

Prescribing patterns of vitamin D and analogues in a private healthcare patient population in South Africa

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Introduction: Numerous studies show the benefits of vitamin D: in the prevention of bone disease, supporting the immune system and the prevention and mitigation of cancer. Until recently, supplementation has been deemed unnecessary. Nonetheless, in the light of emerging evidence, some practitioners are adding vitamin D and its analogues (Anatomic Therapeutic Chemical (ATC) classification code A11CC) to their prescriptions. Therefore, the aim was to determine the medical insurance prescribing patterns of vitamin D in South Africa.

Methods: A retrospective, cross-sectional drug utilisation study was conducted on a South African medical insurance administrator database for 2018. Products in ATC subgroup A11CC (vitamin D and analogues) were extracted and analysed.

Results: A total of 302 patients received 1 164 prescriptions for a vitamin D or analogue product during 2018. The average age of patients was 47.14 (SD = 24.03) years, and the majority were female (58.28%). Very young patients and middle-aged patients received most of the prescriptions. Ergocalciferol (A11CC01) was the most frequently prescribed (59.79%), followed by alfacalcidol (A11CC), colecalciferol (A11CC05) and calcitriol (A11CC04). Ergocalciferol 50 000 IU tablets comprised the most frequently prescribed trade name product (59.45%), followed by alfacalcidol capsules (21.31%).

Conclusion: Vitamin D was used across the age range. Vitamin D supplementation was primarily prescribed in the very young and older age groups, suggesting their need for additional supplementation. As the cost of additional supplements is relatively small compared with the treatment of deficiency disorders, vitamin D supplementation could have broad and positive effects on long-term health for very little outlay.

Keywords prescribing patterns, vitamin D, vitamin D analogues, vitamin supplementation

Introduction

There are two forms of vitamin D. Vitamin D₂ (ergocalciferol) is derived from the irradiation of ergosterol and found in food sources such as fortified foods, plant oils and mushrooms, and vitamin D₃ (cholecalciferol) is derived from animal food sources such as oily fish and egg yolk and the action of sunlight on the subcutaneous layer of the skin.¹ There are numerous studies on the benefits of vitamin D, the role that vitamin D plays in the prevention of bone disease and more recently in the immune system and the prevention and mitigation of cancer. The action of vitamin D is that of a neuro-hormone that regulates both cell growth and immunomodulation.¹ In the former role, vitamin D is well established in its action on bone growth and repair, and the prevention of rickets and osteoporosis.^{1–4} Other studies have implicated vitamin D in the mitigation of bronchiectasis,⁵ prevention of early age-related macular degeneration,⁶ and in support of the immune system in people living with human immunodeficiency virus (HIV).⁷

As an immune modulator, vitamin D₃ has been found to be a factor in the prevention and mitigation of several forms of cancer including breast, ovarian, colorectal, oral, small-cell lung and prostate cancers.^{8–20} The emerging evidence for the therapeutic use of vitamin D in the treatment of cancer warrants attention.^{11,19,21,22} Cancer costs across the world are inestimable, and not all countries can afford to test and treat for the multiple cancers arising within the population. A report on the World Health Organization (WHO) Global Action Plan for the most conservative and cost-effective testing and treatment of breast cancer alone for the east sub-Saharan African region was an estimated US\$ 1 635 per 10 million people per annum, in 2010.²³

The addition of vitamin D and phenylbutyrate to the standard treatment of tuberculosis (TB) has been found to be more effective than standard treatment alone.²⁴ Vitamin D has also been found to be effective alongside vitamin C, zinc and echinacea for the prevention and treatment of the common cold.²⁵ The worldwide increase in fragility fractures in the elderly has been described as catastrophic and potentially directs the cost of medicine away from other critical areas of health.²⁶ As people live longer and women live longer than men, the cost of treating osteoporosis in those at high risk is considerable. Clinical guidelines in the United Kingdom are based on the cost-effective use of bisphosphonates in women over 50 years who are at high risk but do not take into consideration the cost of the longer-term side effects and possible complications.²⁷ Australia, which has a similar climate and number of sunlight hours to South Africa, has focused on both initial fracture management and re-fracture prevention and management. These two strategies reduced the costs of fracture treatment from AU\$ 1.76 billion (US\$ 1.21 billion) to AU\$ 1.58 billion (US\$ 1.09 billion).²⁶

