An analysis of medication adherence among epileptic patients in the private health sector of South Africa

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Proverbs 3:6

"Seek God's will in all you do, and He will show you the path to take"

ABSTRACT

An analysis of medication adherence among epileptic patients in the private health sector of South Africa

Failure to respond to anti-epileptic (AED) treatment and achieving control over epilepsy has severe clinical consequences. The clinical consequences include an increase in the frequency of seizures and increased work and social impairment, poor treatment outcome, increased treatment costs associated with hospitalisation, over-utilisation of health-care systems and ultimately mortality.

The general aim of the study was to measure AED adherence, to determine which factors are closely associated with AED non-adherence and the consequences of prolonged AED non-adherence in the private health sector of South Africa. The empirical study followed a quantitative, descriptive design using longitudinal medicine claims data from 1 January 2008 to 31 December 2013, provided by a nationally representative Pharmaceutical Benefit Management (PBM) company. The study population consisted of all patients registered on the database with an ICD-10 code for epilepsy (G40).

The number of epilepsy patients identified over the study period ranged from 6 634 in 2008 to 7 387 in 2013, representing 0.87 to 0.91% of the total number of registered beneficiaries included in the database. Anti-epileptic drugs were prescribed in 0.92% (n= 62 442) to 1% (n= 67 960) of the total number of patients on the database from 2008 to 2013. The mean number of AED items per epilepsy patient ranged from 1.42 ± 0.86 (95% CI 1.40-1.44) in 2008 to 1.55 ± 1.03 (95% CI 1.52-1.57) in 2013. The active ingredient most prescribed was valproate (ranging from 13.24% to 17.02%), followed by lamotrigine (ranging from 12.73% to 17.80%) and carbamazepine (ranging from 15.54% to 13.82%) during the study period. Patients were predominantly female (female-to-male ratio 1.19:1) (p= 0.478; Cramer's V= 0.010). There were no statistical significant associations observed between the average number of AED prescription per patient and gender. The highest average number of AED prescriptions was observed in the 41 to 65 years age group, increasing with 1.91% from 2008 to 2013. A practical significance was observed between the average number of AED prescriptions and the different age groups (p< 0.0001; Cohen's d ≤ 0.314 in 2008; Cohen's d ≤ 0.244 in 2013).

There were several chronic conditions co-occurring with epilepsy, with hypertension being the most prevalent, followed by hyperlipidaemia and hypothyroidism. The average direct cost per medicine item per patient increased from R237.12 ± R146.93 (95% CI 233.58-240.65) to R522.32 ± R310.62 (95% CI 515.24-529.41) during the study period. A remarkable increase in the average patient contribution was observed during this period (R27.76 ± R46.96 in 2008 to

R264.32 ± R162.61 in 2013). Non-substitutable AEDs (those without generics available) were the most prescribed (39.85% over study period), which could be attributed to the increased medical expenditures by the patients (89.50%). The non-substitutable medication use decreased over the study period ranging from 40.06% in 2008 to 26.92% in 2013

Adherence of only 55.14% (n= 26 214) was observed for anti-epileptic treatment. A statistically significant association was found between the active ingredient consumed and adherence status (*p*= <0.0001), thereby indicating that the use of certain active ingredients resulted in better adherence (Cramer's *V*= 0.071). Only 5.73% of patients receiving clonazepam were adherent compared to 22.96% and 22.54% in the cases of valproate and lamotrigine, respectively. The current study found that the number of co-morbid conditions and the duration of the treatment period had a statistically significant influence on adherence status (*p*= <0.0001; Cramer's *V*= 0.050 and *p*= <0.0001; Cramer's *V*= 0.208 respectively). Non-adherence (undersupply and oversupply of medication) contributed to 20.12% of wasted resources (R32 021 575.77).

In conclusion, the current study confirms that AED non-adherence is an important concern in developing countries similar to developed countries. Several factors were found to be closely associated with AED treatment non-adherence, which include a short treatment period, certain active ingredients and chronic co-morbid conditions. High direct medicine costs of treatment could further contributed to the poor adherence status, which is especially worrying in a country such as South Africa as we do not have the financial capacity to carry such a burden.

Keywords: prevalence, prescribing patterns, epilepsy, private health sector, direct medicine costs, medicine possession ratio modified

UITTREKSEL

’n Analise van geneesmiddelmeewerkendheid onder epileptiese pasiënte in die private gesondheidsektor van Suid-Afrika

’n Onvermoë om te reageer op anti-epileptiese (AE) behandeling of as pasiënte nie beheer oor epilepsie het nie, het ernstige kliniese nagevolge. Die kliniese nagevolge sluit in verhoogde frekwensie van epileptiese aanvalle en ’n verlaagde werk- en sosiale funksionering, swak behandelingsuitkomste, verhoogde behandelingskoste geassosieer met hospitalisering, oorgebruik van gesondheidsisteme en ten einde die dood.

Die sleuteldoelwitte van die studie was om die AE-meewerkendheid te bepaal, asook die faktore wat bydrae by tot AE-nie-meewerkendheid en die nagevolge van langdurige AE-nie-meewerkendheid in die private gesondheidsektor van Suid-Afrika. ’n Kwantitatiewe, beskrywende, longitudinale studie-ontwerp wat medisyne-eise-data ontleed in die empiriese studie, is gebruik. Die data is verkry vanaf ’n nasionaal verteenwoordigende Farmaseutiese Voordelemaatskappy, vir die tydperk 1 Januarie 2008 tot 31 Desember 2013. Die studie populasie het bestaan uit alle pasiënte geregistreer op die databasis met ’n ICD-10-kode vir epilepsie (G40).

Die aantal epilepsie-pasiënte geïdentifiseer oor die studietydperk het gewissel vanaf 6 634 in 2008 tot 7 387 in 2013, met ’n verteenwoordigende voorkoms van 0.87 tot 0.91% van die totale aantal pasiënte geregistreer as begunstigdes ingesluit in die databasis. Anti-epileptiese middels (AEMs) is voorgeskryf in 0.92% (n= 62 442) tot 1% (n= 67 960) van die totale aantal pasiënte op die databasis vanaf 2008 tot 2013. Die gemiddelde aantal AEM-items per epilepsie-pasiënt het gewissel tussen 1.42 ± 0.86 (95% CI 1.40-1.44) in 2008 tot 1.55 ± 1.03 (95% CI 1.52-1.57) in 2013. Die aktiewe bestanddeel wat die meeste voorgeskryf is tydens die studietydperk was valproaat (gewissel vanaf 13.24% tot 17.02%), gevolg deur lamotrigien (gewissel vanaf 12.73% tot 17.80%) en karbamasepien (gewissel vanaf 15.54% tot 13.82%). Pasiënte was oorwegend vroulik (vroulik-tot-manlik-verhouding 1.9:1) (p= 0.478; Cramer se V= 0.010). Daar is geen statistiese betekenisvolle verskille waargeneem tussen die gemiddelde AE voorskrif per pasiënt en geslag nie. Die hoogste gemiddelde aantal AE voorskrifte was waargeneem in die 41 tot 65 jaar ouderdomsgroep, met ‘n verhoging van 1.91% vanaf 2008 tot 2013. ‘n Praktiese betekenisvolheid is waargeneem tussen die gemiddelde aantal AE voorskrifte en die verskeie ouderdomsgroepe (p< 0.0001; Cohen se d ≤ 0.314 in 2008; Cohen se d ≤ 0.244 in 2013).

Daar is verskeie kroniese siektetoestande wat tesame met epilepsie voorkom. Die gemiddelde direkte koste per medisyne-item per pasiënt het toegeneem vanaf R237.12 ± R146.93 (95% CI 233.58-240.65) tot R522.32 ± R310.62 (95% CI 515.24-529.41) gedurende die studietydperk. ’n

Merkwaardige toename in die gemiddelde pasiëntbydrae was waargeneem gedurende die studietydperk (R27.76 ± R46.96 in 2008 tot R264.32 ± R162.61 in 2013). Nie-vervangbare AEM's (geneesmiddels sonder 'n beskikbare generies) was die meeste voorgeskryf (39.85% oor die studietydperk), wat moontlik kan bydra tot die verhoogde mediese uitgawes deur pasiënte (89.50%). Die nie-vervangbare geneesmiddels se gebruik het verminder oor die studietydperk, met 'n wisseling vanaf 40.06% in 2008 tot 26.92% in 2013.

'n Meewerkendheid van slegs 55.14% (n= 26 214) is waargeneem ten opsigte van AE-behandeling. 'n Statisties betekenisvolle verband is gevind tussen die soort aktiewe bestanddeel en die meewerkendheidstatus (*p*= <0.0001), dus 'n aanduiding dat die gebruik van sekere aktiewe bestanddele beter meewerkendheid deur pasiënte meebring (Cramer's *V*= 0.071). Slegs 5.73% van pasiënte wat klonasepam ontvang het, was meewerkend teenoor die 22.96% en 22.54% respektiewelik wat valproaat en lamotrigien ontvang het. Die huidige studie het bevind dat die aantal ko-morbiede chroniese siektetoestande en die duur van behandelingsperiode 'n statistiese betekenisvolle resultaat lewer op die meewerkendheidstatus (*p*= <0.0001; Cramer se *V*= 0.050 en *p*= <0.0001; Cramer se *V*= 0.208 respektiewelik). Nie-meewerkendheid (ondervoorsiening en oorvoorsiening van geneesmiddels) dra by tot 20.12% van vermorste hulpbronne (R32 021 575.77).

Ten slotte, die studie bevestig dat AEM-nie-meewerkendheid 'n probleem in ontwikkelende lande is, soortgelyk aan ontwikkelde lande. Verskeie faktore het 'n statistiese betekenisvolle verabnd met AEM-nie-meewerkendheid insluitend 'n kort behandelingsperiode, sekere aktiewe bestanddele en kroniese ko-morbiditeite. Hoë direkte medisyne behandelingskoste kan verder bydra tot 'n swak meewerkendheidstatus. Dit is veral kommerwekkend in 'n land soos Suid-Afrika, wat nie die finansiële kapasiteit besit om sulke laste te dra nie.

Trefwoorde: voorkoms, voorskryfpatrone, epilepsie, private gesondheidsektor, direkte medisynekoste, veranderde medisynebesit-verhouding

PREFACE

This dissertation was written up in article format. The findings of the study will be presented in Chapter 3 in manuscript format as required by the regulations of the North-west University. Two manuscripts will be submitted for publishing in the following journals:

- *Epilepsia*
- *South African Family Practice*

Each manuscript will contain a reference list cited according to the instructions for authors required by each respective journal. The complete reference list is included at the end of the 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 methodology used to conduct this study.
- Chapter 2 entails a literature review of anti-epileptics (brief summary of the mechanism of action, clinical uses and contra-indications of the various active ingredients) 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 will follow at the end.

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

AUTHOR'S CONTRIBUTIONS (STUDY AND MANUSCRIPT 1)

The contribution of each author to the study and Manuscript 1, entitled "Patient adherence with anti-epileptic drugs in the private health sector of South Africa: 2008-2013" is stipulated in the following table.

Author	Role in studies
Miss K Jacobs	Responsible for the literature review Planning and the design of the manuscript Data and statistical analyses Interpretation of results Writing of dissertation and manuscript
Dr M Julyan (Supervisor)	Supervision of concept of study and manuscript Supervision in the writing of the dissertation and manuscript Revising the manuscript critically for final approval
Prof MS Lubbe (Co-supervisor)	Co-supervision of concept of study and manuscript Co-supervision in the writing of the dissertation and manuscript Programming for statistical analysis Data and statistical analysis Guidance in the interpretation of results Reviewing the manuscript for final approval of the version to be published
Dr JR Burger (Co-supervisor)	Co-supervision of concept of study and manuscript Co-supervision in the writing of the dissertation and manuscript Revising the manuscript for intellectual content and final approval
Mrs M Cockeran (Statistician)	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 (Pharmacy Practice) study of Miss K Jacobs.

.....	.....
Dr M Julyan	Prof MS Lubbe
.....	.....
Dr JR Burger	Mrs M Cockeran

AUTHOR'S CONTRIBUTIONS (MANUSCRIPT 2)

The contribution of each author for manuscript 2 entitled "Anti-epileptic prescribing patterns in the South African private health sector (2008-2013)" is stipulated in the following table.

Author	Role in studies
Miss K Jacobs	Responsible for the literature review Planning and the design of the manuscript Data and statistical analyses Interpretation of results Writing of dissertation and manuscript
Dr M Julyan (Supervisor)	Supervision of concept of study and manuscript Supervision in the writing of the dissertation and manuscript Revising the manuscript critically for final approval
Prof MS Lubbe (Co-supervisor)	Co-supervision of concept of study and manuscript Co-supervision in the writing of the dissertation and manuscript Programming for statistical analysis Data and statistical analysis Guidance in the interpretation of results Reviewing the manuscript for final approval of the version to be published
Dr JR Burger (Co-supervisor)	Co-supervision of concept of study and manuscript Co-supervision in the writing of the dissertation and manuscript Revising the manuscript for intellectual content and final approval
Mrs M Cockeran (Statistician)	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 (Pharmacy Practice) study of Miss K Jacobs.

.....	.....
Dr M Julyan	Prof MS Lubbe
.....	.....
Dr JR Burger	Mrs M Cockeran

LIST OF ACRONYMS AND ABBREVIATIONS

AD	After death
AED	Anti-epileptic drug
AMPA	α-amino-3-hydroxy-5-methyl-isoxazole propionic acid
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
BC	Before Christ
Ca++	Calcium
CDL	Chronic Disease List
CI	Confidence interval
Cl	Chloride
CMG	Continuous measure of medicine gaps
CNS	Central nervous system
EEG	Electroencephalographic
EMD	Electronic monitoring device
EPSP	Excitatory postsynaptic potentials
g	gram
GABA	Gamma-amino-butyric acid
GAD	Generalised anxiety disorder
Glu	Glutamate
HIE	Hypoxic-ischaemic encephalopathy
HIV	Human immunodeficiency virus
ICD	International Classification of Disease

ILAE	International League Against Epilepsy
IQR	Interquartile range
K+	Potassium
Kg	Kilogram
Mg	Milligram
MIMS	Monthly Index of Medicine Specialities
MPR	Medicine possession ratio
MUSA	Medicine Usage in South Africa
Na+	Sodium
NMDA	N-Methyl-D-aspartate
PBM	Pharmaceutical benefit management
RDUR	Retrospective drug utilisation review
SAS	Statistical Analysis System
SD	Standard deviation
SEP	Single exit price
SIGN	Scottish Intercollegiate Guidelines Network
SUDEP	Sudden Unexpected Death in Epilepsy
WHO	World Health Organization

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CHAPTER 1: INTRODUCTION

1.1 Introduction

Chapter 1 focuses on the background, problem statement, research objectives and research methods.

1.2 Background and problem statement

The International League Against Epilepsy and the International Bureau for Epilepsy define epilepsy as “a disorder of the brain that can be characterised by continuing tendency to cause epileptic seizures and the neurobiological, cognitive, psychological and social consequences of this disease”. They also state that an “epileptic seizure is a sudden occurrence of signs and symptoms due to abnormal excessive neuronal activity in the brain that is abnormal” (Fisher *et al.*, 2005:470). Porter and Kaplan (2013) define a seizure as a periodic disturbance in the brain’s normal electrical activity, which results in a temporary brain dysfunction. Epilepsy occurs when these seizures have no obvious trigger or cause and occur repeatedly.

According to the World Health Organization (WHO, 2012), a projected 50 million people globally have epilepsy, with 80% of these cases found in developing countries. The projected proportion of people in the general population suffering from epilepsy at any given time is between four and 10 per 1 000 people. In developed countries, the proportion of patients with epilepsy could reach between six and ten per 1 000. The new cases of epilepsy that are reported annually are between 40 and 70 per 100°000 people. Epilepsy affects people of all ages. According to Epilepsy South Africa (2014), currently 1 to 2% of children in the general population suffer the risk of unprovoked seizures, whereas 6% suffer the risk if a parent has epilepsy. It has been determined that slightly more males than females have epilepsy (WHO, 2012).

Epilepsy is generally divided into two main groups, namely generalised and partial seizures. During generalised seizures, the patient may lose consciousness when the entire organ is affected by the excessive electrical activity in the brain. Partial seizures are defined as the excessive electrical activity limited to one area in the brain, which can result in either simple partial seizures or complex partial seizures (Epilepsy South Africa, 2014).

Table 1-1 shows the two main categories that seizures are divided into (Porter & Kaplan 2013).

Table 1-1: Categorisation of seizures

Generalised seizures	Partial seizures
Tonic-clonic seizures Absence seizures Tonic seizures Atonic seizures Myoclonic seizures Infantile spasms and febrile seizures	Simple partial seizures Jacksonian seizures Complex partial seizure

Patients with a seizure disorder should limit their alcohol intake and should not use illegal drugs. Treatments recommended in a seizure disorder are exercise and social activities. They should, however, avoid activities that could result in sudden loss of consciousness that may lead to injury, for example climbing, swimming, operating power tools etc. Adequate precautions are important, for example to swim where lifeguards are present and prohibit driving until the patient is free from seizures for at least six months. Long-term anti-epileptic medication that eliminates or reduces the frequency of seizures is the mainstay of epilepsy treatment (Elger *et al*., 2008:501). Surgery is recommended if the drugs are ineffective (Porter & Kaplan, 2013). The Medicines Control Council (2003) advocated an algorithm for epilepsy that can be generalised into treatment for primary partial seizure and primary generalised seizure. International algorithms are discussed in the literature review.

It can be a major problem for epileptic patients to manage medication programmes on a daily basis (Yeager *et al*., 2005:679). Non-adherence to medication treatment regimens is a global problem (Dillorio *et al*., 2004:926-927) and may affect the management of epilepsy and carries a significant burden in term of economic and clinical outcomes (Davis *et al.,* 2008:451-453), as well as the occurrence of more seizures and a lack of control in daily activities (Jones *et al.,* 2006:508). According to Epilepsy South Africa (2014), one out of 100 people in South Africa is affected by epilepsy. There was a 100% increase in sudden unexpected death in epilepsy (SUDEP) since 2004 in South Africa (Epilepsy South Africa, 2014). Injuries, increases in doctors' room visits, hospitalisations and decreases in daily work activities (school, work etc.) may be associated with loss of seizure control. These result in an increase in healthcare costs related to epilepsy (Davis *et al.,* 2008:453). Non-adherence to anti-epileptic drugs (AEDs) furthermore leads to reduced treatment benefits and can be associated with unfavourable disease prognoses (Irvine *et al.*, 1999:574) and an increase in the financial burden on patients (Richter *et al.*, 2003:2327). Medical recourse utilisation and costs increase as non-adherence increases, because of higher rates of recurrent seizures. Non-adherence with AEDs has a

statistically significant influence on inpatient costs, emergency department visits and total health care utilisation (Davis *et al.*, 2008:451).

Various factors influence patient adherence to AEDs. These included demographic factors (e.g. age, gender), cultural beliefs about epilepsy, the features of the disease (frequency of the seizures and the severity of the seizures), frequency of medication use, factors that are related to the patient-provider relationship (Hovinga *et al*., 2008:316), and comorbidities (Briesacher *et al.*, 2008:442).

There are different measures available to determine medication adherence on retrospective databases. Continuous measures of medication gaps (CMG) can be defined as the totality of days in the gaps between fill-ups/refills in the observed period divided by the interval between the first and last refills. These gaps are indicated in percentages (Peterson *et al.*, 2007:6). Another method that is commonly used in calculating adherence is the medication possession ratio (MPR). The MPR can be defined as the number of days of medication provided within the refill interval divided by the total number of days in the refill interval. At least two fill dates are required to calculate the medicine possession ratio. Measures based on the MPR provide a better overview of adherence and are less sensitive to occasional intervals in the treatment (Hudson *et al.*, 2007:64). The MPR is furthermore easy to calculate and interpret (Andrade *et al.*, 2006:572). The modified form of MPR, medicine possession ratio modified (MPRm), can be defined as the number of days of medication provided, divided by the sum of the number of days from the first dispensing, excluding the last date of dispensation, and the number of days' supply obtained at the last dispensation. The value is multiplied by 100 to provide a percentage answer of adherence (Hess *et al.,* 2006:1282)

There is limited information available regarding medication adherence of epileptic patients in the South African private health sector. If the factors influencing adherence can be identified, it will allow decision-makers to develop strategies to improve treatment adherence, thereby reducing recurrent seizures and improving the quality of life in patients with epilepsy.

The following research questions can be formulated on the basis of the forgoing discussion:

- What is the prevalence of epilepsy nationally and internationally?
- What are the current treatment guidelines of anti-epileptic drugs nationally and internationally?
- What is the current medication adherence of anti-epileptic medication in the private health sector of South Africa?
- What are the factors influencing medication adherence of epileptic patients in the private health sector of South Africa?

1.3 Research objectives

The research project includes general and specific objectives.

1.3.1 General objective

The general objective of this study is to investigate patient adherence to AEDs in the South African private health sector by using medicine claims data. The research project can be categorised into two phases, namely a literature review and an empirical investigation.

1.3.2 Specific objectives

The specific research objectives of the literature review included the following:

- To investigate the prevalence of epilepsy in South Africa;
- To conceptualise epilepsy, adherence, compliance and treatment of epilepsy;
- To identify possible factors that influence adherence to chronic medication, focusing specifically on anti-epileptic medicine; and
- To investigate the burden of disease for epilepsy focusing on the economic and clinical aspects.

The specific research objectives of the empirical study using a medicine claims database were to:

- determine the prevalence of epilepsy on the database for the period of 2008-2013, stratified by age and gender;
- determine the prescribing patterns and costs for anti-epileptic treatment;
- determine the MPRm as a proxy for adherence, for all epileptic patients; and
- compare database-related variables (demographic, chronic diseases and medicine-related factors) and measurements between adherent and non-adherent epileptic patients to identify factors that influence adherence.

Table 1-2: Specific objectives and the manuscripts in which they were addressed

Manuscript	Objective
3.1 Patient adherence with anti-epileptic drugs in the private health sector of South Africa: 2009-2013 Submitted to journal *Epilepsia*	To determine the medicine possession ratio modified of anti-epileptic use in the private health sector of South Africa. To determine the influence of age, gender, active ingredients, treatment periods, co-morbid conditions and cost on the anti-epileptic treatment adherence.

Manuscript	Objective
3.2 Anti-epileptic prescribing patterns in the South African private health sector (2008-2013) Submitted to journal *South African Family Practice*	To establish the prescribing patterns of anti-epileptics in epilepsy patients in South Africa, with regard to age and gender, using medicine claims data. To determine the cost for anti-epileptic treatment.

1.4 Research methodology

The research consisted of two phases, namely a literature review and an empirical investigation.

1.4.1 Literature phase

The literature review was conducted by using several books and articles. Keywords used for the search were: epilepsy, prevalence, epilepsy statistics, categorisation of epilepsy, burden of disease, epilepsy algorithm, treatment guidelines for epilepsy, medicine treatment cost, compliance, adherence, factors influencing adherence, measures for adherence, medicine possession ratio, medicine possession ratio modified and medicine refill gaps.

1.4.2 Empirical phase

The method employed during the empirical investigation is discussed in detail.

1.4.2.1 Research design

A quantitative, descriptive, longitudinal study was performed using medicine claims data of the central database of a South African Pharmaceutical Benefit Management (PBM) company.

A descriptive design with a time dimension was followed. A longitudinal design can be defined as an "*investigation where the participant outcomes and possible treatments are collected at multiple follow-up times*". The way that variables change over time was examined (Brink *et al.,* 2012:114).

1.4.2.2 Data source and setting

The empirical phase of this study was conducted by extracting data from a medicine claims database from a leading South African Pharmaceutical Benefit Management (PBM) company. Data for a nine-year period, from 1 January 2008 to 31 December 2013 was used. There was no direct manipulation of the data. The research was performed from the assumption that all data from the database is accurate, since only paid claims from prescribed minimum benefits are included.

Data was extracted from a medicine claims database from a PBM company (identity may not be disclosed due to a confidentiality agreement), in the South African private health care sector. The PBM system was opened in 1998 and more than 1.5 million South Africans are currently benefiting from the PBM's services. The company currently provides pharmaceutical benefit management services to 39 medical schemes. The PBM company was the first benefit management company to be accredited by the Council for Medical Schemes as a managed care organisation. The PBM company offers clients a wide range of services, including:

- electronic claims processing services;
- client support services;
- pre-authorisation services;
- management of medicines for the Chronic Disease List (CDL) conditions;
- Prescribed Minimum Benefits (PMB);
- medicine management and other capitation environments, and
- on-line medicine expenditure reporting.

The following data fields on the database are available for research:

- Date of dispensing the prescription
- ICD-10 code (chronic disease list conditions)
- Quantity of medicine items prescribed
- Days supplied (number of days medicine was supplied for)
- Final amount paid by the medical scheme and patient contribution
- Anonymous membership identifier
- Anonymous member dependant identifier
- Prescriber speciality
- Provider type
- Drug trade name
- Date of birth of patient
- Gender of patient

Using an administrative database for research has unique and powerful advantages on key components of healthcare. Administrative data offers a detailed, longitudinal record of

utilisation, diagnosis and prescriptions that are also applicable in this study (Crystal *et al.,* 2007). The advantages are summarised in Table 1-2.

Table 1-3: Strengths and advantages in working with administrative data

Dataset characteristic	Advantages
Very large numbers of covered lives, with relatively comprehensive benefits and information on full continuum of care in most settings.	High statistical power. Supports detailed analyses of demographic data (age and gender), rare conditions and co-morbidities, including individuals with complex combinations of diagnoses. Dataset progress is not inhibited by per-subject costs of primary data collection; large comprehensive analytical datasets on clinically diverse populations can be constructed cost-effectively.
Strong representation of vulnerable populations (epileptic patients).	Important source of knowledge on medication usage patterns for people with epilepsy.
Unobtrusive data collection on entire covered population; medicine prescribing/dispensing data.	Biases are avoided that are related to self-report and differential study participation. Supports studies that include beneficiaries with limited ability to self-report, such as those with cognitive impairment.
Detailed longitudinal histories with dates of healthcare encounters, treatments and diagnosis in epilepsy patients; multiple years of data can be merged for long-term follow-up; it is possible to update datasets cost-effectively as newer years of data become available.	Datasets support detailed longitudinal analyses of medicine possession over time. Long-term follow-up is possible for subjects who are consistently enrolled in the study.
Provides information on expenses from the payer's perspective.	Supports economic analyses of medicine costs and costs of care to the private health market.

1.4.3 Target population

The target population for this study included all epileptic patients on medical aid schemes with the same beneficiary profile within the South African private health sector.

1.4.4 Study population

A discussion of the selection of the study population and the processes followed in selecting the patients follows in subsections 1.4.4.1 to 1.4.4.2.

1.4.4.1 Selection of the study population

The study population consisted of all patients diagnosed with epilepsy according to the ICD-10 code of G40 for epilepsy, paid by the prescribed minimum benefit as part of the chronic disease list (CDL) for anti-epileptic medicine (South Africa, 2003:84). Patients of all ages and genders were included. Data from 1 January 2008 to 31 December 2013 was used.

1.4.4.2 Selection process

The process that was followed to select the patients is depicted in Figure 1-1. The steps in this process were:

- Step 1: Data was obtained from a PMB database
- Step 2: Data was filtered by application of exclusion criteria (refer to Table 1-3)
- Step 3: Application of inclusion criteria (refer to Table 1-4)
- Step 4: Categorised patients from the database into adherent vs. non-adherent

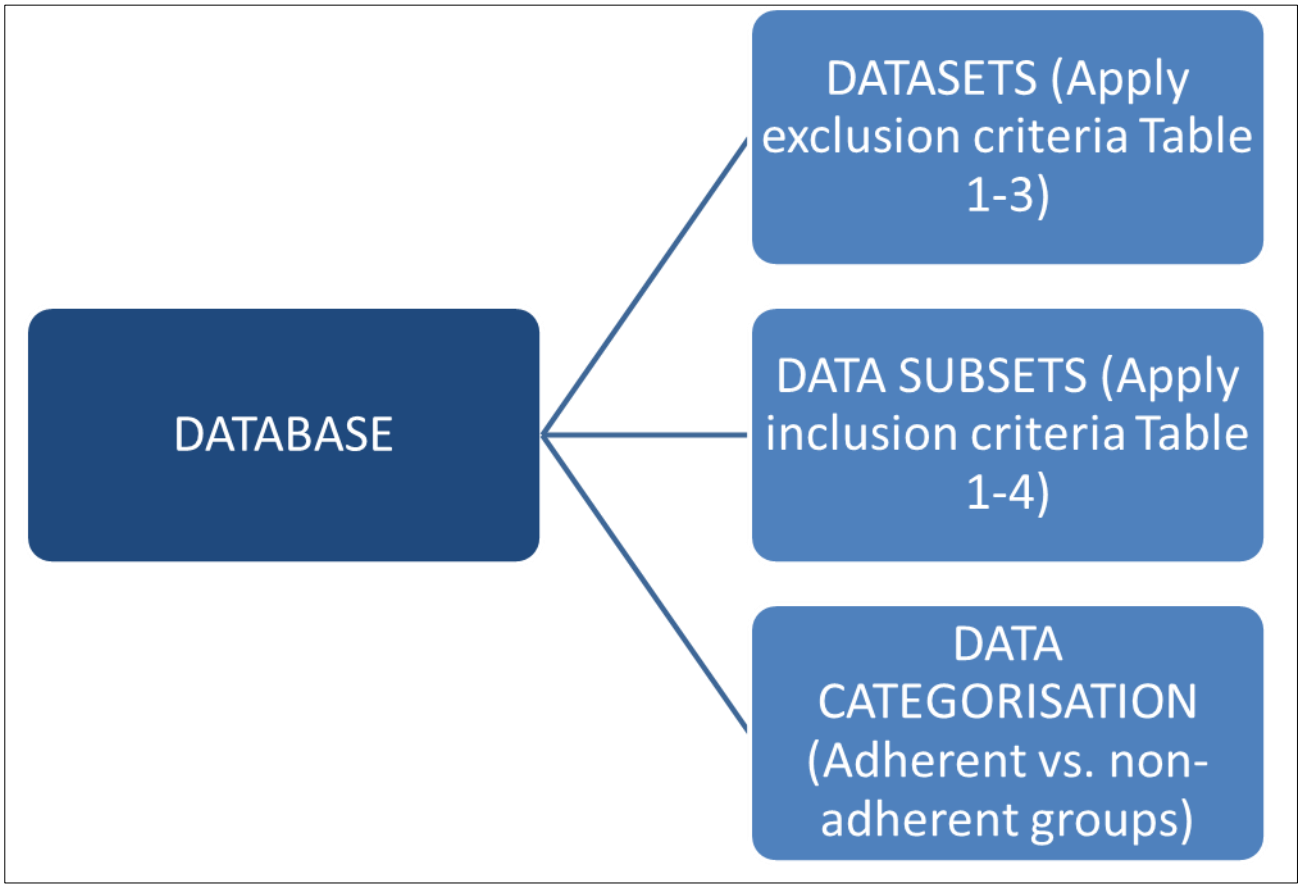

Figure 1-1: Flow diagram illustrating the selection process of study population

The data was filtered by means of the application of exclusion criteria.

Table 1-4: Exclusion criteria for selection

Study period	Criteria
2008-2013	Unknown gender and age Non-medicine items

The data was obtained by means of the application of inclusion criteria.

Table 1-5: Inclusion criteria for selection

Study period	Criteria
2008-2013	Manuscript 1 All patients with an ICD-10 code of G40 in conjunction with a paid claim at any given time during the specific study period. Patients may use more than one AED. Manuscript 2 Received a diagnosis of epilepsy (ICD-10 code G40) during the study period in conjunction with a paid claim paid by the prescribed minimum benefit as part of the chronic disease list (CDL) for anti-epileptic medicine; and Filled a prescription for single or multiple anti-epileptic agents more than once during the study period

Patients were categorised into two groups, namely adherent and non-adherent, based on the MPR of their AEDs. Patients with an MPR of 0.8 or more or MPRm of 80% and more were considered as adherent (Ettinger *et al*., 2009:325). A discussion of the MPR and MPRm follows in paragraph 1.4.5.2.

1.4.5 Data analysis

A quantitative, retrospective drug utilisation review was performed.

1.4.5.1 Retrospective drug utilisation review

Retrospective drug utilisation reviews (RDURs) are defined as organised on-going initiatives that focus on patterns of drug use relative to pre-set criteria in an attempt to minimise inappropriate prescribing. Retrospective drug utilisation review occurs after the prescription has been dispensed and the patient has completed the treatment course (Hennessy *et al.,*

2003:1494). There are several issues commonly addressed by retrospective drug utilisation reviews, namely appropriate generic use, clinical abuse/misuse, drug-disease contra-indications, drug-drug interactions, inappropriate duration of treatment, incorrect drug dosage, use of formulary medications whenever appropriate, over- and underutilisation, and therapeutic appropriateness (Academy of Managed Care Pharmacy, 2009).

The retrospective drug utilisation review is a process by which the quality of drug prescribing is measured against clearly determined criteria. To determine the optimal use, a classification system must be implemented and drug utilisation review criteria must be established. The established criteria are defined to compare the optimal use with the actual use. For the purpose of this study the Anatomical Therapeutic Chemical (ATC) classification system was used to identify all the anti-epileptic medicine. The ATC classified anti-epileptics as central nervous system drugs where anti-epileptics are the sub-pharmacological class. The active ingredients used in this study were defined as drugs from The Anatomical Therapeutic Chemical (ATC) classification group: N03AA, N03AB, N03AE, N03AD, N03AF, N03AG and N03AX. The criteria for adherence status are discussed in paragraph 1.4.5.2.

1.4.5.2 Medicine possession ratio

The medicine possession ratio (MPR) and MPRm were used as proxies to determine the adherence status to anti-epileptic treatment. Patients with an MPR of 0.8 or 80% or more were considered to be adherent (Ettinger *et al*., 2009:325).

In the case of this study, refill dates were calculated from 1 January 2008 to 31 December 2013.

The medicine possession ratio as proxy for patient adherence was determined by:

$$MPR = \frac{Number\ of\ days\ of\ medicine\ supplied\ within\ the\ refill\ interval}{Number\ of\ days\ in\ refill\ interval}$$

The MPR measures a patient's adherence to his/her medication over a specific period. The MPR is a ratio of total number of days of medicine supplied to total days in the refill interval.

The observed period can be defined as the number of days between the prescription date and the expiration of days' supply of the last refill.

Measures based on the MPR provide a better overview of adherence and are less sensitive to occasional intervals in treatment (Hudson *et al.*, 2007:64). The MPR is easy to calculate and interpret (Andrade *et al.*, 2006:572). The disadvantages of the use of medicine possession ratio include that it requires a fixed period of follow-up for the patients to avoid bias (Hudson *et al.*, 2007:60). Secondly, the MPR only provides a global picture of adherence that could be

misleading compared to a gap analysis (Fairman *et al.,* 2000:502). The age, gender, treatment period, co-morbidities and the number of medicine items were measured in terms of the adherence status.

The medicine possession ratio modified as proxy for patient adherence was determined by:

$$MPRm = \frac{Total\ days\ supplied}{last\ claim\ date - first\ claim\ date + days'supplied} \times 100$$

The MPRm is and adherence percentage value.

The following definition pertains to the data analysis for adherence: The guideline adherence status can be divided into three groups regarding the MPR/MPRm, namely undersupply (MPR <0.8 or MPRm <80%), adherent (≤ 0.8 MPR ≤ 1 or ≤ 80% MPRm ≤ 100%) and oversupply (MPR >1 or MPRm >100%). Undersupply- and oversupply are both considered to be forms of non-adherence (Chen *et al*., 2014:3-5).

The mathematical formulas that could be used when calculating the adherence (adapted from Karve *et al*., 2009:991) are shown in Table 1-6.

Table 1-6: Mathematical formulas for various adherence measures

Adherence measure	Formula
Medication possession ratio	Number of days' supply in index period/number of days inthe study period (365 days)
Medication refill adherence	[Number of days' supply in index period/number of days in the study period (365)] x 100
Continuous measure of medication acquisition	Number of days' supply/total days to next fill or end of observation period (365 days)
Proportion of days covered	[Number of days' supply in index period/number of days in the study period (365)] x 100 capped at 1
Refill compliance rate	(Number of days' supply/last claim date - index date) x 100
Days-between-fills adherence rate	[(Last claim date - index date) - total days' supply/last claim date - index date] x 100
Medication possession ratio, modified	[Number of days' supply/(last claim date - index date + last days' supply)] x 100

Adherence measure	Formula
Continuous measure of medication gaps	Total days of treatment gaps/total days to next fill or end of observation period (365 days)
Continuous multiple interval measure of oversupply	Total days of treatment gaps (+) or surplus (-)/total days to next fill or end of observation period
Continuous, single interval measure of medication	Days' supply obtained at the beginning of the interval/days in interval

1.4.5.3 Description of data analysis plan

The data was analysed by using the Statistical Analysis System® SAS 9.3® program (SAS Institute Inc., 2002-2010). Microsoft® Office Excel 2010 was used for general computations.

1.4.6 Study variables

The discussion in this section entails a description of the various variables analysed during the study.

- Age

Age is referred to as a period of time that has passed since the time of birth (Pugh, 2000:34). In this study, age was calculated according to the patient's age on his/her treatment date, in relation to his/her date of birth, using 1 January of the following year as index date.

The age of the patients were categorised as follow:

- 0 ≤ 12 years
- > 12 ≤ 18 years
- > 18 ≤ 40 years
- > 40 ≤ 65 years
- > 65 years

The reason for this division was to compare children/adolescents (0 ≤ 12 years), late adolescents (> 12 ≤ 18 year), young adults (> 18 ≤ 40 years), older adults (> 40 ≤ 65 years) and the age group classified as elderly/geriatric (> 65 years).

The difference in the average age between the non-adherent and adherent groups was determined to determine whether age had an influence on the adherence status.

- Gender

The motivation for the inclusion of gender is to determine the percentage or proportion of males and females, belonging to the adherent and non-adherent groups to observe whether gender had an influence on adherence to anti-epileptic medicine.

- Number of medicine items dispensed

The Medicines and Related Substances Control Act (101 of 1965) of South Africa defines medicine as "*any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man".* The numbers of medicine items as well as the average number of medicine items dispensed per prescription per patient were used to measure the medicine usage and to determine the prescribing patterns.

- Medicine cost

The Merriam-Webster Dictionary (2014) defines cost as "*the amount of money that is needed to pay for or buy something*". In this study, the costs of medicine treatment per patient on the database was calculated by summing the total amount reimbursed by the medical scheme, the patient contribution and the single exit price (SEP), to determine the influence of total direct cost on the adherence status.

The MPRm was also applied to calculate the cost associated with the under- and oversupply of medication. Using the data, the under- and oversupply of medication could be calculated. The following formulas were used to calculate the total cost of under- and oversupply.

$$Cost\ of\ AEDs\ that\ were\ undersupplied =$$

$$Average\ cost\ per\ day\ of\ the\ specific\ AED \times Number\ of\ days\ that\ the\ specific\ AED\ was\ undersupply$$

$$Cost\ of\ AEDs\ that\ were\ oversupplied\ =$$

$$Average\ cost\ per\ day\ of\ the\ specific\ AED \times Number\ of\ days\ that\ the\ specific\ AED\ was\ oversupply$$

- Active ingredient

The active ingredients used in this study were defined as drugs from The Anatomical Therapeutic Chemical (ATC) classification group: N03AA, N03AB, N03AE, N03AD, N03AF, N03AG and N03AX.

- Number of co-morbidities

With each claim for the treatment of any of the 27 chronic disease list conditions (CDL), the PBM allocates a diagnosis code to the specific medicine items claimed, based on the ICD-10 code for the relevant condition. The diagnosis codes were used to determine the prevalence of chronic diseases list conditions as a proxy for co-morbidities. The influence of specific co-morbidities on the adherence status was determined.

Co-morbidity can be defined as the presence of a distinct additional diseases or condition in relation to an index disease in a patient (Valderas *et al*., 2009:358). The number of co-morbid conditions per patient was extracted from the database to determine whether it had an influence on the adherence status.

- Treatment period

The treatment period can be described as the number of days the patient was supposed to receive medication. The treatment period was calculated as the time (in days) from the first prescription for anti-epileptics until the last prescription. In manuscript 3.1, the treatment period was divided into three groups as this article focused on the initial adherence with AEDs. We distinguished between the following treatment periods:

  - ≤ 30 days
  - ≥ 30 days ≤ 120 days
  - > 120 days
- Adherence and non-adherence

For the purpose of this study, the MPRm was used to determine the anti-epileptic adherence in patients diagnosed with epilepsy. A patient was considered to be adherent with his/her AED treatment if the MPRm was ≥ 80% and ≤ 110%. All the epilepsy patients with an anti-epileptic MPRm < 80%, thereby meaning they were undersupplied or an MPRm > 110%, meaning they were oversupplied, were deemed to be non-adherent.

1.4.6.1 Statistical analysis

1.4.6.1.1 Descriptive statistics

Heiman (2011:20) explains descriptive statistics as procedures of organising and summarising data for the purpose of facilitating effective communication and describing their important characteristics.

The following descriptive statistics were used during this study:

- Frequency

The Merriam-Webster Dictionary (2014) defines frequency as "*The number of times that a periodic function repeats the same sequence of values during a unit variation of the independent variable*". Frequency as measurement was used to calculate the number of items and prescriptions.

- Average value (mean)

The average value or arithmetic mean is the sum of all observations in a set of data divided by the total number of measurements (Pagano & Gauvreau, 2000:38). The following equation was used to calculate the average:

$$\bar{X} = \frac{1}{n}\sum_{i=1}^{n} X_i$$

Where:

$\bar{X}$ = mean value

$\sum X_i$= sum of all given X values

n = number of observations in the sample

To analyse the data, the average value (mean) will be used to determine the following:

- Average number of prescriptions per patient per year
- Average number of medicine items per prescription
- Average total cost per prescription
- Average cost per item

- Standard deviation

The standard deviation is the square root of the amount of variability around the mean of the measurements (Pagano & Gauvreau, 2000:47). The standard deviation can be calculated as follows:

$$s = \sqrt{\frac{\sum(x_i - \bar{x})^2}{n-1}}$$

Where:

s = standard deviation

x_i = any value in the dataset

$\bar{x}$ = mean

n = number of observations

The standard deviation was used for the following purposes:

- The standard deviation of the number of prescriptions per patient per year.
- The standard deviation of the number of medicine items per prescription.
- The standard deviation of the total cost per prescription.
- The standard deviation of the cost of all medicine items.

1.4.6.1.2 Inferential statistics

Inferential statistics are procedures performed to make a decision on whether data represents significant differences in a particular population (Heiman, 2011:21).

The following inferential statistical tests were used during this study:

- The *t*-test

The *t*-test can be used to compare means or averages of two groups (Pagano & Gauvreau, 2000:262). The *t*-test was used to determine whether the differences between the two groups' means are statistically significant ($p \leq 0.0001$).

- ANOVA (analysis of variance)

One-way analysis of variance (ANOVA) was used to test whether differences exists between more than two groups' means. It was operationalised with the general linear procedure of the

SAS version 9.3® system. If a difference was indicated, a second procedure, Tukey multiple comparisons procedure was performed to determine which groups most significantly influence the overall differences between the groups. With the one-way analysis of variance, the means of an arbitrary number of groups are compared (Rosner, 2000:512). In this study, the means of more than two distributions were compared, for example items per prescription for different age groups.

- Chi-square test

The Chi-square test (χ^2) compares the observed frequencies in each category of the contingency table with the expected frequencies given that the null hypothesis is true (Pagano & Gauvreau, 2000:345). The Chi-square was calculated as follows:

$$\chi^2 = \sum_{i=1}^{rc} \frac{(O_i - E_i)^2}{E_i}$$

Where:

rc = number of cells in the table (where *r* = number of rows, and *c* = number of columns)

χ^2 = chi-square

(r-1) and (c -1) = degrees of freedom

O = observed frequencies

E = expected frequencies

1.4.6.1.3 Statistical and practical significance

- Statistical significance

The *p*-value is defined as the probability that the null hypothesis is true or correct (Steyn, 2009). In this study, a *p*-value of 0.0001 was used. Observations with *p*-values less than or equal to 0.0001 were considered to be statistically significant; however the *p*-value is sensitive to the population size (Waning & Montagne, 2005:92). The *p*-value does not give strength and association between two groups, and therefore uses the effect size to quantify the degree to which the results should be considered important regardless of the size of the population size or study sample (Kumar, 2013).

- Practical significance: effect sizes
  a) Cohen's *d*-values

Cohen's *d*-value was used to evaluate the effect size between means in order to determine the practical significance of the differences. The practical significance of the differences between the two means was determined when the *p*-value was statistically significant ($p \leq 0.0001$).

Cohen and Lea (2004:60) defined the *d*-value as the difference between two means divided by the largest standard deviation of the two means. The *d*-value can be calculated as follows:

$$d = \frac{\bar{x}_a - \bar{x}_b}{s_{max}}$$

Where:

d = effect size

$\bar{x}_a$ = average value of a

$\bar{x}_b$ = average value of b

s_{max} = the maximum standard deviation of two averages

The following guidelines were used to evaluate the value of *d* (Steyn, 2009):

$|d| = 0.2$: small effect size

$|d| = 0.5$: medium effect size

$|d| = 0.8$: large effect size

  b) Cramer's *V*

The Cramer's *V* value was used to test the strength for any association or practical significance from the Chi-square (Heiman, 2011:352). Cramer's *V* is the most suitable measure of association to use for larger tables with more than two columns and more than two rows (Healey. 2013:292-293). Cramer's *V* is calculated as follow:

$$V = \sqrt{\frac{x^2}{nt}}$$

Where *V* is the Cramer's *V* value

x^2 = chi-square statistic

n = the sample size

t = the minimum number of the number of rows minus one or the number of columns minus one

It could be interpreted as follows: effect size of 0.1 is small; 0.3 effect size is medium and an effect size of 0.5 is large (Ellis & Steyn, 2003:52-53).

