A drug utilisation study investigating prescribed daily doses of hypolipidaemic agents

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Objectives. To estimate average prescribed daily doses (PDDs) for selected hypolipidaemic agents available on the South African market. Comparison of the estimated PDDs with established DDDs (defined daily doses) and international dosage ranges. To investigate the age and gender of the users of the different hypolipidaemic drugs and drug groups.

Design. Retrospective drug utilisation study using data from an organisation involved in the pre-certification of chronic medication.

Setting. Doctors and patients in South Africa.

Participants. A total of 2 336 patients of various medical aids who were using cholesterol-lowering medication on a chronic basis.

Outcome measures. The PDDs, for the complete sample and for the age and gender groups.

Results. More than 90% of all hyperlipidaemic patients in the study were treated with HMG CoA reductase inhibitors or fibrates. The average PDDs for the three most frequently prescribed lipid-lowering drugs were 414.4 mg for bezafibrate, 12.5 mg for pravastatin and 12.6 mg for simvastatin. The PDDs were on average lower than the established DDDs. Differences were observed in the pattern of lipid-lowering drug prescriptions for women and men. Male users were on average 3.9 years younger than female users.

Conclusions. The PDDs used in the patient population studied were within locally and internationally acceptable dosage ranges, but were generally lower than established DDDs for lipid-lowering drugs. Prescription differences exist between female and male patients and between age groups with regard to chronic medication. Further studies should be conducted to investigate hypolipidaemic drug prescribing in patients who are not on chronic medication.

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Various methods exist to measure drug consumption. The traditional measures, viz. volume and cost, have inherent

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limitations when drug consumption patterns are studied over time or between different countries. To overcome these limitations, the defined daily dose (DDD) methodology was introduced as a unit of measurement in drug utilisation studies by the Norwegian Medicinal Depot in the early 1970s.[1] The DDD is defined as the assumed average dose per day for a drug used in its main indication in adults.[2] The DDD system thus allows conversion of prescribed substances into equivalent units of a standard defined volume.[3] The DDD methodology developed into an internationally recognised method to measure and compare drug consumption and is recommended by the Drug Utilisation Research Group (DURG) as a unit of measurement for comparative drug consumption statistics.[2]

It was, however, soon realised that the DDD method in itself had inherent limitations. Variability in dosing, for example, makes the DDD a very crude estimate of true drug exposure in a community. Many drugs have multiple indications, for which different dosage ranges are appropriate. Failure to account for the indications for which a drug was actually prescribed may thus grossly over- or underestimate the number of individuals exposed to it.[4]

An additional measurement unit was subsequently introduced by researchers in the USA to overcome the inherent limitations of the DDD.[5] This is the prescribed daily dose (PDD), to be used alongside the DDD. The PDD represents the average prescribed dose of a drug when used for its main indication.[2] The PDD is thus based on the average dose of the drug actually prescribed, rather than on a dose theoretically most appropriate for its major indication. According to these researchers the PDD reflects drug exposure more accurately than the DDD.

The PDD can be determined from prescription studies, medical records and patient interviews, provided that dosing instructions are available. PDD-based drug consumption measures also have some shortcomings.[4] It is, for example, important to relate the PDD to the diagnosis on which the dosage is based. Studies have shown that although the difference between the DDD and the PDD is relatively small for some drug groups, e.g. antihypertensive drugs and antidiabetic drugs,[6] it may be appreciable in other fields of therapy, e.g. analgesics and psychotropic agents.[7]

PDDs can also vary according to both the illness treated and national therapeutic traditions.[2] In the case of anti-infectives, for example, PDDs can vary according to the severity of the infection. The DDDs for most anti-infectives are based on the treatment of moderately severe infections. In hospital care, however, much higher doses are frequently used and this must be taken into account when PDDs are compared with DDDs as units for drug consumption measurement. When there is a substantial discrepancy between the PDD and the DDD at an individual or average level, caution is needed when comparison is made.

