groups: cognitive behavior therapy and antidepressants, attention control and antidepressants and antidepressants alone. The subjects were followed up over a 15-month period and numerous parameters were assessed. The results suggested that there was overall improvement in depression in all three groups. There was no difference in the overall effectiveness in all three groups, suggesting that antidepressant therapy alone is effective. Additionally in this study, there were improvements noted in various other parameters including sense of helplessness, self efficiency, coping and psychological distress.[24]

Ash et al found the antidepressant Dothiepin, to be effective as an analgesic for RA patients partly due to its antidepressant action. In addition, beneficial effects were also noted on disability and the duration of early morning stiffness in these patients.[25]

This suggests that the benefit of antidepressant therapy may extend beyond the treatment of depressive symptomatology alone and include other disease manifestations of RA as well.

Covic et al in looking at a biopsychosocial model of pain and depression in RA, concluded that the presence of physical disability, sense of helplessness and passive coping have a significant impact on the pain experience and depression in patients with RA. As such, the

authors suggest a biopsychosocial approach to the management of RA, to address not only the physical manifestations of the disease, but also the psychological impact. In this way, better patient health outcomes can be achieved in this group of patients.[26]

In general, the literature on the holistic management of RA, with specific reference to the treatment of depression, supports the use of both antidepressants and psychotherapy; interventions which have traditionally been successfully used in non-medical patients suffering from depression.

2.1.5 The South African Context

The South African RA population presents a unique context in view of its cultural, ethnic and socioeconomic diversity. There appears to be a paucity of literature examining the prevalence of depression and the psychosocial aspects of this RA patient population.[6]

Venter et al in a study looking at coping styles and depression in South African patients with RA and Systemic Lupus Erythematosus (SLE) found that depression was present in 32% of RA patients. The predictors of significant depression were found to be stressful life events unrelated to illness and the use of a passive, acceptant mode of coping. The authors proposed that psychotherapeutic interventions aimed at developing a more active coping strategy may be beneficial to improving the mood of these patients and thereby improving their quality of life.[6]

In another study, reported to be the first South African study to investigate the association between psychosocial, sociodemographic and disease factors; and quality of life in patients with RA, Naidoo et al found that psychological factors, especially coping, were more significant predictors of self-report of pain and functional status than sociodemographic factors. Based on their findings, the authors recommend a holistic and multidisciplinary approach to the care of patients with RA.[27]

Mody G, whilst tending to be more medically based still provides valuable insights into the profile of RA in Black South Africans. One such study in a cohort of Black patients in the city of Cape Town, found that severe RA disease is not as uncommon in this population group as previously believed. The psychological burden of disease can then be expected to be significant and worthy of further investigation.[28]

2.2 RA and Pain

Patients with RA typically describe pain as their most disabling symptom. It is unclear whether depression is a response to pain in RA; or whether the presence of depression results in an exacerbation/elevation of the pain experience. What has clearly emerged from studies is that a reciprocal reinforcing relationship exists between pain and depression in RA.[3, 14]

A more recent study examining the impact of pain on RA patients found that depression and C - reactive protein (CRP) measurements were significantly associated with pain even after adjustments for clinical covariates. In addition it was noted in this study that the risk of severe pain increased with depression and CRP measurements in a linear fashion; illustrating the close association between these parameters.[29] Low et al, however, failed to show the same finding in 173 women with RA. Instead, this study found no significant association between negative mood and CRP and concluded that depressive symptoms in RA may be attributed to an overlap between somatic depressive symptoms and RA; and not due to neuroimmune modulation.[30]

Abeare et al looked at the relationship between pain, executive functioning and the influence of affect and found that increased levels of pain were associated with poor executive functioning, once again highlighting the significance of the role of pain in the overall functioning of RA patients.[31]

One of the challenges facing clinicians managing patients with RA is the measurement of pain which their patients experience. Sokka, in a review of the assessment of pain in patients with rheumatoid disease noted that pain is the most prominent symptom in people with arthritis and should be routinely evaluated as part of clinical monitoring. The author reviewed both early efforts to measure pain tolerance and the later use of patient questionnaires to measure pain; and concluded that the most robust quantitative pain measure that can be speedily completed and scored is the 10-cm visual analogue scale (VAS).[32]

In view of the findings that pain can be easily measured, albeit subjectively, and that it is associated with other important RA and psychosocial outcomes the routine monitoring of pain in a clinical setting and the management thereof; should be viewed as an integral aspect of RA patient care.[33]

2.3 RA and Functional Disability:

Disability is a defined concept, describing the difficulty in functioning; at the body, person or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors. [34]

RA patients experience significant disability that affects all domains of their lives. Studies looking at the factors associated with disability in RA patients have found that co-morbid depression is associated with increased functional disability in these patients.[3, 12, 13] The decline in functional ability in RA patients, particularly with regard to activities of personal valued significance, is thought to herald the onset of depression.[35] Margaretten et al, in a study looking at the socioeconomic determinants of disability and depression also concluded that the presence of RA functional disability, particularly in a low socioeconomic status population, rendered them at high risk of developing depressive symptoms.[36]

The presence of depression, on the other hand, seems to predict a poorer functional outcome and greater general disability. Rupp et al studied the association of disability and health-related quality of life with depressive symptoms, disease activity, pain and radiographic joint damage in 307 RA patients over a two-year period. These authors found that depressive symptoms and pain were more important predictors of disability and impaired quality of life than disease activity or radiographic damage.[37]

In a South African study, examining the functional disability and health-related quality of life of Black patients with RA, a strong and positive correlation was found between disease activity and physical dysfunction as well as poor overall quality of life. Although this study did not specifically look at depression outcomes, it did report that the mental health component summary of the Short Form 36 Disability Questionnaire, also correlated strongly with functional disability. This once again highlighted the relationship between mental health and the outcomes of RA functional disability.[38]

2.4 RA, Morbidity and Mortality

RA is associated with a number of co morbid medical conditions. The most common of these are reported to be depression, hypertension, cardiovascular disease and cerebrovascular disease.[4, 39]

Whilst depression has been noted to be an independent risk factor for incident heart disease its presence in the context of RA is likely to confer an even greater risk of cardiovascular morbidity and even mortality in this patient population.[39, 40] A study on the Department of Veterans Affairs (VA) patients with RA confirmed that depression was a risk factor for incident myocardial infarction, with a 40% higher risk of suffering a heart attack in depressed patients with RA as compared to their non-depressed counterparts.[39]

The median life expectancy of patients with RA is shortened by 3 to 7 years with a 2.5 fold increase in mortality rate.[1] Amongst other factors associated with increased mortality, an association has been found between depression in RA and mortality in a number of studies.[41, 42] In one study looking at this association, co-morbid depression was found to be an independent risk factor for mortality in 1290 RA patients who were followed up over an 18-year period (HR 2.2, 95%CI 1.2-3.9, $p = 0.01$).[4]

Kvien in a review of the epidemiology and burden of illness in RA, reports that the excess mortality seen in RA, has not changed over the past four decades, as may have been seen in other chronic disease entities. Whilst the major contributing factors to mortality are

cardiovascular and cerebrovascular disease, unrecognized and untreated depression should be considered as the mediating factor that sustains this high mortality rate.[42]

With greater awareness of the impact of depression on mortality in RA, clinicians should now actively seek and manage co morbid depression; thereby possibly improving the mortality outcome for future sufferers of RA.

CHAPTER THREE: THE STUDY METHODOLOGY

3.1 Participants:

This study was conducted in the Rheumatology Outpatient clinics at Charlotte Maxeke Johannesburg Academic Hospital. The clinics operate on three days of the week (Monday, Wednesday and Friday). Participants were selected from the Wednesday and Friday clinics, which comprise patients attending routine follow-up. The Friday clinic consists of primarily the treatment- resistant patients. This ensured that the participant sample comprised RA patients with varying levels of disease severity.

