The defined daily dose as a measure of drug consumption in South Africa

A preliminary study

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Objective. To perform a preliminary investigation into the use of the defined daily dose (DDD) as a unit to measure drug utilisation in South Africa. The DDD methodology has been applied in many countries in Western Europe and in other parts of the world. However, research using the DDD method is still lacking in South Africa despite the important role that it can play in economic planning and the improvement of prescribing practices.

Design. A retrospective drug utilisation study using data from a medical aid. Consumption of selected central nervous system drugs included in a formulary system was determined.

Setting. Doctors and patients located in an area of Port Elizabeth.

Participants. The prescribing behaviour of 50 dispensing doctors serving a homogeneous demographic and socio-economic patient population was analysed.

Outcome measures. The DDD/1 000 registered patients/day, the cost per DDD and the relationship between the two units.

Results. Values for the DDD/1 000 registered patients/day were on average lower than international values, but similar trends were observed. The cost per DDD for antipsychotic and antidepressant drugs was on average higher than for hypnotic and anxiolytic drugs. There was an inverse relationship between the DDD/1 000 registered patients/day and the cost per DDD.

Conclusions. The DDD methodology is a useful technique to enable drug consumption data to be measured and compared both nationally and internationally. It can be regarded as a valuable tool for the promotion of rational and cost-effective use of medicine in a future health care system for South Africa.

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There is a growing need for quantitative insight into drug usage in order to identify trends and to enable a base for planning to be established. Drug utilisation studies are a powerful tool that can be used to study the prescribing of drugs, as well as to measure the consumption of drugs.

Various methods exist to measure the consumption of drugs. The traditional measures, viz. cost and volume studies, have inherent shortcomings when drug consumption patterns are studied over time or between different countries.

The defined daily dose (DDD)

To overcome the inherent limitations associated with the traditional units of measurement, the DDD was introduced as a unit of measurement in drug utilisation studies by the Norwegian Medicinal Depot in the early 1970s.[1] The DDD was first mentioned in print in 1975, when a list of DDDs of drugs registered for sale in Norway was prepared.[1]

The DDD is defined as the assumed average dose per day of a drug used for its main indication in adults.[2] DDDs are allocated to drugs by the Nordic Council on Medicines, which works in close association with the World Health Organisation Regional Office for Europe in Copenhagen.[3] A DDD is defined for each active ingredient contained in a product. The dosing levels have been defined according to recommendations in the medical literature, the manufacturer's advice in the data sheet, and experience gained in the field with the product concerned. Examples of DDDs are given in Table I. All newly assigned DDDs are reviewed after 3 years, and all DDDs are reviewed 10 years after their assignment.

Table I. Examples of DDDs[4]

Drug	DDD
Amitriptyline	75 mg
Diazepam	10 mg
Digoxin	0.25 mg
Ibuprofen	0.8 g
Imipramine	0.1 g
Indomethacin	0.1 g
Phenytoin	0.3 g
Propranolol	0.16 g
Tetracycline	1 g
Thioridazine	0.3 g

DDDs are generally based on use in adults. DDDs for plain preparations, i.e. products containing a single active ingredient, are based on the average adult dose if used for the medicine's main indication. For doses related to body weight, 70 kg for adults and 35 kg for children are used. For drugs administered as an initial loading dose, followed by a maintenance dose, the maintenance dose is used. For drugs that are used intermittently, such as cytostatics and some vitamins, the DDD concept is medically meaningless, but can still be used as a technical unit of comparison.

For combined preparations, DDDs are assigned to be on the same therapeutic level as for plain preparations and other combined preparations in the same therapeutic group. If a combined preparation contains auxiliary substances, for example to reduce gastro-intestinal discomfort, the same DDD as for plain preparations is given. In the case of a combined preparation that contains only a few active ingredients, the DDD is based on the main active ingredient. For combination products with many active substances, the DDD should be stated in relation to the total therapeutic effect and the dose of the major ingredient(s) recommended by the manufacturer.