In this study, in order to prevent complications arising from multiple indications, it was decided to calculate PDDs for a very specific and well-defined therapeutic class. Furthermore, in order to obtain reliable results, it was decided to concentrate on a therapeutic drug class that is used nearly exclusively for the treatment of a chronic condition. According to a classification system on the specificity of drug use developed by McGavock *et al.*,[8] prescribing can be classified as specific, symptomatic or often presumptive. According to this classification system, the following criteria for inclusion of a drug or drug group in the 'specific prescription' category must be met:[8] (*i*) before the drug is used there must always be an accurate diagnosis, often confirmed by laboratory or other investigations and often by a second opinion; or (*ii*) the drug must be known to intervene in a specific and well-understood manner to alter the pathophysiology in the patient's favour.

Since hypolipidaemic agents meet both of these criteria, these agents can be classified as 'specific prescription' and are therefore suitable for PDD analysis.

The primary aim of the study was therefore to estimate the PDDs of hypolipidaemic agents in a defined South African population group, and to compare the results with internationally established dosage ranges, as well as with established DDDs.

Subjects and methods

Prescription data were obtained from a South African organisation involved in the pre-certification of chronic medication. Various medical aids are served by this organisation. Data on hyperlipidaemic patients over a 1-year period (28 March 1994 to 27 March 1995) were analysed. Prescription records of 2 336 patients were studied.

All agents that can be used to treat hyperlipidaemia were identified. Other agents prescribed were classified into therapeutic categories by means of the MIMS classification system.[9]

The ages of patients were taken to be those on 1 October 1994 (approximately the middle of the time period under investigation). The actual time period that a patient was using a specific drug was not investigated in detail in this study, since all the patients studied were using the medication on a chronic basis. If the dosage instruction given to a patient was 'use as directed', the standard maintenance dose according to MIMS[9] was taken to be the actual dose.

All the patients in the study were on a chronic medication scheme; they therefore had to apply through their general practitioner to receive the medication on a chronic basis. All prescriptions were screened by a panel of experts for approval (pre-certification). It must be taken into account that treatment of hyperlipidaemic patients who are not on a chronic medication scheme may differ from the treatment of patients in this sample.

Results and discussion

A general drug utilisation study was performed to determine the prescribing frequency of hypolipidaemic drugs, as well as other products that were prescribed together with hypolipidaemic drugs. A total of 2 336 patients were diagnosed as hyperlipidaemic. Of these 2 336 patients, 42.9% were women and 57.1% men. The average age of patients was 57.4 years, with women (average age 59.7 years; first quartile 53.0 years; median 60.7 years; and third quartile 67.5 years) slightly older than men (average age 55.7 years; first quartile 48.4 years; median 56.5 years; and third quartile 64.2 years).

Of the 2 336 patients, 4 received four drugs, 22 three drugs, 161 two drugs and the rest one drug (a total of 2 390 cholesterol-lowering drugs and 163 other drugs) during the period of the study. Most of the other drugs prescribed were agents that acted on the blood and haemopoietic system, endocrine system drugs and cardiovascular system drugs. One-third of all the other drugs prescribed were aspirin (prescribed in a low daily dose).

The frequency of hypolipidaemic drug prescribing (according to trade names) is given in Table I. Hypolipidaemic drugs that were prescribed 20 or fewer times during the period under investigation were grouped together and classified as 'miscellaneous'. Simvastatin 10 mg (Zocor 10 mg) was the single most frequently prescribed drug, representing 36.8% of the total number of hypolipidaemic drugs prescribed. The Pearson chi-square test statistic was used to investigate prescribing differences between women and men. From this test it was inferred that a difference between female and male patients in respect of the bezafibrate prescription pattern is highly probable. Since the cholesterol levels or body weights of patients were not available from the data studied, it is difficult to explain the exact reasons for these differences. A most likely explanation is that the onset of elevated cholesterol levels occurs in women and men at different ages and with different severity.