The sample size was calculated by multiplying the number of study variables by 10 participants per variable. As such, one hundred participants, of Black, African descent and South African nationality, were systematically selected i.e. every third Black patient who presented to the clinic on that specific day. This selection process ensured some degree of randomization as well as a fair spread of the sample over various clinic days by restricting the number of participants selected from each clinic. As patients with a variety of rheumatologic conditions are treated at these clinics, only those who fulfilled the 1987 American College of Rheumatology criteria for RA were invited to participate in the study.[43] Potential participants had to be 18 years and older. Written, informed consent was obtained from each patient who agreed to participate, prior to entering into the study.

In this setting, participants speak a variety of Ethnic languages and have varying levels of formal education. Only participants who spoke and understood English were selected for the study. For those participants who may have encountered some difficulties with this, nursing staff, who routinely manage these clinics, were co-opted to assist with translation. As most of these patients were regular clinic patients, they were also familiar with the process of routine clinical monitoring and the completion of assessment tools used in Rheumatology. As such, they were expected to experience little difficulty with the process.

After selection and completion of the informed consent process, participants completed the Health Assessment Questionnaire – Disability Index (HAQ-DI), Visual Analogue Scales (VAS) for Pain, Fatigue and Disease Activity and Arthritis Impact Measurement Scale (AIMS) for depression (AIMS-D) and tension (AIMS-T). The researcher then administered the Montgomery-Asberg Rating Scale for Depression (MADRS) and verified all demographic data recorded.

Participants were then clinically examined by two experienced rheumatologists and trainee rheumatologists, under the supervision of the qualified rheumatologists. In addition to routine clinical monitoring, the following clinical parameters, relevant to this study, were recorded: HAQ-DI score, 28- and 36- tender, swollen and deformed joint counts, VAS scores for pain, fatigue and disease activity and AIMS score. Participants were then required to provide a blood sample for the C-reactive protein (CRP) measurement. The Rheumatologists were blind to the MADRS scores at the time of conducting the clinical examination.

The researcher assisted with the scoring of the HAQ-DI, AIMS, VAS and Joint Scores. In addition, the author was responsible for recording the C-reactive protein values and calculating the Disease Activity Score (DAS28) using the available clinical parameters.

All information relevant to the study was recorded on the data collection form (Appendix B)

3.2 Materials

3.2.1 Sociodemographic Characteristics:

Sociodemograhic data including age, gender, income status and marital status were recorded for each participant. Age was recorded in actual years; income status as unemployed, employed/pensioner or on a disability pension; and marital status as married or unmarried (single/divorced/widowed)

3.2.2 RA Variables:

3.2.2.1 Disease Duration

This was recorded in number of years. The information was obtained from the patient and then verified by the clinical records. It was not always clear as to whether the disease duration was calculated from the onset of symptoms or from the date of diagnosis of RA.

3.2.2.2 Current Disease Modifying Anti- Rheumatoid Drugs (DMARDS)

DMARDS are delineated pharmacological agents that appear to have the capacity to alter the course of RA and induce true remission in some patients. They constitute the mainstay of treatment for RA, in addition to nonsteroidal anti-inflammatory drugs and analgesia, and are usually used in combination. A list of the DMARDS that the participant was taking at the time of the study was recorded and verified by the most recent prescription chart.

3.2.2.3 Glucocorticosteroid Use

Glucocorticosteroids are used in RA to suppress aspects of the inflammatory process and immunological responses that are characteristic of this disease. In doing so, they provide symptomatic relief for the patient. They are very rarely prescribed for chronic use due to their long term adverse effects. In view of the documented psychiatric adverse effects of glucocorticosteroids, one of which is depression, their use in the study sample population was also recorded.[44]

3.2.2.4 Medical History

RA is commonly associated with other chronic medical conditions. In such patients, the burden of disease is expected to be higher, with an anticipated greater vulnerability to depression. For this reason, the co morbid medical conditions of the study sample were documented.

3.2.2.5 Stanford Health Assessment Questionnaire – Disability Index (HAQ-DI)

The full Stanford Health Assessment Questionnaire was introduced in the 1980s. It was developed specifically for patients with RA, to evaluate a number of outcome parameters including disability, economic costs, pain, adverse effects of medication and death.[45]

For the purposes of this study, the HAQ-DI (Appendix C) was used to evaluate the degree of disability participants experienced at the time of the study. This component of the HAQ consists of questions on the patient's ability to perform twenty activities. These activities are grouped into eight categories and the responses are graded as follows: score 0 – without any difficulty, score 1 – with some difficulty, score 2 – with much difficulty and score 3 – unable to do.

If the patient uses aides or devices or requires the assistance of another person to perform an activity, the score for each category is adjusted accordingly. The total HAQ-DI score is the mean of the scores of the eight categories. The score ranges from 0-3. In this study, patients with a HAQ-DI = 0 were considered not disabled and those with a HAQ-DI $\geq$ 1.5 were considered severely disabled. These cutoff values are in line with those used in a study on a similar study sample and in part, in a similar setting.[7] As reported in this study, the cutoff of a HAQ-DI $\geq$ 1,5 as a marker of severe disability, has been found in other studies to be a strong independent predictor of work disability in early RA.

3.2.2.6 Visual Analogue Scales – for Pain, Fatigue and Disease Activity (VAS-P, VAS-F, VAS-DA)

The visual analogue scale (VAS) was developed for use in Rheumatology by Huskisson et al.[46] This scale comprises a 10-cm horizontal line, anchored with labels at each end. For this study, the patients were instructed to make a mark, along the 10-cm line as to where they rate their pain, fatigue or disease activity respectively, over the past week. The specifiers were as follows: for pain, mark 0 stated 'no pain' and mark 10 stated 'severe pain'; for fatigue – 'fatigue not a problem' and 'fatigue a major problem' respectively and for disease activity – 'disease is not active' and 'disease is very active' respectively (Appendix D).

The VAS is widely used in both clinical and experimental settings and has been found to be valid and reliable.[47] Both strengths and limitations of this type of scale have also been described.[32, 48] The choice of its use in this study was based on its ease of use in an outpatient, time-limited setting and the familiarity with which this study sample has, in completing the VAS.

3.2.2.7 C - reactive protein (CRP)

CRP, together with the erythrocyte sedimentation rate (ESR), is a serum laboratory investigation used widely to assess the presence of acute inflammation and thereby infer information about the level of disease activity.CRP measurements may be used to monitor the response and efficacy of medication and additionally may be used for its prognostic value, as persistently elevated levels can point to higher risk of joint destruction.[49]

Studies report, however, that acute phase reactants like ESR and CRP can be normal in up to 40% of patients at their first visit and may be stable over the long-term course of RA; and may be influenced by individual genetic factors.[50, 51] As such, their use as an indicator of active disease may be limited. Despite these concerns, ESR and CRP measurements remain routinely used laboratory indicators of inflammation in the absence of any proposed alternatives.

There is also some conflicting evidence regarding the association between these inflammatory biomarkers and the presence of depression in patients with RA with some studies finding that CRP is significantly associated with depressive symptoms; and others not.[29, 30]

For the purpose of this study, the recording of the participant's CRP level was two-fold: 1) to determine whether there is an association between the CRP level and the presence of depression and 2) to enable the calculation of the participants' Disease Activity Score
(DAS 28)

Once participants had completed the clinical assessment by the rheumatologist and the depression scale by the author, they were instructed to proceed to the laboratory to provide a serum sample for the CRP level. The reference range for the CRP measurement, for the laboratory used (National Health Laboratory Services – NHLS) was set at 0.0 – 10.0 mg/L with a measurement of >10mg/L indicating the presence of inflammation.

