Influence of antiepileptic treatment changes on adult patients’ clinical outcomes in an outpatient population, North West

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This mini-dissertation was written up in article format. The findings of the study are presented in Chapter 3 in manuscript format as required by the regulations of the North-West University. One manuscript will be submitted for publishing in the following journal:

- *Journal of Clinical Pharmacy and Therapeutics*

The manuscript contains a reference list cited according to the instructions for authors required by the respective journal. The complete reference list is included at the end of the mini-dissertation according to the reference style of the North-West University.

The chapters in this dissertation are stipulated as follows:

- Chapter 1 provides a brief introduction, followed by the research methodology used to conduct this study.
- Chapter 2 entails a literature review of anti-epileptics (brief summary of epilepsy and antiepileptic drugs) and the conceptualisation of adherence.
- Chapter 3 consists of the results and discussions in article format.
- Chapter 4 is the conclusion, recommendations and limitations drawn from the study.
- The annexures and references follow at the end.

The co-authors named in the manuscript were the supervisor and co-supervisors during the study. They gave approval that the manuscript may be used as part of the dissertation. The contributions of each author are subsequently outlined in the next pages.
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ABSTRACT

Influence of antiepileptic treatment changes on adult patients’ clinical outcomes in an outpatient population, North West

Background: Epilepsy, being one of the most common neurological conditions, is undertreated in patients worldwide. The primary treatment goal of antiepileptic drugs (AEDs) is to achieve complete limitation of seizures without side-effects, ensuring an optimal quality of life. Medication adherence is a major problem in epilepsy. The clinical outcomes of epilepsy management and prescribing patterns in the public health sector of the Dr Kenneth Kaunda District were unknown. Little prevalence studies have been done on epilepsy in the public health sector of South Africa. This study could contribute to the knowledge about epilepsy in the public health sector of South Africa.

Objective: The purpose of this study was to investigate the prescribing patterns of antiepileptic drugs and patients’ clinical outcomes, such as adherence, seizure frequency and therapeutic serum drug levels in the adult outpatient department of a public hospital in Dr Kenneth Kaunda District, North West province, South Africa.

Method: A retrospective, quantitative research design was applied to collect data from epileptic patients’ medical files using a pre-developed data collection tool. The inclusion criteria was adult patients (above 18 years) diagnosed with epilepsy and on antiepileptic treatment for six to 24 consecutive months during the study period of 1 January 2014 to 30 June 2016. Patients were excluded if they were diagnosed with medical conditions other than epilepsy for which they received AEDs as treatment. The data collection was conducted from May to August 2016. The medicine possession ratio (MPR) was used to determine adherence status per AED. An MPR $\geq 80\% \text{ and } \leq 110\%$ was considered as adherent. Serum drug levels, as measure of therapeutic drug monitoring (TDM), were compared to the therapeutic range per AED and values were classified as therapeutic, subtherapeutic (below the therapeutic range) and supratherapeutic (above the therapeutic range). The prevalence of seizure breakthrough and regimen change were described using descriptive statistics.

Results: Forty-six epileptic patients complied with the study criteria. Among them 25 were males and 21 were females. Valproate was the drug mostly prescribed (n=41; 53.24%), followed by lamotrigine (n=24; 31.16%) and carbamazepine (n=8; 10.38%). It is important to remember that patients can be on a regimen with more than one AED, therefore the sum of total number of patients per AED will be more than 46 patients. Adherence, according to the medicine possession ratio, was 64.93% (n=50) and seizures occurred in 84.78% (n=39) of patients. According to the serum drug levels, 61.90% (n=13) of the measurements were subtherapeutic, while 14.28% (n=3)
were supratherapeutic. Valproate had the highest rate of seizure breakthrough (n=34; 82.90%) and subtherapeutic serum levels (n=12; 92.31%). More than one regimen changes occurred in 69.56% (n=32) of the population with the change in dose as the most prevalent type of regimen change (n=25; 54.43%).

**Conclusions and recommendations:** The study has attempted to reveal the prescribing patterns and clinical outcomes in the adult outpatient department. Adherence was still poor compared to the ideal of 80%. The number of serum drug levels reported were not sufficient to conclude on the adherence status, although poor adherence and monitoring of patient outcomes, especially in valproate, are suspected. Both sub- and supratherapeutic levels may imply possible non-adherence to antiepileptic treatment. Changes in AED regimen can cause a fluctuation of serum drug levels. Therefore, an expert opinion should be consulted before the initiation of regimen changes. Consequently, the classification of epilepsy, adherence to antiepileptic treatment, the correct documentation of seizure frequency and therapeutic drug level monitoring needs urgent interventions. Therapeutic drug monitoring is fully justified to optimise an individual dosage regimen. Monitoring epilepsy patients, especially patients on valproate, seems to be essential to improve clinical outcomes of anti-epileptic patients in this public hospital.

It is recommended that future research projects on this research topic should be implemented in more hospitals and/or other districts in the public health sector of South Africa. The ‘influence’ of regimen change, according to the study title, could not be measured due to the limitations of this study. Therefore, it is suggested that the title of this mini-dissertation should change to: ‘A retrospective analysis of adult epilepsy patients’ clinical outcomes: adherence, seizure frequency and therapeutic drug monitoring in an outpatient department of a public hospital in the North West Province, South Africa.’

**Keywords:** epilepsy, antiepileptic drugs, regimen change, adherence, clinical outcomes, therapeutic drug levels, public hospital
UITTREKSEL

Die invloed van verandering in anti-epileptiese behandeling in volwasse pasiënte se kliniese uitkomste in ’n buitepasiëntpopulasie, Noordwes

Agtergrond: Epilepsie is een van die algemeenste neurologiese siektes wat wêreldwyd onderbehandel word. Die primêre doel van anti-epileptiese behandeling is om epileptiese aanvalle te voorkom sonder om newe-effekte te veroorsaak en om die lewenskwaliteit van die pasiënt te verbeter. Die meewerkendheid in epilepsie pasiënte is ’n groot probleem. Die kliniese uitkomste van epilepsie beheer en voorskryfpatrone in die publieke gesondheidsorg sektor van die Dr Kenneth Kaunda Distrik is onbekend. Beperkte studies van die voorkoms van epilepsie is bekend in die publieke gesondheidssektor van Suid-Afrika. Hierdie studie kan bydra tot die kennis oor pasiënte met epilepsie in die publieke gesondheidsektor van Suid-Afrika.

Doelwit: Die doel van hierdie studie was om onderzoek in te stel oor die voorskryfpatrone van anti-epileptiese middels en pasiënte se kliniese uitkomste, soos meewerkendheid, voorkoms van epileptiese aanvalle en om terapeutiese geneesmiddel bloedvlakke te bepaal in die volwasse buitepasiëntpopulasie in die Dr Kenneth Kaunda Distrik in die Noordwes provinsie, Suid-Afrika.

Metode: ’n Terugskouende, kwantitatiewe navorsingsontwerp is gevolg om data uit pasiënte se mediese leërs te verkry deur gebruik te maak van ’n voorafopgestelde data versamelingsinstrument. Die insluitingskriteria was volwasse pasiënte (bo die ouderdom van 18 jaar) gediagnoseer met epilepsie wat anti-epileptiese behandeling vir ses tot 24 opeenvolgende maande gedurende die studieperiode, vanaf 1 Januarie 2014 tot 30 Junie 2016, ontvang het. Pasiënte is uitgesluit van die studiepopulasie indien hulle met ’n ander mediese toestand as epilepsie gediagnoseer is waarvoor hulle ook anti-epileptiese behandeling ontvang het. Die dataversameling het plaasgevind tussen Mei en Augustus 2016. Die medikasiebesigtiging is gebruik om die pasiëntmeewerkendheid in die studiepopulasie per anti-epileptiese geneesmiddel te bepaal. ’n Verhouding van ≥80% en ≤110% is as meewerkend beskou. Geneesmiddelbloedvlakke, as middel tot terapeutiese geneesmiddelmonitoring, is vergelyk met die terapeutiese reikwydte per antiepileptiese middel en die waardes is geklassifiseer as terapeuties, sub-terapeuties (onder die terapeutiese reikwydte) of supra-terapeuties (bo die terapeutiese reikwydte). Die voorkoms van epileptiese aanvalle en die verandering in behandelingsriglyne is beskryf met behulp van beskrywende statistiek.

Resultate: Ses-en-veertig pasiënte het aan die insluitingskriteria voldoen, waarvan 25 mans en 21 vrouens was. Valproaat was die geneesmiddel wat die meeste voorgeskryf is (n=41; 53.24%), gevolg deur lamotrigien (n=24; 31.16%) en karbamasepien (n=8; 10.38%). Dit is belangrik om in ag te neem dat pasiënte meer as een anti-epileptiese middel kan gebruik, as deel van die
behandelingsriglyne. Daarom is die som van die totale aantal pasiënte per geneesmiddel meer as 46 pasiënte. Pasiëntmeewerkendheid, volgens die medikasiebesit-verhouding, was 64.93% (n=50) en epileptiese aanvalle het in 84.78% (n=39) van die pasiënte voorgekom. Volgens die geneesmiddelbloedvlakke is 61.90% (n=13) van die waardes as sub-terapeuties en 14.28% (n=3) van die waardes as supra-terapeuties geklassifiseer. Valproaat was die geneesmiddel met die hoogste voorkoms van epileptiese aanvalle (n=34; 82.90%) en sub-terapeutiese bloedvlak waardes (n=12; 92.31%). Meer as een behandelingsriglyn verandering het in 69.56% (n=32) van die populasie voorgekom, waarvoor die rede van verandering in die meeste gevalle dosisverandering (n=25; 54.43%) was.

**Gevolgtrekking en aanbevelings:** Hierdie studie het gepoog om die voorskryfpatrone en kliniese uitkomste van ’n volwasse buitepasiëntpopulasie te bepaal. Pasiëntmeewerkendheid was steeds minder as die ideale meewerkendheid van 80%. Die hoeveelheid geneesmiddelbloedvlakke wat gedokumenteer is, was nie voldoende om die meewerkendheidstatus van die populasie korrek weer te gee nie. Swak pasiëntmeewerkendheid en monitering van pasiëntuitkomste, veral in pasiënte op valproaatbehandeling, word vermoed. Beide sub- en supra-terapeutiese bloedvlakke kan moontlike nie-meewerkendheid aandui.

Veranderinge in anti-epileptiese behandeling kan veranderings in bloedvlakkonsentrasies induseer. Daarom moet ’n kenner se insig eers geraadpleeg word voordat die huidige behandeling verander word. Gevolglik het die klasifisering van epilepsie, pasiëntmeewerkendheid, die korrekte dokumentering van epileptiese aanvalle en terapeutiese geneesmiddelbloedvlakmonitering dringende ingryping nodig. Terapeutiese geneesmiddelmonitering in epilepsie pasiënte is hiermee geregverdig om sodoende die individu se doserings te optimaliseer. Die monitoring van epilepsie pasiënte, veral diegene wat met valproaat behandeld word, is belangrik om sodoende pasiënte in die publieke gesondheidsektor van Suid-Afrika se kliniese uitkomste te verbeter.

Dit word aanbeveel dat navorsingsprojekte in die toekoms in meer hospitale en/of ander distrikte in die publieke gesondheidsektor van Suid-Afrika geïmplementeer word. Verder kon die ‘invloed’ van behandelingsriglyne veranderings, soos die titel aandui, nie bepaal word in hierdie studie nie. Dit word voorgestel dat die titel van hierdie skripsie verander kan word na: ‘n Retrospektiewe ontleiding van volwasse epileptiese pasiënte se kliniese uitkomste: pasiëntmeewerkendheid, epileptiese aanvalfrekwensie en terapeutiese geneesmiddel monitering in ’n buitepasiëntpopulasie in die Noordwes Provincie.’

**Trefwoorde:** epilepsie, anti-epileptiese geneesmiddels, regime verandering, pasiëntmeewerkendheid, kliniese uitkomste, terapeutiese geneesmiddelbloedvlakke, publieke hospitaal.
AUTHOR’S CONTRIBUTIONS (STUDY AND MANUSCRIPT)

The contribution of each author to the study and Manuscript, entitled “Retrospective analysis of adult epilepsy patients’ clinical outcomes: adherence, seizure frequency and therapeutic drug levels in an outpatient department of a public hospital in the North West Province, South Africa” is stipulated in the following table.

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<th>Author</th>
<th>Role in studies</th>
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| Miss R Derksen          | Responsible for the literature review  
                          Planning and design of the manuscript  
                          Data and statistical analysis  
                          Interpretation of results  
                          Writing of dissertation and manuscript |
| Prof MS Lubbe (Supervisor) | Supervision of concept of study and manuscript  
                          Supervision in the writing of the dissertation and manuscript  
                          Guidance in the interpretation of results  
                          Revising the manuscript critically for final approval |
| Dr M Rheeders (Co-supervisor) | Co-supervision of concept of study and manuscript  
                          Co-supervision in the writing of the dissertation and manuscript  
                          Reviewing the manuscript critically for final approval of the version to be published |
| Mrs M Cockeran (Statistician) | Programming for statistical analysis  
                          Data and statistical analysis  
                          Verified all results from statistical analysis  
                          Guidance in the interpretation of results |
The following statement provided by the co-authors confirms their individual roles in the study and their permission that the manuscript may form part of this dissertation:

I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contributions and I hereby give my consent that it may be published as part of the MPharm (Advanced Clinical Pharmacy) study of Miss R Derksen.

Prof MS Lubbe

Dr M Rheeders

Mrs M Cockeran

Miss R Derksen
LIST OF DEFINITIONS

**Adherence** is a term defined by Brodtkorb *et al.* (2016:3) as the “implementation of an agreed medical treatment, its initiation and execution as prescribed.” Therefore it is seen as the active involvement of the patient to achieve therapeutic outcomes and implies that the patient has a choice to follow the medication regimen (Ho *et al.*, 2009:3028) and how well the patient follows the therapeutic plan agreed on (Ettinger & Baker, 2009:60). Adherence has mostly replaced the term compliance. Refer to *compliance* below. In the context of this study, adherence is determined by a medicine possession ratio of $\geq 80\%$ and $\leq 110\%$.

**Change in therapy** in this study refers to any change in antiepileptic drug choice, dosage or dosage interval.

**Clinical outcome** is described as a parameter that involves a diagnosis or assessment by a health care provider (Velentgas *et al.*, 2013:74) and refers to the results of any healthcare intervention (Capuzzo & Moreno, 2010:1). For the purpose of this study clinical outcomes will be described in terms of patient adherence, seizure frequency and therapeutic serum drug levels.

A **comorbid condition** (*comorbidity*) is a condition that occurs during the course of the initial disease (Keezer *et al.*, 2016:106).

**Compliance** is described by Brodtkorb *et al.* (2016:3) as “passive obedience” and according to Peterson *et al.* (2007:3) is a synonym of adherence. Refer to *adherence* above.

**Convulsion** is a term used for a seizure of any type with violent, involuntary and irregular movement of one or more limbs (Angus-Leppan & Parsons, 2008:571-572; Wells, 2009:577).

**Drug interactions** are, according to the Medicines and Related Substances Control Act (Act 101 of 1965), present if an adverse event is suspected to be related to and interaction between two or more medicines (Department of Health, 2012:14).

**Epilepsy** is described by Angus-Leppan and Parsons (2008:572) as the occurrence of two or more unprovoked seizures (Banerjee *et al.*, 2009:32) and active epilepsy is defined as repeated, unprovoked seizures within the last twelve months (Forsgen, 2008:21). Refer to 2.2.1.

A **fit** can entail an outburst of aggression or temper or is a lay term referring to a seizure (Angus-Leppan & Parsons, 2008:572).

**Frequency** is the number or percentage of items in a category in a set of data (Mirriam Webster Dictionary, 2014).
Gingival hyperplasia is swelling of the gums (Schachter, 2008:678).

Incidence is the rate of occurrence of new cases in a population over a specified period in time (Bell et al., 2014:958; Banerjee et al., 2009:33).

Medicine possession ratio (MPR) is described by Faught (2012:289) as “the percentage of time a patient has access to medications.” MPR will be used as a proxy for adherence with therapy.

Modified-release formulation is explained by Encyclopaedia Britannica (2015) as a drug formulation that has been developed to “deliver drug to the part of the body where it will be absorbed, to simplify dosing schedules and to assure that concentration of drug is maintained over an appropriate time interval” and that most modified-release dosage forms are tablets or capsules designed to deliver the drug to the circulating blood over an extended time period.

Monotherapy is described by the Oxford Dictionary (2016a) as the treatment of a disease with a single drug.

Non-adherence can be in the form of intended or non-intentional drug negligence (Brodtkorb et al., 2016:3) and is a growing concern as it is associated with higher cost of care and side-effects (Ho et al., 2009:3028).

Oversupply of medication in this study is an MPR >110%. This is considered to be non-adherent (Jacobs et al., 2016:540).

Persistence is described by Peterson et al. (2007:3) as a factor to determine compliance as the duration of time from initiation of treatment to discontinuation thereof. It is measured in days and assists in monitoring a patient’s refill behaviour.

Polytherapy is described by the Oxford Dictionary (2016b) as treatment with two or more drugs to treat the same condition.

Prescribed daily dose is the total dosage the patient is taking per day per antiepileptic drug.

Postictal phase is the immediate state of consciousness after an epileptic seizure and is recognised by drowsiness, confusion, nausea and hypotension.

Prevalence is described by Keezer et al. (2016:107) as the ratio of individuals at “risk with the condition in question” at a single point in time (Bell et al., 2014:958) to the entire population (Dekker 2002:4).
Proportion of days covered is defined by Peterson et al. (2007:6) as the number of days with drug on hand over a specific time interval. It credits the patient with finishing the current fill of medication before starting the next fill to avoid double counting covered days.

The reference range is a range of drug concentration values, unique for every drug, quoted by the laboratory which can be used by clinicians as a guide for therapeutic response or toxicity (Milosheska et al., 2015:28).

Regimen change refers to the change in antiepileptic drug (AED) dose, frequency of AED administration, switching to another AED and adding another AED or stopping an AED. Consecutive prescriptions were compared to assess whether regimen change had occurred.

Seizure is a term that refers to “the transient alteration of behaviour due to the disordered, synchronous and rhythmic firing of populations of brain neurons” (McNamara, 2006:501).

Seizure frequency is the number of seizures that occur within a specified period. In this study the number of seizures were documented by healthcare practitioners in patients’ medical files during patient consultation. An increased seizure frequency may indicate seizure severity (Schachter, 2008:675). Seizure breakthrough is also used to indicate seizure frequency while on antiepileptic treatment.

The study period in this study was between 1 January 2014 up until 30 June 2016.

Subtherapeutic drug levels refers to the level below therapeutic range and is used during therapeutic drug monitoring (Chan & Beran, 2008:574).

Supratherapeutic drug levels refers to a drug serum level above the therapeutic range and is used during therapeutic drug monitoring (Stepanova & Beran, 2015:8).

Undersupply of medication is determined by an MPR <80% and is considered as non-adherent (Jacobs et al., 2016:540).
### LIST OF ACRONYMS AND ABBREVIATIONS

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>AED</td>
<td>Antiepileptic drug</td>
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<td>AEDs</td>
<td>Antiepileptic drugs</td>
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<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
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<td>ARV</td>
<td>Antiretroviral</td>
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<td>BBB</td>
<td>Blood brain barrier</td>
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<td>CNS</td>
<td>Central nervous system</td>
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<td>CYP450</td>
<td>Cytochrome P450 enzyme</td>
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<td>DoH</td>
<td>Department of Health</td>
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<td>EML</td>
<td>Essential medicine list</td>
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<td>EEG</td>
<td>Electroencephalogram</td>
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<td>EFV</td>
<td>Efavirenz</td>
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<td>g</td>
<td>gram</td>
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<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
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<tr>
<td>GTC</td>
<td>Generalised tonic-clonic</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>ICD</td>
<td>International classification of disease</td>
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<td>ILAE</td>
<td>International league against epilepsy</td>
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<td>kg</td>
<td>kilogram</td>
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<td>LPV</td>
<td>Lopinavir</td>
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<td>mg</td>
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<td>MPR</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<td>MUSA</td>
<td>Medicine Usage in South Africa</td>
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<td>PDD</td>
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<td>SPSS</td>
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<td>Standard treatment guidelines</td>
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CHAPTER 1: INTRODUCTION

1.1 Introduction

With this study the researcher investigated the influence of treatment changes of an adult outpatient population. The researcher evaluated the following clinical outcomes: patient adherence, antiepileptic drug therapeutic levels and seizure frequency. The medication possession ratio (MPR) was used as a proxy to determine patient adherence to antiepileptic drugs. Seizure occurrence throughout the study period was analysed. Antiepileptic drugs that were available in the hospital in the public sector were the following: carbamazepine, phenobarbitone, lamotrigine, topiramate, valproate and phenytoin. Drug use evaluation involved the comprehensive review of patient’s prescriptions and medication and laboratory data to ensure appropriate therapeutic discussion and positive patient outcomes. A retrospective review detected patterns in prescribing, dispensing and medication use and served as means for developing prospective standards and target interventions.

1.2 Background to the study

Epilepsy is a chronic disease experienced by millions and a cause of substantial mortality and morbidity (Banerjee et al., 2009:31). The WHO (2015a) describes it as one of the oldest conditions known to mankind affecting individuals of all ages. Approximately 50 million people worldwide are diagnosed with epilepsy and nearly 80% of these people are found in developing regions, of which 75% do not receive the treatment they need (WHO, 2015a; Banjeree et al., 2009:32). The higher rates in developing countries are thought to be attributable to neuro-cysticercosis caused by: human immunodeficiency virus (HIV)/Acquired immunodeficiency Syndrome (AIDS), trauma and perinatal morbidity (WHO, 2005). It is difficult to keep record of and interpret these cases because of methodological issues. The prevalence of active epilepsy in developing countries is estimated to be four to ten patients per 1 000 people (WHO, 2005). A higher prevalence has been reported in resource-poor countries, such as sub-Saharan Africa and Central and South America (Bell et al., 2014:958-959; WHO, 2005).

A single unprovoked seizure is not an indication for treatment, although 40% of patients may have a subsequent seizure within two years (Department of Health, 2012:14.5). Different parts of the brain can be the site of excessive electrical discharges causing brief lapses of muscle jerks to severe and prolonged convulsions which can occur as frequent as several per day (WHO, 2015a). Available drugs treat symptomatic epilepsy by inhibiting seizures, but no effective prophylaxis or cure is available (McNamara, 2006:501). The primary treatment goal
is to achieve complete control of seizures without side-effects (Pellock et al., 2004:301). According to McNamara (2006:505), the ideal anti-seizure drug would suppress all seizures without causing any unwanted side-effects, however, the available drugs unfortunately frequently cause a range of unwanted effects that may vary from minimal impairment of the central nervous system (Brodtkorb et al., 2016:4; De Boer et al., 2008:542; Wagner et al., 2014:784) to hepatic failure (Milosheska et al., 2015:28) and death (McNamara, 2006:505). Some antiepileptic drugs are indicated in specific epileptic seizure diagnoses and can be classified as simple partial, complex partial, generalised tonic-clonic seizures, myoclonic seizures and absence seizures (McNamara, 2006:502; Wells, 2009:579). Most antiepileptic drugs should be induced gradually (Zabcevic et al., 2002:26). The occurrence of increased epilepsy seizures may correlate with a low drug blood levels.

1.3 Problem statement

In developing countries around 90% of epilepsy patients are not receiving appropriate treatment due to cultural attitude, lack of prioritisation, poor health system infrastructure and inadequate supply of antiepileptic drugs (Scott et al., 2001:344; Bell et al., 2014:958). The clinical outcomes of epilepsy management and prescribing patterns in this public hospital in the Dr Kenneth Kaunda District, during the study period between 1 January 2014 and 30 June 2016, were unknown. Little research has been done on the prevalence of epilepsy, prescribing patterns and the influence of drug therapy changes on patients’ clinical outcomes in the public sector and the Dr Kenneth Kaunda District, in the North West Province. This study could make a contribution to the knowledge about the prevalence of AED prescribing, adherence patterns and seizure frequency to prevent recurrence of inappropriate antiepileptic drug use and assist in the development of prospective standards and target interventions in the public health sector of the North West Province.

