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NEUROPSYCHIATRIC SYMPTOMS IN THYMOMA-ASSOCIATED AND NON-THYMOMA MYASTHENIA GRAVIS

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FRMCAR002

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Thesis presented for the degree of Master of Medicine in Psychiatry in the Department of Psychiatry and Mental Health, University of Cape Town

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DECLARATION

I, Carla Patricia Freeman, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole or any part has been, is being, or is to be submitted for any other degree at this or any other university.

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Signed: _____

Cape Town, February 2012

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Abstract

Background: Myasthenia gravis (MG) is an acetylcholine receptor antibody-mediated disease targeting the neuromuscular junction resulting in fatigable muscle weakness. A number of reports have suggested a high prevalence of psychiatric symptoms amongst MG patients. Approximately 10% of MG subjects are found to have an associated thymoma and despite thymomectomy, the MG persists. The presence of thymoma may lead to other antibody-mediated neuropsychiatric manifestations including limbic encephalitis. We hypothesized that the prevalence of neuropsychiatric symptoms may be higher in MG subjects with thymoma-associated MG when compared with those who have non-thymoma MG.

Aims: This study aims to compare the prevalence of neuropsychiatric symptoms in a South African population of non-thymoma MG and thymoma-associated MG.

Method: A blinded cross-sectional psychiatric evaluation was performed on thirty adults with MG. Twenty-one had non-thymoma MG and nine had thymoma-associated MG. The severity of MG in each participant was assessed by a dedicated MG clinic using the quantified myasthenia gravis score (QMGS). The age at symptom diagnosis, years of symptoms before and on treatment, timing of thymectomy or thymomectomy and current medications were noted.

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Neuropsychiatric assessments included: a self-reported 15-item Quality of Life Scale; the Beck Depression Inventory (BDI-II); the Hamilton Anxiety Rating Scale (HAM-A); the Young Mania Rating Scale (YMRS) and the Brief Psychiatric Rating Scale (BPRS).

Results: Overall, high rates of moderate to severe depression(33.3%) and anxiety(33.3%)symptoms were present across both groups. However, there was no significant difference in the frequency and nature of neuropsychiatric symptoms between thymoma and non-thymoma MG groups. High scores on the BDI-II correlatedpositively with disease severity (p=0.008) as measured by the QMGS and presence of respiratory symptoms and tended to occur in those with a longer duration of illness (p=0.08). The presence of moderate to severe anxiety symptoms was associated with a longer disease duration (p=0.035) and showed significant overlap with symptoms of depression (p=0.001). There was a tendency towards suicidality (p=0.07) and need for psychiatric referral (p=0.08) associated with MG symptoms onset at a younger age.

Conclusion: Neuropsychiatric symptoms such as depression and anxiety are prevalent in this MG population and necessitate identification and subsequent psychiatric referral. No differences could be detected in the prevalence of neuropsychiatric symptoms between thymoma- and non-thymoma MG.

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Abbreviations

Acetylcholine receptor	(AChR)
Beck Depression Inventory	(BDI-II)
Brief Psychiatric Rating Scale	(BPRS)
Groote Schuur Hospital	(GSH)
Hamilton Anxiety Rating Scale	(HAM-A)
Myasthenia Gravis	(MG)
Quality of life	(QOL)
Neuromuscular junction	(NMJ)
Non-thymoma myasthenia gravis	(non-TMG)
Thymoma-associated myasthenia gravis	(TAMG)
University of Cape Town	(UCT)
Young Mania Rating Scale	(YMRS)

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PART A: The protocol

NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH THYMOMA-ASSOCIATED AND NON-THYMOMA MYASTHENIA GRAVIS

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Abstract

Background: Myasthenia Gravis (MG) is an autoimmune disease affecting the nicotinic acetylcholine receptors (nAchRs) of the neuromuscular junction which manifests as fatigability and fluctuating muscle weakness. MG is thought to exclusively involve the "peripheral" nervous system, yet for several decades, physicians have argued that the brain may be affected by MG.

Approximately 10% of patients with MG are associated with the presence of thymoma. Thymoma patients may have several paraneoplastic syndromes including limbic encephalitis (Evoli, 2002), which involves the brain. In this study we wish to explore the prevalence of neuropsychiatric symptoms in MG and hypothesize that these symptoms may be higher in thymoma-MG compared to subjects without thymoma.

Aims: To compare the prevalence and nature of neuropsychiatric symptoms in a sample of patients with thymoma-MG with those of MG without thymoma.

Method: This is a cross-sectional pilot study. A randomly selected sample comprising of 10 patients with thymoma-MG and 20 patients with non-thymoma MG attending the Groote Schuur Hospital (GSH) Myasthenia Gravis Clinic in Cape Town will be studied. As thymoma-MG is rare, the thymoma sample will be randomly selected from the existing UCT/GSH MG clinic database of MG patients known with thymoma.

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Each patient will be assessed by the Neurology team as part of his or her routine clinic visit. Patients who agree to take part in the study will provide written informed consent and complete a self reported Flanagan 15 item Quality of Life Scale (QOL) prior to the psychiatric assessment. The psychiatric assessment will be performed in a private consultation room by a mental health professional in the GSH Neurology ward. Demographic data and a brief medical history will be obtained. The psychiatric interview will be semi-structured and includes the following rating scales: Beck's Depression Inventory (BDI-II); Brief Psychiatric Rating Scale (BPRS); Hamilton Anxiety Rating Scale (HARS) and the Young Mania Rating Scale (YMRS).

Results: The data will be pooled and analyzed with the assistance of a trained statistician employed by the University of Cape Town. The results will be presented to both the Dept. of Psychiatry and the Division of Neurology at the University of Cape Town. The study will be submitted for publication in a peer-reviewed journal.

Conclusion: Should our hypothesis prove correct, we will use the evidence to support the implementation of adequate psychiatric screening services in existing MG clinics. Should the findings reveal that the prevalence of neuropsychiatric symptoms in thymoma-associated is higher than non-thymoma MG, a larger controlled study with further research into the underlying, immune-mediated, neurobiological mechanism will be supported.

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Study Objectives:

- To determine the prevalence of mood, anxiety and psychotic symptoms in a representative sample of the MG population attending the GSH MG clinic.
- To compare the prevalence of neuropsychiatric symptoms i.e. disturbance in mood, perception, thought and behaviour in thymoma-MG vs. MG without thymoma.
- To compare the mean QOL scores of MG patients with those of previously documented scores in other chronic neurological diseases.

Research Questions:

1) To establish the prevalence of neuropsychiatric symptoms in a representative sample of MG patients attending a dedicated quaternary level clinic.
2) To compare the nature and prevalence of neuropsychiatric symptoms in the thymoma MG population versus those with non-thymoma MG.

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1. Introduction

1.1 Myasthenia Gravis

Myasthenia Gravis (MG) is a chronic, potentially debilitating autoimmune disease in which pathogenic antibodies are directed at the neuromuscular

junction (NMJ) of skeletal muscle. The majority of cases with MG are “sero-positive” and have pathogenic antibodies to the acetylcholine receptor (AChR) directed at the alpha-1 subunit of the nAChR. The affected individual can present at any age. The condition is characterized by muscle weakness and fatigability which may fluctuate during the course of the day and is typically worsened by exertion (Fauci, 1998). Approximately 10% of MG cases are associated with thymoma, from here known as thymoma-MG (Evoli, 2002). MG without thymoma will be referred to as MG.

MG is thought to be limited to the peripheral nervous system. As early as the 19th century, a number of physicians have argued that MG involves the central nervous system (CNS) (Keesey 1999). Evidence of central cholinergic involvement in MG has been suggested following several observations. Firstly, EEG changes have been noted in several patients with MG, not accounted for by epilepsy or other clinical parameters e.g. medication. Diffuse slow and focal slow abnormalities were observed in 14 of 118 patients with MG (Tartara, 1982). Secondly, altered rapid eye movement (REM) sleep has been observed in patients with MG, suggesting central involvement. Of a sample of ten patients with MG, all exhibited signs of disturbed REM sleep. One member of this sample was subsequently treated with prednisone and his REM sleep returned to normal limits (Papazian 1976). Thirdly, Fotiou (2000) reports that abnormal pattern-reversal visually evoked potentials have been demonstrated in patients with MG suggesting a disturbance of CNS acetylcholine receptors.