Vitamin D supplementation, however, has until recently been deemed unnecessary and is still not without controversy.²⁸ This factor, alongside the reduction in sunlight-derived vitamin D due to fears of skin cancer, and the increased use of sunscreens, has resulted in an increase in osteoporosis in vulnerable populations.^{29,30} In moderately and heavily pigmented immigrants to countries with fewer hours of sunlight, supplementation of vitamin D has been found to surpass the effectiveness of sunlight exposure for osteoporosis prevention.³¹ In the light of emerging medical evidence of the benefits of vitamin D, some primary care practitioners have recently been

prescribing vitamin D and vitamin D analogues for a number of reasons³² including proactive and preventative use for the multiple effects of deficiency in children and young adults.³³ The prescribing of vitamin D for older women to prevent osteoporosis,³ and the use of vitamin D alongside probiotics for the mitigation of asthma and allergy is not uncommon.³⁴

In some quarters, however, there is still resistance to both testing for deficiency and prescribing of vitamin D, which is viewed as unnecessary health expenditure.³⁵ The safety and efficacy of high doses of vitamin D are also still in question.³⁶ These factors, notwithstanding the adequacy of the current recommendation for the fortification of foods and the supplementation of vitamin D, particularly for children, are being questioned.³⁷ The American Academy of Paediatrics (AAP) has recently doubled its recommended dosage of vitamin D from 200 IU to 400 IU per day for infants, children and adolescents.³⁸

Requirement for vitamin D in South Africa

Adequate blood levels of vitamin D for children in South Africa are considered to be \geq 30 ng/ml acquired through a combination of sunlight and food intake.³⁹ A study conducted in the Western Cape of South Africa found that 16.2% of children on antiepileptic medication required additional vitamin D, due to the possible destruction of vitamin D as a side effect of their treatment.³⁹ This notwithstanding that 8.8% of non-epileptic children with no history of bone metabolism disorders in the control group were also vitamin D deficient.³⁹ A study conducted among hypertensive adults in an urban black community in Mangaung found that, despite the relationship between body mass index (BMI) and hypertension, vitamin D status appeared to have a protective effect, and those with an adequate vitamin D status appeared to be less vulnerable to hypertension despite an elevated BMI.⁴⁰ There appears to be a requirement for increased vitamin D among those with darker skin due to the decreased conversion of vitamin D from sunlight and a reciprocal relationship between vitamin D status and the rate of sputum culture conversion,⁴¹ and seasonal reporting of TB, with higher incidences of TB in the winter months of reduced sunlight.⁴² The need for vitamin D supplementation for all adult South Africans is still under review.⁴³ Variations in pigmentation and vitamin D receptor gene, and changes in lifestyle that reduce sunlight exposure need to be taken into consideration when making recommendations on vitamin D intake and supplementation.⁴³ Considering the connection between vitamin D and immune function, it has been postulated that recommendations for supplementation require a rethink in order to reduce the burden of suffering and the related healthcare costs.⁴³

Prescribing of vitamin D in South Africa

A previous study on the dispensing of vitamins by retail/community pharmacies in South Africa found that ergocalciferol (Anatomic Therapeutic Chemical (ATC) classification code A11CC01), which is available only on prescription, was the most often dispensed (37.48%) of all prescription vitamin products in 2013.^{32,44} Public health prescribing is more difficult to ascertain, as public hospitals and community health centres and clinics do not utilise retail/community pharmacies, medication is given free of charge by the facility and electronic records are not nationally linked; however, there is a tendency for the private healthcare sector to lead the way in the prescribing of nutraceuticals. Establishing private healthcare prescribing patterns may provide an indication of the trend in prescribing of vitamin D and, consequently, the possible future public

healthcare prescribing, expenditure and the cost-benefit ratio of vitamin D supplementation on a broader scale. The primary aim of the study was, therefore, to determine the prescribing patterns of vitamin D and analogues (ATC code A11CC) in a private healthcare setting in South Africa. As South Africa moves into the introduction of the new National Health Insurance (NHI) provision, prescribing of supplements may become public/state expenditure. Knowledge of what is being prescribed and to whom, and for which reasons, will enable future planning of the public needs and government expenditure required for preventive medicine.