Research questions that needed to be answered were:

- What was the relationship between adherence status (as determined with medicine possession ratio) and other clinical outcomes (such as the therapeutic serum drug levels and seizure frequency)?
- What was the level of adherence in patients and the prevalence of regimen change in antiepileptic therapy?
- Could the frequency of seizures documented be related to the change in therapeutic regimen?
1.4 Research aims and objectives

The specific research aims and objectives necessary to conduct this study are discussed next.

1.4.1 Research aims

The general aim of this study was to investigate the prescribing patterns of antiepileptic drugs and patient’s clinical outcomes, such as patient adherence, seizure frequency and therapeutic serum drug levels in the outpatient department of Tshepong Hospital in Dr Kenneth Kaunda District, North West Province, South Africa.

1.4.2 Specific research objectives

The objectives of the literature study were:

- To conceptualise epilepsy and antiepileptic therapy (indications, pharmacokinetic, side-effects and drug-drug interactions) in the public sector of South Africa.
- To identify clinical outcomes in antiepileptic patients, defined in this study as adherence, seizure frequency and therapeutic serum drug levels.

The objectives of the empirical study were:

- To identify prescribing patterns, such as the type of drug and the prescribed daily dose, in the public sector for adult epilepsy patients.
- To establish the adherence, by assessing the medicine possession ratio, of adult epilepsy patients.
- To identify the prevalence of change in antiepileptic drug therapy during the study period, between 1 January 2014 and 30 June 2016, and the type of treatment changes.
- To determine the influence of adherence and/or regimen change on seizure frequency and therapeutic antiepileptic drug levels.

1.4.2.1 Literature review

Literature and research articles included in the literature review of this study were selected as follows:

- An internet search using appropriate databases such as Google Scholar, EBSCOHost, ScienceDirect or Scopus, was conducted.
• Key-words that could be used in the internet search (including applicable journals) related to epilepsy, adherence, antiepileptic drugs and factors that influence adherence and drug therapeutic levels were identified.
• The most appropriate literature from the results was chosen to answer the research objectives.

Key words that were used when conducting a literature research were:

• “Epilepsy”
• “Epilepsy management”
• “Incidence of epileptic seizures with change in therapy”
• “Efficacy of antiepileptic drugs”
• “Medicine possession ratio”
• “Adherence” and “antiepileptic drugs”
• “Adherence” and “change in regimen”
• “Seizure incidence”
• “Antiepileptic drug therapeutic levels”
• “Modified release antiepileptic drugs”
• “Drug interactions” with “carbamazepine”, “phenobarbitone”, “valproate”, “lamotrigine” and “phenytoin”
• “Clinical outcomes” and “epilepsy”

1.4.2.2 Empirical investigation

The research design and study setting are explained in the following section.

1.5 Research methodology

1.5.1 Research design

The most suitable research approach to address this research problem was a descriptive observational, retrospective, cross-sectional, quantitative approach. An observational, or non-experimental study is where the investigator does not have control over the features and does not plan to influence the participants in the study (Johnson, 2011:89). A cross-sectional study examines the data at one point in time and can be used to observe correlations between variables available in the data-set (Johnson, 2011:94). Quantitative data collection was used as method to collect objective data on the variables of interest out of patient files. According to Peterson et al. (2007:5), in a retrospective study, the data of interest has already been collected and stored. A descriptive study describes certain variables, such as medication use
patterns and adherence, as well as laboratory results such as therapeutic drug levels (Peterson et al., 2007:5). The researcher collected data from patient medical records in a reliable manner using the data collection tool (Johnson, 2011:89). The study period was between 1 January 2014 up until 30 June 2016.

1.5.2 Study setting

This study took place in a public hospital complex, namely Klerksdorp/Tshepong Hospital Complex, of the North West Province in the Dr Kenneth Kaunda District. Tshepong Hospital, as one of the hospitals in the complex, was chosen as the research setting because it is the only regional hospital complex in the North West Province. The Hospital Complex has an average of 5 800 patients admitted per month, of which the average length of stay is six days and approximately 20 000 patients visit the outpatient department of the hospital complex annually (North West Department of Health, 2016). Although the study population of each hospital in the Hospital Complex was unknown, these numbers were large enough to suspect significant data in Tshepong Hospital to reflect the study population.

1.5.3 Target and study population

The target population was adult patients (above 18 years) who have been diagnosed with epilepsy, have been on antiepileptic treatment between six and 24 months during the study period between 1 January 2014 up until 30 June 2016 and who attended the outpatient department of the hospital pharmacy during the data capturing period. A six-month to two-year period was chosen to optimise the quality of data that would be captured, as determining adherence needed a longer review period. The target population size was unknown, as neither the hospital nor the hospital pharmacy had a database to verify the number of epilepsy patients to whom they provided treatment. The number of patients on antiepileptic drugs did not provide an indication of the epilepsy patients, as some of the drugs were used to treat other illnesses. The study population involved was all available patients who complied with the inclusion criteria during the study period.

The study population of epilepsy patients in the Dr Kenneth Kaunda District was unknown, especially patients who have had a change in regimen. To represent the estimated statistics of the total population treated at the public hospital, the study population consisted of all epilepsy patients who complied with the selection criteria visiting the hospital pharmacy during the four-month data capturing period to collect their epilepsy medication. This period was chosen to give all participants an equal chance to be selected, as medication was provided to patients on a monthly basis. The study population size was estimated at 30 participants, or
the total participants during the data capturing period. The data capturing period was May 2016 to August 2016.

No sampling was done in this study. All patient files that complied with the selection criteria had been identified by a fieldworker in the outpatient department of the hospital pharmacy. Selection of patient files took place as soon as the study was approved by the Health Research Ethics Committee (HREC) and the North West Department of Health: Policy, Planning, Research, Monitoring and Evaluation (PPRM&E) and the CEO of Tshepong-Klerksdorp Hospital Complex.

1.5.3.1 Inclusion criteria

The following inclusion criteria were used to select the study population:

- All adult patients (above 18 years) with epilepsy on antiepileptic drug therapy between 1 January 2014 up until 30 June 2016 (irrespective of gender and presence of concurrent disease) who visited the outpatient department of the hospital pharmacy during the data capturing period.
- All patients on treatment for longer than six consecutive months.
- All patient files that were available in the hospital in the data collection period, between May and August 2016.

1.5.3.2 Exclusion criteria

The following exclusion criteria were used to deselect patient files in the study population:

- Patients who had been referred to another district or sub-district or clinic within the period between 1 January 2014 and 30 June 2016, causing gaps in the data, with less than six consecutive months' medical records.
- Patients diagnosed with medical conditions other than epilepsy for which they received antiepileptic drugs as treatment, such as anxiety or restless leg syndrome.

1.6 Data collection tool

Data were collected based on information that was visible in the patients' files. The collection tool was only used by the researcher and data were collected using a designed template, after which the data were then transferred into a Microsoft Excel template.
1.6.1 Development of data collection tool

Retrospective data from patient files were used and collected on a Microsoft Excel template, which was designed to collect information for each participant on the data fields as listed below (refer to Annexure A).

The following data fields were captured from patient files:

- Gender
- Date of birth (age)
- Weight (kg)
- Date of epilepsy diagnosis
- Date of prescription refill - this was used to determine the MPR. Refer to 1.8.2
- Treatment
  - Antiepileptic drug, dosage and frequency – this was used to calculate the prescribed daily dose
  - Amount of antiepileptic drugs dispensed to the patient – this was used to determine the MPR
- Seizure frequency
  - Date of consultation where seizure breakthrough is reported and documented by the medical practitioners in the patients’ medical files over a period of six to 24 months
  - Number of seizures documented by the medical practitioners in the patients’ medical files
- Drug serum levels
  - Date of blood specimen collection
  - Value of drug therapeutic levels
- Regimen change
  - Date of regimen change - by comparing consecutive prescriptions
  - Reason for changing antiepileptic treatment regime - reviewing reasons provided by the healthcare professionals
- Other medication used over the study period (which might cause side-effects or drug-drug interactions)

1.6.2 Validity and reliability of the data collection tool

Validity and reliability of the research collection tool influenced the probability of the study significance during the data analysis. Validity and reliability were concerned with how specific
the measurements or indicators for this study were developed (Neuman, 2014: 31). This influenced the conclusion based on the results.

The patients’ medical records are rich sources of data when conducting clinical research (Gregory & Radovinsky, 2012:108; Dhone et al., 2014:182). Research strategies for reliable data collection from the patient’s medical record included the development of a precise data collection tool that correlated with the reliability of the data. Gregory and Radovinsky (2012:108) have also found that patient medical record data that is collected via retrospective study methods contributes to at least 25% of the scientific articles that are published in clinical journals.

Reliability was used to determine what level the instrument could be depended on to provide consistent results if the study should be repeated (Brink et al., 2012:168). Reliability of the data were ensured as only the researcher completed the data collection tool and therefore possible errors that might have occurred if more people were involved in collection had been eliminated. The data collection tool was in a table format and easy to complete (see Annexure A). Personnel from clinical pharmacy and pharmacy practice at the School of Pharmacy, NWU, evaluated the data collection tool to ensure that significant information would be captured. No patient name or ID number were documented during data collection and anonymity of the patient was ensured as discussed in 1.10.2.

1.7 Data collection process

The pharmacy manager gave goodwill permission prior to the start of the study after ethical approval and allocated a pharmacist, working permanently in the hospital pharmacy, as fieldworker to assist in this study by identifying epilepsy patient files that adhered to the inclusion criteria. A pharmacist was an appropriate fieldworker in the study, since the pharmacist had the necessary knowledge to identify the epilepsy patient files that adhered to the inclusion criteria. Training was given by the researcher to the fieldworker on how to identify patient files for the study. Patients presented their medical files at the hospital pharmacy to collect new prescriptions’ medication. This gave the fieldworker the opportunity to identify epilepsy patients, when antiepileptic drugs were dispensed and their files, which revealed if the patient was diagnosed with epilepsy, that complied with the inclusion criteria used in this study.

Once the patient file had been identified in the outpatient department of the hospital pharmacy, the fieldworker recorded the patient file number on a list provided by the researcher. The fieldworker also marked the patient’s medical file with a coloured sticker on the inside of the
file’s cover page. These measures prevented the patient’s information being duplicated by the researcher during the data collection period between May and August 2016. The fieldworker kept the patient files aside on data capturing days and provided these files to the researcher, who analysed and collected the patient data in a private office in the hospital pharmacy. The researcher evaluated if the patient’s medical file complied with the selection criteria. The patient data were recorded by the researcher on a paper document template in the private office of the hospital pharmacy. After the researcher had collected the necessary patient information from the patient’s medical files it was handed to the fieldworker, who returned them to the hospital’s filing room at the end of each day of data collection.

Responsibilities of the fieldworker were:

- To identify files of patients who had been diagnosed with epilepsy and who had six to 24 consecutive month’s patient data between 1 January 2014 and 30 June 2016.
- To document these patient file numbers on a list provided by the researcher.
- To mark the identified files with a coloured sticker on the inside of the cover page to prevent patient data duplication.
- To hand these files to the researcher for documentation of data.

Data capturing took place two days a week on Microsoft Excel in a private office in the pharmacy of Tshepong Hospital in Dr Kenneth Kaunda District, North West Province. The identification of patient files took place over a four-month data capturing period, from May to August 2016, to ensure that all possible participants had an equal chance to be selected. The selection of patient files took place after ethical approval and permission from the Health Research Ethics Committee (HREC), Faculty of Health Sciences, North-West University and the North West Department of Health: Policy, Planning, Research, Monitoring and Evaluation (PPRM&E) and the Klerksdorp-Tshepong Hospital Complex was obtained.

1.8 Study variables

The different study variables were:

- **Age** (using date of birth)
- **Gender**: male or female
- **Prescribing patterns** of antiepileptic regimen
  - Type of antiepileptic drug
  - Dosage and frequency of dosing – used to calculate the prescribed daily dose
  - Treatment period – the number of month’s data per patient
Number of prescriptions per antiepileptic drug per patient during the study period
Number of antiepileptic drugs (AEDs) prescribed per patient – used to determine if a patient was on mono- or polytherapy

### Adherence status
- Number of days supplied with antiepileptic drug by the hospital pharmacy during the study period. This was used to calculate the MPR
- Medicine possession ratio

According to Andrade et al. (2006:567), the medication possession ratio (MPR) is a good measurement to determine patient adherence. Although the calculation of MPR varies, it is estimated by the majority as the proportion or percentage of days’ supply of medication dispensed during a specified follow-up period divided by the number of days from the first dispensing to the end of the follow-up period (Andrade et al., 2006:569).

\[ MPR \% = \frac{\text{Number of days supply of AED (between 1 Jan 2014 and 30 June 2016)}}{\text{Number of days in observation period}} \times 100 \]

This measurement was dependent on the number of prescriptions filled out in the time frame of six to 24 months (between 1 January 2014 and 30 June 2016) and the number of tablets dispensed by the pharmacist at every visit. This was used to determine the proportion of days covered, reflecting the possession of the prescribed medication(s) throughout the year to be able to treat his/her epilepsy. Patients with a MPR of 0.8 or 80% or more were considered to be adherent (Ettinger & Baker, 2009:60).

The MPR was interpreted as follow:

<table>
<thead>
<tr>
<th>Adherence status</th>
<th>As percentage</th>
<th>As ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undersupply</td>
<td>&lt; 80%</td>
<td>&lt; 0.8</td>
</tr>
<tr>
<td>Acceptable</td>
<td>≥80 and ≤110%</td>
<td>≥0.8 and ≤1.1</td>
</tr>
<tr>
<td>Oversupply</td>
<td>&gt; 110%</td>
<td>&gt;1.1</td>
</tr>
</tbody>
</table>

### Serum drug concentration

The value of the serum antiepileptic drug therapeutic level was provided to the hospital by the National Health Laboratory Service (NHLS) and this value was documented in each patient’s file. The researcher collected this therapeutic drug value from the patient file and did not obtain any result from the NHLS. This laboratory results confirmed whether the patient was compliant with his/her antiepileptic drug regime or whether the patient was using the correct therapeutic dosage to prevent an epileptic seizure.

Serum drug levels as tool for therapeutic drug monitoring (TDM) can be used to determine adherence per antiepileptic drug (AED) (Milosheska et al., 2015:25;
Each AED has a therapeutic range, which indicates the therapeutic serum drug levels (Milosheska et al., 2015:36). The serum drug levels per AED can be compared with the therapeutic range and either be classified as therapeutic (within the drug therapeutic range), subtherapeutic (below the therapeutic range) and supratherapeutic (above therapeutic range) (Lertsinudom et al., 2014:83; Gauser & Peppenger, 2000:6).

- **Seizure frequency** was dependent on the antiepileptic regimen, patient adherence and the correct documentation thereof.

- **Change in antiepileptic regimen**
  - Change in regimen occurred: Yes/No – this was determined by comparing consecutive prescriptions
  - Reason for regimen change as documented by healthcare practitioner in the patients’ medical file
  - Type of change that was evident in the prescriptions

### 1.9 Statistical analysis

Data collected were summarised and statistically analysed with the assistance of a statistician employed by the NWU. All variables were expressed using descriptive statistics, such as frequencies (n), percentages (%), means, standard deviations (SD) and 95% confidence intervals (CI). The data were analysed by using SPSS programme version 22.0 (IBM Corp., Armonk, NY:IBM Corp).
### Table 1-1: Statistical analysis

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Measurements</th>
<th>Independent</th>
<th>Dependent</th>
<th>Descriptive</th>
<th>Reference in Chapter 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describe the prescribing patterns of antiepileptic drugs (AEDs)</td>
<td>Gender of patients per AED</td>
<td>-</td>
<td>Gender</td>
<td>Frequency (%)</td>
<td>Table 3-2</td>
</tr>
<tr>
<td></td>
<td>Number of patients per age group</td>
<td>-</td>
<td>Number of patients per age group</td>
<td>Frequency (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment period per patient over the study period</td>
<td>-</td>
<td>Treatment period</td>
<td>Frequency (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency of dosing</td>
<td>-</td>
<td>Frequency of dosing</td>
<td>Frequency (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of patients</td>
<td>-</td>
<td>Number of patients on specific AED/ total number of patients</td>
<td>Frequency (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of patients per gender</td>
<td>Gender</td>
<td>Type of AED</td>
<td>Frequency (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The average number of prescriptions per patient over the study period</td>
<td>Number of prescriptions per patient</td>
<td>Type of AED</td>
<td>Mean ± SD (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PDD per patient per AED</td>
<td>PDD</td>
<td>Type of AED</td>
<td>Mean ± SD (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Establish the adherence</td>
<td>Adherence status per AED over the study period</td>
<td>Adherence status</td>
<td>Type of AED</td>
<td>Frequency (%)</td>
<td>Table 3-4</td>
</tr>
<tr>
<td>Determine the influence of adherence and/or regimen change on serum drug levels and therapeutic drug levels</td>
<td>Prevalence of change in AED regimen per patient</td>
<td>Change in antiepileptic regimen per patient</td>
<td>Type of AED</td>
<td>Frequency (%)</td>
<td>Table 3-6</td>
</tr>
<tr>
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</tr>
<tr>
<td>Identify the prevalence of change in AED regimen and reason(s) for change</td>
<td>Reasons for regimen change</td>
<td>Reasons for regimen change</td>
<td>-</td>
<td>Frequency (%)</td>
<td>Figure 1</td>
</tr>
<tr>
<td></td>
<td>Types of regimen change</td>
<td>Types of regimen change</td>
<td>-</td>
<td>Frequency (%)</td>
<td>Figure 2</td>
</tr>
<tr>
<td>Serum drug levels per AED</td>
<td>Serum drug levels</td>
<td>Type of AED</td>
<td>Frequency (%)</td>
<td>Table 3-5</td>
<td></td>
</tr>
<tr>
<td>Average number of seizures over the study period per AED</td>
<td>Seizure frequency</td>
<td>Type of AED</td>
<td>Frequency (%)</td>
<td>Mean ± SD (95% CI)</td>
<td>Table 3-6</td>
</tr>
<tr>
<td>The influence of regimen change per AED on adherence status and seizure frequency</td>
<td>Regimen change</td>
<td>Adherence status</td>
<td>Frequency (%)</td>
<td>Table 3-7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seizure frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AED: antiepileptic drug; SD: standard deviation
1.10 Ethical considerations

The ethical considerations are discussed next.

1.10.1 Permission and goodwill consent

Permission to use the data in patient medical files at Tshepong Hospital in the Dr Kenneth Kaunda District in the North West Province was obtained from:

- The Health Research Ethics Committee (HREC) of the Faculty of Health Sciences, at the North-West University (Ethics number: NWU-00369-15-S1).
- North West Department of Health: Policy, Planning, Research, Monitoring and Evaluation (PPRM&E) directorate.
- Goodwill permission by the hospital CEO.
- Goodwill permission by the pharmacy manager.

1.10.2 Anonymity

The data were collected only by the researcher from the individual patients’ files in a private office of the hospital pharmacy. No patient file was taken from the hospital premises. The fieldworker did not capture the patients’ names or identification numbers, but only the patient file number, ensuring that anonymity was maintained. The outpatient population was not aware of the coloured stickers that the fieldworker had put on the inside of the patient file’s cover page and therefore the identification of epilepsy patients by the outpatients was eliminated. Anonymity could further be maintained because no patient name was recorded by the researcher. No information was published that could cause any participant to be identified.

1.10.3 Confidentiality

Only the researcher, study leaders and the statistician had access to the data collected from the research participants. The fieldworker, who agreed to assist with this study, only signed the goodwill permission, as the permanent employee contract of the NW DoH already accounted for protecting patient confidentiality in the hospital pharmacy setting. Confidentiality of the patient was reserved as the fieldworker did not have direct contact with the patient, but only identified patients using antiepileptic drugs and handled their medical files. No patient name was recorded by the fieldworker, but only the patient file numbers in order to obtain the files from the hospital’s filing room. This ensured confidentiality of patient data. The fieldworker presented the identified files to the researcher, who only collected the necessary data (as in
the data collection tool) from the patient files. The researcher did not have contact with any of the patients.

All efforts were made to ensure the privacy of the participants. The researcher kept the data anonymous. The hard copy data collection sheet and the electronic Excel sheet were kept safe with the researcher and the research entity Medicine Usage in South Africa (MUSA) after the study (see 1.10.4 on data management and storing).

1.10.4 Data management and storing

The data were collected from the selected patient files in a private office in the hospital pharmacy and the data collection tool was used, which the researcher had designed (see Annexure A). The identified files were presented to the researcher by the fieldworker after the patient had received his/her medication in the outpatient department of the hospital pharmacy or as soon as identified patient files had been retrieved from the hospital's filing room using the list of identified patient file numbers. This data were collected on hardcopies at the pharmacy on data capturing days and converted on the electronic format on a Microsoft Excel data sheet.

Patient files were only in the researcher's possession during data capturing, after which the files were handed back to the fieldworker. The fieldworker was unaware of the type of data the researcher captured and returned the selected files to the hospital's filing room at the end of each work day. The hardcopy of the patient list of file numbers was kept safe in a locked cupboard in the researcher's office and electronic data were protected from unauthorised persons by means of a password protected computer for the duration of the study. According to the NWU guidelines, after the study had been completed, the data were stored at the NWU for safe keeping in the office of the research entity, Medicine Usage in South Africa (MUSA). Hardcopies were shredded and electronic files formatted in the presence of the research assistant of MUSA. The electronic data is stored on a dedicated external hard drive and, according to the NWU guidelines, the data will be destroyed after seven years.

1.10.5 Respect for research participants

Feedback regarding the outcome of the study was provided to the hospital CEO and the pharmacy manager by means of an oral presentation and the manager's time was taken into consideration. The researcher did not demand time from the managers during the study. The researcher respected the time of the fieldworker and data capturing days were corresponded to the fieldworker prior to the onset of the data capturing period. The responsibility of data
catering rested only on the researcher during the data capture period between May and August 2016.

1.10.6 Benefit-risk ratio analysis

1.10.6.1 Anticipated benefits

The anticipated benefits of this study were the contribution to knowledge about patient adherence patterns and the effect on regimen change in epilepsy patients in order to improve healthcare and this could help the North West Department of Health to implement strategies to improve adherence. This could improve patients’ healthcare and wellbeing.

1.10.6.2 Direct benefits

There were no direct benefits to the participants of this research project, because the researcher was not directly involved with the patient.

1.10.6.3 Indirect benefits

- The indirect benefits are that the information used in this study can be used to gain more knowledge and improve health care delivery to epilepsy patients, as health policy decision-makers use observational data.
- This study could contribute to improve patient healthcare and the wellbeing of antiepileptic patients in the Dr Kenneth Kaunda District and the North West Department of Health.

1.10.6.4 Anticipated risks and precautions

The anticipated risks associated with this study were medium.
Table 1-2: Anticipated risks to the participants and precautions taken

<table>
<thead>
<tr>
<th>Risk</th>
<th>Precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>The identification of the patients whose data were used</td>
<td>Neither the name nor the ID number of the patient was captured by the researcher during data collection. The fieldworker only documented the identified patient file numbers on a list provided by the researcher. This list was in the researcher’s possession after the page had been completed by the fieldworker and kept safe and stored with the hard copy data (see 1.10.4 on data management). A coloured sticker was placed on the inside of the patient’s file cover page. These measures were taken to prevent the duplication of data and did not contribute to the identification of the patient. Goodwill permission between the fieldworker, pharmacy manager and the researcher was in place to secure the patients’ identity.</td>
</tr>
<tr>
<td>Financial implications to the participant</td>
<td>There was no economic risk to the patient, as no financial burden rested on the patient to be part of this study.</td>
</tr>
<tr>
<td>Time of fieldworker</td>
<td>Identification of patient files that complied with the criteria for this study and documenting the patient’s file number and date of birth might have been time consuming for the fieldworker. The researcher negotiated and communicated suitable dates for data capturing to the pharmacy manager and the fieldworker.</td>
</tr>
</tbody>
</table>

The benefits for conducting this study **outweighed the risks** associated if anonymity and confidentiality were maintained. There was no conflict of interest regarding the results of the study.