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1.2 Psychiatric symptoms in Myasthenia Gravis

Central involvement of MG has been further argued in both psychiatric and psychological literature, the results of which, remain inconsistent and are criticized for being outdated and making use of unsound methodology. In a study by Rohr (1992), 20% of 200 study sample patients with MG were diagnosed as having a psychiatric illness prior to the diagnosis of MG with symptoms and signs of disturbed perception, thought content, mood or behaviour. More recently, Sitek et al (2009) administered a neuropsychological battery of tests to 33 individuals with MG and 30 healthy controls. They were unable to demonstrate CNS deficit as cognitive tasks independent of motor or visual function remained unimpaired. Although an incidence of axis I and axis II disorders reached as high as 51% in some studies, a number of authors have argued the validity of these results. Their main concerns being that somatic symptoms may interfere with the correct assessment of mood, rating scales were non-specific, sample sizes were small and structured clinical interviews were lacking (Kulaksizogli, 2007). Paul et al. (2000) investigated the severity of mood, self evaluative and vegetative symptoms of depression in patients with MG. They found that the prevalence of depression was statistically significant only in the assessment of vegetative symptoms compared with those in the control group. They recommend that patients with “neuro-immune” disease are assessed using specific scales for the different dimensions of depression i.e. the assessment of cognitive, somatic, affective and behavioural symptoms associated with depression.

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Several contributory factors need to be considered with regard to psychopathology in MG patients. MG is a chronic illness which impacts on an individual's global functioning. Thus neuropsychiatric symptoms may stem from a psychological response to the diagnosis of a chronic neurological illness, the impact it has on one's lifestyle and subsequent physical disability (Kulaksizoglu, 2007). These symptoms may be further complicated by the fluctuating character of MG and the overlap of neurovegetative symptoms such as fatigue, decreased energy levels and shortness of breath posing a challenge to both the patient and the physician (Juel, 2007). Neuropsychiatric symptoms may also be a direct result of the pharmacological treatments used in MG.

Although this proposed pilot study will have a small number of participants, we aim to assess MG patients with a structured interview, taking cognizance of criticism directed at previous work. We will assess neuropsychiatric symptoms using reliable, multi-faceted psychiatric rating scales as well as include both patients severity of MG and concomitant medications.

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1.3 Thymoma associated Myasthenia Gravis

Thymoma may present with a number of paraneoplastic conditions including MG, limbic encephalitis, glomerulonephritis and vitiligo. Thymoma is associated with several antibodies which include those against interferon-alpha, interleukin-12 and muscle antigens, several of which are able to cross the blood brain barrier(Evoli, 2002). Limbic encephalitis presents with a

variety of neuropsychiatric symptoms including: irritability; depression; insomnia; hypersomnia; hallucinations; memory loss and possible progression to dementia (Dalmau, 2006).

To our knowledge, there is no data comparing neuropsychiatric symptoms in patients with MG and thymoma MG. A case series study by Musha et al (1993) reported on three cases of psychosis in thymoma-MG patients. All three patients had undergone a thymectomy in the preceding weeks to months. The neuropsychiatric symptoms appeared homogenous and preceded the onset of MG by several months to years. These symptoms worsened or reappeared during relapses of the MG. The underlying psychopathology is thought to be due to an autoimmuneparaneoplastic limbic encephalitis occurring in patients with thymoma MG.

Our study proposes that neuropsychiatric symptoms are a consequence of CNS involvement in MG. It further attempts to demonstrate that the prevalence of neuropsychiatric symptoms is higher in thymoma MG group.

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1.4 Motivation for the study

A study undertaken by Williams et al. (2003) revealed that one third of patients attending three hospital based general neurology outpatient clinics over a six month period, met the criteria for a depressive episode, yet only 40% of these patients were diagnosed with depression. They found that the prevalence of depression was highest in the neuromuscular and neuropathy

patients. A further study undertaken by Stewart et al. (2007) revealed that the prevalence of depression in MG was equivalent to that in neuromuscular disease, both of which were higher than that in the general population. These findings suggest a need for rigorous screening of neurological outpatients for psychiatric disorders (Williams, 2003).

The results of research on psychiatric symptoms in MG have been equivocal. While it has been reasonably established that psychiatric conditions such as anxiety or depression occur more frequently in MG, we are not aware of any study which compares psychiatric symptoms and quality of life in MG patients with thymoma and those without. The presence of a psychiatric illness may also affect the clinical course of the neurological condition by impacting on both the patient's and their family's quality of life as well as interfering with treatment adherence (Kulaksizoglu, 2007).

A clearer understanding of the neuropsychiatric profile in MG may serve to guide medication regimens. A number of treatment modalities exist, although corticosteroids remain the most widely used agents as immune modulators (Juel, 2007). Mania and hypomania as well as depression are well-recognized adverse effects of steroid use (Kulaksizoglu, 2007). Brown and Chandler (2001) quote a study undertaken by the Boston Collaborative Drug Surveillance Program (BCDSP, N=676) which reported that in subjects free of psychiatric disease prior to steroid therapy, 1.3% developed severe psychiatric disease at low doses of prednisone. The incidence increased to 18.4% if the dose exceeded 80mg/day and thus appeared dose dependent.

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Psychiatric pharmacological treatments e.g. lithium, used in the treatment of Bipolar Mood Disorder, may unmask MG or worsen the existing disease (Alevizos, 2006).

Referral for psychotherapy may also aid treatment and rehabilitation. A case series of four patients with MG who undertook 1-2 years of client-centered psychotherapy demonstrated a significant improvement in their myasthenic symptoms, reduced fluctuations in their clinical course and required less medication compared to controls (Doering, 1993). Thus the treatment of co-existing psychiatric illness may be important in the management of patients with MG.

Should the results of this study reveal that neuropsychiatric symptoms are common in MG, clinician awareness will be raised and the motivation for rigorous psychiatric screening and improved accessibility to mental health services will be supported.

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1.5 Implementation Objectives

The results of this research project will be presented to both the Dept. of Psychiatry and the Division of Neurology at the University of Cape Town. Should the hypothesis prove that the MG population is at risk for psychiatric illness in either the MG, thymoma-MG group or both, the following recommendations will be made:

- A larger, controlled study in this area to be undertaken
- Encourage a collaboration between both departments with regards to the management of patients with MG
- Ensure adequate, simple, screening tools are available to health care workers assessing patients with MG
- Focus on improving the accessibility to the psychiatric services via direct referral routes
- Emphasize the role of the consultant liaison psychiatry team in the management of patients with MG

2. Methods

2.1 Study Design

The pilot study is cross-sectional in design, descriptive in nature with an analytic component. The goal of which, is to examine the relationship between MG and the incidence of neuropsychiatric symptoms in both MG and thymoma-MG. The prevalence of neuropsychiatric symptoms in MG will be determined using a battery of psychiatric rating scales. This data will then be analyzed to further examine potential causative factors and associated variables.

2.2 Study population and sampling

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The study population consists of all patients able to understand English attending the MG clinic at Groote Schuur Hospital (GSH), Cape Town during a three month period. This population includes both patients with thymoma-MG and MG without thymoma. As MG can present at any age, no age limit will be applied to the sample population.

Twenty (N=20) randomly selected patients with MG, attending the clinic during the period of Dec 2009 to June 2010 with MG, will be assessed. Due to the rare nature of thymoma MG (10% of the MG population), a sample of ten (N=10) will be randomly drawn from the UCT-MG database (the last 10 entered into the database representing consecutive clinic attendees). These patients will be contacted telephonically and asked to participate. If they agree, they will be offered an earlier appointment to the clinic.

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2.3 Measurements

Upon arrival at the GSH MG clinic, patients will be briefed about the study and informed consent taken. Participants will be required to sign a consenting document approved by the University of Cape Town Health Science Ethics committee. (See appendix). Participants will be handed the Flanagan Quality of Life Scale to complete before seeing the neurologist (Flanagan, 1982).

Once the neurological assessment has been completed, the participants will be interviewed in a private consultation room in the neurology ward. Dr. Freeman will be blinded to the condition i.e. thymoma-MG or MG without

thymoma. A number of measurement instruments will be used. Documentary sources such as the patient file and assessment sheet will provide basic demographic details. These include: age; gender; address and folder number. Data taken from the assessment sheet will include: onset of illness; quantified MG score based on that by Tindall (1978); pharmacological treatment and non-pharmacological interventions e.g. thymectomy. This data sheet will be obtained from the Neurology folder upon completion of the psychiatric interview so as not to bias the rater to the condition.

Previous studies have reported limitations with regards to the overlap of vegetative symptoms e.g. fatigue, insomnia in both MG and certain psychiatric disorders such as depression and have recommended that the focus on psychiatric symptoms goes beyond somatic complaints (Kulaksizoglu, 2007). We have thus included the BDI-II, which provides an assessment of cognitive, somatic, affective and behavioural symptoms associated with depression (Beck, 1996). Data from the MG clinic score sheet will be recorded which encompasses both reported physical symptoms and objective findings on examination. This data will be correlated with the results from the psychiatric rating scales.