1.4.6.2 Reliability and validity of the data source

There are two possible problems that could arise when using medicine claims databases to provide reliable information, i.e. the quality of the data contained within the database and the ability of the analyses of non-experimental data to provide valid results (Tannen *et al.,* 2009:395). The action taken to prevent these possible problems is addressed in the following paragraphs.

1.4.6.2.1 Data quality

The following validation processes are in place for the PBM to ensure the validity and reliability of the data: data integrity validation, eligibility management services, medicine utilisation management services, clinical management services, price management and real-time benefit management. For the supplementary services of the PBM, refer to paragraph 1.4.2.2. The data was cleaned by deleting all non-paid claims and claims for non-medicine items.

1.4.6.2.2 Assuring validity of results

Using the claims data for retrospective research has several advantages, for example the data is complete, cost efficient, free of recall bias and nonresponse (Muhajarine *et al.,* 1997:711). It is furthermore generally free of drop-out and the database has limited access and subject anonymity within it, which relieves the investigator from the responsibility to obtain individual subject approval to use the data (Baron & Weiderpass, 2000:200).

Unfortunately, using claims data may pose several threats to internal and external validity. Motheral and Fairman (1997:350-351) list the following factors as threats to the internal validity:

- Diagnostic information such as the International Classification of Diseases (ICD) codes may not always be reliable and valid. Under-coding and over-coding of diagnosis occur, which lead to study bias.
- Confounding may occur where it can exaggerate, mitigate or reverse a true effect.

Threats to external validity include the characteristics of the study population, plan design of medical aid scheme benefits, regional practice patterns and cost differences across time and place (Motheral & Fairman, 1997:353-354). Missing data, for example ICD-10 codes, can also pose a threat to external validity.

Hall and colleagues (2011) recommend using a checklist to ensure reliable and valid results when conducting retrospective database studies. Annexure A provides a summary of this list and the approaches followed to achieve each checklist item (adapted from Hall *et al*., 2011; Peterson *et al.,* 2007:4-9).

1.4.7 Ethical considerations

This is a low-risk study since medicine claims data was used. This study was approved by the Health Research Ethics Committee of the North-West University (NWU-00179-14-A1). Goodwill permission for the use of the data was also granted by the Board of Directors of Pharmaceutical Benefit Management (PBM) Company. The data was analysed anonymously. No patient identifiers such as names, identification number or medical aid scheme information, prescriber or pharmacy information were available on the database. There is an eleven-digit reference number (allocated by the Pharmaceutical Benefit Management organisation) that acts as a key to combine fields together. The number is a time stamp of when the transaction was adjudicated. Privacy and confidentiality of the data were maintained at all times, and therefore no patient or medical scheme could be traced. The PBM responsible for providing data in this study was not identified in the study. Confidentiality agreements were signed by the researcher, study supervisor and co-supervisor.

There was no direct contact with patients and individual patients could not be traced. Protection of research data was assured since the database made use of numerical coding systems. Names of medical schemes, prescribers and providers are not available. Leakage of information is possible, but fortunately confidentiality contracts were signed to prevent this. All the data is stored until the contractual agreement with the PBM ends at completion of the study. Data will be deleted from the password protected computer.

CHAPTER 2: LITERATURE STUDY

2.1 Introduction

This chapter contains the background information gathered during the literature review. The specific objectives of this review were to conceptualise epilepsy, adherence and compliance, investigate prevalence of epilepsy, and identify possible factors influencing adherence status and to investigate the burden of the disease on economic and clinical aspects.

2.2 Epilepsy

In this chapter, epilepsy will be defined and classified and a brief overview of the epidemiology, pathophysiology and the management of epilepsy will follow.

2.2.1 Concept of epilepsy

The concept of epilepsy dates back as far as 1000BC, where the Babylonian civilisations discussed a condition in a stone tablet form. This condition discussed can be recognised as epilepsy as we know it today. The tablet contains a detailed portrayal of the symptoms. The Babylonians believed that the aetiology was the result of an invasion of the body by supernatural forces (Chaudhary *et al.,* 2011:109; Wolf, 2014:262). Another early description – which dates back to 770-221 BC – of symptoms associated with epilepsy comes from the Chinese Wade system, where physicians discussed the condition 'Tien-Hs'ien', which is similar to generalised convulsions. They believed that epilepsy in a child was a result of emotional shock bore by the mother during pregnancy. During this time, psychosis, mania and epilepsy were considered to be similar. Bian Que (200 BC) differentiated epilepsy from mania (Chaudhary *et al.,* 2011:109). During the classic Greek Era (500BC to 400AD), the Greeks used the term epilepsy, which means 'to seize' or 'to attack' resulting from the belief that the disease was caused by demonic or godly attacks on humans. They knew epilepsy to be repetitive attacks where the whole body convulsed, which led to impairment of the body functions (Chaudhary *et al.,* 2011:109; Diamantis *et al*., 2010:691). It was only during the 17th and 18th centuries when the concept of epilepsy as brain disorder took root in Europe (De Boer, 2010:631). During these two centuries, the issue of what to include in the concept of epilepsy arose. To include those with motor convulsion with loss of consciousness or those without or to include all periodic convulsion diseases, were a debatable topic. In the 19th century, Robert Bentley Todd in 1894, and John Hughlings Jackson in 1890, gradually separated hysteria, tremors, tetanus, rigors and other paroxysmal movements from epilepsy (Reynolds, 2009:338-339).

The term ‘epilepsy’ originated from the Greek *epilepsis*, meaning ‘to seize’ or ‘to attack’ (Chaudhary, 2011:109), whereas the term ‘seizure’, also deriving from Greek, means ‘to take hold’ (Fisher *et al.,* 2005:471). The Oxford English Dictionary (2015) also described the term epilepsy as “*a disease of the nervous system, characterized by violent paroxysms, in which the patient falls to the ground in a state of unconsciousness, with general spasm of muscles, and foaming at the mouth*”. Stedman’s medical dictionary (2008) adds that a seizure is “*the sudden onset of a disease or of certain symptoms*”. Therefore, the concept of epilepsy can be described as a group of functional disorders that occur in the brain with unpredictable interruptions in the normal activities of the brain, where patients experience repetitive seizures.

According to Fisher *et al.* (2005:471), an epileptic seizure could be defined as “*a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain*”. To simplify the definition of epilepsy, a new operational definition was also proposed by Fisher *et al.* (2014:477), which stated the following standardised, practical approach: “*Epilepsy is a disease of the brain defined by any of the following conditions*:

- *At least two unprovoked (or reflex) seizures occurring > 24 hours apart;*
- *One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and*
- *Diagnosis of an epilepsy syndrome*”.

For those individuals who had an age-dependent epilepsy syndrome and are past the applicable age or are seizure-free for a period of 10 years and did not take any medication for seizures for a period of five years, epilepsy is considered to be resolved. In contrast to earlier concepts, where two unprovoked seizures more than 24 hours apart were required to be considered as epilepsy (Hauser *et al.,* 1998:430), the revised definition now implied that only a single unprovoked seizure could be considered as epilepsy (Hesdorffer *et al.,* 2009:1103). The new definition of epilepsy included those patients with recurrent reflex seizures, such as photosensitive seizures. The diagnosis of epilepsy still relied on the occurrence of two unprovoked seizures, but the definition will become more accurate and precise as more data on recurrence risk of seizures are accumulated (Fisher *et al.,* 2014:476-477).

2.2.2 Defining criteria for the diagnosis of epilepsy

The International League Against Epilepsy (ILAE) proposed a diagnostic scheme, which relied on standard terminology and concepts to describe individual patients. This proposal drastically changed over several years from 1970 when criteria for the classification of epilepsy and seizures were made until 2001, when the Task Force proposed the newly updated diagnostic scheme for seizures and syndromes (Seino, 2006:S28-S30).

The rationale for this new proposal in 2001 was to simplify the classification and terminology associated with epilepsy and epileptic seizures. The new classification will have a major influence on how future generations of neuroscientists think about epilepsy, resulting in changed clinical practice and research results (Engel, 2001:796).

The following criteria changes were implemented from 1970 to 2001 (Seino, 2006:S29):

- Criteria of the 1970 epilepsy and seizure classification

The defining criteria for generalised and focal epilepsy, made by Merlis (1970:116), were divided into two categories; the clinical and the electroencephalographic (EEG) criteria. The clinical criteria consist of the seizure form, presence of neurological or psychological evidence of brain pathology, age of onset and aetiology. The EEG criteria consist of the interictal EEG and the ictal EEG. Gastaut (1970:102) proposed the clinical and EEG classification for epileptic seizures. The classification criteria for the epileptic seizures included the clinical seizure type, the EEG seizure type, the EEG interictal expression, the anatomical substrate, the aetiology and the age.

- Criteria of the 1981 seizure classification and the 1989 syndrome classification

The 1981 classification was a revised edition, which made significant changes to the criteria. The clinical seizure type, ictal EEG and interictal EEG were the only former criteria from 1970 that were recalled. The revised epileptic syndrome classification occurred in 1989.

- Proposed diagnostic scheme for epileptic seizures and epilepsy in 2001

The diagnostic scheme proposed by the ILAE Commission can be divided into five levels or axes (adapted from Engel, 2001:797). These axes were organised in a manner to facilitate a clinical approach in individual patients.

Axis 1: Ictal phenomenology. This axis entails the description of the ictal signs, making use of the standardised ictal terminology. It can be used to describe ictal events in detail for the purpose of research and in cases where patients are candidates for surgical treatment (Engel, 2001:800).

Axis 2: Seizure type. This is the seizure type that the patient experiences resulting from the list of seizure types the Task Force had constructed that represents diagnostic entities with etiological, therapeutic and prognostic implications. Localisation within the brain and triggers for reflex seizures should be specified when appropriate (Engel, 2001:800). The list of epileptic seizures is displayed in Table 2-1, where the different types of seizures are named and classified (extracted from Engel, 2001: 799).

Table 2-1: List of epileptic seizures and stimuli for reflex seizures

Self-limited seizure types	Continuous seizure types	Precipitating stimuli for reflex seizure
<u>Generalised seizure</u> • Tonic-clonic seizures • Clonic seizures with/without tonic features • Typical absence seizures • Atypical absence seizures • Myoclonic absence seizures • Tonic seizures • Spasms • Myoclonic seizures • Eyelid myoclonia with/without absence • Myoclonic atonic seizures • Negative myoclonus • Atonic seizures • Reflex seizures in generalised epilepsy syndromes	<u>Generalised status epilepticus</u> • Generalised tonic-clonic status epilepticus • Clonic status epilepticus • Absence status epilepticus • Tonic status epilepticus • Myoclonic status epilepticus	<u>Visual stimuli</u> • Flickering light: colour to be specified when possible • Patterns • Other visual stimuli
<u>Focal seizure</u> • Focal sensory seizures with elementary sensory or experiential sensory symptoms • Focal motor seizures with elementary clonic motor signs, typical automatisms, hyperkinetic automatisms, focal negative myoclonus, inhibitory motor seizures • Gelastic seizures • Hemiclonic seizures • Secondarily generalised	<u>Focal status epilepticus</u> • Epilepsy partialis continua of Kojevnikov • Aura continua • Limbic status epilepticus Hemiconvulsive status with hemiparesis	Thinking

Self-limited seizure types	Continuous seizure types	Precipitating stimuli for reflex seizure
seizures • Reflex seizures in focal epilepsy syndromes		
		Music
		Eating
		Praxis
		Somatosensory
		Proprioceptive
		Reading
		Hot water
		Startle

Axis 3: Syndrome. This level includes the accepted epilepsy syndromes. A diagnosis of an epilepsy syndrome is not always possible. This list of epilepsy syndromes constructed by the Task Force will continue to be revised based on new information and further deliberations. The following list of classifications of epilepsy syndromes is intended for use by epileptologists (Engel, 2001:802). A more simplified or detailed version can be constructed depending on the user of the list. Table 2-3 describes the classification of epilepsy syndrome (extracted from Engel, 2001:800).

Table 2-2: Classification of epilepsy syndrome

Syndrome group	Specific syndromes
Idiopathic focal epilepsies of infancy and childhood	Benign infantile seizures (non-familial) Benign childhood epilepsy with centrotemporal spikes Early-onset benign childhood occipital epilepsy (Panayiotopoulos type) Late-onset childhood occipital epilepsy (Gastaut type)
Familial (autosomal dominant) focal epilepsies	Benign familial infantile seizures Autosomal dominant nocturnal frontal lobe epilepsy Familial temporal lobe epilepsy Familial focal epilepsy with variable foci
Symptomatic (or probably symptomatic) focal epilepsies	Limbic epilepsies Mesial temporal lobe epilepsy with hippocampal sclerosis Mesial temporal lobe epilepsy defined by a

Syndrome group	Specific syndromes
	specific etiology Other types defined by location and etiology Neocortical epilepsies Rasmussen syndrome Hemiconvulsion–hemiplegia syndrome Other types defined by location and etiology Migrating partial seizures of early infancy
Idiopathic generalised epilepsies	Benign myoclonic epilepsy in infancy Epilepsy with myoclonic astatic seizures Childhood absence epilepsy Epilepsy with myoclonic absences Idiopathic generalised epilepsies with variable phenotypes Juvenile absence epilepsy Juvenile myoclonic epilepsy Epilepsy with generalized tonic-clonic seizures only Generalised epilepsies with febrile seizures plus
Reflex epilepsies	Idiopathic photosensitive occipital lobe epilepsy Other visual sensitive epilepsies Primary reading epilepsy Startle epilepsy
Epileptic encephalopathies (in which the epileptiform abnormalities may contribute to progressive dysfunction	Early myoclonic encephalopathy Ohtahara syndrome West syndrome Dravet syndrome (previously known as severe myoclonic epilepsy in infancy) Myoclonic status in non-progressive encephalopathies*a* Lennox-Gastaut syndrome Landau-Kleffner syndrome Epilepsy with continuous spike-waves during slow-wave sleep
Progressive myoclonus epilepsies	See specific diseases
Seizures not necessarily requiring a diagnosis of epilepsy	Benign neonatal seizures Febrile seizures Reflex seizures Alcohol-withdrawal seizures Drug or other chemically induced seizures Immediate and early posttraumatic seizures Single seizures or isolated clusters of seizures

Syndrome group	Specific syndromes
	Rarely repeated seizures (oligo-epilepsy)

Axis 4: Aetiology. When the aetiology is known, it must be specified. There are several diseases that are frequently associated with epileptic seizures and syndromes; a genetic defect could lead to epilepsy or a specific pathological substrate. Possible diseases associated with the occurrence of epilepsy are listed in Table 2-3Table 2-3, where the specific disease is named (extracted from Engel, 2001:801-802).

Table 2-3: Diseases possibly associated with epileptic seizures and syndromes

Disease group	Specific diseases
Progressive myoclonic epilepsies	Ceroid lipofuscinosis Sialidosis Lafora disease Unverricht-Lundborg disease Neuroaxonal dystrophy MERRF Dentatorubropallidoluysian atrophy Other
Neurocutaneous disorders	Tuberous sclerosis complex Neurofibromatosis Hypomelanosis of Ito Epidermal nevus syndrome Sturge-Weber syndrome
Malformations due to abnormal cortical developments	Isolated lissencephaly sequence Miller-Dieker syndrome X-linked lissencephaly Subcortical band heterotopia Periventricular nodular heterotopia Focal heterotopia Hemimegalencephaly Bilateral perisylvian syndrome Unilateral polymicrogyria Schizencephalies Focal or multifocal cortical dysplasia Microdysgenesis
Other cerebral malformations	Aicardi syndrome PEHO syndrome Acrocallosal syndrome Other
Tumours	DNET

Disease group	Specific diseases
	Gangliocytoma Ganglioglioma Cavernous angiomas Astrocytomas Hypothalamic hamartoma (with gelastic seizures) Other
Chromosomal abnormalities	Partial monosomy 4P or Wolf–Hirschhorn syndrome Trisomy 12p Inversion duplication 15 syndrome Ring 20 chromosome Other
Monogenic Mendelian diseases with complex pathogenetic mechanisms	Fragile X syndrome Angelman syndrome Rett syndrome Other
Inherited metabolic disorders	D-Glyceric acidemia Propionic acidemia Sulphite-oxidase deficiency Fructose 1-6 diphosphatase deficiency Other organic acidurias Pyridoxine dependency Aminoacidopathies (maple syrup urine disease, phenylketonuria, other) Urea cycle disorders Disorders of carbohydrate metabolism Disorders of biotin metabolism Disorders of folic acid and B12 metabolism Glucose transport protein deficiency Menkes' disease Glycogen-storage disorders Krabbe disease Fumarase deficiency Peroxisomal disorders Sanfilippo syndrome Mitochondrial diseases (pyruvate dehydrogenase deficiency, respiratory chain defects, MELAS)
Prenatal or perinatal ischemic or anoxic lesions or cerebral infections causing non-progressive encephalopathy	Porencephaly Periventricular leukomalacia Microcephaly Cerebral calcifications and other lesions due to toxoplasmosis, CVI, HIV, etc.

Disease group	Specific diseases
Postnatal infections	Cysticercosis Herpes encephalitis Bacterial meningitis Other
Other postnatal factors	Head injury Alcohol and drug abuse Stroke Other
Miscellaneous	Celiac disease (epilepsy with occipital calcifications and celiac disease) Northern epilepsy syndrome Coffin-Lowry syndrome Alzheimer's disease Huntington disease Alpers' disease

Axis 5: Impairment: This is an optional description of the degree of impairment caused by the epileptic condition that can be used additionally as a diagnostic parameter which can be derived from the World Health Organization's ICIDH-2 International Classification of Functioning and Disability (Engel, 2001:802).

2.2.3 Classification of epilepsy

The International League Against Epilepsy (ILAE) Commission on Classification and Terminology has revised the concepts, terminology and approaches to classify epilepsy since 1981 (Berg *et al*., 2010:676). The last recorded updated classification of seizures was in 1981 and for epilepsies in 1989 made by the Commission on Classification and Terminology of the ILAE.

The latest revised classification of epilepsy and epileptic syndromes is given in Table 2-4 (adapted from Dekker, 2002:34). In this classification, each of the groups was divided into three subcategories, i.e. idiopathic epilepsies, symptomatic epilepsies and cryptogenic epilepsies. The underlying cause of idiopathic epilepsy is unknown and believed to be of genetic aetiology and is age related. Clinical and electro-encephalographic characteristics are well defined. Symptomatic epilepsies are considered to be of known causes resulting from a suspected disorder of the central nervous system. Cryptogenic epilepsy refers to a disorder where the aetiology is hidden; however, symptoms occur and it is age-related, but does not have electro-encephalographic characteristics (Dekker, 2002:31).

Table 2-4: Revised international classification of epilepsies and epileptic syndromes and seizure disorders

Main group	Sub group
Partial epilepsy and syndromes	Idiopathic • Benign childhood epilepsy with centrotemporal spikes • Childhood epilepsy with occipital paroxysms • Primary reading epilepsy
	Symptomatic • Chronic progressive epilepsy partialis continua • Syndromes characterised by seizures with specific modes of precipitation; temporal lobe epilepsy, frontal lobe epilepsy, parietal epilepsy, occipital epilepsy
	Cryptogenic
Generalised epilepsy and syndromes	Idiopathic • Benign neonatal familial convulsions • Benign neonatal convulsions • Benign myoclonic epilepsy in infancy • Childhood absence epilepsy • Juvenile absence epilepsy • Juvenile myoclonic epilepsy • Epilepsy with grand mal seizures • Other generalised idiopathic epilepsies • Epilepsies with seizures precipitated specific modes of activation
	Cryptogenic • West syndrome (infantile spasms) • Lennox-Gastaut syndrome • Epilepsy with myoclonic-astatic seizures • Epilepsy with myoclonic absences
	Symptomatic • Non-specific aetiology Early myoclonic encephalopathy Early infantile epileptic encephalopathy with suppression bursts Other symptomatic generalised epilepsy • Specific syndromes Epileptic seizures complicating other

Main group	Sub group
	disease states
Epilepsies and syndromes undermined (local or generalised)	With both generalised and focal seizures • Neonatal seizures • Severe myoclonic epilepsy in infancy • Epilepsy with continuous spike waves during slow wave sleep • Acquired epileptic aphasia • Other undermined epilepsies
	Without unequivocal generalised or focal features
Special syndromes	Situation-related seizures • Febrile convulsions • Isolated seizures or isolated status epilepticus • Seizures occurring only with acute metabolic or toxic events

The 1981 classification of seizures proposed by the ILAE Commission on Classification and Terminology (Figure 2-1) presents the classification system for epileptic seizures (adapted from the Commission on Classification and Terminology of the International League Against Epilepsy, 1981:493-495). This system shows a detailed illustration of how the different types of epilepsy are classified as partial, generalised or unclassified seizures.

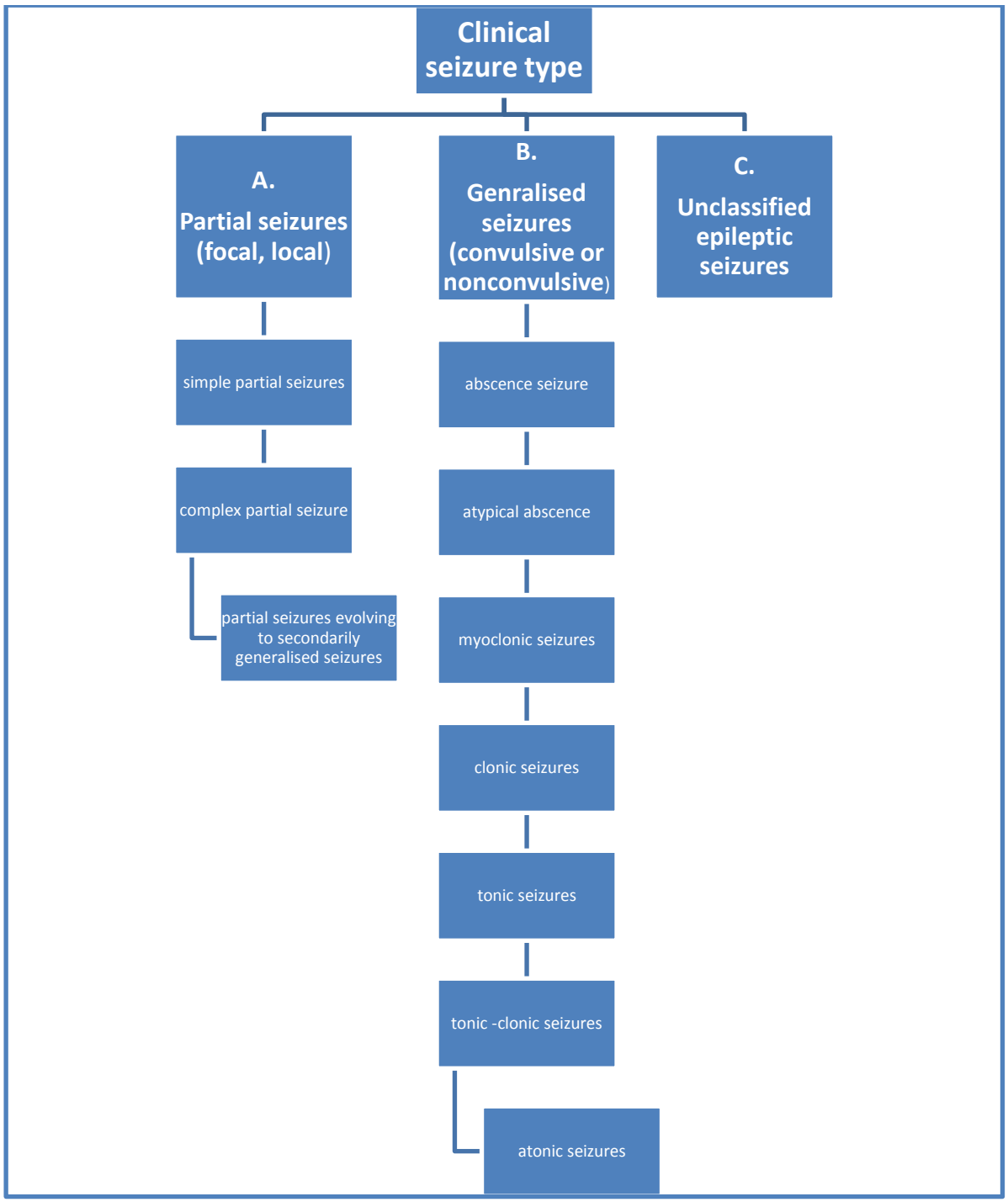

Figure 2-1: Classification system for epileptic seizures

This classification system provided a framework to improve and facilitate the understanding of the different types of seizures and forms the basic foundation to perform clinical and quantitative research on.

A. Partial seizures

Partial seizures can be defined as those seizures where the electro-encephalographic changes are limited to one cerebral hemisphere. The classification of this partial seizure is solely based on whether consciousness is impaired or not during an attack. Partial seizures can be classified into one of the following groups (Commission on Classification and Terminology of the International League Against Epilepsy, 1981:496-498):

- Simple partial seizure, where consciousness is not impaired.
- Complex partial seizure, where consciousness is impaired.
- Partial seizures evolving to generalised tonic-clonic convulsions, where a partial seizure does not terminate and progress to a generalised motor seizure.

In these seizures, the epileptic activity can start as a focal seizure, but can spread through the brain and become a generalised seizure (Dekker, 2002:22).

B. Generalised seizures

These seizures occur when the first clinical changes indicate involvement of both hemispheres. Consciousness is impaired and the motor manifestations are bilateral. Generalised seizures can be classified into the following groups (Commission on Classification and Terminology of the International League Against Epilepsy, 1981:498-500):

- Absence seizure (typical)
  The absence attack is sudden and interrupts on-going activities, include a blank stare and upward rotation of the eyes. Patients are normally unresponsive when spoken to while in this state. These attacks can last up to half a minute. A combination or single component can occur during the attack, which includes impairment of consciousness; mild clonic movements in the eyelids, corner of mouth and other muscle groups; atonic components such as diminution of body tone; tonic muscular contractions may occur, which leads to increased muscle tone; and absence of automatisms, which range from lip licking and swallowing to fumbling clothes.
- Atypical absence
  The atypical absence seizures are less common than the typical absence seizures, but last longer. The jerking movements are more noticeable and the patient is more aware of his/her surrounding and what is happening to him/her. Neurological abnormalities and delays in the development process of the child occurs (Porter & Kaplan, 2013).

- Myoclonic seizures

  The onset of this seizure type is in adolescence and persists through adulthood. Myoclonic seizures usually occur in the morning after awakening, resulting from a photic or sensory stimulation or sleep deprivation. Juvenile myoclonic seizures are the most common form of idiopathic generalised epilepsy, but are rarely reported by patients, because of the infrequent and brief occurrence of myoclonic jerks. In 90% or more of patients, the tonic-clonic seizures occur (Mattson, 2003:3-5). Symptoms include sudden, brief contractions confined to the face, trunk or extremities or individual muscles or groups of muscles. These seizures can be bilateral or single repetitive arrhythmic jerks (Commission on Classification and Terminology of the International League Against Epilepsy, 1981:499; Renganathan & Delanty, 2003:78).
- Clonic seizures

  The seizures include repetitive clonic jerks, and lack a tonic component. As the frequency of the jerks decreases, the amplitude does not (Commission on Classification and Terminology of the International League Against Epilepsy, 1981:500).
- Tonic seizures

  This is a violent muscular contraction. Features are distorted, the colour of the face becomes pale and then flushed as spasms stop the respiration movements, eyes are open or closed and the pupils dilated as cyanosis comes (Commission on Classification and Terminology of the International League Against Epilepsy, 1981:500).
- Tonic-clonic seizures

  Patients who have these seizures lose consciousness and develop a generalised stiffness (tonic phase). All the muscles in the trunk region are in spasms, resulting in breathing that stops, the patient becomes cyanotic, the head is drawn back, the arms are flexed and the legs extended. The clonic phase follows, where the muscles contract and relax alternately. These jerking movements may result in tongue biting, passing of urine or stool. The clonic phase can last up to several minutes, with headache and confusion following when the patient regains consciousness. A deep sleep may follow the episode (Commission on Classification and Terminology of the International League Against Epilepsy, 1981:499; Dekker, 2002:25).
- Atonic seizures

  There is a sudden decrease in muscle tone, which results in head dropping and loss of muscle tone resulting in collapsing to the ground. If consciousness is lost, it is only for a brief moment. There is a high risk of injury that can occur during these seizures, as the patient collapses and has no control over movements.

C. Unclassified epileptic seizures

The primary motivation for revising the classification system in the 2005-2009 Commission terms was so that the classifications of epilepsies were fully reflected; and benefit from the advances made in the neurosciences could be incorporated into clinical practice (Berg *et al*., 2010:677). For seizures to be classified correctly, a more multidimensional approach is needed. In a potential revised classification of epilepsy and seizures, a focus should be placed on factors such as the seizure semiology, frequency of seizures, aetiology, key comorbidities, risk factors associated with epilepsy, and therapeutic response to treatment (Birbeck, 2012:20). Attempts have been made to update the classification system of 1989 and 1981, but no new proposal has yet surfaced.

2.2.4 Aetiology of epilepsy

Determinants that play a role in the origin of epilepsy are briefly mentioned. This section concludes with a brief description of the origin of epilepsy worldwide.

2.2.4.1 Epilepsy aetiological history

Concepts of aetiology have changed over a period of 150 years, from the time of Hughlings Jackson in 1860 to the modern era of 2010. In his study, Shorvon (2011) focuses on the different perceived categories of causation and the nature of this evolution. In the first 50 years (1860-1910), supernatural explanations were put aside and biological and hereditary aetiology came to light as possible factors contributing to epilepsy. During this period, an epileptic seizure was attributed to either an underlying cause or a precipitating cause. The belief was that there was an underlying cause inherited and, in addition, a precipitating cause that varies. Furthermore, a division of causation was made into idiopathic and organic epilepsy. Idiopathic epilepsy was considered to be hereditary, where the term organic epilepsy was used to describe epilepsy of which the cause was clearly identifiable of neurologic or systemic origin. During this century, neuropathologic studies identified organic disorders believed to cause organic epilepsy; these included porencephaly, heterotopy, microcephaly, brain hypertrophy, asphyxia at birth, infantile hemiplegia and cerebral palsy, brain tumours, cerebral trauma causing a cicatrix, cerebral infections (abscess), and degenerative conditions that result in cerebral softening (Shorvon, 2011:1034-1035).

During the period of 1910-1960, attention was diverted to other conditions and theories around epilepsy ceased (Shorvon, 2011:1038). Two themes dominated this period, i.e. the role of heredity and the importance of organic brain disease. The term eugenics played an important role in the neurology concerned with epilepsy. Neurosurgical pathology was being structured and imaging visualised the brain *in vivo*. During the early twentieth century, X-rays were applied

to epilepsy, air encephalography followed in 1919 and contrast ventriculography in 1925 (Shorvon, 2014:2). Neurosurgery expanded based on clinical semiology and the results of these investigations by apparatus and focus were placed on organic theories as causes. Topics on theories focusing on psychological causes of epilepsy, personality development and predisposition were published by Clark (1933:79). Another theory emerged in the 1900, where causation of epileptic seizures was explained by toxins produced within the human body. In 1935, Gibbs and associates published an article regarding the major advances in epilepsy by using the electro-encephalography method.

Moving to the more modern era of 1960-2010, there have been major advances and contributions to the aetiology of epilepsy (Shorvon, 2011:1041). The advances made during this period can be categorised into six headings:

- Clinical and molecular biochemistry
  Identification of most inherited and acquired metabolic disorders.
- Neuro-imaging
  Anatomically abnormal tissue can be viewed by the computed tomography (CT) and magnetic resonance imaging (MRI). The invention of CT allowed specialists to visualise tumours and vascular causes of epilepsy, hydrocephalus and congenital lesions. The MRI allowed the visualisation of hippocampal sclerosis, cortical defective development. These inventions have reduced the use of electroencephalography (Sitoh & Tien, 1998:277).
- Molecular genetics
  The genetic basis of all gene disorders with epilepsy phenotype has been identified.
- Mechanisms of epilepsy
  An understanding of the molecular mechanism of the origin of seizures, the membrane function, receptor function, ionic changes, neuronal networks and the process of developing epilepsy are achieved.
- Methodologies to assess cause-risk factor analysis
  The description of aetiology in terms of risk factors.
- Classification of epilepsy and epileptic seizure
  The ILAE published the first classification of epileptic seizures without consideration of the aetiology. Advances have since been made in the classification by division of aetiology (Berg *et al*., 2010:679-681).

2.2.4.2 Aetiology today

2.2.4.2.1 Inherited epilepsy

Epileptic seizures are classified according to their electro-clinical features as partial or generalised. The seizures are accordingly classified according to their aetiology, where they can be: a) idiopathic (primary, with cause unknown) or b) symptomatic (secondary) (International League Against Epilepsy, 2003:21-22).

a) The discovery of epilepsy genes has resulted in the detection of a specific gene responsible for particular genetic epilepsy and this identification can lead researchers to a specific chromosome region. Seizures of biological inheritance are the neurological consequence of genetic lesion and fall under the classification of idiopathic seizures. These familial epilepsies are characterised by generalised seizures or partial seizures, where an age-related onset is important.

- Generalised epilepsy syndromes
  The International League Against Epilepsy classifies two syndromes, i.e. benign familial neonatal convulsions and benign familial infantile convulsions, where both of the syndromes are inherited by autosomal dominance. Autosomal recessive inheritance is responsible for childhood absence epilepsy and benign myoclonic epilepsy in infants.
- Partial epilepsy syndromes
  Benign partial epilepsies of childhood resolve as the child gets older and the cortical areas mature fully.

b) In the symptomatic inherited epileptic disorders, the seizures are secondary manifestations.

- Metabolic disorders
  This familial disorder is inherited by the autosomal recessive mode. Infantile spasms and generalised or myoclonic seizures may be the result of the cerebral lesion.
- Single gene disorders
  Tuberous sclerosis, neurofibromatosis type 1 and Angelman syndrome are associated with seizures and are acquired by dominant inheritance. Incidence varies among individuals with these disorders, even in those with the same disorder.

2.2.4.2.2 Acquired epileptic disorders

These disorders specifically produce symptomatic epilepsy. Aetiology differs through the stages of life. To treat epilepsy appropriately, the aetiology must be known. Secondary epileptic seizures are most commonly caused by hypoxia or ischemia, trauma, infections and neoplasms.

- Hypoxic-ischaemic encephalopathy

  Hypoxic-ischaemic encephalopathy (HIE), also known as perinatal asphyxia, can be described as a condition characterised by acute or sub-acute brain injury as result of a perinatal hypoxic-ischaemic event in neonates (Paul *et al*., 2014). Neonatal death and neurological disabilities are most frequently caused by HIE. An estimated two per 1 000 births suffer from HIE (Smith *et al*., 2000:463). Statistically, 25% of infants with HIE will have permanent neurological damage, such as cerebral palsy, mental delay and epilepsy (Spitzmiller *et al*., 2007:1069). HIE is the most common cause of seizures during the neonatal period, accounting for more than 40% of all cases with convulsions (Wirrell, 2001:445). In a study done by Pisani and colleagues (2009:66), it was determined that only severe perinatal injuries, in this case HIE, developed post-neonatal epilepsy later on. The more prolonged these seizures are, the more likely the patient is to develop epilepsy (Holmes & Ben-Ari, 2001:322-324). The incidence of post-neonatal epilepsy after neonatal seizures accounts for approximately 50% of cases (Clancy & Legido, 1991:72). Toet and colleagues (2005:243-244) conducted a study on the incidence of post-neonatal epilepsy, and found that 10% of survivors with HIE developed epilepsy over a period of seven years and 7% of the subjects with grade two encephalopathy developed epilepsy.

- Head trauma

  Posttraumatic epilepsy can be defined as two or more unprovoked seizures that occur more than a week after a head injury (Chen *et al*., 2009:686; Frey, 2003:11). The probability of developing posttraumatic epilepsy after an injury depends on the severity of the injury (Chen *et al*., 2009:686). In literature, it is important to distinguish between the different degrees of head trauma: Mild traumatic brain injury is where the patient loses consciousness for a period of less than 30 minutes, but has no skull fracture. Moderate traumatic brain injury is defined by a loss of consciousness that lasts longer than 30 minutes, but less than 24 hours, where the patient has a fractured skull or not. Severe traumatic brain injury is where the patient loses consciousness for more than 24 hours, with contusion, haematoma or skull fracture (Lowenstein, 2009:5). Several studies have been conducted on late unprovoked seizures after a traumatic brain injury. Chen and colleagues (2009) summarised such studies (studies conducted by: Asikainen *et al*., 1999; Englander *et al*., 2003; Annegers *et al*., 1998; Angeleri *et al*., 1999; Jennett & Lewin, 1960) (refer to Figure 2-2: Cumulative probability of late unprovoked seizures). These studies indicated the cumulative probability of late unprovoked seizures.

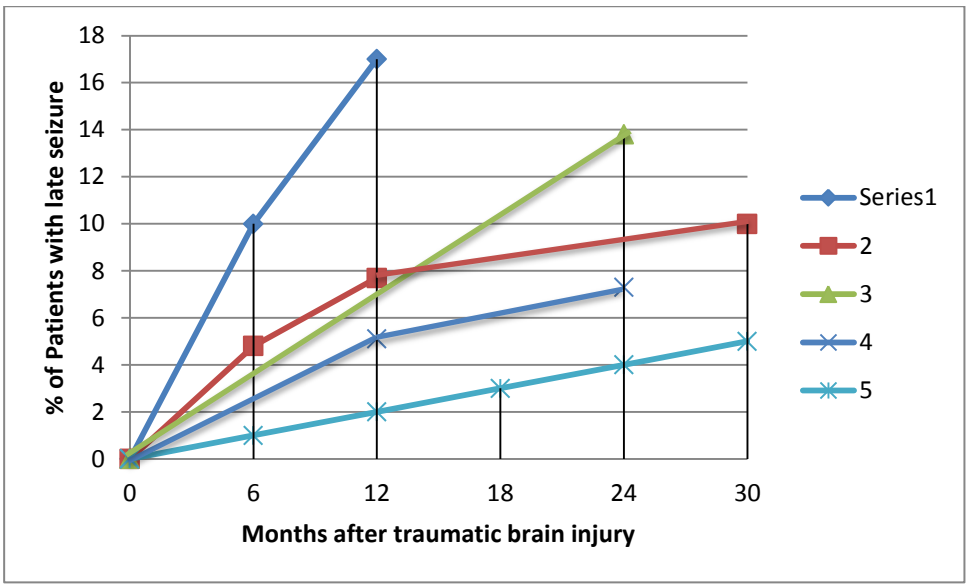

Figure 2-2: Cumulative probability of late unprovoked seizures

Traumatic brain injury or head injury is one of the most common causes of acquired epilepsy and accounts for 20% of symptomatic epilepsy. Posttraumatic epilepsy is difficult to treat medically and surgically, resulting in an increased burden of the illness to the patients and those people involved in the life of the patient. Lowenstein (2009) stated that the likelihood of developing epilepsy after head injury is as high as 50%. Patients with severe head trauma will benefit greatly from anti-epileptic treatment after injury, as it would prevent the development of epilepsy later on (Lowenstein, 2009:4). Posttraumatic injury must be distinguished from repeated seizures, by focusing on the seizures and when they occur. Researchers determined the following: immediate seizures occur less than 24 hours after the traumatic injury, early seizures appear within less than a week after the injury and late seizures occur more than a week after the injury and form the diagnosis of posttraumatic epilepsy.

Late seizures occur in 80% of cases during the first year after injury and over 90% by 18 months after traumatic injury. This period is the highest risk period (Englander *et al*., 2003:371). In a review conducted by Agrawal and colleagues (2006:434), they made a summary of the risk factors for developing posttraumatic epilepsy from five different studies. These risk factors consisted of the following: duration of loss of consciousness, missile injuries, intracerebral haemorrhage, diffuse cerebral contusions, amnesia for more than three days post trauma, acute subdural hematoma with surgical evacuation, early seizure post trauma and a depressed skull fracture.

- Cerebral strokes

  Cerebrovascular disease, such as strokes, is the most common cause of epilepsy in the elderly. Strokes account for up to 40% of epilepsy cases in geriatrics (Stephen & Brodie, 2000:1442). Seizures can occur soon after a stroke or be delayed, depending on the presumed pathophysiology (Camilo *et al*., 2004:1769). In a review conducted by Camilo and colleagues (2004), they focused on different studies on the frequency of seizures after an ischemic stroke. The results of these studies varied somewhat in terms of what an early seizure is compared to a late seizure. Predominantly, early seizures could be defined as those occurring in the first two weeks post stroke (Olafsson *et al*., 2000:1202; Olsen, 2001:340). The only predictor of seizures post stroke is the severity of the initial neurological deficiency (Silverman *et al*., 2002:196). Approximately 10% of stroke patients experience a seizure, whereas half of those patients will further develop epilepsy (Olsen, 2001:343).

  The prognosis for stroke patients prone to seizures is poor. Patients with early-onset seizures have a high incidence of developing status epilepticus, whereas those with late-onset seizures have a recurrence rate of more than 50% (Lamy *et al*., 2003:403).

- Cortical dysplasia

  In a review done by Kabat and Król (2012:35), they defined focal cortical dysplasia as a malformation, which causes refractory epilepsy in paediatrics and intractable epilepsy in adults. This malformation is characterised by cortical thickening and blurring of the grey-white matter boundary when observed on the magnetic resonance imaging (Bastos *et al*., 1999:88; Urbach *et al*., 2002:37). Epilepsy is the main symptom of dysplasia. The symptoms may appear at any age, but mostly occur in childhood, where the epilepsy usually is drug-resistant (Kabat & Król, 2012:37). In recent studies done by Fauser and colleagues (2006:1909), the age at epilepsy onset in a patient population with focal cortical dysplasia was determined to be 61% in patients under the age of five years and 92.5% in patients under the age of 16 years.

- Central nervous system infections

  Central nervous system (CNS) infections, whether they are acute or chronic-recurrent, are the most common cause of epilepsy in the developing world, because of the high incidence of CNS infections in these countries. CNS infections that cause seizures and epilepsy can be categorised into viral, bacterial, fungal and parasitic infections (adapted from Chong, 2004:20; Pradhan & Yadav, 2004:4-8; Sander, 2004:96; Singhi, 2011:601-605).

Table 2-5: Categorisation of CNS infections

Viral	Bacterial	Fungi	Parasitic
Herpes encephalitis Japanese encephalitis Nipah encephalitis Rabies Human immunodeficiency virus	Bacterial meningitis Tubercular meningitis Cerebral abscesses	Cryptococcus neoformans Candida albicans Histoplasmosis Candida Cryptococcosis-fungal meningitis Fungal encephalitis	Neurocysticercosis Malaria Toxoplasmosis Helminths

The types of infections vary through countries. Table 2-6 indicates the summarisation that Singhi (2011:601) made of the geographical distribution of infections worldwide.

Table 2-6: Geographical distribution of central nervous system infections

Infection	Geographical distribution	Comment on type of infection
Malaria	Sub-Saharan Africa; South East Asia, Latin America	Africa– plasmodium falciparum Outside Africa– plasmodium vivax
Neurocysticercosis	Latin America, India, China, South East Asia and some parts of Africa	Extra-parenchymal forms much more common in Latin America than in Asia/ India
Japanese encephalitis	India, China, Japan, South East Asia, eastern Mediterranean region, Papua New Guinea, Australia	Virus spreading continually across regions
Human immunodeficiency virus (HIV)	Sub-Saharan Africa, Central Asia, Latin America, Eastern Europe	Variations of HIV within countries
Tuberculosis	India, China, South East Asia, Sub-Saharan Africa, Latin America	The co-infection with HIV are increasing

The geographical variation determines the most common cause of seizures or epilepsy in a region. However, one must take into account that infections are also transmitted across countries through the migration of carriers, vectors and changes in the pathogenicity of the organism.

The mechanism of epilepsy following CNS infections is attributed to the structural damage caused by cortical necrosis with herpes simplex virus, infarction in meningitis and hypoxic-ischemic injury in cerebral malaria (Singhi, 2011:606). Epilepsy may occur when there is a prolonged stimulation of the pro-inflammatory signals, through chronic inflammation or by the seizure itself, which leads to a permanent pathological state, such as a damaged blood-brain barrier, neuronal death and persistent neuronal hyper-excitability (Choi & Koh, 2008:12-13). It is important to note that seizure disorders after a CNS infection may be a single phenomenon that occurs during the acute phase of the disease or it may be a chronic complication that leads to epilepsy. It all depends on the infectious agent, the duration of the infection, the severity of the infection and brain damage (Singhi, 2011:607). CNS infections are found to be the most common cause of epilepsy globally that can be prevented either through avoidance to exposure and development of vaccines or the quick diagnosis and onset of therapy (Georgakis & Anagnostopoulou, 2014:87; Sander, 2004:98).

- Brain tumours

  The diagnoses of brain tumours are based on four clinical findings:
  Firstly, patients experience partial or generalised seizures, which are more frequent in low-grade gliomas; therefore, slow growing neoplasms (Behin *et al*., 2003:232; Riva, 2005:S40). Secondly, rapidly growing tumours are characterised by increased intracranial pressure (Behin et al., 2003:323; Dunn, 2002:i24). Thirdly, progressive focal neurological deficits show the tumour location (Behin et al., 2003:323). Finally, cognitive dysfunctions are common in frontal syndrome, meningeal spread of the tumour and diffuse brain infiltration (Behin *et al*., 2003:323; Taphoorn & Klein, 2004:160).