1.11 Chapter summary

In this chapter the background to the study was described, as well as the research aims and the research methodology. In the next chapter epilepsy will be discussed under the following headings: background, antiepileptic drugs, treatment changes and seizure frequency.
CHAPTER 2: LITERATURE STUDY

2.1 Introduction

In this chapter the following are discussed:

- Epilepsy: definition, epidemiology, etiology and classification
- The pharmacologic treatment of epilepsy, antiepileptic drugs (AEDs), available in the public hospital setting in South Africa: prescribing patterns according to the Standard Treatment guidelines (STG) and Essential Medicine List (EML) of South Africa, side-effects of AED, drug-drug interactions and stigma in epilepsy patients
- Adherence: different methods of determining adherence, factors that influence adherence and the medicine possession ratio (MPR)
- Therapeutic drug monitoring (TDM)
- Seizure frequency
- Regimen changes

2.2 Background on epilepsy

In this section different aspects of epilepsy are discussed.

2.2.1 Definition of epilepsy

Epilepsy is defined as a neurological disorder characterised by two or more epileptic seizures, with or without unpredictable convulsions (Angus-Leppan & Parsons, 2008:571; Wells, 2009:577; McNamara, 2006:501) and can range from a brief sensory experience to convulsive status epilepticus (Angus-Leppan & Parsons, 2008:571). A seizure, as result of the abnormal functioning in the brain cell’s electrical activity (Dekker, 2002:3), can be measured with an electroencephalogram (EEG), whereas a convulsion is described as a violent, involuntary contraction of the voluntary muscles in the body (Rogers & Cavazos, 2008:928). This change in the brain’s local synaptic environment can cause a focal (or partial) seizure, or when more parts in the body are influenced by this change in synaptic environment a generalised seizure occurs (Angus-Leppan & Parsons, 2008:574). A seizure can also be accompanied by loss of consciousness or control of bowel or bladder function (WHO, 2015a).

2.2.2 Epidemiology

An estimated 50 million people worldwide is diagnosed with epilepsy (Banjeree et al., 2009:32; WHO, 2015a) of whom nearly 80% of these patients are found in developing regions (WHO,
2015a). Epilepsy prevalence is the proportion of any population affected by epilepsy at a given time, whereas incidence is the rate of occurrence of new cases in a population over a given time period (Bell et al., 2014:958). Increased prevalence and incidence of epilepsy may be related to limited access to health care, low socio-economic status and environmental exposures (Banerjee et al., 2009:31). The prevalence of active epilepsy around the world is estimated to be four to ten patients per 1 000 people (Angus-Leppan & Parsons, 2008:571), whereas a higher prevalence of up to 15 patients per 1 000 people has been reported in rural areas of countries in sub-Saharan Africa (Forsgren, 2008:21; WHO, 2005; Bell et al., 2014:958). The incidence of epilepsy differs throughout the world (Bell et al., 2014:958) and in the first world countries it is estimated at 50 per 100,000 people per year (Angus-Leppan & Parsons, 2008:571). According to the government of South Africa’s medical scheme, GEMS (2011), the prevalence of epilepsy in South Africa is 1 in 100 people. The incidence of epilepsy, according to Bell et al. (2014:958), seems to be higher in low income countries, but the lifetime prevalence is the same throughout the world. According to Dekker (2002:6) the African country with the most epilepsy cases is Caberoon with 58 patients per 1 000 people, followed by Tanzania with 38 patients per 1 000 people and Liberia with 28 patients per 1 000 people. The lifetime prevalence of epilepsy is more similar in all countries and is estimated to be 2-5% of a population, excluding the occurrence of febrile seizures (Bell et al., 2014:960; Angus-Leppan & Parsons, 2008:571).

Epilepsy starts at any age, with peak incidences in the early and late stages of life (Angus-Leppan & Parsons, 2008:571; Banerjee et al., 2009:32; De Boer et al., 2008:540). It is difficult to keep record of and interpret these cases because of methodological issues (Bell et al., 2014:958). Some of the other reasons of incorrect prevalence statistics of epilepsy are:

- The difference in the definition of epilepsy is a reason for the uncertainty in epilepsy incidence (Smithson et al., 2012:52; Bell et al., 2014:958).
- Cultural stigma might be a reason for not seeking medical treatment (Zabcevic et al., 2002:26). The prevalence can be inaccurate as a result of not identifying individuals with epilepsy who have not accessed health care for their condition.
- Reported incidences of epilepsy are higher in resource-poor countries (Bell et al., 2014:960).
- Limited comparison about epilepsy incidence around the world is available because of a lack of door-to-door studies (Bell et al., 2014:958).
- The peak incidence of epilepsy is in younger patients, of whom two-thirds go into remission after long antiepileptic treatment and older people (Angus-Leppan & Parsons, 2008:572; Schacther, 2008:676).
Epilepsy is associated with at least twice the standardised mortality ratio in a population and in economically disadvantaged countries epilepsy is even more common (Angus-Leppan & Parsons, 2008:571). This might be because fewer resources in these countries exist. Insufficient health and care delivery systems, limited access to treatment (De Boer et al., 2008:542; Banerjee et al., 2009:31; Forsgren, 2008:22), as well as and poverty (Preux & Druet-Cabanac, 2005:21) can explain the higher incidence of epilepsy in third world countries. The variations in the definitions of active epilepsy are a reason for the uncertainty in epilepsy incidence (Bell et al., 2014:958; Angus-Leppan & Parsons, 2008:571), as well as the absence of sound methods to collect and standardise data (Preux & Druet-Cabanac, 2005:21; Bell et al., 2014:958; Angus-Leppan & Parsons, 2008:571). The management of epilepsy in rural areas is poor, as cultural stigma might be a cause of not seeking medical treatment (Zabcevic et al., 2002:26; Banerjee et al., 2009:32). The social stigma of epilepsy in certain culture groups from western and central Africa, as well as the insufficiency of data collection may be a leading cause of the low incidence reports in South Africa.

2.2.3 Etiology

The causes of epilepsy are categorised (Banerjee et al., 2009:33; Angus-Leppan & Parsons, 2008:574), which include idiopathic (which has an assumed genetic basis and an onset during childhood occurring in a third of patients) symptomatic or congenital (following a known brain injury) and cryptogenic or acquired (cause is unknown, but could be identified with further investigation) (Rogers & Cavazos, 2008:927). Refer to section 2.2.1 for definitions of seizures and epilepsy. The higher rates in developing countries are thought to be caused by conditions such as infections (neuro-cysticercosis, HIV/AIDS and malaria), trauma and metabolic imbalances (WHO, 2005; Banerjee et al., 2009:31; Angus-Leppan & Parsons, 2008:571). The most common cause of epilepsy in the developing world is infection (Angus-Leppan & Parsons, 2008:578; Siddiqi & Birbeck, 2013:531). Causes of seizures in HIV positive patients can be related to infection, such as tuberculous meningitis, toxoplasmosis and encephalopathy (Siddiqi & Birbeck, 2013:531). In developing countries this may be resultant to limited access to health care, low socio-economic status and environmental exposures (WHO, 2005; Banerjee et al., 2009:31; Angus-Leppan & Parsons, 2008:571). In the developed countries the most common causes of epilepsy are vascular disease, trauma and tumors (Angus-Leppan & Parsons, 2008:578). Other causes of seizures can be fever (febrile seizures), intoxication, substance abuse or withdrawal, acute neurological insults (Banerjee et al., 2009:42) or hyperventilation, causing absence seizures (Rogers & Cavazos, 2008:927). Emotional stress, sensory stimuli, sleep disorders and sleep deprivation can trigger or increase seizure frequency (Rogers & Cavazos, 2008:928).
2.2.4 Classification of epilepsy

Accurate classification of seizure type depends on the precision of patient history taking, availability, the correct use of diagnostic tests and the patient’s age at which the seizure type was classified (Banerjee et al., 2009:38). Careful medical history documentation and correct interpretation of clinical information are the cornerstones of accurate diagnosis and patients should be encouraged to keep a seizure dairy as this could assist in the successful treatment of epilepsy (Pellock et al., 2004:305; Department of Health, 2012:14.5; Rogers & Cavazos, 2008:927). Misdiagnosis in epilepsies is a major medical problem, as it has serious repercussions, such as the denial of specific treatment or the provision of inappropriate treatments (Panayiotopoulos, 2005:4).

Seizure types can be classified into two major categories: partial or focal seizures, where the seizures begin in a part of the brain (Gadhoumi et al., 2016:280; Panayiotopoulos, 2005:17; Rogers & Cavazos, 2008:927) and generalised seizures, where the seizure involves the entire brain (Banerjee et al., 2009:38; Schachter, 2008:675; Rogers & Cavazos, 2008:928). The old term ‘focal’ is re-introduced to replace ‘partial’ (Panayiotopoulos, 2005:18) and is sometimes used interchangeable. See Table 2-1 for the international classification of epileptic seizures.

Simple partial seizures occur without the loss of consciousness (Banerjee et al., 2009:33; Panayiotopoulos, 2005:18) and present a subjective sensory experience (auditory, visual, autonomic or touch) or a motor manifestation (myoclonic, clonic, tonic or dystonic) (Angus-Leppan & Parsons, 2008:573; Wells, 2009:579; Schachter, 2008:674; Stephan & Hopfengarter, 2009:564-565). Behavioural manifestations are not always reported and may be difficult to interpret (Mula & Sander, 2007:558).

Generalised seizures can be categorised as myoclonic, tonic-clonic or absence seizures (Schachter, 2008:675) (see Table 2-1). Myoclonic seizures are described as the sudden and irregular movement of the head, trunk and limbs or as a combination that occurs early in the morning (Angus-Leppan & Parsons, 2008:573; Schachter, 2008:676).

Clonic seizures are the rhythmic and symmetrical shaking of limbs, face and neck that can be caused by focal or generalised epilepsy; whereas tonic seizures are associated with stiffness and the extension of limbs and trunk due to focal or generalized epilepsy (Angus-Leppan & Parsons, 2008:573).

Generalised tonic-clonic (GTC) seizures can be preceded by an aura syndrome, which may include symptoms such as nausea, twitching of one side of the body, fear or a metallic taste in the mouth (Schachter, 2008:676; Panayiotopoulos, 2005:15), after which a sudden short
tonic contraction of muscles, followed by a period of clonic movements or muscular contractions of the trunk, face and extremities can occur (Banerjee et al., 2009:33; Rogers & Cavazos, 2008:929). During the seizure the patient may lose sphincter control, bite the tongue or develop cyanosis and after the seizure the patient may be confused or go into a deep sleep (Rogers & Cavazos, 2008:929). Generalised absence seizures, or petit mal, are a sudden loss of awareness which may last less than 10 seconds (ILAE, 2016; Angus-Leppan & Parsons, 2008:572-573) occurring many times a day and may include staring, rapid flickering of the eyes and quick clonus of the eyelids, face or limbs for episodes (Schachter, 2008:675; Angus-Leppan & Parsons, 2008:572-573). These seizures may be underdiagnosed due to its partial onset and the difficulty to determine this type of seizure by clinical methods alone (Preux & Druet-Cabanac, 2005:24-25). Atonic seizures are a sudden loss of muscle tone such as the dropping of a limb, head drop or sudden fall to the ground (Wells, 2009:579; Angus-Leppan & Parsons, 2008:573). Some epilepsies can present an epilepsy syndrome – the combination of clinical manifestations, such as simple partial and tonic-clonic seizures and can be caused by a tumor (Angus-Leppan & Parsons, 2008:571). Unclassified seizures can also occur (Brown et al., 2009:637; Lie et al., 2015:30; Luciano & Shorvon, 2007:377), which are neither focal nor generalised seizures but rather spasms, that cannot be classified due to incomplete or inadequate data (Panayiotopoulos, 2005:17).

See Table 2-1 for the summary on the international classification of epileptic seizures as described above.
Table 2-1: International classification of epileptic seizures – also applicable in South Africa.

<table>
<thead>
<tr>
<th>Classification</th>
<th>ICD10-codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial (or focal) seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple2</td>
<td>G40.1</td>
<td>No alteration of consciousness. Simple partial seizures can develop into secondarily generalised seizures.</td>
</tr>
<tr>
<td>Complex</td>
<td>G40.2</td>
<td>Alteration of consciousness, often with automatisms. Complex partial seizures can develop into secondarily generalised seizures.</td>
</tr>
<tr>
<td>Idiopathic3</td>
<td>G40.0</td>
<td>Benign childhood epilepsy with EEG spikes. Childhood epilepsy with occipital EEG paroxysms.</td>
</tr>
<tr>
<td>Generalised seizures1,2,3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>G40.3</td>
<td>Benign: myoclonic epilepsy in infancy neonatal convulsions (familial) Childhood absence epilepsy Epilepsy with grand mal seizures on awakening Juvenile: absence epilepsy myoclonic epilepsy [impulsive petit mal] Nonspecific epileptic seizures: atonic clonic myoclonic tonic tonic-clonic</td>
</tr>
<tr>
<td>Other</td>
<td>G40.4</td>
<td>Epilepsy with: myoclonic absences myoclonic-astatic seizures</td>
</tr>
<tr>
<td>Special cases3</td>
<td>G40.5</td>
<td>Seizures related to: alcohol drugs hormonal changes sleep deprivation stress</td>
</tr>
<tr>
<td>Unspecified seizures3</td>
<td>G40.9</td>
<td>Epileptic fits or convulsions</td>
</tr>
<tr>
<td>Status epilepticus3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G41.0</td>
<td>Grand mal</td>
<td></td>
</tr>
<tr>
<td>G41.1</td>
<td>Petit mal</td>
<td></td>
</tr>
<tr>
<td>G41.8</td>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>
EEG: Electroencephalogram; ICD: International classification of disease

1: Wells (2009:579)
3: WHO (2015b)
4: Panayiotopoulos (2005:17-20)

Status epilepticus (SE) is prolonged or repeated “seizures without full recovery in between” and convulsive status epilepticus is considered a medical emergency (Schachter, 2008:674; Angus-Leppan & Parsons, 2008:573). Non-adherence to treatment or antiepileptic drug withdrawal is the leading cause of SE, which is associated with sudden death (Brodtkorb et al., 2016:2, 8). Continuous convulsions for more than 30 minutes are seen as a medical emergency as it may cause neurological damage (Angus-Leppan & Parsons, 2008:574; Lie et al., 2015:29).

In most cases, a health care provider will not witness an epileptic seizure and because the epilepsy patient is amnestic to the actual seizure event, an accurate diagnosis is difficult to make, as the health care provider has to rely on accurate history and description of the event (Schachter, 2008:675; Wells, 2009:577). The patient and family should record the frequency and duration of a seizure, as well as precipitating factors, time of occurrence, presence of aura and state of consciousness. There are no point-of-care diagnostic tests for epilepsy. Laboratory tests are used to determine the serum drug concentration (Landmark et al., 2015:90) and may be performed on blood or urine samples to rule out other treatable causes of seizures, such as hypoglycaemia, altered serum electrolyte concentrations or infections (Stefan & Hopfengartner, 2009:653; Rogers & Cavazos, 2008:927). A false diagnosis can be made in the absence of an EEG recording, because the various phenomena are often incorrectly identified as intoxication or a psychotic state (Stefan & Hopfengartner, 2009:655).

2.3 Antiepileptic treatment

The primary treatment goal and desired outcome are to achieve complete limitation of seizures and without causing adverse events ensuring an optimal quality of life (Pellock et al., 2004:301; Rogers & Cavazos, 2008:928; Stefan & Hopfengartner, 2009:653; Wassenaar et al., 2016:421; Dekker, 2002:58). This goal can be achieved by treating the underlying cause (Schachter, 2008:675) and ensuring patient adherence to the treatment, allowing the patient to live as normal as possible (Rogers & Cavazos, 2008:929). Modern medical treatment aims not only to prevent seizures but also to avoid negative effects on cognitive function and emotional, physical and general well-being (Brown et al., 2009:634). To ensure optimal quality of life, the concerns of the patient, such as the future, safety, depression and social stigma
should also receive attention by medical practitioners (Rogers & Cavazos, 2008:928). According to Brown et al. (2009:634), approximately 60% of patients with epilepsy achieve full control of their seizures with antiepileptic drugs.

Accurate diagnosis and classification of the seizure type are critical in selecting the appropriate pharmacotherapy and pharmaceutical care plan (Rogers & Cavazos, 2008:927, 929). A single unprovoked seizure is not an indication for treatment (Department of Health, 2012:14.5). Current medical therapies successfully eliminate seizures in up to two-thirds of patients (Schachter, 2008:674) and up to 35% of patients may be refractory to treatment and seizure freedom not obtained (Rogers & Cavazos, 2008:929). Despite the fact that antiepileptic drugs (AEDs) are highly effective and low-cost treatments are available, as many as 9 out of 10 people with epilepsy in Africa go untreated (De Boer et al., 2008:540). According to Forsgren (2008:21), the estimated number of people that do not receive the appropriate treatment is as high as 90% of the epilepsy population in sub-Saharan Africa. Medication should be given to epileptic patients for many years, sometimes lifelong (Dekker, 2002:58).

2.3.1 Prescribing patterns on antiepileptic drug regime

The drug regime is dependent on the type of epilepsy, the drug-specific side-effects and patient factors, such as preference and adherence ability (Wells, 2009:580; Rogers & Cavazos, 2008:929-930; Stefan & Hopfengartner, 2009:653). Most patients can be maintained on one AED (Rossiter, 2008:440) as it is efficacious in 50-70% of epilepsy patients (Wassenaar et al., 2016:421; Rogers & Cavazos, 2008:930) and should be altered until seizure control is obtained (Department of Health, 2012:14.5). Epilepsy may demand persistent and long-term therapy (Rankovic et al., 2012:69).

The selection of AEDs, by physicians, are according to the following factors (Schachter, 2008:673, 675):

- Seizure type
- Pharmacokinetic properties of the drug
- Patient age
- Comorbid psychiatric and medical conditions
- Woman of childbearing age
- Potential for side-effects and drug-drug interactions
- Dosage of the AED
- Cost
Monotherapy is associated with better adherence than polytherapy (Brodtkorb et al., 2016:6; Bautista & Rundle-Gonzalez, 2012:437). Therapy should be initiated at a low dose and then increased slowly until the seizures are completely controlled, or until side-effects occur, at which time the dose is lowered (Schachter, 2008:676; Dekker, 2002:62). In patients who are unresponsive to monotherapy, a combination of two or more AEDs should be initiated to optimise seizure control (Sake et al., 2010:1056; Schachter, 2008:676; Department of Health, 2012:14.5; Rossiter, 2008:440), keeping in mind that combination therapy may have more side-effects (Patsalos & Perucca, 2003:347; Rossiter, 2008:440). The addition of a second AED results in 10-30% more patients to have seizure control (Wassenaar et al., 2016:421; Rogers & Cavazos, 2008:930). When a new drug is introduced to the treatment regimen, the initial drug should be continued but the dose gradually reduced over a 6-8 week period until the drug can be stopped (Department of Health, 2012:14.5; Rossiter, 2008:440; Dekker, 2002:62). If the second AED fails and alcohol and poor adherence can be excluded, combination treatment may be required. If the drug causes side-effects, such as overly sedation, immediate discontinuation or lowering of the dose should be considered, as a balance in functioning and seizure frequency should be maintained (Schachter, 2008:676; Rogers & Cavazos, 2008:931). Combination treatment should be considered if the second AED fails to achieve adequate seizure control (Department of Health, 2012:14.5). Regular ingestion of the lowest dose of medication and the smallest number of AEDs are most likely to avoid side-effects, but this depends on patients taking their medication as prescribed (Brown et al., 2009:634).

The prescribed daily dose (PDD) is inversely related to compliance, as the adherence in a once-daily dosage is higher than in three-times-daily dosing (Claxton et al., 2001:1297). Despite the relatively good outlook for the majority of people with epilepsy who receive appropriate treatment, some do not benefit from these effective treatments, either because of limited access to effective drugs or because of non-adherence to available treatment (Smithson et al. 2012:49; Manjunath, et al., 2009:372).

According to the Department of Health (2012:14.5), the following Standard Treatment Guidelines (STG) can be followed in South Africa, according to the practicality of dosing frequency and acceptability of side-effects. Therapy for generalised tonic clonic seizures can be initiated with either carbamazepine, lamotrigine or phenytoin (see Table 2-2) (Department of Health, 2012:14.5). The therapy for epilepsy patients with HIV is summarised in Table 2-3.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>General tonic-clonic or partial seizures</th>
</tr>
</thead>
</table>
| Regime 1 (First-line) 1 | Carbamazepine, oral  
Initiate: 100 mg 12 hourly.  
Increase by 100–200 mg/day at weekly intervals according to seizure control and side-events.  
Usual maximal dose: 600 mg 12 hourly                                                                                                                                 |
| Regime 2 (Second-line) 1 | Lamotrigine, oral  
25 mg daily for 2 weeks, then 50 mg daily for 2 weeks.  
Increase by 50 mg every 2 weeks according to response.  
Maintenance dose: 100–200 mg/day as a single dose or 12 hourly.                                                                                                                                 |
| Regime 3 (Third-line) 1 | Phenytoin  
4.5–5 mg/kg (on lean body mass) daily.  
Usual starting dose in an adult male: 300 mg once daily.  
Dose changes above 300 mg should be done in 50mg increments at intervals no shorter than 2 weeks.                                                                 |
Table 2-3: Regimens of AED dosing for generalised tonic-clonic or partial seizures in patients with HIV

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Generalised tonic-clonic or partial seizures in patients with HIV</th>
</tr>
</thead>
</table>
| Regime 1 (First-line)1 | Due to interactions with ARVs, do not use carbamazepine or phenytoin. Lamotrigine, oral  
25 mg daily for 2 weeks, then 50 mg daily for 2 weeks. Increase by 50 mg every 2 weeks according to response.  
Maintenance dose: 100–200 mg/day as a single dose or 12 hourly. If patient is switched to LPV/RTV, double the lamotrigine dose for two weeks. Use this regimen for HIV-infected women of child bearing age. |
| Regime 2 (Second-line)1 | Valproate, oral  
Usual starting dose: 200–300 mg 12 hourly. Increase every 2 weeks to a maximum daily dose of 1200 mg 12 hourly, if required. |
| Regime 3 (Third-line)1 | If above regimens fail: Add on valproate (regimen 1): Lamotrigine, oral  
Start with 25 mg on alternative days for 2 weeks, then 25 mg daily for 2 weeks. Thereafter increase by 25-50 mg every 2 weeks according to response. |

1: Department of Health (2012:14.5)

ARVs: antiretroviral drugs; HIV: human immunodeficiency virus; LPV: lopinavir; RTV: ritonavir

In pregnancy, a single AED is the ideal regimen (Rogers & Cavazos, 2008:938) and the effective regimen before pregnancy should be continued during pregnancy (Rossiter, 2008:440). Valproate should not be initiated during pregnancy, as it is associated with higher teratogenic potential than other first-line AEDs (Department of Health, 2012:14.7; Rossiter, 2008:440). Because some AEDs lower the folate levels, folic acid supplementation is recommended (Rossiter, 2008:440).

HIV positive patients have an increased risk for developing seizures due to immune dysfunction, metabolic disturbances and associated diseases, causing the central nervous system to be vulnerable (Siddiqi & Birbeck, 2013:529). Interactions occur between AEDs and antiretroviral (ARV) drugs (see section 2.3.4.5).

The first step in the management of status epilepticus, is the quick identification and aggressive treatment of the underlying cause which will terminate a seizure and improve the patient outcome (Lie et al., 2015:29). The sudden withdrawal of AEDs is the leading cause of status epilepticus incidence (Lie et al., 2015:31; Rogers & Cavazos, 2008:931).
According to Lie et al. (2015:31), 31% of patients admitted to stopping or reducing their AEDs without medical advice. Lorazepam, when administered intravenously, is an essential component in any AED tapering strategy (Rizvi et al., 2014:764). Patients may want to stop their antiepileptic treatment due to the desire to have children and the possible risk of teratogenic effects and cognitive development, as well as the cost of newer AEDs (Raymond, 2007:27).

After two to four years of seizure freedom, or complete seizure control after one year of onset, drug withdrawal is considered in some patients, although the risk of relapse should be determined first (Rogers & Cavazos, 2008:931; Raymond, 2007:27). Patients with epilepsy can go into remission spontaneously (Bell et al., 2014:960). Remission in epilepsy is seizure freedom for two to five years (Angus-Leppan & Parsons, 2008:572) and stopping AED treatment can be considered (Raymond, 2007:27). Two-thirds of patients go into remission, either spontaneously (Bell et al., 2014:960) or after a few years of antiepileptic treatment (Angus-Leppan & Parsons, 2008:571; Raymond, 2007:27), while up to 90% of children go into remission before reaching adulthood (Schachter, 2008:676; Raymond, 2007:27).