3.2.2.8 28-Joint Disease Activity Score (DAS28)

The original Disease Activity score (DAS) was developed to enable rheumatologists to make treatment decisions based on the disease activity present in the patient. The DAS28 is a modified version of the DAS, using a 28-joint count for both swollen and tender joints. It provides a number on a scale from 0 to 10 to indicate the level of disease activity of RA. A DAS28 above 5.1 indicates high disease activity while a score of below 3.2 indicates low disease activity.[52]

In this study, the DAS28 using CRP measurement [DAS28 (CRP)], as opposed to the usual ESR measurement, was used. The DAS28 (CRP) shows a similar validation profile to the DAS28 (ESR) and is reported to be a useful measure of assessment of disease activity.[53]

The researcher utilized a programme available at the DAS website to calculate the DAS28 score according to a predetermined formula.[54]

3.2.3 Depression Measurements

3.2.3.1 Arthritis Impact Measurement Scale (AIMS)

The AIMS is described as a multidimensional index that measures the health status of persons with arthritis. It was developed to assess all aspects of the RA, including mental and social wellbeing; and not just the physical status of the patient. The scale's validity and reliability has been documented and it is a clinically useful self- administered tool that can be quickly completed in an outpatient setting.[23]

The complete AIMS consists of a total of nine groups of items measuring mobility, physical activity, dexterity, social role, social activity, activities of daily living, pain, depression (mood) and anxiety. For the purpose of this study, only the depression (mood) and anxiety item groups were completed by the study participants (Appendix E). These two groups form part of the assessment tool used routinely by the Rheumatology clinicians to assess health status in their patients; particularly to screen for depression and anxiety symptoms respectively. A score of ≥4 indicates significant depression and/or anxiety symptoms and often prompts the Rheumatologist to commence appropriate psychotropic medication or to refer to appropriate psychiatric services.

3.2.3.2 Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS (Appendix F) is a 10-item clinician-rated depression scale developed in 1979, from a 65-item comprehensive psychopathology instrument.[22] Although the MADRS was developed with the intention to detect change in depressive symptoms with antidepressant use, it has been widely used to measure depression severity.[55, 56, 57]

Although the 17-item Hamilton Rating Scale for Depression is also widely used in clinical trials, the MADRS has been shown to be more precise in estimating depression and is therefore thought to be superior. It is also noted to be briefer and more uniform.[21, 55, 56, 57, 58]

The choice of the MADRS for this study was based on its brevity, inclusion of the item‘Apparent sadness’ which allows the researcher to make an objective assessment of the

participant's mood state and the advantage of a clinician driven scale over a self-report questionnaire. In addition, the relatively few somatic items contained in the MADRS are thought to assist in reducing criterion contamination.[20, 22]

In terms of scoring of the MADRS, literature is variable as to the recommended cut-off score that is most likely to indicate the presence or absence of depression. Whilst the researcher was unable to locate any studies to date using the MADRS on RA cohorts, two studies did report on its use in patients with Parkinson's disease.[56, 57] Both studies justified the use of the MADRS in this medical population, but showed variable cut-off scores that correlate with a diagnosis of depression. Silberman suggested a cut-off of 10, above which patients would be classified as depressed.[57] Leentjies concluded that at a cut-off score of 17 or 18, the MADRS showed high specificity and positive predictive value, hence making it a good diagnostic tool.[56] The use of high cut-off scores for the MADRS was also implied by the WHO cross-sectional, longitudinal study of neuropsychiatric conditions in HIV-AIDS patients. This study found that the symptomatic patients scored higher on the MADRS as compared to asymptomatic patients and controls.[59]

Based on the above reported findings, the author elected to use a cut-off score of ≥20 to indicate the presence of significant depressive symptoms (referred to as depression). This score does not necessarily equate to a clinical diagnosis of a major depressive disorder.

The participants who scored within this range were referred to the psychiatric outpatient clinic for a full psychiatric evaluation to confirm a diagnosis of a depressive disorder. For

those participants who scored ≥ 20, whilst already on antidepressant therapy, referral to psychiatric multidisciplinary services and/or antidepressant dosage adjustments were recommended by the author. In the event of actively suicidal participants, provision was made for them to be immediately referred to emergency consultation-liaison psychiatric services.

3.2.3.3 Psychiatric History

The patients attending the Rheumatology clinics are routinely screened for depression and anxiety using the AIMS. As such, patients found to be depressed are commenced on antidepressant therapy by Rheumatologists. In addition, participants may have a psychiatric history that predates the diagnosis of RA. For these reasons, the psychiatric history of the participants was recorded.

3.2.3.4 Antidepressant Use

The prescription of antidepressant medication was also recorded in this study. Experienced Rheumatologists who manage this clinic seem comfortable prescribing first line antidepressant therapy based on the patients' response to the AIMS depression and anxiety subscales. If a poor response to antidepressant treatment is noted or further psychiatric complications arise, the affected RA patients are then referred to specialized psychiatric services within the hospital.

3.3 Statistical Analysis

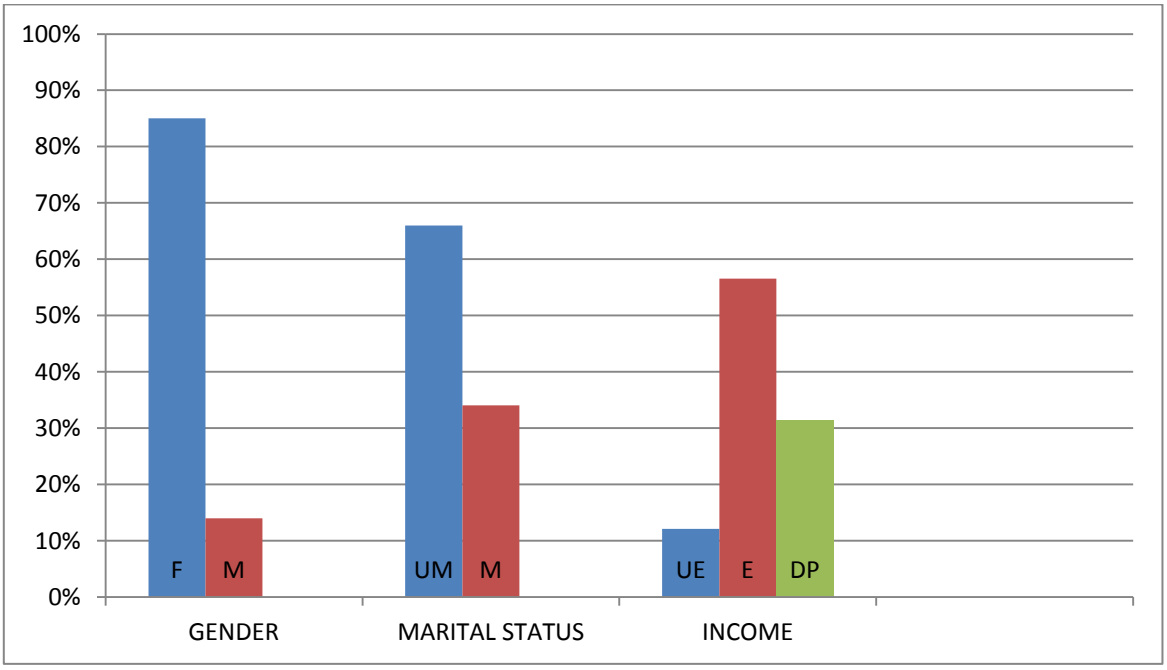
Data was analyzed using the SAS version 9.1 statistical program (SAS, Carey, NC, USA). Results are expressed as mean and standard deviation or median [range] for scores of non-normal distribution; or frequencies and percentages for categorical variables. To determine associations between the presence of depression (MADRS score ≥ 20); and sociodemographic and RA variables, a Wilcoxon-Mann -Witney test was used. Spearman correlation coefficients were used to determine the correlation between the presence of depression (using actual MADRS scores) and age, HAQ-DI, VAS (Pain, Fatigue and Disease Activity), CRP, DAS-28, AIMS-Depression and AIMS-Tension/Anxiety. Significance was assumed at a both-sided value of $p < 0.05$.

CHAPTER FOUR: RESULTS

4.1 Sociodemographic Characteristics

A total of 99 patients participated in the study. One patient was excluded following a diagnostic review that did not find clinical criteria to be consistent with RA. Figure 1 illustrates the sociodemographic profile of the study sample, in which the majority (85%) of the sample was female; unmarried (66%) i.e. single, divorced or widowed and employed or on old age pension (56.6%). The mean age was 54.9 ± 9.9 years, ranging from 19-78 years.