DDDs are, as far as possible, expressed in the amount of active ingredient using the most appropriate units, for example grams, milligrams or millimols. For combined preparations where, for various reasons, the DDD cannot be given in amount of active ingredient, the unit ED (single dose or unit dose) is used. For example, 1 ED of a metered dose preparation is equal to one dose from the original, intact dosage device.

One of the most important advantages of DDDs when quantifying drug consumption is that their use controls for differences between drugs in respect of potency and duration of action, as well as manufactured dosage strengths and package sizes. The DDD can therefore be regarded basically as a unit of measurement for statistical purposes. It must be kept in mind that the DDD is merely a technical unit for the measurement of drug consumption and does not necessarily reflect the recommended or actual dose.

The DDD/population denominator/day

Consumption in a given geographical area is usually expressed as the number of DDDs per 1 000 inhabitants per day. If data are available on the number of units of a drug sold, the number of DDDs consumed is calculated according to the following formula:[3]

$$\frac{\text{Amount of drug sold in 1 year (mg)}}{\text{DDD (mg) x 365 days x No. of inhabitants}} \text{ x 1 000 inhabitants.}$$

The result of the calculation is given as the number of DDDs per 1 000 inhabitants per day. The value obtained is merely a relationship and does *not* refer to actual doses in, for example, milligrams or millilitres.

For example, the DDD for ibuprofen is 0.8 g.[4] If 10% of the total number of inhabitants of a specific area or country take 0.8 g ibuprofen every day for 1 year, the DDD/1 000 inhabitants/day will be 100.

Drug consumption, expressed in DDD/1 000 inhabitants/ day, gives a rough indication of how many patients receive 'standard' treatment with a drug. Thus, in circumstances where a drug is used continually and for one indication only, the DDD/1 000 inhabitants/day should give a rough estimate of the population using the drug. However, in practice, it does not indicate how many patients are treated over a given period of time.

Alternatively, the DDD per 1 000 (registered) patients per day can be calculated. Consumption in hospital is calculated in a similar way, but is expressed as the DDD per 100 bed-days. The days of admission and discharge are usually counted together as one bed-day. The DDD/1 000 inhabitants/day can also be further amended, e.g. the DDD/1 000 inhabitants/month or the DDD/1 000 inhabitants/year can be calculated.

Stanulovic *et al.*[5] investigated the possibility of adapting the DDD methodology to paediatric use. He used the rule of the fraction of the body surface area as the fraction of adult dose, expressed as a DDD. Inesta[6] developed a unit for the determination of drug consumption, the DDD/100 consumers/day (DCD), for community pharmacies in cities where it is difficult to estimate the population covered by each pharmacy.

Limitations of the DDD

1. Drug consumption measured in DDDs gives only a rough estimate of consumption and not a real picture of actual use, because it is based on the assumption that all drugs that are sold are actually consumed. Furthermore, many drugs are used in different dosages and this must be taken into account when drug consumption figures are evaluated.

2. It is important to consider, and adapt if necessary, the size of the population used as a denominator. General consumption is usually calculated for the total population (all age groups), but drug use is often concentrated within certain specific groups, e.g. antihypertensive drugs (only adults) and oral contraceptive drugs (only women between 18 and 44 years of age).

3. For some types of drugs, DDDs are not applicable. Examples are sera and vaccines, antineoplastic drugs and general and local anaesthetics.

4. If drugs are used continuously and for one indication only, consumption given in the DDD per inhabitant may roughly agree with morbidity figures. This has been proved true for antidiabetic drugs and oral hypoglycaemic agents.[7] By contrast, such a relationship for drugs used in several indications (such as benzodiazepines or antipsychotics) or in short or variable courses of treatment (such as analgesics or antibiotics) cannot be expected.[3]

5. The DDD methodology does not provide a means of profiling the extent to which fixed combinations are used. Although a specific unit (ED) has been defined for combined preparations, it is not suitable for comparing the consumption of drugs between countries where different types and dosages of fixed combinations are used.