2.3.2 Antiepileptic drugs

The ultimate goal of AEDs is to eliminate all seizures with no side-effects and an optimal quality of life (Rogers & Cavazos, 2008:929; McNamara, 2006:505). In the past 20 years, eight major new antiepileptic drugs have been licensed that have shown great efficacy in clinical trials (Reijula et al., 2015:29). The optimal doses of AED vary widely between patients due to vulnerability to side-drug effects, variability in seizure responsiveness to medication and the pharmacokinetic properties of the individual drugs (Stefan & Hopfengartner, 2009:653).

In this section, only drugs listed by the STG and EML for South Africa are discussed, which are identified by the Department of Health (2012:14.6) as carbamazepine, lamotrigine, phenytoin, valproate, phenobarbitone and benzodiazepines, such as clonazepam, lorazepam, diazepam, midazolam or oxazepam. Emergency drugs, such as thiopental and propofol are not discussed in this dissertation as these drugs are not seen in repeat prescriptions and are indicated for the acute treatment of status epilepticus (Department of Health, 2012:14.9).

2.3.2.1 Carbamazepine

Carbamazepine is the most common drug in the primary health care setting (Zabcevic et al., 2002:26) and first choice in treating partial and generalised tonic-clonic seizures (Castro et al., 2001:189; Schachter, 2008:677), as well as trigeminal neuralgia (Burianova & Borecka, 2015:886; Schachter, 2008:677). It is generally well tolerated with relatively rare serious side-
effects (Zabcevic et al., 2002:26) (see Table 2-4). The mechanism of action is primarily through the inhibition of voltage-gated sodium channels in the brain (Rogers & Cavazos, 2008:939).

Carbamazepine should be initiated at 100 to 200 mg daily and the dosage increased as needed for seizure control by 100 to 200 mg every 3 to 14 days, which is typically upregulated over a period of 1 to 2 months (Schachter, 2008:677). It is important to remember that carbamazepine underwent auto-induction and that was also the reason for the slow increase of dose over time (Rogers & Cavazos, 2008: 940; Fattore et al., 2006:159). Some patients can be maintained on twice-a-day dosing, while others may need more frequent administration. Bioavailability studies in patients with epilepsy have shown that the carbamazepine modified-release formulations (Tegretol-XR®) administered every 12 hours are bioequivalent to the immediate-release formulations (Degrenol®) when administered 6 hourly (Rogers & Cavazos, 2008: 940; Pellock et al., 2004:304; Garnett et al., 1998:274). The modified-release preparations have shown to simplify the AED regime, improving patient adherence (Pellock et al., 2004:301, 304), while maintaining the drug efficiency to suppress seizures (Garnett et al., 1998:274).

High levels of carbamazepine’s pharmacologically active metabolite, carbamazepine-epoxide can cause symptoms of toxicity, especially in patients with renal disease or in the young with a higher rate of metabolism (Burianova & Borecka, 2015:886). Therefore, the therapeutic and toxic ranges are important. In Table 2-4 the most important pharmacokinetic properties of each AED are summarised. Therapeutic drug monitoring is highly recommended in patients on carbamazepine treatment, as this drug can affect the pharmacokinetics of other AEDs and vice versa, which can cause an increase or decrease of carbamazepine levels – especially in elderly patients (Burianova & Borecka, 2015:886).

2.3.2.2 Phenytoin

Phenytoin is registered for the treatment of partial and generalised tonic–clonic seizures (Schachter, 2008:678). Partial and generalised tonic–clonic seizures are the most frequent seizure types in the elderly and phenytoin is used in this population group because it is a relatively non-sedating drug and it causes less hyponatremia and cardiac rhythm disturbances, especially when compared to carbamazepine (Battino et al., 2004:155-156). The mechanism of action of phenytoin is the inhibition of voltage-dependent sodium channels in the brain (Rogers & Cavazos, 2008:944). Rational prescribing of phenytoin requires an understanding of the non-linear pharmacokinetics (zero order kinetics for its metabolism) of the drug and therefore the narrow therapeutic index of phenytoin (Glauser & Pippenger, 2000:7; Rossiter, 2008:440). This drug is highly protein bound (Milosheska et al., 2015:26)
and enters the brain rapidly, after which it is redistributed to body tissues, breast milk and placenta (Rogers & Cavazos, 2008:944). The bio-availability in a population of healthy volunteers have shown in that the 300-mg modified-release phenytoin sodium is bio-equivalent to three 100 mg capsules of the immediate release formulation of phenytoin (Pellock et al., 2004:304) and oral doses are usually administered once a day at night, while the available intravenous formulation is useful during seizure emergencies (Battino et al., 2004:155). Therapeutic drug monitoring is recommended and the therapeutic range is 10 – 20 µg/ml (Battino et al., 2004:155; Glauser & Pippenger, 2000:13).

2.3.2.3 Phenobarbital

Phenobarbital is registered to be used for partial, generalised tonic-clonic and myoclonic seizures, but is seen as a second-line drug due to its side-effects (Schachter, 2008:678). The mechanism of action of phenobarbital is by interacting with gamma-aminobutyric acid (GABA) receptors which facilitate chloride channel function, as well as inhibiting high voltage-activated calcium channels (Rogers & Cavazos, 2008:944) (see Table 2-4 for pharmacokinetic properties of phenobarbital).

2.3.2.4 Valproate

Valproate or valproic acid is considered as the first-line drug for the treatment of all types of seizures (Doughty et al., 2003:711; Schachter, 2008:678). It is also a registered drug for the treatment of psychiatric disorders such as depression and mania (Fattore et al., 2006:154). Its mechanism of action is to increase GABA, an inhibitory neurotransmitter, reducing glutamate excitation and decreasing the cell stability due to its action on voltage-dependent potassium channels (Rogers & Cavazos, 2008:946; Doughty et al., 2003:710). Valproate is metabolised into ten different metabolites, each with different anticonvulsant activity and the magnitude of clinical response is considered to be related to the unbound valproate concentration in the plasma, which increases during multiple dosing (Fattore et al., 2006:159; Rogers & Cavazos, 2008:946). Valproate is a hepatic enzyme inhibitor, causing various interactions with other drugs (Rossiter, 2008:448). Therapeutic drug monitoring is recommended for valproate (Glauser & Pippenger, 2000:13) and blood drawn for drug levels is best before the morning dose (Rossiter, 2008:448). Patients with a history of myoclonic seizures or typical absence seizures should be treated with valproate as those seizures may be aggravated by phenytoin or carbamazepine (Department of Health, 2012:14.5). According to Fattore et al. (2006:154) valproate is the drug with the most theoretical advantages in elderly patients.
2.3.2.5 Lamotrigine

Lamotrigine might be the best tolerated AED in epilepsy patients and is the most effective first-line treatment for partial seizures and generalised tonic-clonic seizures (Schachter, 2008:677; Rogers & Cavazos, 2008:946). The mechanism of action of lamotrigine is the inhibition of voltage-dependent sodium and high voltage-activated calcium channels in the brain (Rogers & Cavazos, 2008:942). This drug is not an enzyme inducer or inhibitor, but its pharmacokinetics can be affected by other drugs including carbamazepine and valproic acid (Burianova & Borecka, 2015:886). Lamotrigine’s metabolism is induced by some antiretroviral drugs, such as lopinavir, ritonavir and atazanavir and therefore it is advisable to double the lamotrigine dose every 2 weeks when HIV/AIDS patients are switched to a lopinavir/ritonavir- or atazanavir-containing regimen (Department of Health, 2012:14.5) (see Table 2-3).

2.3.2.6 Topiramate

Topiramate is registered for the treatment of partial, generalised tonic-clonic and myoclonic seizures (Schachter, 2008:677-678). Topiramate has various mechanisms of action, such as: the inhibition of voltage-dependent sodium channels, activation of GABA receptors and high voltage calcium channels (Rogers & Cavazos, 2008:946). See Table 2-4 for pharmacokinetic properties of AEDs.

2.3.2.7 Gabapentin

Gabapentin is an available drug in the public hospital sector of South Africa and is indicated in partial seizures and neuropathic pain (Landmark et al., 2015:88; Schachter, 2008:677). This AED is used more in women than in men and routine use of therapeutic drug monitoring (TDM) is most common in patients with epilepsy, because of this drugs’ variable absorption and the individualisation of antiepileptic therapy (Landmark et al., 2015:88).
Table 2-4: Properties of AEDs

<table>
<thead>
<tr>
<th></th>
<th>Carbamazepine</th>
<th>Phenytoin</th>
<th>Phenobarbital</th>
<th>Valproate</th>
<th>Lamotrigine</th>
<th>Topiramate</th>
<th>Gabapentin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>General and partial complex seizures1,5,8</td>
<td>Partial and generalised tonic–clonic2,7</td>
<td>Partial, generalised tonic-clonic and myoclonic seizures7</td>
<td>Partial and generalised seizure types4,7</td>
<td>Partial, generalised tonic-clonic and myoclonic seizures7</td>
<td>Partial, generalised tonic-clonic and myoclonic seizures7</td>
<td>Partial seizures and neuropathic pain9</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>100 mg, 200 mg, 400 mg7</td>
<td>300 mg6</td>
<td>60-240 mg/day7</td>
<td>500-3000 mg/day12</td>
<td>25-50 mg/day7</td>
<td>25-50 mg/day7</td>
<td>Start: 300 mg/day7 Increase every 3 days with 300 mg till tolerated7</td>
</tr>
<tr>
<td><strong>Dosing frequency</strong></td>
<td>Twice daily6</td>
<td>Once daily6</td>
<td>Once or twice7</td>
<td>Once or twice7</td>
<td>Daily to three times per day6</td>
<td>Once or twice6</td>
<td>Daily14</td>
</tr>
<tr>
<td><strong>Vd (L/kg)</strong></td>
<td>0.8-25</td>
<td>0.5-15</td>
<td>0.5-15</td>
<td>0.14-0.235</td>
<td>0.9-1.35</td>
<td>0.6-0.85</td>
<td>0.65-1.45</td>
</tr>
<tr>
<td><strong>t½ (h)</strong></td>
<td>85-3613</td>
<td>305-14013</td>
<td>60-1505,13</td>
<td>12-165,13</td>
<td>15-355</td>
<td>20-305</td>
<td>5-95,9</td>
</tr>
<tr>
<td><strong>Therapeutic serum levels (µmol/L)</strong></td>
<td>12-5010</td>
<td>12-8010</td>
<td>40-13010</td>
<td>350 – 70010</td>
<td>8-8010</td>
<td>6-7510</td>
<td>20-10010</td>
</tr>
<tr>
<td><strong>Time to reach steady state (days)</strong></td>
<td>813</td>
<td>76-3013</td>
<td>14-211</td>
<td>1-31</td>
<td>3-65</td>
<td>4-55</td>
<td>1-25,9,10</td>
</tr>
<tr>
<td>Oral availability (%)</td>
<td>75-855</td>
<td>&gt;805</td>
<td>1005</td>
<td>&gt;905</td>
<td>&gt;955</td>
<td>&gt;805</td>
<td>&lt;605,10</td>
</tr>
<tr>
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<td>---------</td>
</tr>
<tr>
<td>Route of elimination</td>
<td>Carbamazepine</td>
<td>Extensively hepatic5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Extensively hepatic5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
<td>Extensively hepatic5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
<td>Extensively hepatic5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
<td></td>
<td>Renal14</td>
<td></td>
<td>Renal14</td>
<td></td>
<td>Renal14</td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side-effects</td>
<td>Double vision7</td>
<td>Rash7</td>
<td>Headache1,7</td>
<td>Dizziness1,7</td>
<td>Unsteadiness9</td>
<td>Nausea &amp; Vomiting7,11</td>
<td>Rash7</td>
</tr>
<tr>
<td></td>
<td>Headache7</td>
<td>Dizziness1,7</td>
<td>Slurred speech7</td>
<td>Gingival hyperplasia7</td>
<td>Hair growth7</td>
<td>Acne7</td>
<td>Hepatitis7</td>
</tr>
<tr>
<td></td>
<td>Depression7</td>
<td>Sleepiness7</td>
<td>Agitation7</td>
<td>Birth defects7</td>
<td>Tremor7,12</td>
<td>Weight gain7,12</td>
<td>Hair thinning7</td>
</tr>
<tr>
<td></td>
<td>Rash7</td>
<td>Headache7</td>
<td>Nausea &amp; Vomiting7</td>
<td>Insomnia7</td>
<td>Dizziness7</td>
<td>Double vision7</td>
<td>Tremor7</td>
</tr>
<tr>
<td></td>
<td>Numbness7</td>
<td>Weight loss7</td>
<td>Kidney stones7</td>
<td>Glaucoma7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caution</td>
<td>Drug interactions7</td>
<td>Drug interactions7</td>
<td>Drug interactions7</td>
<td>Drug interactions7</td>
<td>1st trimester: cleft lip in babies7</td>
<td>Drug interactions7</td>
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</table>

1: Rogers and Cavazos (2008:940)
2: Battino et al. (2004:155)
4: Fattore et al. (2006:154)
5: Milosheska et al. (2015:27, 36)
6: Pellock et al. (2004:304, 306)
7: Schachter (2008:677-678)
8: Burianova and Borecka (2015:866)
9: Glauser and Pippenger (2000:8)
10: Doughty et al. (2003:712)
11: Castro et al. (2001:189)
12: Siddiqi and Birbeck (2013:536)
14: Rossiter (2008:449-451)
2.3.2.8 Benzodiazepines

Benzodiazepines have been indicated for sleep disorders, anxiety, muscle relaxation and acute convulsions (Griffin et al., 2013:214), especially in status epilepticus (SE) as first-line treatment (Rogers & Cavazos, 2008:957; Yasiry & Shorvon, 2014:167). The public sector in South Africa has certain specific benzodiazepines available, such as diazepam, clonazepam, lorazepam and midazolam (Department of Health, 2012:14.8). These benzodiazepines are indicated for the treatment of epilepsy, especially during acute seizure episodes (Glauser & Pippenger, 2000:7; Brown et al., 2009:635; Patsalos & Perucca, 2003:438).

The mechanism of action of the benzodiazepines is to promote the action of GABA, which is a major inhibitory neurotransmitter in the central nervous system (CNS) by activating the GABA receptors through the activation of the benzodiazepine receptors (Griffin et al., 2013:214; Rossiter, 2008:474). The pharmacodynamic effect of the benzodiazepines is dependent on the GABA concentration and the drug serum concentration (Glauser & Pippenger, 2000:9). Benzodiazepines are excreted via the kidneys and cause less pharmacokinetic interactions with other renal excreted drugs (Landmark et al., 2015:90). Interactions with enzyme inducing drugs, such as carbamazepine, phenytoin and phenobarbital, results in increased metabolism of benzodiazepines, causing potential subtherapeutic levels (Patsalos & Perucca, 2003:350). See table 2-5 for the target serum drug levels of benzodiazepines. These interactions may be of limited clinical significance, due to the high therapeutic index of these drugs (Patsalos & Perucca, 2003:352). Benzodiazepines are metabolised by the cytochrome P450 (CYP450) enzymes and their metabolites are highly protein bound and lipophilic, distributing to the central nervous system and adipose tissue (Griffin et al., 2013:215; Rogers & Cavazos, 2008:957).

Intravenous (IV) administration of one or two doses of a benzodiazepine should stop seizures within 2-3 minutes (Rogers & Cavazos, 2008:957). Diazepam is a long-acting benzodiazepine with extremely lipophilic active metabolites, such as oxazepam, temazepam and desmethyldiazepam (Griffin et al., 2013:216). Because of midazolam’s short half-life, patients can return to consciousness more rapidly than those receiving larger doses of more sedating anticonvulsants, e.g. phenytoin, phenobarbital (Rogers & Cavazos, 2008:960). Benzodiazepines should be administered according to a safety protocol during acute seizures of AED tapering strategies (Rizvi et al., 2014:763).

See table 2-5 for the pharmacokinetic properties of benzodiazepines, including the half-life and target serum drug concentration.
Table 2-5: Pharmacokinetic properties of benzodiazepines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein binding (%)</th>
<th>Half-life (hr)</th>
<th>Initial dose</th>
<th>Max dose</th>
<th>Target serum concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>852</td>
<td>18-502</td>
<td>PO: 1.5 mg/day1 IV: 2 mg5</td>
<td>4 mg3</td>
<td>20–801</td>
</tr>
<tr>
<td>Diazepam</td>
<td>982</td>
<td>20-802</td>
<td>PO: 4–40 mg1 IV: 10-20 mg3</td>
<td>PO: 4–40 mg1 IV: 5–30 mg1</td>
<td>100–1 0001</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>852</td>
<td>10-202</td>
<td>PO: 2–6 mg1 IV: 4 mg3</td>
<td>PO: 10 mg1</td>
<td>10–301</td>
</tr>
<tr>
<td>Midazolam</td>
<td>974</td>
<td>2.3-34</td>
<td>Buccal: 1-5 mg3 IV: 1-5 mg2</td>
<td>IM: 10 mg3</td>
<td>564</td>
</tr>
</tbody>
</table>

IM: intramuscular; IV: intravenously; PO: *per os*, meaning to take orally

1: Rogers and Cavazos (2008:939)
2: Griffin *et al.* (2013:214)
3: Department of Health (2012:14.3)
4: Schwagmeier *et al.* (1998:205)

### 2.3.3 Side-effects

Side-effects are a main cause of medication non-adherence and intolerance and are usually concentration or dose dependent (Schachter, 2008:676). Side-effects occur in 40-80% of all epilepsy patients on antiepileptic treatment (Wassenaar *et al.*, 2016:421). The ideal AED would suppress all seizures without causing any unwanted side-effects (Pellock *et al.*, 2004:301; Rogers & Cavazos, 2008:928; Stefan & Hopfengartner, 2009:653); however, unfortunately, the available drugs frequently cause a range of unwanted effects that may vary from minimal impairment of the central nervous system to hepatic failure and death (McNamara, 2006:505). Combination therapy may increase the risk of side-effects (Patsalos & Perucca, 2003:247). It is commonly thought that newer AEDs have less side-effects and drug interactions (Bautista & Rundle-Gonzalez, 2012:437). The effects of drugs can often be eliminated by decreasing the dose or avoided by increasing the dose very slowly since initiating therapy (Schachter, 2008:676; Rogers & Cavazos, 2008:944). In order to verify if an AED is the possible cause of the side-effect, one way is to withdraw the drug and then re-challenge with it – the patient should be closely monitored and the outcome should be observed (Rogers & Cavazos, 2008:944). The following is the most important side-effects of the AEDs.
2.3.3.1 Central nervous system

Antiepileptic drugs have some effects on the central nervous system (CNS) due to its lipophilicity and crossing of the blood brain barrier (BBB) and side-effects are usually dose-related, for example sleepiness, trouble with balance (e.g. topiramate) and visual disturbances (e.g. carbamazepine) (Schachter, 2008:676-7). Psychiatric and psychological disorders, such as behavioural problems, depression, anxiety, psychoses and attention deficit disorders, are under recognised and undertreated in people with epilepsy (De Boer et al., 2008:543). Comorbidities in epilepsy patients include: depression, anxiety, dementia and migraine which are up to eight times more common in people with epilepsy than in the general population (Keezer et al., 2016:106). There are several possible causes of psychiatric disorders in patients with epilepsy and it is often difficult to determine whether psychopathological manifestations, especially depressive symptoms, are due to drug therapy or to multiple other factors (Mula & Sander, 2007:556).

Side-effects of carbamazepine can cause neurosensory effects such as blurred vision, dizziness and headache, which can occur occur in 35% to 50% of patients (Rogers & Cavazos, 2008:940). The use of phenobarbital is limited by its CNS side-effects and tolerance usually develops (Rogers & Cavazos, 2008:944). Phenobarbital and topiramate show depressive symptoms presenting in up to 10% of all patients on therapy, especially patients receiving polytherapy of CNS depressive drugs (Stefan & Hopfengartner, 2009:656) and patients who have a history of CNS disorders (Mula & Sander, 2007:556). Topiramate can cause impaired concentration and memory difficulties at high doses and during rapid titration (Rogers & Cavazos, 2008:946). When used in combination AED therapy, lamotrigine can cause side-effects such as drowsiness, headache and tremor (Rogers & Cavazos, 2008:942). Carbamazepine, valproate and lamotrigine are associated with a low risk of mood disorders (Mula & Sander, 2007:556). Phenytoin can cause CNS depressive effects, due to bone marrow suppression, such as lethargy, incoordination and drowsiness and topiramate is associated with depression (Brodtkorb et al., 2016:2; Faught, 2012:300), but these effects can be minimised by using slow dose titration (Rogers & Cavazos, 2008:944). Valproate can cause encephalopathy (Yasiry & Shorvon, 2014:171). Common side-effects of benzodiazepines include drowsiness, fatigue, dizziness, slurred speech and blurry vision can occur and tolerance, dependence and withdrawal effects can cause these side-effects that are associated with long-term use (Griffin et al., 2013:220).

According to the study conducted by Brown et al. (2009:638), cognitive problems are a significant reason for non-adherence, more than unwillingness to take medication or carelessness to do so. AEDs may also influence the cognitive development in children.
Learning disability, memory impairment, loss of concentration, disorientation and clouding consciousness can occur in patients and night-time seizures may even disrupt the consolidation of memory and affect language functions (De Boer et al., 2008:542).

Carbamazepine and valproate show signs of mood stabilising properties in primary psychiatric disorders (Fattore et al., 2006:154), epilepsy and behavioural problems, such as aggression (Mula & Sander, 2007:558). Lamotrigine has antidepressant properties (Mula & Sander, 2007:558). Slow titration schedules of AEDs can significantly reduce the incidence of mood disorders as side effect (Brodtkorb et al., 2016:7).

2.3.3.2 Gastrointestinal and weight changes

Patients should be encouraged to report any effects that may be related with the drug use, even weight change (Faught, 2012:301). Alterations in weight can notably affect the quality of life and represent a significant burden to the individual, especially in resource-poor countries (De Boer et al., 2008:542). Weight gain can occur due to the use of AED, such as valproate (Mula & Sander, 2007:562), which can also cause anorexia (Rogers & Cavazos, 2008:946). Ethosuximide may cause a lack of appetite (Schachter, 2008:677). Topiramate has been associated with weight loss (Rogers & Cavazos, 2008:946).

Many AEDs cause nausea and vomiting, due to the irritation of the gastrointestinal tract, for example carbamazepine and valproate (Rogers & Cavazos, 2008:940,946; Schachter, 2008:677,678; Castro et al., 2001:189, Rossiter, 2008:443). These effects can be minimised by administering enteric-coated tablets or giving the drug with food (Dekker, 2002:64).

2.3.3.3 Haematological and cardiovascular

Leukopenia, as well as lymphadenopathy, can occur during carbamazepine therapy and serum sodium concentration should be determined periodically, especially in elderly patients (Rogers & Cavazos, 2008:940; Castro et al., 2001:189). Valproate can cause thrombocytopenia and alterations in platelet aggregation, which is related to the serum concentration (Yasiry & Shorvon, 2014:171-172), although these coagulopathies occur more frequently in children than in adults (Rogers & Cavaos, 2008:947).

According to Brodie et al. (2013:19), the old generation AEDs are associated with increased levels of total cholesterol, low density lipoprotein cholesterol and triglycerides, increasing the risk for hypercholesterolemia and cardiovascular event. Lipoprotein (a), a risk factor for cardiovascular disease, is elevated during carbamazepine treatment (Brodie et al., 2013:19).
2.3.3.4 Hypersensitivity

Carbamazepine may also cause side-effects such as mild or serious rashes and reversible decreases in white blood cells and allergic rashes caused by ethosuximide occur infrequently (Schachter, 2008:677-678). Phenobarbital may cause porphyria and both phenobarbital and phenytoin cause severe rash, such as Stevens-Johnson (Rogers & Cavazos, 2008:944, Rossiter, 2008:442). Monotherapy lamotrigine can cause rash in the first three to four weeks of therapy (Rogers & Cavazos, 2008:942).