FIGURE 1 SOCIODEMOGRAPHIC CHARACTERISTICS



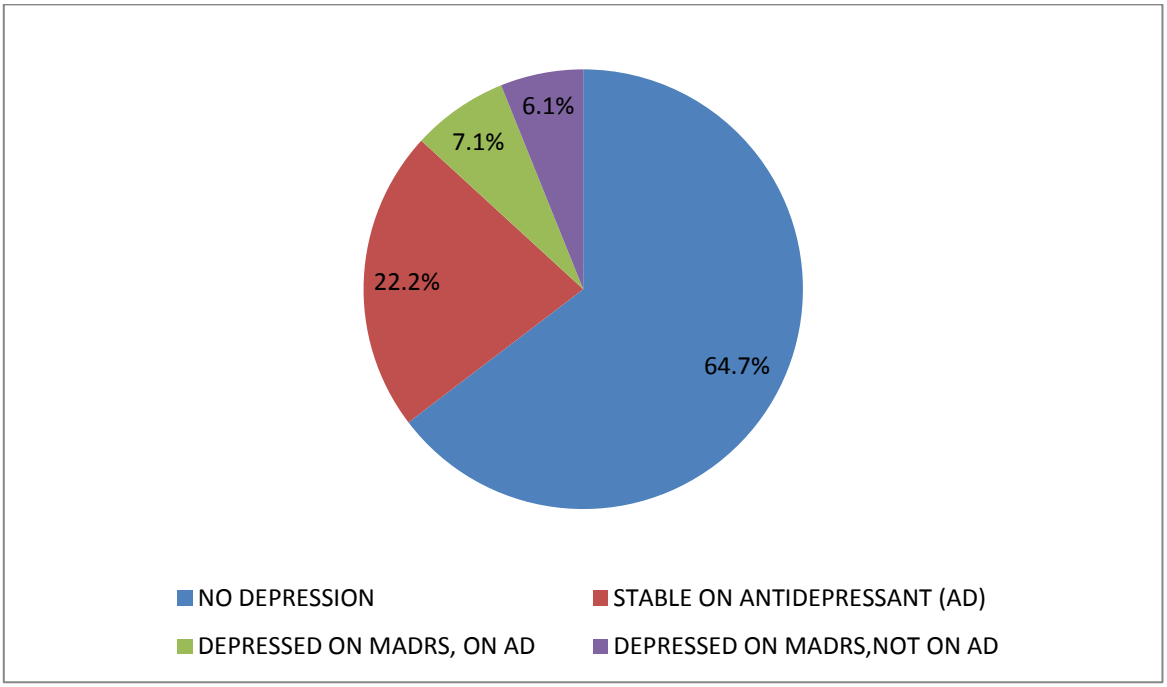
Gender: F – Female, M – Male; Marital Status: UM - Unmarried, M - Married; Income: UE - Unemployed, E - Employed, DP - Disability Pension

4.2 Depression Variables

4.2.1 Prevalence of Depression

Figure 2 illustrates the depression status breakdown. The majority of the sample, 67(64.7%) participants were not found to be depressed, however 35 (35.4%) had an association with depression. Of this a total of 13 (13.2%) participants were found to be currently depressed according to the MADRS (total score ≥20). The remaining 22 (22.2%) participants were not found to be depressed on the MADRS, but were currently stable on antidepressant treatment.

FIGURE 2 DEPRESSION CHARACTERISTICS



MARDS: Montgomery-Asberg Depression Rating Scale; AD: Antidepressants

The prevalence of depression in this study sample was thus calculated at 13.2% (CI 0.06-0.20) if only those participants, who were found to be depressed on the MADRS at the time of the study, were used to determine the prevalence.

4.2.2 Psychiatric History

In terms of the past psychiatric history (Table 1), 29 (29.3%) participants had a history of depression and were currently still on antidepressant treatment; 6 (6.1%) had a previous history of depression and were no longer on treatment; and 2 (2.0%) participants had a history of previous alcohol abuse.

4.2.3 Psychotropic Medication

With reference to antidepressant use (Table 1), the majority of those currently using antidepressants were prescribed Fluoxetine. The only other antidepressant used in this sample for the treatment of depression was Citalopram. Amitriptyline was prescribed, at a low dose, for two participants for the treatment of neuropathic pain only.

Table 1 Psychiatric History and Antidepressant Use

DEPRESSION VARIABLE	*N (%)*
Psychiatric History (N=37)	
Current Depression. On treatment	29 (29.3)
Past Depression. Not on treatment	6 (6.1)
Other Psychiatric Disorder	2 (2.0)
Antidepressant Use (N=31)	
Fluoxetine	15 (15.2)
Citalopram	14 (14.1)
Amitriptyline	2 (2.0)

4.3 RA Variables

Table 2 illustrates the RA clinical variables of the study sample. The mean disease duration was 12.5 ± 9.2 years, the mean HAQ-DI score was 0.92 ± 0.75, the median CRP measurement was 8.1mg/L (0.5 – 189.2mg/L) and the DAS28 had a mean of 3.24 ± 1.13. The mean values of the various visual analogues scales were similar to each other; as were the mean values of the two AIMS subscales. No significant results were found for the use of corticosteroids and DMARDS in study sample. Only one participant was prescribed corticosteroids.

Table 2 Rheumatoid Arthritis (RA) Variables. N=99

RA VARIABLE	*Mean ± SD*	*Range*
Disease Duration (years)	12.5 ± 9.2	1- 41
HAQ – DI (0-3)	1.0 ± 0.8	0 - 3.6
DAS28	3.2 ± 1.1	1.5 - 7.4
CRP (mg/L) median	8.1	0.5 - 189.2
VAS- P	4.8 ± 3.3	0 - 10
VAS-F	4.2 ± 3.2	0 - 10
VAS-DA	4.2 ± 2.9	0 - 10
AIMS-D	3.6 ±1.8	0 - 7.5
AIMS-T	4.1 ± 1.6	1 - 9.5

Table 3 illustrates the frequency distribution of three RA clinical variables; CRP measurement, HAQ-DI, and DAS 28. The majority of the sample, 53 (57.61%) participants had an elevated CRP measurement of >10 mmol/L. A majority of 80 (80.81%) of the participants had a HAQ-DI score of < 1.5, indicating that they were not classified as disabled. For the DAS 28 frequency distribution, a majority of 45 (50%) participants had a low disease activity score of < 3.2; 38 (42.22%) participants had an intermediate disease activity score of

between 3.2 and 5.1 and 7 (7.78%) participants scored in the high disease activity range of >5.2.

Table 3 RA Variables – Frequency Distribution

RA VARIABLE	***N (%)***
CRP (mmol/L):	
≤ 10	39 (42.4)
> 10	53 (57.6)
HAQ-DI:	
< 1.5	80 (80.8)
≥ 1.5	19 (19.2)
DAS 28:	
< 3.2	45 (50.0)
3.2 – 5.1	38 (42.2)
> 5.1	7 (7.8)

4.4 Association between Depression and Sociodemographic Characteristics

This study did not find any significant association between the presence and absence of depression and the age, gender or income of the study sample.

4.5 Association between Depression and RA Disease Variables

Table 4 illustrates the significant associations found in this study between the presence of depression and RA variables. The only significant associations were noted between the presence of depression and the visual analogue scales for fatigue (VAS-F) and disease activity (VAS-DA). Association with AIMS-D and VAS-P were noted to approach significance. No significant associations were found between depression and the use of corticosteroids or DMARDS.

Table 4 Association between Depression and RA Variables

RA VARIABLE	***P VALUE***
HAQ – DI	0.12
DAS28	0.53
CRP	0.32
VAS-P	0.07
VAS-F	0.03†
VAS-DA	0.03†
AIMS-D	0.06
AIMS-T	0.28
Disease Duration	0.74

† Significance $P \leq 0.05$

4.6 Association and Correlation between RA variables and Depression (MADRS) Scores

Table 5 illustrates only the significant relationships found between RA disease variables and the actual MADRS scores for the study sample.

