Chapter 3
Unipolar Mania

3.1 Introduction

Considering the reasons for embarking on this study as explained in the first chapter, it would make sense to discuss the literature on “unipolar mania” in some detail.

3.2 Unipolar mania literature review

In 1966, after the two studies by Angst (52) and Perris (78) referred to in the previous chapter, relatively few studies appeared in the literature on the entity of unipolar mania thereafter. The reluctance to study unipolar mania was probably due to the strong opinion Angst and Perris voiced, both claiming that unipolar and bipolar disorders were distinct entities. Angst and Perris also felt that any assumption made regarding the separation of the group of unipolar mania was an artefact, as unipolar mania was so strongly related to bipolar disorder. (27)

In general, the occurrence of a manic only course in bipolar patients is estimated to be in the region of 10% to 20% (2), but rates have been found to vary substantially from a low of 1,1% (79) to a high of 65,3%. (80)

One of the challenges in the research on recurrent bipolar mania is, however lack of consensus on the defining criteria. Different authors have used different criteria for the diagnosis of recurrent mania with respect to the number of manic episodes, diagnosis of manic episode, and inclusion/exclusion of the depressive symptoms in the intercurrent period. (27)

In studies published in the last three decades, there appears to be some consensus on the presence of at least three manic episodes with no depressive episodes, but there is no consensus on the timeframe for the same.

Abrams and Taylor reported on 50 manic probands of whom 14 had never experienced a depressive episode. These authors concluded that unipolar mania was clinically homogeneous with bipolar disorder. (81) Nurnberger et al reported on 241 patients attending a “Lithium Clinic” of whom 38 had never been treated for depression. There was no difference in the age of onset, family history or response to lithium to support unipolar mania as a distinct clinical entity. (82)

In a more sophisticated replication of their earlier study, Abrams et al examined 77 manic patients. Again there was no significant difference

between bipolars and unipolars on a wide range of variables with two exceptions: the first-degree relatives of unipolar manic patients had a morbidity risk for unipolar depression of 10,5% while the risk for relatives of bipolars was only 3,4%. Abrams et al concluded, however, that unipolar mania clinically, historically and demographically was indistinguishable from bipolar illness. (83)

In a study reporting on chart reviews of 247 patients admitted to the University of Iowa Psychiatric Hospital with a history of at least one manic episode, Pfohl et al found that there were few clinically meaningful differences between patients with unipolar mania and bipolar disorder and that unipolar mania was not supported as a separate entity from bipolar disorder. (84) Considering that some of these study subjects might have been seen to have a unipolar manic course after having had only one manic episode, results may be considered doubtful, as the definition of unipolar mania in this study was “≥ 1 manic episode, no depressive episodes”.

Makanjuola’s study of 45 patients presenting with possible diagnosis of mania to two psychiatric units in Nigeria showed that recurrent manic disorder without depressive episodes is the rule rather than the exception among Yoruba Nigerian patients and that mania appears to

occur predominantly as a recurrent unipolar disorder. (85) In a follow-up study, Makanjuola confirmed his previous impression and found recurrent unipolar mania to be four times as common as bipolar disorder. In this study of 104 patients, 55 exhibited a recurrent unipolar manic course. (86)

Khanna et al found in their study of 95 manic patients admitted to a psychiatric hospital in eastern India that the prevalence of recurrent mania in this sample was high. Sixty percent of the sample had two manic episodes without an episode of depression. Among those with three lifetime episodes of illness, 48% had only manic episodes. Even when unipolar mania was defined as four or more lifetime episodes of mania without any episodes of depression, 44% fulfilled the criterion. (87) At a Lithium Clinic in Hong Kong, in a study by Lee, it was found that 36% of patients manifested manic-only episodes during affective relapse. (88)

In a retrospective cohort study of 50 elderly manic in-patients, Shulman and Tohen identified six (12%) who met criteria for a course of unipolar mania, suggesting that the concept of unipolar mania should not be buried yet and that further investigation of neuro-radiological findings and clinical course is merited. (89)