Table I. Frequency of hypolipidaemic drug prescribing*

Hypolipidaemic drug	Frequency			Total percentage
	Female	Male	Total	
Bezalip Retard	116	116	232	9.7
Bezalip 200 mg	34	27	61	2.6
Lipsin 100 mg	26	28	54	2.3
Lipsin 300 mg	46	55	101	4.2
Lopid 300 mg	12	24	36	1.5
Lopid 600 mg	22	38	60	2.5
Lurselle	34	36	70	2.9
Miscellaneous	18	30	48	2.0
Olbetam 250 mg	10	12	22	0.9
Prava 10 mg	133	201	334	14.0
Prava 20 mg	38	65	103	4.3
Questran	19	44	63	2.6
Zocor 10 mg	364	516	880	36.8
Zocor 20 mg	119	207	326	13.7
Total	991	1 399	2 390	100.0

* $\chi^2_{(13)} = 25.12$; $P < 5\%$.

Nine drugs were classified under 'miscellaneous'. These drugs included colestipol, eicosapentaenoic acid (EPA), fluvastatin, combination products and nicotinic acid. Fluvastatin (Lescol 20 mg and 40 mg) was prescribed to only 4 patients. The reason for this low prescribing frequency is that fluvastatin was a new HMG CoA reductase inhibitor on the South African market and therefore not yet widely in use at the time of the study.

The frequency distribution of the ages of patients on hypolipidaemic drugs for women and men is given in Table II. Most hyperlipidaemic patients were between 50 and 70 years of age. It can be observed in the table that the younger age categories of male users include many more individuals than the corresponding categories of the female group. On average, men therefore received hypolipidaemic drugs at a much younger age. The mean age of the men differed from that of the women by approximately 3.9 years.

Table II. Frequency distribution of the ages of patients on hypolipidaemic drugs*

Age group (yrs)	Frequency			Total percentage
	Female	Male	Total	
0 - 10	2	1	3	0.1
10 - 20	7	4	11	0.5
20 - 30	7	7	14	0.6
30 - 40	31	89	120	5.1
40 - 50	131	306	437	18.7
50 - 60	303	410	713	30.5
60 - 70	353	375	728	31.2
70 - 80	152	132	284	12.2
80 - 90	16	10	26	1.1
Total	1 002	1 334	2 336	100.0

* $\chi^2_{(8)} = 71.85$; $P < 0.01\%$ (after collapsing the top three categories and the bottom two categories).

No association was detected between prescription manufacturer and gender or age. Furthermore, no generic equivalents were available for the hypolipidaemic drugs under investigation at the time of the study.

Frequency of hypolipidaemic drug prescribing in therapeutic subgroups

The hypolipidaemic drugs prescribed were classified into seven therapeutic subgroups. The results are given in Table III. HMG CoA reductase inhibitors represented 68.9% of all the cholesterol-lowering drugs prescribed, followed by fibrates (23.1%). Drugs in these two subgroups therefore represented more than 90% of total hypolipidaemic drug prescription.

Table III. Percentage of hypolipidaemic drugs prescribed in each therapeutic subgroup (N = 2 390)*

Therapeutic subgroup	Percentage		
	Females	Males	Average
Bile acid-binding resins	2.2	3.2	2.8
Fibrates	26.4	20.8	23.1
HMG CoA reductase inhibitors	66.1	70.9	68.9
Nicotinic acid group	1.2	1.7	1.5
Fish oils	0.0	0.1	0.1
Probucol	3.4	2.6	2.9
Combinations	0.7	0.7	0.7
Total	100.0	100.0	100.0

* $\chi^2_{(6)} = 15.32$; $P < 5\%$.

The Pearson chi-square technique was again used to investigate prescribing differences in respect of gender. It was found to be highly probable that prescribing for fibrates differed between women and men ($\chi^2_{(6)} = 15.3$; $P < 5\%$).

Two different combination lipid-lowering drugs were prescribed, viz. clofibrate 500 mg in combination with nicotinyl tartrate 59.5 mg (Lipaten), and a combination product consisting of EPL substances, vitamin B_6, vitamin E and theophylline (Lipostabil). Fish oils (EPAs) were only prescribed to 2 patients.