MADRS scores were initially found to be significantly associated with HAQ-DI ($p = 0.002$, $r = 0.30$); VAS-DA ($p = 0.001$, $r = 0.32$); VAS-F ($p < 001$, $r = 0.43$); AIMS-D ($p < 0.001$, $r = 0.40$) and AIMS-T ($p < 0.001$, $r = 0.35$). A moderately strong correlation was also found between MARDS scores and these RA variables. Upon adjusting for age and clinical status, significant associations remained with MADRS scores and all five above-mentioned RA variables. Correlations between MADRS score and the RA variables HAQ-DI, VAS-DA, VAS-F and AIMS-T weakened slightly upon adjustment.

Table 5 Association and Correlation (Spearman r) between RA variables and MADRS

	MADRS (Unadjusted)		**MADRS (Adjusted[a])**	
Variable	***P*- value**	**Spearman r**	***P*- value**	**Spearman r**
HAQ-DI	0.002	0.30	0.01	0.28
VAS-DA	0.001	0.32	0.02	0.26
VAS-F	< 0.001	0.43	< 0.001	0.40
AIMS-D	< 0.001	0.40	< 0.001	0.40
AIMS-T	< 0.001	0.35	0.002	0.33

[a]Adjusted for age and clinical status

CHAPTER FIVE: DISCUSSION

5.1 Sociodemographic Characteristics

5.1.1 Gender

The study finding of a majority of the sample being female is consistent with literature on gender difference seen in RA, which is reported to be 2- 4-fold higher in women.[1, 42] In Black South Africans a higher prevalence of RA in females was also found, with a female -to- male ratio of 6.9:1.[60]

Kvien also reports that the reason for this gender difference has not been fully established, but that studies have postulated that lower levels of testosterone, high prolactin levels during breastfeeding and greater severity of symptoms, may be possible explanations.[42]

5.1.2 Marital Status

The majority of the sample was noted to be unmarried. The category "unmarried" encompassed study participants that were single, divorced or widowed. This finding may be partially explained by the wide range in the age distribution (19 -78 years) reflecting young adults who are yet to be married; and the older-age adults who have already lost their spouses.

The contribution of the individual components of this category was not further analyzed, hence it is not possible to infer any further information about the contribution of each component to this finding.

5.1.3 Income Status

The finding that the majority of the sample was employed is somewhat unexpected in the context of a condition like RA. Previous studies have illustrated the negative impact of RA on allowing sufferers to sustain employment, particularly in view of the functional disability associated with the disease.[1, 62]

The high employment rate may, however, not truly reflect the status quo, as this category encompassed both participants in formal employment, informal part-time employment and those receiving old age state pensions.

The proportion of each of these groups was not specified in this study. Despite this, those formally employed whilst suffering from a chronic, potentially disabling condition, may reflect the resilience of the study population, the adequate RA disease control and/or the economic demands of a historically disadvantaged population group in a developing country that forces them to continue employment, even in the face of the challenges of living with RA.

5.2 Depression Variables

5.2.1 Prevalence of Depression

In this study, 13.2% (CI 0.06 - 0.20) participants were found to be currently depressed. This prevalence rate, whilst lower than those found in other studies is in keeping with the studies of Pincus et al and Katz which reflect prevalence rates of about 15% after attempting to control for criterion contamination.[8,9,10,11,12,13]

The lower prevalence of depression in this study sample can be partially explained by the attempt to also control for criterion contamination by the selection of a depression screening tool (MADRS) that does not emphasize physical symptoms, that includes an objective item to assess depression and by using a high cut-off score to reflect the presence of depression.

In addition, the depression prevalence rate may also be explained by a study sample which shows adequate RA disease management (Mean HAQ-DI = 1.0 ± 9.2 and DAS28 = 3.2 ± 1.1) and that has routine monitoring and management of depression and anxiety via the AIMS-D and AIMS-T respectively.

It should also be noted, however, that although the 22 (22.2%) participants who were stable on antidepressant treatment were not included in determining the prevalence of depression, their contribution to the overall association between depression and RA in this study remains a meaningful one.

5.2.2 Psychiatric History

A total of 37.3% of the study sample had a psychiatric history and were either still currently on treatment or now stable and no longer taking psychiatric medication. Two participants (2.0%) had a previous history of alcohol abuse, but were stable at the time of the study; whilst the remaining 35.3% reported a history of depression. The history of depression, whether past or present, is relevant not only to the overall prevalence of depression in this sample, but also to the chronic nature of the depression within the context of RA, with some patients requiring long term antidepressant prescription.

5.2.3 Psychotropic Medication

The study finding that the depressed patients who were identified by routine Rheumatology screening, were prescribed Selective Serotonin Reuptake Inhibitors (SSRIs) i.e. Fluoxetine and Citalopram to treat the depression, is expected as these are first- line antidepressant agents that are routinely prescribed by medical specialists other than Psychiatrists, in this hospital setting. Patients requiring other classes of antidepressant treatment or who do not respond adequately to SSRI antidepressants are generally referred for specialized psychiatric management.

The specific use of SSRI antidepressant medication in the treatment of depression in RA was reported on in a case study and review by Krishnadas et al.[3] The report concluded that the

significant interaction between the serotonergic and inflammatory systems is worthy of further study and may explain the benefit and sustained remission of RA with the use of SSRIs.

SSRIs and other serotonergic antidepressants may thus be the most appropriate psychotropic agents to use in this patient population.

5.3 RA Variables

5.3.1 Disease Duration

The mean disease duration of 12.5 years (range 1 – 41 years) is long and probably reflects the wide age distribution of the study sample i.e. 19 – 78 years, as well as the chronic nature of RA.

5.3.2 Disability (HAQ-DI)

The mean HAQ-DI score of 0.92 and the finding that the majority of the sample scored in the "not disabled" range [80 (80.8%) participants scored ≤ 1.5] is somewhat unexpected; as the study sample comprised participants from the routine and treatment – resistant RA clinics.

This low rate of disability may, in part, be explained by the possible unequal distribution of participants recruited from the routine and treatment-resistant clinics. In addition,

consideration must be given to the positive outcomes of close routine monitoring and adequate disease management that this tertiary level academic RA clinic at CMJA Hospital provides.

It may also be tempting to ascribe this finding of a low rate of disability to a milder form of RA disease in Black South African RA patients. Although very early studies thought this to be the case, more recent surveys and studies, as reported by Mody and Meyers, have found that severe RA disease is present in this population group.[28]

5.3.3 Disease Activity Parameters (CRP and DAS 28)

Although a small majority of the study sample had an elevated CRP level i.e. 53 (57.6%) participants, the mean CRP measurement was still low at 8.1mg/L, with a wide range of 0.5 - 189.2mg/L. Again, this seems to indicate a lower level of disease activity in this sample.

The mean DAS28 score of 3.2 with half the sample [45 (50.0%) participants] scoring in this range supports the general finding of a low disease activity. Although this is a favourable outcome in terms of disease management, consideration must still be given to the remaining 50% of the study sample who still have intermediate and high disease activity.

5.3.4 VAS-P, VAS-F and VAS-DA

The findings related to the Visual Analogue Scales for pain, fatigue and disease activity are largely consistent among all three parameters, with values of 4.8, 4.2 and 4.2 respectively.

These relatively lower scores, as indicated subjectively by the participants, seem to support the more objective findings of a generally well controlled RA sample.

5.3.5 AIMS – D and AIMS-T

Both the AIMS-D and AIMS-T mean scores were less than 5, with the mean AIMS-T score being slightly higher at 4.1±1.6. This finding seems to be in keeping with the lower prevalence of depression found in this study sample. As such, it may also indicate a favourable correlation between the MADRS as a psychiatric screening tool and the AIMS-D, as a depression screening tool used specifically for the arthritis population.

5.4 Association between Depression and Sociodemographic Characteristics

The finding of no significant associations between depression and the age, gender, income and marital status of the study sample is not unexpected, as literature is variable with regard to study findings.[9] There is, however, some support for a positive association between the presence of depression and younger age, female sex, lower income; and lack of a significant and supportive relationship. [65, 66, 67]

The difference in findings may possibly be explained by the fact that most published literature on the sociodemographic profile of depressed RA patients, originates from developed countries.[9, 64, 65, 66, 67] The sociodemographic profile of this study sample, on the other hand, is characterized by only Black patients who originate from a formally politically and economically disadvantaged background in a developing country. As such, the findings of this study may be unique to the represented population group.