In response to this study, Lee and Yu emphasise in their letter in the British Journal of Psychiatry that more attention to unipolar mania is plainly in order, as the non-Western cultures make up 80% of the world but are poorly prepared to publish in the English literature. Lee and Yu claimed that there was sufficient evidence of a higher prevalence of unipolar mania in non-Western cultures such as Africa, China and India. (90)

In a study aimed at determining the rate of unipolar mania and comparing its characteristics with those of other affective disorders in a psychiatric hospital in the Fiji Islands, Aghanwa found the rate of recurrent unipolar mania to be 47,2%, thereby adding to the evidence in support of the inclusion of recurrent mania as a useful category in the international psychiatric nosology. (91) Yazici et al found the rate for unipolar mania to be 16,3% with unipolar manic patients tending to have more psychotic features and be less responsive to lithium. Yazici et al concluded that unipolar mania may be a nosologically distinct entity. (92)

In a prospective, longitudinal observational study of mood disorders by Solomon et al, endorsed by the National Institute for Mental Health (NIMH), individuals seeking treatment for mood disorder related symptoms at five academic medical centres in the USA were recruited.

Inclusion criteria for this particular study stipulated that participants had to be at least 17 years of age, with an IQ > 70, able to speak English and of white race for testing of genetic hypotheses.

A total of 163 patients with Bipolar I and 66 with schizoaffective disorder with no history of major depression entered the study. After a minimum of 15 years of prospective follow up, 27 subjects had not suffered any subsequent major depressive episodes. Contrary to expectation is the fact that manic recurrences developed in the five subjects who were treated with a mood stabiliser more than 90% of the follow-up time but no manic recurrences developed in the two subjects who were given very little treatment with a mood stabiliser during follow up.

Solomon et al conclude that, although rare, unipolar mania remains a valid diagnostic entity and that any efforts to understand the biological underpinnings of manic-depressive illness need to account for this. (93)

In a community-based study, looking at the prevalence and characteristics of bipolar I disorder in Butajira, Ethiopia through a door-to-door screening of the district's entire population, 315 cases were identified. Negash et al found that, of the 295 for whom complete information could be collected, 59,8% did not report any depressive

episodes and that their illness started with a manic episode in 77,3% of the cases.

In attempting to explain the high rate of cases not reporting depressive episodes, Negash proposes the reasons to be firstly that it was a community-based sample, secondly that recall bias might have led to under reporting milder episodes of depression, and thirdly that depressive symptoms may be seen as part of normal life rather than as a psychiatric disorder. Lifetime prevalence of bipolar I was estimated to be 0,6% for males and 0,3% for females. (94)

Reporting on this same study, Fekadu et al found that nearly two thirds od cases had relapsed over two and a half years and contrary to expectation, bipolar relapses were characterised by both manic and depressive relapses in almost equal proportion. (95)

Perugi et al also studied unipolar mania in order to define clinical and nosographic utility. From a sample of 155 consecutive inpatients with a DSM-III-R diagnosis of mania seen at the Institute of Psychiatry at the University of Pisa, Italy, patients were selected that had a history of at least three major affective episodes and ten years' duration of illness. Of the 87 patients included in this study, 19 (21,8%) presented a course of

illness characterised by recurrent unipolar manic episodes without a history of major or mild depression.

In spite of some similarities in terms of sex distribution, age of onset and polarity of first episode, some characteristics that were deemed of clinical and prognostic importance in the unipolar manic group included absence of suicidal attempts, more chronic course and less severe social and occupational disability. Perugi et al conclude that their data suggest clinical and prognostic validity of keeping unipolar manic patients as a separate subgroup. These authors also recommend that further research is needed to investigate and explore the possible therapeutic and genetic implications. (96)

A retrospective comparative study by Dakhlaoui et al of medical files of patients admitted with bipolar I (using DSM-IV criteria) between 1997 and 2001 to a psychiatric ward in the Razi Hospital, Tunisia, found that 65,3% of the sample of 72 patients had a unipolar manic course of illness (at least two manic episodes without depression).