Comparison of DDDs and PDDs of selected hypolipidaemic agents

The DDDs and average PDDs for selected hypolipidaemic agents are given in Table IV. The PDDs were generally lower than the internationally established DDDs.[10] The only exception was cholestyramine, with a DDD of 14 000 mg, for which the average PDD was calculated as 18 500 mg. This dose was, however, not excessive, since doses of up to 36 000 mg daily can be used if necessary.[11]

Analysis of PDDs in respect of gender and age

The average PDDs of bezafibrate, pravastatin and simvastatin were estimated for gender and age groups. The results for bezafibrate are given in Table V. The highest prescribing frequency occurred in the 60 - 70-year age group for both women and men. The average PDD for bezafibrate was 414.4 mg, with the average PDD for women and men nearly identical. The DDD for bezafibrate is 600 mg,[10] and the normal dosage range 400 - 600 mg per day.[12] The PDD for bezafibrate in the patient population studied was therefore towards the lower end of the scale. The highest average PDD according to age groups was observed in 40 - 50-year-old patients (458.1 mg).

The PDDs for pravastatin according to gender and age groups are given in Table VI. One-third of all patients on pravastatin were between 50 and 60 years of age. The average PDD for pravastatin was 12.5 mg. As with bezafibrate, only a very small difference was observed between the average PDD for women (12.5 mg) and men (12.6 mg). The highest average PDD was observed for women between the ages of 20 and 30 years. The DDD for pravastatin is 20 mg.[10] The dosage range for pravastatin is considered to be between 10 mg and 40 mg per day.[12] Patients on pravastatin were therefore, on average, using a relatively low dose.

The PDDs of simvastatin according to gender and age groups are given in Table VII. Most women who were prescribed simvastatin were between 60 and 70 years of age (35.5%), followed by the 50 - 60-year age group (32.4%). The average PDD for simvastatin was 12.6 mg. The average PDD for men (12.7 mg) was slightly higher than for women (12.5 mg). The DDD for simvastatin is 15 mg,[10] and the dosage range 10 - 40 mg per day.[12] Seven patients on simvastatin were using both the 10 mg and the 20 mg dosage forms simultaneously, and were thus using a dose higher than the DDD.

The Pearson chi-square technique was used to determine whether prescribing patterns in men and women differed with regard to age for bezafibrate, pravastatin and simvastatin. (The respective chi-square values are shown in Tables V, VI and VII.) From the chi-square values, it seemed that the pattern of hypolipidaemic drug prescribing differed between female and male users. (This finding was also confirmed by *t*-tests executed on the means.) The age of male patients was lower for users of bezafibrate, pravastatin and simvastatin. (The median ages of male users were 59.9, 54.5 and 50.2 years respectively, and for female users 63.9, 59.1 and 63.1 years.)

Conclusion

The study clearly indicated that lipid-lowering drugs were used within locally and internationally accepted dosage ranges. The dosages used were generally closer to the minimum indicated maintenance doses and were therefore not excessive. This was confirmed by the fact that the PDDs were also generally lower than the internationally established DDDs.

Table IV. DDDs and PDDs for selected hypolipidaemic drugs

Hypolipidaemic drug	DDD (mg)[10]	Average PDD (mg)	No.	Standard deviation of average PDD	Coefficient of variation of average PDD
Bezafibrate	600.0	414.4	291	97.9	23.6
Cholestyramine	14 000.0	18 500.0	63	9.0	48.5
Clofibrate	2 000.0	1 250.0	8	378.0	30.2
Fenofibrate	300.0	289.7	155	132.0	45.6
Gemfibrozil	1 200.0	900.0	96	389.3	43.3
Pravastatin	20.0	12.5	433	5.1	40.9
Probucol	1 000.0	660.7	70	272.7	41.3
Simvastatin	15.0	12.6	1 199	5.6	44.0

Table V. Prescribed daily doses of bezafibrate according to gender and age*

	Percentage of patients†			PDD (mg)		
Age group (yrs)	Female	Male	Average	Female	Male	Average
20 - 30	2.0	0.7	1.4	400.0	400.0	400.0
30 - 40	2.0	6.4	4.1	400.0	400.0	400.0
40 - 50	9.3	12.1	10.7	457.1	458.8	458.1
50 - 60	21.3	31.2	26.1	425.0	400.0	410.5
60 - 70	48.7	34.7	41.9	402.7	428.6	413.1
70 - 80	14.7	14.2	14.4	418.2	380.0	400.0
80 - 90	2.0	0.7	1.4	400.0	400.0	400.0
All age groups	100.0	100.0	100.0	414.7	414.2	414.4‡

* 293 drugs were prescribed to 291 patients. (Two patients were using the two dosage strengths simultaneously.)
† $\chi^2_{4} = 7.98$; $P < 10\%$ (after collapsing the top two categories and the bottom two categories).
‡ See Table IV for standard deviation and coefficient of variation.