2.3.3.5 Teratogenic effects

According to Bordtkorb et al. (2016:5) adherence to AEDs is most important during pregnancy and treatment administration should be well-monitored, as seizure breakthroughs may cause damage to both the mother and the foetus. Monotherapy is preferred during pregnancy (Milosheska et al., 2015:28, 36). Phenobarbital and phenytoin administration during pregnancy are associated with congenital heart malfunctions and facial clefts in the unborn baby, especially if lamotrigine is taken in combination during the first trimester of pregnancy, whereas valproate and carbamazepine are associated with spina bifida (Schachter, 2008:677). Although the risk of malformations is twice as high in epileptic mothers as in non-epileptic mothers, 90% of epileptic mothers' pregnancies result in healthy babies (Rogers & Cavazos, 2008:938). The Department of Health (2012.14.7) states that the optimal control of epilepsy in pregnancy is a single AED and that folate supplementation is needed, especially during valproate treatment and valproate should never be initiated during pregnancy. Antiepileptic drug doses should be adjusted in pregnancy according to the drug serum levels.

2.3.3.6 Endocrine effects

Due to the significant weight gain when using valproate, many patients develop increased fasting insulin levels, which can develop to insulin resistance in obese patients (Rogers & Cavazos, 2008:944). The most serious side-effect reported with the use of valproate is hepatitis and therefore liver function should be tested before and every six months during valproate treatment (Schachter, 2008:677; Rogers & Cavazos, 2008:947).

According to Rogers and Cavazos (2008:938-939), reduced fertility in men with epilepsy were associated with carbamazepine and valproate use, as sperm abnormalities occurred. Valproate has been found to cause testicular atrophy (Rogers and Cavazos, 2008:938-939). Enzyme-inducing AEDs can cause sexual dysfunction in women as these drugs affect the reproductive hormones (Brodie et al., 2013:17).
2.3.4 Drug-drug interactions

The comorbidities of epilepsy are found to be a substantial burden for epilepsy patients and some are identified by Keezer et al. (2016:112) as migraine, depression, cardiovascular diseases, anxiety and asthma, which can cause a higher rate in hospital admissions in these patients.

Pharmacokinetic interactions, such as absorption, metabolism and excretion, are the most notable type of interactions of AEDs, but pharmacodynamic interactions involving potentiation of pharmacological effects at the site of action are also important (Patsalos & Perucca, 2003:347).

2.3.4.1 Enzyme inducers

The old generation AEDs (carbamazepine, phenytoin and phenobarbital) are potent inducers (Landmark et al., 2015:88; Burianova & Borecka, 2015:868) of several enzymes involved in drug metabolism’s activity, leading to increased synthesis of the enzyme in the liver and decreased plasma concentration and reduced pharmacological effect, of drugs (Patsalos & Perucca, 2003:347; Burianova & Borecka, 2015:868). By far the most important pharmacokinetic interactions are those involving CYP450 isoenzymes in hepatic metabolism, which is responsible for drug metabolism (Fattore et al., 2006:154-155; Milosheska et al., 2015:26). Carbamazepine is considered a CYP450 substrate with auto- and hetero-induction and therefore carbamazepine should be initiated in low doses and gradually increased for therapeutic effect (Fattore et al., 2006:159) and carbamazepine is an inducer of CYP3A4, that will reduce the plasma concentration of oral contraceptives, ethosuximide and calcium antagonists (Patsalos & Perucca, 2003:348). Because erythromycin is an inhibitor of CYP3A4, the rise in plasma carbamazepine is of clinical importance (Patsalos & Perucca, 2003:348).

Drug-drug interactions exist also with anticoagulants, analgesics, statins, glucocorticoids, ARVs, antihypertensive drugs and immunosuppressant drugs which can cause higher mortality, progressive AIDS, transplant rejection and unwanted pregnancies (Brodie et al., 2013:11). These drugs are expected to have lower serum levels in the presence of the enzyme-inducing drug and higher doses are needed for therapeutic effect (Brodie et al., 2013:21). Polytherapy with AEDs will lead to an increased rate of AED metabolism which causes low antiepileptic efficacy (Burianova & Borecka, 2015:886). Drug-drug interactions are common with carbamazepine administration as this drug increases the metabolism of other drugs (Schachter, 2008:677). Phenytoin is associated with many drug interactions, as it is an inducer of metabolising enzymes, such as CYP450 and uridine glucuronyl transferases (UGT).
(Tomson et al., 2010:86). Food can increase or decrease the bioavailability of phenytoin and the addition of folic acid during treatment enhances the clearance of phenytoin which results in the loss of efficacy (Rogers & Cavazos, 2008:944). The enzyme inducers will decrease the half-life of benzodiazepines (Griffin et al., 2013:221). The sudden withdrawal of these AEDs can cause a risk of toxicity of the induced drug (Brodie et al., 2013:11).

2.3.4.2 Enzyme inhibitors

Interactions involving liver enzyme inhibition can be caused by some AEDs, such as valproate, (Milosheska et al., 2015:26), causing an increase in plasma drug concentration of other co-administered drugs, such as other AEDs or benzodiazepines, such as lorazepam and diazepam (Patsalos & Perucca, 2003:347, 352; Fattore et al., 2006:154, Milosheska et al., 2015:26). Valproate is known to significantly affect the pharmacokinetics of lamotrigine, because valproate is a potent inhibitor of hepatic CYP450 enzymes, causing elevated lamotrigine serum concentration levels compared to lamotrigine in monotherapy (Glauser & Pippenger, 2000:13). Topiramate has a weak inhibitory effect on the CYP2C19 isoform resulting in an increased phenytoin serum concentration when used in combination (Rogers & Cavazos, 2008:946).

2.3.4.3 Binding sites

Phenytoin competes with other drugs, such as valproate, for albumin binding sites (Rogers & Cavazos, 2008:944; Chan & Beran, 2008:574) and therefore the combination of other high protein drugs can cause phenytoin toxicity (Chan & Beran, 2008:574; Patsalos & Perucca, 2003:348). Valproate is highly protein bound and other highly protein-bound drugs, such as free fatty acids and aspirin, can displace valproate from this binding site (Rogers & Cavazos, 2008:947; Chan & Beran, 2008:574). Note that hypoalbuminemia in elderly patients can make the monitoring and adjusting of serum drug levels problematic, especially in high albumin-bound AED (Rogers & Cavazos, 2008:937).

2.3.4.4 Contraception

Hormones can have an influence on the brain’s GABA receptors and protein synthesis and estrogen has a seizure-activating and progesterone a seizure-protecting effect (Wells, 2009:580; Rogers & Canazos, 2008:938).

Special precautions in female patients may affect the choice of AEDs. Antiepileptic drug inducing enzymes may decrease the effectiveness of combination oral contraceptives by enhancing their metabolism (Rossiter, 2008:440). These AEDs can cause treatment failures
of oral contraceptives and breakthrough bleeding or pregnancy can occur (Schachter, 2008:677,678; Wells, 2009:580; Brodie et al., 2013:17). Women with epilepsy should be monitored, according to Pellock et al. (2004:306), especially if they are concerned about the efficacy of their oral contraceptives, pregnancy (due to the potential teratogenic effects of AEDs) and menopause (fluctuations in seizure patterns can occur). Seizures may occur just before or during menses (catamenial epilepsy) or at the time of ovulation due to hormonal changes, even during pregnancy (Rogers & Cavazos, 2008:938) and standard AEDs should be the first-line of therapy (Wells, 2009:583), although, topiramate doses of less than 200 mg/day are unlikely to alter oral contraceptive efficacy (Rogers & Cavazos, 2008:944).

2.3.4.5 Antimicrobial drugs

Antifungals, such as ketoconazole and fluconazole, are potent inhibitors of CYP isoenzymes (CYP3A4), which can increase the serum concentration and bio-availability of AEDs, such as carbamazepine, up to 30% of the normal serum concentration (Besag & Patsalos, 2015:113). Isoniazid, an antituberculosis drug, inhibits the enzyme CYP2E1 (Patsalos & Perucca, 2003:349), responsible for the metabolism of carbamazepine, phenytoin and valproate, causing elevated plasma concentration levels and possible toxicity (Besag & Patsalos, 2015:113). Certain AEDs, such as carbamazepine, can decrease antibiotic efficacy causing recurrent infections in patients and prolonged antibiotic use (Castro et al., 2001:190). When the carbamazepine was replaced with valproate in this specific study, there was a reduction of recurrent infection episodes. The effect of AED on antibiotics will depend on the enzyme inducing or inhibiting effect and the type of antibiotic. Macrolide antibiotics, such as erythromycin or clarithromycin are powerful inhibitors of CYP450 enzymes, such as the CYP3A4 and CYP1A2 enzymes (Patsalos & Perucca, 2003:349) and can cause carbamazepine toxicity (Besag & Patsalos, 2015:117; Patsalos & Perucca, 2003:349). The combination of carbapenem antibiotics in combination with valproate should be avoided, as the valproate concentration will be subtherapeutic (Besag & Patsalos, 2015:117). Note that penicillin may trigger seizures or cause epilepsy (Angus-Leppan & Parsons, 2008:576).

Antiretroviral drugs, such as lopinavir (LPV), ritonavir (RTV), nevirapine (NVP) and efavirenz (EFV) may be compromised when co-administered with enzyme-inducing AEDs and therefore the monitoring of the efficacy of ARVs in patients is essential (Brodie et al., 2013:17). The enzyme-inducing AEDs is recommended to be avoided in patients on protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) as this can result in virologic failure (Brodie et al., 2013:17; Rossiter, 2008:440, 443; Siddiqi & Birbeck, 2013:529), seizure breakthrough and AED toxicity and/or ARV toxicity (Siddiqi & Birbeck, 2013:529, 534).
2.3.4.6 Haematological

Antiepileptic drug inhibitors, such as valproate, may interact with anticoagulants, such as aspirin, warfarin and dipyridamole, causing a prolonged bleeding time (Rossiter, 2008:443, 448).

2.3.4.7 Alcohol

In some communities, alcohol is the most important factor causing seizures, (Brodtkorb et al., 2016:5). Sudden alcohol withdrawal may trigger seizures and susceptibility to the development of epilepsy (Preux & Druet-Cabanac, 2005:26), usually generalised tonic-clonic seizures, due to toxic damage and/or traumatic injury (Angus-Leppan & Parsons, 2008:574,575). High alcohol intake, especially seen in younger age groups, can enhance the drug metabolising capacity, as it is a CYP2E1 inducer (Patsalos & Perucca, 2003:349), shortening the drugs’ half-lives, causing subtherapeutic effects (Fattore et al., 2006:157). Therefore, drug labels provide warnings regarding the co-administration of AEDs with alcohol (Faught, 2012:301) and should best be avoided (Rossiter, 2008:441). An occasional drink is not harmful to a patient concerning their epilepsy, but becoming drunk should be avoided (Dekker, 2002:75). New-onset epilepsy patients, especially in the elderly population are of significant greater risk of medical admission due to alcohol dependency (Keezer et al., 2016:112; Schachter, 2008:674). Alcohol withdrawal can also be a precipitating factor in status epilepticus (SE) and treatment of non-adherence has been associated with alcohol-related SE (Lie et al., 2015:31).

2.3.5 Stigma

The management of epilepsy in rural areas is poor and cultural stigma might be a reason for patients not seeking medical treatment (Zabcevic et al., 2002:26). The number of missing cases of epilepsy could be due to families hiding the condition from the society or medical help, either because of social stigma, loss of employment and loss of driver’s license (Banerjee et al., 2009:33). According to De Boer et al. (2008:543), epilepsy is a hidden disability causing these patients to be more vulnerable in their community and the stigmatisation of these patients leads to discrimination, causing people with epilepsy to be the target of prejudicial behaviour, over time and in many cultures.

The social stigma of epilepsy in certain culture groups in western and central Africa may be a leading cause of the low incidence reports in South Africa (Faught, 2012:300; WHO, 2005) and the prevalence can be inaccurate as a result of not identifying individuals with epilepsy who have not accessed health care for their condition (WHO, 2005). The impact of epilepsy is
greater for disadvantaged groups, even in high-income countries, but this burden is higher in low-income countries and the burden for anyone with epilepsy can be reduced by good seizure control (Smithson et al., 2012:49). The burden of epilepsy is not only on the individual patient (Mula & Sander, 2007:556; Schachter, 2008:679; Smithson et al., 2012:52), but also on the family and indirectly on the community (De Boer et al., 2008:542). Because seizures are unpredictable, social exclusion, because of other people’s negative attitudes and the stigma thereof, may cause children to be banned from school, adults barred from marriage or employment denied (De Boer et al., 2008:540). Stigma due to epilepsy is poorly understood by professionals and is associated with an increased risk of depression, suicide, accidents and death (Smithson et al., 2012:49; De Boer et al., 2008:543).

De Boer et al. (2008:543) state that there are two ways to reduce the stigma of epilepsy. The first relates to people with epilepsy themselves, who need support from epilepsy associations to counter prevailing negative stereotypes and reduce their experience of stigma. The second way is to support people with epilepsy individually to develop resourcefulness, by means of educational programs and counselling, to increasing their knowledge (De Boer et al., 2008:543).

2.4 Adherence to antiepileptic treatment

Medication adherence continues to be a problem for patients with epilepsy and non-adherence is considered to be one of the most serious obstacles in the current medical practice (Hovinga et al., 2008:316) with up to 60% of epilepsy patients being non-compliant (Rogers & Cavazos, 2008:930). Adherence to prescribed medications is a key factor in effective disease management of many chronic conditions (Andrade et al., 2006:565). Medication compliance behaviour, according to Ho et al. (2009:3028), is divided into two concepts, namely adherence (the intensity of drug use during the duration of therapy) and persistence (the overall duration of drug therapy).

Non-adherence to AED treatment is common and often leads to seizure breakthrough (Brodtkorb et al., 2016:1; Krause et al., 2007:14a). Hospital admissions, in the case of status epilepticus, can occur due to non-adherence, which is a major cause of sudden death (Brown et al., 2009:634; Smithson et al., 2012:49; Doughty et al., 2003:710; Krause et al., 2007:14b; Stepanova & Beran, 2015:8). Suboptimal adherence can be classified as non-adherence and occurs in up to 50% of epilepsy patients on AED medication (Smithson et al., 2012:49). In South Africa only 55% of patients of the private health sector was found to be adherent according to the MPR status (Jacobs et al., 2016a:539), while in the public health sector 42.9% and 54.9% has been reported respectively (Krause et al., 2007:14c; Egenasi et al., 2015:329).
According to Brown et al. (2009:634) 70% of patients with epilepsy stated that they never missed a dose and the majority of patients admit to missing only one or two doses per month, but in their study it was revealed that less than 80% of the AEDs were collected at the right time for the prescription refill. Adherence among older patients with epilepsy has been found to be suboptimal and is associated with increased seizure frequency and total health care costs (Ettinger & Baker, 2009:62). Adherence can be classified if the medication possession ratio is more than 80% (Faught, 2012:297). It is important to note that adherence to medication is the responsibility of the patient.

The level of patient adherence for chronic conditions can be classified into three categories (Claxton et al., 2001:1298):

- full compliers - who take adequate amounts of medication to control the disorder (80-100%);
- partial compliers, who take many doses, but not regularly enough to control the disorder (50-80%); or
- non-compliers, who take few or no doses and whose disorder are unaltered (<50%).

2.4.1 Factors influencing adherence to antiepileptic drugs

The following factors may contribute to adherence or non-adherence in epilepsy:

- **Prescribing patterns.** An inverse linear relationship has been found between the dose frequency and drug adherence, as regimens can be complicated (Doughty et al., 2003:710; Rogers & Cavazos, 2008:930). This is reasonable since the act of remembering to take the drug several times per day is more likely to fail compared with taking a drug once per day (Faught, 2012:300). A decreased dosing frequency and use of monotherapy are thought to favourably influence adherence (Bautista & Rundle-Gonzalez, 2012:437) and therefore modified-release AED formulations, with once daily dosing frequency, can be advantageous for patients with epilepsy (Pellock et al., 2004:307; Ettinger & Baker, 2009:61). Personalising regimen interventions can improve patient adherence (Brodtkorb et al., 2016:10-11; Ettinger & Baker, 2009:61; Dekker, 2002:68).

- **Age.** In young adults polytherapy can cause a drug burden, because of possible multiple dosing and side-effects (Bordtkorb et al., 2016:2), while in older patients, if cognitive disturbances and fatigue occur, it may lead to non-adherence (Ettinger & Baker, 2009:61).
• **Persistence of medication taking.** A higher rate of missed doses was found with a longer duration of treatment (Faught, 2012:300).

• **Comorbidities.** About 50% of adults with epilepsy have at least one comorbid disorder (Keezer et al., 2016:106). Depression is associated with non-adherence and is also a potential side-effect of some AEDs (Brodtkorb et al., 2016:2, 6; Faught, 2012:300).

• **Polytherapy with AEDs or other chronic medication.** Polytherapy with AEDs has been associated with lower adherence than monotherapy (Brodtkorb et al., 2016:6; Bautista & Rundle-Gonzalez, 2012:437).

• **Lack of knowledge and health literacy** about epilepsy may cause non-adherence in patients (Faught, 2012:300; Ettinger & Baker, 2009:61; Krause et al., 2007:14d).

• **Beliefs.** Different patient and doctor beliefs about the efficacy of AEDs and side effects may influence patient adherence (Faught, 2012:300; Ettinger & Baker, 2009:61).

• **Psychological.** Efficacy refers to a patient being able to believe that a medication will help for the epilepsy to be treated and it suggests dependence on treatment (Faught, 2012:300).

• **Cost.** Not only financial cost - newer drugs are more expensive (Ettinger & Baker, 2009:61) - but costs of convenience, stress and stigma associated with medication taking can influence patient adherence (Faught, 2012:300). Transportation cost may limit visits to health care facilities (Krause et al., 2007:14c). Refer to section 2.3.4.3 for more information on stigma.

• **Forgetfulness.** Forgetfulness can lead to missed drug dosage, but a recent study has shown an association between the patient’s mood and adherence rather than memory loss (Brodtkorb et al., 2016:6).

• **Pregnancy.** Adherence to AED regimen is essential during pregnancy and because the mother wants to protect the unborn child, adherence may be enhanced (Brodtkorb et al., 2016:5). In pregnancy, a monotherapy is the ideal regimen (Rogers & Cavazos, 2008:938).

The non-adherence of patients should be recognised by the treating clinicians and medical practitioners during a new consultation or prescription renewal (Smithson et al., 2012:49-50; Ettinger & Baker, 2009:62). Non-adherence results in the failure of seizure control and is a waste of healthcare resources (Smithson et al., 2012:52). The determination of patient medication adherence and the use of interventions to improve adherence are rare in routine clinical practice (Ho et al., 2009:3028; Smithson et al., 2012:52).
2.4.2 Methods of determining adherence

All methods to determine patient adherence have merits and shortcomings (Andrade et al., 2006:273; Ettinger & Baker, 2009:60). See table 2-6 for the limitations of methods used to measure adherence. Combined methods may enhance the recognition of non-adherence, as, according to Andrade et al. (2006:273), no single method can be considered as the ‘best’ method. Electronic monitoring methods, such as the prescription refill patterns and patient reported data can be used to evaluate non-adherence (Manjunath et al., 2009:372).

A visual analogue scale (VAS) is described as a neutral clinical instrument to visualise variables for the recording of an individual’s perception or satisfaction (Biraben & Allaf, 2015:24; Agrawal et al., 2016:247), ranging from ‘best health state’ with a rating of 100 and the ‘worst health state’ at zero (Agrawal et al., 2016:247). Questionnaires can be used to score the individual’s quality of life in epilepsy (Agrawal et al., 2016:248) or satisfaction on AEDs (Biraben & Allaf, 2015:24).

Methods of measuring adherence in epilepsy patients are listed below.
**Table 2-6: Methods of measuring adherence in epilepsy patients**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Limitation</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reports, questionnaires, visual analogue scale (VAS)</td>
<td>This source may not be accurate because the patient might feel embarrassed about not complying. Patient education and a trusting patient-physician relationship have repeatedly been demonstrated to be a key factor in medication adherence. Self-reports, or medication diaries, are indirect and subjective and inaccurate.</td>
<td>Inexpensive method and easy to use. Visual analogue scale is easy and quick to complete and can be used to quantify a patient’s opinion.</td>
</tr>
<tr>
<td>Pill-counts</td>
<td>Short periods of observation (1 month or quarterly) are associated with higher levels of adherence and a very large number of patients fail to maintain adherence over a period even as short as a single year. Subject to manipulation and is not an indication if the correct intervals were followed.</td>
<td>This is a more sound method than asking the patient. An objective, inexpensive and easy to use method.</td>
</tr>
<tr>
<td>Medication possession ratio (MPR) Or prescription refill rates</td>
<td>Medication records are not always accurate. The MPR will not identify all those patients who do not take their medication as prescribed, but only the quantity of medication they receive per month or over the study period. Pharmacy records are objective as they do not guarantee that the patient has taken the medicine.</td>
<td>Non-adherence can be identified by reviewing accurate medication records. This method is objective and inexpensive.</td>
</tr>
<tr>
<td>Therapeutic drug monitoring (TDM)</td>
<td>Determining can be very complex and is requested by a medical professional, only when non-adherence or toxicity is expected. Antiepileptic drug levels can give false reassurance about adherence.</td>
<td>Drug therapy can be optimised and individualised in general and special populations. This method is objective, direct, easy to understand and part of routine in many countries.</td>
</tr>
</tbody>
</table>

1: Faught (2012:297)  
2: Bautista and Rundle-Gonzalez (2012:437, 438)  
3: Smithson et al. (2012:50)  
4: Bordtkorb et al. (2016:2, 17)  
5: Milosheska et al. (2015:25, 36)  
6: Ettinger and Baker (2009:60-61)
2.4.2.1 Medication possession ratio

Medicine possession ratio (MPR) is an accepted, reliable and indirect method of determining medication adherence by using the prescription refill rate and the received pill count (Ho et al., 2009:3028; Ettinger & Baker, 2009:61; Briesacher et al., 2008:440). Interruptions of therapy are short-term non-adherence. It is used to assess the patient’s exposure to treatment over the observation period (Ettinger & Baker, 2009:61) and is defined as the ratio of total days between refills (28 days for our patient population) for a specific drug in the observation period to the total days of the observation period (Bautista & Rundle-Gonzalez, 2012:438; Ettinger & Baker, 2009:61; Andrade et al., 2006:267). For example, if an AED was refilled after 36 days, the MPR would be 28/36 or 0.78. The MPR of each AED prescription would give an indication of the adherence over the study period (from 1 January 2014 up until 30 June 2016) between six months and two years. According to Andrade et al. (2006:267), the MPR can also be estimated by calculating the day’s supply of medication dispensed (excluding the last refill) divided by the number of days between the first and last prescription refill.

Two main equations (Andrade et al., 2006:269; Ettinger & Baker, 2009:61):

1) \[ MPR = \frac{\text{number of days supply obtained during observation period}}{\text{number of days in observation period}} \times 100 \]

2) \[ MPR = \frac{\text{number of days supply obtained (excluding last refill)}}{\text{number of days between first and last dispense date}} \times 100 \]

Measuring adherence using MPR is a common method in clinical retrospective or longitudinal studies (Briesacher et al., 2008:441). The MPR was interpreted as follows:

<table>
<thead>
<tr>
<th>Adherence status</th>
<th>As percentage</th>
<th>As ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undersupply</td>
<td>&lt; 80%</td>
<td>&lt; 0.8</td>
</tr>
<tr>
<td>Acceptable</td>
<td>≥80 and ≤110%</td>
<td>≥0.8 and ≤1.1</td>
</tr>
<tr>
<td>Oversupply</td>
<td>&gt; 110%</td>
<td>&gt; 1.1</td>
</tr>
</tbody>
</table>

An MPR of ≥80 and ≤110% is considered adherent (Andrade et al., 2006:272; Ho et al., 2009:3029), with MPR <80% defining non-adherence (Manjunath et al., 2009:374; Smithson et al., 2012:49). The MPR, used to calculate adherence status, was assessed cumulatively at the end of each month following AED initiation throughout the six month and two year period, between 1 January 2014 and 30 June 2016. In addition, MPRs higher than 100% were classified as compliant, but over-adherence (>110%) was difficult to interpret (Briesacher et al., 2008:440).
Medication gaps may occur when reviewing the patient file and are described by Andrade et al. (2006:270) as the number of days a patient had been without medication during a specified period of observation. This can be determined by using the information on AED days’ supply or refills obtained during specified time intervals (Andrade et al., 2006:272). The correct measuring of adherence depends on the accuracy of information available of the days’ medication supply in patient files (Briesacher et al., 2008:442). Patients may dispose their medication or save the medication for future use, which might lead to inaccurate estimation of adherence (Manjunath et al., 2009:377).

