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

Karen Jacobs*, Marlene Julyana, Martie S Lube*, Johanita R Burger**, and Marike Cockeran**

*Medicine Usage in South Africa, Faculty of Health Sciences, North-West University, Potchefstroom Campus, Potchefstroom, South Africa
**Corresponding author. Email: Johanita.Burger@nwu.ac.za

Background: Little is known about longitudinal prescribing practices for anti-epileptic drugs (AEDs) in South Africa. The prescribing patterns and associated direct medicine costs of AEDs in the private health sector were investigated, using claims data from January 1, 2008 to December 31, 2013.

Methods: The annual prevalence of prescriptions, AEDs and AED generics per patient with epilepsy (ICD-10 code G40) was determined. Cost analyses conducted included the calculation of the total direct cost of AEDs (medical scheme contribution, patient co-payment, and single exit price (SEP)), and the average cost per AED per year.

Results: Prevalence of patients claiming anti-epileptics ranged between 0.87% and 0.91% from 2008 to 2013. AED prescriptions/patient ranged from 11.76 (95% CI, 11.56–11.95) in 2008 to 11.90 (95% CI, 11.71–12.09) in 2013. Patients aged 40–65 years had the highest number of AED prescriptions/year. Valproate was most prescribed, followed by lamotrigine and carbamazepine. Average cost per AED increased from R237.12 (95% CI, 233.58–240.65) in 2008 to R522.32 (95% CI, 515.24–529.41) in 2013, while the average patient co-payments increased from R27.76 (95% CI, 26.63–28.89) to R264.32 (95% CI, 260.61–268.03). Prescribing of generics increased by 12.84%.

Conclusions: Generic prescribing increased over time; however, patient co-payments increased dramatically.

Keywords: anti-epileptic, direct medicine costs, longitudinal, medicine claims database, prescribing patterns, South Africa

Introduction
Approximately 50 million people worldwide suffer from epilepsy.1 Based on a meta-analysis by Ngugi and colleagues,2 the median prevalence of lifetime epilepsy is 5.8 per 1 000 in developed countries, 10.3 per 1 000 in lower-income or developing countries and 15.4 per 1 000 in rural areas of developing countries. Prevalence studies conducted in South Africa have reported a lifetime prevalence of 7.3 per 1 000 in children of a rural district and an estimated prevalence of 7.0 per 1 000 in a rural north-east district, respectively.3,4

Anti-epileptic drugs (AEDs) are increasingly being prescribed to patients of all ages in populations worldwide,5,6 either as monotherapy or polytherapy.7 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.8,9 The prescribing of first-choice AEDs in particular has changed over the last decade,10 with prescribers tending to prescribe newer AEDs (e.g. gabapentin, lamotrigine, levetiracetam and pregabalin) to patients due to their improved tolerability.11

Anti-epileptic drugs, in particular those that are still under patent such as some of the newer AEDs, are relatively expensive.12–14 Generic substitution of many drug classes is a common health care cost-saving practice;15 however, use of generic antiepileptic drugs in patients with epilepsy is controversial.16

Little is known about the longitudinal prescribing practices for anti-epileptic drugs (AEDs) in South Africa. The aim of this study was therefore firstly to investigate the prescribing patterns of AEDs in the private health sector of South Africa and secondly to determine the total direct 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 (January 1, 2008 to December 31, 2013). Data were obtained from a privately owned South African Pharmaceutical Benefit Management (PBM) company. The PBM currently manages the medicine benefits of 1.7 million beneficiaries on behalf of 40 medical schemes. All of South Africa’s pharmacies and 98% of all dispensing doctors are on this service provider database. Data for 758 505 patients from 2008 were obtained, compared with 1 033 057 from 2009, 968 158 from 2010, 864 977 from 2011, 815 810 from 2012, and 809 857 from 2013. In 2008 these patients represented 9.6% of all beneficiaries covered by medical aid schemes registered in terms of the Medical Schemes Act (Act 131/1998) in South Africa, compared with 13% in 2009, 11.7% in 2010, 10.3% in 2011, 9.5% in 2012, and 9.3% in 2013.17

Data fields used in this study included the following: patients’ member number, patients’ date of birth, treatment date, ICD-10 codes, active ingredients, the quantity of medicine items prescribed and the number of days for which the medicine items were supplied.

