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To cite this article: Karen Jacobs, Marlene Julyan, Martie S Lubbe, Johanita R Burger & Marike Cockeran (2016) Anti-epileptic prescribing patterns in the South African private health sector (2008–2013), South African Family Practice, 58:4, 142–147, DOI: [10.1080/20786190.2016.1148337](https://doi.org/10.1080/20786190.2016.1148337)

To link to this article: <http://dx.doi.org/10.1080/20786190.2016.1148337>



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Published online: 29 Feb 2016.



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

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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 1000 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 comorbidities, 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 ($0 \leq 12$ years), late adolescents ($> 12 \leq 18$ years), young adults ($> 18 \leq 40$ years), older adults ($> 40 \leq 65$ 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 (χ^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 ($> 40 \leq 65$ 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

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.

$d = 0.152$ between 2011 and 2012; Cohen's $d = 0.131$ between 2009 and 2012) was observed in the group older than 65 years ($p < 0.0001$). It is likely that the use of AEDs increased with an increase in age (Table 2).

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

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

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

^aAEP = anti-epileptic prescription; no. = number.

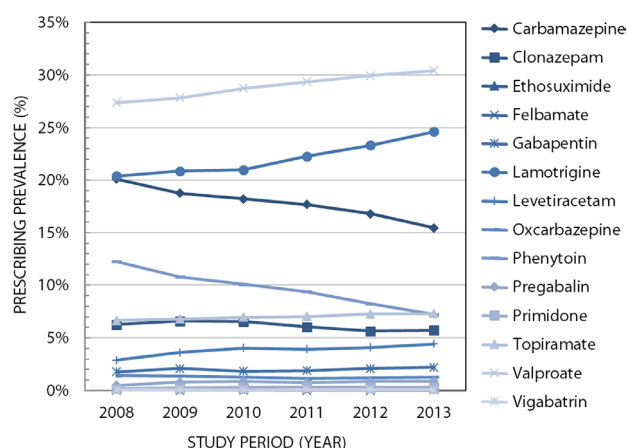


Figure 1: Trends in prescribing of active ingredients over study period.

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).

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.^{21–23} This trend also confirms findings from other international studies.^{8,24–26}

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

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

[†]Percentages were calculated according to the total medical scheme contribution in each respective year.

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

^{**}SC = Medical scheme contribution

^{††}PC = Patient contribution.

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.⁶ The shift toward the use of newer AEDs may be attributed to the broader spectrum of action of the new AEDs in epileptic patients⁸ and wider marketing attributes. The use of these newer AEDs may also be attributed to their improved effectiveness, reduced side effects and ease of use (once-a-day dosing).²¹ The newer AEDs may not be more effective in suppressing seizures alone, but they are more effective overall in treating patients with epilepsy and coexisting conditions.⁹ The shift towards the use of newer AEDs is also supported by national and international treatment algorithms.^{21–23}

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.¹⁶ For example, according to Jobst and Holmes,³⁴ 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 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

^{||||} Single exit price

Table 5: Variance based on the generic indicator (%)

Medicine indicator ^{†††}	Number of items, <i>n</i> (%)	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
<i>p</i> -value		< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	
Cramer's <i>V</i>		0.70	0.68	0.67	0.68	0.68	0.63	

†††Non-generic: medicine without a generic alternative; original: medicine with a generic alternative available; generic: alternative medicine for original.

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.

Acknowledgements – The authors wish to thank Ms Anne-Marie Bekker for administrative support with regard to the database.

Conflict of interest – None to declare.

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Received: 14-10-2015 Accepted: 13-01-2016