Methods

A retrospective, cross-sectional drug utilisation study was conducted on a South African medical insurance administrator database for accepted and paid claims for the year 2018. The administrator oversees the claims for several medical insurance schemes. The database contained 4 191 138 records for medicine, medical devices and procedures. The ATC,⁴⁵ Monthly Index of Medical Specialities (MIMS)⁴⁶ and the South African Medicines Formulary⁴⁷ were used to classify medicines. Products in ATC subgroup A11CC (vitamin D and analogues) were extracted and analysed. As this study relates only to prescribed medications and the diagnoses of the individual patients were not disclosed the authors assumed that the prescriptions were given due to there being a clinical indication for their use. It must also be noted that the study did not include the numerous multivitamin products containing low-dose vitamin D that are available over the counter (OTC) from pharmacies, health shops and other distributors in South Africa. The focus of this study was specifically to determine which products containing vitamin D or a vitamin D analogue were prescribed to patients and paid for by the medical insurance schemes.

The study focused only on the private healthcare sector, which constitutes about 17.4% of the total healthcare sector in South Africa.⁴⁸ Data for the public healthcare sector are not readily available.

Each medication record contained information on the age and gender of the patient, with a unique number to identify each patient, the date of the prescription, detailed information on the dispensed drug (name, package size, formulation, strength and quantity) and gross sales value. The diagnostic ICD-10 codes were not available in the database. Microsoft Access® and Excel® (Microsoft Corp, Redmond, WA, USA) were used to analyse the data. Descriptive statistics were calculated using SPSS V 20® (IBM Corp, Armonk, NY, USA).

Ethical approval to conduct studies on prescription databases has been obtained from the Research Ethics Committee (Human) of the Nelson Mandela University (ethics clearance number: H08-HEA-PHA-005).

Results

A total of 302 patients (176 female and 126 male) received a total of 1 164 prescriptions for a vitamin D or analogue product during 2018 (an average of four [3.85 SD = 3.77] products per year per patient) (Figure 1). The median age of patients was 47.14 (SD = 24.03) years. The age and gender distribution of patients are given in Figure 1.

In total, 123 patients received a single prescription, 238 patients received six or fewer products, and 7 patients received more than 12 prescriptions over the period of one year (Table 1).

Providers of products and cost of claims

Table 2 indicates the provider where each prescription was dispensed. As expected, most prescriptions (69.76%) were dispensed by retail or community pharmacies. This was followed by private hospitals (21.82%), where it was vitamin D drops especially that were dispensed to young children.

Pharmacy dispensing of private practitioner prescriptions outweighed all other dispensers of vitamin D products (69.76% of

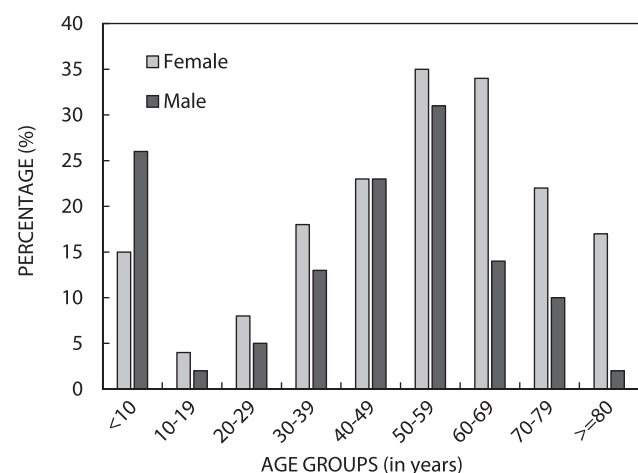


Figure 1: Age and gender distribution of patients who were prescribed a vitamin D or analogue product (n = 302).