Study population
The study population consisted of all patients with an ICD-10 code for epilepsy (G40) as recorded on the database, in
association with a paid claim for an AED during the study period January 1, 2008 to December 31, 2013. Active ingredients (AEDs) were chosen according to the MIMS® classification system.

**Variables**

Variables (age groups and name of active ingredient) were expressed using descriptive statistics such as frequencies, percentages, means and 95% confidence intervals (CI). Patient’s age was calculated according to the patient’s age on his/her treatment date, in relation to his/her date of birth, using January 1 of the following year as an index date. Patients were divided into five age groups: children/adolescents (0 ≤ 12 years), late adolescents (> 12 ≤ 18 years), young adults (> 18 ≤ 40 years), older adults (> 40 ≤ 65 years) and the elderly/geriatrics (> 65 years).

Cost analyses included the calculation of the total direct cost of AEDs (defined as the total amount reimbursed through prescribed minimum benefit, consisting of the medical scheme contribution, the patient co-payment, and the single exit price (SEP)), and the average cost per AED per year, stratified by SEP medical scheme contribution, and patient contribution. The SEP can be defined as the price set by the manufacturer and/or importer for medicines or scheduled substances in terms of regulations, combined with both logistic fee and VAT.18 This is the lowest price of medicines and scheduled substances of a unit within a pack and is multiplied by the number of units in the pack.

Prevalence of AEDs was further determined based on registration status and categorised as ‘generic’, ‘non-substitutable’ or ‘original’. Non-generic medications were those medicines that did not have a generic substitution available on the market during the study period, whereas original medications were defined as brand-name products with an available generic alternative.

**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 ($\chi^2$) was used to determine whether an association exists between proportions of the 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 statistically significant. Cramer’s $V$ was 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.19

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 test 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 was 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.20

**Results**

Patients who received anti-epileptic prescriptions ranged between 0.87% and 0.91% over the study period. AEDs claimed ranged between 0.54% ($n = 90\,086$) and 0.63% ($n = 104\,011$) of the total number of medicine items claimed over the study period. The average number of anti-epileptic prescriptions per patient per year ranged from 11.76 (95% CI 11.56–11.95) in 2008 to 11.90 (95% CI 11.71–12.09) in 2013 (Cohen’s $d = 0.02$). The average number of anti-epileptics per prescription per year increased slightly from 1.42 (95% CI 1.40–1.44) in 2008 to 1.55 (95% CI 1.52–1.57) in 2013, representing a small difference between these years (Cohen’s $d = 0.13$) (Table 1).

The mean age of patients in the study population was 45.61 (95% CI, 45.30–45.93), with slightly more than half of these patients being women (53.82%). 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 $d ≤ 0.314$) to 2013 (Cohen’s $d ≤ 0.244$) ($p < 0.0001$). A very small effect size (Cohen’s

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

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

*Patients claiming at least one prescription for an AED in conjunction with a ‘G40’ diagnosis code.
† ‡ Percentages were calculated according to the total in each respective year.
The active ingredient most frequently prescribed was valproate with a relative increase from 27.39% (n = 24 672) in 2008 to 30.43% (n = 31 729) in 2013. This was followed by lamotrigine with an increased prescribing prevalence from 20.39% in 2008 to 24.63% in 2013. A notable decrease in the prescribing of phenytoin and carbamazepine was observed (Figure 1). The prescribing of these two active ingredients decreased by 5.04% and 4.66%, 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).