  Epileptogenesis in patients with brain tumours are affected by various factors including the tumour type, the location of the tumour, changes in the peritumoral environment and genetic factors. The incidence of brain tumours varies depending on the type of tumour (Van Breemen *et al*., 2007:421). The World Health Organization made a grading of tumours of the central nervous system (Table 2-8) (extracted from Louis *et al*., 2007:107).

Table 2-7: WHO grading of tumours of the CNS

Tumour type	I	II	III	IV
Astrocytic tumours				
Subependymal glant cell astrocytoma	X			
Pilocytic astrocytoma	X			
Pilomyxoid astrocytoma		X		
Diffuse astrocytoma		X		
Pleomorphic xanthoastrocytoma		X		
Anaplastic astrocytoma			X	
Glioblastoma				X
Giant cell glioblastoma				X
Gliosarcoma				X
Oligodendroglial tumours				
Oligodendroglioma		X		
Anaplastic oligodendroglioma			X	
Oligoastrocytic tumours				
Oligoastrocytoma		X		
Anaplastic oligoastrocytoma			X	
Ependymal tumours				
Subependymoma	X			
Myxopapillary ependymoma	X			
Ependymoma		X		
Anaplastic ependymoma			X	
Choroid plexus tumours				
Choroid plexus papilloma	X			
Atypical choroid plexus papilloma		X		
Choroid plexus carcinoma			X	

Tumour type	I	II	III	IV
Other neuroepithelial tumours				
Angiocentric glioma	X			
Chordoid glioma of the third ventricle		X		
Neuronal and mixed neuronal-glial tumours				
Gangliocytoma	X			
Ganglioglioma	X			
Anaplastic ganglioglioma			X	
Desmoplastic infantile astrocytoma and ganglioma	X			
Dysembryoplastic neuroepithelial tumour	X			
Central neurocytoma		X		
Extraventricular neurocytoma		X		
Cerebellar liponeurocytoma		X		
Paraganglioma	X			
Papillary glioneuronal tumour	X			
Rosette-forming glioneuronal tumour of the fourth ventricle	X			
Pineal tumours				
Pineocytoma	X			
Pineal parenchymal tumour of intermediate differentiation		X	X	
Pineoblastoma				X
Papillary tumour of the pineal region		X	X	
Embryonal tumours				
Medulloblastoma				X
CNS primitive neuroectodermal tumour				X
Atypical teratoid				X

Tumour type	I	II	III	IV
Tumours of cranial and paraspinal nerves				
Schwannoma	X			
Neurofibroma	X			
Perineurioma	X	X	X	
Malignant peripheral		X	X	X
Meningeal tumours				
Meningioma	X			
Atypical meningioma		X		
Anaplastic (malignant) meningioma			X	
Haemangiopericytoma		X		
Anaplastic haemangiopericytoma			X	
Haemangioblastoma	X			
Tumours of the sellar region				
Craniopharyngioma	X			
Granular cell tumour	X			
Pituicytoma	X			
Spindle cell oncocytoma of the adenohypophysis	X			

In a clinical study conducted by Iuchi and colleagues (2015:88), the incidence of seizures in patients with Grade II tumours was 47.4%, in Grade III tumours 28.6% and 19.8% in patients with Grade IV tumours. Epilepsy occurred in 33.9% of patients with brain tumours before any surgical treatment was done (Iuchi *et al*., 2015:87). In several incidence studies conducted on seizures and epilepsy in patients with brain tumours, predominantly low-grade gliomas, it can be concluded that approximately 50% of cases present with seizures and epilepsy (Brahimaj *et al*., 2014:1385; Iuchi *et al*., 2015:88; Posti *et al*., 2015:90). Brain tumour-related epilepsy is well characterised by its resistance to treatment (Klein *et al*., 2003:519).

2.2.5 Pathophysiology of epilepsy

Epileptogenesis is the process where a neuronal network develops recurrent epileptic seizures and where these seizures become more frequent and severe in chronic epilepsy (Rakhade & Jensen, 2009:380). Epileptic seizures develop when there is an excessive synchronous and sustained discharge of neurons. All epileptic syndromes are characterised by a persistent

increase of neuronal excitability. These abnormal cellular discharges may be due to several causative factors, including trauma, a lack of enough oxygen, tumours, infections and metabolic imbalances. In approximately half of patients with epilepsy, no specific causative factor can be identified (Engelborghs *et al*., 2000:201). Seizures and epilepsy are a result of a disturbed balance between excitation and inhibition (Treiman, 2001:8).

2.2.5.1 Neurochemical mechanisms underlying epilepsy

The neurochemical mechanisms involved in the development of epilepsy are discussed in the following section.

2.2.5.1.1 Gamma-amino-butyric acid (GABA)

GABA is the major inhibitory neurotransmitter in the central nervous system (Penderis, 2014:4; Schwartz, 1988:3369). Lowering GABA levels with agents that block glutamate decarboxylase leads to epileptic activity (Bradford, 1995:482; Engelborghs, 2000:206).

2.2.5.1.2 Glutamate

Glutamate is the major excitatory neurotransmitter in the central nervous system (Penderis, 2014:4). The potentiation of glutamate promotes seizure activity. The glutamate receptors can be divided into inotropic and metabotropic and the activation of these postsynaptic receptors can lead to convulsions (Engelborghs *et al.,* 2000:207; Penderis, 2014:4). The glutamate system is involved at three levels when causing epilepsy: in the chronic sub-convulsive hyperactivity, which occurs in the epileptic focus; in the intensified excitatory activity, which results in the initiation of a convulsion; and finally, in the generalisation of the hyperactivity and spread of it to lead to a full convulsion (Bradford, 1995:483).

2.2.5.1.3 Ictal and interictal transition mechanisms

The Stedman's Medical Dictionary for the Health Professions and Nursing (2008) defines ictal as *"relating to or caused by a stroke*" and interictal as *"the period between convulsions*". Epileptiform electro-encephalography are categorised as ictal (during a seizure), interictal (between seizures) and postictal (after a seizure) activity (Fisher *et al*, 2014:6).

The following summarisation of the non-synaptic mechanisms involved in interictal-ictal transition can be made (adapted from Engelborghs *et al.*, 2000:206):

- alterations in the ionic microenvironment. There is an increase in extracellular K^+ and a decrease in extracellular Ca^{++};
- decrease in the size of extracellular space;
- there is a failure in the ion transport: the Na^+-K^+ pump or Cl^-K^+ co-transport;
- presynaptic terminal bursting;
- ephatic interactions.

Synaptic mechanism can be summarised as:

- depression of the GABA-ergic inhibition
- NMDA receptor activation; voltage-dependant excitatory postsynaptic potentials (EPSPs);
- frequency potentiation of EPSPs
- actions of modulators

2.2.5.2 Mechanism of epileptogenesis

Table 2-8 (extracted from Engelborghs *et al.*, 2000:208) describes the different mechanisms that take place at the neurotransmitter sites. Understanding the pathophysiology of epilepsy and the neurochemical alterations has contributed to the development of anti-epileptic medicines and interventions in the disease.

Table 2-8: Mechanism of epileptogenesis

	Mechanism of epileptogenesis
GABA	• Reduced GABA in microgyric cortex • Reduced benzodiazepine receptor binding in medial thalamic nucleus (mesial temporal lobe epilepsy) • Reduced benzodiazepine receptor density in CA1 region (hippocampal sclerosis) • Reduced GABA levels and GAD activity (epileptic foci) • Auto-antibodies to GAD (Stiff-man syndrome)
Glu	• Upregulation of hippocampal ionotropic glutamate receptors (temporal lobe epilepsy) • Anti-gluR3 antibodies (Rasmussen encephalitis) • Increased plasma glutamate levels (absence seizures)
Na^+	• Mutation voltage-gated Na^+ channel (generalised epilepsy with febrile seizures)
K^+ **Ca^+**	• Mutation voltage-gated K^+ channel (benign familial neonatal convulsions) • Reduced Ach-mediated Ca flux (nocturnal frontal lobe epilepsy)
	→ Increased membrane excitability

2.2.6 Epidemiology of epilepsy

A discussion of the prevalence of epilepsy in worldwide populations is provided here. A discussion of the epidemiology in sub-Saharan Africa and South Africa proceeds thereafter.

2.2.6.1 General trends and prevalence rates across continents

Various studies have documented the prevalence of epilepsy in worldwide populations. Prevalence can be defined as a diagnosis of epilepsy prior to a prevalence date or period (Banerjee *et al*., 2009:33). The number of diseased persons in a population at one point in time divided by the total number of persons in that population and expressed as a number of cases per 1 000 people in the population can be used as a calculation of prevalence (Sander, 2003:166; Sridharan, 2002:665). An active prevalence case can be described as one that continues to experience the burden of epilepsy based on experiencing a seizure lately (generally in the year prior to prevalence date) or the use of anti-seizure medication (Banerjee *et al*., 2009:33).

- Asia

The lifetime prevalence of epilepsy varies among different countries in the Asian region. According to Mac and colleagues (2007:534), a door-to-door survey conducted in Pakistan determined that the prevalence was 10 per 1 000 people. Several other studies done in Pakistan confirmed this figure (Kathria *et al*., 2003:594; Khan *et al*., 2011:44). According to epidemiological studies on the prevalence of epilepsy in China, the overall prevalence was 2.89 per 1 000 (Gu *et al*., 2013:201). Although there are no prevalence statistics available for Bangladesh regarding the epilepsy figure, it can be estimated that approximately two million people suffer from epilepsy; therefore, approximately 10 to 12 per 1 000 people (Shakirullah *et al*., 2014:33). A study conducted in India revealed that the prevalence was five per 1 000 (Radhakrishnan *et al.,* 2000:1031). The prevalence of epilepsy in Iran is high when compared to India, but low in comparison to the figure of Pakistan. Iran had a prevalence of 7.87 per 1 000 (Ebrahimi *et al.,* 2012:119). Saudi Arabia had a prevalence of 6.5 per 1 000 (Benamer & Grosset, 2009:2302).

- Australia

The overall prevalence of the Asia-Oceania region, which includes New-Zealand and Australia, is three to eight per 1 000 (D'Souza, 2008:99). In an old study conducted 30+ years ago in Sydney, it was determined that the prevalence of epilepsy was 7.5 per 1 000 (Beran *et al*., 1982:201). A study conducted from 2001 to 2002 in Tasmania, Australia, estimated a prevalence of 4.36 per 1 000 (D'Souza *et al*., 2012:102).

- North America

In the Ontario health survey in Canada, the prevalence of self-reported epilepsy was 5.8 per 1 000 (Wiebe *et al*., 1999:264). The prevalence of epilepsy in Medicare beneficiaries older than 65 years in the United States was 10.8 per 1 000 (Faught *et al*., 2012:450). In 1995, a study was conducted in rural Honduras, where 11 counties in Honduras took part in the analyses. A prevalence rate of 23.3 per 1 000 was identified for all epilepsies and 15.4 per 1 000 for active epilepsy cases (Medina *et al*., 2005:127).

- South America

In a study conducted by Bruno and colleagues (2013:3), they determined in a meta-analysis of the literature, that the median lifetime prevalence of epilepsy covering all age groups was 15.8 per 1 000 and the median prevalence for active epilepsy was 10.7 per 1 000. The prevalence of epilepsy in an Argentine city with good sanitation facilities and access to healthcare services was 3.8 per 1 000 population (Melcon *et al*., 2007:10). In a rural village, Atahualpa, Ecuador, the prevalence is reported to be 9.94 per 1 000 (Brutto *et al*., 2005:584). In another systematic

review and analysis of published literature, a study done by Burneo and colleagues (2005:65) determined that the median lifetime prevalence of all the countries in South America was 17.8 per 1 000 people and the median prevalence of active epilepsy was 12.4 per 1 000 people. The high reported prevalence figures are seen in those populations with serious health problems that can cause epilepsy (Melcon *et al*., 2007:8).

- Europe

In a study done in a French population, the overall prevalence of epilepsy was 6.06 per 1 000 (Picot *et al*., 2008:1233). Research done in Ireland indicated a nationwide prevalence of 10 per 1 000 people aged 18 years and older and nine per 1 000 for children aged five years and older (Linehan *et al*., 2010:848).

In 1997, the International League Against Epilepsy reported a prevalence of five to 10 cases per 1 000 in Europe (Brodie *et al*., 1997:1245). In 2004, the estimated prevalence of epilepsy was 4.3 to 7.8 per 1 000 in Europe (Pugliatti *et al*., 2007:2226-2227).

2.2.6.2 Sub-Saharan Africa and South Africa

Numerous studies have been done in sub-Saharan Africa on the prevalence of epilepsy. These studies all followed the door-to door survey method (Preux & Druet-Cabanac, 2005:22). In a survey conducted in rural Zambia, a prevalence rate of 12.5 per 1 000 was observed. The prevalence rates were the highest among children and adolescents in this community (Birbeck & Kalichi, 2004:93-94). In a review done by Diop and colleagues (adapted 2003:151), they compiled a table (Table 2-9) of reported prevalence studies in sub-Saharan African countries.

Table 2-9: Prevalence rate in different regions of sub-Saharan countries

Country	Prevalence (per 1000)
Cameroon	11
Ethiopia	14.2
Malawi	5.2
Nigeria	5.3
Rwanda	4.5
Tanzania	10.2
Togo	18.6
Zimbabwe	7.4

Prevalence rates vary among African countries between 2.2 to 58 per 1 000 cases (WHO, 2004:5). In a recent study done by Christianson and colleagues (2000:264) in a rural environment in the Northern Province of South Africa, the active prevalence of epilepsy in children aged two to nine years was found to be 6.7 per 1 000.

2.2.7 Management and treatment of epilepsy

The management of epilepsy is not only based on the pharmacological treatment of seizures, but on the lifestyle and daily diet as well.

2.2.7.1 Diet and lifestyle

Dietary interventions in epilepsy are used to maximise the health of patients combined with the use of medicinal treatment (Stern, 2006:281). Specific guidelines for these diets do not exist, but recommendations are made by healthcare professionals. The diet therapy is focused on restricting carbohydrate intake and increasing the caloric source of the diet to fat. This diet is termed the ketogenic diet (Huffman & Kossoff, 2006:332; Stern, 2006:282). The ketogenic diet consists of high fat, moderate protein and low carbohydrates (Huffman & Kossoff, 2006:332; Lee & Kossoff, 2011:115). Evidence from two randomised control trials proves that the ketogenic diet has a significant impact on children with treatment-intractable epilepsy. Results have shown that 38% of children in the diet group had a greater than 50% reduction in seizures and 7% of children in the diet group had more than a 90% reduction in seizures respectively compared to control groups, not receiving the diet (Neal *et al*., 2008:503-504). Results from the blinded crossover study show that 65% of patients had more than a 50% reduction in seizures over the study period of 12 days, and 80% of those patients still had more than 50% reduction in reported seizures after a period of six months (Freeman *et al*., 2009:323). In a meta-analysis done by Henderson and colleagues (2006:194), 24% of patients were reported to have complete control of seizures and 52% have more than 90% reduction or control of seizures.

Diet and lifestyle are synonymous in the management of epilepsy. The Scottish Intercollegiate Guidelines Network (SIGN) recommends that patients must avoid sleep deprivation, excessive alcohol intake and recreational drugs (SIGN, 2015:63). Other factors that may lower the seizure threshold include photic stimulation, metabolic disturbance and the abrupt withdrawal of AEDs. There are several safety precautions that must be incorporated into the daily life of patients with epilepsy, especially those where loss of consciousness without warning is a risk. These patients must avoid swimming alone, where the onset of a seizure may result in drowning; they must also avoid unguarded heights and machinery (Hart, 2012:480-481; Stern, 2006:282).

2.2.7.2 Pharmacological treatment

There is a variety of algorithms available (Annexure C to F). A variety of medication is used in the treatment of epilepsy and can be classified into the following types (refer to Table 2-10 (adapted from Reynolds, 1993:292; Rossiter, 2014:453-466)):

Table 2-10: Types of anti-epileptic drugs available in South Africa

Type of anti-epileptics	Active ingredient
Barbiturates and derivatives	Phenobarbitone Primidone
Benzodiazepine derivatives	Clonazepam Clobazam Diazepam Lorazepam Midazolam
Carboxamide derivatives/ iminostilbenes	Carbamazepine Oxcarbazepine
Hydantoin derivatives	Phenytoin
Succinimide derivatives	Ethosuximide
Miscellaneous/ other anti-epileptics	Gabapentin Lamotrigine Levetiracetam Topirimate Vigabatrin
Fatty acids	Valproic acid

2.2.7.2.1 Carbamazepine

Carbamazepine blocks voltage-dependent sodium channels, thereby blocking the high-frequency repetitive firing of action potentials (French & Gazzola, 2013:644; Kwan *et al*., 2001:22; Perucca, 2005:32; Stafstrom, 2010:158). It is used in the treatment of generalised tonic-clonic epilepsy (Rossiter, 2014:459).

The initial dose of carbamazepine in adults starts at 100 to 200 mg orally twice a day, which can be increased by weekly intervals of 100 to 200 mg/day until the target dose is reached (Rossiter, 2014:460). Maintenance doses of 600 to 1 200 mg/day or even up to 1600 mg/day are continued over a period of time (Perucca & Tomson, 2011:452; Reynolds, 1993:297-298; Rossiter, 2014:460). The paediatric doses for epilepsy are 100 to 200 mg/day for infants up to one year of age, 10 to 20 mg/kg/day in two divided doses for toddlers aged one to five years

and 100 mg twice a day for children aged six to 12 years. An increase can be made of 100 mg/day at weekly intervals until the maximum maintenance dose of 400 mg/day is reached for toddlers up to five years and 400 to 800 mg/day for children older than six years (Rossiter, 2014:460).

Patients with a history of atrioventricular heart block, bone marrow depression, porphyria and concurrent monoamine oxidase inhibitor therapy should not use this medication (Rossiter, 2014:459).

2.2.7.2.2 Clobazam

Clobazam is a benzodiazepine that acts as an off-label AED by enhancing the GABA-ergic inhibition, when it binds to the benzodiazepine receptor on the $GABA_A$ receptor (Pastalos, 2005:140). Clobazam has an off-label use for all types of epilepsy (Rossiter, 2014:457).

Clobazam can initially be given in a dose of 10 mg per day orally, which can be increased to a target of 20 to 30 mg daily for adults after a period of two weeks (Perucca & Tomson, 2011:452; Rossiter, 2014:459).

Patients with a hypersensitivity to benzodiazepines and myasthenia gravis should not use clobazam (Hoechst Marion Roussel, 1984).

2.2.7.2.3 Clonazepam

Clonazepam binds to the benzodiazepine receptor on the $GABA_A$ receptor and enhances the GABA-ergic inhibition (Pastalos, 2005:142). It is used in cases of myoclonic seizures and as an alternative to diazepam in status epilepticus (Rossiter, 2014:457).

Clonazepam should be started in small doses and increased gradually according to the individual's response to the treatment. The initial dose is 1.5 mg/day in three divided doses, which can be increased gradually to a maintenance dose of 3 to 6 mg/day after four weeks. The dose is increased by 0.5 mg every third day. A maximum of 20 mg/day can be given to an adult patient and children older than 10 years. In case of status epilepticus, 1 mg must be slowly injected intravenously over a period of 30 seconds. A maximum of 10 mg/day can be injected. Children under the age of 10 years or 30 kg must start with an oral dose of 0.01 to 0.03 mg/kg/day in three divided doses and can be increased to a maintenance dose of 0.1 mg/kg/day. A maximum dose of 0.2 mg/kg/day is acceptable. In paediatrics with status epilepticus, a dose of 0.5 mg must be injected slowly (Reynolds, 1993:299; Rossiter, 2014:457).

The use of clonazepam is contra-indicated in patients with myasthenia gravis chronic obstructive pulmonary disease and in severe hepatic diseases (Rossiter, 2014:490).

2.2.7.2.4 Diazepam

Diazepam, like the other benzodiazepines, does not activate the $GABA_A$ receptor directly in the absence of GABA. Both the drug and transmitter must be present to facilitate a neurotransmission. Diazepam enhances the $GABA_A$-mediated inhibition in the neurons of the nucleus reticularis thalam (Davies, 1995:268; White, 1999:S5).

Diazepam is used in status epilepticus. In first-line therapy, an intravenous dose of 2 mg/minute is given for adults until the seizure stops or a maximum target of 20 mg is reached. Second-line therapy includes an infusion of 100 mg of the diazepam in 1 litre of 0.9% sodium chloride solution at a rate of 8 mg/hour. A maximum dose of 3 mg/kg can be given in 24 hours. When the seizures stop, the infusion must be continued for two hours and be discontinued after another two to three hours. Rectally, 10 mg of the intravenous solution can be given in adults and repeated after five minutes if it is deemed to be necessary. Half of the adult dose must be given in cases of elderly or debilitated patients. An initial paediatric dose of 0.2 mg/kg is given intravenously over a period of three minutes. This procedure can be repeated after two to five minutes until a maximum target dose of 5 mg is reached in children under the age of five years and 10 mg in children over the age of five years. If the intravenous route is not an option, 5 mg of the intravenous solution for children under the age of three years and 10 mg of the intravenous solution for children over the age of three years can be given rectally (Rossiter, 2014:458).

Diazepam is contraindicated in patients with myasthenia gravis, chronic obstructive pulmonary disease and severe hepatic disease (Rossiter, 2014:490).

2.2.7.2.5 Ethosuximide

Ethosuximide acts as an antiepileptic agent by blocking the T-type voltage-gated calcium channels in thalamic neurons (Coulter *et al*, 1989:582; French & Gazzola, 2013:644). It is used in the management of absence seizures (Rossiter, 2014:458).

An initial dose of 500 mg daily, with an increase of 250 mg every four to seven days if needed, is given until a maximum target dose of 1.5 g/day in divided doses is reached. The usual maintenance dose is 20 mg/kg or 1.5 g/day. An initial paediatric dose of 250 mg/day for children aged three to six years and 500 mg daily for children aged over six years is given according to their plasma levels. The usual maintenance dose is 20 mg/kg/day (Perucca & Tomson, 2011:452; Reynolds, 1993:300; Rossiter, 2014:459).

Ethosuximide is contra-indicated in cases where patients have porphyria (Reynolds, 1993:293; Rossiter, 2014:458).

2.2.7.2.6 Gabapentin

Gabapentin is used as monotherapy and add-on therapy in partial seizures in adults and children older than 12 years (Rossiter, 2014:462).

Start with 300 to 400 mg as a single or divided doses on day one, 300 to 400 mg twice a day on day two, 300 to 400 mg three times a day on day three and gradually increase it thereafter according to response and a target dose is reached after approximately 10 days. The initial maintenance dose ranges from 900 to 1 800 mg/day in three divided doses with a maximum maintenance dose of 3600 mg. This dose accounts for both adults and children over the age of 12 years.

Patients with a hypersensitivity to gabapentin should not use this product (Pharmaplan, 2005).

2.2.7.2.7 Lamotrigine

Lamotrigine may be used as monotherapy or add-on therapy in partial epilepsy with or without secondary generalised tonic-clonic seizures and is used in primary generalised tonic-clonic seizures (Rossiter, 2014:462). It primarily acts as an anticonvulsant by blocking sodium channels, where it inhibits continuous repetitive firing of action potentials and it inhibits the high voltage-activated calcium channels via the N-type and P-type channels in the neurotransmitter (French & Gazzola, 2013:644; Stefani *et al*., 1996:116; Zona & Avoli, 1997:522).

In monotherapy for adults, an initial dose of 25 mg daily for a period of two weeks should be given, followed by 50 mg daily for two weeks and thereafter an increase of 50 to 100 mg every one to two weeks until the desired response is achieved. The usual maintenance dose is 100 to 200 mg/day and can go up to 500 mg/day. In therapy with lamotrigine and enzyme-inducing co-medication (add-on therapy without valproate), an initial dose of 50 mg/day for two weeks, then 50 mg twice a day for the next two weeks should be given followed by an increase of 100 mg every one to two weeks according to the response. The usual maintenance dose is 200 to 400 mg/day in two divided doses. Add-on therapy with valproate requires an initial dose of 25 mg on alternate days for two weeks, followed by 25 mg daily for the next two weeks, and an increase thereafter of 25 to 50 mg every one to two weeks according to the response. The usual maintenance dose is 100 to 200 mg/day in a single dose or two divided doses (Perucca & Tomson, 2011:452; Rossiter, 2014:464).

The initial paediatric dose of lamotrigine with valproate for children aged two to 12 years is 0.15 mg/kg/day for two weeks, then 0.3 mg/kg/day for the next two weeks, followed by an increase of 0.3 mg/kg every one to two weeks until the desired response is achieved. The usual maintenance dose is 1 to 5 mg/kg/day as a single or multiple doses, with a maximum dose of

200 mg/day. Initial add-on therapy without valproate for children aged two to 12 years is 0.6 mg/kg/day in two divided doses for two weeks, then 1.2 mg/kg/day in two divided doses for the next two weeks, followed by an increase of 1.2 mg/kg every one to two weeks according to the response. The usual maintenance dose is 5 to 15 mg/kg/day in two divided doses, with a maximum dose of 400 mg/day (Rossiter, 2014:464).

Lamotrigine is contraindicated in cases of severe impaired hepatic or renal function (Rossiter, 2014:463).

2.2.7.2.8 Levetiracetam

Levetiracetam is used in adults and children older than 16 years as monotherapy or add-on therapy for partial seizures, with or without secondary generalised seizures and primary generalised seizures. It can be used as add-on therapy for myoclonic seizures in adults and children older than 12 years. The precise mechanism of this anticonvulsant is not known and fully understood, but the antiepileptic effects involve the following:

- Levetiracetam binds to the synaptic vesicle protein 2A and directly inhibits the presynaptic neurotransmission (Lyseng-Williamson, 2011:491; Yang *et al*., 2007:1867).
- It reduces the release of calcium from intraneuronal stores (Cataldi *et al*., 2005:278; Nagarkatti *et al*., 2008:292).
- It partially inhibits N-type calcium channels, which results in changes of intraneuronal calcium levels (Lukyanetz *et al*., 2002:16).
- Levetiracetam strengthens the GABA inhibition by blocking the receptor run-down in the cortex (Palma *et al*., 2007:1848).
- It inhibits hypersynchrony between neurons (Margineanu & Klitgaard, 2000:285) and inhibits the burst firing of neurons without affecting normal neuronal excitability (Lyseng-Williamson, 2011:492).

An initial monotherapy dose for adults of 250 mg twice a day is given, with an increase to 500 mg twice a day therapeutic dose. Adjustments can be made with increases of 500 mg twice daily according to response every two to four weeks, with a maximum of 1 500 mg twice daily. In add-on therapy, 500 mg twice a day can be given, with an increase of 500 mg twice daily every two to four weeks according to response. A maximum of 3 g/day can be given The initial paediatric dose for add-on therapy is 10 mg/kg twice daily for children aged 12 to 17 years or under 50 kg. Increments of 10 mg/kg twice daily is allowed until the therapeutic response is reached or a maximum of 30 mg/kg/day (Perucca & Tomson, 2011:452; Rossiter, 2014:464-465).

Levetiracetam is contraindicated in pregnancy and lactation and those patients hypersensitive to the ingredients of this product (Snyman, 2009:35).

2.2.7.2.9 Lorazepam

Lorazepam is used in status epilepticus (Rossiter, 2014:458). Lorazepam is a fast-acting anticonvulsant that primarily acts by binding to the benzodiazepine receptor and enhances the GABA-ergic inhibition and limits continuous repetitive neuronal firing (Lowenstein & Alldredge, 1998:974).

The adult dose for status epilepticus is 4 mg of lorazepam slowly injected intravenously into a large vein at a rate of 2 mg/minute. This procedure may be repeated after 10 to 14 minutes if deemed necessary. The maximum dose is 8 mg in 12 hours. The paediatric dose is an intravenous dose of 0.05 to 0.1 mg/kg injected over two minutes with a maximum single dose of 4 mg. It can be repeated. The maximum total dose is 8 mg in 12 hours. The contraindication profile is the same as for diazepam – not suitable in patients with myasthenia gravis, chronic obstructive pulmonary disease and severe hepatic disease (Rossiter, 2014:458; 491).

2.2.7.2.10 Midazolam

Midazolam has an off-label use for status epilepticus (Rossiter, 2014:458). It binds to the benzodiazepine receptor and enhances the $GABA_A$ inhibitory action (Lowenstein & Alldredge, 1998:974; Meldrum & Chapman, 1986:S3).

A slow intravenous dose of 0.1-0.2 mg/kg is given to adults followed by a maintenance infusion of 0.75 to 10 mcg/kg/minute. Midazolam can be given rectally or intramuscular as well in a dose of 5 to 10 mg. The intravenous dose for paediatrics is 0.1 to 0.2 mg/kg, followed by the infusion of 0.5 to 5 mcg/kg/minute. Midazolam is contraindicated in myasthenia gravis, chronic obstructive pulmonary disease and severe hepatic disease (Rossiter, 2014:458; 491).

2.2.7.2.11 Oxcarbazepine

Oxcarbazepine is indicated for partial seizures with or without secondary generalised tonic-clonic seizures (Rossiter, 2014:459). Oxcarbazepine exerts its effects by blocking voltage-dependent sodium channels, which results in the stabilisation of hyper-excited neural membranes; it inhibits repetitive neuronal firing, it increases potassium conductance and reduces glutaminergic transmission and finally modulates calcium channel function by acting on N-type calcium channels (French & Gazzola, 2013:644; Perucca, 2005:32; Shorvon, 2000:75).

An initial dose for adults of 600 mg/day is given in two divided doses, with increases of 600 mg/day at weekly intervals according to response, up to 2 400 mg/day. The usual

maintenance range is 900 to 1 200 mg/day. The paediatric dose for children over the age of three years is eight to 10 mg/kg/day in two divided doses, which can be increased to 10 mg/kg/day at weekly intervals according to response. A maximum dose of 46 mg/kg/day is allowed. As adjunctive therapy, a maintenance dose of 30 mg/kg/day can be given (Perucca & Tomson, 2011:452; Rossiter, 2014:460).

Oxcarbazepine is contraindicated in patients with atrioventricular heart block, bone marrow depression, porphyria and concurrent monoamine oxidase inhibitor therapy (Reynolds, 1993:296 and Rossiter, 2014:459).

2.2.7.2.12 Phenobarbitone

Barbiturates, unlike benzodiazepines, can directly activate the $GABA_A$ receptor in the absence of GABA. Therefore, it enhances the GABA inhibition by increasing the duration of chloride channel opening (French & Gazzola, 2013:644; Perucca, 2005:32; Rho *et al*., 1996:510). Phenobarbital is used for all forms of epilepsy, except in cases of absence seizures and myoclonic seizures (Rossiter, 2014:454).

The usual oral dose for adults is 60 to 80 mg taken at night. Treatment can be started with low doses of 30 to 50 mg at night and be increased after 10 to 15 days according to the needs of the patient to achieve adequate control of the seizures. In cases of status epilepticus, an intravenous dose of 15 to 20 mg/kg can be given at a rate not faster than 100 mg/minute, until the seizure is controlled. A maximum dose of 1 000 to 1 500 mg is allowed in adults. The paediatric dose for phenobarbital is 3 to 8 mg/kg daily. The intravenous loading dose for termination of seizures is 10 to 20 mg/kg (Reynolds, 1993:303; Perucca & Tomson, 2011:452; Rossiter, 2014:455).

Phenobarbital is contraindicated in patients with porphyria and severe renal and hepatic impairment (Rossiter, 2014:454).

2.2.7.2.13 Phenytoin

Phenytoin can be used in all forms of epilepsy, except for absence and myoclonic seizures (Rossiter, 2014:455). It is primarily active in the blockade of voltage-dependent sodium channels, thus blocking the repetitive firing of action potentials (French & Gazzola, 2013:644; Perucca, 2005:31; Tunnicliff, 1996:1092).

The initial oral dose for adults is 150 to 300 mg daily as a single dose or given in divided doses. After a period of five to 10 days, an increment can be made of not more than 50 mg/day. The usual maintenance dose range is 5 to 7 mg/kg/day. An intravenous loading dose of 18 mg/kg is

given at a rate not exceeding 50 mg/minute in status epilepticus. After the seizure is controlled, an oral dose of 100 mg should be continued every eight hours in less than 12 hours after the loading dose. The intravenous dose should not exceed 25 mg/minute in special cases where patients have impaired liver function or the elderly. The initial paediatric dose is 5 mg/kg/day given in three divided doses. A maximum of 300 mg daily can be given. The usual maintenance range in paediatrics is 5 to 8 mg/kg/day. The intravenous loading dose in status epilepticus is 15 to 20 mg/kg given at a rate of 1 to 3 mg/kg/minute (Perucca & Tomson, 2011:452; Reynolds, 1993:308; Rossiter, 2014:457).

It is contraindicated in patients with impaired cardiac function and porphyria (Rossiter, 2014:456).

2.2.7.2.14 Primidone

Primidone is partly converted to the active metabolite phenobarbitone. It is used orally in the control of tonic-clonic seizures and partial seizures (Reynolds, 1993:309; Rossiter, 2014:455). Therefore, it has the same mechanism as phenobarbital and enhances the GABA inhibition and reduces the high-frequency repetitive neuronal firing. There is allosteric modulation via the barbiturate receptor and prolonged chloride channel opening (Czuczwar & Patsalos, 2001:343; French & Gazzola, 2013:644).

Start with an initial dose of 62.5 mg per day and increase over a period of three weeks until the target dose is reached or the maintenance dose of 750 to 1 500 mg/day in two divided doses. The usual paediatric maintenance dose is 250 to 500 mg/day in two divided doses for children over the age of two years, 500 to 750 mg/day in two divided dose for children aged two to five years, 750 to 1 000 mg/day in two divided doses for children age seven to nine years and the dose is the same as for adults in children aged nine years and older (Perucca & Tomson, 2011:452; Reynolds, 1993:310; Rossiter, 2014:455).

Primidone is contraindicated in patients with hypersensitivity to the ingredient, acute intermittent porphyria, and severe hepatic, renal or respiratory impairment. Concomitant use with phenobarbitone should be avoided (Pharmaplan, 1993).

2.2.7.2.15 Topirimate

Topirimate is used as monotherapy or add-on therapy in primary generalised tonic-clonic seizures, partial seizures with or without secondary generalisation and in Lennox-Gastatut syndrome (Rossiter, 2014:465). Topirimate blocks the kainate/ α-amino-3-hydroxy-5-methyl-isoxazole propionic acid (AMPA) glutamate receptor subtype, it blocks voltage-activated sodium channels, reduces the high voltage-activated calcium currents, and activates potassium

conduction. It has a secondary effect on GABA where it potentiates the GABA-mediated chloride flux by binding on the $GABA_A$ receptor (Czuczwar & Patsalos, 2001:343; French & Gazzola, 2013:644; White *et al*., 1997:176).

As adjunctive therapy, topirimate is initially given to adults in a dose of 25 to 50 mg at night for a period of one week, followed by a weekly increase of 25 to 50 mg/day in two divided doses. The minimum effective dose is 200 mg/day with a usual range of 200 to 400 mg daily and a maximum of 800 mg per day. In monotherapy, an initial dose of 25 mg is given at night for a week, with increases of 25 to 50 mg/day at weekly intervals in two divided doses. The usual dose is 100 mg/day in two divided doses, with a maximum dose of 500 mg/day. In paediatric adjunctive therapy, an initial dose of 1 to 3 mg/kg is given for one week for children aged four years and over. It can be increased by 1 to 3 mg/kg/day weekly in two divided doses. The recommended dose range is 5 to 9 mg/kg/day with a maximum of 30 mg/kg daily. The monotherapy for children aged two years and over is initially 0.5-1 mg at night for one week, with increases of 0.5-1 mg/kg/day at weekly intervals given in two divided doses. The usual dose is 3 to 6 mg/kg/day with a maximum of 16 mg/kg daily (Perucca & Tomson, 2011:452; Rossiter, 2014:465-466).

Topirimate is contraindicated in patients known to have a hypersensitivity reaction to the product (Janssen Pharmaceutica, 2001).

2.2.7.2.16 Valproic acid

It is indicated in all forms of epilepsy and is the first choice drug in the treatment of tonic-clonic seizures (Rossiter, 2014:461). Valproic acid has several anticonvulsant mechanisms. It inhibits histone deacetylase, inhibits GABA catabolism and enhances GABA synthesis as a secondary effect and it is an antagonist of NMDA receptor-mediated neuronal excitation (Czuczwar & Patsalos, 2001:343; French & Gazzola, 2013:644; Löscher, 2002:689).

The initial adult dose is 600 mg daily in three divided doses, increased by 200 mg/day every third day until control is achieved over seizures. The usual dosing range is 1 to 2 g/day with a maximum of 2.5 g/day. If the oral route is not possible, a slow initial intravenous infusion of 400 to 800 mg over a rate of three to five minutes can be given, followed by an infusion up to a maximum of 2.5 g/day. The initial dose for children over 20 kg is 400 mg/day, with increases until control is achieved. The usual dosing range is 20 to 30 mg/kg/day. For children under 20 kg, 20 mg/kg/day can be given with a maximum of 40 mg/kg/day in severe cases (Perucca & Tomson, 2011:452; Rossiter, 2014:644).

Valproic acid is contraindicated in patients with porphyria and liver diseases (Rossiter, 2014:461).

2.2.7.2.17 Vigabatrin

Vigabatrin is used as an add-on therapy in resistant partial epilepsy with or without secondary generalisation (Rossiter, 2014:466). Vigabatrin targets the GABA transaminase enzyme and binds to this enzyme, resulting in a permanent irreversible inactivation of the enzyme. This action of vigabatrin results in an enhancement of GABA neurotransmission and an increased inhibition of the neurons that are involved in seizure activity (Ängehagen *et al*., 2003:335; French & Gazzola, 2013:644; Stafstrom, 2010:158; White, 1999:S8).

The initial dose for vigabatrin when added to current antiepileptic therapy in adults is 1 g daily in a single dose or two dived doses. An increase of 0.5 g weekly can be made. The usual dose is 2 to 3 g daily with a maximum of 3 g daily. The initial paediatric dose is 40 mg/kg/day, which can be increased to 80 mg/kg/day depending on the response of the patient. The maintenance dose of 0.5 to 1 g/day for children weighing 10 to 15 kg, 1 to 1.5 g/day for children 15 to 30 kg, 1.5 to 3 g/day for children 30 to 50 kg, and for children weighing more than 50 kg is the same as for adults (Perucca & Tomson, 2011:452; Rossiter, 2014:466).

Vigabatrin is contraindicated in patients with a pre-existing visual defect, renal impairment, pregnancy and lactation (Ängehagen *et al.*, 2003:335; Rossiter, 2014:466).

2.2.8 Burden of disease

Determining the burden of disease is important in the decision-making and planning of health processes (Lopez *et al*., 2006:1747). Guidance is needed to estimate the need for health services, the cost associated with it and effectiveness. The global burden of disease serves as an indicator of the above mentioned (Leonardi & Ustun, 2002:21).

- Social burden

The impact of epilepsy on the daily lives of patients and their caregivers, whether they are family, friends or acquaintances, is characterised by negative social consequences and emotional influences (Elliot *et al*., 2005:668-669). Patients with epilepsy tend to have negative self-image, a low self-esteem and have difficulties in keeping up good relationships (Camfield *et al*., 2001:110). They are more isolated and often victims of prejudice that can result in unemployment (Baker *et al*., 2005:560). The psychosocial impact of epilepsy depends on several factors, including the severity of the epilepsy; complexity of the therapy and management; the meaning of the illness and how family, friends and society in whole perceives it; the possible restrictions in daily activities caused by epilepsy; the coping abilities of caregivers and patients; and the resources available and social support to deal with epilepsy

(Camfield *et al*., 2001:104). It is important to note that epilepsy is not only a burden to those who suffer from it, but also to those who are caregivers of these patients (Karakis *et al*., 2014:8).

- Medical burden

The clinical aspects of epilepsy include the seizure duration, therapy and frequency (Johnson *et al*., 2004:545). A poor health-related quality of life is associated with a high seizure frequency (Birbeck *et al*., 2002:535). Patients with a high seizure frequency tend to develop depression and anxiety. In a study done by Boylan and colleagues (2004:258), the conclusion was that 50% of inpatients suffered from depression, where 19% of the patients with severe depression had suicidal thoughts. O'Donoghue and colleagues (1999:214) determined that 33% of patients with recurrent seizures had depression. As the burden of epilepsy increases, the severity of mood disorders increases (Kimiskidis *et al*., 2007:6).

In South Africa, the lack of medical treatment for epilepsy is affected by the lack of resources in the healthcare system, such as healthcare workers trained to manage epilepsy (Eastman, 2005:10); challenges to reach medical facilities; communication barriers due to the different languages pose a major burden on the patient and health professionals; cultural differences, where patients do not believe in modern medical treatment; and limited financial capacity due to unemployment and support (Williams *et al*., 2015:184).

- Economic burden

Sinha and Bhaumik (2014:1-2) describe epilepsy as a cost-intensive disorder, where 90% of the financial burden rests on the shoulder of developing countries. Being healthy is a very important economic resource and where health is deteriorating, a heavy economic burden follows. The cost of epilepsy involves the application of cost of illness methods, where direct, indirect and intangible costs are calculated, which are attributable to epilepsy (Begley & Beghi, 2002:3-4; Sinha & Bhaumik, 2014:2). Direct costs include medical costs used to treat, diagnose, and prevent illness, and nonmedical expenditures such as travel costs to medical facilities etc. Indirect costs can be defined as loss of productivity associated with morbidity and mortality. Intangible costs are related to the social and emotional impact the illness has on the economy (Begley & Beghi, 2002:3; Begley *et al*., 2002:669; Thomas *et al*., 2001:1052). Table 2-11 summarises the different costs associated with epilepsy (adapted from Thomas *et al*., 2001:1053).

Table 2-11: Cost associated with epilepsy

Direct costs	Indirect costs	Intangible costs
• Medical costs Hospital services Home care services Ancillary service • Nonmedical costs Care provided by caregivers (family and friends) Transportation to and from facilities Child care Housekeeping Social services	Time and productivity loss Income lost by family members Forgone leisure time Unemployment underemployment	Pain, suffering, social stigma etc.

The economic burden of epilepsy depends on many factors, including the age of onset of the illness, the impact of the illness on the quality of life, the cost associated with treatment and therapy, the risk of mortality and many more factors. The introduction of new AEDs and other medical treatment such as surgical treatment increases the direct cost of epilepsy many fold (Thomas *et al*., 2001:1052). In a study performed in Denmark by Jennum and colleagues (2011:950), it was possible to evaluate the economic consequences of epilepsy, since all information of the Danish population is registered in a central database. When the average annual costs of epilepsy patients versus the control group (people without epilepsy) were compared, a significant result emerged. The average annual cost for an epilepsy patient was €14 575 and €1 163 for the control (Jennum *et al*., 2011:951). Research conducted by Ivanova and colleagues (2010:842) under the privately-insured patients in the United States of America determined that the annual direct cost of patients diagnosed with epilepsy is $11 276 versus the $4 087 for the control group patients.

The 2010 Global Burden of Disease study estimated that epilepsy accounts for approximately 0.75% of the global disease burden (Murray *et al*., 2012:2203). The greater the percentage of people living with epilepsy without treatment, the greater the burden of the disease and a higher disability weight is reflected (Leonardi & Ustun, 2002:25).

Studies on the burden of epilepsy are more focused on the developing world and public sector. More studies need to be done on the burden regarding the private sector, to understand the factors affecting these patients.

2.3 Adherence/ compliance/ concordance

2.3.1 Adherence

Adherence is defined by Horne *et al*. (2005:12) as the "*extent to which the patient's behaviour matches agreed recommendations from the prescriber*". Adherence, in contrast with compliance, emphasises the empowerment of the patient to decide whether he/she wants to adhere to the prescriber's recommendations. The term adherence is more an expectation of the patient to follow the regimen in mutual agreement with the health professional, as opposed to compliance where the patient is told what to do (Eatock *et al*., 2007:118).

2.3.1.1 Importance of adherence

Adherence to any drug regimen reflects behaviour aspects, such as medical attention, filling of prescriptions, and the appropriate ingestion of medication, obtaining immunisations and attending follow-up appointments. Therapeutic behaviours address personal hygiene, smoking, unhealthy diets and lack of physical activity (WHO, 2003:3). The accurate assessment of the patient's adherence behaviour is essential for effective and efficient treatment planning to ensure positive health outcomes (WHO, 2003:4).

Statistically, 20 to 60% of patients are non-adherent to medication regimens, with the highest rates of non-adherence occurring in chronic conditions (Dunbar-Jacob & Mortimer-Stephens, 2001:S57; Kripilani *et al.,* 2007:540). These higher non-adherence rates have a significant influence on healthcare costs as it increases hospitalisation, emergency room treatment, use of other medical resources and ultimately cause poorer health outcomes and quality of life (DiMatteo, 2002:794-795; Sokol *et al.,* 2005:521).

Adherence to medication regimens improves the effectiveness of interventions designed to encourage healthy lifestyles (Clark, 2001:409; Cutler *et al*., 2010:1553-1555). Not only does adherence improve health outcomes, it also contributes to economic benefits; whether they are direct or indirect benefits. The direct benefits include expenses saved on expensive health services, such as hospitalisation. The indirect benefits of adherence may be the improvement of quality of life (WHO, 2003:20).