Medication adherence, which is an essential component for a successful health outcome, is largely the responsibility of the patient. As Claxton et al. (2001:1298) stated, standard measures of medication adherence include accurate patient self-report, blood-level monitoring, number of prescription refills, pill count and electronic monitoring (EM). Using retrospective data to determine adherence to AEDs, such as MPR, remains an accepted source to payers and providers to see how medication adherence varies among patients and how that variation impacts health outcomes in epilepsy (Manjunath et al., 2009:377).

2.4.2.2 Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) is a multi-disciplinary clinical speciality aimed at improving patient care by adjusting dosages based upon blood levels, certain pharmacokinetic equations and individual characteristics of the patients (Milosheska et al., 2015:25,36; Hiemke, 2016:353). According to Bordtkorb et al. (2016:2), TDM is the best way of measuring patient adherence, because it is a direct, objective and understandable method (Bordtkorb et al., 2016:2; Department of Health, 2012:14.5; Stepanova & Beran, 2015:7).

Therapeutic drug monitoring is a tool that can guide physicians to individualise treatment in prescribing effective and safe AEDs to the patient (Milosheska et al., 2015:26, 28; Landmark et al., 2015:88, 91) by establishing non-adherence, the lack or loss of efficacy and to guide therapy in patients (Rogers & Cavazos, 2008:929; Department of Health, 2012:14.5). During pregnancy, TDM is advised to occur monthly to prevent drug toxicity (Rossiter, 2008:440). The method of using the ratios of concentration/dose introduces a new standard for measuring non-adherence over the observation period - even with changed dosing, especially if there are linear pharmacokinetics of the analysed drugs (Bordtkorb et al., 2016:4).

The first generation of AEDs had complex and variable pharmacokinetics, as well as a higher toxicity and side-effect profile and therefore TDM was initially used for these drugs (Milosheska et al., 2015:26; Hiemke, 2016:353). Phenytoin is one of the earliest examples of drugs for
which TDM is essential due to the drug’s non-linear pharmacokinetics (Milosheska et al., 2015:26). Monitoring the AED or the active metabolite, such as carbamazepine-epoxide, can be useful to decrease the risk of toxicity, especially in polypharmacy cases (Burianova & Borecka, 2015:88). The level of free valproic acid can assist with the identifying of concentration related side-effects (Milosheska et al., 2015:26). The use of TDM for the newer AEDs is limited, according to Striano et al. (2008:173), as the pharmacokinetics of these drugs are better and more predictable. During disease pathology, such as chronic renal failure, liver disease, hypoalbuminemia, burns, pregnancy and malnutrition, the free rather than total serum AED concentration should be measured, especially for highly protein bound AED, such as valproate and phenytoin (Rogers & Cavazos, 2008:934; Burianova & Borecka, 2015:886; Striano et al. (2008:173).

Indications for TDM, according to Minshall et al. (2011:126,127) and Department of Health (2012:14.5) are:

- Detection of non-adherence to the prescribed medication - values are taken in the postictal phase and compared with trough values in seizure-free periods (Bordtkorb et al., 2016:2).
- Poor seizure control (Rossiter, 2008:440).
- After the initiation of treatment or regimen change, the TDM can establish individual therapeutic range (Milosheska et al., 2015:36).
- Adjustment of dose, for example phenytoin due to its dose-related toxicity, or carbamazepine, causing time-related toxicity (Milosheska et al., 2015:36).
- Management of pharmacokinetic interactions with other drugs (Milosheska et al., 2015:28, 36; Rossiter, 2008:440).
- Specific clinical conditions: by implementing TDM at admission of status epilepticus or the signs of organ failure, the severity of the failed treatment can be identified (Lie et al., 2015:28).
- Certain patient factors: renal and/or hepatic impairment, pregnancy (Milosheska et al., 2015:28; Hiemke, 2016:353) and age - elderly patients may be more sensitive to changes in the AED serum levels (Pellock et al., 2004:306).
- When to change AED regimen (Glauser & Pippenger, 2000:6).

In TDM, the patient’s own pharmacokinetic parameters are calculated and can then be compared to the population values. This is a very good indication of adherence and can then
be used to individualise the patient’s dosing regimen (Milosheska et al., 2015:26; Landmark et al., 2015:88, 91).

Oral clearance can be calculated according to the following equation (Fattore et al., 2006:154):

\[
\frac{Cl}{F} (ml \ h^{-1} \ kg^{-1}) = \frac{AED \ daily \ dose \ (mg. \ kg^{-1})}{C_{ss} (\mu g. \ ml^{-1})}
\]

In this equation, \(Cl\) is the total body clearance, \(F\) the value of oral bioavailability and \(C_{ss}\) is the total serum AED concentration at steady-state (Fattore et al., 2006:154).

The clearance can be used to determine the ideal AED maintenance dose (MD) per patient with the following equation (Bauer, 2008:20):

\[
MD = Cl \times C_{ss}
\]

At steady state the following equation can be used (Bauer, 2008:38) to determine different parameters, such as the dosing interval (\(\tau\)), body clearance or steady state drug concentration in the blood.

\[
C_{ss} = [F(D/\tau)] / Cl
\]

Genetic polymorphisms of the drug metabolising enzymes and the CYP450 enzymes, especially of the first generation AEDs, explain the variability in drug response (Milosheska et al., 2015:26). The therapeutic range for each AED may be different for different seizure types and the optimal serum concentration should be calculated for each patient by the physician (Rogers & Cavazos, 2008:929; Department of Health, 2012:14.5). See Table 2-4 on reference ranges of therapeutic serum levels for AEDs).

According to Lertsinudom et al. (2014:83), TDM can be used in epilepsy patients to evaluate adherence and determine the optimal regimen dosage (Rankovic et al., 2012:69). Therapeutic drug monitoring can assist the clinician to assess whether breakthrough seizures are caused by a change in AED formulation, subtherapeutic drug levels or poor adherence, pharmacokinetics or drug-drug interactions (Lertsinudom et al., 2014:83; Glauser & Pippenger, 2000:13). Therapeutic drug monitoring can aid a multidisciplinary team to make dosage recommendations and evaluate the clinical status of the patient to improve epilepsy treatment and seizure control (Lertsinudom et al., 2014:84-85). Causes for subtherapeutic AED levels can be non-adherence to treatment, polytherapy causing enzyme induction (Patsalos & Perucca, 2003:347; Burianova & Borecka, 2015:868; Ettinger & Baker, 2009: 60), underdosing, the metabolizing status of a patient and clinical signs such as diarrhoea,
preventing AED absorption (Dekker, 2002:65). It is important that serum drug levels should be taken in the morning (Chan & Beran, 2008:573) as this reflects the drug-fasting levels and the steady state trough levels in the patient (Landmark et al., 2015:89).

The goal of TDM is to improve patient care and enhance the quality of life of patients living with epilepsy (Glauser & Pippenger, 2000:14). Interventions in treatment should be applied in the most cost-effective, rational and clinically useful manner (Milosheska et al., 2015:28). It is important to remember that all results should always be interpreted according to the clinical state of the patient in response to therapy (Glauser & Pippenger, 2000:6, 12; Rossiter, 2008:440).

2.5 Seizure frequency

Unfortunately, the most important outcome measurement in epilepsy is seizure frequency, which can be documented in hospital monitoring units or on patient reports (Faught, 2012:298). Patient adherence is essential to reduce seizure frequency. As a retrospective observational trial demonstrated, the risk of seizure occurrence was 21% higher in a non-adherent patient within the first year of AED use, with an adherence of less than 50% after twelve months of treatment (Bautista & Rundle-Gonzalez, 2012:437).

The lack of seizure control is believed to be a primary driver in the underlying increased morbidity and mortality in the epilepsy population, as well as a lower quality of life (Manjunath et al., 2009:372; Bautista & Rundle-Gonzalez, 2012:437). The loss of seizure control includes injury, such as bone fractures and burns (Schachter, 2008:674), the decrease in productivity and increased healthcare costs related to epilepsy (Hovinga et al., 2008:316). Death is the worst consequence of non-adherence and the risk of death is found to be three times higher during quarters of non-adherence (defined as <80% MPR) (Faught, 2012:299). Brodtkorb et al. (2016:2, 6) state that uncontrolled seizures may discourage a patient causing a mistrust in epilepsy treatment and refers to a study which revealed that epilepsy patients were non-adherent to treatment after a recent seizure episode (Smithson et al., 2013:109). According to Rankovic et al. (2012:69) even patients who suffer from a single seizure per year have a decreased quality of life.

The development of neuroimaging had contributed significantly to the better management of seizures as the severity and frequency of seizures can be reduced or prevented (Gadhoumi et al., 2016:270). Electroencephalogram analysis is successful in detecting changes from minutes to hours before a seizure onset (Gadhoumi et al., 2016:271). Besides the quantity,
duration and severity of seizures, the testing of neurophysiological changes is also of importance during the course of epilepsy treatment (Stefan & Hopfengartner, 2009:654).

Achieving seizure freedom is influenced by the issues associated with toxicity and poor adherence to AED therapy (Pellock et al., 2004:301). If a patient is ‘seizure free’ it means the patient has been without seizure occurrence for a period of 12 months (Rankovic et al., 2012:69).

### 2.6 Treatment change

Changes in AED regime may indicate unsatisfactory results in treatment, such as failed seizure control or side-effects, which cause a lower quality of life (Wassenaar et al., 2016:421). According to Fattore et al. (2006:154) the choice of an AED or the change in regimen in a patient is dependent on a number of factors, including age-related differences in response and the type of epilepsy. Refer to section 2.3.1 for more information on AED regimens. Potential drug interactions can determine the regimen choice and clinical signs of interactions will influence the next step in treatment to change the regimen (Glauser & Pippenger, 2000:13). Antiepileptic drug regime changes are an objective marker for epilepsy severity (Wassenaar et al., 2016:424). Treatment changes include: changing in dose or frequency of current medication, switching to another AED, adding another AED and switching to a new formulation of the same AED.

According to Hovinga et al. (2008:318), patients with a loss of seizure control had their epilepsy treatment regime changed as a result of seizure frequency or breakthrough (72% of patients). Many experts on epilepsy advise medical practitioners to switch all patients from the older to newer generation AEDs due to the overall better drug tolerability, without using caution, as this switch is associated with a higher risk of seizure (Manjunath et al., 2009:376; Faught, 2012:299; Hovinga et al., 2008:320; Luciano & Shorvon, 2007:379). Changing a regimen to a modified-release formulation or administering this drug twice a day will significantly decrease the incidence of tremors and side-effects caused by fluctuations in serum drug concentrations (Pellock et al., 2004:303; Doughty et al., 2003:711). Patients who are initiated on generic formulations of the AEDs can be switched to a branded formulation or an alternative generic (Manjunath et al., 2009:376). Modified-release formulations and generic products of the same AED may have different pharmacokinetic properties and a change in product type can result in breakthrough seizures (Glauser & Pippenger, 2000:13).

The assessment of treatment change is useful to evaluate AED efficacy for seizure control and patient adherence (Andrade et al., 2006:272). It is assumed that regimen changes occur
due to breakthrough or increased seizure frequency, rather than the vice versa situation (Manjunath et al., 2009:376). Non-adherence should always be considered before regimen change is implemented due to suspected poor seizure control (Stepanova & Beran, 2015:7).

If the failure of adherence is not considered as a reason for treatment failure it may result in the unnecessary adjustment of regimen as an increase in AED dosage or the addition of another AED, causing potential side-effects and complications (Hovinga et al., 2008:320). The number or regimen changes during the study period is important for the interpretation of treatment outcomes in the clinical practice (Wassenaar et al., 2016:424). Therapeutic drug monitoring can also assist to determine the effect of drug regimen change during a withdrawal stage (Stefan & Hopfengartner, 2009:655). Withdrawal of AEDs should occur gradually, according to protocol (Rizvi et al., 2014:763) and preferably within six weeks (Raymond, 2007:27). According to Hovinga et al. (2008:320), non-adherence is related to a loss of seizure control and these patients are likely to have their treatment regime changed in some way by their medical practitioner. A study conducted by Wassenaar et al. (2016:423) found that patients who had antiepileptic regimen changes had less seizure control. The change of regimen is usually driven in a hope to find effective and well-tolerated therapy (Wassenaar et al., 2016:423).

2.7 Chapter summary

Chapter 2 provided an overview of the concept of epilepsy and epileptic seizures. Topics addressed were the definition of epilepsy, classification of epilepsy types; epidemiology and etiology, as well as antiepileptic treatment in the public sector of South Africa. Patient adherence, by investigating the MPR, TDM and seizure frequency were also reviewed. Hereby the specific objectives of the literature review have been answered. In the following chapter the results will be discussed in a manuscript format.
CHAPTER 3: RESULT AND DISCUSSION

3.1 Introduction

This chapter contains the general findings and discussion of the empirical investigation of the study and is represented in the form of one manuscript.

The manuscript, entitled “Retrospective analysis of adult epilepsy patients’ clinical outcomes: adherence, seizure frequency and therapeutic drug levels in an outpatient department of a public hospital in the North West Province, South Africa” was submitted to the “Journal of Clinical Pharmacy and Therapeutics”.

Instructions to the author can be viewed in Annexure D or with the following link:

http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1365-2710/homepage/ForAuthors.html
3.2 Manuscript

Title
Retrospective analysis of adult epilepsy patients’ clinical outcomes: adherence, seizure frequency and therapeutic drug levels in an outpatient department of a public hospital in the North West Province, South Africa

Short title
Adult epilepsy patients’ clinical outcomes

Authorship
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Department where study was conducted:
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Conflicts of interest
No conflicts of interest have been declared.

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Keywords
Antiepileptic; clinical outcomes; adherence; seizure frequency; therapeutic drug levels; regimen change; South Africa
SUMMARY

WHAT IS KNOWN AND OBJECTIVE
Medication adherence is a major problem in epilepsy patients. Non-adherence is a cause of poor seizure control and a decrease in quality of life. The prevalence of seizure frequency and effective therapeutic drug monitoring (TDM) in the public health sector of South Africa is unknown. Any change in antiepileptic drug (AED) regimes is an indication of treatment failure. This study aimed to investigate the prevalence of adherence, treatment change, seizure frequency and therapeutic serum drug levels as adult patient’s clinical outcomes measures in an outpatient department of a public hospital.

METHODS
A retrospective research design was applied to collect data from medical records in a public hospital in the Dr Kenneth Kaunda District of the North West Province, South Africa. Forty-six patients complied with the inclusion criteria: adult patients (>18 years), diagnosed with epilepsy and on antiepileptic treatment. The study period was between 1 January 2014 and 30 June 2016. Patients who had been diagnosed with medical conditions other than epilepsy for which they received antiepileptic drugs as treatment, were excluded in this study. Medicine possession ratio (MPR) was used as proxy to determine the adherence status per antiepileptic drug (AED). The MPR of ≥80% and ≤110% were considered as adherent. Serum drug levels, as function of therapeutic drug monitoring (TDM) were compared to the therapeutic range of each AED. The prevalence of seizure frequency, regimen change and the type of changes for each AED were described using descriptive statistics.

RESULTS
Among the study population of 46 patients, 25 were males and 21 were females. Valproate was the drug mostly prescribed (n=41; 53.23%), followed by lamotrigine (n=24; 31.16%) and carbamazepine (n=8; 10.38%). Adherence to antiepileptic treatment, according to the MPR, was 64.93% (n=50) and one or more seizures occurred in 84.78% (n=39) of the patients. According to the serum drug levels, only 23.81% (n=5) of the measurements were in the therapeutic range and 61.90% (n=13) were subtherapeutic. Valproate has shown the highest concentration of levels outside the therapeutic range, of which most levels (92.31%; n=12) were subtherapeutic and 14.28% (n=3) were toxic levels. More than one regimen changes occurred in 69.56% (n=32) of the study population, with change in dosage as the most prevalent regimen change (n=25; 54.43%).
DISCUSSION
Non-adherence in patients on antiepileptic treatment is a major concern. The adherence rate described in this study was still relatively poor compared to the ideal of 80%. Valproate was the drug mostly prescribed, followed by lamotrigine and carbamazepine. Valproate was the AED with most levels outside the therapeutic range and the highest incidence of seizure frequency. Both sub- and supratherapeutic serum levels can indicate possible poor adherence to AED treatment and be a causative factor for seizure breakthrough.

WHAT IS NEW AND CONCLUSION
Non-adherence has a negative impact on patients’ clinical outcomes. Although the TDM performed was not sufficient to conclude on the adherence status of the population, poor adherence and monitoring of patient outcomes are suspected. Consequently, the classification of epilepsy, patient education on adherence and the importance of therapeutic drug levels in uncontrolled epilepsy patients, especially on valproate in this population, need urgent interventions to improve quality of life in epileptic patients.
WHAT IS KNOWN AND OBJECTIVE
Epilepsy is one of the most common neurological conditions\textsuperscript{1,2} and 80\% of epilepsy patients are found in developing countries.\textsuperscript{1} Patients with epilepsy are undertreated worldwide.\textsuperscript{1,3-4} The prevalence of epilepsy in the public sector of South Africa is unknown, but up to 15 patients per 1 000 people have been reported in rural areas of third world countries in sub-Saharan Africa.\textsuperscript{1,5-7} Medication adherence is a problem in epilepsy patients and non-adherence, up to 60\%,\textsuperscript{8} is considered to be one of the most serious obstacles in the current medical practice.\textsuperscript{8,9}

Antiepileptic drug (AED) therapy is not a permanent cure to epilepsy\textsuperscript{10} and the primary treatment goal is to achieve complete cessation of seizures without causing side-effects.\textsuperscript{8,11-15} The choice of drug depends on the accurate classification of seizures, drug availability, patient factors, cost and side-effect profile.\textsuperscript{16} Medicine possession ratio (MPR) is an accepted, reliable and indirect method of determining medication adherence by using the prescription refill rate and the received pill count.\textsuperscript{18-20} Medication adherence is essential for a successful treatment outcome and is largely the responsibility of the patient.\textsuperscript{15,21} The undersupply of medication leads to inadequate treatment of epilepsy, resulting in seizure breakthrough and poor quality of life.\textsuperscript{22}

Therapeutic drug monitoring (TDM) is a clinical specialty aimed at improving patient care and seizure control.\textsuperscript{26-28} It is described to be the best way of measuring patient adherence\textsuperscript{15,19,29-30} and to determine individual optimal regimen doses.\textsuperscript{2,26,31} Because the first generation of AEDs had complex variable pharmacokinetics, a higher toxicity and side-effect profile TDM was initially used just for these drugs.\textsuperscript{26-27} The current trend is not to use TDM in all epilepsy patients.\textsuperscript{30} It is important that all serum drug levels should always be interpreted according to the clinical state of the patient in response to therapy.\textsuperscript{32-33}

A loss of seizure control is associated with epilepsy treatment regimen changes.\textsuperscript{9} Unfortunately, the most important outcome measurement in epilepsy is seizure frequency.\textsuperscript{17} Non-adherence or underdosing of AED can cause seizure breakthrough.\textsuperscript{22,28,32} Patients who suffer from a single seizure per year have a decreased quality of life.\textsuperscript{2}

Regimen changes may indicate unsatisfactory results in treatment, such as failed seizure control or side-effects, both causing a lower quality of life.\textsuperscript{2,9,11} Newer AEDs are better tolerated\textsuperscript{9,17,24} and have a broader spectrum of action\textsuperscript{34} compared to older AEDs. Without using caution during a switch from an old to a new AED, the risk for seizure frequency can increase.\textsuperscript{9,17,24,35} The assessment of switching is useful to evaluate AED efficacy for seizure
control and patient adherence and is an objective marker to indicate epilepsy severity. The number of regimen changes during the study period was important for the interpretation of treatment outcomes in the clinical practice. Treatment changes included: changing the dose or frequency of current medication, switching to another AED, adding another AED and switching to a new formulation of the same AED.

The objectives of this study were to determine the prescribing patterns and to investigate the prevalence of adherence, by assessing the MPR, seizure frequency and serum drug levels in an outpatient department of a public hospital in Dr Kenneth Kaunda District in the North West province, South Africa.

METHODS

Study setting and population
This study took place in the pharmacy of Tshepong hospital, a public hospital in the Dr Kenneth Kaunda District of the North West province, South Africa. Forty-six patients complied with the inclusion criteria. The study was approved by the Health Research Ethics Committee (HREC) of the Faculty of Health Sciences, at the North-West University, South Africa (Ethics number: NWU-00369-15-S1), the North West Department of Health: Policy, Planning, Research, Monitoring and Evaluation (PPRM&E) directorate and goodwill permission was obtained from the hospital’s chief executive officer (CEO) and pharmacy manager.

Research design
The study followed a retrospective, cross-sectional research design. The following data fields were captured from patients’ medical records using a data collection form: gender, date of birth, prescription refill dates, type of AED, dosage and frequency of dosing, number of day’s supply of treatment, number of seizures indicated by healthcare professionals on date of prescription, reason for regimen change as indicated by the prescriber and drug serum levels. The study period was between 1 January 2014 and 30 June 2016. Data were collected in a private office of the hospital pharmacy between May and August 2016.

Eligibility criteria
Patients were eligible for inclusion if they met the following criteria: (i) adult patients (>18 years) diagnosed with epilepsy (irrespective of gender and presence of concurrent disease) who had visited the outpatient department of the hospital pharmacy during the data capturing period and (ii) patients on between six and 24 months of consecutive antiepileptic drug treatment. Patients were excluded if they were diagnosed with medical conditions other than epilepsy for which they received antiepileptic drugs as treatment.
Statistical analysis

Descriptive statistics, such as frequencies, percentages, mean, standard deviation (SD) and 95% confidence interval (CI) were calculated by using SPSS programme version 22.0 (IBM Corp., Armonk, NY:IBM Corp). No inferential statistics were used in the study due to subgroups having a small number of participants.

Prescription patterns were investigated by determining the prevalence of AEDs, the frequency of dosing and the number of AED prescribed per patient. The prescribed daily dose (PDD) and the average prescription per patient were determined per AED.

The adherence status was determined by the MPR as a percentage. The MPR is defined as the ratio of total days between refills (28 days for our patient population) for a specific drug in the observation period to the total days of the observation period.\textsuperscript{19,23,36} It is assumed that the consumption of medication follows from the possession.\textsuperscript{22} The MPR is categorised as adherent, if the calculated value is ≥80% and ≤110%.\textsuperscript{18,22-23} An undersupply with an MPR <80% and an oversupply with an MPR >110% are categorised as non-adherence.\textsuperscript{4,19,22,24-25} The MPR is calculated by using the following formula:\textsuperscript{22-23}

\[
MPR = \frac{\text{Number of days supply of AED (between 1 Jan 2014 and 30 June 2016)}}{\text{Number of days in observation period}} \times 100
\]

Measuring serum drug levels as a tool of TDM, can be used to determine patient adherence.\textsuperscript{8,26,29} It is important to evaluate the drug level in the context of the clinical status and dosing regimen. The serum drug levels can be compared to the therapeutic range per AED\textsuperscript{29} (Table 3-1) and either be classified as therapeutic, subtherapeutic (below the therapeutic range) or supratherapeutic (above therapeutic range).\textsuperscript{28,32}

<table>
<thead>
<tr>
<th>Antiepileptic drug</th>
<th>Therapeutic range (µmol/L)\textsuperscript{38}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>12-50</td>
</tr>
<tr>
<td>Valproate</td>
<td>350-700</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>8-80</td>
</tr>
</tbody>
</table>

Table 3-1: Therapeutic serum levels of the most prevalent AEDs

The number of seizures was obtained from the patient medical files as indicated by the prescriber and analysed per AED. The prevalence of regimen change was determined by comparing consecutive months’ prescription information and the reason for regimen change were obtained from patient medical files as documented by prescribers.
RESULTS

Demographic characteristics and prescribing patterns

Forty-six patients were included in this study, composing of 54.30% (n=25) males and 45.70% (n=21) females with a relative equal female-to-male ratio (1:1.13). The patients were divided in the following age groups: ≥18 and ≤29 years (n=9); ≥30 and ≤49 years (n=15); ≥50 and ≤64 years (n=16) and older than 65 years (n=6). Refer to table 3-3. The average age of the patients was 46.98 ± 15.53 years (95% CI= 42.36-51.58) (Table 3-2).

