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# **Benzodiazepine Usage in the North Eastern Health Board Region of the Republic of Ireland**

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## ABSTRACT

**Introduction:** Benzodiazepines are a large group of drugs used as hypnotics, anxiolytics, and tranquillisers, anti convulsants, pre-medication and for intravenous sedation. Extended use of benzodiazepines may lead to dependence and misuse. Use of benzodiazepines, for anxiety disorder and insomnia, is therefore just recommended for short-term use. Current European prescribing guidelines for usage of benzodiazepines for general anxiety is 4 weeks and 1-2 weeks for acute insomnia. Despite prescribing recommendations long-term use is widespread in medical practice, especially among elderly. For many years now concerns have been expressed over the inappropriate use of benzodiazepines in Ireland.

**Aim:** The objective of this study was to determine the feasibility of exploiting government General Medical Services (GMS) data to provide periodic drug utilisation reports, and assess benzodiazepine and related drug usage in the North Eastern Health Board (NEHB) region during the period January 2001 to June 2003.

**Method:** Prescription data over the GMS population, NEHB, from the GMS Payments Boards data records was interrogated by using the database program Filemaker pro 5, and the database analysis program SPSS11.

**Results:** The results shows that the prescribing of benzodiazepines and related drugs gradually increased during the study period and was mainly due to an increasing for the benzodiazepine-related drugs zolpidem and zopiclone. The total average number of Defined Daily Doses (DDD) per prescription items for all included drugs was for the period for 22 days supply. All the hypnotics had average number of DDDs per prescription higher than the recommend, for 14 days supply. As an example, Flunitrazepam, which is classified as a Schedule 3 controlled drug was on average prescribed for 33 days supply. In 2002 48.9% of the users had prescriptions in 3 or more consecutive months, 30.3% received prescriptions in  $\geq 6$  consecutive months and 9.7% had prescriptions in every month during 2002.

**Conclusion:** Although this study has several limitations the results show that the prescribing of benzodiazepines and related drugs in the GMS population, NEHB during January 2001 to June 2003 are high and that many patients seems to be long-term users, which is in conflict with best clinical practice.

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## **1. INTRODUCTION**

Benzodiazepines are a large group of drugs used as anxiolytics, hypnotics, tranquilisers, anticonvulsants, and as intravenous sedatives and for premedication in surgical procedures [4]. They were introduced during the early 1960s as a safer and less toxic alternative to barbiturates. Benzodiazepines are among the most commonly prescribed medications today because of their effectiveness in relieving anxiety and insomnia [3,4,5].

In 1980's it became clear that extended use of benzodiazepines may lead to dependence, misuse and withdrawal reactions [3,5]. Therefore, use of benzodiazepines for anxiety disorder and insomnia is recommended for short-term use[21,22]. Current European prescribing guidelines for benzodiazepines indicated for acute insomnia is for 1-2 weeks and 4-weeks for general anxiety. Symptoms of dependence are characterised by anxiety, dysphoria, perceptual changes, headaches, muscle spasms and sleep disturbance. Other less common symptoms include seizures and episodes of confusion [3,4,5,16]. Abrupt withdrawal after long-term use can induce acute anxiety, psychosis and convulsions. Short-acting benzodiazepines cause more abrupt withdrawal effects than long-acting [4,22]. Long-acting agents are more likely to affect performance and co-ordination the following day.

Studies have suggested that up to 40% of the people who use benzodiazepines for 3 months or longer will develop dependence, but dependence can occur even with shorter periods of 3-6 weeks. Therefore, the duration of treatment is an important factor in preventing dependence [5]. Despite the existence of benzodiazepine prescribing recommendations for some years and the widespread acceptance that prolonged benzodiazepine usage can cause dependence, long-term prescribing is common in medical practice. Long-term use of benzodiazepines for the treatment of anxiety and insomnia has therefore become a major cause for concern. [3, 16, 21, 22]. For example in the Netherlands in 1998 there were 1.9 million benzodiazepine users, a third used benzodiazepines chronically (defined in that study as at least 90 days[7]). The number of chronic users in the Netherlands was estimated to have been

increasing by 50,000 each year, and steps were been taken to decrease the use of benzodiazepines by employing restricted prescribing rules. Despite the prescribing restrictions, the number of prescriptions increased each year by 1.7% from 1993 to 1998 [7]. Other studies had reported that the benzodiazepine consumption is increasing in Spain and Italy, while the UK, Germany and the USA have decreased their total benzodiazepine usage [2, 5, 22].