The neuropsychiatric symptom assessment will include four rating scales administered by a mental health professional. These include: The Young Mania Rating Scale (YMRS) – a widely used, reliable instrument used in the assessment of mania (Altman, 1994); Beck Depression Inventory (BDI-II) – serves as an instrument to identify the presence and severity of symptoms

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consistent with criteria of the DSM-IV (Beck, 1996); Brief Psychiatric Rating Scale (BPRS) – a rapid assessment of global psychiatric symptomatology (Overall, 1962); Hamilton Anxiety Rating Scale (HARS) – used to measure severity of anxiety symptoms in both clinical and research settings (Hamilton, 1959).

The interview is estimated to take between 40-45 minutes.

2.4 Pilot studies

The battery of psychiatric rating scales will be piloted on 2 patients attending the GSH MG clinic. Logistical and implementation difficulties will then be assessed and adjusted accordingly.

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3. Data management and analysis

Once the data has been collected in a clinical interview, the data will be systematically filed for later processing. The actual scores of each rating scale will be calculated and recorded on the completed questionnaire at the time of interview. The Quality of Life score sheet will be collected at the start of the interview. Copies will be made of the clinical data score sheet acquired by the neurology team and filed with the results of the psychiatric interview.

Once the data collection has been completed, it will be processed with the assistance of a trained statistician.

4. Logistics and time schedule

4.1 Responsibilities of investigators/staff

- Both A/Prof. Heckmann and Dr Lewis to advise on both needs and discrepancies in the study protocol
- A/Prof. Heckmann will assist with the simple random sample collection of patients with thymoma MG from her existing data base of patients
- DrHeckmann will contact these patients to arrange a suitable appointment time at GSH. Transport costs of these patients will be covered if not part of the patients routine assessment
- A/Prof. Heckmann to alert neurology team of the data collection location and periods and direct patients to the waiting area following their assessment
- Dr Freeman to ensure informed consent is taken from each patient
- Dr Freeman to collect data during the period of 07h00 to 11h30 on Friday mornings during the GSH MG clinic
- Data will be assimilated and pooled by Dr Freeman. This data will be analyzed with assistance from Dr'sHeckmann and Lewis. The department may be consulted for additional input from a recommended statistician

4.2 Time schedule

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October 2009:	Protocol completion, submission to the University of Cape Town Dept. of Psychiatry, Dept. of Neurology and Ethics Committee.
November 2009:	Pilot study rating scales with 2 patients attending the GSH MG clinic
December 2009 to June 2010:	Data collection and measurement
July 2010:	Assimilation of data: checking and summarizing
August/Sept 2010:	Analyzing and interpreting data
September/October 2010:	Writing up and presentation of data

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5. **Resources**

5.1 Available resources

- Personnel include A/Prof. Jeannine Heckmann (Dept. of Neurology) and Dr Ian Lewis (Dept. of Psychiatry) for information, experience and guidance.
- Professor Landon Myers to advise on study design and statistical analyses

- The University of Cape Town Library to access both textbooks and journals.
- The Internet.
- R2000.00 Research Grant provided by the Dept. of Psychiatry, UCT. Fund managed by Dr John Joska and allocated to M Med Research projects that have been approved by the University of Cape Town's Ethics Committee.

5.2 Budget and budget motivation

- R2000.00 Research grant to assist with transport fees of the patients seen outside of their routine clinic follow-up. The remainder will be spent on printing costs, the purchase of a printer and petrol costs.

6. Ethical and legal considerations

The protocol will be submitted to the University of Cape Town Health Science Ethics Committee to ensure that the study safeguards patient's rights and welfare.

Each patient participating in the study will be required to give informed consent in writing. Each participant must have full capacity to sign consent and this consent must be given voluntarily. The consent procedure will include disclosure of the purpose of the study as well as the possibility of subsequent referral to the psychiatric services if indicated.

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Should a participant require further psychiatric intervention or care, a referral will be made to either the psychiatric emergency services at Groote Schuur Hospital or the Neuropsychiatric outpatient clinic run by Dr Ian Lewis on a Thursday morning at Ward C23, Groote Schuur Hospital.

In the event whereby a patient may need to come in for assessment outside of the usual clinic time, the patient's transportation costs e.g. bus or taxi fare, will be covered by the research grant of R2000 given to each psychiatric registrar who has successfully submitted a research protocol.

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7. Reporting of results

A written report will be submitted to the Department of Psychiatry at The University of Cape Town as part of the MMed requirements. This will take the form of a dissertation.

Results will also be reported back to the scientific community by means of a presentation to both the Psychiatry and Neurology Departments at the University of Cape Town. Both target groups will play an instrumental role in implementing the recommendations formulated from the research findings.

The study and dissertation will form the basis of a paper to be submitted to a peer-reviewed journal.

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PART B: Structured literature review

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NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH THYMOMA-ASSOCIATED AND NON-THYMOMA MYASTHENIA GRAVIS

i. Objectives of the literature review

- To acquire up-to-date knowledge pertaining to the intended field of study i.e. the presence or absence of neuropsychiatric symptoms in myasthenia gravis, studies already undertaken in this area and recommendations for future research
- To identify key terminology used in this field
- To identify limitations and difficulties experiencedby researchers in previous studies examining this area in order to improve the methods and study design of the intended study
- To identify conflicting viewpoints within this field
- To assist us in identifyingsuccessful methods used in previous studies which could be employed in the intended study allowing us to draw comparison
- To identify needs and gaps of knowledge in the field of neuropsychiatry pertaining to myasthenia gravis
- To identify experts within the field of myasthenia gravis with a view to establishing contact for future collaboration

ii. Literature search strategy

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The search strategy involved identifying keywords relevant to this study and embarking on an online search making use of an established database.

The following keywords were used: **myasthenia gravis + psychiatric symptoms; neuropsychiatry; depression; anxiety; mania; hypomania.**All reviews, descriptive and controlled studies, published in this area, were included.

Pubmed Central is a well-known repository of peer-reviewed research reports/articles pertaining to the life-sciences and provided a sound database for the online search.(1)As some of the studies in this area were performed several decades ago, we did not limit the search to a particular time period. Once a number of articles were identified, the abstracts were obtained in order to assess the relevance of the article to the intended study. Irrelevant studies were excluded and the main body/text of the remaining articles were sourced via open access or using the University of Cape Town's 'easyproxy' server.

In addition, a hand-search was performed using the bibliographies of the selected articles to ensure that a broad range of information was accessed.

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iii. Summary and interpretation of the literature, and its implications for research

Introduction

Myasthenia Gravis (MG) is a chronic, potentially debilitating, autoimmune disease in which pathogenic antibodies are directed at the neuromuscular junction (NMJ) of skeletal muscle. The condition can present at any age and is characterized by muscle fatigability, which may fluctuate during the course of the day and is typically worsened by exertion. MG is classified as ocular MG when weakness is limited to the eyelids and extraocular muscles or generalized MG when other muscle groups are involved e.g. limbs, bulbar or respiratory muscles. The majority of MG subjects have detectable pathogenic antibodies to the acetylcholine receptor (AChR) directed at the alpha-1 subunit of the nicotinic AChR on the skeletal muscle endplate. Approximately 15% of these cases are associated with thymoma. MG is the most commonparaneoplastic manifestation affecting up to 50% of thymoma cases (known as thymoma-MG from this point). Thymoma may worsen the prognosis of the MG and symptoms often persist despite thymectomy for removal of the tumour (as reviewed in Evoli et al).(2)A number of other paraneoplastic syndromes are associated with thymoma including neuromyotonia, limbic encephalitis, polymyositis, psychosis, hearing loss and sleep disturbance.(3)Limbic encephalitis is known to present with a variety of neuropsychiatric symptoms including depression, irritability and psychosis.(4)

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Psychiatric symptoms in myasthenia gravis

Occasional reports dating back to the 19th century propose that MG also involves central nervous system cholinergic neurotransmission.(5,6)This follows observable electroencephalographic (EEG) changes in MG patients not accounted for by epilepsy or other clinical parameters(7), as well as, altered rapid eye movement sleep and abnormal pattern-reversal visually evoked potentials in MG patients.(8,9)More recently, several reports have demonstrated an increased prevalence of psychiatric disorders in this population in an attempt to support this hypothesis.