Comparing two groups (Group 1 comprising those with unipolar mania who presented with at least two manic episodes without depression and Group 2 the rest of the sample) in terms of socio-demographic profile,

family psychiatric history and comorbidity, it was found that there were no significant difference in terms of socio-demographic features and family psychiatric history.

However, it was found that the bipolar group tended to abuse substances significantly more that the unipolar group. A significant difference was also observed regarding the 'first episode season' with the unipolar group presenting with their first episode more in "summer-autumn" and the bipolar group in "winter-spring".

Insisting that unipolar mania was a clinical reality in their daily practice, Dakhlaoui et al also suggested it was the "predominant presentation of bipolar disorder in Tunisia". (80)

3.3 Unipolar mania research – Western- vs. non-Western Countries

It thus becomes clear that there seems to be a considerable difference in findings regarding the entity of unipolar mania when one compares studies from Western vs. non-Western countries as shown in Table 3.1 and Table 3.2.

3.3.1 Table 3.1: Studies from Western countries

Table 3.1				
Author	**Country**	**Year**	**Definition**	**Rate of Unipolar Mania**
Perris (78)	Sweden	1966	≥ 1 manic episode, no depressive episodes	4,5%
Abrams & Taylor (81)	USA	1974	"never had a depressive episode"	28%
Abrams et al. (83)	USA	1979	2 manic episodes with no depressive episodes	18%
Nurnberger et al. (82)	USA	1979	≥ 1 manic episode with no treatment for depression	15,7%
Perris(79)	Sweden	1982	≥ 1 manic episode, no depressive episodes	1,1%
Pfohl et al. (84)	USA	1982	≥ 1 manic episode, no depressive episodes	33,6%
Shulman & Tohen (89)	Canada	1994	3 manic episodes with no depressive episodes and 10 years elapsed since hospitalisation for 1st manic episode	12%
Solomon et al. (97)	USA	2003	No depressive episode in 15-year prospective follow-up study of manic patients	16,5%
Perugi et al. (96)	Italy	2007	≥ 3 manic episode, 10 years of illness with no depressive episodes	21,8%
Average				**16,8%**

3.3.2 Table 3.2: Studies from non-Western countries

Table 3.2				
Author	**Country**	**Year**	**Definition**	**Rate of Unipolar Mania**
Makanjuola (86)	Nigeria	1985	≥ 2 manic episode, no depressive episodes	53%
Khanna et al. (87)	India	1992	≥ 4 manic episode, no depressive episodes	44%
Lee (98)	China	1992	≥ 2 manic episode, no depressive episodes	36%
Aghanwa (91)	Fiji Islands	2001	≥ 3 manic or hypomanic episodes, no depressive episodes and affective illness of at least 4 years	47,2%
Yazici et al. (92)	Turkey	2002	≥ 4 manic episode, no depressive episodes in 4 year follow-up	16,3%
Negash et al. (94)	Ethiopia	2005	Non report of depressive episode in a community-based study	59,8%
Dakhlaoui et al. (80)	Tunisia	2008	≥ 2 manic episodes without depression	65,3%
Average				**45,94%**

The high percentage (28%) found by Abrams and Taylor (81) and Pfohl et al (33,6%) (84), could be attributed to their generous definition of unipolar mania. With regard to the study by Yazici et al (92) in Turkey, the authors failed to describe the selection of his cohort in sufficient detail.

Selection bias could in fact be an important limiting factor in almost all studies mentioned, as the majority of studies, with the exceptions of Makanjuola (85), Solomon et al. (93) and Negash (94), were all retrospective chart reviews of patients admitted for manic episodes.

One should also consider the fact that not all patients with manic episodes would necessarily be admitted to or present in a hospital. Some could be seen by private practitioners or traditional healers and yet others may not present for help at all. The other studies mentioned also appear to have some selection flaws for example, the subjects in the study by Makanjuola were all in-patients (85) and in Solomon's study only white patients were included. (93)

From the abovementioned studies and comments by the various authors, it becomes clear that there is a need to continue to investigate the course of illness of bipolar disorder in South Africa and pay particular attention to a unipolar manic course. It should be interesting to see whether findings will replicate those from other non-Western countries and, in particular those from Africa.