2.3.1.2 Adherence in epilepsy therapy

It is estimated that approximately 50 million people worldwide are affected by epilepsy, of whom 40 million live in developing countries (WHO, 2004:1-5). Approximately 80 to 90% of those living in developing countries with epilepsy do not receive appropriate treatment or in some cases have never been diagnosed (Meinardi *et al.,* 2001:137). The majority of people suffering from

epilepsy in Africa do not seek medical attention as they are intended to. The reason for this is that in several of the developing countries, there is only one neurologist for up to 4 million people. The diagnostic means for epilepsy is consequently poor in the sub-Saharan African countries. Table 2-12 is a representation of the personnel and means for diagnostic epilepsy in sub-Saharan African countries (Diop *et al.,* 2003:152-153).

Table 2-12: Personnel, means of diagnosis for epilepsy in sub-Saharan African countries

Country	Neurologists	Neurosurgeons	Psychiatrists
Angola	3	3	2
Benin	4	0	14
Botswana	0	0	0
Burkina Faso	2	2	7
Burundi	2	0	1
Cameroon	4	2	3
Cape Verde	0	0	0
Cent. Afr. R.	2	0	2
Chad	0	1	1
Comores	1	0	0
Congo D.R.	25	1	25
Congo	3	1	2
Côte d'Ivoire	9	7	40
Equ. Guinea	0	0	1
Eritrea	0	0	1
Ethiopia	4	3	10
Gabon	4	1	-
Gambia	0	0	2
Ghana	3	5	-
Guinea	3	2	8
Guinea-Bis.	0	0	0
Kenya	11	7	30
Lesotho	0	0	2
Liberia	-	-	-
Madagascar	5	2	12
Malawi	0	0	0
Mali	3	2	5

Country	Neurologists	Neurosurgeons	Psychiatrists
Mauritania	2	2	4
Mauritius	2	0	1
Mozambique	0	1	1
Namibia	0	0	-
Niger	1	1	4
Nigeria	10	-	-
Rwanda	1	1	1
Sao Tome Pr.	0	0	1
Senegal	9	5	12
Seychelles	0	0	-
Sierra Leone	0	0	-
South Africa	111	12	474
Swaziland	0	0	1
Tanzania	2	5	10
Togo	5	1	4
Uganda	6	2	9
Zambia	2	-	10
Zimbabwe	1	5	10

Many of the world's poor, who live in developing countries, become part of a discouraging cycle that contributes to poor adherence or non-adherence: being healthy requires money for food, sanitation and medical care, but to earn money, one must be healthy. The result of this cycle forces poor families to face the burden of caring for loved ones, due to inadequate healthcare (WHO, 2003:8). The high cost of epilepsy treatment, the lack of availability of antiepileptic drugs, distance to health facilities and cultural beliefs of people are all contributors to the large epilepsy treatment gap (Meinardi *et al.,* 2001:140-143).

2.3.1.3 Barriers to adherence in epilepsy treatment

There are many factors involved in the adherence status to anti-epileptic therapy, and these factors can be grouped into five dimensions, namely (Dassa *et al*., 2010:926; Moosa *et al*., 2007:42-44; WHO, 2003:89):

- Socio-economic-related factors;
- Health system-related factors;
- Condition-related factors;

- Treatment-related factors, and
- Patient-related factors

The different dimensions will be discussed briefly.

2.3.1.3.1 Social and economic factors

A low social and economic status in developing countries puts patients in a delicate situation, where a lack of prioritisation occurs. These priorities include a choice that patients need to make regarding limited resources available and to direct these resources to family members for whom they care and believe are in more need of it (WHO, 2003:28). There are several factors that could be included in the socio-economic dimension that affects adherence, namely (Jin *et al.*, 2008:280; WHO, 2003:28):

- Poor socio-economic status
- Poverty and unemployment
- Illiteracy and a low level of education
- Lack of social support
- Long distances to treatment centres and high cost of transport
- High cost of therapy
- Time commitment

2.3.1.3.2 Health system factors

Although relatively little research has been conducted in the field of health systems and their effect on adherence status, there are various factors that affect the adherence negatively, that are known. These factors are (Jin *et al*., 2008:281; Moore *et al*., 2004:429; Ponnusankar *et al*., 2004:58; WHO, 2003:29):

- Lack of accessibility to healthcare
- Health services are not well developed and have inadequate or non-existent reimbursement by health insurance plans
- A poor medication distribution system
- Healthcare providers are not well trained and have limited knowledge about chronic disease management
- Healthcare providers are overworked
- Lack of incentives and feedback on performance
- Long waiting time for clinic visits and brief consultations
- The ability of the system is poor to educate patients and provide follow-up

- Unable to establish a community support system and a self-management capacity
- Lack of adequate knowledge on adherence and the possible effective intervention for improving adherence

2.3.1.3.3 Condition factors

This dimension includes the illness-related demands the patient must face. Adherence to medication can be influenced by the severity of disease symptoms, level of physical, psychological and social impact of the disease, the severity and disease progress and the availability of specific disease treatment. Comorbidities contribute furthermore to the adherence status (Jin *et al.,* 2008:274; 281; WHO, 2003:30).

2.3.1.3.4 Treatment factors

Treatment of a disease can have an enormous influence on adherence status, depending on the complexity of the medicine regimen, the duration of therapy, previous failures with the treatment, frequent therapy alterations, proximity of positive effects, possible side-effects with the treatment and the availability of medical support to deal with these side-effects (WHO, 2003:30).

The complexity of medication treatment is a threat to patient compliance. The number of dosing times per day has a significant influence on the compliance behaviour. As the doses increase daily, the compliance decreases (Claxton *et al*., 2001:1301; Cockburn *et al*., 1987:817). Together with the complexity of the regimen is the duration of therapy. A longer duration of the illness may compromise the patient's adherence to therapy (Morris & Schulz, 1992:285). When patients experience a side-effect of medication that causes discomfort, they tend to lose trust in the effectiveness of therapy and trust in the healthcare provider (Christensen, 1978:175).

2.3.1.3.5 Patient factors

Patients have different beliefs, knowledge, perceptions and expectations about therapy for a specific disease. Adherence to a medication regimen depends on the patient's beliefs about the illness, their knowledge of the illness and how they perceive the prognosis of their disease. The motivation to manage their regimen and the confidence they have in themselves predict how successful the outcome of therapy will be. If that expectation is not met, the consequence is poor adherence (WHO, 2003:30).

Table 2-13 summarises several of the patient characteristics associated with poor adherence (adapted from Conthe *et al*., 2014:339; Jin *et al*., 2008:274).

Table 2-13: Patient-centred factors that influence adherence to treatment

Patient characteristics
An indifferent attitude toward the disease or the treatment or forgetfulness in terms of taking medication
Inadequate knowledge about the disease or therapy and health literacy
Do not rely on a success outcome or effectiveness of treatment
Not motivated to recuperate health
Perception of disease that it is not serious
Age extremes: children to adolescents to the elderly all have different perceptions of the disease
Uneducated or low level of education and poor economic status
Do not understand the consequences of poor compliance to medication
Emotional instability or physical difficulty/ disability

2.3.1.4 Methods for measuring adherence

When adherence is measured it falls into two categories, namely direct and indirect measures. The direct method includes electronic monitoring devices (EMDs), pill counts, the detection of the drug in the biological fluids and direct observation of the patient taking the medicine (Mitchell, 2014:565). These direct measures provide evidence of medication consumption. Direct monitoring has the advantage that it is more reliable and accurate than the indirect measurements, but is more labour-intensive and costly compared to the indirect methods. Another limitation to using these direct methods is that it is only useful in in-patient settings and that the variation in patients' metabolism can be problematic for drugs with short half-lives, since adherence is only measured at one point in time (Fairman & Motheral, 2000:500).

Fairman and Motheral (2000:500) further describe the more commonly used method in practice, namely the indirect measure. This method includes medication monitoring, self-reporting and prescription claims data. These indirect methods are more useful in assisting the researcher in understanding why patients do not adhere to medication regimens and their behavioural aspect. Pill counts are not the best method to represent adherence status, as they fail to prove whether the medication was taken on schedule. The self-report measures have the advantage that it provides reasons for non-adherence by obtaining information from the patient's perspective (Farmer, 1999:1078; Paschal *et al*, 2008:1117). The problem with surveys is that the 'Hawthorne effect' can occur at any given time. The *"Hawthorne effect is the tendency of patients to increase compliance because they know they are being observed*". The prescription claims data is more accessible and inexpensive, but has the disadvantage that it can only be used in chronic diseases, because it relies on prescription refills on a monthly basis (Fairman & Motheral, 2000:500).

2.3.2 Compliance

The use of the term '*medication compliance'* is declining because it is paternalistic, where the patient has a lack of involvement in the decision-making process and the patient's behaviour agrees with the prescriber's medical advice (Horne *et al.,* 2005:12). The proposed definition by Cramer *et al.* (2008:46) of medication compliance refers to *"the act of conforming to the recommendations made by the provider with respect to timing, dosage and frequency of medication taking*." Cramer *et al*. (2008:46) defines it as *"the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen*."

Non-compliance suggests that a patient has stopped taking medication and does not follow the recommendations given by the health professional (Gray *et al.,* 2002:277).

The following diagram illustrates the various ways in which medication dosing can deviate from the recommended provider's prescription.

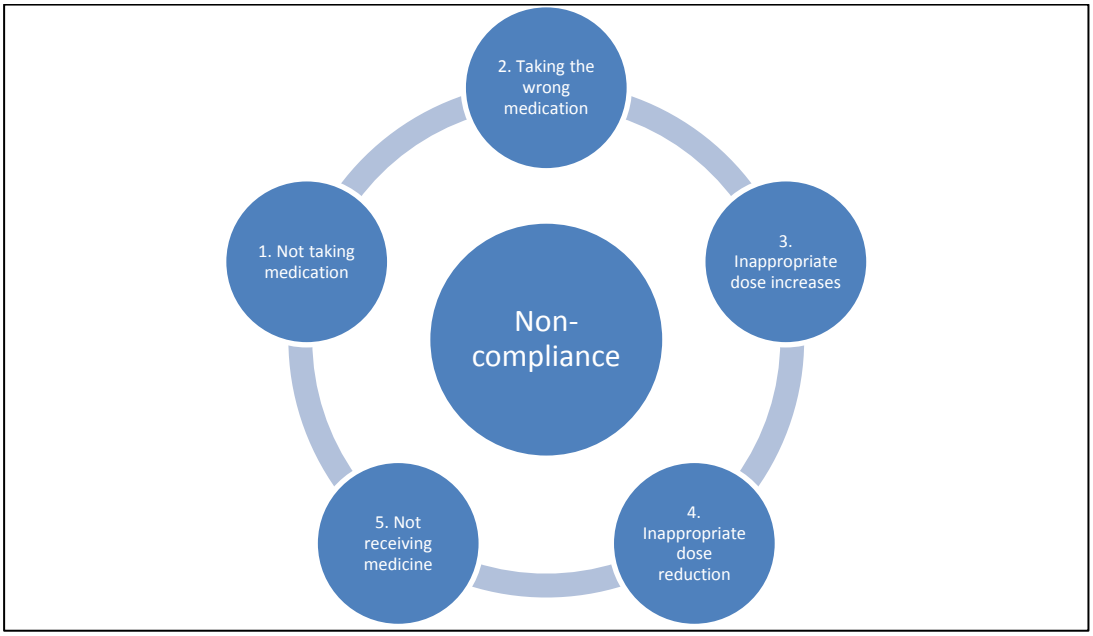

Figure 2-3: Diagram of medication non-compliance

The non-compliance diagram (Figure 2-3) can be explained as follows (Abbott, 2007:2648):

- Not taking the medication: where the patients do not take the medications, despite having the medication in their possession.
- Taking the wrong medication: this could be a medication error where the medication dispensed by the pharmacist is wrong or where the patient takes the wrong medication if they use other acquaintances', like family members', medications.

- Inappropriate dose increases: patients take extra doses to make up for missed doses, which causes more harm than missed doses.
- Inappropriate dose reduction: where the patient autonomously decreases his/her dose without the knowledge and directions of the prescriber.
- Not receiving medicine: where the patient did not collect his/her prescription.

To summarise, compliance is understood as professional dominance, where the patient is expected to do as directed. The great area of change that has been included lately is the inclusion of the patient in the decision-making process, where they become partners with the healthcare professionals in their therapy. The term 'adherence' indicates this action of partnership more accurately than "compliance" (Tilson, 2004:161).

2.3.3 Concordance

According to Chatterjee (2006:509), *"concordance encompasses the idea that the doctor and the patient are equals, and that the patient makes informed decisions*".

The term concordance, together with the terms compliance and adherence, is commonly used in relation to medication taking. However, these terms are different from each other (Mitchell, 2014:564). Concordance is not synonymous with compliance or adherence. The term adherence focuses on the aspect of medicine-taking, while concordance does not take the medicine-taking behaviour into consideration, but rather the interaction between the patient and prescriber (De la Cuevas, 2011:75). Applying concordance means that the prescriber and the patient must form a unity in therapeutic decisions. Concordance is indeed synonymous with patient-centred care, which focuses on the health practitioner's acknowledgement of the patient's perspective on therapy, and his/her ability to make his/her own decisions about healthcare. The main difference between adherence and concordance is that adherence encompasses the whole process of shared decision-making, whereas concordance is the outcome of that process. Compliance and adherence describe patient behaviour in terms of the recommended therapeutic regimen, whereas concordance is more useful in describing what is right and should happen in relation to medicine-taking, but does not address medication taking directly (De la Cuevas, 2011:75-76).

2.4 Chapter summary

Chapter 2 provided an overview of the concept of epilepsy and epileptic seizures. Topics addressed were the history of the development of epilepsy, including the aetiology of epilepsy, the defining criteria for the diagnosis of epilepsy, the pathophysiology and epidemiology and the management and treatment of epilepsy. The impact of non-adherence on the utilisation and

cost of healthcare services were furthermore addressed. Hereby, the specific objectives of the literature review have been answered.

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 two manuscripts.

Manuscript one, entitled “Anti-epileptic prescribing patterns in the South African private health sector (2008-2013)” was submitted to the journal “*South African Family Practice*”.

Instructions to the author can be viewed with the following link: http://www.safpj.co.za/index.php/safpj/about/submissions#authorGuidelines

Manuscript two, entitled “Patient adherence with anti-epileptic drugs in the private health sector of South Africa: 2008-2013” was submitted to the journal “*Epilepsia*”.

Instruction to the author can be viewed with the following link: http://onlinelibrary.wiley.com/store/10.1111/(ISSN)1528-1167/asset/homepages/EPI_Instructions_for_Authors.pdf?v=1&s=c30ad6ab6adadabfea22c97fbe15342a2be84168&isAguDoi=false b

3.2 Manuscript 3.1

Title

Anti-epileptic prescribing patterns in the South African private health sector (2008-2013)

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Keywords

Anti-epileptic; South Africa; prescribing patterns; longitudinal; medicine claims database; direct medicine costs

Abstract

Background

Newer anti-epileptic drugs (AEDs) are increasingly prescribed. Epilepsy is associated with high direct cost. This study will investigate the prescribing patterns and direct medicine costs associated with epilepsy treatment in the private health sector of South Africa.

Methods

A quantitative analysis of medicine claims data from 1 January 2008 to 31 December 2013 for patients with a diagnosis of epilepsy (G40) was performed. Descriptive statistics were used to analyse and interpret data.

Results

Prevalence ranged between 0.87% and 0.91% during the study period. The average number of AED prescriptions per patient ranged from 11.76 ± 8.07 in 2008 to 11.90 ± 8.39 in 2013. Patients aged 40 to 65 years had the highest average number of AED prescriptions/year. Valproate was prescribed most (increasing from 13.24% to 17.02%). The average cost per item increased by 54.6% from 2008 to 2013, while the average patient contribution increased by 89.50%. Prescribing of non-substitutable drugs decreased by 13.14 %, whereas generics increased by 12.84%.

Conclusions

An increase in the use of newer AEDs can be attributed to their broad spectrum of action. Generic substitution and dose optimisation should be encouraged to minimise cost.

Introduction

Approximately 50 million people globally suffer from epilepsy.[1] Ngugi and colleagues,[2] concluded that the median prevalence of lifetime epilepsy was 5.8 per 1 000 in developed countries, 10.3 per 1 000 in lower-income countries and 15.4 per 1000 in rural areas. Prevalence studies conducted in South Africa reported a lifetime prevalence of 7.3 per 1 000 in children of a rural district and a crude adjusted prevalence of 7.0 per 1 000 in a rural northeast district respectively.[3,4]

Anti-epileptics are increasingly prescribed to patients of all ages in populations worldwide,[5,6] either as monotherapy or polytherapy.[7] The prescription of first-choice AEDs has been especially changing over the last decade.[8] Prescribers tend to prescribe newer AEDs (e.g. gabapentin, lamotrigine, levetiracetam and pregabalin) to patients due to their tolerability and fewer side-effects.[9] Prescribing patterns and exposure of AEDs to different patient population groups are important factors to consider regarding the safety aspects of the drug.[10] Although AEDs are primarily prescribed for epileptic seizures, they are also used for other co-morbidities, such as neuropathic pain, particularly diabetic neuropathy and postherpetic neuralgia, migraine prophylaxis and bipolar disorder.[11,12]

Mental healthcare in South Africa has been relying on psychiatric hospitals for the past decades, with little attention to mental health care provision in primary care. Currently, psychiatric care for disorders such as epilepsy is minimal in primary care facilities, as South Africa does have a substantial shortage of mental healthcare workforce. According to Jack and colleagues,[13] there are only 1.2 psychiatrists per 100 000 people available in South Africa, which is almost ten times less than higher income countries. This leads to great disparities, which could possibly lead to higher direct costs associated with treatment. The average AED treatment cost was R4 632.[14]

The aim of this study was to determine the prevalence of epilepsy in the private health sector of South Africa; secondly, to investigate the prescribing patterns of AEDs; and lastly, to determine the impact and difference in cost of anti-epileptic treatment during the study period.

Methods

Study design

A quantitative, retrospective drug utilisation review was conducted using nationally representative medicine claims data for a six-year period (1 January 2008 to 31 December 2013). Data were obtained from a privately-owned South African Pharmaceutical Benefit Management (PBM) company. The target population consisted of 6 634 945 patients of whom 46 829 patients (0.7%) (study population) claimed anti-epileptic prescriptions during this study period. Data fields used in this study included patients' member number, date of birth of patients, gender, treatment date, ICD-10 codes of claims, active ingredients, the quantity of medicine items prescribed and the number of days medicine items was supplied for.

Study population

The study population was identified as all patients with an ICD-10 code for epilepsy (G40), in association with a paid claim for an AED during the study period 1 January 2008 to 31 December 2013.

Variables

Variables (age groups, gender and name of active ingredient) were expressed using descriptive statistics such as frequencies, percentages, means, standard deviations and 95% confidence intervals (CI). Patients' ages were calculated according to the patient's age on his/her treatment date, in relation to his/her date of birth, using 1 January of the following year as index date. Patients were divided into five age groups: children/adolescents (0 ≤ 12 years), late adolescents (> 12 ≤ 18 year), young adults (> 18 ≤ 40 years), older adults (> 40 ≤ 65 years) and the elderly/geriatrics (> 65 years). AEDs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system N03AA, N03AB, N03AE, N03AD, N03AF, N03AG and N03AX.

The following cost analyses were conducted: total directs cost of AEDs, single exit price (SEP), medical scheme contribution, and patient contribution.

Statistical analyses

Descriptive and inferential statistics were used to analyse the data during this study period, using the SAS program version 9.3®. The Chi-square test (χ^2) was used to determine whether an association exists between proportions of two groups. Results were considered to be statistically significant when the probability was $p < 0.0001$. Cramer's *V* statistic was used to test the practical significance of the results or associations if the *p*-value was statistical significant

(p<0.0001). Cramer's V could be interpreted as follows: effect size of 0.1 is small; 0.3 effect size is medium and an effect size of 0.5 is large.[15]

A two-sample independent t-test was used to compare the average number of anti-epileptic prescriptions per patient per year by gender. The one-way ANOVA, expressed by the general linear model (GLM), was used to compare the differences between the average number of anti-epileptic prescriptions per patient per year between the five different age groups and in the cost analysis between the different years in the study period. Tukey's studentised range was performed to determine which groups differ significantly from each other. Cohen's d-value was used to determine the size of the difference between these groups. Cohen's d-value can be interpreted as follows: 0.2 is a small effect size; 0.5 is a medium effect size and 0.8 is a large effect size.[16]

Results

The prevalence of patients who received anti-epileptic prescriptions of the total number of patients on the database over the study period 2008 to 2013 ranged between 0.87% and 0.91%. AEDs represented 0.59% (n= 653 780) of the 109 279 335 medicine items claimed during the study period. The average number of anti-epileptic prescriptions per patient per year ranged from 11.76 ± 8.07 (95% CI 11.56-11.95) in 2008 to 11.90 ± 8.39 (95% CI 11.71-12.09) in 2013 (Cohen's d = 0.02). The number of anti-epileptics per prescription per year fairly increased from 1.42 ± 0.86 (95% CI 1.40-1.44) in 2008 to 1.55 ± 1.03 (95% CI 1.52-1.57) in 2013, representing a small difference between the years (Cohen's d = 0.13).

Table 1: Distribution of patients claiming anti-epileptics, prescriptions and number of AEDs claimed during the study period

Year	Total number of patients in database	Number of patients claiming anti-epileptics, n (%)*	Total number of prescriptions in database	Number of anti-epileptic prescriptions, n (%) †	Average number of anti-epileptic prescription per patient ± SD (95% CI)	Total number of medicine items dispensed in database	Number of AEDs claimed, n (%) ‡	Average number of AED per prescription ± SD (95% CI)
2008	758 505	6634 (0.87)	6 775 863	62 442 (0.92)	11.76 ± 8.07 (11.56-11.95)	16 439 253	90 086 (0.54)	1.42 ± 0.86 (1.40-1.44)
2009	1 033 057	8958 (0.87)	9 023 237	84 080 (0.93)	11.82 ± 8.30 (11.65-11.99)	21 648 991	125 066 (0.57)	1.44 ± 0.90 (1.42-1.46)
2010	968 158	8569 (0.89)	8 515 428	79 924 (0.93)	11.82 ± 8.36 (11.64-11.99)	20 527 777	117 496 (0.57)	1.47 ± 0.95 (1.45-1.49)
2011	864 977	7827 (0.90)	7 371 213	74 944 (1.01)	12.22 ± 8.51 (12.03-12.41)	17 766 594	111 541 (0.62)	1.49 ± 0.99 (1.47-1.51)
2012	815 810	7454 (0.91)	6 770 703	69 819 (1.03)	12.00 ± 8.73 (11.80-12.20)	16 409 292	105 580 (0.64)	1.51 ± 0.99 (1.48-1.53)
2013	809 857	7387 (0.91)	6 794 490	67 960 (1.00)	11.90 ± 8.39 (11.71-12.09)	16 487 428	104 011 (0.63)	1.55 ± 1.03 (1.52-1.57)
Total			**45 250 934**	**439 169 (0.97)**		**109 279 335**	**653 780 (0.59)**	

*† ‡ Percentages were calculated according to the total in each respective year

The ratio of females to males over the study period remained relatively similar at 1.19:1. The highest average number of anti-epileptic prescriptions was observed in the older age group (> 40 ≤ 65 years), increasing by 1.91% from 2008 to 2013. A small practical significance was observed between the average number of anti-epileptic prescriptions per patient and the different age groups from 2008 (Cohen's $d \leq 0.314$) to 2013 (Cohen's $d \leq 0.244$) ($p < 0.0001$). A very small effect size (Cohen's $d = 0.152$ between 2011 and 2012; Cohen's $d = 0.131$ between 2009 and 2012) was observed in the group older than 65 years ($p < 0.0001$). There were no statistical significant difference between the average number of anti-epileptic prescriptions per patient and gender. It is likely that the use of AEDs increased with an increase in age.

Table 2: Anti-epileptic prescription per patient stratified by gender and age

Variable	Gender			Age groups (years)					
	Female	Male	*p*-value (*t*-test)	0 - 12	13 -18	19 - 40	41 - 65	> 65	*p*-value (ANOVA)
2008 (N)	3552	3082	**0.903**	433	405	1568	2662	1566	**<0.0001**
Average nr of AEP per patient ± SD	12.05 ± 8.07	11.42 ± 8.05		9.95 ± 7.75	10.29 ± 8.31	12.48 ± 9.18	12.07 ± 8.09	11.39 ± 6.60	
2009 (N)	4818	4140	**0.854**	591	552	2265	3524	2026	**<0.0001**
Average nr of AEP per patient ± SD	12.09 ± 8.29	11.50 ± 8.31		9.94 ± 8.05	10.56 ± 8.38	11.82 ± 9.15	12.32 ± 8.47	11.84 ± 6.82	
2010 (N)	4660	3909	**0.270**	540	480	2102	3384	2063	**<0.0001**
Average nr of AEP per patient ± SD	11.97 ± 8.29	11.65 ± 8.44		9.55 ± 7.44	10.29 ± 8.32	12.26 ± 9.41	12.30 ± 8.61	11.54 ± 6.75	
2011 (N)	4258	3569	**0.551**	472	381	1909	3052	2013	**<0.0001**
Average nr of AEP per patient ± SD	12.29 ± 8.48	12.14 ± 8.56		9.78 ± 7.44	10.81 ± 8.15	12.28 ± 9.57	12.90 ± 8.90	11.98 ± 6.84	
2012 (N)	4060	3394	**0.266**	427	366	1783	2906	1972	**<0.0001**
Average nr of AEP per patient ± SD	12.01 ± 8.80	11.99 ± 8.64		10.00 ± 8.15	10.78 ± 7.86	12.65 ± 9.89	12.77 ± 8.87	10.94 ± 7.39	
2013 (N)	4070	3317	**0.979**	428	360	1846	3035	1718	**<0.0001**
Average nr of AEP per patient ± SD	12.10 ± 8.38	11.65 ± 8.38		10.26 ± 8.18	11.00 ± 8.14	12.16 ± 9.49	12.30 ± 8.48	11.51 ± 6.85	
***p*-value**	**0.566**	**0.001**		**0.822**	**0.771**	**0.104**	**0.001**	**<0.0001**	

Variable	Gender			Age groups (years)					
	Female	Male	*p*-value (*t*-test)	0 - 12	13 -18	19 - 40	41 - 65	> 65	*p*-value (ANOVA)
(ANOVA)									
[§]AEP=	anti-epileptic			prescription;		nr	=		number

The active ingredients most frequently prescribed was valproate with a relative increase in use from 13.24% (n=24 672) in 2008 to 17.02% (n= 31 729) in 2013. This was followed by lamotrigine whose use increased from 12.73% in 2008 to 17.80% in 2013 and gabapentin whose use increased from 12.42% in 2008 to 17.59% in 2013. A notable decrease in the prescribing of phenytoin and carbamazepine was observed (Table 3). The prescribing of these two active ingredients decreased by 6.03% and 1.72%, respectively. Though statistically significant, there was a small practically significant association between the type of active ingredient claimed and the study period ($p< 0.001$; Cramer's $V = 0.24$).

Table 3: Prescribing prevalence of specific anti-epileptic active ingredients from 2008 to 2013, n(%)

Active ingredient	2008 N(%)	2009 N(%)	2010 N(%)	2011 N(%)	2012 N(%)	2013 N(%)	Difference between 2008 and. 2013 ǁ	*p*-value
Carbamazepine N(%)	18 118 (15.54) (20.11)	23 464 (20.13) (18.76)	21 393 (18.35) (18.21)	19 726 (16.92) (17.68)	17 750 (15.23) (16.81)	16 109 (13.82) (15.49)	-1.72	
Clonazepam N(%)	5629 (13.99) (6.25)	8259 (20.53) (6.60)	7700 (19.14) (6.55)	6734 (16.74) (6.04)	5950 (14.79) (5.64)	5955 (14.80) (5.73)	0.81	
Ethosuximide N(%)	138 (13.07) (0.15)	184 (17.42) (0.15)	163 (15.44) (0.14)	215 (20.36) (0.19)	197 (18.66) (0.19)	159 (15.06) (0.15)	1.99	
Felbamate N(%)	0	0	0	0	7 (35.00) (0.01)	13 (65.00) (0.01)	65	
Gabapentin N(%)	1609 (12.42) (1.79)	2620 (20.23) (2.09)	2156 (16.65) (1.83)	2092 (16.15) (1.88)	2196 (16.96) (2.08)	2278 (17.59) (2.19)	5.17	<0.0001
Lamotrigine N(%)	18 368 (12.73) (20.39)	26 096 (18.09) (20.87)	24 641 (17.08) (20.97)	24 839 (17.22) (22.27)	24 635 (17.08) (23.33)	25 685 (17.80) (24.69)	5.07	
Levetiracetam N(%)	2594 (10.32) (2.88)	4502 (17.91) (3.60)	4726 (18.80) (4.02)	4384 (17.44) (3.93)	4315 (17.16) (4.09)	4622 (18.38) (4.44)	8.06	
Oxcarbazepine N(%)	1269 (15.22) (1.41)	1725 (20.68) (1.38)	1493 (17.90) (1.27)	1265 (15.17) (1.13)	1270 (15.23) (1.20)	1318 (15.80) (1.27)	0.58	
Phenytoin N(%)	11 043 (17.58) (12.26)	13 508 (21.50) (10.80)	11 857 (18.87) (10.09)	10 463 (16.65) (9.38)	8692 (13.84) (8.23)	7529 (11.55) (6.98)	-6.03	
Pregabalin N(%)	434 (8.59) (0.48)	983 (19.46) (0.79)	1022 (20.23) (0.87)	819 (16.21) (0.73)	879 (17.40) (0.83)	915 (18.11) (0.88)	9.52	
Primidone Metabolites N(%)	154 (8.93) (0.17)	310 (17.97) (0.25)	312 (18.09) (0.27)	351 (20.35) (0.31)	300 (17.39) (0.28)	298 (17.28) (0.29)	8.35	
Topiramate N(%)	6004 (13.11) (6.66)	8500 (18.55) (6.80)	8197 (17.89) (6.98)	7821 (17.07) (7.01)	7677 (16.76) (7.27)	7614 (16.62) (7.32)	3.51	

Valproate N(%)	24 672 (13.24) (27.39)	34 828 (18.69) (27.85)	33 778 (18.12) (28.75)	32 740 (17.57) (29.35)	31 639 (16.97) (29.97)	31 729 (17.02) (30.51)	3.78
Vigabatrin N(%)	54 (12.83) (0.06)	87 (20.67) (0.07)	58 (13.78) (0.05)	92 (21.85) (0.08)	73 (17.34) (0.07)	57 (13.54) (0.05)	0.71
p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Cramer's *V*	0.113	0.111	0.113	0.151	0.128	0.132	
Total	**90 086**	**125 066**	**117 496**	**111 541**	**105 580**	**104 011**	

[‖] Differences between 2008 and 2013 was calculated from the percentages representing each respective active ingredient

The direct cost of anti-epileptic medicine increased over the study period from 1.28% of the total cost on the database in 2008 to 1.55% of the total cost on the database in 2013. The medical scheme contribution increased by 22.62% from 2008 to 2013, but decreased marginally by 0.59% from 2012 to 2013. The patient contribution increased with 71.43% from 2008 to 2013, with a 4.35% increase from 2012 to 2013.

Table 4: Cost associated with treatment for each respective year (%)**

Year	Total cost on database (R)	Total cost of anti-epileptic agent (R)	SC †† on database (R)	SC †† of anti-epileptic agent (R)	PC ‡‡ on database (R)	PC ‡‡ of anti-epileptic agent (R)
2008	1 785 871 014	22 857 737.74 (1.28)	1 478 548 229	20 282 534.38 (1.37)	307 322 784.90	2 575 203.36 (0.84)
2009	2 509 210 770	34 647 380.19 (1.38)	2 033 702 485	30 369 600.24 (1.50)	475 508 284.70	4 277 779.94 (0.90)
2010	2 460 225 811	33 871 840.37 (1.38)	1 984 537 142	29 747 585.15 (1.50)	475 688 669	4 124 255.22 (0.87)
2011	2 010 783 076	31 653 025.09 (1.57)	1 756 837 350	28 103 478.23 (1.60)	253 945 726	3 549 546.86 (1.40)
2012	1 840 364 908	30 473 131.03 (1.65)	1 620 250 087	27 432 224.07 (1.69)	220 114 821	3 040 906.96 (1.38)
2013	3 607 147 617.90	55 938 332.60 (1.55)	1 643 102 147	27 609 323.87 (1.68)	1 964 045 470	28 329 008.73 (1.44)

** Percentage was calculated according to the total cost in rand (R) on the database in each respective year
†† Medical scheme contribution; ‡‡ Patient contribution

The average cost per item increased by 54.6% from 2008 to 2013, with an increase of 46.98% between 2012 and 2013. The SEP increased by 21.75%, whereas the medical scheme contribution increased by 18.85% from 2008 to 2013. The patient contribution increased drastically by 89.50% from 2008 to 2013, with most of the increase observed between 2012 and 2013.

Table 5: Average cost per item for each respective year from 2008 to 2013

Year	Cost per items (R)		SEP *** (R)		Medical scheme contribution (R)		Patient contribution (R)	
	(mean ± SD)	95% CI	(mean ± SD)	95% CI	(mean ± SD)	95% CI	(mean ± SD)	95% CI
2008	237.12 ± 146.93	233.58 - 240.65	2.95 ± 1.79	2.91 – 2.99	209.36 ± 135.47	206.10 – 212.62	27.76 ± 46.96	26.63 – 28.89
2009	259.24 ± 152.36	256.09 - 262.40	3.32 ± 2.09	3.28 – 3.36	227.72 ± 142.34	224.77 – 230.67	31.52 ± 49.48	30.50 – 32.55
2010	271.49 ± 159.48	268.11 - 274.86	3.50 ± 2.16	3.45 – 3.55	237.62 ± 148.72	234.47 – 240.77	33.87 ± 55.81	32.69 – 35.05
2011	272.42 ± 158.17	268.92 - 275.92	3.60 ± 2.02	3.56 ± 3.65	241.72 ± 146.26	238.48 – 244.96	30.70 ± 52.76	29.53 – 31.87
2012	276.91 ± 162.38	273.22 - 280.60	3.69 ± 2.02	3.64 – 3.73	249.28 ± 154.45	245.78 – 252.79	27.63 ± 49.38	26.50 – 28.75
2013	522.32 ± 310.62	515.24 - 529.41	3.77 ± 2.26	3.71 – 3.82	258.00 ± 153.46	254.50 – 261.50	264.32 ± 162.61	260.61 – 268.03

*** Single exit price

The prescribing of non-generic medication over the study period of 2008 to 2013 has decreased by 13.14%, whereas the percentage of the overall generic substitution increased by 12.84% from 2008 to 2013. Original medication prescribing has remained relatively constant. Non-generic medications were the most prescribed (39.85%) medication overall between the medicine indicators. There was a practical significant association between the proportions of drugs within each group based on the medicine indicator over the study period.

Table 6: Variance based on the medicine indicator (%)

Medicine indicator	Number of items n (%)	2008	2009	2010	2011	2012	2013	Difference between 2008 and 2013
Non-generic	260 526 (39.85)	36 084 (40.06)	55 432 (44.32)	50 831 (43.26)	46 174 (41.40)	44 005 (41.68)	28 000 (26.92)	-13.14
Original	215 980 (33.04)	33 455 (37.14)	40 836 (32.65)	38 283 (32.58)	34 698 (31.11)	29 781 (28.21)	38 927 (37.43)	0.29
Generic	177 274 (27.12)	20 547 (22.81)	28 798 (23.03)	28 382 (24.16)	30 669 (27.50)	31 794 (30.11)	37 084 (35.65)	12.84
***p*-value**		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Cramer's *V*		0.70	0.68	0.67	0.68	0.68	0.63	

Discussion

The prevalence of epilepsy in the private health sector of South Africa ranged between 8.7 per 1 000 and 9.1 per 1 000 over the study period. This figure corresponds with other studies conducted in Italy,[5] Sweden and South Africa.[3,4] For example, Giussani and colleagues,[18] observed a prevalence of 7.9 per 1 000 on The Health Search CSD Longitudinal Patient Database (HSD), whereas Wagner and colleague,[4] reported a crude adjusted prevalence of 7 per 1 000 in a rural Agincourt health sub-district in South Africa.

This longitudinal study showed that the total anti-epileptic use by patients increased by approximately 0.40% from 2008 to 2013. The fatty acid derivate and other anti-epileptic groups (according to ATC® classification system) were the most prescribed pharmacological groups of anti-epileptics in this section of the private health sector of South Africa. This trend confirms other studies conducted in Norway and Germany.[10,19] Landmark and colleagues,[10] determined that the most commonly used AEDs in epilepsy for the period of 2008 to 2009 were lamotrigine, carbamazepine and valproate. Hamer and colleagues,[19] concluded that 83.1% of all patients filled a prescription with at least one of the four most popular active ingredients: valproate, carbamazepine, lamotrigine or levetiracetam. It was interesting to note the gradual increase in the use of new AEDs and a decline in the use of older AEDs, confirming the trend from a study conducted in Europe.[6] The shift to the use of newer AEDs is attributed to the fact that the new AEDs have a broader spectrum of work in epileptic patients, and is not only indicated for epilepsy anymore but for the additional co-morbid symptoms such as neuropathic pain, especially in the elderly.[11] Furthermore, the use of these newer AEDs may be attributed to better effectiveness, fewer side-effects and being easier to use (once-a-day dosing). The newer AEDs may not be more effective in supressing seizures alone, but they are overall more effective in treating patients with epilepsy and co-existing conditions.[9]

This modification in the treatment of epilepsy from older to newer AEDs may explain the increase in cost of AEDs over the study period.[19] Although these newer AEDs are more expensive, they are more cost-effective in the end, due to their tolerability, minimal drug-drug interactions and fewer adverse events.[20]

It was furthermore determined that the majority of medications prescribed during the study period were attributed to non-generic medication. These non-generic medications are extremely costly and are the potential drivers for increased medical expenditures, as they do not have any generic equivalents available on the market. The escalation in medicine cost

between 2013 and the previous study years can be attributed to a 5.8% increase in the maximum SEP by the Department of Health in 2013. In the previous years the SEP was not a factor as no increase was permitted.[21] Epilepsy South Africa,[22] states that South Africa grants patents on almost every patent application it receives, thereby allowing companies to maintain lengthy control over medicines. This results in medication prices being higher in South Africa when compared to many other countries. Charlene Sunkel from the South African Federation for Mental Health stressed the following "high medicine prices prevent mental health patients from accessing the medicines that they need – especially the new generation of medications which often have fewer side effects and cover a broader spectrum of symptoms".[22]

There were no practically significant associations between gender and prescribing patterns. This trend confirms studies done in Norway and Germany. The study observed the highest anti-epileptic use in older adults aged between 41 and 65 years. Older adults are more prone to epilepsy than the younger generation, due to their risk in developing strokes, brain tumours or Alzheimer's disease, which can all cause epilepsy.[23]

Conclusion

From our study, gender and age were weak predictors of anti-epileptic use. The increase in the use of newer AEDs such as gabapentin, lamotrigine, levetiracetam etc., can be attributed to its use in the treatment of epilepsy and its co-morbid conditions. Generic substitution should be encouraged through the implementation of formularies, reference pricing and benefit design strategies. We therefore recommend that effective interventions be instituted nationwide to reduce the cost of the newer AEDs, to ensure access for all epilepsy patients. Examples of these cost containment strategies include: generic substitution, mandatory generic substitution by healthcare plans, and dose optimisation (thereby giving a higher single dose and replacing multiple doses resulting in cost-savings). Interventions should focus on incorporating mental health care into primary care facilities, without the use of specialised workers.

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Ethical considerations

This study was approved by the Health Research Ethics Committee of the North-West University (NWU-00179-14-A1). Permission for the use of the data was granted via the contract between Medicine Usage in South Africa (MUSA) and the South African Pharmaceutical Benefit Management Company (PBM). The data were analysed anonymously. Privacy and confidentiality of the data were maintained at all times, and therefore no patient or medical scheme could be traced. The PBM responsible for providing data in this study was not identified in the study. Confidentiality agreements were signed by the researcher, study supervisor and co-supervisor.

Conflict of interest

None to declare.

References

1. WHO (World Health Organization). Epilepsy. Available from: http://www.who.int/mediacentre/factsheets/fs999/en/index.html [Accessed 19 August 2015].
2. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analysis approach. Epilepsia. 2010;51(5):883-890.
3. Christainson AL, Zwane ME, Manga P, Rosen E, Venter A, Kromberg JGR. Epilepsy in rural South African children: prevalence, associated disability and management. S Afr Med J. 2000;90(3):262-266.
4. Wagner RG, Ngugi AK, Twine R, Bottomley C, Kamuyu G, Gómez-Olive FX, et al. Prevalence and risk factors for active convulsive epilepsy in rural northeast South Africa. Epilepsy Res. 2014;108(4):782-791.
5. Alacqua M, Trifirò G, Spina E, Moretti S, Tari DU, Bramanti P, et al. Newer and older antiepileptic drug use in Southern Italy: a population-based study during the years 2003-2005. Epilepsy Res. 2009;85(1):107-113.
6. De Groot MCH, Schuerch M, De Vries F, Hesse U, Olivia B, Gil M, et al. Antiepileptic drug use in seven electronic health record databases in Europe: a methodological approach. Epilepsia. 2014;55(5):666-673.
7. Stephen LJ, Brodie MJ. Antiepileptic drug monotherapy versus polytherapy: pursuing seizure freedom and tolerability in adults. Curr Opin Neurol. 2012;25(2):164-172.

8. Pickrell WO, Lacey AS, Thomas RH, Lyons RA, Smith PEM, Rees MI. Tends in the first antiepileptic drug prescribed for epilepsy between 2000 and 2010. Seizure. 2014;23(1):77-80.
9. Faught E, Helmers SL, Begley CE, Thurman DJ, Dilley C, Clark C et al. Newer antiepileptic drug use and other factors decreasing hospital encounters. Epilepsy Behav. 2015;45:169-175.
10. Landmark CJ, Fossmark H, Larsson PG, Rytter E, Johanessen SI. Prescription patterns of antiepileptic drugs in patients with epilepsy in a nation-wide population. Epilepsy Res. 2011;95(1-2):51-59.
11. Italiano D, Capuano A, Alibrandi A, Ferrara R, Cannata A, Trifiro G, et al. Indications of newer and older anti-epileptic drug use: findings from a southern Italian general practice setting from 2005-2011. Br J Clin Pharmacol. 2015;79(6):1010-1019.
12. Spina E, Perugi G. Antiepileptic drugs: indications other than epilepsy. Epileptic Disord. 2004;6(2):57-75.
13. Jack H,Wagner RG, Petersen I, Thom R, Newton CR, Stein A, et al. Closing the mental health treatment gap in South Africa: a review of costs and cost-effectiveness. Glob Health Action. 2014;15(7):23431.
14. McCleod H, Rothberg A, Pels L, Eekhout S, Mubangizi DB, Fish T. The costing of the proposed chronic disease list benefits in South African Medical Schemes in 2001. https://www.commerce.uct.ac.za/Research_Units/CARE/RESEARCH/Papers/Chronic%20Disease%20List%20Report.pdf (Accessed 1/10/2015)
15. Ellis SM, Steyn HS. Practical significance (effect sizes) versus or in combination with statistical significance (p-values). Management dynamics. 2003; 12(4):51-53.
16. Steyn HS. Handleiding vir bepaling van effekgrootte-indekse en praktiese betekenisvolheid. Potchefstroom: Statistiese Konsultasiediens, NWU. http://www.puk.ac.za/opencms/export/PUK/html/fakulteite/natuur/skd/handleiding/Hoofstuk_1.pdf (Accessed 15/9/2015).
17. Bolin K, Berggren F, Landtblom AM. Prevalence and cost of epilepsy in Sweden: a register-based approach. Acta Neurol Scand. 2015;131(1):37-44.
18. Giussani G, Cricelli C, Mazzoleni F, Cricelli I, Pasqua A, Pechcioli S, et al. Prevalence and incidence of epilepsy in Italy based on a nationwide database. Neuroepidemiology. 2014;43(3-4):228-232.
19. Hamer HM, Dodel R, Strzelczyk A, Balzer-Geldsetzer M, Reese JP, Schöffsko O, et al. Prevalence, utilization and costs of antiepileptic drugs for epilepsy in Germany: a nationwide population-based study in children and adults. J Neurol. 2012;259(11):2376-2384.

20. Kirmani BT, Robinson DM, Kikam A, Fonkem E, Cruz, D. Selection of antiepileptic drugs in older people. Curr Treat Options Neurol. 2014;16(295):1-16.
21. BHF Southern Africa. SA medicine expenditure reflects increase for the first time in three years. http://ftp.bhfglobal.com/sa-medicine-expenditure-reflects-increase-first-time-three-years (Accessed 10/09/2015).
22. Epilepsy South Africa. 2015. Leading SA health organisations join fight for affordable medicines. http://epilepsy.org.za/new/ (Accessed 1/10/2015).
23. Schacter SC, Shafer PO, Sirven JI. Who gets epilepsy? http://www.epilepsy.com/learn/epilepsy-101/who-gets-epilepsy (Accessed 10/9/2015).

3.3 Manuscript 3.2

Title

Patient adherence with anti-epileptic drugs in the private health sector of South Africa: 2008-2013

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Abstract

Objective: To evaluate the adherence status and predictors of adherence with epilepsy in the private sector of South Africa.