In the early 1990's Rohr and colleagues undertook a retrospective study in 200 patients with confirmed MG.(10)Up to 20% of this sample had been misdiagnosed with a psychiatric disorder at the onset of their myasthenic illness. Young women were noted to be most at risk of a misdiagnosis. A number of older studies exist supporting an increased prevalence of psychiatric disorders within the MG population. (11,12)However, these studies have been criticized due to their small sample sizes, lack of structured clinical interviews and overlap of neurovegetative and physical symptoms associated with MG.(13,14)

More recently, a number of groups, both in the developed and developing world have re-examined psychopathology within the MG population. A Brazilian research group employed a structured

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psychiatric interview (MINI-Plus) and demonstrated high rates of depression (26.1%) and anxiety symptoms (46.3%) in their MG population (n=41).(15)Their results were similar to those found by Qui et al. who, using a larger sample (n=161), found that up to half oftheir Chinese MG sample suffered from either depression or dysthymia and 45.3% had anxiety symptoms.(16)An even larger MG sample (n=251) was studied by Suzuki et al.(17)Their group found a depression frequency of 13.6% in their study population, pooled from multiple sites, and concluded that the dose of oral corticosteroids was a major contributing factor.(17)Other groups, such as Paul et al. found that 17% of their MG sample were depressed and that this result was independent of daily dose of prednisone or disease duration.(18)

Although the above studies report a frequency of depression and anxiety that is higher than that of the general population, a number of factors should be considered. Firstly, up to one-third of newly referred neurology outpatients meet the criteria for a major depressive episode.(19)A study undertaken by Stewart et al. demonstrated that the frequency of depression in MG was equivalent to that in neuromuscular disease.(20)Thus, we cannot infer that the increased frequency of psychopathology is unique to MG patient populations. Secondly, groups such as Sitek et al. were unable to demonstrate neurocognitive deficits in this population once vision and motor function were controlled for.(21)They concluded that they were unable to confirm a CNS deficit within the MG population based on their findings.

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However, they did find an elevated mean Beck Depression Inventory (BDI-II) score compared to their control group. Finally, several contributory factors should be considered with regards to the development of psychopathology in MG patients. Neuropsychiatric symptoms may stem from a psychological response to the diagnosis of a chronic neurological illness, the impact it has on one's lifestyle and subsequent physical disability.(22)In addition, pharmacological agents used in the treatment e.g. corticosteroids may further contribute to the development of neuropsychiatric symptoms.(23)

Thymomaand psychiatric symptoms in myasthenia gravis

Little is known about the nature and frequency of neuropsychiatric symptoms in thymoma-MG. A number of antibody-mediated paraneoplasticsyndromes have been associated with thymoma,two of which, may present with psychiatric symptoms i.e. limbic encephalitis and psychosis. Limbic encephalitis may present with prominent neuropsychiatric symptoms including: depression; insomnia; hypersomnia; irritability; hallucinations; memory loss and possible progression to dementia.(4)

Interestingly, in thymoma-MG the disease frequently persists despite thymoma removal requiring further immunosuppressant therapy. Musha and colleagues report on three case studies of thymoma-MG, all of which demonstrate persistence of neuropsychiatric symptoms despite thymomectomy.(24)More recently, a Chinese MG cohort

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(n=151) found that prominent anxiety symptoms correlated with thymoma, prednisone dose and severity of MG.(16) Apart from the above-mentioned studies and the association with limbic encephalitis, most of the larger studies assessing psychiatric manifestation in MG cohorts do not comment on the differences between thymoma-MG and non-thymoma MG subjects.

iv. Gaps or needs for further research

Almost all of the studies undertaken in this area highlight the necessity for further research. Authors emphasize the need for larger study samples with control groups. A detailed quantitative assessment of disease severity should be included in all future studies. This includes classification into certain subtypes, e.g. thymoma-MG, and an attempt to delineate vegetative features of MG vs. depression, e.g. insomnia and appetite disturbance.

An important area of research in this field includes the provision of evidence-based guidelines on the safety and efficacy of psychotropic prescribing in MG factoring in adverse effects, disease progression and quality of life of MG patients.

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Part C: Publication-ready manuscript

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Neuropsychiatric symptoms in patients with thymoma-associated and non-thymoma myasthenia gravis

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ABSTRACT

Background: Myasthenia gravis (MG) is an acetylcholine receptor antibody-mediated disease targeting the neuromuscular junction resulting in fatigable muscle weakness. A number of reports have suggested a high prevalence of psychiatric symptoms amongst MG patients. Approximately 10% of MG subjects are found to have an associated thymoma and despite thymomectomy, the MG persists. The presence of thymoma may lead to other antibody-mediated neuropsychiatric manifestations including limbic encephalitis. We hypothesized that the prevalence of neuropsychiatric symptoms may be higher in MG subjects with thymoma-associated MG when compared with those who have non-thymoma MG.

Aims: This study aims to compare the prevalence of neuropsychiatric symptoms in a South African population of non-thymoma MG and thymoma-associated MG.

Method: A blinded cross-sectional psychiatric evaluation was performed on thirty adults with MG. Twenty-one had non-thymoma MG and nine had thymoma-associated MG. The severity of MG in each participant was assessed by a dedicated MG clinic using the quantified myasthenia gravis score (QMGS). The age at symptom diagnosis, years of symptoms before and on treatment, timing of thymectomy or thymomectomy and current medications were noted.

Neuropsychiatric assessments included: a self-reported 15-item Quality of Life Scale; the Beck Depression Inventory (BDI-II); the Hamilton Anxiety Rating

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Scale (HAM-A); the Young Mania Rating Scale (YMRS) and the Brief Psychiatric Rating Scale (BPRS).

Results: Overall, high rates of moderate to severe depression(33.3%) and anxiety(33.3%)symptoms were present across both groups. However, there was no significant difference in the frequency and nature of neuropsychiatric symptoms between thymoma and non-thymoma MG groups. High scores on the BDI-II correlatedpositively with disease severity (p=0.008) as measured by the QMGS and presence of respiratory symptoms and tended to occur in those with a longer duration of illness (p=0.08). The presence of moderate to severe anxiety symptoms was associated with a longer disease duration (p=0.035) and showed significant overlap with symptoms of depression (p=0.001). There was a tendency towards suicidality (p=0.07) and need for psychiatric referral (p=0.08) associated with MG symptoms onset at a younger age.

Conclusion: Neuropsychiatric symptoms such as depression and anxiety are prevalent in this MG population and necessitate identification and subsequent psychiatric referral. No differences could be detected in the prevalence of neuropsychiatric symptoms between thymoma- and non-thymoma MG.

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INTRODUCTION

Myasthenia Gravis (MG) is a chronic, potentially debilitating, autoimmune disease in which pathogenic antibodies are directed at the neuromuscular junction (NMJ) of skeletal muscle. The condition can present at any age and is characterized by muscle fatigability, which may fluctuate during the course of the day and is typically worsened by exertion. MG is classified as ocular MG when weakness is limited to the eyelids and extraocular muscles or generalized MG when other muscle groups are involved e.g. limbs, bulbar or respiratory muscles. The majority of MG subjects have detectable pathogenic antibodies to the acetylcholine receptor (AChR) on the skeletal muscle endplate.

Between 10%-15% of generalized, antibody positive MG cases have an associated tumour of the thymus or thymoma, with late-onset patients being more commonly affected. MG is the commonest paraneoplastic manifestation of thymoma affecting about 50% of patients. A number of additional antibody-mediated paraneoplastic syndromes have been associated with thymoma including neurological disorders such as neuromyotonia, polymyositis, limbic encephalitis, psychosis and sleep disturbance as well as autoimmune diseases to non-neurological target organs such as haematological and skin.(1) Limbic encephalitis frequently presents with neuropsychiatric symptoms, which may include depression, irritability, cognitive impairment and psychosis.(2) The treatment of thymoma involves surgical removal of the tumour (thymomectomy), but despite this, the MG and other paraneoplastic

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syndromes may persist requiring additional immunosuppressive pharmacotherapy. Although psychosis is rare (1) in thymoma, there is a report of three cases with persistence of psychotic symptoms despite thymomectomy.(3)

In MG, muscle fatigability is mediated largely by the effects of pathogenic antibodies directed at the alpha-1 subunit of the nicotinic AChR. Occasional reports dating back to the 19th century propose that MG also involves central nervous system cholinergic neurotransmission.(4,5)This follows observable electroencephalographic (EEG) changes, altered rapid eye movement sleep and abnormal pattern-reversal visually evoked potentials in MG patients.(6-8) More recently, several reports have demonstrated an increased prevalence of psychiatric disorders in this population.(9) Despite these positive findings, many MG studies of this nature have been criticized due to their small sample sizes, lack of structured clinical interviews and lack of distinction in the overlap of neurovegetative symptoms seen in depression and physical symptoms associated with MG.(10) In addition, Sitek et al were unable to demonstrate neurocognitive deficits in this population once they controlled for vision and motor dysfunction.(11) Apart from a small case series (3) and the association with limbic encephalitis (1), most of the larger studies assessing psychiatric manifestation in MG cohorts do not comment on the differences between thymoma-and non-thymoma MG subjects.