6. A DDD is not necessarily equivalent to the average doses actually prescribed or to the average dose actually ingested every day. The doses prescribed and taken in a particular community will vary with the actual predominating indications, national or regional therapeutic traditions and the attitude of patients.

7. The DDD has limited potential for the evaluation of the effectiveness of the drugs consumed.

Subjects and methods

The prescribing data of a sample of 50 dispensing doctors serving a homogeneous patient population in an area of Port Elizabeth were analysed retrospectively. The study was carried out over 4 months in a cycle of 1 year (July 1992, October 1992, January 1993 and April 1993) to detect and account for any possible seasonal effects. The sample of doctors was using a formulary system. On average, 93.63% of the total number of drugs prescribed by the sample of doctors were formulary drugs. Selected central nervous system drugs were analysed in respect of DDD methodology.

Three calculations were made, viz. the DDD/1 000 registered patients/day, the cost per DDD (in South African rands), and the relationship between the cost per DDD and the DDD/1 000 registered patients/day.

The DDD/1 000 registered patients/day was calculated by means of the given formula. Because data were obtained from a medical aid, the total number of inhabitants could not be used in the calculation, since only a sample of doctors who were serving only a portion of the total number of inhabitants of the area was chosen. It was therefore decided to calculate the DDD/1 000 registered patients/day. The sample of 50 dispensing doctors was randomly selected from a total of 136 dispensing doctors. The total number of registered patients (principal members plus dependants) for the 136 doctors was known and from this the number of registered patients for the sample of doctors could be calculated proportionally. By using this method of calculation, the possibility that a patient can visit more than one doctor in the group of 136 dispensing doctors was indirectly accounted for.

The cost per DDD refers to the price that a patient will have to pay per day for a particular drug if the drug is used in the dose that was established as an international norm, viz. the DDD. The March 1993 prices, as indicated in the formulary, were used in the calculations. All prices are in South African rands.

Results and discussion

DDD/1 000 registered patients/day

The DDDs/1 000 registered patients/day for selected hypnotic and anxiolytic drugs are given in Table II. The DDD/1 000 registered patients/day for diazepam (4.81) was the highest. There were marked fluctuations in the values obtained for the different months. The differences could not be readily explained, and since they did not fall within the scope of this preliminary study, seasonal differences were not investigated further.

Table II. DDD/1 000 registered patients/day for selected hypnotic and anxiolytic drugs

	DDD/1 000 registered patients/day				
Drug	July	October	January	April	Average
Bromazepam	0.46	0.39	0.33	0.44	0.41
Diazepam	5.30	5.54	4.43	3.96	4.81
Lorazepam	2.10	1.91	1.87	1.37	1.81
Nitrazepam	2.00	1.94	1.71	1.49	1.79
Oxazepam	0.22	0.60	0.36	0.31	0.37

The values obtained for the calculation of the DDD/1 000 registered patients/day for selected antipsychotic and antidepressant drugs are given in Table III. These values were on average much lower than the values calculated for hypnotic and anxiolytic drugs. The fluctuations in the values are most probably due to the low number of patients using these drugs, which are more often prescribed by psychiatrists.

Table III. DDD/1 000 registered patients/day for selected antipsychotic and antidepressant drugs

	DDD/1 000 registered patients/day				
Drug	July	October	January	April	Average
Amitriptyline	0.86	1.08	0.55	1.44	0.98
Clomipramine	0.21	0.17	0.25	0.02	0.16
Desipramine	0.00	0.00	0.00	0.00	0.00
Dothiepin*	0.01	0.02	0.01	0.01	0.01
Flupenthixol	0.03	< 0.01	< 0.01	0.01	0.01
Haloperidol	0.07	0.01	0.01	0.00	0.02
Imipramine	< 0.01	0.01	< 0.01	0.04	0.01
Trimipramine	0.09	0.04	0.11	0.07	0.08

* Estimated by Jacobson *et al.*[8]