In addition, the mean age of the sample was older i.e. 54.9 ± 9.9 years. As literature seems to support an association between depression and a younger age group, this may explain the lack of significant association with age in this study.

Dickens et al, in a study looking at the association of Depression and RA, found depressed RA patients to be significantly more likely to belong to a lower social class ($p = 0.002$).[64] Whilst this study did not categorize patients into social classes per se, it did consider income status. Unemployment would have been expected to be associated with depression in this study sample, however, this was not the case. A possible explanation may lie in the high unemployment rate in South Africa (25.0% - 3rd Quarter, October 2011); hence unemployment amongst patients attending a public sector hospital may be the norm rather than the exception.[68] Additionally, it is possible that a change in employment status, as opposed to a long standing status quo of unemployment may represent a greater stressor; that then renders the RA patient more vulnerable to depression.

Literature on the subject of depression in RA and marital status suggests that the quality of the relationship as opposed to the status of marriage is a more significant associate and correlate. Both Reese and Waltz highlight this aspect of marital status and, in particular, its impact on the clinical outcomes of the patient.[33, 67]

The lack of a significant association between depression and marital status in this study may further be explained by two reasons. Firstly, the participants were divided into two categories only i.e. married and unmarried. Whist the "unmarried" category included only single, divorced and widowed individuals, it may have also included those who were in a significant and supportive relationship, but not lawfully married. This is not an uncommon practice among certain South African cultural groups, where partners may be "culturally and religiously married" but not legally so. In doing so, participants who were categorized as single may have, in fact, been in a meaningful and supportive relationship. Secondly, this study did not explore the quality of the marital relationship and can therefore not infer any other information regarding the impact of marital status on depression except for the noted findings.

5.5 Association between Depression and RA Disease Variables

5.5.1 Depression and Disability (HAQ-DI)

The significant association between MADRS and HAQ-DI scores as well as the positive correlation (r = 0.30) between these two measures, even after adjustment, is in keeping with most of the literature on disability and RA.[3, 12, 36, 37]

Lowe, Willand and Eich et al, studied the relative contribution of psychiatric co morbidity to work disability (as measured by physical disability scales). They found depression to be an independent risk factor of work disability and that this finding was particularly relevant to patients with severe RA.[69]

In this study, participants had predominantly mild to moderate RA disease. Based on the findings of Lowe et al, this may explain the lack of a strong correlation between MADRS scores and disability. Nevertheless, the significant association between these two measures is a meaningful one and may indicate a greater need for active management of depression as well as physical and vocational rehabilitation.

5.5.2 Depression and VAS-Disease Activity (VAS-DA)

Despite the lack of finding a significant association and correlation between depression and the DAS 28 scores and CRP measurement, both of which are used as a measure of disease

activity, the VAS-DA was found to be both significantly associated with and positively correlated with MADRS scores.

This finding should be interpreted with caution as the VAS-DA is a subjective measure of the patient's impression of their overall disease activity. As such, it may be influenced by other factors including co-morbid medical illness, medication adverse-effects, psychosocial stressors and the negative cognitions associated with depression. Conversely, visual analogue scales are noted to be both sensitive and clinically useful measures of the subjective aspects of RA disease outcomes.[46, 47] In considering this, the study's finding of significant association between MADRS scores and VAS-DA, is worthy of further exploration.

5.5.3 Depression and VAS- Fatigue (VAS-F)

There is extensive literature documenting and exploring the symptom of fatigue in patients with RA and other musculoskeletal disorders.[70, 71, 72, 73, 74, 75, 76]

Stebbings, Herbison, et al investigated the correlates of fatigue amongst RA and OA patients; and found fatigue to be common and severe in both disorders. In RA, fatigue was significantly associated with depression and anxiety, but not with pain, disease activity or disability.[70]

The findings in this study were similar, with a significant association between MADRS scores and VAS-F ($p = < 0.001$). A positive correlation was also noted between these two parameters ($r = 0.43$), which weakened slightly after adjustment ($r = 0.40$).

Whilst fatigue may also represent one of the neurovegetative or physical symptoms of depression, it is also widely accepted as a significant symptom of rheumatic disease that is frequently reported by patients.[71]

RA patients differentiate fatigue related to disease from general tiredness in that fatigue seems to encompass both a physical and a mental/cognitive component; typically described as a lack of motivation, difficulty concentrating and an inability to think clearly.[72] The prevalence of clinically relevant fatigue is reported to be between 40 and 80%.[70, 73] Fatigue has also been reported to be a common reason for discontinuing work.[74]

Although, fatigue may well be difficult to conceptualize particularly as it is subjective, and may represent either an independent symptom of RA disease or a part of other disease outcomes, its significant association with depression warrants further consideration. RA patients with a past history of depression and suffering from a current "dysphoric" mood were found to experience higher levels of fatigue. In addition, the most robust predictor of fatigue was found to be, amongst other parameters, a greater number of depressive symptoms ($r = 0.51$; $p < 0{,}0001$).[75]

Hence the findings of this study are in keeping with international published literature on fatigue and depression in RA. This warrants further investigation of this symptom in this cohort of RA patients, particularly in view of the negative impact of fatigue on the patient; and the reported benefit of cognitive behavioural therapy and psychosocial interventions in

managing fatigue; not withstanding the positive impact of the active management of depression.[76]

5.5.4 MADRS, AIMS-D and AIMS-T Scores

The significant association and positive correlation between MADRS scores and both AIMS-D and AIMS-T respectively provides useful information regarding the use of these AIMS subscales as a good psychological screening tool for depression and anxiety. Whilst the AIM-D and AIMS-T do not presume to indicate a diagnosis of a depressive or anxiety disorder, their use in the RA population is invaluable in alerting and sensitizing the Rheumatologist to the possibility of co-existing psychiatric pathology.

This finding is also important for aligning the MADRS, a depression screening tool used predominantly on a psychiatric and general population, with the AIMS, a screening tool developed for and used specifically on an arthritis population. Further research into the correlation between these screening instruments and their findings on different patient cohorts may assist us in developing a better understanding of the depression characteristics within and between depression and arthritis patient populations.

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

Depression within the context of a chronic, potentially, disabling condition like RA is a significant, but complex phenomenon to understand and investigate.

Extensive published literature exploring these two disease entities, while providing both contradictory and compelling evidence of the interaction between them, illustrates that this area of research is worthy of our understanding and study, in order to achieve the most favourable outcomes in RA.

The prevalence of depression in RA, despite concerns about criterion- contamination, suitability of measurement instruments and confounding psychosocial and RA disease factors, still remains higher than the general population. In addition to this, the negative health impact of depression in RA patients is significant and cannot be ignored if favourable health outcomes are to be achieved.

As such, an important goal of comprehensive RA disease management should be to sensitize the clinician to the need and the means to detect depression in RA patients. Whilst the AIMS subscales for depression (AIMS-D) and tension (AIMS-T) are valuable and validated screening tools, there appears to be a need to develop more comprehensive measurement tools that may assist in diagnosing psychiatric disorders, like depression, in the unique medical population.

Despite some of the challenges faced with screening for, detecting and diagnosing depression; when identified, depression has been found to be responsive to antidepressant medication. However, for those patients who are not responsive or partially responsive to antidepressants, the role of psychological interventions like cognitive behavioural therapy and psychosocial support need to be considered. In order to facilitate this, a multidisciplinary team approach to the management of RA patients with depression, should be employed.[26, 77]

Whilst South African literature regarding depression in RA patients is minimal, there is sufficient evidence to indicate that the prevalence and correlates of depression in RA, is in keeping with research findings from other developed and developing countries. The challenges facing the management of these complex disorders within South Africa are unique though, especially in the face of the country's political history. The active pursuit of more extensive research into this area will assist in developing a better understanding of depression within the South African RA population.