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 on AEDs increased by 22.62% from 2008 to 2012, thereafter remaining relatively constant from 2012 to 2013. The patient contribution on AEDs increased by 71.43% from 2008 to 2013, with a 4.35% increase from 2012 to 2013 (Table 3).

The average cost per AED increased by 120.28% from 2008 to 2013, with an increase of 88.62% between 2012 and 2013. The SEP increased by 27.80%, whereas the medical scheme contribution increased by 23.23% from 2008 to 2013. The patient contribution increased drastically by 852.16% from 2008 to 2013, with most of the increase observed between 2012 and 2013 (Table 4).

The prescribing of non-generic medication decreased by 13.14%, whereas that of the generic substitution increased by 12.84% from 2008 to 2013. Prescribing of original medication remained relatively constant. Non-generic medications were the most prescribed (39.85%) overall between the medicine indicators. Based on the medicine indicator, there was a practically significant association between the proportions of drugs within each group over the study period (Table 5).

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

| Variable       | Age groups (years) | 0–12 | 13–18 | 19–40 | 41–65 | > 65 | p-value(ANOVA) |
|----------------|--------------------|------|-------|-------|-------|------|----------------|
|                |                    |      |       |       |       |      |                |
| 2008 (n)       |                    | 433  | 405   | 1568  | 2662  | 1566 | < 0.0001       |
| Average no. of | Average no. of     | 9.95 | 10.29 | 12.48 | 12.07 | 11.39 |                |
| AEPs§ per      | AEPs§ per patient  | (9.22–10.68) | (9.49–11.11) | (12.02–12.93) | (11.76–12.38) | (11.06–11.71) |                |
| patient (95% CI)|                    |      |       |       |       |      |                |
| 2009 (n)       |                    | 591  | 552   | 2265  | 3524  | 2026 | < 0.0001       |
| Average no. of | Average no. of     | 9.94 | 10.56 | 11.82 | 12.32 | 11.84 |                |
| AEPs§ per      | AEPs§ per patient  | (9.29–10.59) | (9.86–11.26) | (11.44–12.19) | (12.04–12.60) | (11.54–12.14) |                |
| patient (95% CI)|                    |      |       |       |       |      |                |
| 2010 (n)       |                    | 540  | 480   | 2102  | 3384  | 2063 | < 0.0001       |
| Average no. of | Average no. of     | 9.55 | 10.29 | 12.26 | 12.30 | 11.54 |                |
| AEPs§ per      | AEPs§ per patient  | (8.92–10.18) | (9.55–11.04) | (11.86–12.66) | (12.01–12.59) | (11.25–11.83) |                |
| patient (95% CI)|                    |      |       |       |       |      |                |
| 2011 (n)       |                    | 472  | 381   | 1909  | 3052  | 2013 | < 0.0001       |
| Average no. of | Average no. of     | 9.78 | 10.81 | 12.28 | 12.90 | 11.98 |                |
| AEPs§ per      | AEPs§ per patient  | (9.11–10.45) | (9.99–11.63) | (11.85–12.71) | (12.58–13.22) | (11.68–12.28) |                |
| patient (95% CI)|                    |      |       |       |       |      |                |
| 2012 (n)       |                    | 427  | 366   | 1783  | 2906  | 1972 | < 0.0001       |
| Average no. of | Average no. of     | 10.00| 10.78 | 12.65 | 12.77 | 10.94 |                |
| AEPs§ per      | AEPs§ per patient  | (9.23–10.78) | (9.98–11.59) | (12.20–13.11) | (12.45–13.09) | (10.61–11.26) |                |
| patient (95% CI)|                    |      |       |       |       |      |                |
| 2013 (n)       |                    | 428  | 360   | 1846  | 3035  | 1718 | < 0.0001       |
| Average no. of | Average no. of     | 10.26| 11.00 | 12.16 | 12.30 | 11.51 |                |
| AEPs§ per      | AEPs§ per patient  | (9.48–11.03) | (10.17–11.85) | (11.72–12.59) | (12.00–12.60) | (11.18–11.83) |                |
| patient (95% CI)|                    |      |       |       |       |      |                |

AEP = anti-epileptic prescription; no. = number.