Methods: A retrospective study analysing medicine claims data obtained from a nationally represented South African pharmaceutical benefit management (PBM) company. Patients of all ages (N = 19 168), who received more than one prescription for an anti-epileptic drug (AED), were observed from 2008 to 2013.

Results: Only 55% of AEDs prescribed to 19 168 patients during the study period could be categorised as the adherent group. The top ten active ingredients dispensed accounted for 90.98% of all AED items dispensed. There was an increasing trend in the number of AEDs in the acceptable adherence group parallel with an increase in the number of co-morbid conditions ($p < 0.0001$; Cramer's $V = 0.05$). The total direct cost of non-adherence (wasted resources) amounted to 20.12% of the total direct cost of all AEDs included in the study. Oversupply of AEDs contributed to 3.7% ($736 376.23) of these wasted resources in South Africa.

Significance: Non-adherence to anti-epileptic treatment is a major problem. Various variables (treatment period, cost of undersupply and oversupply) were identified in this study as potentially important factors for a poor adherence status. Epilepsy is associated with high additional costs that affect individuals and society.

KEYWORDS: medicine possession ratio, adherence, direct medicine costs, treatment period, anti-epileptic drugs

KEY POINTS

- Failure in prescription refills and co-morbidities were predictors of non-adherence in patients with epilepsy.
- Wasted direct cost of undersupply and oversupply amounted to $3 964 271.08 (20.12%) of total epilepsy cost during the study period of 2008 to 2013.

Introduction

Approximately 50 million people globally suffer from epilepsy.[1] The most recent prevalence studies conducted in South Africa in 2000 and 2014 reported a lifetime prevalence of 7.3/1000 in children of a rural district and a crude adjusted prevalence of 7.0/1000 in a rural northeast district, respectively.[2-3] Epilepsy has a major impact on the general health of patients and influences the quality of life, performance at work and school and everyday social life.[4] Epilepsy carries an increased risk for seizure-related injuries and mortality compared with the general population.[5] There are several causes of injuries and death directly related to seizures, such as burns, soft tissue injuries, fractures, concussions, intracranial haemorrhages, spinal fractures, drowning, trauma and in some cases, suicide.[6-9]

The introduction of anti-epileptic therapy has been successful in improving morbidity and decreasing the mortality rate of epilepsy patients. AEDs help to maintain a healthy lifestyle. Importantly, however, seizure control or freedom is associated with excellent adherence and persistence to the correct anti-epileptic therapy. Patients with epilepsy must maintain a good

adherence rate in order to prevent a relapse or risk for a recurrent seizure. Several studies have been conducted in the field of adherence to epilepsy treatment, [10-13] all showing a correlation between poor adherence and the increase in frequency of seizures and poor quality of life. In addition Faught et al.[14] found a threefold increased risk of mortality in non-adherent patients when compared to adherent patients.

To ensure optimal therapy, adequate adherence to the given prescription is necessary. Insufficient monthly supply (undersupply) of medication leads to inadequate treatment and the therapeutic effect of chronic diseases, whereas the oversupply of medication consequently leads to potential toxicities.[15-17] Both undersupply and oversupply lead to wasted resources. Undersupply of antipsychotic medication is quite common and Mojtabai and colleagues [18] found 51% of the patients had a treatment gap of 30 days or longer. The assessment of adherence should be a routine action in the management of epilepsy. There are only a few studies in which the economic consequences of non-adherence have been studied.[15,19] There are even fewer studies about the oversupply of medication in South Africa.

This study will firstly strive to determine the adherence status of epilepsy patients in the private health sector of South Africa and observe whether there is any association with age, gender, active ingredient and co-morbidities, and secondly, investigate the cost implication of non-adherence to epilepsy treatment.

Methods

Patients and study design

We conducted a retrospective, longitudinal study analysing nationally representative medicine claims data obtained from a South African pharmaceutical benefit management (PBM) company. Continuously enrolled patients of all ages, who were prescribed any AED over a six-year period from 1 January 2008 to 31 December 2013, were eligible for analysis.

We extracted data for patient demographics (gender and date of birth) and pertinent prescription information (such as drug trade name, days supplied, dispensing date, quantity of medicine prescribed and ICD-10 code per claim). The quality of the data was ascertained by means of several automated validation processes applied by the PBM, such as data integrity validation, eligibility management, medicine utilisation and clinical management, pricing and formulary management.

Inclusion criteria

Patients were included in the study if they i) received a diagnosis of epilepsy (ICD-10 code G40) during the study period in conjunction with a paid claim paid by the prescribed minimum benefit as part of the chronic disease list (CDL) for anti-epileptic medicine; and ii) filled a prescription for single or multiple anti-epileptic agents more than once during the study period (Figure 1).

Study population

A total of 45 250 902 prescriptions on the database were analysed. The study population was narrowed down to 20 210 patients receiving anti-epileptic medication (defined as drugs from the ATC-classification group: N03AA, N03AB, N03AE, N03AD, N03AF, N03AG and N03AX) during the study period by applying the inclusion criteria (refer to Figure 1). Of these 20 210 patients for AED over the study period, 19 168 patients received more than one prescription.

Adherence measure

The medicine possession ratio modified (MPRm) measure was used as proxy to determine adherence. The MPRm is an internationally accepted and well-documented method to calculate drug adherence in pharmacoepidemiological studies and in chronic diseases.[20-23] The MPRm was calculated from the medicine claims data by using the following formula [24]:

$$MPRm = \frac{Total\ days\ supplied}{Last\ claim\ date - first\ claim\ date + days'supplied} \times 100$$

The MPRm is an adherence percentage value.

Adherence measures based on the MPRm provide an indication of the possession of the medicine by the patient; however, the consumption of the medication by the patient can only be assumed to follow from the possession. [25] The MPRm is considered acceptable if the calculated value is ≥ 80%, but ≤ 110%. An MPRm of less than 80% indicates undersupply of medication or the presence of refill gaps, so that possession is considered unacceptably low and non-adherent, whereas an MPRm greater than 110% (oversupply) is also deemed unacceptably high and non-adherent due to the oversupply of medicine. Both undersupply and oversupply represent possible waste and exhaustion of resources. [26]

The MPRm was used to identify the undersupply and oversupply of medication. The direct cost associated with the undersupply and oversupply of medication was also calculated. The cost of oversupply was calculated by multiplying the average direct medicine cost per day with the total number of days' supplied, subtracting the number of days the patient was supposed to receive the medication. The cost of the undersupply was determined by calculating the average direct medicine cost per day with the number of days the patient was supposed to have received the medication, subtracting the total number of days' supplied. The medicine cost was calculated in South African rand and converted to US dollars (average conversion rate 2008-2013: 0.1238). [27]

Study variables

Variables (age, gender, treatment period, active ingredients and other co-morbidities) were expressed by using descriptive statistics. Frequencies, means, percentages, standard deviations (SD) and the 95% confidence interval (95% CI) were used. Patient age was calculated at the date of the first dispensing on the database in relation to his/her date of birth. Patients were categorised into five age groups: 0 ≤ 12 years; > 12 ≤ 18 years; > 18 ≤

40 years; > 40 ≤ 65 years and > 65 years and older. Treatment duration was calculated as the days from the first prescription for AEDs until the date of the last prescription and divided into three groups: ≤ 30 days; > 30 - ≤ 120 days and > 120 days. The treatment period can be described as the number of days the patient was supposed to receive medication. The co-morbid conditions were considered to be those chronic conditions registered on the CDL. The South African prescribed minimum benefit chronic disease list (CDL) conditions were identified based on the presence of the following ICD-10 codes on claims reimbursed from patients' PMB benefits: Addison's disease (ICD-10 code E27.1), asthma (J45, J45.8), bronchiectasis (J47, Q33.4), cardiac failure (I50, I50.0, I50.1), cardiomyopathy (I42, I42.0, I25.5), chronic obstructive pulmonary disease (J43, J44), chronic renal disease (N03, N11, N18), coronary artery disease (I20, I20.0, I25), Crohn's disease (K50, K50.8), diabetes insipidus (E23.2), diabetes mellitus (E11.0- E11.9), dysrhythmias (I47, I47.2, I48), epilepsy (G40, G40.8), glaucoma (H40, Q15.0), haemophilia (D66, D67), hyperlipidaemia (E78.0-E78.5), hypertension (I10.0, I11.0, I12.0, I13.0, I15.0), hypothyroidism (E02, E03, E03.8), multiple sclerosis (G35), Parkinson's disease (G20, G21), rheumatoid arthritis (M05, M06, M08.0), schizophrenia (F20), systemic lupus erythematous (M32, L93, L93.2) and ulcerative colitis (K51, K51.9).

Statistical analysis

Data management and analysis were performed by the SAS program version 9.3®. A probability of $p < 0.0001$ was considered statistically significant. The practical significance of the results was computed when the *p*-value was statistically significant.

The Chi-square test was used to compare the statistically significant associations between two categorical variables. The Cramer's *V* value was used to test the strength for any association or practical significance from the Chi-square. It could be interpreted as follows: effect size of 0.1 is small; 0.3 effect size is medium and an effect size of 0.5 is large. [28]

Results

In this study, 95% of the patients were aged between 45.30 and 45.93 years, with more than half of these patients being women. In total, more than three quarters of the population received AEDs for a period longer than four months (Table 1). The mean MPRm of the 47 407 AEDs was 96.35% (SD 143.49) (95% CI: 95.06-97.64). Of the anti-epileptics dispensed, more than half were associated with an acceptable adherence (MPRm of > 80% and more, but less than 110%) (Table 1).

The treatment period had a statistically and practically significant influence on the MPRm of anti-epileptics (Table 2). Patient adherence status was independent of gender, but a statistically significant association was observed between the adherence status and the different age groups (Table 2) ($p < 0.0001$; Cramer's $V = 0.067$). The number of co-morbid conditions may influence the adherence to AEDs, although there were a very small practical association ($p \leq 0.0001$; Cramer's $V = 0.05$).

The top ten most dispensed active ingredients accounted for 90.98% of all AED items dispensed during the study period. These active ingredients include valproate, lamotrigine, carbamazepine, topirimate, phenytoin, clonazepam, levetiracetam, gabapentin, valproic acid and oxcarbazepine. A statistically significant difference was observed between the type of active ingredient and adherence status (Table 2). The active ingredient with the highest adherence prevalence was oxcarbazepine (64.5%), followed by valproic acid (63.7%) and phenytoin (58.7%) (Table 2). Most of the undersupply, adherent and oversupply groups were found in situations where the patient only suffered from epilepsy, without a co-morbid condition.

Of the 44.86% items (undersupply and oversupply items), the total wasted resources from 2008 to 2013 due to non-adherence amounted to $3 964 271.08 (20.12%) of the total cost of AEDs. During this period, a third of AEDs were undersupplied, with oversupply

corresponding to 3.7% of the total direct cost of epilepsy prescriptions during the study period (Table 3).

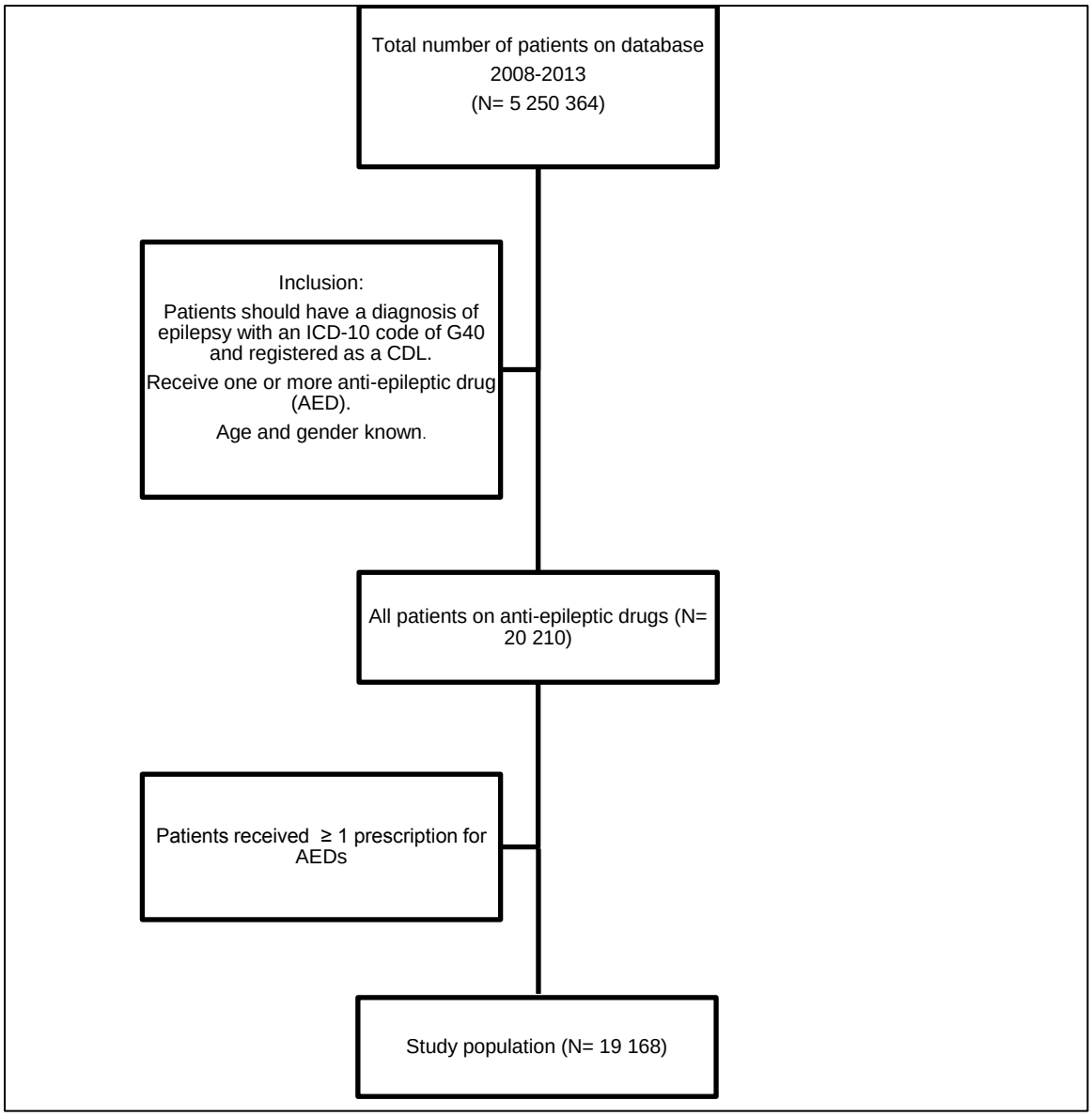

Figure 1: Selection of the study population

Table 1: Patient demographics

Variable	N (%)
Total number of patients	19 168
Age	
Mean (SD) (years)	45.61 (21.96)
Age groups (years)	
0-12 years	1 411 (7.36)
13-18 years	1 163 (6.07)
19-40 years	5 067 (26.43)
41-65 years	7 424 (38.73)
> 65 years	4 103 (21.41)
Gender	
Male	8 852 (46.18)
Female	10 316 (53.82)

All values are presented as frequencies and percentages, except where specifically stated otherwise.

Table 2: Adherence to AEDs by age group, gender and active ingredient

Variable	N	Adherent [n (%)]	Undersupply [n (%)]	Oversupply [n (%)]	*p*-value	Cramer's *V*
Overall active ingredients	47 407	26 142 (55.14)	14 498 (30.58)	6 767 (14.27)		
Age group (years), n (%)					<0.0001	0.067
0-12 years	2 812	1 305 (4.99)	1 142 (7.88)	365 (5.39)		
13-18 years	2 762	1 367 (5.23)	1 034 (7.13)	361 (5.33)		
19-40 years	13 571	7 071 (27.05)	4 430 (30.56)	2 070 (30.59)		
41-65 years	18 760	10 555 (40.38)	5 496 (37.91)	2 709 (40.03)		
> 65 years	9 502	5 844 (22.35)	2 396 (16.53)	1 262 (18.65)		
Gender, n (%)					0.182	0.009
Male	21 138	11 752 (44.95)	6 416 (44.25)	2 970 (43.89)		
Female	26 269	14 390 (55.05)	8 082 (55.75)	3 797 (56.11)		
Top ten active ingredients initiated					<0.0001	0.071

Variable	N	Adherent [n (%)]	Undersupply [n (%)]	Oversupply [n (%)]	*p*-value	Cramer's *V*
Valproate	10 690	5 931 (22.69)	3 329 (22.96)	1 430 (21.13)		
Lamotrigine	10 411	5 748 (21.99)	3 268 (22.54)	1 395 (20.61)		
Carbamazepine	7 404	4 158 (15.91)	2 203 (15.20)	1 043 (15.41)		
Topirimate	3 892	2 006 (7.67)	1 251 (8.63)	635 (9.38)		
Phenytoin	3 814	2 240 (8.57)	1 060 (7.31)	514 (7.60)		
Clonazepam	2 528	1 355 (5.18)	831 (5.73)	342 (5.05)		
Levetiracetam	1 795	977 (3.74)	467 (3.22)	351 (5.19)		
Gabapentin	1 077	492 (1.88)	410 (2.83)	175 (2.59)		
Valproic acid	1 066	679 (2.60)	273 (1.88)	114 (1.68)		
Oxcarbazepine	456	294 (1.12)	102 (0.70)	60 (0.89)		
Treatment period (days)					<0.0001	0.208
≤30	2 587	986 (3.77) (38.11)	210 (1.45) (8.12)	1 391 (20.56) (53.77)		
>30 - ≤120	8 750	4 336 (16.59) (49.55)	2 711 (18.70) (30.98)	1 703 (25.17) (19.46)		
>120	36 070	20 820 (79.64)	11 577 (79.85)	3673 (54.28)		

Variable	N	Adherent [n (%)]	Undersupply [n (%)]	Oversupply [n (%)]	*p*-value	Cramer's *V*
		(57.72)	(32.10)	(10.18)		
Number of co-morbidities					<0.0001	0.050
No co-morbidities	27 692	14 752 (56.43)	9 155 (63.15)	3 785 (55.93)		
1	10 736	6 252 (23.92)	2 962 (20.43)	1 522 (22.49)		
2	5 508	3 220 (12.32)	1 427 (9.84)	861 (12.72)		
3	2 469	1 365 (5.22)	696 (4.80)	408 (6.03)		
4	783	444 (1.70)	188 (1.30)	151 (2.23)		
5	184	88 (0.34)	63 (0.43)	33 (0.49)		
>6	32	18 (0.07)	7 (0.05)	7 (0.10)		

Table 3: Direct medicine cost associated with non-adherence

	Adherence status			
	Non-adherent		Adherent	
	Undersupply	**Oversupply**	**Appropriate**	**Total**
Number of items (%)	14 498 (30.58)	6 767 (14.27)	26 142 (55.14)	**47 407**
Total cost ($)	3 227 894.85	736 376.23	15 743 643.24	**19 707 905.31**
Medical scheme contribution ($) (%)	2 486 430.34 (77.02)	5 576.98 (0.76)	12 480 157.30 (79.27)	**14 972 164.61**
Patient contribution ($) (%)	741 464.51 (22.97)	730 799.25 (99.24)	3 263 476.94 (20.73)	**4 735 740.70**

Discussion

The purpose of this study was to evaluate the adherence status and to determine the predictors of adherence.

The most important findings of this study were that: 1) adherence with chronic anti-epileptic treatment is poor (55.14%) in the study population; 2) a longer period of treatment was a predictor of adherence; and 3) patients aged between 41 and 65 years and predominantly females were in the adherent group.

Non-adherence in patients taking AEDs is a major concern, not only in developed countries, but also in middle-income countries such as South Africa. The 55.14% adherence rate described in this study was especially poor when compared to other studies [29,30], and had a major economic influence on the total healthcare, contributing to $3 964 271.08 of wasted resources. Briesacher and colleagues [31] used a secondary database of employer-sponsored medical care claims in the United States of America and found that 61% of patients on AED treatment are adherent, whereas Faught and colleagues conducted a study using Medicaid claims data from Florida, Iowa and New Jersey [14], and found a 71% adherence rate. The observation of poor adherence rates has prompted studies to investigate possible reasons for non-adherence, such as side-effects, complex drug regimens, patients' beliefs and severity of the disease.

Our study further revealed that only 40.38% of the items dispensed in the older adult group (41-65 years) were associated with an acceptable adherence. The trend in this study of increase in age parallel to an increase in adherence status is supported by several other studies. [32-34] In a study performed in the United Kingdom by Buck et al., patients aged 60 years and older were more adherent to their treatment than those younger than 60 years of age (86% *vs*. 66%, respectively). Buck and colleagues showed that the reason for this non-adherence observed between the two age groups could be attributed to a lack of understanding of the importance of

adherence to treatment especially by teenagers and ultimate denial of the disease and having a disease that is not comprehended by other peers. [35]

The majority of anti-epileptic items prescribed in the undersupply, adherent and oversupply group were prescribed for more than 120 days. This observation may be explained by the fact that epilepsy is a chronic condition and automatically falls in the longer treatment period. An increase was observed in the percentage of items dispensed associated with an acceptable adherence and undersupply over the period of treatment, whereas the percentage of items dispensed associated with oversupply decreased.

The top three active ingredients that represented the highest adherence rate were oxcarbazepine, valproic acid and phenytoin, which can possibly be attributed to the fact that they are first-line treatment, have available generics and the extended release forms that make once a day dosing possible. [36-37] Adherence status was independent of generic status.

The number of co-morbidities may also pose a threat to adherence. The mean prevalence of co-morbid conditions in this study was found to be 0.89, implying that epilepsy patients had an occurrence of one additional chronic condition. The top five co-morbid conditions occurring with epilepsy was hypertension, hyperlipidaemia, hypothyroidism, diabetes mellitus type 2 and asthma. Current literature studies report conflicting results. Some of these studies reported a lower adherence with multiple co-morbid conditions [38-40], whereas others indicated a better adherence rate as the number of co-existing conditions increased. [31] As noted earlier, non-adherence is associated with a higher frequency of seizures. Patients with a higher seizure frequency tend to develop depression and anxiety, as it has a psychological impact on them. [7] Patients who have had active seizures, have a significantly increased mortality and morbidity rate. [9] Non-adherence to medication does not only have a negative impact on clinical outcomes, but also on the economic consequences. We observed that non-adherence contributed to 20.12% of wasted resources, which is especially worrying in a country such as South Africa, as we do not have the financial capacity to carry such a burden. Patients who were undersupplied

in terms of the total cost of medicine items (16.38%) did possibly not receive adequate treatment and did not reach optimal therapeutic effect. We observed that the oversupply of medication contributed to 3.7% of the total direct costs on the database over the study period. This corresponds more or less with another study conducted by Kingsman and colleagues [19], which focused on the cost of oversupply, indicating a 4.5% extra cost of the total sales. The extra supply of medication leads to a waste of medical resources and potential hazards to the patient if medication is overused, leading to side-effects. Medication oversupply reflects a poor communication system between the prescriber and patient, where these patients believe they are fully adhering to their prescriptions. Undersupply of medication may lead to a greater probability of visits to emergency departments or admissions to the hospital, as a result of poor control over seizures. [41]

Conclusion

We showed that the adherence with AEDs in the South African private health sector, as determined on the claims database, was relatively poor. To improve this poor adherence status, strategies must be implemented. Reminders such as telephone monitoring or automated alert, simpler regimens, value-based insurance designs, such as lowering co-payments and patient education about the disease can all lead to improvement in adherence by patients. Pharmacists and other healthcare providers play an essential role in contributing to the patients' adherence status. These pharmacists must implement routine communication with the providers and follow-up consultations to encourage the adherence to medications after changes in regimens. [42]

We established that poor adherence with AED treatment contributes significantly to a waste of cost in the treatment of epilepsy in a middle-income country such as South Africa. To lower the cost of medication, mandatory generic substitutions must be implemented and cost-effective therapy initiated by healthcare providers to ensure that patients adhere to regimens on a monthly basis.

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Disclosure of conflicts of interest

None.

Ethical publication statement

This study was approved by the Health Research Ethics Committee of the North-West University (NWU-00179-14-A1). Permission for the use of the data was granted by the board of directors of Pharmaceutical Benefit Management (PBM) company. The data were analysed anonymously. Privacy and confidentiality of the data were maintained at all times, and therefore no patient or medical scheme could be traced. The PBM responsible for providing data in this study was not identified in the study. Confidentiality agreements were signed by the researcher, study supervisor and co-supervisor.

References

1. WHO (World Health Organization). Epilepsy. Available from: http://www.who.int/mediacentre/factsheets/fs999/en/index.html [Accessed 19 August 2015].
2. Christainson AL, Zwane ME, Manga P, et al. Epilepsy in rural South African children: prevalence, associated disability and management. S Afr Med J. 2000; 90(3):262-266.
3. Wagner RG, Ngugi AK, Twine R, et al. Prevalence and risk factors for active convulsive epilepsy in rural northeast South Africa. Epilepsy Res. 2014; 108(4):782-791.
4. Birbeck GL, Hays RD, Cui X, et al. Seizure reduction and quality of life improvements in people with epilepsy. Epilepsia. 2002; 43(5):535-538.
5. Tiamkao S, Kaewkiow N, Pranbul S, et al. Validation of a seizure-related injury model. J Neurol Sci. 2014; 336(1-2):113-115.
6. Bellon M, Walker C, Peterson C. Seizure-related injuries and hospitalizations: self-report data from the 2010 Australian Epilepsy Longitudinal Survey. Epilepsy Behav. 2013; 26(1):7-10.
7. Boylan LS, Flint LA, Labovits DL, et al. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. Neurology. 2004; 62(2):258-261.
8. Camfield C, Camfield P. Injuries from seizures are a serious, persistent problem in childhood onset epilepsy: a population-based study. Seizure. 2015; 27:80-83.
9. Nei M, Bagla R. Seizure-related injury and death. Curr Neurol Neurosci Rep. 2007; 7(4):335-341.
10. Hovinga CA, Asato MR, Manjunath R, et al. Association of non-adherence to antiepileptic drugs and seizures, quality of life, and productivity: survey of patients with epilepsy and physicians. Epilepsy Behav. 2008; 13(2):316-322.
11. Jones RM, Butler JA, Thomas VA, et al. Adherence to treatment in patients with epilepsy: associations with seizure control and illness beliefs. Seizure. 2006; 15(7):504-508.

12. Ladner TR, Morgan CD, Pomerantz DJ, et al. Does adherence to epilepsy quality measures correlate with reduced epilepsy-related adverse hospitalization: a retrospective experience. Epilepsia. 2015; 56(5):e63-e67.
13. Samsonsen C, Reimers A, Brathen G, et al. Nonadherence to treatment causing acute hospitalizations in people with epilepsy: an observational, prospective study. Epilepsia. 2014; 55(11):e125-e128.
14. Faught E, Duh MS, Weiner JR, et al. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM study. Neurology. 2008; 71(20):1572-1578.
15. Frediani F, Cannatà AP, Magnoni A, et al. The patient with medication overuse: clinical management problems. Neurol Sci. 2003; 24(2):s108-s111.
16. Hedna K, Hägg S, Andersson Sundell K, et al. Refill adherence and self-reported adverse drug reactions and sub-therapeutic effects: a population-based study. Pharmacoepidemiol Drug Saf. 2013; 22(12):1317-1325.
17. Stroupe KT, Murray MD, Stump TE, et al. Association between medication supplies and healthcare costs in older adults from an urban healthcare system. J Am Geriatr Soc. 2000; 48(7):760-768.
18. Mojtabai R, Lavelle J, Gibson PJ, et al. Gaps in use of antipsychotics after discharge by first-admission patients with schizophrenia, 1989 to 1996. Psychiatr Serv. 2002; 53(3):337-339.
19. Kingsman K, Melander A, Carlsten A, et al. Refill non-adherence to repeat prescriptions leads to treatment gaps or to high extra costs. Pharm World Sci. 2007; 29(1):19-24.
20. Andrade SE, Kahler KH, Frech F, et al. Methods for evaluation of medication adherence and persistence using automated databases. Pharmacoepidemiol Drug Saf. 2006; 15(8):565-574.
21. Marcum ZA, Gurwitz JH, Colón-Emeric C, et al. Pills and ills: methodologic issues in pharmacologic research. J Am Geriatr Soc. 2015; 63(4):829-830.

22. Park H, Rascati KL, Lawson KA, et al. Adherence and persistence to prescribed medication therapy among medicare part D beneficiaries on dialysis: comparisons of benefit type and benefit phases. J Manag Care Spec Pharm. 2014; 20(8):862-876.
23. Thier SL, Yu-Isenberg KS, Leas BE, et al. In chronic disease, nationwide data show poor adherence by patients to medication and by physicians to guidelines. Manag Care. 2008; 17(2):48-57.
24. Karve S, Cleves MA, Helm M, et al. Prospective validation of eight different adherence measures for use with administrative claims data among patients with schizophrenia. Value Health. 2009; 12(6):989-995.
25. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. Am J Manag Care. 2005; 11(7):449-457.
26. Ettinger AB, Manjunath R, Candrilli SD, et al. Prevalence and cost of non-adherence to anti-epileptic drugs in elderly patients with epilepsy. Epilepsy Behav. 2009; 14:324-329.
27. OANDA Corporation. Currency converter. Available from: http://www.oanda.com/currency/converter/ [Accessed 27 August 2015].
28. Ellis SM, Steyn HS. Practical significance (effect sizes) versus or in combination with statistical significance (p-values). Management dynamics. 2003; 12(4):51-53.
29. Davis KL, Candrilli SD, Edin HM. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. Epilepsia. 2008; 49(3):446-454.
30. Manjunath R, Davis KL, Candrilli SD, et al. Association of antiepileptic drug nonadherence with risk of seizures in adults with epilepsy. Epilepsy Behav. 2009; 14(2)372-378.
31. Briesacher BA, Andrade SE, Fouayzi H, et al. Comparison of drug adherence rates among patients with seven different medical conditions. Pharmacotherapy. 2008; 28(4):437-443.
32. Hertz RP, Unger AN, Lustik MB. Adherence with pharmacotherapy for type 2 diabetes: a retrospective cohort study of adults with employer-sponsored health insurance. Clin Ther. 2005; 27(7):1064-1073.

33. Kim YS, Sunwoo S, Lee HR, Lee KM, Park YW, Shin HC, Kim CH, Kim DH, Kim BS, Cha HS, Huh BY, Korea post-marketing surveillance research group. Determinants of non-compliance with lipid-lowering therapy in hyperlipidemic patients. Pharmacoepidemiol Drug Saf. 2002; 11(7):593-600.
34. Sirey JA, Bruce ML, Alexopoulos GS, et al. Perceived stigma and patient-rated severity of illness as predictors of antidepressant drug adherence. Psychiatr Serv. 2001; 52 (12):1615-1620.
35. Buck D, Jacoby A, Baker GA, et al. Factors influencing compliance with antiepileptic drug regimes. Seizure. 1997; 6(2):87-93.
36. South Africa. Medical Schemes Act, 1998 (Act no. 131 0f 1998). Regulations made in terms of the Medical Scheme Act, 1998 therapeutic algorithms for chronic conditions. (Notice 1402). Government gazette, 25537:53.
37. Uthman BM. Extended-release antiepilepsy drugs: review of the effects of once-daily dosing on tolerability, effectiveness, adherence, quality of life, and patient preference. US neurology. 2014; 10(1):30-37.
38. Marcum ZA, Gellad WF. Medication adherence to multi-drug regimens. Clin Geriatr Med. 2012; 28(2):287-300.
39. Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. Clinical medicine & research. 2013; 11(2):54-65.
40. Saadat Z, Nikdoust F, Aerab-Sheibani H, Bahremand M, Shobeiri E, Saadat H, Moharramzad Y, Morisky DE. Adherence to antihypertensives in patients with comorbid condition. Nephro-Urology monthly. 2015; 7(4):1-6.
41. Krause SR, Van Rooyen FC, Van Vuuren MVJ, Jenkins L. Non-compliance with treatment by epileptic patients at George Provincial Hospital. South African family practice. 2007; 49(9):14-14d.
42. Iuga AO, McGuire MJ. Adherence and health care costs. Risk Manag Health Policy. 2014; 7:35-44.

CHAPTER 4: CONCLUSION AND RECOMMENDATIONS

4.1 Introduction

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

The aim of this study was to investigate and determine the adherence status with AEDs in epilepsy patients in the private health sector of South Africa. The study was divided into two phases; the literature review and the empirical investigation phase.

4.2 Content of dissertation

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

Chapter 2 focused on the general summary of anti-epileptics and their use from literature. Adherence was also conceptualised.

Chapter 3 represented the results and discussions of the study in manuscript form. Two manuscripts were presented with the following titles:

- Anti-epileptic prescribing patterns in the South African private health sector (2008-2013)
- Patient adherence with anti-epileptic drugs in the private health sector of South Africa: 2008-2013

4.3 Literature review

The specific objectives of this study's literature review were to:

- Investigate the prevalence of epilepsy in South Africa.
- Conceptualise epilepsy, adherence, compliance and treatment of epilepsy.
- Investigate possible factors that influence adherence to chronic medication, focusing specifically on anti-epileptic medicine.
- Investigate the burden of disease for epilepsy focusing on the economic and clinical aspects.

The conclusion from the literature study was as follow:

4.3.1 Investigate the prevalence of epilepsy in South Africa

The prevalence of epilepsy in the different continents was studied, where the difference in the socio-economic state is evident (section 2.2.6). It was found that the worldwide median prevalence of lifetime epilepsy was 5.8 per 1 000 of the population in developed countries, 10.3 per 1000 in lower-income countries and 15.5 per 1 000 in rural areas (Ngugi *et al*., 2012:886). Very little research has been done regarding the prevalence of epilepsy in South Africa. A lifetime prevalence of 7.3 per 1 000 in children of a rural district and a crude adjusted prevalence of 7.0 per 1 000 in a rural northeast district were found, respectively (Christianson *et al*., 2000:264; Wagner *et al*., 2014:786).

4.3.2 Conceptualisation of epilepsy, adherence, compliance and treatment thereof

Adherence was used as the preferred term in this study as it focuses on the empowerment of the patient to decide whether he/she wants to adhere to the recommendations regarding therapy by the prescriber in mutual agreement (Eatock *et al*., 2007:118; Horne *et al*., 2005:12). The effective management of epilepsy is based on exercise, a healthy ketogenic diet and lifestyle and effective pharmacological treatment (sections 1.2; 2.2.7.1 and 2.2.7.2). Up to 80% of epileptic patients should have their epilepsy controlled with medicine (Epilepsy South Africa, 2014). The newer AEDs are similar in their effectiveness when compared to older AEDs, but more tolerable (Kirmani *et al*., 2014:2). It was interesting to note in the results that there was a gradual increase in the use of newer AEDs and a decrease in the use of older AEDs (Chapter 3). This trend was confirmed by another study in 2014 conducted in Europe (De Groot *et al*., 2014:668). Gabr and Shams (2015:33) agree with a previous study (Eatcock & Baker, 2007:121) that the estimated non-adherence rate of epilepsy worldwide ranges from 30% to

50%. Non-adherence to AED treatment results in a significant burden in term of economic and clinical outcomes, such as injuries, increases in doctors' room visits, hospitalisation, decreases in daily work activities (school, work etc.) and ultimately increased healthcare costs (Davis *et al*., 2008:451-453; Richter *et al.*, 2003:2327).

4.3.3 Investigation of possible factors that influence adherence to chronic medication, focusing specifically on anti-epileptic medicine

There are several factors that may contribute to poor adherence or non-adherence. These factors were grouped into five dimensions: socio-economic, health system-related, condition-related, treatment-related and patient-related factors (section 2.3.1.3). To mention a few of these factors belonging to the five dimensions: lack of social support, high cost of therapy, inadequate reimbursement by health insurance plans, lack of adequate knowledge on adherence and the possible effective intervention for improving adherence, the level of physical, psychological and social impact of the disease on the patient, complex drug regimens, indifferent attitude toward the disease by the patient and patient does not understand the consequences of poor adherence to therapy. Factors associated with non-adherence to epilepsy treatment, specifically, could be contributed to the unwillingness to pay the high cost of medicine, low income and the language barrier, inadequate reimbursement by health insurance plans, lack of education about epilepsy and the consequences of not adhering to treatment, duration of treatment and high frequency of seizures, poly-therapy and the patients who feel stigmatised by suffering from epilepsy (WHO, 2003:91).

4.3.4 Investigation of the burden of disease for epilepsy focusing on the economic and clinical aspects

High seizure frequency is associated with a poor health-related-quality-of-life (Birbeck *et al*., 2002:535). For those patients suffering from a high seizure frequency, developing depression and anxiety may be inevitable (section 2.2.8). Epilepsy is a cost-intensive disorder, where the financial burden rests on the shoulders of developing countries such as South Africa. In a country where financial stress is unavoidable, the burden of medical costs follows. To ensure optimal health, patients often have to face the hard reality of expensive medical treatment. Jennum and colleagues (2011:951), found that the average annual cost for an epilepsy patient was €14 575, whereas Ivaanova and colleagues (2010:842) determined that the annual direct cost of epilepsy patients was $11 276 and McCleod and colleagues (2002:25) determined an average cost for AED treatment of R4 632.

4.4 Empirical study objectives

The specific objectives of the empirical study using the medicine claims database were to:

- Determine the prevalence of epilepsy on the database for the period of 2008 to 2013 stratified by age and gender.
- Determine the prescribing patterns and costs for anti-epileptic treatment.
- Determine the MPRm as proxy for adherence for all epileptic patients.
- Compare database-related variables (demographic, chronic diseases and medicine-related factors) and measurements between adherent and non-adherent epileptic patients to identify factors that influence adherence.

The conclusion from the empirical investigation was as follow:

4.4.1 Determination of the prevalence of epilepsy on the database for the period of 2008 to 2013 stratified by age and gender

With regard to determining the prevalence of epilepsy over the study period, it was found that epilepsy patients represented 8.7 per 1 000 to 9.1 per 1 000 from 2008 to 2013 of the total population on the database. This finding agrees with other studies conducted in the private health sector (Giussani *et al*., 2014:229; Hamer *et al*., 2012:2378) and other prevalence studies in South Africa (refer to paragraph 4.3). Anti-epileptic prescriptions represented 0.97% (n= 439 169) out of the 45 250 934 number of prescriptions on the database and AED represented 0.59% (n= 653 780) out of the 109 279 335 medicine items claimed on the database. The female-to-male ratio (1.19:1) remained relatively similar over the study period. The highest prevalence of anti-epileptic prescriptions was observed in the older age group (patients between the age of 40 and 65 years), increasing by 1.91% from 2008 to 2013, supporting literature suggesting that older adults are more prone to epilepsy than the younger generation, due to risks of developing strokes and brain tumours which can lead to epilepsy (Schachter *et al*., 2013). Small practical significant differences was observed between the age groups and the average number of anti-epileptic prescriptions per patient in 2008 (Cohen's $d \leq 0.314$) to 2013 (Cohen's $d \leq 0.244$) ($p < 0.0001$). The results indicated that there was no practically significant association between the gender and the prescribing patterns (average number of AED prescriptions per patient).

4.4.2 Determination of the prescribing patterns and costs for anti-epileptic treatment

The active ingredient most frequently prescribed was valproate with a relative increase in prescribing from 2008 to 2013 (ranging from 13.24% to 17.02%). This was followed by an increase in the prescribing of newer AEDs, such as lamotrigine (ranging from 12.73% in 2008 to 17.80% in 2013) and confirms the trend from a study conducted in Europe (De Groot *et al*., 2014:668). The shift towards the use of newer AEDs can be contributed to the fact that the newer AEDs have a broader spectrum of action in epilepsy patients and are more tolerable.

The direct cost of AED treatment increased over the study period from 1.28% of the total cost of all the medication on the database in 2008 to 1.55% in 2013. The medical scheme contribution increased with 22.62% and the patient contribution increased with 71.43% over the study period. The modification in the treatment of epilepsy with newer AEDs may explain the increase in cost (with 54.6%) observed between 2008 and 2013 (ranging from an average cost of R237.12 per item to an average cost of R522.32 per item).This increase in the average cost had a significant impact on the patient contribution (ranging from an average patient contribution of R27.76 in 2008 to an average patient contribution of R264.32 in 2013). The SEP increased with 21.75% and the medical scheme contribution increased with 18.85% over the study period.

The majority of medications prescribed during this study period were attributed to non-substitutable medication (39.85%), which are extremely costly and who is the potential drivers for increased medical expenditures by patients (89.50%). The non-substitutable medication use decreased over the study period ranging from 40.06% in 2008 to 26.92% in 2013, with an increase in the prescribing of generic medicine (ranging from 27.12% in 2008 to 35.65% in 2013). The escalation in the medicine cost between 2013 and the previous years can be attributed to the 5.8% increase in SEP by the Department of Health in 2013 (BHF Southern Africa).

4.4.3 Determination of the MPRm as proxy for adherence for all epileptic patients

The MPRm is an internationally accepted and well-documented method to calculate drug adherence in pharmacoepidemiological studies and in chronic diseases (Andrade *et al*., 2006:567; Marcum *et al*., 2015:829; Park *et al*., 2014:864 & Thier *et al*., 2008:50). The adherence to AED treatment was 55.14%, which was especially poor when compared to other studies (Briesacher *et* al., 2008:443; Davis *et* al., 2008:449; Faught *et* al., 2008:1572; Manjunath *et al*., 2009:374). The MPRm did not only provide an overview of the possession of the AEDs during the study period, but were also used to identify the undersupply and oversupply of AEDs. Of all AED items dispensed, 44.86% were corresponding to wasted

resources (undersupply and oversupply). The direct cost associated with the undersupply and oversupply amounted to 20.12% (R32 021 575.77) of the total cost (R159 191 480.70) of AEDs during the study period.

4.4.4 Comparison of database-related variables (demographic, chronic diseases and medicine-related factors) and measurements between adherent and non-adherent epileptic patients to identify factors that influence adherence

Patient adherence to AED treatment was independent of gender, whereas the age, the number of co-morbid conditions and the treatment period and active ingredients had a possible influence on the adherence status ($p< 0.0001$; Cramer's $V= 0.067$; $p <0.0001$; Cramer's $V= 0.050$; $p <0.0001$; Cramer's $V= 0.208$ and $p< 0.0001$; Cramer's $V= 0.071$, respectively). There was a trend of an increase in age parallel to an increase in adherence status, which is supportive of other studies (Hertz *et al*., 2005:1068; Kim *et al*., 2002:595; Sirey *et al*., 2001:1617). An increase was observed in the percentage of items dispensed associated with acceptable adherence as the treatment period increased. The highest adherence rate was observed with ingredients categorised as first-line treatment in epilepsy (e.g. oxcarbazepine 64.5%; valproic acid 63.7% and phenytoin 58.7%), as they have available generics, available in once-a-day dosing regimens. The results indicated that several co-morbid conditions co-occur with epilepsy, with hypertension the most prevalent, followed by hyperlipidaemia and hypothyroidism, which affect the adherence status very poorly ($p< 0.0001$; Cramer's $V= 0.067$).

4.5 Limitations of the research

There are several limitations regarding the database employed in the study. It lacks clinical data; the clinical effects of the different AED dosages on the epilepsy patients could therefore not be analysed. The consumption of AED by patients is not known for sure, as there is no guarantee that the patient actually took the medicine that was dispensed and claimed. When using the medicine claims data, the causality of epilepsy could not be determined. Not all registered epilepsy patients could have had a paid claim for an AED during the study period; this data would be lost to analysis, consequently leading to an underreporting of prevalence.

4.6 Strengths

The strengths of this study include the provision of a large, nationally representative study population extracted from a pharmaceutical claims database. This is a low-risk study since depersonalised data was used, resulting in minor ethical implications. Reliability and validity of

data were ensured by performing random data checks and assuring that all items on the checklist (refer to Annexure A) were achieved. This study will provide the following benefits:

- Information to the South African health sector regarding the prevalence and co-morbidities of patients with epilepsy. The data will be presented in accredited South African journals.
- Provision of expenditure data to the private health market regarding treatment costs of patients with epilepsy.
- Valuable information will be provided to the private health market regarding the compliance with or adherence to standard treatment guidelines, including the level of compliance by ambulatory patients to refill.
- This study provides an improvement in healthcare delivery to epileptic patients and can improve the prescribing practice of anti-epileptic medicine to patients.

4.7 Recommendations

Future research must focus on the following aspects:

- The current study focused only on the private health sector using medicine claims data. It is recommended that research on populations that do not have medical aid benefits be undertaken in order to assess the direct cost-impact of adherence of AEDs.
- It is recommended that research on populations in more rural areas (developing countries) is undertaken to assess the influence of infective causes of epilepsy on adherence, as developing countries have a high incidence of central nervous system infections and these infections are the most common cause of epilepsy (Singhi, 2011:601-605).
- The current study focused on the under- and oversupply of medication in the private health sector. It is suggested that research is undertaken to determine the cost of undersupply and oversupply of chronic medication in the public sector.
- Patient surveys must be initiated to establish the perception of the patient regarding the gaps in refills of medical supplies and early claiming of medication in the private health sectors and to find the possible reasons for it.
- Future research must focus on generic substitution to minimise the cost associated with epilepsy treatment, as this study established a high cost associated with newer AEDs.
- Further research can focus on the scope of replacing non-substitutable medicines (those without generics available) with alternative therapies for possible cost-savings to the benefit of the patient.

- More research focusing on the prescribing patterns must be performed concerning epilepsy patients in South Africa, because there is minimal literature available.
- It is recommended that future studies focus on the trends of medical scheme and patient contributions towards anti-epileptics over a certain period.

4.8 Chapter summary

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

REFERENCE LIST

Abbott, K. 2007. Medication compliance in transplantation. *American journal of transplantation*, 7:2647-2649.