Table 1: Frequency distribution of vitamin D or analogue products prescribed per patient during the year (n = 302)

Number of products per year	Number of patients	Percentage of patients (%)
1	123	40.73
2	40	13.25
3	29	9.60
4	17	5.63
5	15	4.97
6	14	4.64
7	14	4.64
8	9	2.98
9	4	1.32
10	9	2.98
11	12	3.97
12	9	2.98
> 12	7	2.31
Total	302	100.00

Table 2: Providers of vitamin D and analogues (n = 1 164)

Providers	Percentage (%)
Community pharmacies	69.76
Private hospitals	21.82
General medical practices and specialists	5.67
Mental health institutions	1.72
Physical rehabilitation hospitals and sub-acute facilities	0.86
Dieticians	0.17
Total	100.00

all prescriptions), suggesting that most vitamin D was prescribed to ambulatory patients as opposed to hospitalised patients (Table 2). Private hospitals would dispense to inpatients in addition to patients leaving the hospital on discharge, although no distinction between these patients was made or was possible in this study. The private medical insurers received claims for vitamin D or analogue products to the value of ZAR 152 243, of which ZAR 119 337 was covered by the insurer, and the rest constituted out-of-pocket expenses for patients. Given the number of prescriptions dispensed, this constitutes a relatively small average expenditure for the individual (ZAR 28.27 or US\$ 2.02) per prescription.

Active ingredients dispensed

Table 3 shows the four different ATC groups of products that were dispensed, according to gender.⁴⁷ Ergocalciferol constituted 59.79% of all prescriptions. Table 3 shows that the most often prescribed trade name product was ergocalciferol 50 000 IU tablets (59.45%), followed by alfacalcidol 0.25 µg capsules (21.31%) and colecalciferol (400 IU/0.5 ml) drops (6.27%). With respect to the number of dosage units dispensed, most prescriptions (65.95%) for ergocalciferol tablets were for only four or five tablets, while 67.19% of prescriptions for alfacalcidol were for 30 capsules. All seven prescriptions for calcitriol were for 60 capsules.

Table 3: Number of trade-name products dispensed in the different ATC groups to female and male patients

ATC code and active ingredient	Female	Male	Total	%
A11CC01—Ergocalciferol (vitamin D₂)	536	160	696	59.79
Calciferol® (50 000 IU) tablets	534	158	692	59.45
Calciferol® Oily drops	2	2	4	0.34
A11CC03—Alfacalcidol	73	244	317	27.23
One-Alpha® (0.25 mcg) capsules	72	176	248	21.31
One-Alpha® (1 mcg) capsules	1	68	69	5.93
A11CC04—Calcitriol	7	0	7	0.60
Rocaltrol® (0.25 mcg) capsules	7	0	7	0.60
A11CC05—Colecalciferol	57	87	144	12.37
Biogen Platinum Series Vitamin D3® (1000 IU)	1	0	1	0.09
Clicks Essentials Vitamin D3® (480 IU) tablets	0	2	2	0.17
D3® (1000 IU) tablets	1	2	3	0.26
D3 5000® tablets	17	10	27	2.32
D-drops® 3.816 ml drops	2	5	7	0.60
D-drops® 30 ml (400 IU/0.5ml) drops	24	49	73	6.27
D-tabs® (1000 IU) tablets	2		2	0.17
D-vit® (400 IU) tablets	1	4	5	0.43
Sentry D® (1000 IU) films	1	3	4	0.34
Solal Vitamin D3® (1000 IU) tablets	7	11	18	1.55
Vitamin D3® effervescent tablets	1	0	1	0.09
Xymogen D3 liquid® (1000 IU) drops	0	1	1	0.09
Total	673	491	1 164	100.00

Table 4: Dosage forms and quantities dispensed

Age groups in years	Capsules	Drops	Effervescent tablets	Orodispersible films	Tablets	Total	%
< 10		53	1		1	55	4.73
10–19		11			12	23	1.98
20–29		3			45	48	4.12
30–39	37	9			58	104	8.93
40–49	104	1			83	188	16.15
50–59	89	3			177	269	23.11
60–69	79	6		2	144	231	19.85
70–79	16			2	145	163	14.00
≥ 80					83	83	7.13
Total	325	86	1	4	748	1 164	100.00

Most prescriptions shown in Table 4 (64.26%) were for tablets, followed by capsules (27.92%) and drops (7.39%). Orodispersible films accounted for 0.24% of prescriptions and effervescent products for only 0.09% (one product). Most drops were dispensed to children, while the prescriptions for the orodispersible film were dispensed to older patients. No capsules were dispensed to children.