## **2. BACKGROUND**

The first benzodiazepine, chlordiazepoxide was produced by chance in 1961 after combining a heterocyclic 6-membered ring with methylamine [13]. Soon after that, diazepam was introduced onto the market. Today there are about 20 different benzodiazepines available for clinical use around the world [4]. All the benzodiazepines share the same 7-membered ring and differ by their substituent groups [19].

Benzodiazepine dependence and withdrawal reactions became apparent in the 1980's [3,5]. The risk of developing benzodiazepine dependence increases with the dose and the duration of treatment, the severity of symptoms, the nature of the illness, the expectation of beneficial effect and the intensity of stress factors. The risk is highest among patients with a history of addiction, chronic physical illness, personality disorders and chronic sleep disorders [23]. Benzodiazepine abuse has been a growing problem since the last decade [23]. Exceeding the prescribed dosage and obtaining prescriptions from several different doctors is common, especially among anxious patients with a history of alcohol misuse and among drug abusers [23].

### **2.1 Indications, Definitions and Clinical use**

Benzodiazepines have a wide range of usage. The most common indications are anxiety, insomnia, panic, epilepsy, muscle spasms and pre-surgical stress [4,13,23].

Insomnia and anxiety are the most frequently seen symptoms in general practice [23]. Insomnia is characterised by difficulties with falling asleep or staying asleep. Insomnia is twice as common in women than in men, and increases with age (30-40%

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of people over 65 years are dissatisfied with their sleep)[23]. Anxiety is a normal response to stress, and refers to a feeling of fear or apprehension, together with symptoms of increased sympathetic activity. There are several different types of anxiety. The most common include panic disorder, agoraphobia, other phobias and generalized anxiety. Anxiety disorders are also twice as common in females than male. The onset of most anxiety disorder is in young adulthood, but most cases of generalized anxiety and agoraphobia-panic occurs in the 50-64 year age group [23].

All benzodiazepines have principally the same pharmacological effects - hypnotic, anxiolytic, and anticonvulsant, though they differ in their selectivity and in their duration of action. Most benzodiazepines are well absorbed and rapidly penetrated into the brain due to their high lipid solubility. Hypnotic effects are seen within half-an-hour, and anxiolytic effects within an hour after oral administration. Some of the benzodiazepines indicated for the treatment of muscle spasm and epilepsy can be administered intravenously or rectally for a more rapid effect [13,19, 23]. Benzodiazepines bind strongly to plasma protein, but because of their high lipid solubility they can accumulate in body fat. Their elimination half-lives vary from 6 to 100 hours. Benzodiazepines are all inactivated by hepatic metabolism via oxidation or conjugation, and are excreted as glucuronide conjugates in the urine. Oxidative metabolism of benzodiazepines is decreased in the elderly, in patients with hepatic impairment and in combination with some drugs including alcohol [13, 19, 23].

Benzodiazepines vary greatly in their duration of action, mainly because of their differences in pharmacokinetic behaviour [22]. They can be divided into short-, and long-acting benzodiazepines. Short-acting benzodiazepines (e.g. flurazepam) are used as hypnotics and longer acting ones (e.g. chlordiazepoxide and diazepam) as anxiolytics and tranquillizers. Some anxiolytics can also have hypnotic effects and they are generally divided into:

- Anxiolytics, tranquillizer (anti-anxiety drugs) include:
  - diazepam (Valium®)
  - alprazolam (Alprox®, Calmax®, Gerax® and Xanax®)
  - bromazepam (Lexotan®)

- 
- chlordiazepoxide (Librium®)
  - clobazam (Frisium®)
  - clorazepate (Tranxene®);
  - prazepam (Centrax®)
  - Hypnotics (sleep-inducing drugs) include:
    - flunitrazepam (Rohypnol®)
    - flurazepam (Dalmane®)
    - lorazepam (Dormonox®)
    - lormetazepam (Noctamid®)
    - nitrazepam (Mogadon®, Somnite®)
    - temazepam (Nortem®, Tenox®)
    - triazolam (Halcion®,) [4]

The long-acting benzodiazepine Diazepam (Anxicalm®, Valium®) is also used for the treatment of muscle spasm. Diazepam (Valium®, Sobril®, Diazemuls®) is also used in the treatment of all forms of epilepsy. Clonazepam (Rivotril®), Clobazam (Frisium®) are other benzodiazepines particularly indicated for treatment of different forms of epilepsy, and Lorazepam (Ativan®) may also be used. Midazolam (Hypnovel®) is indicated for premedication. [4,6].