Academy of Managed Care Pharmacy. 2009. Drug utilization review. http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=9296 Date of access: 23 May 2014.

Agrawal, A., Timothy, J., Pandit, L. & Manju, M. 2006. Post-traumatic epilepsy: an overview. *Clinical neurology and neurosurgery*, 108(5):433-439.

Alacqua, M., Trifirò, G., Spina, E., Moretti, S., Tari, D.U., Bramanti, P., Cuputi, A.P. & Arcoraci, V. 2009. Newer and older antiepileptic drug use in Southern Italy: a population-based study during the years 2003-2005. *Epilepsy research*, 85(1):107-113.

Andrade, S.E., Kahler, K.H., Frech, F. & Chan, K.A. 2006. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiology and drug safety*, 15:565-574.

Ängehagen, M., Ben-Menachem, E., Rönnbäck, L. & Hansson, E. 2003. Novel mechanisms of action of three antiepileptic drugs, vigabatrin, tiagabine, and topiramate. *Neurochemical research*, 28(2):333-340.

Angeleri, F., Majkowski, J., Cacchiò, G., Sobieszek, A., D' Acunto, S., Gesuita, R., Bachleda, A., Polonara, G., Królicki, L., Signorino, M. & Salvolini, U. 1999. Posttraumatic epilepsy risk factors: one-year prospective study after head injury. *Epilepsia*, 40(9):1222-1230.

Annegers, J.F., Hauser, W.A., Coan, S.P. & Rocca, W.A. 1998. A population-based study of seizures after traumatic brain injuries. *The New England journal of medicine*, 338(1):20-24.

Asikainen, I., Kaste, M. & Sarna, S. 1999. Early and late posttraumatic brain injury rehabilitation patients: brain injury factors causing late seizures and influence of seizures on long-term outcome. *Epilepsia*, 40(5):584-589.

Baker, G.A., Spector, S., McGrath, Y. & Soteriou, H. 2005. Impact of epilepsy in adolescence: a UK controlled study. *Epilepsy & behaviour*, 6(4):556-562.

Banerjee, P.N., Filippi, D. & Hauser, W.A. 2009. The descriptive epidemiology of epilepsy: a review. *Epilepsy research*, 85(1):31-45.

Baron, J.A. & Weiderpass, E. 2000. An introduction to epidemiological research with medical databases. *Annals of epidemiology*, 10(4):200-204.

Bastos, A.C., Comeau, R.M., Andermann, F., Melanson, D., Cendes, F., Dubeau, F., Fontaine, S., Tampieri, D. & Olivier, A. 1999. Diagnosis of subtle focal dysplasia lesions: curvilinear reformatting from three-dimensional, magnetic resonance imaging. *Annals of neurology*, 46(1):88-94.

Begley, C.E. & Beghi, E. 2002. The economic cost of epilepsy: a review of the literature. *Epilepsia*, 43(Suppl.4):3-9.

Begley, C.E., Beghi, E., Beran, R.G., Heaney, D., Langfitt, J.T., Pachlakto, C., Silfvenius, H., Sperling, M.R. & Wiebe, S. 2002. ILAE Commission on the burden of epilepsy, subcommission on the economic burden of epilepsy: final report 1998-2001. *Epilepsia*, 43(6):668-673.

Behin, A., Hoang-Xuan, K., Carpentier, A.F. & Delattre, J. 2003. Primary brain tumours in adults. *The lancet*, 361(9354):323-331.

Bellon, M., Walker, C. & Peterson, C. 2013. Seizure-related injuries and hospitalizations: self-report data from the 2010 Australian Epilepsy Longitudinal Survey. *Epilepsy & behavior*, 26(1):7-10.

Benamer, H.T.S. & Grosset, D.G. 2009. A systematic review of the epidemiology of epilepsy in Arab countries. *Epilepsia*, 50(10):2301-2304.

Beran, R.G., Hall, L., Pesch, A., Ho, P., Lam, S., Leung, P., Cheung, P. & Fung, M. 1982. Population prevalence of epilepsy in Sydney, Australia. *Neuroepidemiology*, 1(4):201-208.

Berg, A.T., Berkovic, S.F., Brodie, M.J., Buchhalter, J., Cross, J.H., van Emde Boas, W., Engel, J., French, J., Glauser, T.A., Mathern, G.W., Moshé, S.L., Nordli, D., Plouin, P. & Scheffer, I.E. 2010. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*, 51(4):676-685.

BHF Southern Africa. 2014. Sa medicine expenditure reflects increase for the first time in three years. http://ftp.bhfglobal.com/sa-medicine-expenditure-reflects-increase-first-time-three-years Date of access: 10 Sep. 2015.

Birbeck, G.L. 2012. Revising and refining the epilepsy classification system: priorities from a developing world perspective. *Epilepsia*, 53(2):18-21.

Birbeck, G.L. & Kalichi, E.M.N. 2004. Epilepsy prevalence in rural Zambia: a door-to-door survey. *Tropical medicine and international health*, 9(1):92-95.

Birbeck, G.L., Hays, R.D., Cui, X. & Vickrey, B.G. 2002. Seizure reduction and quality of life improvements in people with epilepsy. *Epilepsia*, 43(5):535-538.

Bolin, K., Berggren, F. & Landtblom, A-M. 2015. Prevalence and cost of epilepsy in Sweden: a register-based approach. Acta neurologica Scandinavica, 131(1):37-44.

Borneo, J.G., Tellez-Zenteno, J. & Wiebe, S. 2005. Understanding the burden of epilepsy in Latin America: a systematic review of its prevalence and incidence. *Epilepsy research*, 66(1-3):63-74.

Boylan, L.S., Flint, L.A., Labovits, D.L., Jackson, S.C., Starner, K. & Devinsky, O. 2004. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology*, 62(2):258-261.

Bradford, H.F. 1995. Glutamate, GABA and epilepsy. *Progress in neurobiology*, 47(6):477-511.

Brahimaj, B., Greiner, H.M., Leach, J.L., Horn, P.S., Stevenson, C.B., Miles, L., Byars, A., Holland, K., Sutton, M. & Mangano, F.T. 2014. The surgical management of pediatric brain tumors causing epilepsy: consideration of the epileptogenic zone. *Child's nervous system*, 30(8):1383-1391.

Briesacher, B.A., Andrade, S.E., Fouayzi, H. & Chan, K.A. 2008. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy*, 28(4):437-443.

Brink, H., Van der Walt, C. & Van Rensburg, G. 2012. Fundamentals of research methodology for healthcare professionals. 3rd ed. Cape Town: Juta.

Brodie, M.J., Shorvon, S.D., Canger, R., Halász, P., Johannessen, S., Thompson, P., Wieser, H.G. & Wolf, P. 1997. Commission on European affairs: appropriate standards of epilepsy care across Europe. *Epilepsia*, 38(11):1245-1250.

Bruno, E., Bartoloni, E., Zammarchi, L., Strohmeyer, M., Bartalesi, F., Bustos, J.A., Santivanez, S., Garcia, H.H. & Nicoletti, A. 2013. Epilepsy and neurocysticercosis in Latin America: a systematic review and meta-analysis. *PLOS neglected tropical diseases*, 7(10):1-11.

Brutto, O.H.D., Santibáñez, R., Idrovo, L., Rodrìguez, S., Díaz-Calderón, E., Navas, C., Gilman, R.H., Cuesta, F., Mosquer, A., Gonzalez, A.E., Tsang, V.C.W. & García, H.H. 2005. Epilepsy and neurocysticercosis in Atahualpa: a door-to-door survey in rural coastal Ecuador. *Epilepsia*, 46(4):583-587.

Buck, D., Jacoby, A., Baker, G.A. & Chadwick, D.W. 1997. Factors influencing compliance with antiepileptic drug regimes. *Seizure*, 6(2):87-93.

Camfield, C. & Camfield, P. 2015. Injuries from seizures are a serious, persistent problem in childhood onset epilepsy: a population-based study. *Seizure*, 27:80-83.

Camfield, C., Breau, L. & Camfield, P. 2001. Impact of paediatric epilepsy on the family: a new scale for clinical and research use. *Epilepsia*, 42(1):104-112.

Camilo, O. & Goldstein, L.B. 2004. Seizures and epilepsy after ischemic stroke. *Stroke*, 35:1769-1775.

Cataldi, M., Lariccia, V., Secondo, A., di Renzo, G. & Annunziato, L. 2005. The antiepileptic drug levetiracetam decreases the inositol 1,4,5-trisphosphate-dependent [Ca^{2+}] increase induced by ATP and bradykinin in PC12 cells. *The journal of pharmacology and experimental therapeutics*, 313(2):720-730.

Chatterjee, J.S. 2006. From compliance to concordance in diabetes. *Journal of medical ethics*, 32(9):507-510.

Chaudhary, U.J., Duncan, J.S. & Lemieux, L. 2011. A dialogue with historical concepts of epilepsy from the Babylonians to Hughlings Jackson: persistent beliefs. *Epilepsy & behaviour*, 21:109-114.

Chen, C., Blank, R.H. & Cheng, S. 2014. Medication supply, healthcare outcomes and healthcare expenses: longitudinal analysis of patients with type 2 diabetes and hypertension. *Health policy* (In press).

Chen, J.W.Y., Ruff, R.L., Eavey, R. & Wasterlain, C.G. 2009. Posttraumatic epilepsy and treatment. *Journal of rehabilitation research & development*, 46(6):685-696.

Choi, J. & Koh, S. 2008. Role of brain inflammation in epileptogenesis. *Yonsei medical journal*, 49(1):1-18.

Chong, H.T. 2004. Seizures and epilepsies secondary to central nervous system infection. *Neurology Asia*, 9(Suppl.1):20-23.

Christainson, A.L., Zwane, M.E., Manga, P., Rosen, E., Venter, A. & Kromberg, J.G.R. 2000. Epilepsy in rural South African children: prevalence, associated disability and management. *South African medical journal*, 90(3):262-266.

Christensen, D.B. 1978. Drug-taking compliance: a review and synthesis. *Health service research*, 13(2):171-187.

Christianson, A.L., Zwane, M.E., Manga, P., Rosen, E., Venter, A. & Kromberg, J.G.R. 2000. Epilepsy in rural South African children: prevalence, associated disability and management. *South African medical journal*, 90(3):262-266.

Clancy, R.R. & Legido, A. 1991. Postnatal epilepsy after EEG-confirmed neonatal seizures. *Epilepsia*, 32(1):69-76.

Clark, D.O. 2001. Issues of adherence, penetration and measurement in physical activity effectiveness studies. *Medical care*, 39(5):409-412.

Clark, L.P. 1933. What is the psychology of organic epilepsy. *Psychoanalytic review*, 20:79-85.

Claxton, A.J., Cramer, J. & Pierce, C. 2001. A systematic review of the associations between dose regimens and medication compliance. *Clinical therapeutics*, 23(8):1296-1310.

Cockburn, J., Gibberd, R.W., Reid, A.L. & Sanson-Fisher, R.W. 1987. Determinants of non-compliance with short term antibiotic regimens. *British medical journal*, 295(6602):814-818.

Cohen, B.J. & Lea, R.B. 2004. Essentials of statistics for the social and behavioural sciences. Hoboken, NJ: Wiley.

Commission on Classification and Terminology of the International League Against Epilepsy. 1981. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*, 22(4):489-501.

Conthe, P., Márquez Contreras, E., Aliaga Pérez, A., Barragán García, B., Fernández de Cano Martín, M.N., González Jurado, M., Ollero Buturone, M. & Pinto, J.L. 2014. Treatment compliance in chronic illness: current situation and future perspectives. *Revista clínica Espanola*, 214(6):336-344.

Coulter, D.A., Huguenard, J.R. & Prince, D.A. 1989. Characterization of ethosuximide reduction of low-threshold calcium currents in thalamic neurons. *Annals of neurology*, 25(6):582-593.

Cramer, J.A., Roy, A., Burrell, A., Fairchild, C.J., Fuldeore, M.J., Ollendorf, D.A. & Wong, P.K. 2008. Medication compliance and persistence: terminology and definitions. *Value in health*, 11(1):44-47.

Crystal, S., Akincigil, A., Bilder, M.S. & Walkup, J.T. 2007. Studying prescription drug use and outcomes with medicaid claims data: strengths, limitations and strategies. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2486436/pdf/nihms49963.pdf Date of access: 16 May 2014.

Cutler, D.M. & Everett, W. 2010. Thinking outside the pillbox: medication adherence as a priority for health care reform. *The New England journal of medicine*, 362(17):1553-1555.

Czuczwar, S.J. & Pastalos, P.N. 2001. The new generation of GABA enhancers. *CNS drugs*, 15(5):339-350.

D'Souza, W.D. 2008. Epidemiology of epilepsy in Tasmania. Wellington: Massey University. (Thesis - PhD).

D'Souza, W.J., Quinn, S.J., Fryer, J.L., Taylor, B.V., Ficker, D.M., O'Brien, T.J., Pearce, N. & Cook, M.J. 2012. The prevalence and demographic distribution of treated epilepsy: a community-based study in Tasmania, Australia. *Acta neurologica Scandinavica*, 125(2):96-104.

Dassa, D., Boyer, L., Benoit, M., Bourcet, S., Raymondet, P. & Bottai, T. 2010. Factors associated with medication non-adherence in patients suffering from schizophrenia: a cross-sectional study in a universal coverage health-care system. *Australian and New Zealand journal of psychiatry*, 44(10):921-928.

Davies, J.A. 1995. Mechanisms of action of antiepileptic drugs. *Seizure*, 4(4):267-272.

Davis, K.L., Candrilli, S.D. & Edin, H.M. 2008. Prevalence and cost of non-adherence with anti-epileptic drugs in adult managed care population. *Epilepsia*, 49(3):446-454.

De Boer, H.M. 2010. Epilepsy stigma: moving from a global problem to global solutions. *Seizure*, 19(10):630-636.

De Groot, M.C.H., Schuerch, m., De Vries, F., Hesse, U., Olivia, B., Gil, M., huerta, C., Requena, G., De abajo, F., Afonso, A.S., Souverein, P.C., Alvarez, Y., Slattery, J., Rottenkolber, M., Schmiedl, S., Van Dijk, L., Schlienger, R.G., Reynolds, R. & Klungel, O.H. 2014. Antiepileptic drug use in seven electronic health record databases in Europe: a methodological aproach. *Epilepsia*, 55(5):666-673.

De las Cuevas, C. 2011. Towards a clarification of terminology in medicine taking behaviour: compliance, adherence and concordance are related although different terms with different uses. *Current clinical pharmacology*, 6:74-77.

Dekker, P.A. 2002. Epilepsy: a manual for medical and clinical officers in Africa. Geneva.

Diamantis, A., Sidiropoulou, K. & Magiorkinis, E. 2010. Epilepsy during the middle ages, the renaissance and the enlightenment. *Journal of neurology*, 257(5):691-698.

Dillorio, C., Shafer, P.O., Letz, R., Henry, R.T., Schomer, D.L. & Yeager, K. 2004. Project EASE: a study to test a psychosocial model of epilepsy medication management. *Epilepsy & behaviour*, 5:926-936.

DiMatteo, M.R., Giordani, P., Lepper, H.S. & Croghan, T.W. 2002. Patient adherence and medical treatment outcomes. *Medical care*, 40(9):794-811.

Diop, A.G., de Boer, H.M., Mandlhate, C., Prilipko, L. & Meinardi, H. 2003. The global campaign against epilepsy in Africa. *Acta Tropica*, 87:149-159.

Dunbar-Jacob, J. & Mortimer-Stephens, M.K. 2001. Treatment adherence in chronic disease. *Journal of clinical epidemiology*, 54:S57-S60.

Dunn, L.T. 2002. Raised intracranial pressure. *Journal of neurology, neurosurgery & psychiatry*, 73(Suppl.1):i23-i27.

Eastman, R. 2005. Epilepsy in South Africa. *Acta neurologica Scandanavica*, 112(Suppl.181):8-11.

Eatock, J. & Baker, G.A. 2007. Managing patient adherence and quality of life in epilepsy. *Neuropsychiatric disease and treatment*, 3(1):117-131.

Ebrahimi, H., Shafa, M. & Asl, S.H. 2012. Document prevalence of active epilepsy in Kerman, Iran: a house based survey. *Acta neurologica Taiwanica*, 21(3):115-124.

Elger, C.E. & Schmidt, D. 2008. Modern management of epilepsy: a practical approach. *Epilepsy & behaviour*, 12:501-539.

Elliot, I.M., Lach, L. & Smith, M.L. 2005. I just want to be normal: a qualitative study exploring how children and adolescents view the impact of intractable epilepsy on their quality of life. *Epilepsy & behaviour*, 7(4):664-678.

Ellis, S.M. & Steyn, H.S. 2003. Practical significance (effect sizes) versus or in combination with statistical significance (p-values). *Management dynamics*, 12(4):51-53.

Engel, J. 2001. A proposed diagnostic scheme for people with epileptic seizures and epilepsy: report of the ILAE Task Force on classification and terminology. *Epilepsia*, 42(6):796-803.

Engelborghs, S., D'Hooge, R. & De Deyn, P.P. 2000. Pathophysiology of epilepsy. *Acta neurologica Belgica*, 100(4):201-213.

Englander, J.,Bushnik, T., Duong, T.T., Cifu, D.X., Zafonte, R., Wright, J., Hughes, R. & Bergman, W. 2003. Analyzing risk factors for late posttraumatic seizures: a prospective, multicentre investigation. *Archives of physical medicine and* rehabilitation, 84(3):365-373.

Epilepsy South Africa. 2014. Facts about epilepsy. http://www.epilepsy.org.za/facts/index.php Date of access: 03 Mar. 2014.

Ettinger, A.B., Manjunath, R., Candrilli, S.D. & Davis, K.L. 2009. Prevalence and cost of non-adherence to anti-epileptic drugs in elderly patients with epilepsy. *Epilepsy & behaviour*, 14:324-329.

Fairman, K. & Motheral, B. 2000. Evaluating medication adherence: which measure is right for your program? *Journal of managed care pharmacy*, 6(6):499-506.

Farmer, K.C. 1999. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clinical therapeutics*, 21(6):1074-1090.

Faught, E., Duh, M.S., Weiner, J.R., Guérin, A. & Cunnington, M.C. 2008. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM study. *Neurology*, 71(20):1572-1578.

Faught, E., Helmers, S.L., Begley, C.E., Thurman, D.J., Dilley, C., Clark, C. & Fritz, P. 2015. Newer antiepileptic drug use and other factors decreasing hospital encounters. Newer. Epilepsy & behaviour, 45:169-175.

Faught, E., Richman, J., Martin, R., Funkhouser, E., Foushee, R., Kratt, P., Kim, Y., Clements, K., Cohen, N., Adoboe, D., Knowlton, R. & Pisu, M. 2012. Incidence and prevalence of epilepsy among older US Medicare beneficiaries. *American Academy of Neurology*, 78(7):448-453.

Fauser, S., Huppertz, H., Bast, T., Strobl, K., Pantazis, G., Altenmueller, D., Feil, B., Rona, S., Kurth, C., Rating, D., Korinthenberg, R., Steinhoff, B.J., Volk, B. & Schulze-Bonhage, A. 2006. Clinical characteristics in focal cortical dysplasia: a retrospective evaluation in a series of 120 patients. *Brain*, 129(7):1907-1916.

Fisher, R.S., Acevedo, C., Arzmanoglou, A., Bogacz, A., Cross, H., Elger, C.E., Engel, J., Forsgren, L., French, J.A., Glynn, M., Hesdorffer, D.C., Lee, B.I., Mathern, G.W., Moshé, S.L., Perucca, E., Scheffer, I.E., Tomson, T., Watanabe, M. & Wiebe, S. 2014. A practical clinical definition of epilepsy. *Epilepsia*, 55(4):475-482.

Fisher, R.S., Scharfman, H.E. & deCurtis, M. 2014. How can we identify ictal and interictal abnormal activity. *Advances in experimental medicine and biology*, 813:3-23.

Fisher, R.S., Van Emde Boas, W., Blume, W., Elger, C., Genton, P., Lee, P. & Engel, J. 2005. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*, 46(4):470-472.

Frediani, F., Cannatà, A.P., Magnoni, A., Peccarisi, C. & Bussone, G. 2003. The patient with medication overuse: clinical management problems. *Neurological sciences*, 24(2):s108-s111.

Freeman, J.M., Vining, E.P.G. Kossoff, E.H., Pyzik, P.L., Ye, X. & Goodman, S.N. 2009. A blinded, crossover study of the efficacy of the ketogenic diet. *Epilepsia*, 50(2):322-325.

French, J.A. & Gazzola, D.M. 2013. Antiepileptic drug treatment: new drugs and strategies. *Continuum: lifelong learning in neurology*, 19(3):643-655.

Frey, L.C. 2003. Epidemiology of posttraumatic epilepsy: a critical review. *Epilepsia*, 44(Suppl.10):11-17.

Gabr, W.M. & Shams, M.E.E. 2015. Adherence to medication among outpatient adolescents with epilepsy. *Saudi pharmaceutical journal*, 23(1):33-40.

Gastaut, H. 1970. Clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*, 11(1):102-113.

Georgakis, M. & Anagnostopoulou, S. 2014. Epilepsy: what is the responsibility of central nervous system infections for its occurrence. *Encephalos*, 51:79-91.

Gibbs, F.A., Davis, H. & Lennox, W.G. 1935. The electro-encephalogram in epilepsy and in conditions of impaired consciousness. *Archives of neurology and psychiatry*, 34(6):1113-1148.

Giussani, G., Cricelli, C., Mazzoleni, F., cricelli, I., Pasqua, A., Pechcioli, S., Lapi, F. & Beghi, E. 2014. Prevalence and incidence of epilepsy in Italy based on a nationwide database. *Neuroepidemiology*, 43(3-4):228-232.

Gray, R., Wykes, T. & Gournay, K. 2002. From compliance to concordance: a review of the literature on interventions to enhance compliance with antipsychotic medication. *Journal of psychiatric and mental health nursing*, 9:277-284.

Gu, L., Liang, B., Chen, Q., Long, J., Xie, J., Wu, G., Yan, Y., Tan, J., Dou, W., Chen, W., Wu, P., Wang, J. & Su, L. 2013. Prevalence of epilepsy in the People's Republic of China: a systematic review. *Epilepsy research*, 105(1-2):195-205.

Hamer, H.M., Dodel, R., Strzelczyk, A., Balzer-Geldsetzer, M., Reese, JP., Schöffsko, O., Graf, W., Schwab, S., Kanke, S., Oertel, W.H., Rosenow, F. & Kostev, K. 2012. Prevalence, utilization and costs of antiepileptic drugs for epilepsy in Germany: a nationwide population-based study in children and adults. *Journal of neurology*, 259(11):2376-2384.

Hart, Y.M. 2012. Management of epilepsy. *Medicine*, 40(9):477-483.

Hauser, W.A., Rich, S.S., Lee, J.R.J., Annegers, J.F. & Anderson, V.E. 1998. Risk of recurrent seizures after two unprovoked seizures. *The New England journal of medicine*, 338(7):429-434.

Healey, J.F. 2013. The essential of statistics: a tool for social research. 3rd ed. California: Wadsworth.

Hedna, K., Hägg, S., Andersson Sundell, K., Petzold, M. & Hakkarainen, K.M. 2013. Refill adherence and self-reported adverse drug reactions and sub-therapeutic effects: a population-based study. *Pharmacoepidemiology and drug safety*, 22(12):1317-1325.

Heiman, G.W. 2011. Basic statistics for behavioural sciences. 6th ed. California: Wadsworth.

Henderson, C.B., Filloux, F.M., Alder, S., Lyon, J.L. & Caplin, D.A. 2006. Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis. *Journal of child neurology*, 21(3):193-198.

Hennessy, S., Warren, B.B., Zhou, L., Weber, A.L., Bresinger, C., Wang, Y. & Strom, B.L. 2003. Retrospective drug utilization review, prescribing errors and clinical outcomes. *Journal of the American Medical Association*, 290(11):1494-1499.

Hertz, R.P., Unger, A.N. & Lustik, M.B. 2005. Adherence with pharmacotherapy for type 2 diabetes: a retrospecive cohort study of adults with employer-sponsored health insurance. *Clinical therapeutics*, 27(7):1064-1073.

Hesdorffer, D.C., Benn, E.K.T., Cascino, G.D. & Hauser, W.A. 2009. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia*, 50(5):1102-1108.

Hess, L.M., Raebel, M.A., Conner, D.A. & Malone, D.C. 2006. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *The annals of pharmacotherapy*, 40:1280-1289.

Hoechst Marion Roussel. 1984. Urbanol 5 mg capsules and Urbanol 10 mg tablets, http://home.intekom.com/pharm/hmr/urbanol.html Date of access: 13 May 2015.

Holmes, G.L. & Ben-Ari, Y. 2001. The neurobiology and consequences of epilepsy in the developing brain. *Pediatric research*, 49(3):320-325.

Horne, R., Weinman, J., Barber, N., Elliot, R. & Morgan, M. 2005. Concordance, adherence and compliance in medicine taking. Brighton: Centre for Health Care Research. http://www.google.co.za/url?url=http://www.aph.gov.au/DocumentStore.ashx%3Fid%3Ddefbfbc9-5206-42c1-8093-3d408ebbe09f&rct=j&frm=1&q=&esrc=s&sa=U&ved=0CB4FjABahUKEwiLitPfkpHGAhWMF9sKHTg3AOU&usg=AFQjCNGpLaIeAYdq_jmRlM1U9IgCGVTY3Q Date of access: 17 Mar. 2015.

Hovinga, C.A., Asato, M.R., Manjunath, R., Wheless, J.W., Phelps, S.J., Sheth, R.D., Pina-Garza, J.E., Zingaro, W.M. & Haskins, L.S. 2008. Association of non-adherence to antiepileptic drugs and seizures, quality of life, and productivity: survey of patients with epilepsy and physicians. *Epilepsy & behavior*, 13(2):316-322.

Hudson, M., Rahme, E., Richard, H. & Pilote, L. 2007. Comparison of measures of medication persistency using a prescription drug database. *American heart journal*, 153(1):59-65.

Huffman, J. & Kossoff, E.H. 2006. State of the ketogenic diets(s) in epilepsy. *Current neurology and neuroscience reports*, 6(4):332-340.

International League Against Epilepsy. 2003. Causation: Aetiology of epilepsy. *Epilepsia*, 44(Suppl.6):21-22.

Irvine, J., Baker, B., Smith, J., Jandciu, S., Paquette, M., Cairns, J., Connolly, S., Roberts, R., Gent, M. & Dorian, P. 1999. Poor adherence to placebo or amiodarone therapy predicts mortality: results from the CAMIAT study. *Psychosomatic medicine*, 61(4):566-575.

Italiano, D., Capuano, A., Alibrandi, A., Ferrara, R., Cannata, A., Trifiro, G., Sultana, J., Ferrajolo, C., Tari, M., Tari, D.U., Perrotta, M., Pagliaro, C., Rafaniello, C., Spina, E. & Arcoraci, V. 2015. Indications of newer and older anti-epileptic drug use: findings from a southern Italian general practice setting from 2005-2011. *British journal of clinical pharmacology*, 79(6):1010-1019.

Iuchi, T., Hasegawa, Y., Kawasaki, K. & Sakaida, T. 2015. Epilepsy in patients with gliomas: incidence and control of seizures. *Journal of clinical neuroscience*, 22(1):87-91.

Iuga, A.O. & McGuire, M.J. 2014. Adherence and health care costs. Risk management and healthcare policy, 7():35-44.

Ivanova, J.I., Birnbaum, H.G., Kidolezi, Y., Qui, Y., Mallett, D. & Caleo, S. 2010. Direct and indirect costs associated with epileptic partial onset seizures among the privately insured in the United States. *Epilepsia*, 51(5):838-844.

Janssen Pharmaceutica. 2001. Topamax. http://home.intekom.com/pharm/janssen/topamax.html Date of access: 13 May 2015.

Jennett, W.B. & Lewin, W. 1960. Traumatic epilepsy after closed head injuries. *Journal of neurology, neurosurgery and psychiatry*, 23(4):295-301.

Jennum, P., Gyllenborg, J. & Kjellberg, J. 2011. The social and economic consequences of epilepsy: a controlled national study. *Epilepsia*, 52(5):949-956.

Jin, J., Sklar, G.E., Oh, V.M.S. & Li, S.C. 2008. Factors affecting therapeutic compliance: a review from the patient's perspective. *Therapeutics and clinical risk management*, 4(1):269-286.

Johnson, E.K., Jones, E.J., Seidenberg, M. & Hermann, B.P. 2004. The relative impact of anxiety, depression and clinical seizure features on health-related quality of life in epilepsy. *Epilepsia*, 45(5):544-550.

Jones, R.M., Butler, J.A., Thomas, V.A., Peveler, R.C. & Prevett, M. 2006. Adherence to treatment in patients with epilepsy: associations with seizure control and illness beliefs. *Seizure*, 15(7):504-508.

Kabat, J. & Król, P. 2012. Focal cortical dysplasia: review. *Polish journal of radiology*, 77(2):35-43.

Karakis, I., Cole, A.J., Montouris, G.D., San Luciano, M., Meador, K.J. & Piperidou, C. 2014. Caregiver burden in epilepsy: determinants and impact. *Epilepsy research and treatment*, 2014:1-9.

Karve, S., Cleves, M.A., Helm, M., Hudson, T.J., West, D.S. & Martin, B.C. 2009. Prospective validation of eight different adherence measures for use with administrative claims data among patients with schizophrenia. *Value in health*, 12(6):989-995.

Kathria, I.A., Iannaccone, S.T., Ilyas, M.S., Abdullah, M. & Saleem, S. 2003. Epidemiology of epilepsy in Pakistan: review of literature. *Journal of the Pakistan Medical Association*, 53(12):594-597.

Khan, N., Jehan, B., Khan, A. & Khan, H. 2011. Audit of 100 cases of epilepsy in a tertiary care hospital. *Gomal journal of medical sciences*, 9(1):42-45.

Kim, Y.S., Sunwoo, S., Lee, H.R., Lee, K.M., Park, Y.W., Shin, H.C., Kim, C.H., Kim, D.H., Kim, B.S., Cha, H.S., Huh, B.Y. & Korea post-marketing surveillance research group. 2002. Determinants of non-compliance with lipid-lowering therapy in hyperlipidemic patients. *Pharmacoepidemiology and drug safety*, 11(7):593-600.

Kimiskidis, V.K., Triantafyllou, N.I., Kararizou, E., Gatzonis, S., Fountoulakis, K.N., Siatouni, A., Loucaidis, P., Pseftogianni, D., Vlaikidis, N. & Kaprinis, G.S. 2007. Depression and anxiety in epilepsy: the association with demographic and seizure-related variables. *Annals of general psychiatry*, 6(28):1-8.

Kingsman, K., Melander, A., Carlsten, A., Ekedahl, A., Nilson, J.L.G. 2007. Refill non-adherence to repeat prescriptions leads to treatment gaps or to high extra costs. *Pharmacy world & science*, 29(1):19-24.

Kirmani, B.T., Robinson, D.M., Kikam, A., Fonkem, E. & Cruz, D. 2014. Selection of antiepileptic drugs in older people. *Current treatment options in neurology*, 16(295):1-16.

Klein, M., Engelberts, N.H., van der Ploeg, H.M., Kasteleijn-Nolst Trenité, D.G.A., Aaronson, N.K., Taphoorn, M.J.B., Baaijen, H., Vandertop, W.P., Muller, M., Postma, T.J. & Heimans, J.J. 2003. Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life. *Annals of neurology*, 54(4):514-520.

Krause, S.R., Van Rooyen, F.C., Van Vuuren, M.V.J. & Jenkins, L. 2007. Non-compliance with treatment by epileptic patients at George Provincial Hospital. *South African family practice*, 49(9):14-14d.

Kripilani, S., Yao, X. & Haynes, B. 2007. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Journal of the American Medical Association*, 167:540-550.

Kumar, P. 2013. Statistical significance and practical significance in statistics education. http://iase-web.org/documents/papers/sat2013/IASE_IAOS_2013_Poster_2.7.5_Pranesh.pdf Date of access: 15 Sep. 2015.

Kwan, P., Sills, G.J. & Brodie, M.J. 2001. The mechanisms of action of commonly used antiepileptic drugs. *Pharmacology & therapeutics*, 90(1):21-34.

Ladner, T.R., Morgan, C.D., Pomerantz, D.J., Kennedy, V.E., Azar, N., Haas, K., Lagrange, A., Gallagher, M., Singh, P., Abou-Khalil, B.W. & Arain, A.M. 2015. Does adherence to epilepsy quality measures correlate with reduced epilepsy-related adverse hospitalization: a retrospective experience. *Epilepsia*, 56(5):e63-e67.

Lamy, C., Domigo, V., Semah, F., Arquizan, C., Trystram, D., Coste, J. & Mas, J.L. 2003. Early and late seizures after cryptogenic ischemic stroke in young adults. *Neurology*, 60(3):400-404.

Landmark, C.J., Fossmark, H., Larsson, P.G., Rytter, E. & Johanessen, S.I. 2011. Prescription patterns of antiepileptic drugs in patients with epilepsy in a nation-wide population. *Epilepsy research*, 95(1-2):51-59.

Lee, P.R. & Kossoff, E.H. 2011. Dietary treatments for epilepsy: management guidelines for the general practitioner. *Epilepsy & behavior*, 21(2):115-121.

Leonardi, M. & Ustun, T.B. 2002. The global burden of epilepsy. *Epilepsia*, 43(Suppl.2):21-25.

Linehan, C., Kerr, M.P., Walsh, P.N., Brady, G., Kelleher, C., Delanty, N., Dawson, F. & Glynn, M. 2010. Examining the prevalence of epilepsy and delivery of epilepsy care in Ireland. *Epilepsia*, 51(5):845-852.

Lopez, A.D., Mathers, C.D., Ezzati, M., Jamison, D.T. & Murray, C.J.L. 2006. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *The lancet*, 367(9524):1747-1757.

Löscher, W. 2002 Basic pharmacology of valproate: a review after 35 years of clinical use for the treatment of epilepsy. *CNS drugs*, 16(10):669-694.

Louis, D.N., Ohgaki, H., Wiestler, O.D., Cavenee, W.K., Burger, P.C., Jouvet, A., Scheithauer, B.W. & Kleihues, P. 2007. The 2007 WHO classification of tumours of the central nervous system. *Acta neuropathologica*, 114(2):97-109.

Lowenstein, D.H. 2009. Epilepsy after head injury: an overview. *Epilepsia*, 50(Suppl.2):4-9.

Lowenstein, D.H. & Alldredge, B.K. 1998. Status epilepticus. *The New England journal of medicine*, 338(14):970-976.

Lukyanetz, E.A., Shkryl, V.M. & Kostyuk, P.G. 2002. Selective blockade of N-type calcium channels by levetiracetam. *Epilepsia*, 43(1):9-18.

Lyseng-Williamson, K.A. 2011. Levetiracetam: a review of its use in epilepsy. *Drugs*, 71(4):489-514.

Mac, T.L., Tran, D., Quet, F., Odermatt, P., Preux, P. & Tan, C.T. 2007. Epidemiology, aetiology, and clinical management of epilepsy in Asia: a systematic review. *The lancet neurology*, 6(6):533-543.

Manjunath, R., Davis, K.L., Candrilli, S.D. & Ettiger, A.B. 2009. Association of antiepileptic drug nonadherence with risk of seizures in adults with epilepsy. *Epilepsy & behavior*, 14(2)372-378.

Marcum, Z.A. & Gellad, W.F. 2012. Medication adherence to multi-drug regimens. *Clinics in geriatric medicine*, 28(2):287-300.

Marcum, Z.A., Gurwitz, J.H., Colón-Emeric, C. & Hanlon, J.T. 2015. Pills and ills: methodologic issues in pharmacologic research. *Journal of the American geriatrics society*, 63(4):829-830.

Margineanu, D.G. & Klitgaard, H. 2000. Inhibition of neuronal hypersynchrony in vitro differentiates levetiracetam from classical antiepileptic drugs. *Pharmacological research*, 42(4):281-285.

Mattson, R.H. 2003. Overview: idiopathic generalized epilepsies. *Epilepsia*, 44(Suppl.2):2-6.

McNicholas, F. 2012. To adhere or not, and what we can do to help. *European child & adolescent psychiatry*, 21:657-663.

Medina, M.T., Durón, R.M., Martínez, L., Osorio, J.R., Estrada, A.L., Zúniga, C., Cartagena, D., Collins, J.S. & Holden, K.R. 2005. Prevalence, incidence and etiology of epilepsies in rural Honduras: the Salamá study. *Epilepsia*, 46(1):124-131.

Meinardi, H., Scott, R.A., Reis, R. & Sander, J.W.A.S. 2001. The treatment gap in epilepsy: the current situation and ways forward. *Epilepsia*, 42(1):136-149.

Melcon, M.O., Kochen, S. & Vergara, R.H. 2007. Prevalence and clinical features of epilepsy in Argentina: a community-based study. *Neuroepidemiology*, 28(1):8-15.

Meldrum, B.S. & Chapman, A.G. 1986. Benzodiazepine receptors and their relationship to the treatment of epilepsy. *Epilepsia*, 27(Suppl.1):S3-S13.

Merlis, J.K. 1970. Proposal for an international classification of the epilepsies. *Epilepsia*, 11(1):114-119.

Merriam-Webster's Medical Dictionary. 2014. Cost. http://www.merriam-webster.com/dictionary/cost Date of access: 30 Apr. 2014.

Mitchell, G. 2014. Adherence to medications: towards a shared understanding. *Nurse prescribing*, 12(11):564-568.

Mojtabai, R., Lavelle, J., Gibson, P.J., Sohler, N.L., Craig, T.J., Carlson, G.A. & Bromet, E.J. 2002. Gaps in use of antipsychotics after discharge by first-admission patients with schizophrenia, 1989 to 1996. *Psychiatric services*, 53(3):337-339.

Moore, P.J., Sickel, A.E., Malat, J., Williams, D., Jackson, J. & Adler, N.E. 2004. Psychosocial factors in medical and psychological treatment avoidance: the role of the doctor–patient relationship. *Journal of health psychology*, 9(3):421-433.

Moosa, M.Y.H., Jeenah, F.Y. & Kazadi, N. 2007. Treatment adherence. *South African journal of psychiatry*, 13(2):40-45.

Morris, L.S. & Schulz, R.M. Patient compliance: an overview. *Journal of clinical pharmacy and therapeutics*, 17(5):283-295.

Motheral, B., Brooks, J., Clark, M.A., Crown, W.H., Davey, P., Hutchins, D., Martin, B.C. & Stang, P. 2003. A checklist for retrospective database studies: report of the ISPOR Task Force on Retrospective Databases. *Value in health*, 6(2):90-97.

Muhajarine, N., Mustard, C., Roos, L.L., Young, T.K. & Gelskey, D.E. 1997. Comparison of survey and physician claims data for detecting hypertension. *Journal of clinical epidemiology*, 50(6):711-718.

Murray, C.J., Vos, T., Lozano, R., Naghavi, M., Flaxman, A.D., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J.A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S.Y., Ali, M.K., Alvarado, M., Anderson, H.R., Anderson, L.M., Andrews, K.G., Atkinson, C., Baddour, L.M., Bahalim, A.N., Barker-Collo, S., Barrero, L.H., Bartels, D.H., Basáñez, M.G., Baxter, A., Bell, M.L., Benjamin, E.J., Bennett, D., Bernabé, E., Bhalla, K., Bhandari, B., Bikbov, B., Bin Abdulhak, A., Birbeck, G., Black, J.A., Blencowe, H., Blore, J.D., Blyth, F., Bolliger, I., Bonaventure, A., Boufous, S., Bourne, R., Boussinesq, M., Braithwaite, T., Brayne, C., Bridgett, L., Brooker, S., Brooks, P., Brugha, T.S., Bryan-Hancock, C., Bucello, C., Buchbinder, R., Buckle, G., Budke, C.M., Burch, M., Burney, P., Burstein, R., Calabria, B., Campbell, B., Canter, C.E., Carabin, H., Carapetis, J., Carmona, L., Cella, C., Charlson, F., Chen, H., Cheng, A.T., Chou, D., Chugh, S.S., Coffeng, L.E., Colan, S.D., Colquhoun, S., Colson, K.E., Condon, J., Connor, M.D., Cooper, L.T., Corriere, M., Cortinovis, M., de Vaccaro, K.C., Couser, W., Cowie, B.C., Criqui, M.H., Cross, M., Dabhadkar, K.C., Dahiya, M., Dahodwala, N., Damsere-Derry, J., Danaei, G., Davis, A., De Leo, D., Degenhardt, L., Dellavalle, R., Delossantos, A., Denenberg, J., Derrett, S., Des Jarlais, D.C., Dharmaratne, S.D., Dherani, M., Diaz-Torne, C., Dolk, H., Dorsey, E.R., Driscoll, T., Duber, H., Ebel, B., Edmond, K., Elbaz, A., Ali, S.E., Erskine, H., Erwin, P.J., Espindola, P., Ewoigbokhan, S.E., Farzadfar, F., Feigin, V., Felson, D.T., Ferrari, A., Ferri, C.P., Fèvre, E.M., Finucane, M.M., Flaxman, S., Flood, L., Foreman, K., Forouzanfar, M.H., Fowkes, F.G., Fransen, M., Freeman, M.K., Gabbe, B.J., Gabriel, S.E., Gakidou, E., Ganatra, H.A., Garcia, B., Gaspari, F., Gillum, R.F., Gmel, G., Gonzalez-Medina, D., Gosselin, R., Grainger, R., Grant, B., Groeger, J., Guillemin, F., Gunnell, D., Gupta, R., Haagsma, J., Hagan, H., Halasa, Y.A., Hall, W., Haring, D., Haro, J.M., Harrison, J.E., Havmoeller, R., Hay, R.J., Higashi, H., Hill, C., Hoen, B., Hoffman, H., Hotez, P.J., Hoy, D., Huang, J.J., Ibeanusi, S.E., Jacobsen, K.H., James, S.L., Jarvis, D., Jasrasaria, R., Jayaraman, S., Johns, N., Jonas, J.B., Karthikeyan, G., Kassebaum, N., Kawakami, N., Keren, A., Khoo, J.P., King, C.H., Knowlton, L.M., Kobusingye, O., Koranteng, A., Krishnamurthi, R., Laden, F., Lalloo, R., Laslett, L.L., Lathlean, T., Leasher, J.L., Lee, Y.Y., Leigh, J., Levinson, D., Lim, S.S., Limb, E., Lin, J.K., Lipnick, M., Lipshultz, S.E., Liu, W., Loane, M., Ohno, S.L., Lyons, R., Mabweijano, J., MacIntyre, M.F., Malekzadeh, R., Mallinger, L., Manivannan, S., Marcenes, W., March, L.,

Margolis, D.J., Marks, G.B., Marks, R., Matsumori, A., Matzopoulos, R., Mayosi, B.M., McAnulty, J.H., McDermott, M.M., McGill, N., McGrath, J., Medina-Mora, M.E., Meltze,r M., Mensah, G.A., Merriman, T.R., Meyer, A.C., Miglioli, V., Miller, M., Miller, T.R., Mitchell, P.B., Mock, C., Mocumbi, A.O., Moffitt, T.E., Mokdad, A.A., Monasta, L., Montico, M., Moradi-Lakeh, M., Moran, A., Morawska, L., Mori, R., Murdoch, M.E., Mwaniki, M.K., Naidoo, K., Nair, M.N., Naldi, L., Narayan, K.M., Nelson, P.K., Nelson, R.G., Nevitt, M.C., Newton, C.R., Nolte, S., Norman, P., Norman, R., O'Donnell, M., O'Hanlon, S., Olives, C., Omer, S.B., Ortblad, K., Osborne, R., Ozgediz, D., Page, A., Pahari, B., Pandian, J.D., Rivero, A.P., Patten, S.B., Pearce, N., Padilla, R.P., Perez-Ruiz, F., Perico, N., Pesudovs, K., Phillips, D., Phillips, M.R., Pierce, K., Pion, S., Polanczyk, G.V., Polinder, S., Pope, C.A., Popova, S., Porrini, E., Pourmalek, F., Prince, M., Pullan, R.L., Ramaiah, K.D., Ranganathanm D., Razavi, H., Regan, M., Rehm, J.T., Rein, D.B., Remuzzi, G., Richardson, K., Rivara, F.P., Roberts, T., Robinson, C., De Leòn, F.R., Ronfani, L., Room, R., Rosenfeld, L.C., Rushton, L., Sacco, R.L., Saha, S., Sampson, U., Sanchez-Riera, L., Sanman, E., Schwebel, D.C., Scott, J.G., Segui-Gomez, M., Shahraz, S., Shepard, D.S., Shin, H., Shivakoti, R., Singh, D., Singh, G.M., Singh, J.A., Singleton, J., Sleet, D.A,. Sliwa, K., Smith, E., Smith, J.L., Stapelberg, N.J., Steer, A., Steiner, T., Stolk, W.A., Stovner, L.J., Sudfeld, C., Syed, S., Tamburlini, G., Tavakkoli, M., Taylor, H.R., Taylor, J.A., Taylor, W.J., Thomas, B., Thomson, W.M., Thurston, G.D., Tleyjeh, I.M., Tonelli, M., Towbin, J.A., Truelsen, T., Tsilimbaris, M.K., Ubeda, C., Undurraga, E.A., van der Werf, M.J., van Os, J., Vavilala, M.S., Venketasubramanian, N., Wang, M., Wang, W., Watt, K., Weatherall, D.J., Weinstock, M.A., Weintraub, R., Weisskopf, M.G., Weissman, M.M., White, R.A., Whiteford, H., Wiebe, N., Wiersma, S.T., Wilkinson, J.D., Williams, H.C., Williams, S.R., Witt, E., Wolfe, F., Woolf, A.D., Wulf, S., Yeh, P.H., Zaidi, A.K., Zheng, Z.J., Zonies, D., Lopez, A.D, AlMazroa, M.A., Memish, Z.A. 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *The lancet*, 380(9859):2197-2223.