A significant number of prescriptions were given to younger patients; the average number of repeat prescriptions was four in the 10–19-year age group. Nonetheless, there is a direct positive correlation between the number of repeat prescriptions given to any individual patient and the age of the patient ($r = 0.826$ $p = 0.006$) (Pearson's two-tailed correlation).

Discussion

Vitamin D appears to be prescribed across the age range. Although a significant number of prescriptions were dispensed to children, the largest number of prescriptions appears to be among women in the 50–59-year age group. Younger patients received vitamin D in the form of drops, which are easier to administer for very young children, while older persons received more capsules or tablets and the soluble orodispersible film was given only occasionally to those in late middle age. Except for patients under the age of 10 years where prescriptions were more common for young boys and the 40–49-year age group where the prescriptions were equal for both genders, vitamin D is more commonly given to women.

It is the very young and the older predominantly female population that appear to be the recipients of higher dose prescriptions for calciferol. Infants are often born with low levels of vitamin D, which were not a concern when breastfed and exposed to sunlight; this situation, however, is no longer the norm.⁴⁹ As the vitamin D content of breast milk is dependent on maternal vitamin D status, which is often low, and sun exposure may be restricted for infants living at higher latitudes or for cultural or other reasons, infants are particularly vulnerable to vitamin D deficiency.⁴⁹ The prescribing of vitamin D in the youngest age group, and for boys, may be in line with the increased recommendations for children, which doubled from 200 IU to 400 IU for infants, children and adolescents to accommodate the decrease in sunlight exposure and increased incidence of rickets for inner-city children.³⁸ The problem of vitamin D deficiency during pregnancy, which can increase the risk of pre-term and low birthweight infants, has arisen⁵⁰ and in light of concerns over possible risks of giving pregnant women higher doses of vitamin D, supplementation for preterm and low-birthweight infants has been recommended

to curb the complications of infant vitamin D deficiency.⁵¹ Breastfeeding under such circumstances may not be protective if mothers have low vitamin D levels.⁴⁹ The WHO has added its voice to the recommendations for infant supplementation.⁴⁹ The guidelines are, however, not implemented across the board, and less than half of United States primary care practitioners recommend paediatric supplementation.³³ Not everyone agrees with the necessity for childhood supplementation, and in the United Kingdom, where costs of testing and supplementation are borne by the state, there are concerns about unnecessary testing and prescribing, and the concomitant additional expenditure.³⁵

At the other end of the age scale, there is research proposing that vitamin D supplementation is associated with decreased cardiovascular mortality, diabetes, risk of infection and multiple cancers,^{12,13,36,52} all associated with increasing age. Vitamin D has been found to play a crucial role in the health of the immune system and in promoting the production of antimicrobial monocytes and neutrophils, which tends to decline with increasing age.¹ With increasing age, exposure to sunlight may be limited due to reduced outdoor activity and increased skin sensitivity, and dermal production of vitamin D is reduced because of atrophic skin changes and decreased renal function.⁵³ The changes place both genders at risk and have been postulated to lead to severe adverse consequences such as osteoporosis, breast, colon and prostate cancers and hypertension.⁵³ Chronic kidney disease equally places both genders at increased risk of osteoporosis and increased requirement for vitamin D.⁵⁴ Clinical trials have demonstrated that 800 IU (20 µg) per day of vitamin D in combination with 1 200 mg calcium reduced the risk of fractures due to falls in the institutionalised elderly, who are not ambulatory or exercising, and that single doses of 100 000 IU orally every fourth month, without calcium, reduces fracture risk in mobile community-dwelling individuals over 65 years of age.⁵³ Another study suggested a three-year combined programme of denosumab (a monoclonal antibody) and vitamin D supplementation for the treatment of osteoporosis and rheumatoid arthritis.⁵⁵ Vitamin D and calcium combinations are frequently self-prescribed for osteoporosis but were not investigated for this study as the aim was to focus on the increased and multiple prescribing recommendations for vitamin D alone. It is acknowledged, however, that vitamin D and calcium combinations with or without other pharmaceuticals are often prescribed for women concerned about osteoporosis.⁵⁵