Following the observation of psychopathology in thymoma-MG by an experienced clinician, we questionedwhether we, as clinicians, need to be

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more vigilant about an increased frequency of neuropsychiatric symptoms amongst thymoma -associated MG compared with non-thymoma MG. To answer this we performed a pilot study in which both thymoma and randomly selected non-thymoma-MG subjects were blindly assessed using several neuropsychiatric questionnaires.

Methods

The present study is a cross-sectional analysis of 30 MG patients attending a dedicated, quaternary, outpatient MG clinic at Groote Schuur Hospital in Cape Town, South Africa. Following a routine clinic visit, each participant wasinformed of the study and invited to participate. No patient refused to take part in the study. Written informed consent was obtained from each study participant prior to entry into the study. The University of Cape Town Health Sciences Ethics Committee approved the study protocol in compliance with the guidelines of The Declaration of Helsinki, sixth revision, 2008.

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Study population

Patientsattending the MG clinic between November 2009 and August 2010 were invited to take part in our study. All participants had a confirmed diagnosis of MG based on fatigable weakness with either a positive anti-AChR assay (≥0.2nmol/l), a significant clinical response to neostigmine or a >10% decremental response on 2 Hz repetitive nerve stimulation.(12) All patients attending the clinic followed a standard treatment protocol as referenced in Heckmann et al.(13) At the time of diagnosis, patients with thymoma-MG were stabilized on prednisone (± plasma exchange or

intravenous immune globulin) and a thymomectomy was performed at the earliest possible time. Non-thymoma, acetylcholine receptor antibody-positive, generalized MG ≤45 years, with significant disease are offered a thymectomy as standard of care.

Although the hospital generally serves an adult population, we did not limit the sample to a particular age-group. During the study period all thymoma-MG patients attending the clinic were invited to participate. In addition, prior to each clinic the unblinded neurologist randomly identified three to four subjects from the booking list to be approached for possible study participation. Participants were required to be able to converse in English.Only patients who had generalized MG and who were not critically ill e.g. requiring hospitalization for decompensating MG, were approached. The interviewer (CF) was blinded to presence or absence of thymoma in study participants.

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Interviews & tools

Individuals were interviewed by a psychiatrist (CF) in a private consultation room within the clinic. A 16-item self-reported Flanagan Quality of Life Scale (QOL) was completed at the beginning of the interview.(14) The neuropsychiatric symptom assessment consisted of three validated rating scales. These included: the Beck Depression Inventory, second edition (BDI-II); the Young Mania Rating Scale (YMRS) and the Hamilton Anxiety Rating Scale (HAM-A).(15-17) The Brief Psychiatric Rating Scale (BPRS) was included to provide a global psychiatric impression of the participant during the course of the interview.(18) (See Table 1 for description).

A brief enquiry was made into previous history of psychiatric diagnosis, past or current medical or psychological treatment and history of suicide attempts. Participants were referred for further psychiatric assessment and management if they expressed current suicidal ideation or scored in the moderate to severe range of symptomatology on any of the psychiatric scales. Upon completion of the psychiatric interview, each participant's medical folder was retrieved in order to obtain the Quantified Myasthenia Gravis Score (QMGS), as used by Heckmann et al.(13)calculated on the day of interview. The most recent thyroid stimulating hormone (TSH) level and other pertinent data such as comorbid conditions, treatments and dosing were also obtained.Age at symptom onset, duration of symptoms prior to diagnosis, duration of illness and thymic histology i.e. thymoma or not, were obtained from a MG database recorded by the clinic.

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Statistical analysis

Normally distributed data are presented as means and standard deviations (SD) whereas ordinal data such as the QMGS score are presented as medians and interquartile ranges (IQR). Results from the psychiatric rating scales are presented in Table 2 as means, in keeping with broader psychiatric literature. Due to the small study sample, non-parametric tests such as the Mann-Whitney U Test were used for comparison of longitudinal data between two unpaired groups. Fisher's exact test was used for categorical data on www.openEpi.com.(19) The Spearman rank-order correlation coefficient (rs) was employed to assess relationships between ordinal data between two

groups e.g. BDI-II scores and prednisone dose. A significance level of <0.05 was chosen for p-values (2-tailed). Statistical analysis was performed using Statistica10 (Statsoft®).

Results

Of the total sample (n=30) included in the study, 21 (70%) participants had non-thymoma MG and 9 (30%) had thymoma- MG. The demographic and clinical characteristics are included in Table 2. Both groups were predominantly female with 16 (76%) females in the non-thymoma MG group and 6 (66%) in the thymoma-MG group (p=0.61). At the time of interview, the groups were similar in age distribution with an average age of 44.7 years (SD±9.8) in the thymoma-MG and 45.0 years (SD±16.9) years in the non-thymoma group (median for both 46 years; p=0.89). Both groups had a mean age of disease onset in their early thirties (non-thymoma MG median onset age= 25.0 years; IQR 16.0; 43.0; thymoma-MG median= 39.0; IQR 29.0; 44.0; p=0.50).There was no difference in the disease duration prior to the interview between the non-thymoma MG group (mean=135.9 months; median 89.0; IQR 49.0; 154.0) compared to the thymoma-MG group (mean=65.6 months; median=36.0; IQR 13.0; 118.0) (p=0.14). Although the non-thymoma MG group was symptomatic for a longer period of time prior to the diagnosis of MG being made with an average wait of 11.9 months (SD±25.3; median=6.0) vs. 6.3 months (SD±7.5; median=4.0) in the thymoma-MG group, this was not significant (p=0.39).

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At the time of interview the thymoma-MG group reported predominantly limb symptoms (77%) whereas over half the non-thymoma MG group suffered from bulbar (52%) and ocular (57%) symptoms; however, the distribution of symptoms was not significantly different between the two groups (Table 1; p=0.47). The QMGS of disease severity was similar across both groups with a median score of 8 (IQR 4.5; 11) in the non-thymoma MG and 10 in the thymoma MG group (IQR 4; 11; p=0.76). As expected, higher QMGS scores correlated with respiratory symptoms (rs=0.39, p=0.031), higher doses of prednisone (rs=0.39, p=0.034) and worse Flanagan QOL scores (rs=-0.51, p=0.004).

Six participants (66%) with thymoma-MG and sixteen (76%) with non-thymoma MG were on corticosteroids. The average daily dose of prednisone was similar with 16.3mg/day (SD±16.7) in the non-thymoma- and 17.2mg/day (SD±17.2) in the thymoma MG group (p=0.86). Four (19%) with non-thymoma-MG and two (22%) with thymoma MG were on antidepressant therapy (p=0.37). At the time of interview, eight (88%) of the nine subjects with thymoma-MG had undergone surgery for thymoma removal and one subject wished it to be postponed until after his intended wedding. Ten (47%) subjects with non-thymoma MG had undergone a thymectomy for removal of their thymus.

When comparing neuropsychiatric symptoms across the thymoma and non-thymoma groups, no statistical difference was seen in depression, anxiety or manic symptoms (Table 3)(p=0.16). However, when examining the study

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sample as a whole, one third of the total sample demonstrated moderate to severe symptoms of depression (n=10; 33%) and anxiety (n=10; 33%). Moderate to severe depression and anxiety symptoms were associated with lower Flanagan QOL scores (rs=-0.69, p=0.0001). At the time of interview more severe disease, as measured by the QMGS, was associated with higher BDI-II scores (rs=0.47, p=0.008) but not anxiety symptoms (rs=0.08, p=0.69). A longer duration of MG disease was associated with both significant anxiety (rs=0.38, p=0.035) and depression symptoms (rs=0.37; p=0.045). There was no association between duration of symptoms before diagnosis in either of these categories (anxiety or depression) suggesting that it was not the duration of symptoms pre-treatment but rather duration of disease that contributed to depressive state.

Subjects with high BDI scores also had higher scores on the BPRS (rs=0.72, $p=\leq 1x10^{-5}$) and HAM-A (rs=0.56, p=0.001). They were also more likely to have been placed on antidepressant therapy by their medical attendants (rs=0.42, p=0.019). Four subjects were identified with moderate to severe depression at the time of interview, which had not previously been detected by the attending neurological team. Subjects who had been diagnosed with depression and placed on antidepressants prior to the study demonstrated high scores on the BDI-II (p=0.012). These subjects were also highly associated with suicidal behaviour (rs=0.68, $p=\leq 1x10^{-4}$) and required subsequent psychiatric referral (rs=0.54, p=0.002).