## **2.2 Mechanism of Action and Dependence**

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter, and one of the most common transmitter substances in the central nervous system (CNS). GABA is used as a transmitter in 20-50% of all the synapses in the brain by binding to specific binding sites on GABA receptors, which control chloride channels. When GABA binds to the receptor, chloride channels open, allowing chloride to flow in. This leads to membrane hyperpolarization and synaptic inhibition. Benzodiazepines enhance GABA's effect, through increasing the affinity for its binding site. The enhancement increases GABA's neuro-inhibitory effect, which leads to a decrease in the firing rate of several different neuron in many regions of the CNS. There are three different types of GABA receptors; GABA<sub>A</sub>, GABA<sub>B</sub> and GABA<sub>C</sub>. The benzodiazepines

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interact with specific binding sites on GABA<sub>A</sub> receptors. All benzodiazepines bind to these sites but they differ in their degrees of affinity. There are different subtypes of both GABA<sub>A</sub> receptors and benzodiazepine binding sites, which are expressed in different areas of the CNS. Depending on which area of the brain the inhibitory effect takes place, different pharmacological effects (hypnotic, anxiolytic, and anticonvulsant) occurs [13,19,23,11]. The mechanism of benzodiazepine dependence is due to down-regulation of the expression of the different subunits of the GABA<sub>A</sub> receptor complex [10].

**Zolpidem**, (Stilnoct®) is a non-benzodiazepine with an intermediate hypnotic effect, indicated for short-term treatment of insomnia. This imidazopyridine derivate, binds to one benzodiazepine receptor subtype (omega-1;benzodiazepine-1), where as benzodiazepines binds to three known subtypes. The half-life for Zolpidem is very short, around 2 hours. Therefore, hangover effects are rare but withdrawal effects and tolerance have been reported in patients taking high doses. **Zaleplon** (Sonata®) is a pyrazolopyrimidine indicated for treatment of insomnia. This short acting hypnotic binds selectively to the omega-1;benzodiazepine-1 receptor. The half-life for this substance is around 1 hour. As with benzodiazepines tolerance may develop following repeated use for a few weeks. **Zopiclone**, (Zimoclone®, Zimovane®, Zileze®, Zopitan®,Zorclone®) a cyclopyrrolone, is indicated for short term treatment of insomnia. It binds to two of the benzodiazepine receptor subtypes and has an half-life around 4-6 hours. Zopiclone may have the same potential for dependence and withdrawal effects as benzodiazepines [23,6].

### **2.3 Prevalence, patterns of use and risk factors for use**

The role of benzodiazepines in medical practice is controversial. There are many who consider that benzodiazepine consumption is too high and that the risk of dependence and withdrawal reactions outweighs the positive effects of the drugs, others argue that benzodiazepines are inexpensive, safe and effective in short-term therapy [21]. The reason for this controversy is that benzodiazepines are often used inappropriately and their use has been associated with a number of adverse effects [21].

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The prevalence of benzodiazepine use in different countries varies from 1-10% of the adult population [3,22]. The highest prevalence of usage has been found in females and elderly people [4,16,20]. An Italian study of the use of benzodiazepines in the general population showed that their usage occurred in 9% of the population [16]. Fifty six percent were chronic users receiving daily benzodiazepine for more than six-months (their definition), and seventy percent of the long-term users were over 65 years of age [16]. Another Italian study reported that the use of benzodiazepines has increased by 53% from 1984 to 1999 and showed a prevalence of use of approximately 10% [2].

Several studies have found an association between driving impairment and benzodiazepine use [1, 12, 21]. A Canadian case control study on elderly drivers involved in crashes resulting in injury concluded that long half-life benzodiazepines, such as diazepam and nitrazepam were associated with an increased risk of road traffic accidents [1]. The study did not find the same relationship for short half-life benzodiazepines. A Scottish study of drivers (aged 18 and older) involved in road traffic accidents also found that long half-life benzodiazepines were associated with an increased risk of traffic accidents [12].

Benzodiazepines are mainly prescribed by general practitioners [22]. A Spanish study (from 1996) of the general practitioner's (GP) prescribing patterns concluded that while GPs were knowledgeable about the therapeutic indications for benzodiazepine prescribing, they were far less aware of their potential to induce dependence [5]. Sixty five percent of the doctors thought that the use of benzodiazepines in therapeutic doses was not associated with a risk of dependence, 35% believed that high doses were not likely to induce dependence and 78% thought that use for up to 4 weeks had no risk of dependence.