Chapter 4
Purpose and Methodology

4.1 Purpose of the study

The purpose of this study was to investigate and describe the course of illness and clinical features in a cross-section of patients diagnosed with bipolar disorder and attending public hospitals in Limpopo Province, South Africa.

From this information, the author wanted to determine the rate of a unipolar manic course in this specific sample and to ascertain whether it is possibly an entity distinct from bipolar mood disorder as it is generally conceptualised in modern-day psychiatric literature. The issue of unipolar mania as a clinical entity remains unresolved and research in this area from South African may assist in clarifying this conundrum. If unipolar mania is found to be as prevalent in South Africa as compared to the rest of Africa, it will have diagnostic and treatment implications, as well as implications for genetic research.

4.2 Study design

Descriptive, cross-sectional study.

4.3 Methodology

A purposeful sample of 103 patients presenting with a history of mania between October 2009 and April 2010, to three hospitals in the Limpopo Province namely Mankweng-, Mokopane- and George Masebe hospitals, was recruited and interviewed using the Affective Disorders Evaluation (ADE). (99)

4.4 Background to the hospitals

For clarification, it needs to be explained that there are three categories of hospitals in South Africa. The most common names used to refer to these categories are “District”, “Regional” and “Tertiary” although these names are at present being changed to “Level 1”, “Level 2” and “Level 3” hospitals and, as their names imply, they offer different levels of service. Unfortunately the national Department of Health has yet to adopt a firm definition of each category or to define what services should be available at each facility. A district hospital is defined as a facility at which a range of outpatient and inpatient services are offered. This is the first level of referral and generalist staff (ordinary general practitioners) are available and patients have access to basic diagnostic and therapeutic services.

Regional hospitals are Level 2 facilities that provide care requiring the intervention of specialists and general practitioners. Tertiary Hospitals or

Level 3 facilities provide specialist and sub-specialist care. Most of the care here requires the expertise of clinicians working as sub-specialists or in rarer specialties (e.g. sub-specialties such as urology, neurosurgery, plastic surgery and cardiothoracic surgery). (100)

Apart from this, there are also specialised hospitals that cater for high incidence chronic conditions for example psychiatric hospitals and TB hospitals.

All Level 1- or district hospitals should provide psychiatric services but only some of them will be allowed to admit patients in accordance with the Mental Health Care Act (No. 17 of 2002). These facilities are known as “designated facilities” and mental health care users (MHCUs) are admitted for 72 hours before being transferred to a “listed facility”, which will then provide intermediate- to long-term care. The purpose of the 72-hour observation period is to rule out and/or treat any medical conditions that could mimic psychiatric illness. (101)

Limpopo Province has the fourth largest population in South Africa with roughly five million people. It is considered to be a poor province, with approximately 87% of its people living in rural areas and with 23% of households having no access to piped water.

Mankweng Hospital is part of the Polokwane-Mankweng Hospital Complex (PMHC) situated in the Capricorn District of Limpopo Province. The PMHC comprises two hospitals, Pietersburg Campus and Mankweng Campus, 30 kilometres north east of Polokwane, the largest town in the province. The combined bed capacity is 1 016. PMHC provides tertiary services to all district and regional hospitals in Limpopo Province and also serves as a regional hospital to the Capricorn District.

Mankweng Psychiatric Unit is a 40-bed adult unit making provision for 20 males and 20 females. It is known as the ”Mankweng Child and Family Unit” as this is what the original intention for the unit was, but the unit was subsequently never utilised as such since its establishment in 1998. It functions as a “designated” psychiatric facility, admitting patients in accordance with the Mental Health Care Act.

Mokopane Hospital is a Level 2 Hospital in the Mokgalakwena Municipality of the Waterberg area of Limpopo Province. It renders services at Level 2, providing specialist services for psychiatry, obstetrics and gynaecology, internal medicine, surgery and orthopaedics as well as paediatrics. It has a bed capacity of 260 and has made beds available for psychiatric patients in the medical wards. Mokopane

Hospital also functions as a designated facility, also admitting patients under the Mental Health Care Act.