Valproate was the active ingredient most frequently prescribed (n=41; 53.24%), followed by lamotrigine (n=24; 31.16%) and carbamazepine (n=8; 10.39%). Polytherapy was prescribed for 50% (n=23) of the study population. Twice-a-day prescribing occurred in most patients (n=45; 97.82%), while daily dosing was only observed in n=10 (21.7%) patients. The average treatment period for the study population was 20.10 ± 6.29 months. The average PDD was 841.92 mg ± 426.72 for carbamazepine, 1003.83 mg ± 415.48 for valproate, 205.39 mg ± 104.37 for lamotrigine and 239.45 mg ± 137.82 for topiramate (Table 3-3).
Table 3-2: Demographic characteristics of the study population

<table>
<thead>
<tr>
<th>Demographic information</th>
<th>Number of patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong> (n=46)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (54.3)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (45.7)</td>
</tr>
<tr>
<td><strong>Age distribution in years</strong></td>
<td></td>
</tr>
<tr>
<td>(n=46; $\bar{x}$= 46.98, SD= 15.53, 95% CI= 42.36-51.58)</td>
<td></td>
</tr>
<tr>
<td>$\geq$18 and $\leq$29</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td>$\geq$30 and $\leq$49</td>
<td>15 (32.6)</td>
</tr>
<tr>
<td>$\geq$50 and $\leq$64</td>
<td>16 (34.8)</td>
</tr>
<tr>
<td>$\geq$65</td>
<td>6 (13)</td>
</tr>
<tr>
<td><strong>Treatment period in months</strong></td>
<td></td>
</tr>
<tr>
<td>($\bar{x}$= 20.10, SD= 6.29)</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>31 (67.39)</td>
</tr>
<tr>
<td>$\geq$12 and &lt;24</td>
<td>8 (17.39)</td>
</tr>
<tr>
<td>&lt;12</td>
<td>7 (15.21)</td>
</tr>
<tr>
<td><strong>Frequency of dosing</strong></td>
<td></td>
</tr>
<tr>
<td>Once-a-day</td>
<td>10 (17.85)</td>
</tr>
<tr>
<td>Twice-a-day</td>
<td>45 (80.35)</td>
</tr>
<tr>
<td>Three-times-a-day</td>
<td>1 (1.78)</td>
</tr>
</tbody>
</table>

* Patients can be on a regimen with more than one AED, therefore the total number of patients will be more than 46.
Table 3-3: Prescribing patterns per antiepileptic drug for the study population

<table>
<thead>
<tr>
<th>Gender</th>
<th>Carbamazepine</th>
<th>Valproate</th>
<th>Lamotrigine</th>
<th>Topiramate</th>
<th>Phenytoin</th>
<th>Gabapentin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>5 (62.5)</td>
<td>23 (56.1)</td>
<td>14 (58.3)</td>
<td>0</td>
<td>1 (100-)</td>
<td>1 (100)</td>
<td>44 (57.1)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (37.5)</td>
<td>18 (43.9)</td>
<td>10 (41.7)</td>
<td>2 (100)</td>
<td>0</td>
<td>0</td>
<td>33 (42.9)</td>
</tr>
<tr>
<td>Total</td>
<td>8 (10.38)</td>
<td>41 (53.24)</td>
<td>24 (31.16)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>77*</td>
</tr>
</tbody>
</table>

Average number of prescriptions per patient ± SD (95% CI)
- Carbamazepine: 20 ± 10.04 (11.60-28.40)
- Valproate: 18.44 ± 7.44 (16.09-20.79)
- Lamotrigine: 21.25 ± 6.16 (18.65-23.85)
- Topiramate: 23.50 ± 2.12 (4.44-42.56)

Average PDD (mg) per patient ± SD
- Carbamazepine: 841.92 ± 426.72
- Valproate: 1003.83 ± 415.48
- Lamotrigine: 205.39 ± 104.37
- Topiramate: 293.45 ± 137.82

* Patients can be on a regimen with more than one AED, therefore the total number of patients will be more than 46.

PDD: prescribed daily dose; SD: standard deviation
Evaluation of adherence

According to the MPR, 64.93% of patients were adherent to their antiepileptic treatment. The MPR was also used to identify the undersupply (MPR <80%) and oversupply (MPR >110%) of AEDs. Undersupply of AEDs was seen in 2.59% (n=2) of patients, while 32.46% (n=25) were oversupplied (Table 3-4).

A total of 21 serum drug levels was documented in 13 patients and only 23.81% (n=5) of the measurements were in the therapeutic range (Table 3-5). Subtherapeutic levels were found in 61.9% (n=13) of the measurements, of which 92.31% (n=12) were for valproate and 7.69% (n=1) for carbamazepine. Supratherapeutic levels are also in toxic range and were observed 14.28% (n=3) for valproate.
Table 3-4: Evaluation of adherence using the medicine possession ratio

<table>
<thead>
<tr>
<th>MPR category</th>
<th>Carbamazepine</th>
<th>Valproate</th>
<th>Lamotrigine</th>
<th>Topiramate</th>
<th>Phenytoin</th>
<th>Gabapentin</th>
<th>Total number of patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 80%</td>
<td>0</td>
<td>1 (2.43)</td>
<td>1 (4.17)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (2.59)</td>
</tr>
<tr>
<td>80-110%</td>
<td>4 (50)</td>
<td>26 (63.41)</td>
<td>16 (66.67)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>50 (64.93)</td>
</tr>
<tr>
<td>&gt;110%</td>
<td>4 (50)</td>
<td>14 (34.14)</td>
<td>7 (29.16)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>25 (32.46)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8 (10.38)</strong></td>
<td><strong>41 (53.24)</strong></td>
<td><strong>24 (31.16)</strong></td>
<td><strong>2 (2.59)</strong></td>
<td><strong>1 (1.29)</strong></td>
<td><strong>1 (1.29)</strong></td>
<td><strong>77 (100)</strong>*</td>
</tr>
</tbody>
</table>

* Patients can be on a regimen with more than one AED, therefore the total number of patients will be more than 46.
Table 3-5: Evaluation of adherence using serum drug levels

<table>
<thead>
<tr>
<th></th>
<th>Carbamazepine</th>
<th>Valproate</th>
<th>Lamotrigine</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of serum drug levels measured, n (%)</td>
<td>1 (4.76)</td>
<td>19 (90.48)</td>
<td>1 (4.76)</td>
<td>21</td>
</tr>
<tr>
<td>Number of patients measured, n (%)</td>
<td>1 (7.69)</td>
<td>11 (84.62)</td>
<td>1 (7.69)</td>
<td>13</td>
</tr>
<tr>
<td>Therapeutic levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (19.04)</td>
<td>1 (4.76)</td>
<td></td>
<td>5 (23.81)</td>
</tr>
<tr>
<td>Subtherapeutic levels measured, n (%)</td>
<td>1 (7.69)</td>
<td>12 (92.31)</td>
<td></td>
<td>13 (61.90)</td>
</tr>
<tr>
<td>Supratherapeutic levels measured, n (%)</td>
<td>0</td>
<td>3 (14.28)</td>
<td></td>
<td>3 (14.28)</td>
</tr>
</tbody>
</table>
Seizure frequency
One or more than one seizure was documented in 84.78% (n=39) patients’ medical files (Table 3-6). Seizure frequency was also calculated per AED, and valproate had the highest rate of seizure breakthrough (64.73%).

Regimen change
Regimen changes occurred in 69.56% (n=32) patients. See Table 3-6. The AED with the most regimen changes was lamotrigine 91.70% (n=22), followed by valproate 70.70% (n=29) and then carbamazepine 62.50% (n=5). The main reasons for regimen change were due to seizure breakthrough (62.50%; n=55), followed by a decrease in dose (13.63%; n=12) and incorrect repeat prescribing (10.22%; n=9). See Figure 1 for the reasons for regimen change. The type of regimen change that occurred the most was change in dose in 54.43% (n=25) patients. A decrease in dose (n=12; 26.08%) occurred in the same 25 patients. See Figure 2 for the type of regimen changes. Dosages fluctuated in consecutive months.

See Table 3-7 on the effect of regimen change on MPR and seizure frequency per AED in the study population. Regimen changes occurred in 20.77% (n=16) of patients who were classified by the MPR as non-adherent. Seizures frequency of more than once was recorded in 74.02% (n=57) of patient cases with regimen changes.
Figure 3.1: Reasons for regimen change

Figure 3.2 Type of regimen changes
<table>
<thead>
<tr>
<th>Regimen change</th>
<th>Carbamazepine</th>
<th>Valproate</th>
<th>Lamotrigine</th>
<th>Topiramate</th>
<th>Phenytoin</th>
<th>Gabapentin</th>
<th>Total number of cases, n (%)</th>
<th>Total number of patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen change</td>
<td>5 (62.5)</td>
<td>29 (70.7)</td>
<td>22 (91.7)</td>
<td>2 (100)</td>
<td>1 (100)</td>
<td>0</td>
<td>59 (76.62)</td>
<td>32 (69.56)</td>
</tr>
<tr>
<td>No regimen change</td>
<td>3 (37.5)</td>
<td>12 (29.3)</td>
<td>2 (8.3)</td>
<td>0</td>
<td>0</td>
<td>1 (100)</td>
<td>18 (23.38)</td>
<td>14 (30.43)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>8</td>
<td>41</td>
<td>24</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td><strong>77</strong></td>
<td><strong>46</strong></td>
</tr>
</tbody>
</table>

| No seizures     | 2 (25)        | 7 (17.1)  | 1 (4.2)     | 0          | 0         | 0          | 10 (12.98)                  | 7 (15.21)                     |
| ≥1 seizure      | 6 (75)        | 34 (82.9) | 23 (95.8)   | 2 (100)    | 1 (100)   | 1 (100)    | 67 (87.02)                  | 39 (84.78)                    |
| **Total**       | 8             | 41        | 24          | 2          | 1         | 1          | **77**                      | **46**                        |

**Average number of seizures per patient over the study period ± SD**

<p>| | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Average number of</td>
<td>9.13 ± 8.72</td>
<td>13.61 ± 24</td>
<td>19.83 ± 27.38</td>
<td>28.5 ± 20.51</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>seizures per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>over the study period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Number of seizures reported**

|                        | 73 (8.46)      | 558 (64.73) | 88 (10.20) | 57 (6.61)  | 2 (0.23)   | 84 (9.74)   | 862            |                |

* Patients can be on a regimen with more than one AED, therefore the total number of patients will be more than 46.
Table 3-7: Prevalence of regimen change on MPR status and seizure frequency per AED in the study population

<table>
<thead>
<tr>
<th>Regimen change</th>
<th>MPR</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Total number of patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;110%</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>25 (32.46)</td>
</tr>
<tr>
<td></td>
<td>≥80 and ≤110%</td>
<td>4</td>
<td>0</td>
<td>20</td>
<td>6</td>
<td>16</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>50 (64.93)</td>
</tr>
<tr>
<td></td>
<td>&lt;80%</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (2.59)</td>
</tr>
<tr>
<td>Seizure frequency</td>
<td>No seizures</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10 (10.92)</td>
</tr>
<tr>
<td></td>
<td>≥1 seizure</td>
<td>5</td>
<td>1</td>
<td>27</td>
<td>7</td>
<td>22</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>67 (87.02)</td>
</tr>
<tr>
<td>Total patients</td>
<td></td>
<td>8</td>
<td>41</td>
<td>24</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td>77*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patients can be on a regimen with more than one AED, therefore the total number of patients will be more than 46.
DISCUSSION

Adherence to prescribed medications is a key factor in effective disease management and non-adherence in epilepsy is a major concern\textsuperscript{23,39} affecting clinical outcomes negatively.\textsuperscript{22} Adherence can be influenced by various factors, which can be patient, medication or disease related.\textsuperscript{15,22} According to the MPR, the adherence (64.93\%) is higher than in other studies in the public health sector (54.9\% and 42.90\%)\textsuperscript{40-41} and 55\% in the private health sector of South Africa,\textsuperscript{22} but still poor compared to the ideal 80\%.\textsuperscript{17,19} Valproate was the drug with the highest adherence rate, and this might be due to the modified-release formulation available,\textsuperscript{12,22} twice daily dosing and because most patients were treated with valproate. It is interesting to mention that the highest percentage of subtherapeutic levels and most seizures were reported for valproate.

Serum drug levels can be used to determine possible adherence to treatment,\textsuperscript{19,26,29} to assist in clinical decision making\textsuperscript{30} and is also an indicator of the quality of antiepileptic treatment.\textsuperscript{42} Serum samples are usually taken in the morning\textsuperscript{43-44} and because these levels should be drug-fasting they should reflect through values at steady state.\textsuperscript{31,43,45} Sub- and supratherapeutic drug levels can indicate possible non-adherence.\textsuperscript{30} This, however, cannot be conclusive in this study as the measurement of serum drug levels was only performed in 28.26\% (n=13) of the study population. Subtherapeutic levels can be an indication of either non-adherence or underdosing.\textsuperscript{28}

Although criteria for defining uncontrolled epilepsy vary,\textsuperscript{40} one seizure per year is considered to be causative of a decreased quality of life in the majority of patients.\textsuperscript{2,17,24,36,40} Most patients (84.78\%) had more than one seizure over the study period. Non-adherence is one of the most common causes of breakthrough seizures\textsuperscript{19,30} and should not be interpreted as poor seizure control.\textsuperscript{30} Seizure frequency increases the risk for sudden death in epilepsy, which is considered as the most important directly epilepsy related cause of death.\textsuperscript{39} Seizure frequency due to non-adherence should not be interpreted as poor seizure control\textsuperscript{30} and adherence should first be established before regimen change is initiated.

Regimen change can influence therapeutic outcomes\textsuperscript{15} such as serum drug concentrations, seizure frequency\textsuperscript{39} and the quality of life.\textsuperscript{8,11,15,22} The type of regimen change that occurred the most was the change in AED dosage. This has been found to be one of the risk factors for sudden unexpected death in epilepsy.\textsuperscript{39} Generic substitution in the public sector of South Africa occurs without the documentation thereof in patient medical records and the switching between generic products has been indicated as a possible cause of change in serum drug concentrations.\textsuperscript{34} Regimen change occurred the most during valproate treatment and could be a possible cause of the seizure frequency. Regimen change in antiepileptic treatment should
always depend on the individual’s clinical presentation and the advice of an expert prescriber or specialist.34

The available literature on the association between age and adherence to AEDs is conflicting.19,22,29,46 The age group with the most patients was ≥50 and ≤64 years and this might be due to the presence of other chronic conditions, which may or may not influence patient adherence.22,47 Women are less likely to be adherent to their AEDs22,48 and this may be due to the side-effect profile of some of the AEDs22 causing cognitive difficulty or weight gain,49-50 such as valproate.22,44 During the evaluation of PDD against the Standard Treatment Guidelines in South Africa, it was evident that valproate was underdosed in the study population. Underdosing is a reason for seizure incidence,14,22,28,32 which might explain the large number of seizures documented. Monotherapy is still important for maintenance therapy as adherence is better,19,22,29,36,46,49 side-effects less and the risk of drug-drug interactions lower14,16,29,33 when compared to polytherapy, which is associated with an increased risk of sudden unexpected death in epilepsy39 and toxicity.25,29 Polytherapy was prescribed for half of the study population, which might explain non-adherence17,36 and the number of seizures documented.36

This study adds to the limited literature on adherence and clinical outcomes in epilepsy patients in the public sector of South Africa. Limitations that should be considered when interpreting the results include firstly, that the accuracy of patient outcomes depended on clear and correct descriptions made by healthcare professionals in patients’ medical files. Secondly, the serum drug levels provided by the National Health Laboratory Service (NHLS) were not documented in all patient files. The measured serum levels lacked valuable information such as the time of last dose and time of sample taken. This is important in TDM and could have caused gaps in the data. Thirdly, a relatively small number of patients with uncontrolled epilepsy were enrolled in the present study.

WHAT IS NEW AND CONCLUSION
This study investigated the clinical outcomes of adult epilepsy patients in a public hospital in the North West Province of South Africa, not previously reported. The serum drug levels measured were not sufficient to conclude on the adherence status of the study population. The monitoring of patients on valproate was problematic and performing TDM was invaluable and fully justified for optimising the dosage regimen and the quality of life. Poor monitoring of epilepsy and poor history taking by prescribers prevented optimal patient outcomes. The monitoring of adult epilepsy patients in this public health setting needs urgent interventions, which can be improved by classifying the type of epilepsy, determining adherence to treatment, correct documentation of seizure occurrence and TDM, especially in unstable
epilepsy patients. Further studies need to be performed to determine the association between regimen change, non-adherence and seizure frequency. Larger retrospective studies in more hospitals in the North West Province are warranted to enhance the importance of TDM in epilepsy patients.
REFERENCES


CHAPTER 4: CONCLUSION AND RECOMMENDATIONS

4.1 Introduction

The focus of this chapter is to draw conclusions from the specific objectives outlined in Chapter 1. A brief overview is provided of the content of the mini-dissertation and a brief summary of the findings. The limitations and strengths of the study are listed with a conclusion and recommendations for future studies.

The aim of this study was to investigate the prescribing patterns of antiepileptic drugs and adult patients’ clinical outcomes, such as patient adherence, seizure frequency and therapeutic drug levels in the outpatient department of a public hospital in Dr Kenneth Kaunda District, in the North West province, South Africa.

4.2 Content of dissertation

This dissertation consists of four chapters. Chapter 1 provided a general overview of the study, addressing a background, a problem statement, research questions, as well as the aim of the study, specific objectives and the research methodology used in the study.

Chapter 2 focused on epilepsy and antiepileptic drugs used in the public sector of South Africa. The change of regimen, patient adherence and seizure frequency were investigated from the literature.

Chapter 3 represented the results and discussion of the study in manuscript form. One manuscript was presented with the following title:

- Retrospective analysis of adult epilepsy patients’ clinical outcomes: adherence, seizure frequency and therapeutic drug levels in an outpatient department of a public hospital in the North West Province, South Africa

This manuscript is submitted to the “Journal of Clinical Pharmacy and Therapeutics.”

4.3 Literature review

The specific objectives for this study’s literature review were to:

- Conceptualise epilepsy and antiepileptic therapy (indications, pharmacokinetic properties, side-effects and drug-drug interactions) in the public sector of South Africa.
• Identify clinical outcomes in antiepileptic patients, focusing on adherence, seizure frequency and therapeutic serum levels.

The conclusion from the literature study was as follows:

4.3.1 Conceptualise epilepsy and antiepileptic therapy in the public sector of South Africa

Epilepsy is a common neurological condition which can be characterised by two or more seizures (Angus-Leppan & Parsons, 2008:571; McNamara, 2006:501) as result of abnormal functioning of brain cell activity (Dekker, 2002:3). Worldwide prevalence of epilepsy is 50 million people (Banjeree et al., 2009:32) of which almost 80% is found in developing countries (WHO, 2015a). According to GEMS (2011), the government of South Africa’s medical scheme, the prevalence of epilepsy the public sector of South Africa is 1 in 100 people. Epilepsy can be idiopathic, congenital or acquired (Rogers & Cavazos, 2008:927). In developing countries the main causes of epilepsy is caused by infections that influence brain function, such as HIV/AIDS, malaria, neuro-cysticercosis and trauma (Banerjee et al., 2009:31). Epilepsy can be classified as partial or generalised seizures (Gadhoumi et al., 2016:280; Schachter, 2008:675) and sub-classification is described by the WHO (2015b).

Antiepileptic treatment aims to achieve complete suppression of seizures, without causing side-effects (Pellock et al., 2004:301; Stefan & Hopfengartner, 2009:653), promoting an optimal quality of life (Glauser & Pippenger, 2000:14). The selection of AEDs are determined by the seizure type, patient factors, such as age, gender and comorbidities, potential side-effects and cost (Schachter, 2008:673).

Antiepileptic drugs that were available in the hospital in the public sector were the following: carbamazepine, phenobarbitone, lamotrigine, topiramate, valproate and phenytoin. Refer to section 2.3.1 for the South African treatment regime for epilepsy as stated by the Department of Health. Monotherapy is preferred over polytherapy due to better adherence patterns (Brodtkorb et al., 2016:6) and the risk of side-effects lower (Patsalos & Perucca, 2003:247). See Table 2-4 for the indications and pharmacokinetic parameters per AED. Side-effects occur in 40-80% of all epilepsy patients on antiepileptic treatment (Wassenaar et al., 2016:421) and range from neurosensory effects (De Boer et al., 2008:543) to weight change (Faught, 2012:301) and hypersensitivity effects (Rossiter, 2008:442). Drug interactions with AEDs are common, as most of these drugs are enzyme inducers or enzyme inhibitors, affecting drug absorption, metabolism and excretion (Patsalos & Perucca, 2003:347). The old AEDs are potent inducers, causing decrease plasma drug concentrations (Landmark et al., 2015:88).
Enzyme inducers, such as valproate, causes an increase in plasma concentration of co-administered drugs (Fattore et al., 2006:154).

4.3.2 Identify clinical outcomes in antiepileptic patients, focusing on adherence, seizure frequency and therapeutic serum levels

Adherence was the preferred term used in this study as it focused on the patient’s decision to adhere to the recommended treatment by the prescriber (Ho et al., 2009:3028; Ettinger & Baker, 2009:60). Medication adherence continues to be a problem for patients with epilepsy. Non-adherence is considered to be one of the most serious obstacles in the current medical practice (Hovinga et al., 2008:316) with up to 60% of epilepsy patients being non-adherent worldwide (Rogers & Cavazos, 2008:930). Non-adherence results in the failure of seizure control (Brodtkorb et al., 2016:1) and is a waste of healthcare resources (Smithson et al., 2012:52). According to Jacobs et al. (2016a:539), 55% of patients in the private sector of South Africa are adherent to their antiepileptic regime. Other studies conducted in the public sector of South Africa found that the adherence rate for epilepsy patients was 54.9% and 42.9% respectively (Egenasi et al., 2015:329; Krause et al., 2007:14c). The determination of patient medication adherence and the use of interventions to improve adherence are rare in routine clinical practice (Ho et al., 2009:3028; Smithson et al., 2012:52). Apart from patient factors, such as age, stigma and forgetfulness, disease-related factors, such as comorbidities and disease severity and medication-related factors, such as side-effects and polytherapy can affect adherence to medication (Garnett et al., 1998:274; Doughty et al., 2003:710; Rogers & Cavazos, 2008:930). Personalising regimen interventions can improve patient adherence (Brodtkorb et al., 2016:10-11, Ettinger & Baker, 2009:61).

Unfortunately, the most important treatment outcome measurement in epilepsy is seizure occurrence. Achieving seizure freedom is influenced by the issues associated with AED toxicity and poor adherence to AED therapy (Pellock et al., 2004:301). Inadequate seizure control is a primary driver to increase morbidity and mortality, reducing the lower quality of life (Manjunath et al., 2009:372; Bautista & Rundle-Gonzalez, 2012:437). The risk of epilepsy-related death is three times higher during non-adherence (Faught, 2012:299).

The monitoring of serum drug levels, as function of TDM, is a good measurement of patient adherence (Brodtkorb et al., 2016:2; Stepanova & Beran, 2016:2015) and the optimal individual dosage (Rankovic et al., 2012:69). The effectivity of treatment can be evaluated by comparing the serum drug value to the therapeutic drug range (Milosheska et al., 2015:26). Breakthrough seizures can be explained by TDM (Lersinudom et al., 2014:83; Glauser & Pippenger, 2000:13). Serum levels should always be interpreted according to the clinical state

4.4 Empirical study objectives

The specific objectives of the empirical study using patient medical files were to:

- Identify prescribing patterns, such as the type of drug and the prescribed daily dose (PDD) in the public sector for adult epilepsy patients.
- Establish the adherence, by assessing the medicine possession ratio, of adult epilepsy patients.
- Identify the prevalence of change in antiepileptic drug therapy between 1 January 2014 up until 30 June 2016.
- Determine the influence of adherence and/or drug therapy change on seizure frequency and therapeutic antiepileptic drug levels.

The conclusion from the empirical investigation was as follows:

4.4.1 Identify antiepileptic prescribing patterns

The study population was 46 adult patients (mean age of 47 years ± 15.53), with more than half of these patients being male (54.30%). The female-to-male ratio (1:1.13) was relatively equal in all patients. Although the association between gender and adherence was not measured in this study, studies have found that women are less likely to be adherent to AED, especially if side-effects, such as weight gain and cognitive changes occur (Manteuffel et al., 2014:112; Brown et al., 2009:635). The majority of antiepileptic patients was between the ages of 50 and 64 years. Older adults are more prone to be adherent than younger adults to AEDs (Jacobs et al., 2016b:4), due to increased risk of comorbidities or other chronic conditions (Jacobs et al., 2016b:540; Keezer et al., 2016:106).