#### **2.4 Elderly patients**

Benzodiazepines are the most commonly prescribed psychotropic drugs among elderly patients [4,15]. An Irish study of an area in Dublin, from 1999, examined benzodiazepine use among the elderly ( $\geq 65$ years) and reported that the drugs were

used by 17.3% of the study population and that the use was twice as common in females as in men [15]. Many elderly take benzodiazepines on a long-term basis and have been shown to become both physiologically and psychologically dependent [21]. The benzodiazepines used by elderly patients are associated with several other adverse outcomes. The most frequently reported adverse effects includes impaired psychomotor performance and cognitive impairment (especially memory), daytime sedation, motor vehicle accidents and increased risk of falls and fractures. Many studies have reported that the use of benzodiazepines is independently associated with an increased risk of falls among elderly [8,17,18]. Some studies have shown that the use of short-acting benzodiazepines by elderly people is linked to a greater risk of falls, while others have demonstrated a relationship between long-acting benzodiazepines and the risk of falls among the elderly leading to hip fracture. [18]

Long-acting benzodiazepines are likely to accumulate in older people, due to their decreasing metabolic function, which can result in an increased risk for sedative effects and psychomotor impairment [4, 23].

### **2.5 Benzodiazepine Use in The Republic of Ireland**

All benzodiazepines are controlled by Misuse of Drugs Regulations in Ireland and are classed as Controlled Drugs. Two of the benzodiazepine drugs, flunitrazepam and temazepam are classed as Schedule 3 in the Misuse of Drugs Regulations, the rest are listed in Schedule 4 of these regulations [4]. Benzodiazepines and related drugs can only be prescribed on a single prescription and cannot exceed a maximum of 30 days supply [15].

For many years now, concerns have been expressed over the inappropriate use of benzodiazepines in Ireland. The major medical bodies in Ireland (the Irish college of General Practitioners, the Royal College of Psychiatrists and the Royal College of Physicians) recommend that benzodiazepines should not be prescribed for more than 2-4 weeks. However evidence remains of many long-term benzodiazepine users in Ireland and in June 2000 the Benzodiazepine Committee was established by Mr

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Micheal Martin, T.D., and Minister for Health and Children [4]. The aims of the committee were:

- To examine the current prescribing and usage of benzodiazepines and related drugs (zaleplon, zolpidem and zopiclone)
- To consider recommendations on good prescribing and dispensing practice, paying particular attention to the management of drug misusers;
- To make recommendations as appropriate [4].

At the request of the Benzodiazepine Committee, two studies examined the use of benzodiazepines in the Irish GMS population. Both studies used data from the General Medical Services (GMS) scheme records. The first study examined the use of benzodiazepines and related drugs (related drugs = ATC Code N05CF which includes: zaleplon, zolpidem and zopiclone) in the whole adult GSM population over the years 1995 to 2000. Results from this study indicated that the prescribing of benzodiazepines and related drugs are increasing and that the usage in this population was high. Usage of the benzodiazepine and related drugs increased gradually from 87 Defined Daily Doses (DDDs) per 1000 of the adult ( $\geq 15$  years) GMS population (for definition, see below) in 1995 to 116 DDDs in 2000. According to this study 11.6% of the adult GMS population used benzodiazepines and related drugs in 2000 [4].

The other study looked at the benzodiazepine use in the GMS population, Eastern Regional Health Authority area (one of Ireland's eight health authority areas) for two six-month periods (January to June 1999 and January to June 2000). This study showed that the use of benzodiazepines increased with age. The highest prevalence of usage was found in females and among patients in their late 60s and early 70s. Almost 14% of the study population were prescribed benzodiazepines at least once over the six month period in 1999. For the same six month period in 2000, this figure has decreased to 9.9%, which could indicate that the prescribing was reducing slowly over time. The two studies were acknowledged to have had several limitations and the Committee concluded that further evaluations of the prescribing of benzodiazepines in Ireland must be carried out [4].