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In our sample, higher doses of prednisone did not show an association with a depressed state (rs=0.28, p=0.14) or prominent anxiety symptoms (rs=-0.08, p=0.66). Interestingly, three subjects (10%) in our study met the criteria for hypomania and two (6%) were manic at the time of interview, but these features were negatively associated with prednisone dose (rs=-0.38; p=0.034). The underlying cause or precipitant of the manic/hypomanic features remains unknown and four or these subjects required referral for further psychiatric evaluation.

As mentioned, current suicidal ideation or previous history of suicide attempt was strongly associated with higher scores on the BDI-II (rs= 0.68; $p \leq 1x10^{-4}$), higher BPRS scores (rs=0.49, p=0.006) and a significant number of these had already been diagnosed with depression and were on antidepressants (rs=0.58; p=0.006). A younger age of onset revealed a positive trend to suicidal behavior (p=0.07) and need for psychiatric referral (p=0.08). Subjects who were younger at the time of onset of MG had higher scores on the BPRS (rs=-0.47, p=0.007). A number of factors were not associated with suicidal behaviour. These include: anxiety symptoms (p=0.25); mania or hypomania (p=0.65); QMGS (p=0.18); prednisone dose (p=0.18) and duration of MG (p=0.11).Overall, fourteen (46%) of the participants who were interviewed required further psychiatric evaluation and management with emphasis on those with early age of onset.

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Discussion

Although we did not find a significant difference in the frequency of neuropsychiatric symptoms between thymoma-associated and non-thymoma MG, we did reveal prominent psychiatric symptomatology in the group as a whole. One third of our total sample were found to be either in a clinically depressed state or scored in the moderate to severe range of anxiety symptoms on the HAMA-A (Table 2). A third of our subjects reported one or more past suicide attempts or exhibited suicidal ideation at the time of interview and almost half of the sample required additional psychiatric evaluation and management, particularly those with younger age of onset. Although 19-20% of our sample had been treated with antidepressants by the attending neurologists, they remained symptomatic for depression and/or anxiety and required further psychiatric review.

The high prevalence of psychiatric symptoms in MG, particularly depressive and anxiety disorders, is well described. Our results corresponded with a South American group who evaluated a similar sample size, using a structured psychiatric interview (MINI-Plus), and diagnosed 26% of their sample with a depressive disorder and 46% with an anxiety disorder.(20) We used the BDI-II as a measure of a depressed state and found higher overall scores compared to two larger groups, North American (11) and Japanese (21) who used the same assessment tool. Although the Japanese cohort was older, their myasthenia was less severe based on the MG Foundation of America (MGFA) quantitative MG score compared with our cohort whereas the US cohort was similar in age and duration of MG to our sample.

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Our findings revealed a number of factors associated with a depressed state in MG. These included: more severe disease with or without the presence of respiratory symptoms; co-morbid anxiety symptoms; suicidality and concurrent antidepressant therapy. The Japanese group found an association with corticosteroid dose and depression, but their doses appeared far lower than our patients' current dose(21) We, and others (22) could not demonstrate an association between prednisone dose and severity of depression. Although our results stated otherwise, treatment with corticosteroids is a well-known precipitant of psychiatric disturbance, particularly affective disorders, and should be considered in the aetiology of psychopathology in MG.(22)

Six (20%) of our subjects reported that they were on antidepressant therapy at the time of interview, five of whom required psychiatric referral due to inadequate control of symptoms. These five subjects all scored in the moderate to severe range of depression symptoms on the BDI-II despite antidepressant therapy. Although depression had been identified and antidepressant therapy commenced in several subjects with severe depression prior to our assessment, a proportion of participants, not previously diagnosed, were found to be depressed at the time of interview. MG subjects with high scores on the BDI-II were also at significantly increased risk for suicidality, as defined by one or more previous suicide attempts, or current suicidal ideation. Suicidal behaviour is not widely reported in MG literature and highlights the importance of a psychiatric assessment in this potentially vulnerable group.

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One-third of our sample reported moderate to severe anxiety symptoms at the time of interview which is lower than the 46% seen in a large Chinese cohort using the same anxiety rating scale (HAM-A).(23) In contrast to our findings, their high frequency of anxiety correlated with both the presence of thymoma and prednisone dose. Some reports have suggested that anxiety symptoms such as dyspnoea are more prevalent in MG patients with bulbar and respiratory symptoms, as reviewed in Kulaksizoglu.(10) Despite the association of respiratory symptoms with depression, we could not find an association with anxiety symptoms in our cohort.

Five subjects with manic/hypomanic features were identified in our sample (16%) and to our knowledge, this has not been previously reported in MG. The reliability of the YMRS is limited as this scale reflects the clinical picture over a short period and not over the several days needed to make the diagnosis of mania or hypomania. Mania and hypomania are often thought to arise as a consequence of corticosteroid therapy, but in our sample the presence of these features did not correlate with prednisone dose. Furthermore, we could not find an association with antidepressant therapy as only one of these five individuals was on antidepressants at the time of interview, and only two subjects (both hypomanic) had thymoma. In order to judge its relevance, this finding would need to be examined in greater depth using a large sample and rigorous assessment of all aspects of mood.

Neuropsychiatric symptoms may arise from factors other than the myasthenic illness. These factors include a possible psychological response to the

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diagnosis of a chronic neurological illness, the impact that the illness has on one's lifestyle and subsequent physical disability.(24) Although the frequency of depression in our study is higher than the lifetime prevalence of the South African population (9.7%) (25), it is similar to that seen in a general neurology outpatient population (33%).(26) Thus, we cannot infer from our results that MG underlies the pathogenesis of psychopathology in MG subjects.(27)

This study has several limitations. Our study sample was small as this was a pilot study to assess the viability of a larger study examining the MG patient population attending a clinic in a tertiary level hospital. The study was undertaken over a relatively short period and patients with active/unstable disease or more symptoms are more likely to have more frequent follow-up visits introducing a selection bias.Due to limited resources, a battery of validated psychiatric rating scales were used in the interview to assess depressive, anxiety and manic symptoms based on those used in similar MG studies. A detailed psychiatric assessment examining broader psychopathology e.g. cognitive impairment, personality disorders and substance abuse was not undertaken and the authors recommend the inclusion of these aspects in future MG studies of this nature. A further limitation pertains to the BDI-II, which is a subjective measure of the cognitive and neurovegetative aspects of depression. However our findings, using brief rating scales, reflect similar results to that seen in the few studies that have employed structured psychiatric interviews, which are often time-consuming and require specialized training. As part of our QOL assessment we enquired about social and occupational function but did not use a specific tool

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assessing daily function in MG. We did not assess socioeconomic status, which could impact on psychopathology, and this quaternary referral MG clinic may represent a biased patient population due to the selective referral of more severe cases.

Conclusion

We found a high frequency of psychiatric disorders, particularly depression and anxiety, in this South African population with myasthenia gravis. Our results highlight the need for systematic depression screening within the outpatient clinic in order to detect all depressed patients as well as to monitor ongoing symptoms. Particular attention should focus on subjects with severe MG and those with a long duration of illness. Simple screening tools, such as the BDI-II and HAM-A, are widely accessible and will detect subjects with both depression and anxiety as well as those who are experiencing suicidal ideation. Once identified, these subjects should be assessed for pharmacotherapy and possible referral to psychiatric services.

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Acknowledgements

The authors wish to thank the staff of The Division of Neurology, Groote Schuur Hospital for their assistance with this study.

Dr. CP Freeman is a recipient of a Discovery Foundation Academic Award

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Table 1. Psychiatric rating scales and measurements

Scale	Measure	Cut off values
1. BDI-II	Depression	0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; 29–63: severe depression
2. HAM-A	Anxiety symptoms	14-17: mild anxiety 18-24: moderate anxiety 25-30: severe anxiety
3. YMRS	Mania/hypomania	8-12: hypomania 13-60: mania
4. BPRS	Measures multiple domains in psychopathology and is used to assess change in severity over time.	0-31: mildly ill 32-41: moderately ill 42-53: markedly ill

BDI-II, Beck Depression Inventory; HAM-A, Hamilton Anxiety Rating Scale; YMRS, Young Mania Rating Scale; BPRS, Brief Psychiatric Rating Scale

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Table 2. Clinical and demographic characteristics of 30 myasthenia gravis (MG) patients attending the Myasthenia Gravis Clinic of Groote Schuur Hospital, South Africa.