Nagarkatti, N., Deshpande, L.S. & DeLorenzo, R.J. 2008. Levetiracetam inhibits both ryanodine and IP3 receptor activated calcium induced calcium release in hippocampal neurons in culture. *Neuroscience letters*, 436(3):289-293.

Neal, E.G., Chaffe, H., Schwartz, R.H., Lawson, M.S., Edwards, N., Fitzsimmons, G., Whitney, A. & Cross, J.H. 2008. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *The lancet neurology*, 7(6):500-506.

Nei, M & Bagla, R. 2007. Seizure-related injury and death. *Current neurology and neuroscience reports*, 7(4):335-341.

Ngugi, A.K.,Bottomley, C., Kleinschmidt, I., Sander, J.W. & Newton, C.R. 2010. Estimation of the burden of active and life-time epilepsy: a meta-analysis approach. *Epilepsia*, 51(5):883-890.

NICE (National Institute for Health and Care Excellence). 2015. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. (NICE clinical guideline 137). https://www.nice.org.uk/guidance/cg137/chapter/guidance Date of access: 5 May 2015.

O'Donoghue, M.F., Goodridge, D.M., Redhead, K., Sander, J.W. & Duncan, J.S. 1999. Assessing the psychosocial consequences of epilepsy: a community-based study. *British journal of general practice*, 49(440):211-214.

OANDA corporation. 2015. Currency converter. http://www.oanda.com/currency/converter/ Date of access: 27 Aug. 2015.

Olafsson, E., Gudmundsson, G. & Hauser, W.A. 2000. Risk of epilepsy in long-term survivors of surgery for aneurysmal subarachnoid hemorrhage: a population-based study in Iceland. *Epilepsia*, 41(9):1201-1205.

Olsen, T.S. 2001. Post-stroke epilepsy. *Current atherosclerosis reports*, 3(4):340-344.

Oxford English Dictionary. 2015. Epilepsy. http://www.oed.com.nwulib.nwu.ac.za/view/Entry/63398?redirectedFrom=epilepsy#eid Date of access: 2 Mar. 2015.

Pagano, M. & Gauvreau, K. 2000. Principles of biostatistics. 2nd ed. Pacific Grove, CA: Duxbury.

Palma, E., Ragozzino, D., Di Angelantonio, S., Mascia, A., Maiolino, F., Manfredi, M., Cantore, G., Esposito, V., Di Gennaro, G., Quarato, P., Miledi, R. & Eusebi, F. 2007. The antiepileptic drug levetiracetam stabilizes the human epileptic $GABA_A$ receptors upon repetitive activation. *Epilepsia*, 48(10):1842-1849.

Park, H., Rascati, K.L., Lawson, K.A., Barner, J.C., Richards, K.M. & Malone, D.M. 2014. Adherence and persistence to prescribed medication therapy among medicare part D beneficiaries on dialysis: comparisons of benefit type and benefit phases. *Journal of managed care & speciality pharmacy*, 20(8):862-876.

Paschal, A.M., Hawley, S.R., St. Romain, T. & Ablah, E. 2008. Measures of adherence to epilepsy treatment: review of present practices and recommendations for future directions. *Epilepsia*, 49(7):1115-1122.

Pastalos, P.N. 2005. Properties of antiepileptic drugs in the treatment of idiopathic generalized epilepsies. *Epilepsia*, 46(Suppl.9):140-148.

Paul, S.P., Abdelrhim, H. & Heep, A. 2014. Management of hypoxic-ischemic encephalopathy. *Indian journal of pediatrics*. http://download.springer.com/static/pdf/709/art%253A10.1007%252Fs12098-014-1592-3.pdf?auth66=1427701946_56656c80d52bc877b375621b8ce5b99f&ext=.pdf Date of access: 30 Mar. 2015.

Penderis, J. 2014. Pathophysiology of epileptic seizures. *In practice*, 36(Suppl.1):3-9.

Perucca, E. 2005. An introduction to antiepileptic drugs. *Epilepsia*, 46(Suppl.4):31-37.

Perucca, E. & Tomson, T. 2011. The pharmacological treatment of epilepsy in adults. *The lancet neurology*, 10(5):446-456.

Peterson, A.M., Nau, D.P., Cramer, J.A., Benner, J., Gwadry-Sridhar, F. & Nichol, M. 2007. A checklist for medication compliance and persistence studies using retrospective databases. *Value in health*, 10(1):3-12.

Pharmaplan. 1993. Mysoline tablets. http://home.intekom.com/pharm/pharmpln/mysoline.html Date of access: 13 May 2015.

Pharmaplan. 2005. Epleptin 100 mg, 300 mg and 400 mg (capsules). http://home.intekom.com/pharm/pharmpln/epleptin.html Date of access: 13 May 2015.

Pickrell, W.O., Lacey, A.S., Thomas, R.H., Lyons, R.A., Smith, P.E.M. & Rees, M.I. 2014. Tends in the first antiepileptic drug prescribed for epilepsy between 2000 and 2010. *Seizure*, 23(1):77-80.

Picot, M.C., Baldy-Moulinier, M., Daurès, J.P., Dujols, P. & Crespel, A. 2008. The prevalence of epilepsy and pharmacoresistant epilepsy in adults: a population-based study in a Western European country. *Epilepsia*, 49(7):1230-1238.

Pisani, F., Orsini, M., Braibanti, S., Copioli, C., Sisti, L. & Turco, E.C. 2009. Development of epilepsy in newborns with moderate hypoxic-ischemic encephalopathy and neonatal seizures. *Brain & development*, 31(1):64-68.

Ponnusankar, S., Surulivelrajan, M., Anandamoorthy, N. & Suresh, B. 2004. Assessment of impact of medication counseling on patients' medication knowledge and compliance in an outpatient clinic in South India. *Patient education and counseling*, 54(1):55-60.

Porter, R.S. & Kaplan, J.L., *eds*. 2013. The Merck manual: home health handbook. http://www.merckmanuals.com/home/brain_spinal_cord_and_nerve_disorders/seizure_disorders/seizure_disorders.html?qt=epilepsy&alt=sh. Date of access: 13 Mar. 2014.

Porter, R.S. & Kaplan, J.L., *eds*. 2013. The Merck manual: home health handbook. http://www.merckmanuals.com/home/brain_spinal_cord_and_nerve_disorders/seizure_disorders/seizure_disorders.html?qt=epilepsy&alt=sh. Date of access: 17 Mar. 2015.

Posti, J.P., Bori, M., Kauko, T., Sankinen, M., Nordberg, J., Rahi, M., Frantzén, J., Vuorinen, V. & Sipilä, J.O.T. 2015. Presenting symptoms of glioma in adults. *Acta neurologica Scandinavica*, 131(2):88-93.

Pradhan, S. & Yadav, R. 2004. Seizures and epilepsy in central nervous system infections. *Neurology Asia*, 9(Suppl.1);4-9.

Preux, P.M. & Druet-Cabanac, M. 2005. Epidemiology and aetiology of epilepsy in sub-Saharan Africa. *Lancet neurology*, 4(1):21-31.

Pugliatti, M., Beghi, E., Forsgren, L., Ekman, M. & Sobocki, P. 2007. Estimating the cost of epilepsy in Europe: a review with economic modeling. *Epilepsia*, 48(12):2224-2233.

Radhakrishnan, K., Pandian, J.D., Santhoshkumar, T., Thomas, S.V., Deetha, T.D., Sarma, P.S., Jayachandran, D. & Mohamed, E. 2000. Prevalence, knowledge, attitude, and practice of epilepsy in Kerala, South India. *Epilepsia*, 41(8):1027-1035.

Rakhade, S.N. & Jensen, F.E. 2009. Epileptogenesis in the immature brain: emerging mechanisms. *Nature reviews neurology*, 5(7):380-391.

Renganathan, R & Delanty, N. 2003. Juvenile myoclonic epilepsy: under-appreciated and under-diagnosed. *Postgraduate medical journal*, 79(928):78-80.

Reynolds, E.H. 2009. Milestones in epilepsy. *Epilepsia*, 50(3):338-342.

Reynolds, J.E.F., *ed*. 1993. Martindale: the extra pharmacopoeia. 30th ed. London: The Pharmaceutical Press.

Rho, J.M., Donevan, S.D. & Rogawski, M.A. 1996. Direct activation of $GABA_A$ receptors by barbiturates in cultured rat hippocampal neurons. *Journal of physiology*, 497(2):509-522.

Richter, A., Anton, S.E., Koch, P. & Dennett, S.L. 2003. The impact of reducing dose frequency on health outcomes. *Clinical therapeutics*, 25(8):2307-2335.

Riva, M. 2005. Brain tumoral epilepsy: a review. *Neurological sciences*, 26(1):S40-S42.

Rolnick, S.J., Pawloski, P.A., Hedblom, B.D., Asche, S.E. & Bruzek, R.J. 2013. Patient characteristics associated with medication adherence. *Clinical medicine & research*, 11(2):54-65.

Rosner, B. 2000. Fundamentals of biostatistics. 5th ed. Pacific Grove, CA: Duxbury.

Rossiter, D., *ed*. 2014. South African medicines formulary. 11th ed. Cape Town: Health and Medical Publishing Group of the South African Medical Association.

Saadat, Z., Nikdoust, F., Aerab-Sheibani, H., Bahremand, M., Shobeiri, E., Saadat, H., Moharramzad, Y. & Morisky, D.E. 2015. Adherence to antihypertensives in patients with comorbid condition. *Nephro-Urology monthly*, 7(4):1-6.

Samsonsen, C., Reimers, A., Brathen, G., Helde, G. & Brodtkorb, E. 2014. Nonadherence to treatment causing acute hospitalizations in people with epilepsy: an observational, prospective study. *Epilepsia*, 55(11):e125-e128.

Sander, J.W. 2003. The epidemiology of epilepsy revisited. *Current opinion in neurology*, 16(2):165-170.

Sanders, J.W. 2004. Infectious agents and epilepsy. (*In* Knobler, S.L., O'Connor, S., Lemon, S.M. & Najafi, M., *eds*. The infectious etiology of chronic diseases: defining the relationship, enhancing the research and mitigating the effects. Washington, DC.: The National Academies Press. p. 93-99).

SAS (Statistical Analyses System®). 2012. SAS for windows 9.3®. Cary: North Carolina.

Schacter, S.C., Shafer, P.O. & Sirven, J.I. 2013. Who gets epilepsy? http://www.epilepsy.com/learn/epilepsy-101/who-gets-epilepsy Date of access: 10 Sep. 2015.

Schwartz, R.D. 1988. The $GABA_A$ receptor-gated ion channel: biochemical and pharmacological studies of structure and function. *Biochemical pharmacology*, 37(18):3369-3375.

Seino, M. 2006. Classification criteria of epileptic seizures and syndromes. *Epilepsy research*, 70S:S27-S33.

Shakirullah., Ali, N., Khan, A. & Nabi, M. 2014. The prevalence, incidence and etiology of epilepsy. *International journal of clinical and experimental neurology*, 2(2):29-39.

Shorvon, S. 2000. Oxcarbazepine: a review. *Seizure*, 9(2):75-79.

Shorvon, S. 2014. The concept of symptomatic epilepsy and the complexities of assigning cause in epilepsy, *Epilepsy & behavior*, 32:1-8.

Shorvon, S.D. 2011. The causes of epilepsy: changing concepts of etiology of epilepsy over the past 150 years. *Epilepsia*, 52(6):1033-1044.

SIGN (Scottish Intercollegiate Guidelines Network). 2015. Diagnosis and management of epilepsy in adults: a national clinical guideline. Edinburgh: SIGN.

Sikka, R., Xia, F. & Aubert, R.E. 2005. Estimating medication persistency using administrative claims data. *The American journal of managed care*, 11(7):449-457.

Silverman, I.E., Restrepo, L. & Mathews, G.C. 2002. Poststroke seizures. *Archives of neurology*, 59(2):195-202.

Singhi, P. 2011. Infectious causes of seizures and epilepsy in the developing world. *Developmental medicine & child neurology*, 53(7):600-609.

Sinha, A. & Bhaumik, D.K. 2014. Treatment expenditure pattern of epileptic patients: a study from a tertiary care hospital, Kolkata, India. *Neurology research international*, 2014(869572):1-6.

Sirey, J.A., Bruce, M.L., Alexopoulos, G.S., Perlick, D.A., Friedman, J.S. & Meyers, B.S. 2001. Perceived stigma and patient-rated severity of illness as predictors of antidepressant drug adherence. *Psychiatric services*, 52 (12):1615-1620.

Sitoh, Y.Y. & Tien, R.D. 1998. Neuroimaging in epilepsy. *Journal of magnetic resonance imaging*, 8(2):277-288.

Smith, J., Wells, L. & Dodd, K. 2000. The continuing fall in incidence of hypoxic-ischaemic encephalopathy in term infants. *British journal of obstetrics and gynaecology*, 107(4):461-466.

Snyman, J.R., *ed*. 2011. MIMS monthly index of medical specialities. 49(4):402p.

Sokol, M.C., McGuigan, K.A., Verbrugge, R.R. & Epstein, R.S. 2005. Impact of medication adherence on hospitalization risk and healthcare cost. *Medical care*, 43(6):521-530.

South Africa. 2003. Medical Schemes Act, 1998 (Act no. 131 0f 1998). Regulations made in terms of the Medical Scheme Act, 1998 therapeutic algorithms for chronic conditions. (Notice 1402). *Government gazette*, 25537:53, 3 Oct.

South Africa. 2004. Medicines and Related Substances Act, 1965 (Act No. 101 of 1965). Regulations relating to a transparent pricing system for medicines and scheduled substances. (Notice R 553). *Government Gazette*, 26304:3-24, 30 Apr.

Spitzmiller, R.E., Phillips, T., Meinzen-Derr, J. & Hoath, S.B. 2007. Amplitude-integrated EEG is useful in predicting neurodevelopmental outcome in full-term infants with hypocix-ischemic encephalopathy: a meta-analysis. *Journal of child neurology*, 22(9):1069-1078.

Sridharan, R. 2002. Epidemiology of epilepsy. *Current science*, 82(6):664-670.

Stafstrom, C.E. 2010. Mechanisms of action of antiepileptic drugs: the search for synergy. *Current opinion in neurology*, 23(2):157-163.

Starks, H., Diehr, P. & Curtis, J.R. 2009. The challenge of selection bias and confounding in palliative care research. *Journal of palliative medicine*, 12(2):181-187.

Stedman's medical dictionary. 2000. 27th ed. Baltimore, MD: Lippincott Williams & Wilkins.

Stefani, A., Spadoni, F., Siniscalchi, A. & Bernardi, G. 1996. Lamotrigine inhibits Ca^{2+} currents in cortical neurons: functional implications. *European journal of pharmacology*, 307(1):113-116.

Stephen, L.J. & Brodie, M.J. 2000. Epilepsy in elderly people. *The lancet*, 355(9213):1441-1446.

Stephen, L.J. & Brodie, M.J. 2012. Antiepileptic drug monotherapy versus polytherapy: pursuing seizure freedom and tolerability in adults. *Current opinion in neurology*, 25(2):164-172.

Stern, J.M. 2006. Overview of treatment guidelines for epilepsy. *Current treatment options in neurology*, 8(4):280-288.

Steyn, H.S. 2009. Handleiding vir bepaling van effekgrootte-indekse en praktiese betekenisvolheid. Potchefstroom: Statistiese Konsultasiediens, NWU. http://www.puk.ac.za/opencms/export/PUK/html/fakulteite/natuur/skd/handleiding/Hoofstuk_1.pdf Date of access: 15 Sep. 2015.

Stroupe, K.T., Murray, M.D., Stump, T.E. & Callahan, C.M. 2000. Association between medication supplies and healthcare costs in older adults from an urban healthcare system. *Journal of American geriatrics society*, 48(7):760-768.

Tannen, R.L., Weiner, M.G. & Xie, D. 2009. Use of primary care electronic medical record database in drug efficacy research on cardiovascular outcomes: comparison of database and randomised controlled trial findings. *British medical journal*, 338(81):395-399.

Taphoorn, M.J.B. & Klein, M. 2004. Cognitive deficits in adult patients with brain tumours. *The lancet neurology*, 3(3):159-168.

Thier, S.L., Yu-Isenberg, K.S., Leas, B.E., Cantrell, C.R., DeBussey, S., Goldfarb, N.I. & Nash, D.B. 2008. In chronic disease, nationwide data show poor adherence by patients to medication and by physicians to guidelines. *Managed care*, 17(2):48-57.

Thomas, S.V., Sarma, P.S., Alexander, M., Pandit, L., Shekhar, L., Trivedi, C. & Vengamma, B. 2001. Economic burden of epilepsy in India. *Epilepsia*, 42(8):1052-1060.

Tiamkao, S., Kaewkiow, N., Pranbul, S. & Sawanyawisuth, K. 2014. Validation of a seizure-related injury model. *Journal of neurological sciences*, 336(1-2):113-115.

Tilson, H.H. 2004. Adherence or compliance? Changes in terminology. *The annals of pharmacotherapy*, 38:161-162.

Toet, M.C. Groenendaal, F., Osredkar, D., van Huffelen, A.C. & de Vries, L.S. 2005. Postneonatal epilepsy following amplitude-integrated EEG-detected neonatal seizures. *Pediatric neurology*, 32(4):241-247.

Treinman, D.M. 2001. GABAergic mechanisms in epilepsy. *Epilepsia*, 42(Suppl.3):8-12.

Tunnicliff, G. 1996. Basis of the antiseizure action of phenytoin. *General pharmacology: the vascular system*, 27(7):1091-1097.

Urbach, H., Scheffler, B., Heinrichsmeier, T., von Oertzen, J., Kral, T., Wellmer, J., Schramm, J., Wiestler, O.D. & Blümcke, I. 2002. Focal cortical dysplasia of Taylor's balloon cell type: a clinicopathological entity with characteristic neuroimaging and histopathological features, and favorable postsurgical outcome. *Epilepsia*, 43(1):33-40.

Uthman, B.M. 2014. Extended-release antiepilepsy drugs: review of the effects of once-daily dosing on tolerability, effectiveness, adherence, quality of life, and patient preference. *US neurology*, 10(1):30-37.

Valderas, J.M., Starfield, B., Sibbald, B., Salisbury, C. & Roland, M. 2009. Defining comorbidity: implications for understanding health and health services. *Annals of family medicine*, 7(4):357-363.

Van Breemen, M.S.M., Wilms, E.B. & Vecht, C.J. 2007. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *The lancet neurology*, 6(5):421-430.

Wagner, R.G., Ngugi, A.K., Twine, R., Bottomley, C., Kamuyu, G., Gómez-Olive, F.X., Connor, M.D., Collinson, M.A., Kahn, K., Tollman, S. & Newton, C.R. 2014. Prevalence and risk factors for active convulsive epilepsy in rural northeast South Africa. *Epilepsy research*, 108(4):782-791.

Wanning, B. & Montagne, M. 2005. Pharmacoepidemiology: principles and practices. New York, NY: McGraw Hill.

White, H.S. 1999. Comparative anticonvulsant and mechanistic profile of the established and newer antiepileptic drugs. *Epilepsia*, 40(Suppl.5):S2-S10.

White, H.S., Brown, S.D., Woodhead, J.H., Skeen, G.A. & Wolf, H.H. 1997. Topiramate enhances GABA-mediated chloride flux and GABA-evoked chloride currents in murine brain neurons and increases seizure threshold. *Epilepsy research*, 28(3):167-179.

WHO (World Health Organization). 2003. Adherence to long-term therapies: evidence for action. Geneva.

WHO (World Health Organization). 2003. Introduction to drug utilization research. Geneva.

WHO (World Health Organization). 2004. Epilepsy in the WHO African region: bridging the gap. Brazzaville.

WHO (World Health Organization). 2012. Epilepsy. http://www.who.int/mediacentre/factsheets/fs999/en/index.html Date of access: 03 Mar. 2014.

WHO (World Health Organization). 2015. Epilepsy. http://www.who.int/mediacentre/factsheets/fs999/en/index.html Date of access: 19 Aug.

Wiebe, S., Bellhouse, D.R., Fallahay, C. & Eliasziw, M. 1999. Burden of epilepsy: the Ontario health survey. *The Canadian journal of neurological sciences*, 26(4):263-270.

Williams, N., Nefdt, W.M. & Wilmshurst, J.M. 2015. Epilepsy South Africa: turning obstacles into true potential. *Epilepsia*, 56(2):184-187.

Wirrell, E.C., Armstrong, E.A., Osman, L.D. & Yager, J.Y. 2001. Prolonged seizures exacerbate perinatal hypoxic-ischemic brain damage. *Pediatric research*, 50(4):445-454).

Wolf, P. 2014. History of epilepsy: nosological concepts and classification. *Epileptic disorders*, 16(3):261-269.

Yang, X., Weisenfeld, A. & Rothman, S.M. 2007. Prolonged exposure to levetiracetam reveals a presynaptic effect on neurotransmission. *Epilepsia*, 48(10):1861-1869.

Yeager, K.A., Dillorio, C., Shafer, O.P., McCarthy, F., Letz, R., Henry, T. & Schomer, D.L. 2005. The complexity of treatments for persons with epilepsy. *Epilepsy & behaviour*, 7:679-686.

Zona, C. & Avoli, M. 1997. Lamotrigine reduces voltage-gated sodium currents in rat central neurons in culture. *Epilepsia*, 38(5):522-525.

ANNEXURE A: CHECKLIST FOR RETROSPECTIVE DATABASE

Checklist for retrospective database studies to assess quality

Element	Aspect	Description of checklist item	Approach followed
Database selection	Population covered	Does the resource include an appropriate population in terms of size, coverage and representativeness?	Refer to paragraph 1.4.2.2.
	Capture of study variables	Are all exposures and study variables captured in sufficient detail, without bias and accessible for research?	Refer to paragraph 1.4.5.3.
	Continuous and consistent data capture	Are there any changes or breaks in data collection over time during the observation period? Are there any inconsistencies in the provision of healthcare or capture of study variables across the database population?	Not applicable.
	Record duration and data latency	Are the average patient record and the time between the occurrence of the exposure and data collection sufficiently long for the study event?	Refer to paragraphs 1.4.2.1 and 1.4.2.2.
	Database expertise	Is the expertise required to use the resource available in-house or elsewhere?	In-house.
Data source/ multiple resources	Relevance	Have the data attributes been described in detail for decision-makers to determine whether there	The following data attributes were describe: health-care profile, available services and

Element	Aspect	Description of checklist item	Approach followed
		was a good rationale for using the data source?	advantages of administrative data (refer to paragraph 1.4.2.2).
	Reliability and validity	Description of reliability and validity of data, including data quality checks and data cleansing procedures.	The datasets were cleaned by deleting non-paid claims and non-medicine items. The PBM providing the data had certain validation processes in place to assure validity (refer to paragraphs 1.4.2.2 and 1.4.5.2.2).
	Linkages	Have the necessary linkages among data sources and/or different care sites been carried out appropriately?	Patient claims data received will be imported into the SAS® for Windows 9.3 analytical program. Encrypted number provided by the PBM links the patient record to the claims data. This number stays the same over the eight-year period.
	Eligibility	Description of the type of data used to determine member eligibility.	Patients' health plans data was not available due to patient confidentiality agreement. Therefore, eligibility could not be assessed.
	Data storage and analyses	In multi-institutional studies, should a central or distributed system be used?	Central system.
Methods	Data analysis	Was a data analysis plan developed *a priori*?	Not applicable.

Element	Aspect	Description of checklist item	Approach followed
	Design selection	Was a rationale for the research design provided?	Yes, refer to paragraphs 1.4.2.1, 1.4.4.1 and 1.4.5.2.
	Research design limitations	Were potential limitations of the design identified and addressed?	
	Treatment effect	Does the study include a comparison group? Does the study include a description of the process to identify the comparison group and the characteristics of the comparison group as they relate to the intervention group?	Not applicable.
Measurements	Measure of compliance	Was a method to measure adherence to medication included in this study? Was the method clearly described? Is the measure consistent with the objective of the study?	Yes, refer to paragraph 1.4.5.1.
Study population and variable	Sample selection	Description of the inclusion and exclusion criteria and the steps used to derive the final sample from the initial population.	Refer to paragraph 1.4.4.2.
	Eligibility	Are subjects eligible for the time period over which measurements are occurring?	Due to patient confidentiality agreement data on patients' health plans was not available. Eligibility could not be assessed. The PBM providing the data had certain validation processes in place to assure validity (refer to paragraph 1.4.2.2 and 1.4.5.2.2).
	Censoring	Were inclusion or exclusion or eligibility criteria used to address censoring and was the impact on the study findings discussed?	

Element	Aspect	Description of checklist item	Approach followed
definitions/ Study population extraction and analyses Privacy and security Quality and validation procedures	Definition validity	Were a rationale and/or supporting literature provided for the definitions and criteria used? Were sensitivity analyses performed for definitions or criteria that are controversial, uncertain or novel?	Refer to paragraphs 1.4.4.1 and 1.4.4.2.
	Timing of outcome	Is there a clear temporal relationship between the exposure and outcome?	Not applicable.
	Event capture	Is the collected data able to identify the intervention and outcomes if they actually occurred?	Only data for medicine items claimed is available and assessed.
	Specification of extraction	Are the following specified in detail: how to extract the study population and variables, code lists and non-coded systems, retrieval and merging of additional external data, output and final analyses?	Refer to paragraphs 1.4.2.2, 1.4.4.1 and 1.4.4.2.
	Compliance with privacy and security policy	Have all relevant local, regional and national policies been complied with?	Refer to paragraph 1.4.6.
	Limited use of identifying information	Have all direct identifiers been removed or masked?	Refer to paragraph 1.4.6.
	Secure data storage and transfer	Is there a formal data security policy and has it been adhered to?	Refer to paragraph 1.4.6.
	Review policy and procedures	Are regular privacy reviews adhered to? Have the use of a new database and collection of patient data impacted confidentiality?	Refer to paragraph 1.4.6.
	Overall database	Have appropriate general quality	Refer to paragraph 1.4.5.5 and

Element	Aspect	Description of checklist item	Approach followed
		checks been completed?	Table 1-6.
	Study population	Which study-specific quality checks are needed: extraction process, data merging, study variables, assumptions, etc.?	Refer to paragraphs 1.4.4.1 and 1.4.4.2 and Table 1-3 and Table 1-4.
	Testing	The checks can be external, logical or internal and should be cross-sectional, longitudinal and up to date.	Longitudinal.
Documentation	Format	Are rules of Guidelines for Good Pharmacoepidemiology Practice followed, including storage and indexing?	Refer to paragraph 1.4.6.3.
	Specifics	Have extraction specification, output, quality testing, merging resources, responsibility for privacy and annotated programming code for data extraction and final analyses been documented?	Not applicable

ANNEXURE B: ALGORITHM OF MEDICINE CONTROL COUNCIL

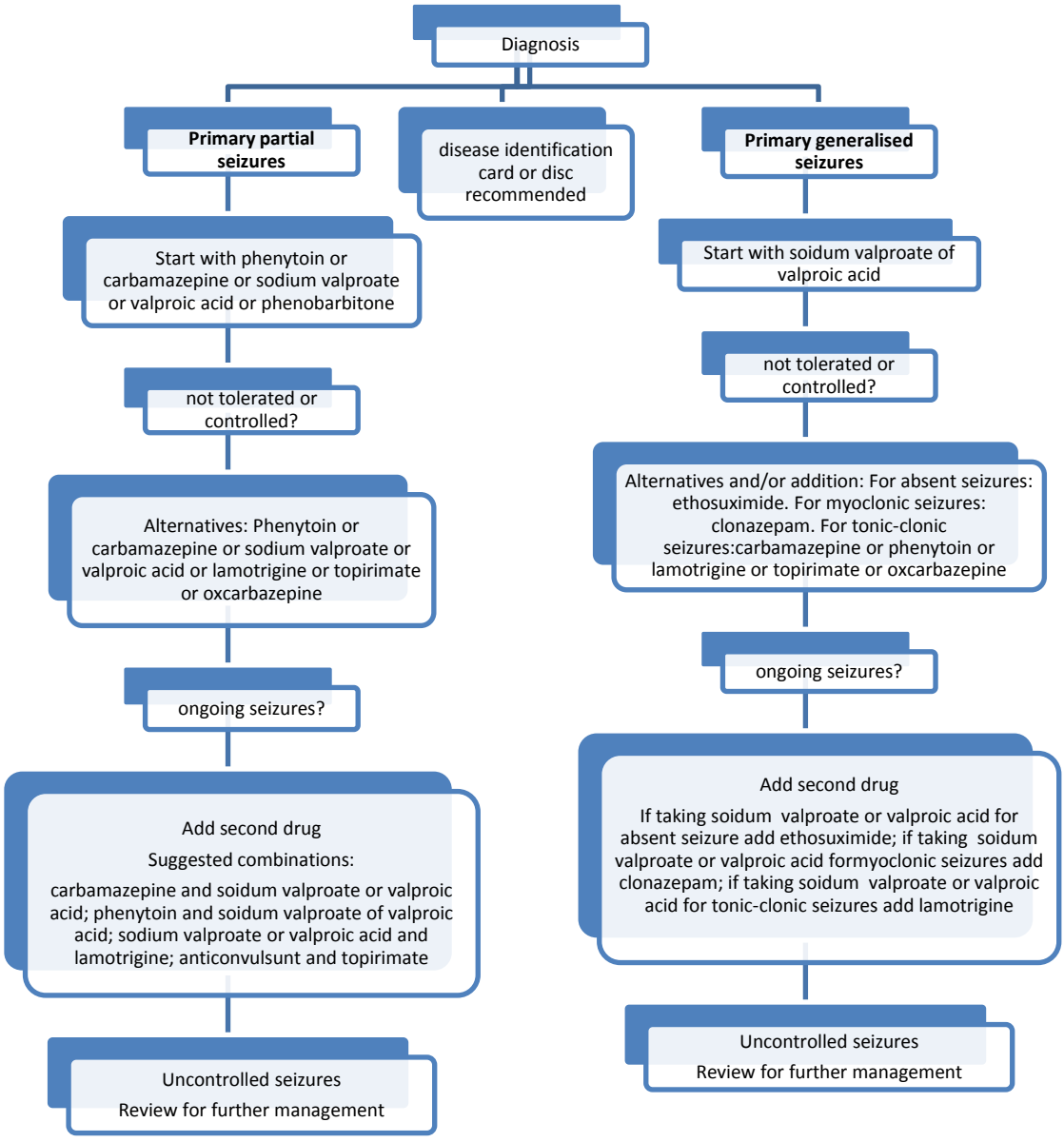
The Medicines Control Council advocates the following algorithm for the treatment of epilepsy (South Africa, 2003:84).

Epilepsy algorithm

	Diagnosis	
Primary partial seizure	Disease identification card or disc recommended	**Primary generalised seizures**
Start with phenytoin or carbamazepine or sodium valproate or valproic acid or phenobarbitone		Start with sodium valproate or valproic acid
Not tolerated or controlled?		Not tolerated or controlled?
Alternatives: Phenytoin or carbamazepine or sodium valproate or valproic acid or lamotrigine or topirimate or oxcarbazepine		Alternatives and/or addition: For absent seizures: ethosuximide, for myoclonic seizure: clonazepam, for tonic-clonic seizures: carbamazepine or phenytoin or lamotrigine or topirimate or oxcarbazepine
On-going seizures?		On-going seizures?
Add second drug Suggested combinations: Carbamazepine and sodium valproate or valproic acid; phenytoin and sodium valproate or valproic acid; sodium valproate or valproic acid and lamotrigine; anticonvulsant and topirimate		Add second drug If taking sodium valproate or valproic acid for absent seizures add ethosuximide; if taking sodium valproate or valproic acid for myoclonic seizures add clonazepam; if taking sodium valproate or valproic acid for tonic-clonic seizures add lamotrigine.
Uncontrolled seizures Review for further management		Uncontrolled seizures Review for further management

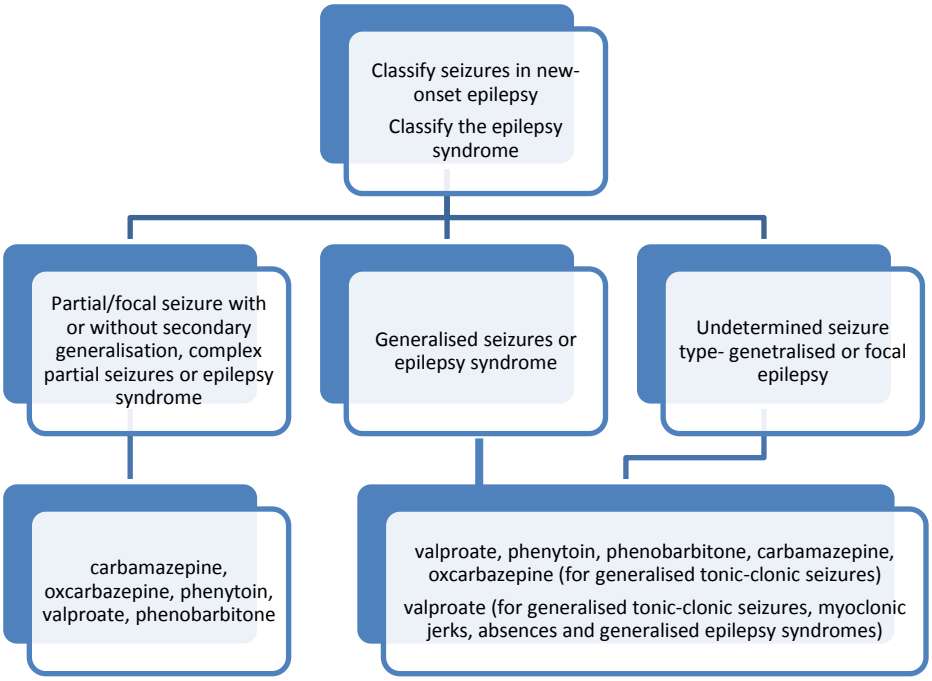
ANNEXURE C: SOUTH AFRICAN ALGORITHM

The following algorithms from three different countries can be compared (extracted from South Africa, 2003:84; Roy & Das, 2013:529; The National Institute for Health and Care Excellence, 2012:76):



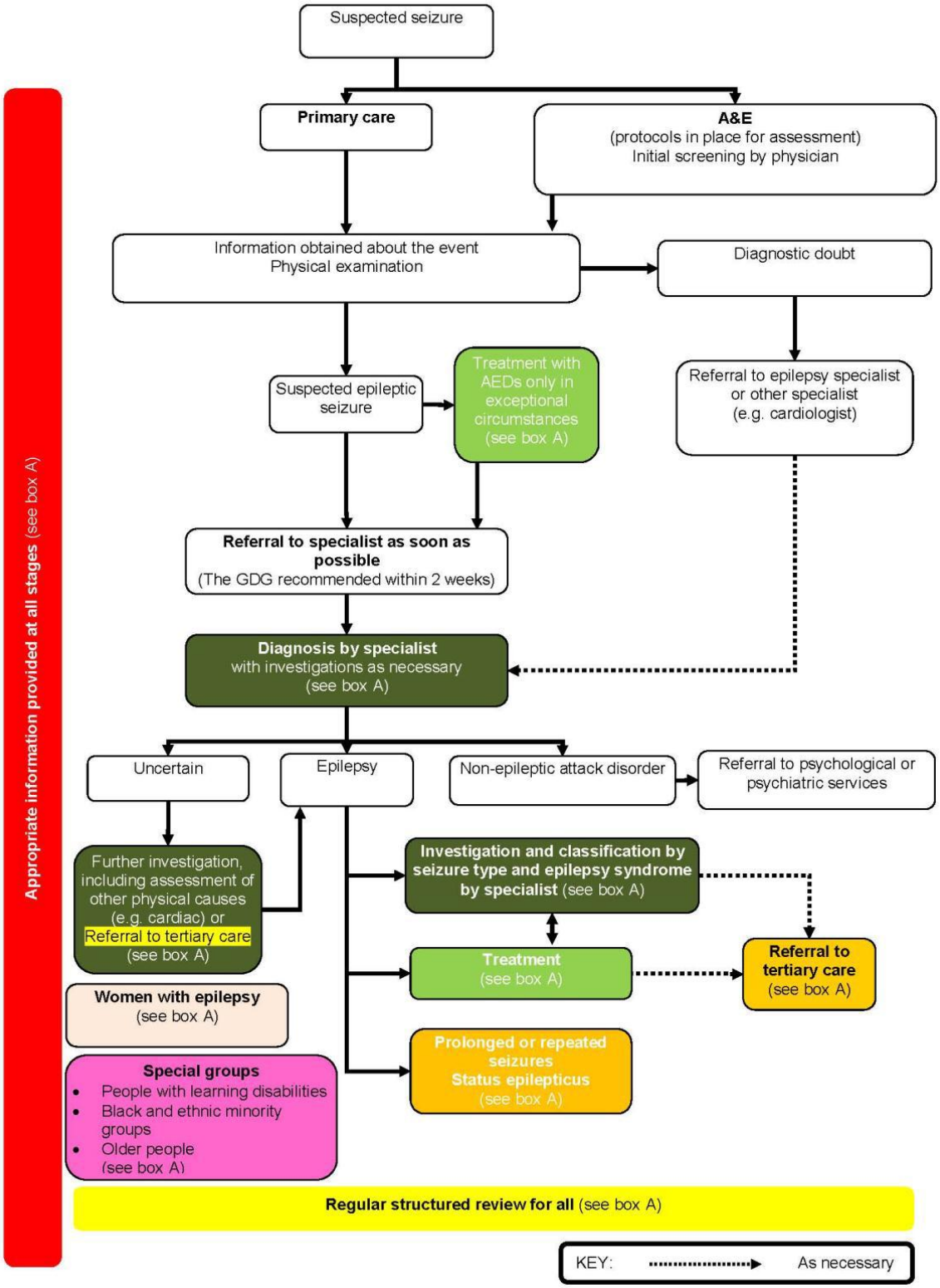
South African algorithm

ANNEXURE D: INDIAN ALGORITHM



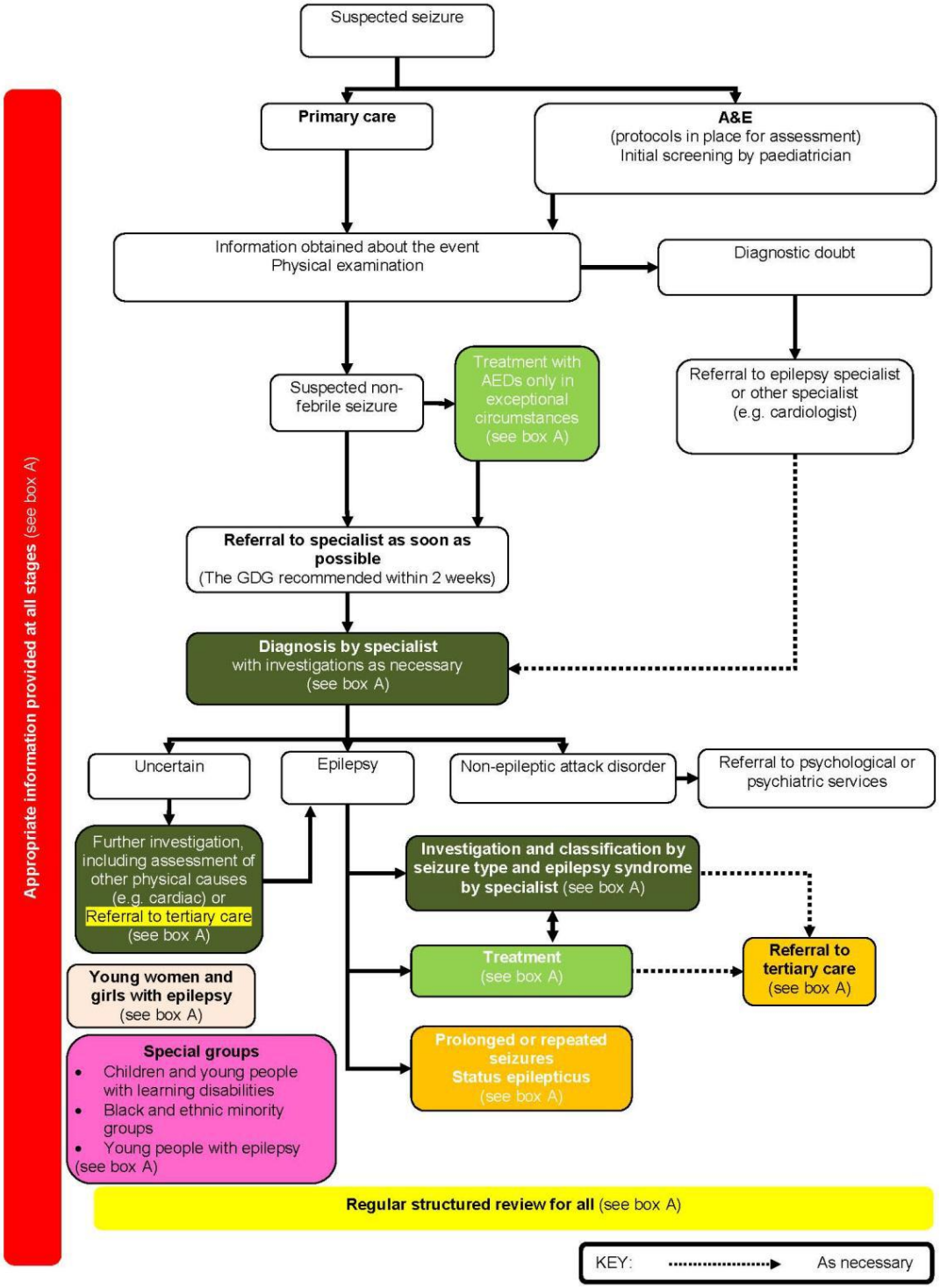
Indian algorithm for new-onset epilepsy

ANNEXURE E: BRITISH ALGORITHM FOR ADULTS



British algorithm for adults

ANNEXURE F: BRITISH ALGORITHM FOR CHILDREN



British algorithm for children

ANNEXURE G: NICE GUIDELINES FOR SPECIFIC SEIZURE TYPES

The National Institute for Health and Care Excellence compiled a table indicating what treatment/active ingredient is appropriate to use in specific seizure types (extracted from NICE, 2015:78-80).

NICE guideline on epilepsy treatment

Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
Generalised tonic-clonic	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate	Clobazam Lamotrigine Levetiracetam Sodium valproate Topiramate		(If there are absence or Myoclonic seizures, or if JME suspected) Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Tonic or atonic	Sodium valproate	Lamotrigine	Rufinamide Topiramate	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin
Absence	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Clobazam Clonazepam Levetiracetam	Carbamazepine Gabapentin Oxcarbazepine

Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
			Topiramate Zonisamide	Phenytoin Pregabalin Tiagabine Vigabatrin
Myoclonic	Levetiracetam Sodium valproate Topiramate	Levetiracetam Sodium valproate Topiramate	Clobazam Clonazepam Piracetam Zonisamide	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Focal	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Eslicarbazepine acetate Lacosamide Phenobarbital Phenytoin Pregabalin Tiagabine Vigabatrin Zonisamide	
Prolonged or repeated seizures and convulsive status epilepticus in the community	Buccal midazolam Rectal diazepam Intravenous lorazepam			
Convulsive status epilepticus in hospital	Intravenous lorazepam	Intravenous phenobarbital		

Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
	Intravenous diazepam Buccal midazolam	Phenytoin		
Refractory convulsive status epilepticus	Intravenous midazolam Propofol (not in children) Thiopental sodium			

ANNEXURE H: SOUTH AFRICAN FAMILY PRACTICE

Author guidelines

Submissions can only be made online at www.editorialmanager.com/safpj. Authors need to register online with the journal prior to submitting a manuscript. Once registered, simply log in and begin an easy 5 step process to upload your manuscript. All manuscripts must be submitted in MS Word®, Open Office, or RTF format using Times New Roman font size 10 and single-spacing. Headings must be in Bold.

The author must always retain a copy. All the named authors must have approved the final manuscript. Pages should be numbered consecutively in the lower right corner. Please note that the Original Research section will follow a ";print-short, web-long"; policy, which means that only the abstracts will be published in print, with the full article published on the web. Some review articles may also be published under these provisions.

The following contributions are accepted (word counts exclude abstracts, tables and references):

1. Original research (Between 1000 and 3500 words):

2. Letters to the Editor (Up to 400 words):

3. Scientific Letters (Less than 600 words): A short abstract is required (125-150 words) and should be structured under the following headings: background, methods, results and conclusion. One table or graph and not more than 5 references.

4. Review/CPD articles (Up to 1800 words): Most review articles are published as part of the continuous professional development (CPD) programme of SAFP. A scientific editor is appointed to approve topics, invite authors and to review the articles before they are independently peer-reviewed. All articles are reviewed by a family physician as well a topic specialist. Review articles outside the CPD programme are welcomed. Once accepted they may be published in full in the printed journal OR a 250 word abstract will be published in print with the full article available online.

5. Opinions (Open Forum) (Between 1000 and 3500 words).

6. Editorials (Between 600 - 800 words): Scientific editorials can be used to highlight progress in any scientific field related to family medicine.

Please consult the Section Policies for more details regarding CPD articles.