George Masebe Hospital is a district (Level 1) hospital in the Waterberg area and renders a service to the local community, which consists of Bakenberg and Rebone. It is a 143-bed hospital and renders a psychiatric service as a “listed” facility making provision for 72 hours observation. Psychiatric patients are admitted to the medical wards and managed by medical officers. The hospital has a community psychiatric nurse who is very involved in the management of the inpatients as well. Outreach by a specialist psychiatrist to the psychiatric clinic is provided by a visiting psychiatrist from Mokopane Hospital.

For the purpose of orientation Figure 4.1 shows the map of South Africa and neighbouring countries. Figure 4.2 shows the nine provinces and the location of Limpopo Province in particular. Figure 4.3 is a map of Limpopo Province, indicating the location of the three hospitals where the study was conducted.

Figure 4.1 Map of Southern Africa

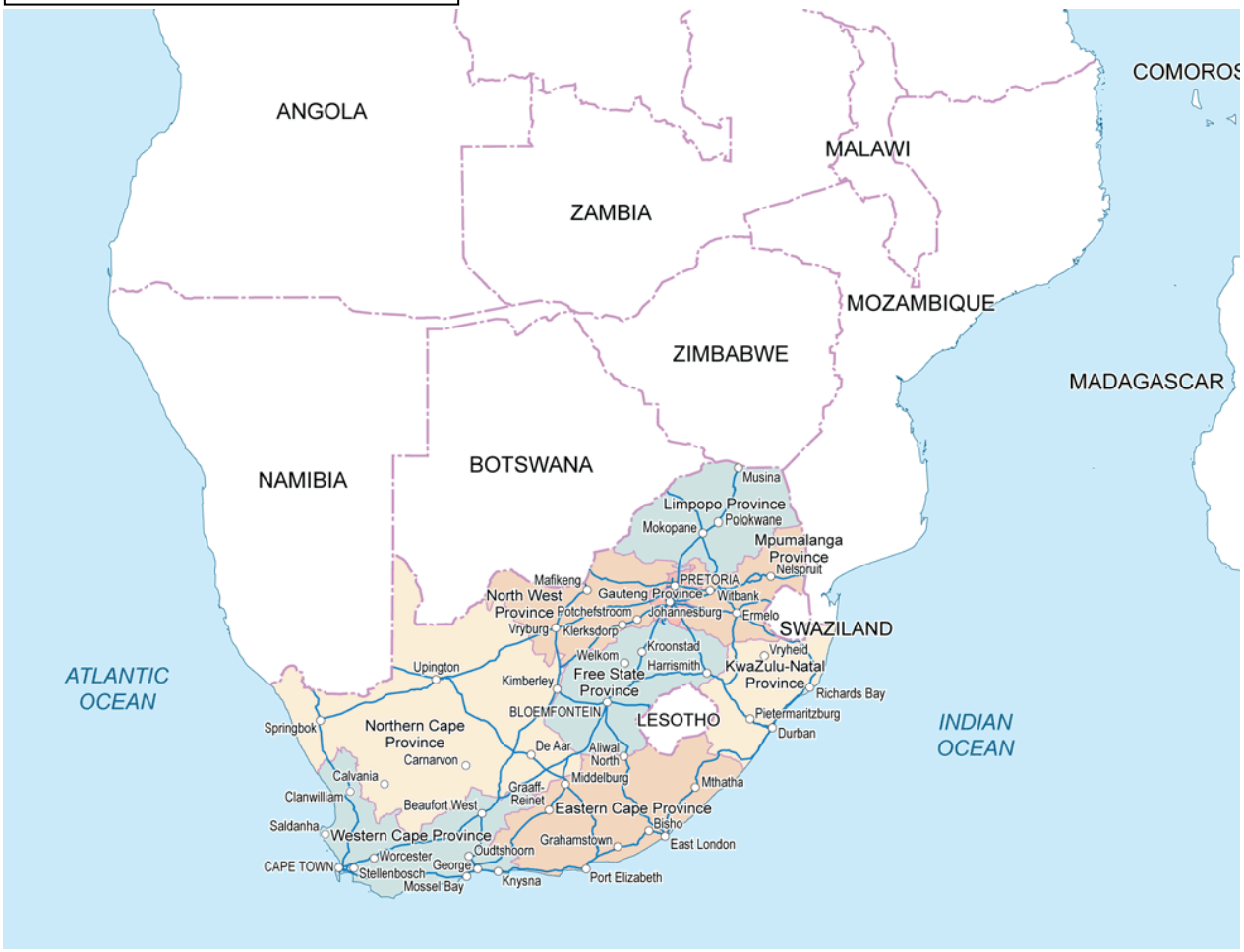


Figure 4.2 Map of South Africa

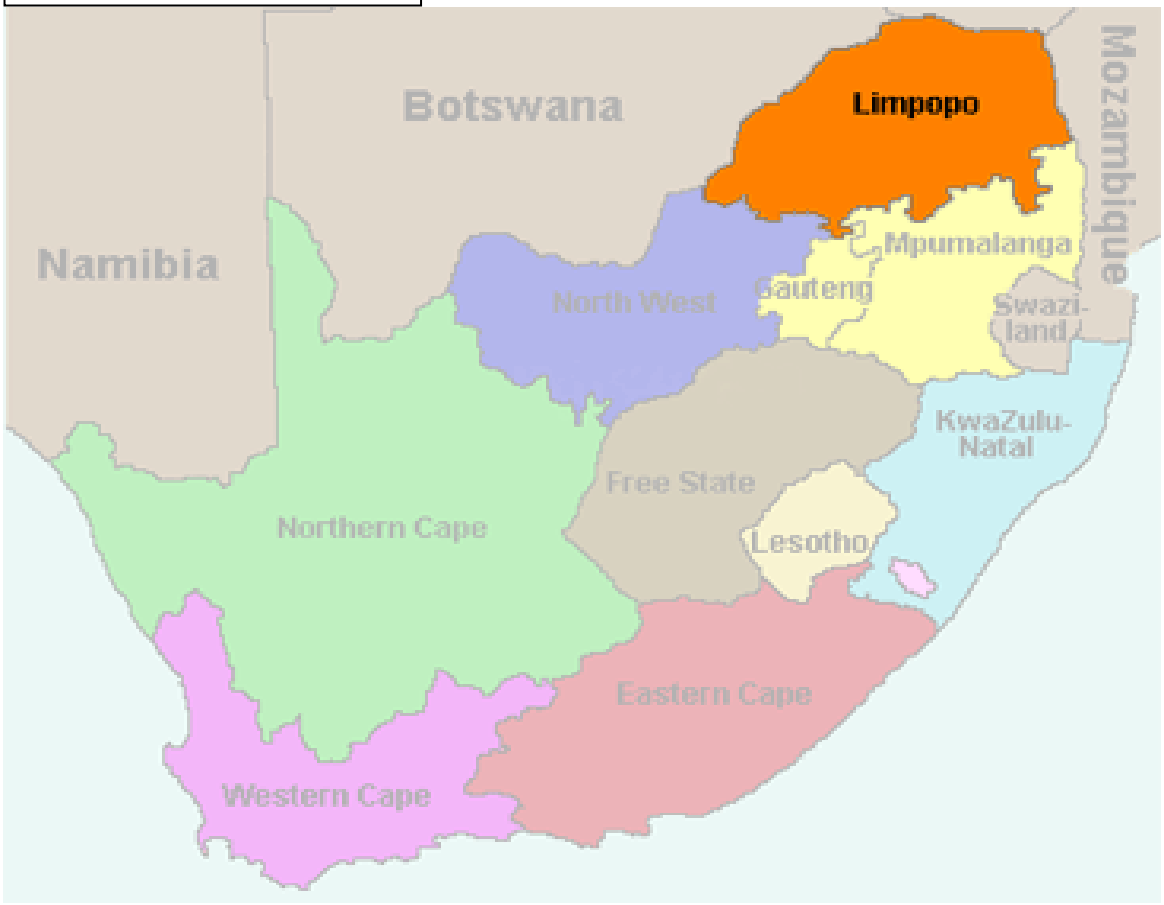
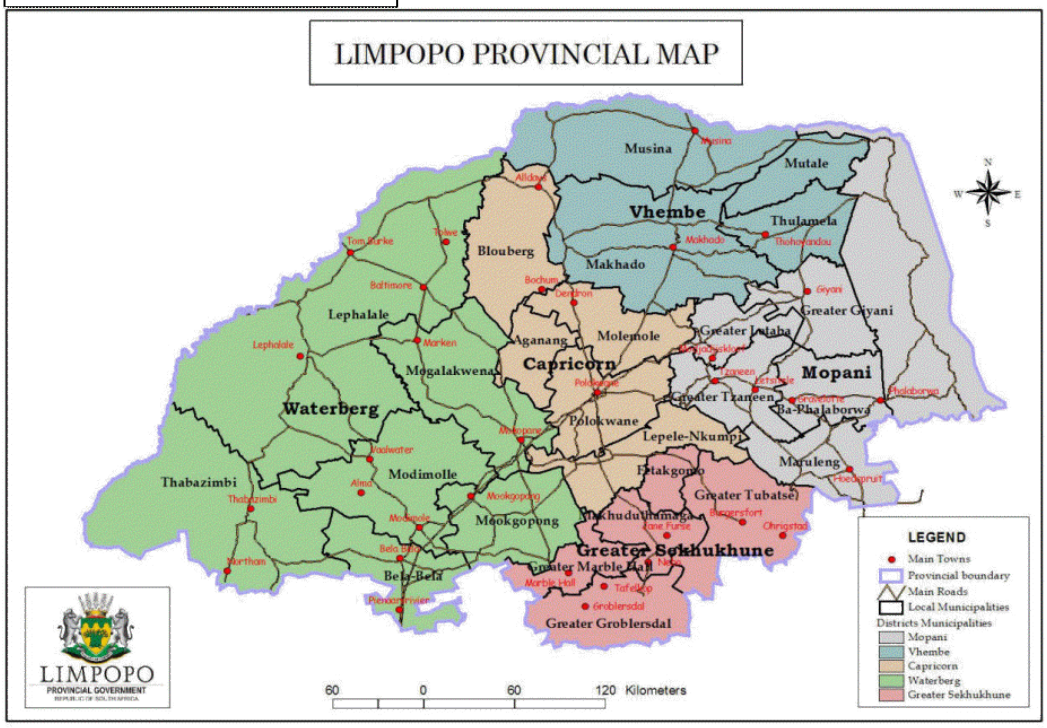