Table VI. PDDs of pravastatin according to gender and age*

	Percentage of patients†			PDD (mg)		
Age group (yrs)	Female	Male	Average	Female	Male	Average
20 - 30	0.6	0.4	0.5	20.0	10.0	15.0
30 - 40	4.1	5.7	5.1	14.3	11.3	12.3
40 - 50	15.4	28.4	23.3	13.9	13.2	13.3
50 - 60	33.1	33.3	33.3	13.2	12.6	12.9
60 - 70	27.2	22.4	24.2	11.5	12.0	11.8
70 - 80	17.8	9.8	12.9	11.0	12.5	11.7
80 - 90	1.8	0.0	0.7	10.0	N/A	10.0
All age groups	100.0	100.0	100.0	12.5	12.6	12.5‡

* 437 drugs were prescribed to 433 patients. (Four patients were using the two dosage strengths simultaneously.)
† $\chi^2_{.05}$ = 15.91; $P < 0.5\%$ (after collapsing the top two categories and the bottom two categories).
‡ See Table IV for standard deviation and coefficient of variation.

Table VII. PDDs of simvastatin according to gender and age*

	Percentage of patients†			PDD (mg)		
Age group (yrs)	Female	Male	Average	Female	Male	Average
20 - 30	1.3	1.0	1.1	13.3	12.9	13.1
30 - 40	2.7	6.8	5.2	15.4	12.5	13.1
40 - 50	13.7	24.9	20.4	14.5	14.6	14.6
50 - 60	32.4	31.1	31.6	12.6	12.8	12.7
60 - 70	35.5	27.7	30.9	12.2	11.6	11.9
70 - 80	13.1	8.1	10.1	10.7	10.8	10.7
80 - 90	1.3	0.4	0.7	9.2	10.0	9.4
All age groups	100.0	100.0	100.0	12.5	12.7	12.6‡

* 1 206 drugs were prescribed to 1 199 patients. (Seven patients were using the two dosage strengths simultaneously.)
† $\chi^2_{.05}$ = 39.53; $P < 0.01\%$ (after collapsing the top two categories and the bottom two categories).
‡ See Table IV for standard deviation and coefficient of variation.

Important differences in cholesterol-lowering drug prescribing were observed with regard to gender and age groups. Male users of hypolipidaemic drugs were on average 3.9 years younger than female users. From Table II it is evident that hyperlipidaemia and the treatment thereof are more prevalent in men than women. The faster reduction in the number of men aged over 60 years in Table II is probably due to their accelerated mortality. It also seemed that the style of prescribing was influenced within each gender group by the ages of patients. Since cholesterol levels were not investigated, it was very difficult to explain the reasons for these differences. It can, however, be speculated that the onset of elevated cholesterol levels occurred in women and men at different ages and with different severity.

The coefficient of variation in Table IV provides insight into the therapeutic window of the different hypolipidaemic agents (as interpreted by the medical practitioners). Almost all the coefficients of variation were in the 41 - 49 interval, except for bezafibrate and clofibrate.

It must be noted that all the patients in the study were using the medication on a chronic basis. The possibility exists that different dosages are used by patients who are not using hypolipidaemic drugs chronically. It is recommended that further drug utilisation studies on the use of lipid-lowering agents be undertaken, incorporating those patients who are not on a chronic medication scheme.

The study clearly showed that the PDD methodology can be a useful tool to determine the actual dosages in which specific drugs are prescribed. It is, however, important to note that drug consumption based on the PDD methodology must only be regarded as a proxy for actual drug consumption or utilisation, and that it will be directly influenced by the patient population studied and the severity of the disease state. It is recommended that further studies on the PDD methodology in South Africa be undertaken in order to follow treatment patterns over time and also to facilitate comparison between regions or countries.

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