## **2.6 General Medical Services (GMS) scheme**

The Irish National Health Service is a combination of state supported and private practice service [9]. Approximately 31% (1.24 million) of the Irish population are eligible for General Medical Services (GMS) scheme which supplies all medicines without any cost to socially disadvantaged persons and their dependants, based upon a means test. All persons  $\geq 70$  years of age are also entitled to GMS membership. The GMS population received about 70% of all medications prescribed in general practices at a cost of 340 million Euros in 2000. Community pharmacies providing services for GMS patients use computer software for dispensing and processing the claims information to the GMS Payments Board. The Payments Board then processes the pharmacist's claims and keeps a record of them. The GMS Payments Board data records contains information such as: claim number-, patient GMS number-, prescribing doctor-, pharmacy number, drug name, drug code, ATC level, pharmaceutical form, strength, Defined Daily Doses (DDD), price, month and year. The drugs are classified according to the World Health Organizations (WHO) Anatomical Therapeutic Chemical (ATC) classification system. The quantitative unit Defined Daily Doses (DDDs) is the assumed average maintenance dose per day for a drug used for its main indication in adults [24]. For each drug a theoretical daily dose (DDD) has been defined based on the recommended daily use by an adult for the drugs main indication. The DDDs for the drugs are updated by the WHO Collaborating Centre for Drug Statistics methodology in Oslo, Norway.

## **2.7 GMS in North Eastern Health Board (NEHB)**

The North Eastern Health Board covers the Republic of Ireland counties of Louth, Meath, Cavan and Monaghan (see map below) with a total population of 344.965 persons in November 2003. In Nov 2003 30.09% (103454/344.965) of the NEHB population was eligible for GMS and of those 77.6% (80.503/103.787) were  $\geq 15$  years old. For the same period there was 154 GMS Panel Agreements in NEHB (154 General Practitioners in the area available for the GMS population).



The white area show the North Eastern Health Board area, Ireland.

### **3. AIM**

The objective of this study was to determine the feasibility of exploiting government General Medical Services (GMS) data to provide periodic drug utilisation reports, and assess benzodiazepine and related drug usage in the North Eastern Health Board (NEHB) region during the period January 2001 to June 2003.

### **4. METHOD**

Prescription data from the GMS Payments Boards data records were available for evaluation and analysis. The GMS Payments Board data records from the period of January 2001 to June 2003 was interrogated by using the database program Filemaker pro 5 and the database analysis program SPSS11 to study prescribing and usage patterns of benzodiazepines and related drugs; zaleplon, zolpidem and zopiclone among the Republic of Ireland's NEHB region GMS patients. The GMS population in the NEHB constitute approximately 30% of the total population in NEHB (for more details see Table 1 Population Data). The GMS Payments Board data records contain information such as; claim-, patient-, prescribing doctor-, pharmacy number, drug name, drug code, ATC level, pharmaceutical form, strength, Defined Daily Doses (DDD), price, month and year. The drugs were classified according to the World Health Organisations (WHO) Anatomical Therapeutic Chemical (ATC) classification system.

In this study records with ATC codes N05BA (anxiolytics containing benzodiazepine derivatives), N05CD (hypnotics containing benzodiazepine derivatives), N03AE01 (Clonazepam, antiepileptic) and N05CF (hypnotics containing benzodiazepine related drugs) were included and examined. The drugs with ATC code N05CF (Zaleplon, Zolpidem and zopiclone) were included since they have similar effects as benzodiazepines, use of them are increasing and they may cause dependence, withdrawal effects and abuse.

The data record files were available on the database File maker pro 5 on a Macintosh computer and included two six months files with 2001 data (Jan-Jun) and (Jul-Dec) and one file for every month, for 2002 and for the first six month in 2003 (Jan-Jun). After collecting all the useful data from the File maker pro and creating and converting it into new files, the data were transferred to a PC. On the database analysis program SPSS 11 the files were merged together into six-month files, (Jan-Jun: 2001, 2002 and 2003) and (Jul-Dec: 2001, 2002) and year files (2001 and 2002). There were no data available for the second six months period in 2003 at the time for the study. All the descriptive statistics which for example included frequencies and cross-tabulations of the data were then made on SPSS11.

As a quantitative unit Defined Daily Doses (DDD) was used, which is the unit normally used in drug utilisation studies. DDDs are the assumed average maintenance dose per day for a drug used for its main indication in adults. The number of DDDs per prescription was calculated with following formula:

Quantity/ (DDD (mg)/Strength (mg)). To estimate the proportion of the population treated daily with benzodiazepines, and to compare the results with other studies, the drug consumption were expressed in terms of the number of DDDs per 1000 of the adult ( $\geq 15$  years), and overall GMS population in North Eastern Health Board Region, Ireland.