Without the active detection and management of depression in RA patients, the health outcomes are expected to be characterized by patients who experience higher levels of pain and fatigue, a greater degree of physical disability and higher rates of both medical co-morbidity and mortality. The net result of which again points to poorer health outcomes and resultant personal and economic strain.[78]

In this study, the sociodemographic characteristics of the study sample revealed a predominantly female, unmarried and employed profile. The gender distribution was not unexpected in terms of the predominance of female RA sufferers in general.

The unexpected high level of employment amongst these sufferers of a potentially debilitating illness may be unique to the South African developing economic climate and the limited availability of state financial assistance; which results in RA sufferers being forced to continue employment.

A higher prevalence of depression as compared to the general worldwide population was also found in this study cohort; in keeping with published literature on the subject. In addition, more than one third of the study cohort reported a current or past psychiatric history, mostly related to depression. This represents a significant burden of co morbid disease and may also attest to the chronic nature of depression.

The RA variables of this study sample, despite a long duration of RA disease, revealed that the majority of participants were not clinically disabled. This was an unexpected finding and may be explained by chance, unequal distribution of participant RA disease severity during selection and/or good overall disease management and control.

In addition, other RA disease parameters suggested a RA disease cohort with generally low disease activity and relatively low visual analogue scale (VAS) scores for pain, fatigue and disease activity. This once again indicates a cohort with a lower level of RA disease burden.

In the analysis of association and correlation, no significant associations were found between depression and the sociodemographic factors studied. However, significant associations and positive correlation were found between depression scores (not depressive disorder) and disability (HAQ-DI), subjective assessment of disease activity (VAS-DA) and subjective assessment of fatigue (VAS-F). Not only are these findings in keeping with some published literature, but they are also useful in assisting with the identification RA disease parameters that are associated with co morbid depression. In so doing, these parameters may then be actively targeted and managed, so as to achieve more effective management of co morbid depression and consequent improved RA disease and patient health outcomes. Conversely, the associations of these RA parameters with depression may further sensitize the rheumatologist to actively seek depression in RA patients presenting with persistently elevated disability, subjective disease activity and fatigue scores.

The significant association and positive correlation between RA psychological screening tools (AIMS-D and AIMS-T) and those used traditionally in Psychiatry (MADRS) may assist in developing a unique measurement tool that can be used to not only screen, but preferably help diagnose depressive disorders in this patient population.

The finding of 7.1% of the study cohort being depressed on MADRS despite being currently on antidepressant treatment (Figure 2) is an area of concern. This may indicate a need for closer monitoring of depression, more regular referral to specialist psychiatric services of patients who are not optimally responsive to first-line antidepressant treatment and/ or the need for a multidisciplinary approach to the management of depression in these patients.

This would ultimately include the additional input of psychologists, occupational therapists and social workers to address the comprehensive needs of these patients who have a high burden of disease.

CHAPTER SEVEN: LIMITATIONS

Whilst being the first known study to look at depressive symptoms, using a psychiatric screening tool in this cohort of Black South Africans with RA, attending this specific public health institution, the study nevertheless has a number of limitations.

The study cohort was confined to a specific sector of the South African population i.e. Black South Africans attending a tertiary, academic, public health institution. The findings may therefore, not be generalisable to the greater South African population where access and standard of healthcare may be dependant on resources and settings (provincial variations, public versus private healthcare and rural versus urban). In addition, sociodemographic and socioeconomic variations between different racial population groups that exist in South Africa, may translate into unique RA disease parameters and depression profiles.

Whilst an attempt was made to include a study population that encompassed RA patients with variable disease severity, no attempt was made to ensure that the contribution of the "treatment-resistant" clinic equaled that of the routine clinic. As such, the lower prevalence of depression seen in this study may have arisen from an unequal distribution of RA disease severity.

A control group was not used to provide a comparison of the sociodemographic characteristics and the depressive symptom prevalence of the study cohort with other Black South Africans. Instead, the sociodemographic, RA disease and depression characteristics were simply

compared to those described in international, published literature from other developed and developing countries.

Although attempts were made to ensure that all RA disease measurement outcomes were completed for each participant, there were missing data across all variables, but most notably in the CRP measurement, where the patient was expected to proceed to the laboratory to provide a blood sample. Ensuring that this sample was taken may have reduced the number of lost data and possibly influenced the final data analysis.

The use of a depression screening tool (MADRS) as opposed to a depression diagnostic tool, whilst providing useful information regarding depression symptom prevalence, did not equate to a diagnosis of a depressive disorder, differentiation of various depressive disorders or individual depression characteristics. As such, the comprehensive profile and description of depressive disorders in these RA patients was not addressed in this study.

In addition, the high cut-off score of ≥ 20 as a measure of significant depressive symptoms may have failed to detect participants experiencing mild to moderate, yet still significant depressive symptoms. This, in turn, may be reflected in the low prevalence rate of depression found in this study.

What this study does provide is the beginning of a descriptive pathway into the interaction between the psychiatric entity of depression and the chronic, potentially disabling condition of RA, in a largely understudied population group. In addition, it provides useful findings that

may be of influence in the diagnosis and management of depression in chronic medical conditions like RA, and in so doing, improve health and health-related economic outcomes in South Africa. Lastly, but not least of all, this study may provide a gateway to further research into the complex interaction between the human immune system and the human psyche.[79]

APPENDIX A

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Pillay

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M070624**
PROJECT	Depressive Symptoms in African Patients with Rheumatoid Arthritis
INVESTIGATORS	Dr A Pillay
DEPARTMENT	Psychiatry/Neurosciences
DATE CONSIDERED	07.06.29
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 07.08.16 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr U Subramaney

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX B

DATA COLLECTION FORM
DEPRESSION/ RHEUMATOID ARTHRITIS STUDY

DATE		
PATIENT CODE		
CONSENT	Y	N

MARITAL STATUS	S	D
	M	W

1. SOCIODEMOGRAPHIC DATA (tick where applicable)

AGE IN YEARS				
GENDER	F	M		
INCOME STATUS	EMP	U/E	DG	RETIRED/PENS
DISEASE DURATION	YEARS		MONTHS	

2. DISEASE OUTCOME

HAQ - DI						
TENDER JOINTS	36		28			
SWOLLEN JOINTS	36		28			
DEFORMED JOINTS	36					
VAS PAIN		VAS FATIGUE			VAS DIS.AC. Pt.	
AIMS (TENSION)		AIMS (DEPRESSION)				
CRP (AT VISIT)						
DAS						

3. TREATMENT

CURRENT DMARDS			
CURRENT REGULAR CORTICOSTERIODS	YES	NO	
CURRENT PSYCHOTROPIC MEDS			

4. CURRENT CO-MORBIDITIES (tick where applicable)

CVD	MI	CVA	HF	PVD	CMP	HT
ONCOLOGY	TU	METASTATIC		SPECIFY TYPE		
MSK	OSTEOP		FM	OTHER	SPECIFY OTHER	
SUBSTANCE USE/ABUSE	ALCOHOL			DRUGS		
INFECTIONS	TB		GEN		RETRO	
GENITOURINARY	PROST		UTEUS		OVAR	
NEURO	STROKE		DEM	PARK	SEIZURE	
	OTHER	SPECIFY OTHER				
ENDOCRINE	DIAB		THYROID		OBESITY	
	OTHER		SPECIFY OTHER			
PSYCHIATRIC	DEPRESSION		BIPOLAR		SCZ	
	OTHER		SPECIFY OTHER			

5. PSYCHIATRIC SCREEN

MADRS	
CLIN DEP	

APPENDIX C

Name_____ Date_____

This questionnaire includes information from you to provide a record of your health status.