Figure 4.3 Map of Limpopo



4.5 Ethical considerations

The research protocol (Protocol no. 136/2009) and informed consent document (Appendix B) were presented to the University of Pretoria, Faculty of Health Sciences Research Ethics Committee and approved on 26/08/2009 (Appendix C).

Letters requesting permission to see patients and access patient records were sent to the Chief Executive Officers of the three hospitals involved and permission was obtained (Appendix D).

Ethical approval to conduct the study was requested and obtained from the Limpopo Department of Health and Social Development Research Ethics Committee on 04/11/2009 (Appendix E).

Patients admitted under the Mental Health Care Act as either assisted or involuntary patients were not requested to participate in the study until such time that they were deemed able to give informed consent and provide an adequate history.

Personal information, names and file numbers of patients were handled with utmost confidentiality but were documented for future reference, follow up and verification of information.

4.6 Informed consent

Subjects agreeing to participate in the study signed informed consent. Those not conversant in English had the informed consent form explained to them in Northern Sotho by an interpreter fluent in the native language. The interpreter was asked to read through the informed consent document first and was given an opportunity to ask questions to clarify content. Hereafter the interpreter then explained the content of the informed consent document to the study subject and the study subject would be given an opportunity to ask questions as well. Study participants were also given the researcher's personal cell phone number so that they could request any additional information at a later stage should they wish to.

Informed consent included: purpose of the study, procedure, potential risks, benefits to the individual and others, consent to family members being interviewed, an invitation to ask questions, name and address of researcher and a statement to the effect that the person was free to choose not to participate without incurring displeasure or disadvantage.