In most international drug utilisation studies, the DDD/1 000 inhabitants/day is calculated. Because the DDD/1 000 registered patients/day was calculated in this study, it was not possible to compare the results of this study directly with most overseas studies. However, in a study by Balestrieri *et al.*,[9] antidepressant drug prescription rates of general practitioners working in Verona, Italy, over a 6-year period (1983 - 1988) were analysed using registered patients as the population denominator. The results of their study are compared with the results of the South African study (Table IV). It was found that the values obtained in the South African study were lower. There was, however, a weak relationship between the results of the two studies. In both studies, amitriptyline rated highest, followed by clomipramine.

Table IV. Comparison of the DDD/1 000 registered patients/day for antidepressant drugs in the South African and Italian drug utilisation studies

Antidepressant	Italy[9]	South Africa
Amitriptyline	1.35	0.98
Clomipramine	0.64	0.16
Desipramine	0.01	0.00
Dothiepin	0.13	0.01
Imipramine	0.64	0.01
Trimipramine	0.06	0.08

Cost per DDD

A similar study with regard to the cost per DDD was done by Lucioni and Rossi[10] in 1991. Because of fluctuations in currency values, it is difficult to compare the cost per DDD internationally. However, the cost per DDD is suitable for cost comparisons between different strengths of the same drug, and also between a drug and its generic equivalents.

The cost per DDD for selected hypnotic/anxiolytic drugs and for selected antipsychotic/antidepressant drugs is illustrated in Table V. The highest cost per DDD for hypnotic and anxiolytic drugs was for bromazepam 3 mg (R1.30). Therefore, if bromazepam 3 mg tablets were used according to the daily dose indicated as an international guideline, it would cost the patient R1.30 per day. The cost per DDD was the lowest for diazepam 10 mg and nitrazepam 5 mg (both R0.24 per day).

Table V. Cost per DDD for selected hypnotic and anxiolytic drugs and for selected antipsychotic and antidepressant drugs

Drug	DDD	Strength	Cost per DDD (in rands)
Hypnotic and anxiolytic drugs			
Bromazepam	10 mg	3 mg	1.30
		6 mg	0.93
Diazepam	10 mg	2 mg	0.49
		5 mg	0.46
		10 mg	0.24
Lorazepam	2.5 mg	1 mg	0.50
		2.5 mg	0.45
Oxazepam	50 mg	10 mg	0.40
		15 mg	0.45
		30 mg	0.64
Nitrazepam	5 mg	5 mg	0.24
Antipsychotic and antidepressant drugs			
Amitriptyline	75 mg	10 mg	2.96
		25 mg	1.90
Chlorpromazine	300 mg	25 mg	6.60
		100 mg	4.14
Clomipramine	100 mg	10 mg	10.84
		25 mg	7.68
Desipramine	100 mg	25 mg	7.65
Dothiepin*	100 mg	25 mg	5.88
		75 mg	5.20
Flupenthixol	6 mg	0.25 mg	35.58
		0.5 mg	20.28
		1 mg	18.45
Haloperidol	8 mg	1.5 mg	0.96
Imipramine	100 mg	10 mg	1.32
		25 mg	3.74
Thioridazine	300 mg	10 mg	19.20
		25 mg	14.08
Trimipramine	150 mg	50 mg	4.45

* Estimated by Jacobson *et al.*[8]

It is noticeable that the costs per DDD for antipsychotic and antidepressant drugs are considerably higher than for hypnotic and anxiolytic drugs. The highest cost per DDD for antipsychotic and antidepressant drugs was for flupenthixol 0.25 mg (R35.58).

Relationship between the cost per DDD and the DDD/1 000 registered patients/day

The relationship between the cost per DDD and the DDD/1 000 registered patients/day gives an indication of how consumption of more expensive drugs compares with that of less expensive drugs.