During investigation of AED the tendency of increased prescribing of new AED around the world (Bautista & Rundle-Gonzalez, 2012:437; Jacobs et al., 2016b:1; De Groot et al., 2014:668) was not seen in this study. Valproate, an old AED (Rogers & Cavazos, 2008:946; Bautista & Rundle-Gonzalez, 2012: 437), was the active ingredient most frequently prescribed (n=41; 53.24%), followed by lamotrigine (n=24; 31.16%) and carbamazepine (n=8; 10.39%). These drugs are first-line treatment for epilepsy in the public health sector (Department of Health, 2012:14.5). See section 2.3.1 on the regimens for AEDs in South Africa. Newer AEDs, such as lamotrigine and topiramate, have a broader spectrum of action and are more tolerable with less side-effects (De Groot et al., 2014:668). The evaluation of PDD against the STG in
South Africa, revealed that valproate was underdosed in the study population. Underdosing is a reason for seizure breakthrough (Dekker, 2002:65). Treatment with AED monotherapy in maintenance therapy is beneficial, as patient adherence is better and less side-effects and drug-drug interactions may occur compared to polytherapy (Bautista & Rundle-Gonzalez, 2012:437; Ettinger & Baker, 2009:60; Rossiter, 2008:440). Polytherapy was prescribed to half of the study population and is associated with inadequate seizure control (Bautista & Rundle-Gonzalez, 2012:437), toxicity (Brodtkorb et al., 2016:7; Kingsman et al., 2007:20), an increased risk of sudden unexpected death in epilepsy (Nilsson et al., 2001:667) and therefore the need for TDM services (Burianova & Borecka, 2015:88; Chan & Beran, 2008:573). Complex regimens are found to decrease patient adherence to antiepileptic treatment (Claxton et al., 2001:1297; Faught, 2012:297).

4.4.2 Establish the adherence, by assessing the medicine possession ratio, of adult epilepsy patients

Non-adherence in epileptic patients is a major concern as adherence is a key factor in the effective treatment to manage this condition (Andrade et al., 2006:565; Nilsson et al., 2001:67). The prevalence of non-adherence in epilepsy patients tends to be high in the world (Smithson et al., 2012:49; Jacobs et al., 2016a:540; Rogers & Cavazos, 2008:930; Brown et al., 2009:634). In the private health sector of South Africa, only 55% of patients were adherent to their AED treatment (Jacobs et al., 2016a:539), while in the public health sector 42.9% and 54.9% have been reported (Krause et al., 2007:14c; Egenasi et al., 2015:329). The adherence to AED treatment in this study (64.9%) was higher than these other studies, but still relatively poor compared to the ideal 80% (Faught, 2012:297; Ettinger & Baker, 2009:62) (see Chapter 3 on adherence per AED). The over- and undersupply of medication can be seen as a waste of medical resources (Jacobs et al., 2016a:543).

Valproate was the AED with the highest adherence (63.41%) which might be due to the consistent twice daily dosing and modified-release formulation available (Pellock et al., 2004:307; Jacobs et al., 2016a:544).

4.4.3 Identify the prevalence of change in antiepileptic drug therapy between 1 January 2014 and 30 June 2016

Therapeutic outcomes can possibly be influenced by regimen change, as it may affect seizure frequency (Jacobs et al., 2016b:4), serum drug levels (Nilsson et al., 2001:67) and the patient’s quality of life (Wassenaar et al., 2016:421; Rogers & Cavazos, 2008:92). More than one regimen change occurred in 69.56% (n=32) of the study population, with the main cause
for regimen change due to seizure breakthrough. The type of regimen change that occurred the most was the change in AED dose. The frequent changing of AED dose is found to be one of the risk factors for sudden unexpected death in epilepsy (Nilsson et al., 2001:670). Generic substitution occurs without the documentation thereof in medical files of the public hospital. Switching between generic products has been indicated as a possible cause for seizure breakthrough and a change in serum drug levels (Jacobs et al., 2016b:5). Regimen change occurred mostly during valproate treatment (70.69%) and could be a possible cause for the high seizure frequency. The expert opinion of a prescriber should be considered before initiating a regimen change (Jacobs et al., 2016b:5). Further investigation is needed to determine the association between regimen change and seizure breakthrough.

4.4.4 Determine the influence of adherence and/or drug therapy change on seizure frequency and therapeutic antiepileptic drug levels

Therapeutic drug monitoring (TDM), by evaluating serum drug levels, can be used to determine patient adherence (Bordtkorb et al., 2016:2; Pudifin et al., 2012:14.5; Stepanova & Beran, 2015:7) and to individualise treatment (Milosheska et al., 2015:26, 28; Landmark et al., 2015:88, 91). The evaluation of serum drug levels must be used in context with the patient’s dosage, time of last dose and the time the sample was taken (Chan & Beran, 2008:573; Fattore et al., 2006:155). Both sub- and supratherapeutic levels may imply possible non-adherence (Stepanova & Beran, 2015:8) or underdosing (Lertsinudom et al., 2014:83; Dekker, 2002:65). Possible reasons for subtherapeutic levels are non-adherence, polytherapy which can cause enzyme induction (Patsalos & Perucca, 2003:347; Burianova & Borecka, 2015:868), the metabolising status of a patient and clinical signs such as diarrhoea which can prevent drug absorption (Dekker, 2002:65). The subtherapeutic levels measured can only indicate the possibility of poor adherence, which, however, cannot be concluded by this study due to too few serum drug levels measured and documented in patient medical files by healthcare professionals. This highlights the role of serum AED level determinations in evaluating adherence (Ettinger & Baker, 2009:60; Bordtkorb et al., 2016:2; Rogers & Cavazos, 2008:929). Although TDM is recommended for valproate (Glauser & Pippenger, 2000:13), it is troublesome that only 19 serum levels were measured from the 41 patients on valproate during the study period.

The definition of uncontrolled epilepsy is unclear (Egenasi et al., 2015:329) and therefore studies have considered one seizure per year as a cause in decreasing the quality of life in an epileptic patient (Rankovic et al., 2012:69; Manjunath et al., 2009:372; Bautista & Rundle-Gonzalez, 2012:437). Most patients (84.78%) had more than one seizure during the study period. Non-adherence to AED treatment is one of the most common causes of seizure
breakthroughs (Faught, 2012:299; Smithson et al., 2013:109). Seizure frequency can increase the risk for sudden death in epilepsy, which is considered as the most important directly epilepsy-related cause of death (Nilsson et al., 2001:667). Seizure frequency was also determined per AED and more than 75% of patients on the different AEDs experienced seizures. A change in AED regime could be a possible cause of the seizure frequency. According to Stepanova and Beran (2015:7) seizure breakthrough as a result of non-adherence should not be interpreted as poor seizure control and adherence should first be established before regimen change is initiated.

Valproate was the drug mostly prescribed in the study population and was used as the forth regime of treatment for complicated or uncontrolled epilepsy and as second regime in HIV patients (Department of Health, 2012:14.5). This may suggest that most of the outpatient population with epilepsy were uncontrolled or that epilepsy was a comorbidity in HIV patients. The highest percentage of subtherapeutic levels and the most seizures were reported for valproate. Monitoring of epilepsy patients on valproate seems to be essential to improve clinical outcomes and performing TDM is fully justified to optimise the dosage regimen.

This study adds to the limited literature on adherence and clinical outcomes in epilepsy patients of South Africa. The monitoring of epilepsy patients need urgent investigations. Patient outcomes can be improved by determining adherence to treatment, correct documenting of seizure breakthrough and to perform TDM, especially in patients on valproate treatment. Larger retrospective studies in more hospitals in the North West Province will enhance the importance of TDM in epilepsy patients. This concludes that non-adherence to their antiepileptic treatment is suspected and therapeutic drug monitoring in epilepsy patients is required in this public hospital of the North West Province.

4.5 Limitations of the research

There are several limitations regarding the study. The outcomes depended on the clear and correct descriptions made by healthcare professionals in patient medical files on the date of visit to the hospital. These descriptions were used to document seizure frequency, serum drug levels and side-effects of AED during the study period.

The type of epilepsy was not indicated in the medical records. Serum drug levels, provided by the National Health Laboratory Service (NHLS), were not documented or attached in all patient files. This could have caused gaps in the data, leading to inaccurate conclusions. All laboratory values available were documented per AED for each patient.
Antiepileptic regimen change during the last month of the study period (June 2016) might be a limitation to the study, because the clinical outcomes, such as seizure frequency, adherence and drug therapeutic levels, were not documented in the patient file, unless the patient visited the hospital twice in the last month.

The number of patients that complied with the inclusion criteria is not sufficient to make conclusions on practical and statistical significance associations. Therefore, only descriptive interpretations of the results could be made.

4.6 Strengths

This was a low-risk study, since depersonalised data were used, resulting in minor ethical implications. Reliability and validity of data were ensured (see section 1.6.2).

The study provided the following benefits:

- Information to the South African health sector regarding the prevalence of antiepileptic treatment changes and the investigation of on clinical outcomes, such as adherence, seizure frequency and serum drug levels to therapeutic ranges per AED in this public hospital in the Dr Kenneth Kaunda District in the North West province.
- Contribution to knowledge about patient adherence patterns, by investigating the MPR and serum drug levels, in order to improve healthcare and well-being of patients.
- This study provides an improvement in healthcare delivery to epileptic patients and can improve the prescribing practice of antiepileptic treatment to patients in this public hospital in the Dr Kenneth Kaunda District and the North West Department of Health.

4.7 Recommendations

Future research must focus on the following aspects:

- This study focused on one hospital in the public health sector of the Dr Kenneth Kaunda District, North West province. It is recommended that future research projects should be implemented in more hospitals in this and/or other districts of the province to reflect a greater population.
- It is recommended that research on epilepsy adherence and prescribing patterns should be conducted in the primary healthcare level of South Africa. Many patients of primary health care facilities are diagnosed with infections, such as HIV and Tuberculosis (TB) meningitis, which are identified as common causes of epilepsy in
developing countries (Angus-Leppan & Parsons, 2008:578; Siddiqi & Birbeck, 2013:531).

- More research focusing on the prescribing patterns for epilepsy patients must be performed in South Africa, because there is minimal literature available.
- The ‘influence’ of regimen change on patient level, according to the study title, could not be measured due to the limitations of a small study population size. It is suggested that the title should change to: ‘A retrospective analysis of adult epilepsy patients’ clinical outcomes: adherence, seizure frequency and therapeutic drug levels in an outpatient department of a public hospital in the North West Province, South Africa.’

4.8 Chapter summary

This final chapter completed the study by discussing the conclusions drawn from the specific objectives outlined from the literature review and the empirical investigation. The strengths and limitations of the study were described and recommendations for future research were made.
REFERENCES


Department of Health, South Africa see South Africa.


Medicines and Related Substances Control Act see South Africa.


# ANNEXURE A: DATA COLLECTION TOOL

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ANNEXURE B: THE HEALTH RESEARCH ETHICS COMMITTEE CERTIFICATE

ETHICS APPROVAL CERTIFICATE OF PROJECT

Based on approval by Health Research Ethics Committee (HREC), the North-West University Institutional Research Ethics Regulatory Committee (NWU-IERC) hereby approves your project as indicated below. This implies that the NWU-IERC grants its permission that, provided the special conditions specified below are met and pending any other authority that may be necessary, the project may be initiated, using the ethics number below.

Project title: Influence of antiepileptic treatment changes on adult patients’ clinical outcomes in an outpatient population.

Project Leader: Prof M6 Lubbe
Student: R Derksen

Ethics number: NWU-IERC-2016-041-S-A11

Approval date: 2016-02-22 Expired date: 2017-02-21 Risk: Medium

Special conditions of the approval (if any):
- Translation of the informed consent document to the languages applicable to the study participants should be submitted to the HREC if applicable.
- Any research at governmental or private institutions, permission must still be obtained from relevant authorities and provided to the HREC. Ethics approval is required before approval can be obtained from these authorities.
- Any further information and any report template is obtainable from Carolin van Zyl at Carolin.VanZyl@nwu.ac.za

General conditions:
- While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, please note the following:
  - The project leader (principal investigator) must report to the prescribed format to the NWU-IERC and HREC:
    - Annually or as otherwise required on the progress of the project, and upon completion of the project;
    - Without any delay in case of any adverse events (or not event that interrupts sound ethical principles) during the course of the project;
    - Annually a number of projects may be randomly selected for an external audit;
  - The approval applies strictly to the protocol as stipulated in the application form. Should any changes to the protocol be deemed necessary during the course of the project, the project leader must apply for approval of these changes at the HREC and NWU-IERC. Would there be deviation from the project protocol without the necessary approval of such changes, the ethics approval is immediately and automatically forfeited;
  - The date of approval indicates the first date that the project may be started. Would the project have to continue after the expiry date, a new application must be made to the NWU-IERC and new approval be received before or on the expiry date.
  - In the interest of ethical responsibility the NWU-IERC and HREC retains the right to:
    - Request access to any information or data at any time during the course of after completion of the project;
    - To ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process;
    - Withdraw or postpone approval if:
      - any unethical principles or practices of the project are revealed or suspected;
      - it becomes apparent that any relevant information was withheld from the NWU-IERC or that information has been false or misrepresented;
      - the required annual report and reporting of adverse events was not done timely and accurately, new institutional rules, national legislation or international conventions demand it necessary.

The IERC would like to remain at your service as scientist and researcher, and wishes you well with your project. Please do not hesitate to contact the IERC for any further enquries or requests for assistance.

Yours sincerely

Prof LA Du Plessis

Prof Linda du Plessis

Chair NWU Institutional Research Ethics Regulatory Committee (IERC)
ANNEXURE C: NORTH WEST DEPARTMENT OF HEALTH:
POLICY, PLANNING, RESEARCH, MONITORING AND EVALUATION
(PPRM&E) PERMISSION LETTER

POLICY, PLANNING, RESEARCH, MONITORING AND EVALUATION

Name of researcher : Ms. R. Derksen
North West University

Physical Address : Hoffman Street
Potchefstroom Campus
Potchefstroom

Subject : Research Approval Letter- Influence of antiepileptic treatment changes on adult patients' clinical outcomes in an outpatient population.

This letter serves to inform the Researcher that permission to undertake the above mentioned study has been granted by the North West Department of Health. The Researcher is expected to arrange in advance with the chosen facilities, and issue this letter as proof that permission has been granted by the Provincial office.

This letter of permission should be signed and a copy returned to the department. By signing, the Researcher agrees, binds himself/herself and undertakes to furnish the Department with an electronic copy of the final research report. Alternatively, the Researcher can also provide the Department with electronic summary highlighting recommendations that will assist the department in its planning to improve some of its services where possible. Through this the Researcher will not only contribute to the academic body of knowledge but also contributes towards the bettering of health care services and thus the overall health of citizens in the North West Province.

Kindest regards

[Signature]
Mr. L.P. Mosiel
Acting Director: PPRM&E

[Signature]
Researcher

[Stamp] LEPAPHA LA SOTHEKANELO
DEPARTMENT OF HEALTH
NORTH WEST PROVINCE
12 MAR 2016

Healthy Living for All

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ANNEXURE D: JOURNAL OF CLINICAL PHARMACY AND THERAPEUTICS

Author Guidelines

3. General

The Journal of Clinical Pharmacy and Therapeutics (JCPT) provides a forum for clinicians, pharmacists and pharmacologists to explore and report on issues of common interest. It welcomes five main types of articles

- Editorials
- Original research
- Review articles (including Mini-reviews)
- Commentaries
- Case reports

As our main interest is on novelty, irrespective of the type of contribution, the sub-headings should identify what is known and what is new. A clear description of these aspects is important as they are used by us to filter submissions at the very first stage. This helps us to return manuscripts quickly to authors for submission elsewhere.

Please read the instructions below carefully for details on the submission of manuscripts, the Journal's requirements and standards as well as information concerning the procedure after a manuscript has been accepted for publication in JCPT.

4. Ethical Guidelines

JCPT has adopted the following ethical guidelines for publication and research.

2.1 Authorship and Acknowledgements

Authorship: Authors submitting a paper do so on the understanding that the manuscript has been read and approved by all authors and that all authors agree to the submission of the manuscript to the Journal.

JCPT adheres to the definition of authorship set up by The International Committee of Medical Journal Editors (ICMJE). According to the ICMJE authorship criteria, all named authors should meet the following conditions: 1) substantial contributions to conception and design of, or
acquisition of data or analysis and interpretation of data, 2) drafting the article or revising it critically for important intellectual content and 3) final approval of the version to be published. Participation solely in the acquisition of funding or the collection of data does not justify authorship. All people who fulfil the criteria for authorship should be listed as authors. Contributors who do not qualify as authors should be mentioned in Acknowledgements.

The Editors recognise that complex, large-scale and multi-centre research will often result in a significant number of people fulfilling the authorship criteria. However, they reserve the right to ask the lead author to justify the inclusion of more than six authors.

**Acknowledgements:** Under Acknowledgements please specify contributors to the research/article other than the authors accredited. Please note that research funders are now listed separately under Source of Funding.

### 2.2 Conflict of Interest and Source of Funding

*JCPT* requires that sources of financial support for the work reported within the manuscript are fully acknowledged, and any potential conflicts of interest noted.

**Conflict of Interest:** All manuscripts submitted to the Journal require a statement about authors' conflicts of interest. Please disclose any possible conflict of interest under the heading 'Conflicts of Interest' on the title page of your manuscript. Any reported conflicts of interest will be published in a highlighted box as part of the article. If no conflicts of interest are reported, the box will include the statement "No conflicts of interest have been declared". Possible conflicts of interest include financial interests relating to issues discussed in the manuscript (e.g. patent ownership, stock ownership, consultancies and speaker's fees).

**Source of Funding:** Authors are required to specify the sources of funding for their research when submitting a manuscript. These include the individuals and organisations that supplied resources for interventions as well as those that funded researcher time and other research costs. All sources of funding should be named and their location (town, state/county, country) included. The information should be provided on the title page of the manuscript and will be disclosed in the published article.

### 2.3 Appeal of Editorial Decisions

The Editors make careful judgements about the selection of manuscripts for publication, taking into account the extent to which the manuscript is consistent with the aims and scope of the Journal and their own and referees' assessments of the quality of the work and the contribution it is likely to make to knowledge, policy and practice. We are able to accept only a proportion
of the manuscripts that are submitted to the Journal, and recognise that authors are often disappointed when we decline to publish their manuscripts. We strongly discourage routine appeals against such decisions. Authors who believe there were serious flaws in our editorial judgement may appeal decisions by e-mailing the editorial office with a detailed explanation of their concerns.

2.4 Permissions

If all or parts of previously published illustrations are used, permission must be obtained from the copyright holder concerned. It is the author's responsibility to obtain these permissions in writing and provide copies to the Publishers.

2.5 Copyright Assignment

If your paper is accepted, the author identified as the formal corresponding author for the paper will receive an email prompting them to login into Author Services; where via the Wiley Author Licensing Service (WALS) they will be able to complete the license agreement on behalf of all authors on the paper.

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If the OnlineOpen option is not selected the corresponding author will be presented with the copyright transfer agreement (CTA) to sign. The terms and conditions of the CTA can be previewed in the samples associated with the Copyright FAQs below:


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If the OnlineOpen option is selected the corresponding author will have a choice of the following Creative Commons License Open Access Agreements (OAA):

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5. Submission of Manuscripts

Manuscripts should be submitted electronically via http://mc.manuscriptcentral.com/jcpt. Authors may track the status of their own manuscripts. Complete instructions for submitting papers are available online and a user ID and password can be obtained from the first visit. Further assistance can be obtained from: support@scholarone.com. If you cannot submit online or have a general query, please contact Professor Alain Li Wan Po (Editor-in-Chief) at alainliwanpo@yahoo.com

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Prior to acceptance you should not inform the Editorial Office that you intend to publish your paper OnlineOpen. All OnlineOpen articles are treated in the same way as any other article. They go through the Journal's standard peer-review process and will be accepted or rejected based on their own merit.

6. Manuscripts Types Accepted

**Original research:** Reports in this section should have a structured summary and a main text, both of which must have the following sub-headings: What is known and Objective; Methods; Results and discussion; What is new and Conclusion.
The maximum word-length for reports of original research is 3000 words excluding tables, figures, references and summary. We encourage submission of additional supporting material for online-only publication but this should be clearly identified and labeled as ‘Online appendix A1’ etc. within the text.

**Review articles:** These contributions should have a structured summary and a main text both of which must have the following sub-headings: What is known and Objective; Methods; Results and discussion; What is new and Conclusion. If your review is not a systematic review, then it should be submitted as a commentary. A mini-review can be submitted either as a commentary or as a systematic review depending on the methodology used.

The maximum word-length for a Review is 5000 words excluding tables, figures, references and summary. A mini-review is by definition shorter than this but we impose no specific word-length. We encourage submission of additional supporting material for online-only publication but this should be clearly identified and labeled as ‘Online appendix A1’ etc. within the text.

**Commentaries:** A commentary should have:

(i) a structured summary of no more than 150 words with the following subheadings: What is known and Objective; Comment; What is new and Conclusion.

(ii) a main text with the same sub-headings as the summary but with a maximum of 2000 words excluding references.

In both the summary and the main text, the Comment section should make up the bulk of the contribution (> 90%).

**Editorials:** Generally these are contributed by our own Editors to describe specific developments at the Journal but may also include invited contributions from leading experts on highly topical subjects for which the novelty is obvious. These expert contributions may vary considerably in length and style so as to ensure particularly rapid publication.

**Case reports:** A case report should have:

(i) a summary of not more than 100 words

(ii) a main text of not more than 1500 words excluding references.

Both sections should have the following sub-headings: What is known and objective; Case description; What is new and Conclusion. In both sections the case-description should make up the bulk (> 90%) of the contribution. We encourage submission of additional supporting
material for online-only publication but this should be clearly identified and labelled as ‘Online appendix A1’ etc. within the text.

**Letters:** Correspondence is invited. Letters will only be considered if they contain constructive comments on published articles and if they are received in time to allow the authors a right of reply. Publication of correspondence is at the discretion of the Editor.

7. **Manuscript Format and Structure**

5.1 **Format**

**Language:** The language of publication is English. Authors for whom English is a second language should have their manuscript professionally edited by an English speaking person before submission to make sure the English is of high quality. A list of independent suppliers of editing services can be found at http://authorservices.wiley.com/bauthor/english_language.asp. All services are paid for and arranged by the author, and use of one of these services does not guarantee acceptance or preference for publication.

**Units and Spellings:** Système International (SI) units should be used, as given in *Units, Symbols and Abbreviations* (4th edition, 1988), published by the Royal Society of Medicine Services Ltd, 1 Wimpole Street, London W1M 8AE, UK. Other abbreviations should be used sparingly and only if a lengthy name or expression is repeated throughout the text. Spelling should conform to that used in *The Concise Oxford Dictionary*, published by Oxford University Press. Authors should strenuously avoid the use of jargon or obscure technical terms.

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**ANNEXURE E: SUBMISSION OF MANUSCRIPT**

**Journal of Clinical Pharmacy and Therapeutics**

Retrospective analysis of adult epilepsy patients' clinical outcomes: adherence, seizure frequency and therapeutic drug levels in an outpatient department of a public hospital in the North West Province, South Africa

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<td>Complete List of Authors:</td>
<td>Derksen, Rachelle; North West University School of Pharmacy, Clinical Pharmacy</td>
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<td>Lubbe, Martha; North West University, Medicine Usage in South Africa</td>
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<td>Khadrew, Malia; North West University, Centre of Excellence for Pharmaceutical Sciences</td>
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<td>Coolahan, Markle; North-West University, Medicine Usage in South Africa (MUSA)</td>
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ANNEXURE F: PROOF OF LANGUAGE EDITING

DECLARATION

I, C Vorster (ID: 710924 0034 084), Language editor and Translator, and member of the South African Translators' Institute (SATI member number 1003172), herewith declare that I did the language editing of the mini-dissertation of ms R Derksen (student number 21619557) from the North-West University.

Title of the mini-dissertation: Influence of antiepileptic treatment changes on adult patients' clinical outcomes in an outpatient population, North West

C Vorster

16/11/2016

Date

(BA (1992), NDBI (1993), Hons Translation Studies (2015))