Patients who were incapable of giving either informed consent or providing a good history of their illness were not included in the study.

4.7 Measuring instrument

After signing the informed consent form, a questionnaire, the Affective Disorder Evaluation (ADE) (99), was completed by the researcher for every study subject. See Appendix F for an example of the ADE. The researcher was assisted by registered nurses fluent in Northern Sotho, who translated the questions to non-English-speaking participants.

The ADE is a standardised tool for initial clinical assessment of patients possibly suffering from bipolar disorder. Developed for the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), the main objective of the ADE is to provide an efficient way of making a reliable current and lifetime diagnosis of bipolar disorder. (102) The ADE uses an adaptation of the mood disorder modules from the Structured Clinical Interview for DSM-IV (SCID). (103) These modules assess current mood episode and lifetime mood disorder diagnosis and flow in an orderly sequence designed to reflect the DSM-IV mood disorder classification.

4.8 Sample size

The sample size was calculated with the objective of prevalence of a unipolar manic course determination in mind. Under the assumption that the expected prevalence of a unipolar manic only course in the study

population is 35%, a sample size of 88 patients was considered to be able to estimate the prevalence to an accuracy of 10% with 95% confidence.

4.9 Data analysis

The data summary covered descriptive statistics like mean, standard deviation, median, range and 95% confidence intervals for continuous variables whilst for categorical variables (nominal and ordinal) use was made of proportion, percentages cross-tables and 95% confidence intervals. Survival curves comparing subgroup, e.g. sex, age categories etc., employed hazard ratios. Testing was done at the 0,05 level of significance.

4.10 Methodological limitations

As the researcher is not a speaker of Northern Sotho, interpreters were used for those study subjects not fluent in English. Language and the use of interpreters constitute a challenge in all cross-cultural research situations. In this population specifically there are frequently no specific translations available for a word and the interpreter then had to explain concepts to the study subjects.

Interpreters were mostly registered nurses whose native language was Northern Sotho and who worked in the particular psychiatric unit providing care for psychiatric patients. When possible, use was made of registrars training to become psychiatrists, who were fluent in Northern Sotho.

Selection bias could be a limiting factor as not all patients with manic episodes may necessarily seek help at a hospital but might go to either private practising doctors or traditional healers. Only those presenting to hospital were included in the study.

As with most questionnaires, when history is being taken, patients might not be able to remember everything about their illness in detail and recall bias is therefore a definite limitation of this study. In order to avoid recall bias, information from clinical records in hospital files as well as collateral information from family members was obtained if available.

4.11 Definition of recurrent unipolar mania

One of the challenges in the research of recurrent bipolar mania is a lack of consensus on the defining criteria. Different authors have used different criteria for the diagnosis of recurrent mania with respect to the number of manic episodes, diagnosis of manic episode, and

inclusion/exclusion of the depressive symptoms in the intercurrent period. (27)

In the studies published in the last decade there appears to be some consensus on the presence of at least three manic episodes with no depressive episodes, but there is no consensus on the timeframe for the same.

Aghanwa defined “recurrent mania” as three previous episodes of mania or hypomania (ICD-10) and the presence of affective illness for at least four years. (91)

On the other hand, Yazici et al defined recurrent mania by the occurrence of at least four episodes of mania (DSM-IV) and at least four years of follow up without any depressive episode.(92)

Thus, a critical issue that remains unresolved concerns the maximum number of manic/hypomanic episodes that a person must experience in a particular timeframe without any depressive episodes so as to enable a psychiatrist to make a confident diagnosis of recurrent unipolar mania. One should consider however that this issue is not unique to making a

diagnosis of only recurrent unipolar mania but is equally important when making a diagnosis of recurrent unipolar depression.

For the purposes of this study, a unipolar manic course was considered in all patients who had never experienced a major depressive episode. However, the rate of unipolar mania was also established for those in the sample who were diagnosed with bipolar disorder in particular and had three or more lifetime number of phases without the occurrence of any depressive episodes.