	Non-thymoma MG (n=21)	**Thymoma MG (n=9)**	**p value**
Male/female	5/16	3/6	0.61
Age, mean (±SD), years**	45.0 (16.9)	44.7 (9.8)	0.89
Age of onset, mean (±SD), years	30.9 (18.9)	34.9 (17.2)	0.50
Marital status			0.23
Married/partner	7 (33%)	6 (66%)	
Single	8 (38%)	2 (22%)	
Divorced	6 (28%)	1 (11%)	
Educational level			0.20
Primary school	2 (9%)	2 (22%)	
Secondary school	12 (57%)	2 (22%)	
Tertiary study	7 (33%)	5 (55%)	
Disease duration*, mean (±SD), months	135.9 (131.0)	65.6 (73.3)	0.14
Duration of symptoms prior to diagnosis, mean (±SD), months	11.9 (25.3)	6.3 (7.5)	0.39
QMGS median**, (IQR)	8 (IQR 4.5; 11)	10 (IQR 4; 11)	0.76
MG symptoms**:			0.47
Bulbar	11 (52%)	2 (22%)	
Respiratory	5 (24%)	2 (22%)	
Ocular	12 (57%)	4 (44%)	
Limbs	10 (48%)	7 (78%)	
Prednisone			
Prednisone	16 (76%)	6 (66%)	0.61
Daily dose, mean (±SD), mg	16.3 (16.7)	17.2 (17.2)	0.86
Antidepressant Therapy n, (%)	4 (19%)	2 (22%)	0.37
Thymectomy/Thymomectomy	n=10 (52%)	n=8 (88%)	**0.043**

Legend: *refers to duration prior to interview
**On day of interview
QMGS, Quantified Myasthenia Gravis Score; IQR, Interquartile Range

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Table 3. Neuropsychiatric symptoms in thymoma-associated MG vs. non-thymoma MG

	All MG subjects (n=30)	**Non-thymoma MG (n=21)**	**Thymoma-MG (n=9)**	**P value***
BPRS score, mean (SD)	12.2 (6.5)	13.1 (6.8)	10.3 (5.9)	0.30
BDI-II score, mean (SD)	16.3 (9.1)	17.8 (9.8)	12.8 (6.2)	0.16
HAM-A score, mean (SD)	13.7 (8.8)	14.2 (9.1)	12.7 (8.7)	0.67
YMRS score, mean (SD)	4.0 (4.3)	3.9 (4.4)	4.2 (4.0)	0.87
Suicidality n, (%)	9 (30)	7 (33)	2 (22)	0.65
Psychiatric referral n, (%)	14 (46)	11 (52)	3 (33)	0.42

BPRS, Brief Psychiatric Rating Scale; BDI-II, Beck Depression Inventory; HAM-A, Hamilton Anxiety Rating Scale; YMRS, Young Mania Rating Scale

*Refers to comparison of non-thymoma MG and thymoma-MG

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Part D: Appendices

Appendix A Ethics Approval Letter

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za

28 September 2009

REC REF: 353/2009

Dr C Freeman
Psychiatry

Dear Dr Freeman

PROJECT TITLE: NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH THYMOMA AND NON-THYMOMA MYASTHENIA GRAVIS

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 03 October 2010.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

pp

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

sAriefdien

Appendix B Annual Renewal Ethics Letter

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Annual Progress Report

Date	14 October 2010
HREC REF number	353/2009
Project number (if applicable) & Protocol title	Title: NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH THYMOMA AND NON-THYMOMA MYASTHENIA GRAVIS (protocol remains unchanged)
Principal Investigator	Dr Carla Patricia Freeman
Department / Office / Internal Mail Address	Department of Psychiatry and Mental Health, J2, Groote Schuur Hospital, Anzio Rd, Observatory, 7925

List of documentation

Approval requested for additional year for study titled:

NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH THYMOMA AND NON-THYMOMA MYASTHENIA GRAVIS

Protocol remains unchanged and additional time is required to complete the data analysis and write-up.

RESEARCH ETHICS COMMITTEE
14 OCT 2010
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

HREC office use only: (FWA00001429, IRB0001938)

☐ Approved ✓	This serves as official notification of annual approval, with additional documentation checked above.		
☐ Not approved	Specific required comments:		
Type of review	☐ Expedited ✓	☐ Full committee	
Expiry date	15 October 2011		
Signature of Chairperson of the HREC	Wally Henley	Date	15·10·10

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Appendix C

Permission from Division of Neurology, Department of Medicine, University of Cape Town

UNIVERSITY OF CAPE TOWN

Department of Medicine
Division of Neurology

JD Heckmann FCP (SA) Neurology PhD (UCT)
ASSOCIATE PROFESSOR JD HECKMANN
E8 - 74 Groote Schuur Hospital
Observatory - 7925 - Cape Town - South Africa
Telephone : +27 21 404 3263
Fax : +27 21 406 6251
Email: jeanine.heckmann@uct.ac.za

12 June 2009

Prof. M. Blockman
Chairperson, HSF Human Ethics Committee
Room E52-24, GSH
OMB

PROJECT TITLE: NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH THYMOMA AND NON-THYMOMA MYASTHENIA GRAVIS

Dear Prof. Blockman

This letter serves to indicate my support for the application of Dr Carla Freeman from the Department of Psychiatry, to perform a study in the Division of Neurology towards a MMed. Dr Freeman hopes to recruit about 30 patients for neuropsychiatric evaluations from the Myasthenia Gravis clinic at UCT/GSH, during their regular clinic visits. I have also agreed to provide supervision for the project together with Dr Ian Lewis from Psychiatry.

Yours sincerely

.....

PROF. J. HECKMANN
SPECIALIST NEUROLOGIST
DIVISION OF NEUROLOGY
WARD E7/E8 GROOTE SCHUUR HOSPITAL/UCT

"OUR MISSION is to be an outstanding teaching and research university, educating for life and addressing the challenges facing our society."

Appendix D Informed Consent Form (ICF)

Consent and information pamphlet

NEUROPSYCHIATRIC SYMPTOMS IN THYMOMA AND NON-THYMOMA MYASTHENIA GRAVIS

Dr CP Freeman (Dept. of Psychiatry, UCT), A/Prof J Heckmann (Neurology, Groote Schuur Hospital) and Dr IS Lewis (Dept. of Psychiatry, UCT)

Dear Participant

We would like to invite you to participate in a research study, the aim of which is to answer the following question:

Myasthenia Gravis (MG) is often, although not always, a chronic, debilitating autoimmune disease characterized by muscle weakness which may fluctuate during the course of the day and is worsened by exertion. Some patients suffer from psychiatric problems such as depression and anxiety at the same time as their MG symptoms. Also, some patients develop a thymoma, which may sometimes be associated with psychiatric symptoms. Our study aims to determine how often these symptoms occur in MG and whether these symptoms differ in patients with or without thymoma. This will be important in deciding who needs psychiatric evaluation and to improve the treatment offered to our patients.

Myasthenia Gravis is a disease that can affect an individual at any age. Many people with myasthenia gravis report great difficulty adjusting to the impact that the disease has on their day to day lives. They may even experience mild to severe psychiatric symptoms such as low mood, anxiety, insomnia and feelings of hopelessness. Our study intends to determine how many people with myasthenia gravis suffer from psychiatric symptoms and whether the actual disease may be responsible for them.

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If you agree to participate in the study, you will be asked to sign this consent form, giving permission for us to include your information in the study. You will be interviewed by a mental health professional in a private room on the same morning as the Myasthenia Clinic at Groote Schuur. The interview will take 35-40 minutes. Your routine clinic visit will go ahead as planned. Should we find during the course of the interview that you are suffering from a psychiatric illness and in need of further help, we will refer you to your local psychiatric service with a comprehensive letter requesting a full assessment.

The information gathered in the interview will remain confidential. This research project has been formally approved by the University of Cape Town Health Science Ethics Committee. Please contact their offices at (021) 406-6338 or **Dr Carla Patricia Freeman at (021) 440-3111, for more information.**

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I, _____

(Name of participant in block letters)

have read and understand all of the information given to me about my participation in this study. I have been given the opportunity to discuss it and ask questions. I voluntarily agree to take part in the study and have received an information sheet outlining the details of the study. I understand that I am able to withdraw from this study at any time knowing that this will not affect the quality of my subsequent clinical management or care.