The cost per DDD versus the DDD/1 000 registered patients/day for selected central nervous system drugs on the formulary is illustrated in Fig. 1. From the figure, it can be seen that there was an inverse relationship between the cost per DDD and the DDD/1 000 registered patients/day. This relationship was especially evident in the case of flupenthixol. The DDD/1 000 registered patients/day for flupenthixol was calculated to be 0.01. Flupenthixol was the drug with the highest cost per DDD (R35.58, R20.28 and R18.45 respectively for the 0.25 mg, 0.5 mg and 1 mg strengths). The DDD/1 000 registered patients/day for diazepam was the highest (4.81) for all the values calculated. The cost per DDD of diazepam was, however, low (R0.49, R0.46 and R0.24 for the respective strengths of 2 mg, 5 mg and 10 mg). Drugs with a low cost per DDD were therefore used more than drugs with a high cost per DDD, and vice versa.

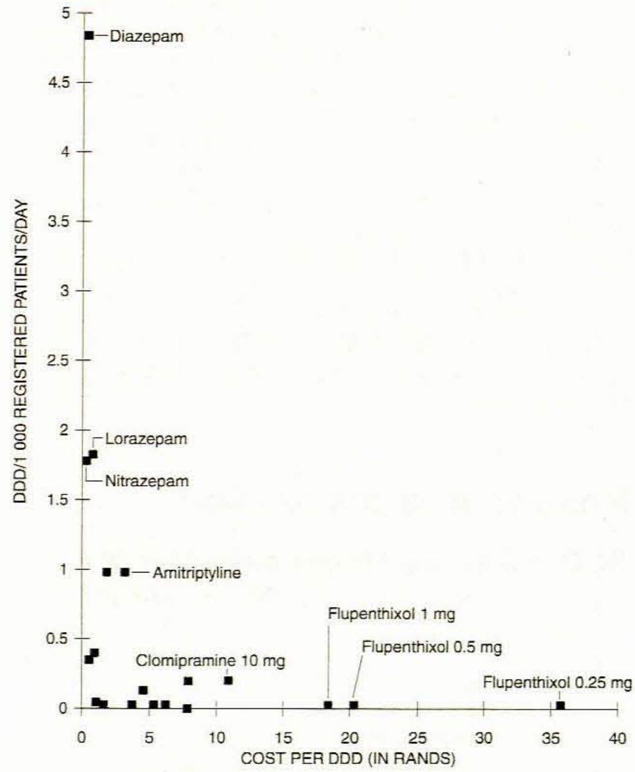

Fig. 1. Cost per DDD versus DDD/1 000 registered patients/day for selected central nervous system formulary drugs.

Conclusion

Drug consumption studies, especially ones that use the DDD methodology, have been undertaken in many countries in Western Europe and elsewhere in the world since the early 1970s. However, research using the DDD method is still lacking in South Africa, despite the important role that it can play in economic planning and the improvement of prescribing practices.

This preliminary study showed that valuable information can be obtained by using the DDD methodology on a retrospective basis. Because DDD calculations are independent of dosage form and price differences, the calculation of DDDs makes it possible to study national and international data retrospectively. Another important advantage of the DDD method is that it is a relatively easy and inexpensive method of calculating drug consumption.

Although the DDD is recognised internationally, the inherent limitations of the DDD as a unit for the measurement of drug consumption must be realised and taken into account when calculating and comparing drug consumption data. Despite its limitations, the DDD methodology is a valuable first step in overall drug use measurement. For more precise estimates of drug use it can and should be supplemented by other drug consumption techniques, e.g. the prescribed daily dose (PDD). The PDD of a drug is the average daily amount that is actually prescribed.

This was the first study of its kind in South Africa and it was therefore not possible to compare the results of this study with those of other local studies. However, the results of this study can be used as a basis for comparison of drug consumption patterns over time if a follow-up study is conducted.

It can be concluded from this study that the DDD methodology is a useful technique to measure and compare drug consumption data nationally and internationally. It can also be regarded as a valuable tool for the promotion of rational and cost-effective use of medicine in a South African future health care system.

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