**Figure 1:** Trends in prescribing of active ingredients over study period.

Discussion

This longitudinal study showed that total anti-epileptic prescribing increased by approximately 0.40% from 2008 to 2013. The active ingredients most frequently prescribed in our study were valproate, lamotrigine and carbamazepine. These AEDs are considered first-line treatment for epilepsy by international and national treatment guidelines. The trend also confirms findings from other international studies.

The majority of patients in the study population were adults (mean age 45 years), with more than half of these patients being women. We observed the highest anti-epileptic prescribing in 2011 and 2012; Cohen’s d = 0.131 between 2009 and 2012) was observed in the group older than 65 years (p < 0.0001). It is likely that the use of AEDs increased with an increase in age (Table 2).
older adults between the ages of 41 and 65 years. Older adults are more prone to epilepsy than the younger generation, due to their risk of developing strokes or brain tumours, which can all cause epilepsy.27 Potential causes of secondary epilepsy can further be attributed to infections such as neurocysticercosis, head traumas and neoplasms. Traumatic brain injury or head injury is one of the most common causes of acquired epilepsy and accounts for 20% of symptomatic epilepsy. According to Lowenstein the likelihood of developing epilepsy after head injury may be as high as 50%.28 Cerebrovascular disease, such as stroke, is the most common cause of epilepsy in the elderly, accounting for up to 40% of epilepsy cases in geriatrics.29 Central nervous system (CNS) infections, whether acute or chronic-recurrent, are the most common cause of epilepsy in the developing world, because of the high incidence rate of CNS infections in these countries. The types of infections vary from country to country.30 A study conducted in 2004 in St Elizabeth’s Hospital in the Eastern Cape of South Africa indicated that 61.1% of their patients had neurocysticercosis-associated epilepsy.31

We also noted a gradual increase in the use of new AEDs with a subsequent decline in the use of older AEDs, confirming trends from a recent European study.1 The shift toward the use of newer AEDs may be attributed to the broader spectrum of action of the cause epilepsy.27 Potential causes of secondary epilepsy can further be attributed to infections such as neurocysticercosis, head traumas and neoplasms. Traumatic brain injury or head injury is one of the most common causes of acquired epilepsy and accounts for 20% of symptomatic epilepsy. According to Lowenstein the likelihood of developing epilepsy after head injury may be as high as 50%.28 Cerebrovascular disease, such as stroke, is the most common cause of epilepsy in the elderly, accounting for up to 40% of epilepsy cases in geriatrics.29 Central nervous system (CNS) infections, whether acute or chronic-recurrent, are the most common cause of epilepsy in the developing world, because of the high incidence rate of CNS infections in these countries. The types of infections vary from country to country.30 A study conducted in 2004 in St Elizabeth’s Hospital in the Eastern Cape of South Africa indicated that 61.1% of their patients had neurocysticercosis-associated epilepsy.31

Similar to a recent study conducted in Germany,25 the move from older to newer AEDs for the treatment of epilepsy may explain the increase in cost of AEDs observed in our study. It was furthermore determined that the majority of medications prescribed or dispensed during the study period were non-generic medications. These non-generic medications are extremely costly and are the potential drivers for increased medical expenditure, as they do not have any generic equivalents available on the market. The escalation in direct medicine costs between 2013 and the previous study years can be attributed to an increase in the maximum SEP, but also to high launch prices for new products and inflation. This cost escalation, however, is much higher in comparison with the ~6% change in the general inflation rate from 2008 to 2013.32 In conjunction with the increase in medicine costs, patient co-payments increased by more than 800% over the study period.