Participant signature: _____ Date: _____

Signature of Researcher: _____Date:_____

Appendix E Data collection sheet

DATA COLLECTION SHEET **DATE:_____**

NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH THYMOMA-ASSOCIATED AND NON-THYMOMA MYASTHENIA GRAVIS

Dr Carla Patricia Freeman, Email: freecarla@gmail.com

Patient information:
Name:
DOB:
M/F
Folder number:
Marital status:

1.	Date of onset of MG symptoms:	Year	Month	Day	duration
2.	Date of MG diagnosis:	Year	Month	Day	duration
3.	Antibody level at diagnosis:				
4.	Initial diagnosis at onset of symptoms:				
5.	**MESTINON**	YES - 1	NO – 0		
	Current dose:				
6.	**PREDNISONE**				
	Current dose:	YES - 1	NO – 0		
	Daily dose:	YES - 1	NO – 0		
	Alternate daily dose:				
	Duration current dose: months				
	Duration of prednisone: years				
	Steroid sparing agent: (name)				
	Duration of steroid sparing agent:				
7.	**CURRENT SYMPTOMS (MG)**				
	Eye Symptoms	YES – 1	NO – 0		
	Bulbar symptoms	YES – 1	NO – 0		
	Limb symptoms	YES – 1	NO – 0		
	Respiratory symptoms	YES - 1	NO – 0		
8.	Flanagan Quality of life: score				
9.	Beck's Depression Inventory: score				
10.	Brief Psychiatric Rating Scale: score				

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11.	Hamilton Anxiety Rating Scale: score			
12.	Young Mania rating scale: score			
13.	Co – morbid illness: Treatment:			
14.	Psychiatric diagnosis: Treatment:			
	Previous suicide attempt:	YES - 1	NO - 0	
	Seeing psychiatrist/psychologist at present:	YES - 1	NO - 0	
15.	TSH level: Date checked:	Month:	Year:	
16.	Requires psychiatric referral:	YES - 1	NO – 0	

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Appendix F Flanagan Quality of Life Scale

QUALITY OF LIFE SCALE (QOL)

Please read each item and circle the number that best describes how satisfied you are at this time. Please answer each item even if you do not currently participate in an activity or have a relationship. You can be satisfied or dissatisfied with not doing the activity or having the relationship.

	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
1. Material comforts home, food, conveniences, financial security	7	6	5	4	3	2	1
2. Health - being physically fit and vigorous	7	6	5	4	3	2	1
3. Relationships with parents, siblings & other relatives- communicating, visiting, helping	7	6	5	4	3	2	1
4. Having and rearing children	7	6	5	4	3	2	1
5. Close relationships with spouse or significant other	7	6	5	4	3	2	1
6. Close friends	7	6	5	4	3	2	1
7. Helping and encouraging others, volunteering, giving advice	7	6	5	4	3	2	1
8. Participating in organizations and public affairs	7	6	5	4	3	2	1
9. Learning- attending school, improving understanding, getting additional knowledge	7	6	5	4	3	2	1
10. Understanding yourself - knowing your assets and limitations - knowing what life is about	7	6	5	4	3	2	1
11. Work - job or in home	7	6	5	4	3	2	1
12. Expressing yourself creatively	7	6	5	4	3	2	1
13. Socializing - meeting other people, doing things, parties, etc	7	6	5	4	3	2	1
14. Reading, listening to music, or observing entertainment	7	6	5	4	3	2	1
15. Participating in active recreation	7	6	5	4	3	2	1
16. Independence, doing for yourself	7	6	5	4	3	2	1

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Appendix G Beck Depression Inventory (BDI-II)

Roche

V 0477

Beck Depression Inventory

CRTN: _____ CRF number: _____

Page 14 patient inits: _____

Baseline

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

Subtotal Page 1

Continued on Back

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0154018392
NR15645

Young Mania Rating Scale (clinician administered)

Rater: ..... Date: .....

Patient's personal details

Name: ..... Age: ..... Gender: M/F

Guide for scoring items:

The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating.

The keys provided are guides. One can ignore the keys if that is necessary to indicate severity, although this should be the exception rather than the rule.

Scoring between the points given (whole or half points) is possible and encouraged after experience with the scale is acquired. This is particularly useful when severity of a particular item in a patient does not follow the progression indicated by the keys.

1. Elevated mood

Absent	0
Mildly or possibly increased on questioning	1
Definite subjective elevation, optimistic, self-confident, cheerful, appropriate to content	2
Elevated, inappropriate to content, humorous	3
Euphoric, inappropriate laughter, singing	4

2. Increased motor activity energy

Absent	0
Subjectively increased	1
Animated, gestures increased	2
Excessive energy, hyperactive at times, restless (can be calmed)	3
Motor excitement, continuous hyperactivity (cannot be calmed)	4

3. Sexual interest

Normal, not increased	0
Mildly or possibly increased	1
Definite subjective increase on questioning	2
Spontaneous sexual content, elaborates on sexual matters, hypersexual by self-report	3
Overt sexual acts (towards patients, staff or interviewer)	4

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4. Sleep

Reports no decrease in sleep	0
Sleeping less than normal amount by up to 1 hour	1
Sleeping less than normal by more than 1 hour	2
Reports decreased need for sleep	3
Denies need for sleep	4

5. Irritability

Absent	0
Subjectively increased	2
Irritable at times during the interview, recent episodes of anger or annoyance on ward	4
Frequently irritable during interview, short and curt throughout	6
Hostile, uncooperative, interview impossible	8

6. Speech (rate and amount)

No increase	0
Feels talkative	2
Increased rate or amount at times, verbose at times	4
Push, consistently increased rate and amount, difficult to interrupt	6
Pressured, uninterruptible, continuous speech	8

7. Language–thought disorder

Absent	0
Circumstantial, mild distractibility, quiet thoughts	1
Distractible, loses goal of thoughts, changes topic frequently, racing thoughts	2
Flight of ideas, tangentiality, difficult to follow, rhyming, echolalia	3
Incoherent, communication impossible	4

8. Content

Normal	0
Questionable plans, new interests	2
Special project(s), hyperreligious	4
Grandiose or paranoid ideas, ideas of reference	6
Delusions, hallucinations	8

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9. Disruptive–aggressive behaviour

Absent, cooperative	0
Sarcastic, loud at times, guarded	2
Demanding, threats on ward	4
Threatens interviewer, shouting, interview difficult	6
Assaultative, destructive, interview impossible	8

10. Appearance

Appropriate dress and grooming	0
Minimally unkempt	1
Poorly groomed, moderately dishevelled, overdressed	2
Dishevelled, partly clothed, garish make-up	3
Completely unkempt, decorated, bizarre garments	4

11. Insight

Present, admits illness, agrees with need for treatment	0
Possibly ill	1
Admits behaviour change, but denies illness	2
Admits possible changes in behaviour, but denies illness	3
Denies any behaviour change	4

Total score .....

Appendix I Brief Psychiatric Rating Scale (BPRS)

Scoring Procedure

Please enter the score for the term which best describes the patient's condition 0 = not assessed, 1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = extremely severe

1. SOMATIC CONCERN	
Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

2. ANXETY	
Worry, fear, or over-concern for present or future. Rate solely on the basis ot verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defense mechanisms.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

3. EMOTIONAL WITHDRAWAL	
Deficiency in relating to the interviewer and to the Interviewer situation. Rate only the degree to which the patient gives the impression of tailing to be in emotional contact with other people in the interview situation.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

4. CONCEPTUAL DISORGANIZATION	
Degree to which the thought processes are confused, disconnected, or disorganized. Rate on the basis of integration of the verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

5. GUILT FEELINGS	
Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not inter guilt feelings from depression, anxiety or neurotic defenses.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

6. TENSION	
Physical and motor manifestations of tension "nervousness', and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

7. MANNERISMS AND POSTURING	
Unusual and unnatural motor behavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

8. GRANDIOSITY	
Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation-to-others, not on the basis of his demeanor in the interview situation.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

9. DEPRESSIVE MOOD	
Despondency in mood. sadness. Rate only degree of despondency; do not rate on the basis 0 inferences concerning depression based upon general retardation and somatic complaints.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

10. HOSTILITY	
Animosity, contempt, belligerence, disdain for other people outside the interview situation. Pate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defenses, anxiety, nor somatic complaints. (Rate attitude toward interviewer under uncooporativeness").☐	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

11. SUSPICIOUSNESS	
Belief (delusional or otherwise) that others have now, w have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstanes.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

12. HALLUCINATORY BEHAVIOR	
Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

13. MOTOR RETARDATION	
Reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient only; do not rate on the basis of patient's subjective impression of own energy level.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

14. UNCOOPERATIVENESS	
Evidence d resistance, unfriendliness, resentment and lack of readiness to cooperate with the interviewer. Rate only on the basis of the patients attitude and responses to the interviewer and the interview situation; do not rate on basis of reported resentment or uncooperativeness outside the interview situation.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

15. UNUSUAL THOUGHT CONTENT	
Unusual, odd, strange or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganizations of thought processes.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

16. BLUNTED AFFECT	
Reduced emotional tone, apparent lack of normal feeling or involvement	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

17. EXCITEMENT	
Heightened emotional tone, agitation. increased reactivity.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

18. DISORIENTATION	
Contusion or lack of proper association for person, place or time.	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Appendix J Hamilton Anxiety Rating Scale (HAM-A)

Hamilton Anxiety Rating Scale (HAM-A)

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

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

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

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

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

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

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

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

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

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

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

Difficulty in concentration, poor memory.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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