Format

Title page: All articles must have a title page with the following information and in this particular order: Title of the article; surname, initials, qualifications and affiliation of each author; The name, postal address, e-mail address and telephonic contact details of the corresponding author; at least 5 keywords. Please do not use capital letters only for headings and names, but stick to the normal use of capital letters.

Abstract. All articles should include an abstract. The structured abstract for an Original Research article should be between 200 and 250 words and should consist of four paragraphs labelled "Background, Methods, Results, and Conclusions".

Only the abstract of Original Research articles will be published in print, and the abstract with the full article will be published online. It should briefly describe the problem or issue being addressed in the study, how the study was performed, the major results, and what the authors conclude from these results.

The abstracts for other types of articles should also be no longer than 250 words and need not follow the structured abstract format.

Keywords. All articles should include keywords. Up to five words or short phrases should be used. Use terms from the Medical Subject Headings (MeSH) of Index Medicus when available and appropriate. Key words are used to index the article and may be published with the abstract.

Acknowledgements. In a separate section, acknowledge any financial support received or possible conflict of interest. This section may also be used to acknowledge substantial contributions to the research or preparation of the manuscript made by persons other than the authors.

References. Cite references in numerical order in the text, in superscript format. Do not use brackets. In the References section, references must be numbered consecutively in the order in which they are cited, not alphabetically.

The style for references should follow the format set forth in the ";Uniform Requirements for Manuscripts Submitted to Biomedical Journals"; prepared by the International Committee of Medical Journal Editors.

Abbreviations for journal titles should follow Index Medicus format. Authors are responsible for the accuracy of all references. Personal communications and unpublished data should not be referenced. If essential, such material should be incorporated in the appropriate place in the text. List all authors when there are six or fewer; when there are seven or more, list the first three, then ";et al.";

When citing URLs to web documents, place in the reference list, and use following format: Authors of document (if available). Title of document (if available). URL. (Accessed [date]).

The following are sample references:

1. London L, Baillie R. Notification of Pesticide Poisoning: Knowledge, Attitudes and Practices of Doctors in the Rural Western Cape. S A Fam Pract 1999;20(1):117-20.

2. FDA Talk Paper: http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01151.html (Accessed 04/10/2002).

Click here for more sample references.

Tables. Tables should be self-explanatory, clearly organised, and supplemental to the text of the manuscript. Each table should include a clear descriptive title on top and numbered in Roman numerals (I, II, etc) in order of its appearance as called out in text. Tables must me inserted in the correct position in the text. Authors should place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations. For footnotes use the following symbols, in sequence: *,†,‡,§,||,,**,††,‡‡

Figures. All figures must be inserted in the appropriate position of the electronic document. Symbols, lettering, and numbering (in Arabic numerals e.g. 1, 2, etc. in order of appearance in the text) should be placed below the figure, clear and large enough to remain legible after the figure has been reduced. Figures must have clear descriptive titles.

Photographs and images: If photographs of patients are used, either the subject should not be identifiable or use of the picture should be authorised by an enclosed written permission from the subject. The position of photographs and images should be clearly indicated in the text. Electronic images should be saved as either jpeg or gif files. All photographs should be scanned at a high resolution (300dpi, print optimised). Provision is made to upload individual images on the website as supplementary files. Please number the images appropriately.

Permission. Permission should be obtained from the author and publisher for the use of quotes, illustrations, tables, and other materials taken from previously published works, which

are not in the public domain. The author is responsible for the payment of any copyright fee(s) if these have not been waived. The letters of permission should accompany the manuscript. The original source(s) should be mentioned in the figure legend or as a footnote to a table.

Review and action. Manuscripts are initially examined by the editorial staff and are usually sent to independent reviewers who are not informed of the identity of the author(s). When publication in its original form is not recommended, the reviewers' comments (without the identity of the reviewer being disclosed) may be passed to the first author and may include suggested revisions. Manuscripts not approved for publication will not be returned.

Ethical considerations. Papers based on original research must adhere to the Declaration of Helsinki on ";Ethical Principles for Medical Research Involving Human Subjects"; and must specify from which recognised ethics committee approval for the research was obtained.

Conflict of interest. Authors must declare all financial contributions to their work or other forms of conflict of interest, which may prevent them from executing and publishing unbiased research. [Conflict of interest exists when an author (or the author's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her opinions or actions.]* **Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA 2001: 286(10)*

The following declaration may be used if appropriate: ";I declare that I have no financial or personal relationship(s) which may have inappropriately influenced me in writing this paper.";

Submissions and correspondence. All submissions must be made online at www.safpj.co.za and correspondence regarding manuscripts should be addressed to:

The Editor, South African Family Practice, PO Box 14804, Lyttelton, 0140. Telephone: (012) 664 7460

General Facsimile: (012) 664 6276. href="mailto:editor@safpj.co.za"> editor@safpj.co.za

ANNEXURE I: EPILEPSIA THE JOURNAL OF THE INTERNATIONAL LEAGUE AGAINST EPILEPSY

Author guidelines

INSTRUCTIONS *for* AUTHORS

Epilepsia is the official journal of the **International League Against Epilepsy (ILAE)**. The Journal publishes original articles on all aspects of epilepsy, clinical and experimental, especially of an International importance. Manuscripts should be the work of the author(s), must not have been previously published elsewhere, and must not be under consideration by another journal. If you have a question not addressed in these pages then contact the journal at epilepsia@epilepsia.com.

EDITORIAL POLICIES

(1) The Editors-in-Chief of *Epilepsia* invite manuscripts in all areas of epilepsy-related research, especially if useful for an international audience. Manuscript submission is free. As a general guide, manuscripts will be considered for publication if they contribute significant new findings to the field. The primary aim of *Epilepsia* is to publish innovative and high quality papers that provide clinical and/or basic science insights. The Editors will make an initial evaluation of all manuscripts to determine whether they provide new important information and in the field, are in the proper format, and are appropriate for the Journal (editorial review). Reports are unlikely to be accepted for publication if they are not based in sound science and/or they provide only incremental knowledge of limited general usefulness. To assist authors in deciding whether to submit a manuscript to *Epilepsia*, we provide the following commonly encountered examples of reports which we are unlikely to publish:

(a) Papers that describe clinical features or epidemiology in a given region of the world that do not provide new insights into epilepsy not already published;

(b) Correlative studies where the sample size is too low to provide statistically sound findings;

(c) Genetic association studies in which the association has already been confirmed;

(d) Investigatory articles describing the application of a new technical variation which is not likely to have clinical utility or impact;

(e) Correlative clinical studies, which are conceived without clear hypotheses and the results of which are of little clinical utility;

(f) Basic research studies that are not grounded in epilepsy relevant hypotheses;

(g) Single group, before-after evaluations of therapeutic interventions and programs that do not include a control group;

(h) Small case series which largely replicate what is already known;

(i) Case reports (highly unlikely to be accepted unless they provide novel findings of theoretical or clinical importance).

Epilepsia will accept, review, and publish studies with negative results, provided that appropriate controls have been used, the study is adequately powered, and the results are important and or useful to others in their search community.

(2) Manuscripts describing original research, and passing the initial editorial screen, will be subject to external peer review. Acceptance of these manuscripts is never guaranteed. At least two reviews are generally obtained for these submissions; additional reviews may be sought at the discretion of the Editors. Appeals of rejection decisions will be considered by the Editors-in-Chief; decisions of the Editors-in-Chief are final.

(3) In the cover letter, authors should indicate that the material described in the manuscript is the work of the author(s), has not been previously published, except in abstract form, and that it is not simultaneously under consideration by any other journal.

(4) As a condition of publication, *Epilepsia* requires authors to transfer copyright to the ILAE. Authors will be asked to login into Author Services and complete the appropriate license agreement via Wiley Author Licensing Service.

(5) *Epilepsia* complies with recommendations of the International Committee of Medical Journal Editors (http://www.ICMJE.org). Authors are required to include a statement at the end of their manuscript affirming that the work described is consistent with the JournalÊs guidelines for ethical publication (see below). *Epilepsia* is a member of the Committee on Publication Ethics (COPE), and we adhere to itsprinciples (http://publicationethics.org/).

(6) Data reporting should follow appropriate checklists and guidelines (e.g., STROBE for observational trials; CONSORT for clinical trials), and other checklists should be consulted for other reports including diagnostic accuracy (STARD) or meta-analyses (PRISMA). Checklists can be downloaded from the following: STROBE http://strobe-statement.org CONSORT http://www.consort-statement.org/consortstatement/ STARD http://www.stard-statement.org/ PRISMA http://www.prisma-statement.org/

(7) For animal experiments, the authors need to state that the experiments have been performed in accordance with all applicable national and/or international guidelines/laws. The authors should also provide their allowance number for performing animal experiments when available and should add a statement indicating that the principles outlined in the ARRIVE

guidelines and the Basel declaration (http://www.basel.declaration.org) including the 3R concept have been considered when planning the experiments.

(8) Authors are also required to provide full disclosure of any conflict of interest as a part of the submitted manuscript (see Disclosure of Conflicts of Interest in the Manuscript Format section under Manuscript Preparation). Manuscripts that do not conform to these guidelines will not be considered for publication. Discovery of or failure to comply will result in rejection of the manuscript, retraction of the published article, and/or a ban on future submissions by the author(s).

(9) In submitting a manuscript, the submitting/corresponding author must acknowledge that: a) all co-authors have been substantially involved in the study and/or the preparation of the manuscript; b) no undisclosed groups or persons have had a primary role in the study and/or in manuscript preparation (i.e., there are no ghost-writers); and c) all co-authors have seen and approved the submitted version of the paper and accept responsibility for its content. The Editors reserve the right to require authors to submit their original data for comparison with the manuscripts illustrations, tables, and results.

(10) Sometimes editors make mistakes. If an author believes an editor has made a decision in error we welcome an appeal. Please contact the editor and in your appeal letter, clearly state why you think the decision is a mistake and set out specific responses to any comments related to the rejection. An appeal does not guarantee a re-review.

TYPES OF MANUSCRIPTS

The following types of material may be considered for publication:

(1) Peer-reviewed papers (to be submitted by uploading online via Scholar One Manuscript Central http:// mc.manuscriptcentral.com/epilepsia).

a. Critical Reviews and Commentaries. The Editors-in- Chief encourage submission of reviews and commentaries on topical and controversial issues. Authors planning/ proposing such papers should contact the Editors-in-Chief at epilepsia@epilepsia.com before submitting their manuscripts. Authors can also approach one of *Epilepsia's* Associate Editors about possible reviews. While there are no strict length limits on this type of paper, manuscripts generally should be around 4-5000 words. Ample figures and tables are encouraged. Longer manuscripts will be considered at the discretion of the Editors-in-Chief, but justification should be provided by the authors.

b. Full-length Original Research Articles. These articles should be limited in length to 4000 words and no more than 6 figures and tables (combined). Additional figures and tables will be

permitted at the discretion of the Editors or can be submitted as online only Supporting Information (which will be linked to the online version of the published article). Authors should aim for presenting material clearly and completely, in the most concise and direct form possible; the Introduction should be brief (typically less than 600 words), and the Discussion should be restricted to issues directly relevant to the Results (typically less than 1200 words).

c. Brief Communications. These articles including short studies, small series, case reports, etc. should describe previously unpublished material, including original research and/or clinical observations. The papers are limited generally to 1800 words (excluding the summary), 15 references, and no more than 2 figures and tables (combined). Please note that the Editors may use their discretion to request that brief communications be shortened to a length that they feel is appropriate, and may provide for a larger number of figures and tables if justified. Brief Communications may be published online only (not in the print version of the journal) depending on their impact. They will appear in a specific issue in the electronic (online) version, and will be identified and described (Short Summary) in the Table of Contents of the printed version of that issue. The online versions will be dealt with by Pub- Med/Medline and other indexing/citation systems, exactly the same way as print articles; they will be referenced by their DOI number and date of online publication (which will continue to be approximately 35 working days following acceptance).

d. Controversy in Epilepsy: For emerging areas related to epilepsy care and research for which there is more opinion than high quality data, Epilepsia uses the Controversy series as a venue. Authors can propose a pro- con-position each limited to 2000 words. Contact the editors at epilepsia@epilepsia.com before submitting in this series.

(2) Editorially-reviewed material (to be submitted by email to the Editors-in-Chief at epilepsia@epilepsia.com, except letters and commentaries which should be submitted online at http://mc.manuscriptcentral.com/epilepsia). Other contributions that do not report original research will be published at the discretion of the Editors-in- Chief, with only editorial review. Such material includes: workshop reports and conference summaries, obituaries, letters/commentary to the Editors (500 word limit, and only exceptionally figures or tables), special (brief) reports from ILAE Commissions or other working groups, and announcements. Such material will usually be published in **Gray Matters**.

(3) Supplements (to be submitted as directed by the Editors-in-Chief) Supplements, including meeting abstracts, will be published only after advance arrangements are made with the Editors-in-Chief. Guidelines for preparing supplements are given below. Proposal for, and questions about supplements should be directed to one of the Editors-in-Chief

(epilepsia@epilepsia.com). Such proposals must be explicitly approved by the Editors-in-Chief, who will also confirm the page rate charge for the proposed supplement.

(4) Special reports: In some cases, special reports from ILAE Commissions or other broadly constituted working groups will be published after peer review. The corresponding author of such papers should confer with the Editors-in-Chief to determine if the full manuscript will be peer-reviewed, or whether only a short version will be considered for publication in *Epilepsia's* Gray Matters (see below).

MANUSCRIPT PREPARATION

General Style Guidelines

Manuscripts are to be submitted (and will be published) in English. Writers not fluent in English should seek assistance to ensure proper grammar and syntax, and to help generate a manuscript organization that facilitates reader understanding. Authors for whom English is a second language may choose to have their manuscript professionally edited before submission, to improve the English. A list of independent suppliers of editing services can be found at http://wileyediting services.com/en/. 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. The Editors will not re-write papers submitted in unacceptable English, and will return such manuscripts for revision before sending them out for review. Use international non-proprietary (generic) names when referring to drugs; avoid proprietary (brand) names. All acronyms should be spelled out at first mention. Spell out numbers below 10 and all numbers that are used to begin a sentence; use Arabic numerals for numbers above 10 and for units of measure. Manuscript text should be double spaced with at least 1 inch margin on all sides using size 12 font. Word limits for each type of submission will generally be enforced unless there are good reasons not to do so. If manuscripts exceed these guidelines, authors should submit a cover letter explaining why the additional length is necessary. Authors are encouraged to use the most recent terminology of seizures and epilepsy (Fisher et al., 2014) and epilepsy classification of the ILAE (Berg et al., 2010). Studies involving treatments should adhere to ILAE's classification of medically refractory epilepsy (Kwan et al., 2011).

Manuscript Format

a. Critical Reviews and Invited Commentaries

Title Page (see Full-Length Original Research below)

Summary and Key Words

Reviews and commentaries should generally begin with a summary (less than 300 words) of the content. The summary (structured) should provide the reader with the main points of the paper, and be divided into Objective, Methods, Results, and Significance. The Summary should be followed by a list of 3-6 Key Words; please provide Key Words that will assist in the indexing of your article (i.e., make it easy for individuals who are searching PubMed to find your paper). Do not use words already incorporated into your title (those words are picked up automatically by the indexing service).

Body of review

There is no designated structure for the body of Reviews or Commentaries. Authors are encouraged, however, to use sub-headings to separate major sections and to facilitate clarity and to use figures and tables to illustrate the key issues of the document. Tables, figures, figure legends, references, acknowledgements, statement of compliance with the Journal's guidelines for ethical standards in publishing, disclosure of conflicts of interest, and Supplementary material as for *Full-Length Original Research* (see below)

b. Full-Length Original Research, Special Reports, and

Brief Communications

Title Page

Include the following information: Full title of the manuscript which generally should be as concise and precise as possible; authors' names (first and last names, middle initial when commonly used by that author); institutional affiliation for each author (use superscripted numbers after each author's name, and a corresponding superscripted number before each institutional affiliation); contact information for the corresponding author (name, address, telephone number, fax number, e-mail address); running title (no more than 40 characters and spaces in length); Key Words for use by abstracting services (same as following summary); number of text pages; number of words; number of references; number of figures; number of tables.

Summary and Key Words

Provide a summary of no more than 300 words (200 words for Brief Communications). The summary for Full Length Original Research reports should consist of four sections, labelled: Objective; Methods; Results; Significance. This structured summary should concisely and

specifically describe why and how the study was performed, the essential results, and what the authors conclude from the results. To promote brevity, authors may use phrases rather than complete sentences. The summary for Special Reports, Invited Commentaries, and Brief Communications is not structured, but should cover the same topics as the structured summary. The summary (structured or unstructured) should be followed by 3-6 Key Words (see above). A second short summary (less than 100 words) is required for Brief Communications that can be used in the print issue Table of Contents. Submit the second short summary as a Supporting Document.

Key Point Box

Include 3 to 5 key bullet points that summarize your article after the main body of text. Please ensure each bullet point is no longer than 140 characters. (A key point box is not needed for Brief Communications). An example of a key point box can be found on the Epilepsia Scholar One Manuscripts website (http://mc.manuscriptcentral.com/Epilepsia); please click “Instructions and Forms” at the top right-hand corner of the homepage.

Introduction

State the objectives of the study clearly and concisely, and provide a context for the study by referring judiciously to previous work in the area. Do not attempt to present a comprehensive view of the field. Provide a statement about the significance of this research for understanding and/or treating epilepsy.

Methods

Describe the research methods in sufficient detail that the work can be duplicated; alternatively, give references (if they are readily accessible) to previous comprehensive descriptions. Identify the statistical procedures that were used and the rationale for choosing a particular method, especially if it is not standard. Reports of experimental studies on humans must explicitly certify that the research received prior approval by the appropriate institutional review body and that informed consent was obtained from each volunteer or patient. Studies involving animals must include an explicit statement that animal care and use conformed to institutional policies and guidelines. When animals are subjected to invasive procedures, details must be provided regarding the steps taken to eliminate/minimize pain and suffering, including the specific anesthetics, analgesics, or other drugs used for that purpose (amounts, mode of delivery, frequency of administration). If extensive descriptions of methods are needed, provide basic information with in the text and submit supplementary information for online Supporting Information.

Results

Results should be reported fully and concisely, in a logical order. Do not repeat methodological details from the Methods section. Where possible, use figures and/or tables to present the data in a clear and concise format. Do not repeat data in the text that are given in a table, but refer to the table. Provide textual explanations for all figures, with clear reference to the figure(s) under discussion. Descriptive information provided in figure legends need not be repeated in the text; use the text, however, to describe key features of the figures. When appropriate, give sample numbers, the range and standard deviation (or mean error) of measurements, and significance values for compared populations.

Discussion

Provide an interpretation of the results and assess their significance in relation to previous work in the field. Do not repeat the results. Do not engage in general discussion beyond the scope of the experimental results. Conclusions should be supported by the data obtained in the reported study; avoid speculation not warranted by experimental results, and label speculation clearly. Discuss the significance of the data for understanding and/or treating epilepsy.

Statistical Methods

The following guidelines assume familiarity with common statistical terminology and methods. We recommend that authors consult a biostatistician during the planning stages of their study, with further consultations during the analytical and interpretational stages.

1. Analysis guidelines:

- Use robust analytic methods when data are skewed.
- Use Kaplan Meier methods, Cox Proportional Hazards, and mixed models analyses for longitudinal data.
- Account properly for statistical outliers.
- Use exact methods as much as possible in analyses of categorical data.
- Use appropriate correction procedures to account for multiple comparisons, and conduct post-hoc comparisons with statistically appropriate methods.

2. Presentation guidelines:

- Report means accompanied by standard deviations standard errors should not be used.
- Present results with only as much precision as is appropriate.
- Present confidence intervals, whenever possible, including in figures.

- Describe quantity of missingness and methods used for handling such missingness.
- In general, present two-sided p-values. P-values larger than 0.01 should be reported to two decimal places, those between 0.01 and 0.001 to three decimal places, and those smaller than 0.001 should be reported as $p<0.001$.
- In reporting clinical trials, include a flow diagram, a completed trial checklist, and trial registration information. The CONSORT flow diagram and checklist are recommended (http://www.consortstatement.org/).

Acknowledgements

Acknowledge sources of support (grants from government agencies, private foundations, etc.); including funds obtained from private industry. Also acknowledge(consistent with requirements of courtesy and disclosure) participation of contributors to the study who are not included in the author list.

Disclosure of Conflicts of Interest

In addition, each author should provide full disclosure of any conflicts of interest. One of the following sentences must be included at the end of the paper: either “Author A has received support from, and/or has served as a paid consultant for .... Author B has received support from.... The remaining authors have no conflicts of interest” Or “None of the authors has any conflict of interest to disclose.” Note: Disclosure is needed for financial income/payment from commercial sources, the interests of which are relevant to this research activity. Please identify sources from which financial assistance/income was obtained during the period of the research activity and generation of the current report. Grants from government and/or private agencies should be identified in the Acknowledgements section.

Ethical Publication Statement

All papers must include the following statement to indicate that the authors have read the Journal’s position on issues involved in ethical publication (see below) and affirm that their report is consistent with those guidelines: “We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.”

References

Authors are responsible for the accuracy of their references. References should follow a modified Vancouverstyle format. Citation of references in the text should be in superscript

numbers (including those in figure legends and tables). Cite the end references in numerical order. The first three authors should be listed and followed by et al. Use journals' PubMed abbreviations in the reference list at the end of the paper (as opposed to journals' names being written out in full). Reference program patches are available on the Epilepsia Scholar One Manuscripts website (http://mc.manuscriptcentral.com/Epilepsia); please click "Instructions and Forms" at the top right-hand corner of the homepage.

Number of references is limited to the following:

Full Length Original Research Paper - 40

Brief Communications - 15

Reviews - 80

Special Reports - 80

Sample References:

Journal Article

Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia2010; 51: 676-685.

Journal article published electronically ahead of print version

Reilly C, Atkinson P, Das KB et al. Academic achievement in school-aged children with active epilepsy: A population-based study. Epilepsia Epub 2014 Oct 20.

Journal article In Press

Battino D, Tomson T, Bonizzoni E, et al. Seizure control and treatment changes in pregnancy: Observations from the EURAP epilepsy pregnancy registry. Epilepsia (in press 2013)

Letter

Marucci G. Commentary on the new ILAE classification system for focal cortical dysplasias. Epilepsia2012; 1:219-220. Letter

Published Abstract

Noe K, Drazkowski J. Safety of Long-Term Video EEG Monitoring. Epilepsia 2008; 59 (suppl 7):1.125. Abstract

Book

Shorvon S. Handbook of the treatment of epilepsy. Oxford: Blackwell Publishing; 2005

Chapter in a Book

Fraser RT, Gumnit RJ, Thorbecke R, et al. Psychosocial rehabilitation: A pre- and postoperative perspective. In Engel J (Ed) Surgical treatment of the epilepsies.2nd Ed. New York: Raven, 1993:669-667

Online

Russo CA, Elixhauser A. Hospitalizations for Epilepsy and Convulsions, 2005: Statistical Brief #46. Availableat:http://www.hcup-us.ahrq.gov/reports/statbriefs/sb46.jsp. Accessed February 12, 2011.

Figure legends

Number each legend sequentially to conform to the figure number (e.g., Figure 1, Figure 2...). The legend should provide a brief description of the figure, with explanation of all symbols and abbreviations. Written permission to use non-original material must be obtained(from the original authors (where possible) and publishers) by the authors. Credit for previously published material (author(s), date, journal/book title, and publisher) must be included in the legend.

Tables

Tables should be formatted as the authors wish the table to appear in print. Present all tables together at the end of the manuscript, with each table on a separate manuscript page. Each table should be given a number and a descriptive title. Provide notes and explanations of abbreviations below the table, and provide clear headings for each column and row. Do not duplicate data given in the text and/or in figures. Written permission to use non-original material must be obtained (from the original authors (where possible) and publishers) by the authors. Credit for previously published material (author(s), date, journal/book title, and publisher) must be included in the table notes.

□Figures

All figures should be prepared with care and professionalism. Submissions that do not comply with the following formatting requirements will be returned for correction and re-submission. Figures should be submitted as TIFF files in the size expected for final publication-approximately 3 inches (7-8 cm) for half column and 6 to 7 inches (15-17 cm) for double columns. Submit black and white figures with a minimum of 300 dpi (MRI scans)and for line drawings or figures that included imbedded text (bar graphs with numbers) at least 600 dpi. Complex figures (including photographs, micrographs, and MR-related images), either in colour, in half-tones, or in black and white, should also be submitted in TIF format with a resolution of at least 600 dpi. We recommend saving the TIF files with LZW compression (an option when you 'save as' in packages like Photoshop), which will make the files smaller and quicker to upload without reducing the resolution/quality. Save each TIF file with a name that includes the first author's last name and the figure number as referenced in the text (e.g., Smith-fig1.tif). Provide clear labels on the ordinate and abscissa. Figures with more than one part should be combined by the authors in the correct orientation and labelled with A,B, C etc. When relevant, include calibration information. Label figures using Calibri font and be sure that all labels are large enough to be clearly legible when the figure is reduced to fit onto a journal page. The maximum size of any figure is 7x9 in (17□22.5 cm) and 40 mega pixels; the total number of pixels for each figure (i.e., height□width) must be less than 40 megapixels otherwise the image will not convert to PDF for review. There is no charge for colour figures. We strongly encourage authors to generate figures in colour (to enhance clarity of presentation and aesthetic appeal), using the following colour palette:

Color #	RGB Definition	CMYK Definition
#e4b8b4	228/184/180	0/25/15/9
#ce8080	206/128/128	0/50/30/18
#a30234	163/2/52	0/100/60/37
#511d24	81/29/36	42/85/67/60
#f1b682	241/182/130	0/29/50/4
#e37c1d	227/124/29	0/58/100/8
#ffdf76	255/223/118	0/11/64/0
#abb47d	171/180/125	13/0/47/27
#67771a	103/119/26	27/0/94/55
#a1c5cb	161/197/203	25/0/7/16
#5698a3	86/152/163	50/0/14/32
#00545f	0/84/95	100/0/28/64
#002f30	0/47/48	87/34/47/77
#bacfec	186/207/236	25/11/0/0
#0076c0	0/118/192	100/46/0/0
#002157	0/33/87	100/75/0/60
#7a5072	122/80/114	50/73/30/18

Photographs or videos of patients should not reveal patient identity; masking eyes and/or other identifiers is compulsory unless the eyes are essential to the meaning of the photograph or video. In addition, such photographs and videos must be accompanied by a letter saying that signed consent forms authorizing publication have been obtained for all identifiable patients, and that the consents will be maintained by the author for seven years or until the patient reaches 21 year sof age, whichever is longer. Do not send Epilepsia the consent forms; U.S. Federal privacy rules prohibit sending signed consent forms to Epilepsia or Wiley-Blackwell Publishing without written permission from the patient to do so. A sample signed consent form can be found on the Epilepsia Scholar One Manuscripts website (http://mc.manuscriptcentral.com/Epilepsia);please click ‘Instructions and Forms’ at the top right-hand corner of the homepage.

Supporting Information

Supporting information, to be published online only, can be submitted for review. Such material may include: additional figures, large tables, videos, etc. that cannot be accommodated within the normal printed space allocation for an article-but provide important complementary information for the reader. As determined by the reviewers and Editors, supporting information will be posted on the Wiley Online Library Epilepsia server and directly integrated into the full-text HTML article. Explicit reference to the supporting information in the main body of the text of the article is recommended, and the material must be captioned at the foot of the text, below the reference list. Supporting information will be published as submitted and will not be corrected or checked for scientific content, typographical errors or functionality. Although hosted on Wiley Online Library, the responsibility for scientific accuracy and file functionality remains entirely with the authors. A disclaimer will be displayed to this effect with any supporting information published. Supporting Information files should be accompanied by detailed information (if relevant) about what they are and how they were created (e.g., a native data set from a specific piece of apparatus). Acceptable formats for supporting information include: General Standard MS Office format (Word, Excel, PowerPoint, Project, Access, etc.); PDF Graphics GIF; TIF (or TIFF); EPS; PNG; JPG (or JPEG); BMP; PS (postscript); embedded graphics(e.g. a GIF pasted into a Word file) are also acceptable. Video-QuickTime; MPEG; AVI. All video clips must be created with commonly-used codecs, and the codec used should be noted in the supplementary material legend. Video files should be tested for playback before submission, preferably on computers not used for its creation, to check for any compatibility issues. Video clips are likely to be large; try to limit their size to less than10 MB.

c. Gray Matters

Title

Letters, workshop reports, etc. should be given a brief title. Letters should start with the opening *To the Editors*:

Authors and affiliations

Provide authors' names (first and last names, middle initial when commonly used by that author); institutional affiliation for each author (use superscripted numbers after each author's name, and a corresponding superscripted number for each institutional affiliation);e-mail contact address for the corresponding author.

Body of submission

Letters and commentaries should be restricted to 500words or less, unless otherwise allowed by the Editors. Figures and tables will be included only in exceptional cases. Gray Matters will not be used to publish case reports. Tables, figures, figure legends, references, acknowledgements, disclosure of conflicts of interest, ethical publication statement and Supporting Information-as for *Full Length Original Research* (see above).

(3) Details of Preparation

Detailed instructions for all aspects of electronic manuscript submission (including useful information on image files) is available on the Epilepsia Scholar One Manuscripts website (http://mc.manuscriptcentral.com/Epilepsia); please click 'Instructions and Forms' at the top right-hand corner of the home page; then click on the link 'Instructions to Authors'.

a. Text

Manuscripts should be prepared using a word processing program. Save text and tables as a Microsoft Word document. Place the lead author's name and the page number in the upper right hand corner of each page. Begin numbering with the Title Page as #1, and number pages consecutively including references, figure legends, and tables. Text (including acknowledgements, disclosure statement, and figure legends) and references should be double-spaced, and be composed in 12 point font (preferably Times New Roman). When generating a revised manuscript, identify the altered portions of the manuscript with highlighted text, underlined, colored or bold font to indicate where changes to the original version of the text have been made.

b. Tables, Figures, and Supporting Information

See above.

MANUSCRIPT SUBMISSION

(1) Online submission via Manuscript Central Manuscripts should be submitted via the Journal's website on Scholar One Manuscripts at http://mc.manuscriptcentral.com/epilepsia. Instructions at the site will guide the author through the submission process. Separate files should be submitted for: Cover letter to editors, manuscript text, tables, each figure, supplemental material, permissions to use previously published material, patient consent declaration.

(2) Cover letter

All manuscripts should be submitted with a cover letter, addressed to the Editors-in-Chief, which explains why the manuscript should be published in *Epilepsia*. In particular, authors should identify novel findings, innovative approaches, and important insights that would make the manuscript of particular value to the broad readership of *Epilepsia*.

(3) Text, table and figure files

All files should be given a label that includes the first author's last name and the nature of the file (e.g.,Smith-manuscripttext.doc; Smith-Fig1.tif).

(4) Other materials/forms

At the time of submission, all other materials (e.g., permission forms, supplemental material, patient consent) must be uploaded onto Manuscript Central, faxed to the editorial office (Fax: +1-702-548-0706) or emailed to epilepsia@epilepsia.com.

(5) Questions/Contacts

Questions and request for assistance should be addressed to the Journal at epilepsia@epilepsia.com. The Managing Editor, Ms. Laurie Beninsig will in most cases be able to provide direction, or will contact the Editors-in-Chief for further assistance.

MANUSCRIPT PUBLICATION

(1) Once accepted for publication, authors are required to provide a portrait colour photograph of the first author (1.5 inches-1.5 inches (3 -3 cm), 300 dpi light coloured background) along with a one sentence line describing who they are (limited to 100 characters with spaces) to be included in the title page

(2) The Editors may approach authors to provide one or two of their figures as possible cover material for the printed journal. These figures will need to be large enough and with the appropriate dpi.

(3) Online tracking of your article

Online production tracking of your article is available through Blackwell's Author Services. Author Services enables authors to track their article once it has been accepted through the production process to publication online and in print. Authors can check the status of their articles online and choose to receive automated e-mails at key stages of production. The

corresponding author will receive an e-mail with a unique link that enables him/her to register and have the article automatically added to the system. To facilitate this service, please ensure that you provide a complete e-mail address when submitting the manuscript. Visit http://authorservices.wiley.com/bauthor/ for more details on online production tracking and for other publication resources (including FAQs and tips on article preparation, submission and more).

(4) Proofs

Proofs are sent electronically in a PDF format, and must be returned within 48 hours of receipt. Late returns of proofs will cause substantial delay in article publication. It is the corresponding author's responsibility to see that the proof is accurately checked and corrected, and to return the proofs promptly to avoid publication delays. Please check the spelling of co-authors' names and affiliations, text, tables, legends, and references carefully. It is the authors' responsibility to make sure that the information is accurate. Indicate corrections either using the PDF editor function (so as to return proofs electronically to eeeproofs@aol.com), or with clear hard-copy indications which should be faxed to +1 508-586-4024. The proof corrections stage is not the time for fine-tuning language or making any other substantive changes. Confine corrections to errors in printing; authors may be charged for major author-initiated changes.

(5) Early View

The publication-ready PDF of an article will be published initially online. Early View publication will precede print publication by a variable time period. The online publication date will be considered the official publication date. Early View published material will be indexed by PubMed, and can be cited by DOI number. In general, manuscripts will be published on Early View within 35 business days of the publisher's receipt of the complete accepted manuscript (including CAF and permission forms).

(6) Print issue publication

Publication of an article in a print issue will typically occur after Early View publication. Print issue articles carry their electronic publication date.

(7) Public access of accepted/published articles

Prior to acceptance, articles may be shared (print or electronic copies) with colleagues; at this time the article may be posted on the author's personal website, on his/her employer's website, and/or on free public servers in the author's subject area - with the acknowledgement that the article has been submitted to Epilepsia. After an article has been accepted, authors may share

print or electronic copies of the article (accepted and revised to address peer review) with colleagues, and may use the material in personal compilations, other publications of his/her own work, and for educational/research purposes. Articles published in Epilepsia are freely accessible to the public via the Wiley Online Library website one year after publication. Epilepsia will automatically upload NIH-supported studies to PubMed Central after a 12 month moratorium (provided the appropriate funding acknowledgement has been provided). Similarly, at this time authors may post an electronic version of the article on their own personal websites, on their employer's website/repository, and on free public servers in the relevant subject area. Electronic versions of the accepted (or published) article must include a link to the published version of the article, together with the following text: "The definitive version is available at http://www3.interscience.wiley.com/journal/117957420/home." Authors can also choose to make their articles open access and available free for all readers through the payment of an author fee. This facility allows authors to fulfil the requirements for studies supported by agencies requiring open access before 12 months. For full details visit http://authorservices.wiley.com/Bauthor/onlineopen.asp

(8) Reprints

An order form for reprints will be included with the electronic transmission of initial proofs. For pricing of quantities in excess of 500 copies, please contact Beverly Lawrence at Wiley-Blackwell Publishing (blawrence@wiley.com).

SUPPLEMENT PUBLICATION

(1) Policy

A decision to publish a supplement is based on the topic, Guest Editor, proposed table of contents and contributing authors, and availability of necessary funding. Supplement topics must be of importance to Epilepsia readers, and supplements will be published only if there is scientific or educational rationale for combining papers on a given theme within one publication. The number and quality of the articles must be sufficient to constitute a body of important information. Each supplement will have a Guest Editor who is an expert on the theme of the supplement. The Guest Editor is responsible for compiling articles and assisting with the editorial process, and is responsible for the overall quality and integrity of the supplement. The publication of a supplement usually incurs charges, payable to Wiley-Blackwell Publishing.

(2) Publishing guidelines

Articles in a supplement are subject to the same copyright regulations and ethical publishing guidelines that apply to articles published in regular issues of Epilepsia. All supplement articles are peer-reviewed; the first level of review is carried out by the Guest Editor and his/her designates. The second level of review will include the articles being sent out for peer review.

(3) Online only and print supplements

Abstract supplements, from meetings or congresses sponsored by the ILAE or its chapters, will generally be published online only. Longer articles will be published in print supplements (these articles will also appear online). Print supplements may be generated from proceedings of symposia organized by an independent body of professionals in which the funding organization does not have a controlling voice on scientific content. The Guest Editor and/or organizers of such symposia should be members of ILAE chapters. Supplements from other sources including invited supplements initiated by the Editors-in-Chief will also be considered.

(4) Supplement content

The content of supplements must not be biased in the interest of any sponsor. Epilepsia does not permit presentations that extol a commercial product, and supplements should not be perceived as endorsing a particular product. Publication of supplements does not constitute product or sponsor endorsement by Epilepsia or ILAE. In most cases, supplements should not focus on a single product; however, when a new product is introduced, a single product focus will be considered by the Editors-in-Chief. In all cases, the content of a supplement must be determined by a body of professionals working independently of the sponsor. The Guest Editor is charged with assuring that the material presented in the supplement is not biased toward the interests of the product manufacturer.

(5) Supplement sponsorship

Most supplements require external sponsorship. When a supplement proposal is presented to the Editors-in-Chief, they will fix appropriate fees. Supplement costs may be negotiated with the Editors-in-Chief and the publisher’s supplement representative. The Editors-in-Chief may choose to publish a supplement of particular academic and clinical value without external sponsorship.

(6) Instructions for submitting supplements

Agreement to publish a supplement must be obtained from the Editors-in-Chief prior to submission. Proposals for supplements should be submitted to the Editors-in-Chief (Epilepsia@epilepsia.com) well in advance of desired publication date, so that the proposal can be evaluated and discussed. Timing is especially critical if the supplement is linked to a symposium or congress, since rapid publication is often important to assure that the information is current. The proposals should identify the Guest Editor and include a list of topics and potential authors. The proposal should include an estimate of supplement length so that the Editors-in-Chief can provide reasonable information about the cost of publication. The cost of any supplement, and related financial issues, should be discussed with Michael Targowskiat Wiley-Blackwell Publishing (mtargowski@wiley.com). Collection of manuscripts, as well as initial editing and reviewing should be carried out by the Guest Editor on a schedule predetermined in discussion with the Editors-in-Chief. The Guest Editor is responsible for timely submission of articles, and should expect to assist the Editors-in-Chief in collecting final revised manuscripts (including any required permissions).

(7) Format of supplement articles

In general, articles should follow the format described above for Critical Reviews (in regular issues of the Journal). Contact the Editors-in-Chief for additional information and special instructions.

Epilepsia'*s* POSITION ON ISSUES INVOLVED IN ETHICAL PUBLICATION

(1) Authorship/Credit

Epilepsia follows the guidelines of the International Committee of Medical Journal Editors regarding criteria for authorship (http://www.icmje.org/). The author list should include those who have made substantial intellectual/conceptual contributions to the work. Such contributions should include participation in: (a) experimental design, data acquisition, and analysis and interpretation of data; (b) drafting and/or critically revising the article with respect to intellectual content; and (c) final approval of the manuscript version to be published. We strongly discourage the inclusion of “honorary” authors (individuals who are listed as authors but have not contributed to the work/manuscript - e.g., heads of departments) and „ghost‰ authorship (individuals who have substantively contributed to the work and/or manuscript but are not listed as authors or contributors). In cases where writing support is necessary, the writer(s)should be acknowledged in the Acknowledgements section, and the source of funding for writing support should be provided under Disclosure of Conflicts of Interest. The corresponding/ submitting

author must, when submitting a manuscript, give assurance that all authors have read and approved the submitted manuscript. The corresponding/ submitting author should also give assurance that all authors have seen and approved the final (accepted) manuscript, and that the manuscript includes all conflict of interest declarations. All individuals who have contributed to the work but do not meet criteria for authorship should be cited in the Acknowledgement section.

(2) Funding

Sources of funding (for the research, data analysis, and manuscript generation) should always be disclosed in the Acknowledgements section. Sources may include government funding agencies, institutions and departments, private industry, and charitable organizations and foundations. Funding for all authors should be acknowledged.

(3) Procedures involving Human and Animal Subjects

The authors should include within the manuscript an explicit statement indicating that the submitted study was approved by the relevant research ethics committee or institutional review board (IRB). When the study involves human participants (including material from human subjects), authors should also provide assurance that appropriate consent was obtained. When studies involve animal subjects, authors should provide methodological details about steps taken to minimize pain/discomfort. Such papers must contain a statement that affirms that the experimental protocols were approved by the institutional animal care and use committee (IACUC).

(4) Confidentiality

In all cases, information and images derived from individual patients must be presented with assurance of appropriate consent and with details removed that might reveal identity of the individual.

(5) Disclosure

All authors are required to disclose associations which might affect their ability to present and/ or interpret data objectively, particularly financial ties to funding sources for the work under review (e.g., membership on corporate scientific boards, stock ownership, consultant arrangements, patent ownership or application, etc.). Disclosure of such associations for the Editorial personnel of Epilepsia (Editors-in-Chief, Associate Editors, Editorial Board members) will be published each year. Reviewers will also be asked to affirm that they have no conflict of interest when critiquing a manuscript.

(6) Research Misconduct (Data Fabrication/ Falsification)

Epilepsia will attempt to ensure that any allegations of misconduct are properly investigated. In the case of any allegations, authors will be given a right to respond. While the Journal is limited in its ability to investigate misconduct, we will seek COPEÊs advice and alert appropriate bodies and encourage them to investigate.

(7) Plagiarism, Duplication, and Redundant Publication

Epilepsia requires that work submitted for publication is the authors' own work and has not been misappropriated. When previously published material is used, appropriate credit must be given and written permission obtained (for use of copyrighted material). Epilepsia also explicitly discourages duplication of published material and redundant publication. All manuscripts submitted to Epilepsia are checked with the iThenticate software to detect instances of overlapping and similar text. In the case of apparent or substantial overlap, authors will be asked to rewrite their article.

(8) Corrections of Erroneous Information

Authors are expected to proof-read their articles carefully before returning page proofs for publication. They should make needed corrections at this time. We recognize that it is only human to err occasionally, and the Journal is committed to correcting mistakes when those errors affect the interpretation of data or information presented in an article. Such corrections will be published in the form of an Erratum, and linked to the original article electronically. Errors that result from author oversight in the proofing process, and that do not affect data interpretation, will not be corrected.

(9) Peer Review

Epilepsia is committed to a peer-review system that is fair to the author and enhances the value of the articles published in the Journal. In order to encourage qualified reviewers to offer their time and efforts to the Journal, reviewer identity is kept confidential. Reviewers are chosen for their expertise in the field; conflicts of interest are avoided whenever the Editors are aware of such issues, and reviewers are asked to affirm that they have no conflicts of interest in reviewing a given Epilepsia manuscript. Authors are encouraged to identify specific individuals who, they believe, cannot provide unbiased review. While the Editors-in-Chief reserve the right to make the final decision to accept or reject an article, appeals will be seriously considered. Address appeals to the Editors-in-Chief, who will examine the reviews and the author

responses, consult the relevant Associate Editor, and seek additional reviewer input if deemed necessary.

ANNEXURE J: SUBMISSION OF MANUSCRIPT 1

Dr Johanita Riétte Burger:

Thank you for submitting the manuscript, "Anti-epileptic prescribing patterns in the South African private health sector (2008-2013)" to South African Family Practice. Please note that we have changed the journal platform to Editorial Manager. Please register as a new user of this platform and upload your submission there.

Editorial Manager website: http://www.editorialmanager.com/safpj

Your manuscript will be placed in the review process from that platform.

Please note that we will archive this submission on this platform within one week of today's date.

Thank you and kind regards
Robyn Marais
South African Family Practice

South African Family Practice journal
http://www.safpj.co.za

ANNEXURE K: SUBMISSION OF MANUSCRIPT 2

Dear Dr. Burger:

This is a computer generated message.

Thank you very much for submitting your manuscript to EPILEPSIA. Your manuscript entitled, Patient adherence with anti-epileptic drugs in the private health sector of South Africa: 2008-2013 has been successfully uploaded to Manuscript Central.

Please make note of your manuscript number: EPI-00909-2015. We will direct all future communications to you, the corresponding author, via e-mail.

We attempt to complete the review process as fast as possible, and EPILEPSIA is making strenuous efforts to ensure as short a turn-around time as is compatible with a high quality peer review process. Manuscript processing is entirely dependent on the timeliness of our reviewer feedback. It typically takes one week to assign reviewers and another 2-3 weeks to obtain reviews. If a reviewer does not return his/her comments within four weeks, another reviewer may be invited. Reminders are sent to tardy reviewers, but I'm sure you can understand that the requested deadline cannot be enforced.

Revised manuscripts are sent to the original reviewers unless the revisions are minor, in which case the Editor will usually make a final decision on the manuscript him/herself.

You can keep track of your manuscript by logging on
and checking the status in your Author Center.
URL: https://mc.manuscriptcentral.com/epilepsia
User ID: johanita.burger@nwu.ac.za
Password: https://mc.manuscriptcentral.com/epilepsia?URL_MASK=5ade10cf48324d12ada0c8cd043971be

Thank you for your interest in EPILEPSIA.

Sincerely,

Gary Mathern, Astrid Nehlig and Michael Sperling
Editors-in-Chief, Epilepsia

ANNEXURE L: PROOF OF LANGUAGE EDITING

To whom it may concern

Cecile van Zyl
Language editing and translation
Cell: 072 389 3450
Email: Cecile.vanZyl@nwu.ac.za

6 October 2015

Dear Mr / Ms

Re: Language editing of dissertation: **An analysis of medication adherence among epileptic patients in the private health sector of South Africa**

I hereby declare that I language edited the above-mentioned dissertation (in article format) by Ms K Jacobs (student number:22061320) during October 2015.

Please feel free to contact me should you have any enquiries.

Kind regards

Cecile van Zyl

Language practitioner

BA (PU for CHE); BA honours (NWU); MA (NWU)