Age-related vitamin D deficiency has been found to be prevalent in South Africa, with those over 65 years being particularly

vulnerable to deficiency.⁴³ This study showed that private practitioner prescribing of vitamin D in South Africa increased with age and, except for the 40–49-year age group, prescriptions for women outweighed those for men. This might suggest that practitioners are reacting to older female patient concerns regarding the impact of vitamin D deficiencies, or are themselves concerned about vitamin D deficiencies in this population group, thus initiating the conversation about supplementation of vitamin D. Vitamin D deficiency has been associated with higher incidences of breast cancer among women and lower survival rates.^{16,17,52} Women have a lower bone density than men and are more prone to fall-related fractures due to osteoporosis, particularly in the post-menopausal years.⁵⁶ Vitamin D-related osteopenia and osteoporosis are not uncommon, and vitamin D deficiency appears to be more common in women, but treatable with supplementation.⁵⁷ There is a case for additional vitamin D for older people, of both genders;⁵³ however, in this study, prescriptions were more frequently given to women.

There is a lack of consensus on the appropriate vitamin D supplement dosage.¹ Although the higher dose of 50 000 IU capsules or tablets appears to be the predominant prescribing practice for South Africa, not all researchers agree that this is necessary. One study found that a single loading dose followed by a low daily maintenance dose was equally effective with the possibility of fewer high-dose risks.³⁶ Another study by Kearns et al. (2014), however, found that daily intake may be difficult to comply with and larger single doses were more effective for eradication of vitamin D deficiency.⁵⁸ They also found that single vitamin D3 doses in excess of 300 000 IU are most effective at improving vitamin D status and suppressing compensatory parathyroid hormone concentrations, which draw calcium from bones, although gastrointestinal complaints were reported by a few patients at higher doses of vitamin D intake.

In South Africa, there is a wide population group variation in vitamin D receptor genes, ethnicity, and ability to absorb ultraviolet rays and synthesise vitamin D, in addition to variations in disease or treatment responses.⁴³ South Africa spans latitudes from 22.34 S to 34.28 S and has a wide variation in ultraviolet light exposure, which further impacts upon the synthesis of vitamin D, a situation that demonstrates the complex interactions between genetics and the environment.⁴³ Although there appears to be a correlation between frequent sun exposure and a reduction in certain cancers, such as colorectal, prostate, breast cancer and non-Hodgkin's lymphoma, this may or may not be due to the effects of the conversion of sunlight to vitamin D.⁵⁹ Sunlight also has an effect on circadian rhythms and the degradation and utilization of folic acid, the beneficial effects of which may not have been taken into account.⁵⁹ It should also be considered that in the right hands prescribed supplementation is generally safe, but high doses of Vitamin D have the potential for cumulative toxicity. The public perception of need might drive potentially dangerous over-the-counter self-medication.⁶⁰ Whether vitamin D plays an important role in protection against the range of diseases that currently constitute a burden on the health services in South Africa or whether there are more complex factors at play needs further investigation before global population-based recommendations can be made.⁴³

The study had limitations in that it covered a period of only one year, and focused only on private prescribing of vitamin D and vitamin D analogues and with a single medical aid administrator, which did not disclose the patient ICD-10 codes and as such can

only provide a snapshot picture of the total vitamin D prescribing practice for this specific population. Furthermore, no clinical information, such as the patient vitamin D blood levels, were available in the database. There are also numerous registered and unregistered products available OTC in South Africa that contain low doses of vitamin D in combination with other vitamins, minerals and/or herbal products. This is a large market in South Africa and difficult to quantify as these products are sold through various distribution channels. The use of these products did not form part of this study.

Conclusion

Vitamin D is used across the age range, and there are numerous prescribers and dispensers. Most patients received their prescriptions from a pharmacy as opposed to a hospital or medical practitioner. The number of patients receiving prescribed vitamin D or vitamin D analogues was directly correlated with increasing age. The practice appears to be that of repeat and long-term use of vitamin D, in older age groups and particularly women, suggesting the perceived efficacy of the additional supplementation. Preventing the most common cancers and fragility fractures with better nutritional intervention could potentially save not only lives but a large amount of money that could be redirected towards other prevention and treatment strategies. As the cost of additional supplements is relatively small compared with treatment of deficiency disorders, vitamin D could have broad and positive effects for very little outlay (ZAR 130.79/US\$ 9.06 per prescription), thus the strategy of a wider cost-effective rollout of supplementation may be worth consideration. Further investigations of the current total use and possible future benefits of vitamin D supplementation may be warranted.

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