Please check (√) the response which best describes your abilities OVER THE PAST WEEK

	Without ANY difficulty	With SOME difficultly	With MUCH difficulty	UNABLE to do
DRESSING & GROOMING – Are you able to:				
1 Dressing yourself, including typing shoelaces and doing buttons?	_____	_____	_____	_____
2 Shampoo your hair?	_____	_____	_____	_____
ARISING – Are you able to:				
3 Stand up from a straight chair?	_____	_____	_____	_____
4 Get in and out of bed?	_____	_____	_____	_____
EATING – Are you able to:				
5 Cut your meat?	_____	_____	_____	_____
6 Lift a full cup or glass to your mouth:	_____	_____	_____	_____
7 Open a new milk carton?	_____	_____	_____	_____
WALKING – Are you able to:				
8 Walk outdoors on flat ground?	_____	_____	_____	_____
9 Climb up five steps?	_____	_____	_____	_____

Please check (√) any AIDS OR DEVICES that you usually use for any of these activities:

_____Cane _____Devices used for dressing (button hook, zipper pull, long shoe horn etc.)
_____Walker _____Built up or special utensils
_____Crutches _____Special or built up chair
_____Wheelchair _____Other (Specify:_____)

Please check (√) any categories for which you usually need HELP FROM ANOTHER PERSON:

_____Dressing and Grooming _____Eating
_____Arising _____Walking

Please check (√) the response which best describes your abilities OVER THE PAST WEEK

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
HYGIENE – Are you able to:				
10 Wash and dry your body?	_____	_____	_____	_____
11 Take a tub bath?	_____	_____	_____	_____
12 Get on and off the toilet?	_____	_____	_____	_____
REACH – Are you able to:				
13 Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	_____	_____	_____	_____
14 Bend down to pick up clothing from the floor?	_____	_____	_____	_____
GRIP - Are you able to:				
15 Open car doors?	_____	_____	_____	_____
16 Open jars which have been previously opened?	_____	_____	_____	_____
17 Turn taps on and off?	_____	_____	_____	_____
ACTIVITIES – Are you able to:				
18 Run errands and shop?	_____	_____	_____	_____
19 Get in and out of a car?	_____	_____	_____	_____
20 Do chores such as vacuuming or yardwork?	_____	_____	_____	_____

Please check (√) any AIDS OR DEVICES that you usually use for any of these activities:

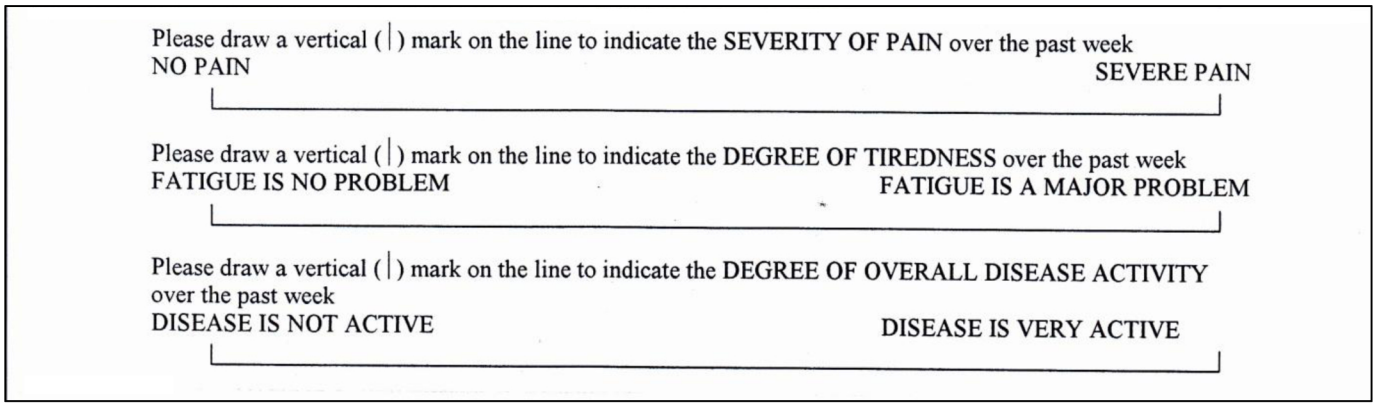
_____Raised toilet seat _____Bathtub bar
_____Bathtub seat _____Long-handled appliances for reach
_____Jar opener (for jars previously opened?) _____Long handled appliances in bathroom
_____Other (Specify:_____)

Please check (√) any categories for which you usually need HELP FROM ANOTHER PERSON:

_____Hygiene _____Grip
_____Reach _____Activities

PLEASE TURN TO THE NEXT PAGE

APPENDIX D



Calculation of the VAS scores:

The distance from mark 0 to the point at which the patient inserts a mark is measured with a ruler. The centimetre value obtained is then reflected as a numerical value indicating the level of severity of the symptom measured. The higher the value the greater the severity of the symptom. For example, a value of 6 (6cm) indicates greater pain than a value of 2 (2cm).

APPENDIX E

Please check (√) the most appropriate answer for each question

TENSION – DURING THE LAST MONTH....

	Always	Very often	Sometimes	Almost never	Never
1 How often have you felt tense or highly strung?	____	____	____	____	____
2 How often have you been bothered by nervousness or your nerves?	____	____	____	____	____
3 How often were you able to relax without difficulty?	____	____	____	____	____
4 How often have you felt relax and free of tension?	____	____	____	____	____
5 How often have you felt calm and peaceful?	____	____	____	____	____

MOOD – DURING THE LAST MONTH....

6 How often have you enjoyed the things you do?	____	____	____	____	____
7 How often have you been in low or very low spirits?	____	____	____	____	____
8 How often did you feel that nothing turned out the way you wanted?	____	____	____	____	____
9 How often did you feel that others would be better off if you were dead?	____	____	____	____	____
10 How often did you feel so down in the dumps that nothing would cheer you up?	____	____	____	____	____

APPENDIX F

Montgomery-Åsberg Depression Rating Scale (MADRS)

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.	☐
2 = Looks dispirited but does brighten up without difficulty.	☐
4 = Appears sad and unhappy most of the time.	☐
6 = Looks miserable all the time. Extremely despondent	☐

2. Reported sadness Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope.	
0 = Occasional sadness in keeping with the circumstances.	☐
2 = Sad or low but brightens up without difficulty.	☐
4 = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.	☐
6 = Continuous or unvarying sadness, misery or despondency.	☐

Montgomery-Åsberg Depression Rating Scale (MADRS)

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.	☐
2 = Occasional feelings of edginess and ill-defined discomfort.	☐
4 = Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.	☐
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 normal.	☐
2 = Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.	☐
4 = Moderate stiffness and resistance	☐
6 = Sleep reduced or broken by at least 2 hours.	☐

5. Reduced appetite Representing the feeling of a loss of appetite compared with when-well. Rate by loss of desire for food or the need to force oneself to eat.	
0 = Normal or increased appetite.	☐
2 = Slightly reduced appetite.	☐
4 = No appetite. Food is tasteless.	☐
6 = Needs persuasion to eat at all.	☐

6. Concentration difficulties Representing difficulties in collecting one's thoughts mounting to an incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.	
0 = No difficulties in concentrating.	☐
2 = Occasional difficulties in collecting one's thoughts.	☐
4 = Difficulties in concentrating and sustaining thought which reduced ability to read or hold a conversation.	☐
6 = Unable to read or converse without great difficulty.	☐

Montgomery-Åsberg Depression Rating Scale (MADRS)

7. Lassitude Representing difficulty in getting started or slowness in initiating and performing everyday activities.	
0 = Hardly any difficulty in getting started. No sluggishness.	☐
2 = Difficulties in starting activities.	☐
4 = Difficulties in starting simple routine activities which are carried out with effort.	☐
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.	☐
2 = Reduced ability to enjoy usual interests.	☐
4 = Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.	☐
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.	☐

Montgomery-Åsberg Depression Rating Scale (MADRS)

9. Pessimistic thoughts Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.	
0 = No pessimistic thoughts.	☐
2 = Fluctuating ideas of failure, self-reproach or self- depreciation.	☐
4 = Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.	☐
6 = Delusions of ruin, remorse or irredeemable 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. Suicide attempts should not in themselves influence the rating.	
0 = Enjoys life or takes it as it comes.	☐
2 = Weary of life. Only fleeting suicidal thoughts.	☐
4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intenstion.	☐
6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.	☐

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