While switching to generic formulations is generally considered to be a cost-saving initiative,15 generic substitution with AEDs in patients with epilepsy is controversial because of the narrow therapeutic index of some of the AEDs, which requires very precise dosing.16,33 The controversy surrounding AED substitution is not only limited to brand name to generic product substitution; switching patient medication from one generic product to another generic product has also been indicated as a potential cause of changes in plasma drug concentrations.15 For example, according to Jobst and Holmes,16 changing patients to generic phenytoin and carbamazepine can be problematic as a result of differences in bioavailability and possible loss of seizure control. Fosphenytoin may further only be cost-effective in certain clinical situations compared with intravenous phenytoin. Substituting AEDs in clinical practice should, therefore, still depend on the individual clinical situation and expert opinion of the prescriber.

### Table 3: Total direct medicine cost stratified by study period (%)

| 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 | 20 282 534.13 (1.37) | 307 322 784.90 | 2 575 203.36 (0.84) |
| 2009 | 2 509 210 770 | 34 647 390.19 (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) |

††PC = Patient contribution.

### Table 4: Average cost per item for each respective year from 2008 to 2013

| Year | Average cost per item (R) | SEP (R) | Medical scheme contribution (R) | Patient contribution (R) |
|------|-------------------------|---------|-------------------------------|-------------------------|
|      | (mean) | 95% CI | (mean) | 95% CI | (mean) | 95% CI | (mean) | 95% CI |
| 2008 | 237.12 | 233.58–240.65 | 2.95 | 2.91–2.99 | 209.36 | 206.10–212.62 | 27.76 | 26.63–28.89 |
| 2009 | 259.24 | 256.09–262.40 | 3.32 | 3.28–3.36 | 227.72 | 224.77–230.67 | 31.52 | 30.50–32.55 |
| 2010 | 271.49 | 268.11–274.86 | 3.50 | 3.45–3.55 | 237.62 | 234.47–240.77 | 33.87 | 32.69–35.05 |
| 2011 | 272.42 | 268.92–275.92 | 3.60 | 3.56 ± 3.65 | 241.72 | 238.48–244.96 | 30.70 | 29.53–31.87 |
| 2012 | 276.91 | 273.22–280.60 | 3.69 | 3.64–3.73 | 249.28 | 245.78–252.79 | 27.63 | 26.50–28.75 |
| 2013 | 522.32 | 515.24–529.41 | 3.77 | 3.71–3.82 | 258.00 | 254.50–261.50 | 264.32 | 260.61–268.03 |

§§Percentages were calculated according to the total patient contribution in each respective year.

**SC = Medical scheme contribution**

††PC = Patient contribution.
Conclusion
The findings of this longitudinal study suggest that prescribers in the South African private health sector generally followed treatment guidelines for epilepsy in terms of first-line drugs prescribed, and the shift towards the use of newer AEDs with broader generic prescribing over time. AEDs were shown to be relatively expensive, with patient co-payments increasing dramatically over the study period. Further studies including prescriber preference and patients’ willingness-to-pay data as factors influencing generic AED substitution would be a logical next step in this field of research. To ensure that every patient with epilepsy receives the best, but also the most affordable health care possible, awareness should be created amongst prescribers and pharmacists with regard to current prescribing patterns of AEDs and subsequent cost implications.

Limitations of study
Since the study population was based solely on ICD codes, it may lead to under-estimation of prevalence in claims data. As per confidentiality agreement with the PBM, all identifying information regarding beneficiaries, medical schemes and health plans was encrypted or removed by the PBM before data were released for analysis. It was therefore not possible to determine the number of schemes administered per year for each year of the study, or whether significant changes in the schemes or treatment formularies under administration occurred in this time period that may potentially influence the calculation of prevalence. Because the claims database reflects only electronically captured reimbursed claims, it was not possible to determine where a generic product is dispensed that is different from the one prescribed.

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 through 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; therefore no patient or medical scheme can be traced.

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Conflict of interest – None to declare.

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