The literature search used the database PubMed and searches for articles with the keywords: benzodiazepine use, benzodiazepines AND prescription patterns, benzodiazepines AND elderly, benzodiazepines AND long-term use, benzodiazepines

AND withdrawal, benzodiazepines AND dependence were carried out. Trinity College library on-line ([www.tcd.ie](http://www.tcd.ie)) was used to search for literature about the subject and the British National Formulary web-site ([www.bnf.org](http://www.bnf.org)) was used to search for information about all the included substances.

## **5. RESULTS**

### **North Eastern Health Board (NEHB) Populations**

<b>Time Period</b>	<b>NEHB Region</b>	<b>GMS Patients</b>	<b>Adult GMS (&gt;15 yrs.)</b>	<b>% Adults GMS Patients</b>	<b>Benzodiazepine patients*</b>	<b>Adult Benzodiazepine patients*</b>	<b>% Adult Benzodiazepine patients</b>
<b>2001</b>	<b>No Statistics Available</b>	105,247 (Dec)	81,802	77,7	20,114	19892	98,9
<b>2001 (Jan-June)</b>	-	-	-		14,081	13,962	99,1
<b>2001 (July-Dec)</b>	-	-	-		16,149	16,029	99,3
<b>2002</b>	344,926 (Dec)	104,445 (Dec)	81,061	77,6	21,513	21,273	98,9
<b>2002 (Jan-June)</b>	-	-	-		16,527	16,391	99,2
<b>2002 (July-Dec)</b>	-	-	-		16,724	16,600	99,3
<b>2003</b>	344,965 (Nov)	103,787 (Nov)	80,503	77,6	N/A	N/A	
<b>2003 (Jan-June)</b>	-	-	-		16,815	16,695	99,3

\* GMS Patients prescribed benzodiazepine or related drug (N05BA, N05CD, N05CF, N03AE01)

**Table 1. Population Data North Eastern Health Board (NEHB).**

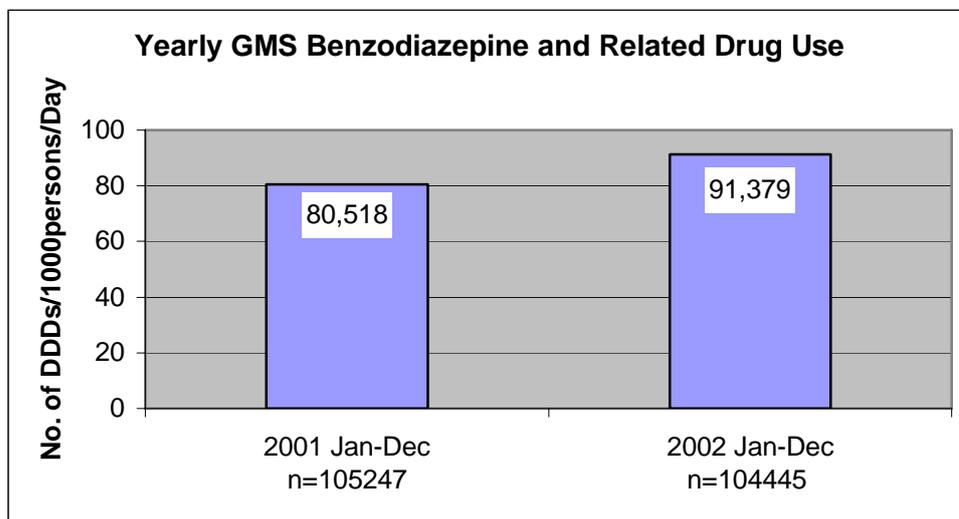
The North Eastern Health Board covers the counties of Louth, Meath, Cavan and Monaghan with a total population of 344926 persons in December 2002 and 344965 persons in November 2003. In 2002 and 2003 approximately 30% of the total NEHB population was eligible for the GMS scheme. Prior to 2002, the most recent population survey of the NEHB region was conducted in 1996, therefore the proportion of the population eligible for the General Medical Services could not be determined for 2001.

Throughout the period January 2001 to July 2003 about 78% of the GMS population were adults ( $\geq 15$  years). Of the prescribed benzodiazepines and related drugs 99% were for adult persons.

### **5.1 Analysis of the prescribing of GMS Benzodiazepine and Related Drug Usage**

#### **Yearly Data**

In 2001 the use of benzodiazepines and related drugs, expressed as the total number of DDDs/1000 GMS Patients/Day dispensed was 80.52. In 2002 this figure had increased by 13.5% to 91.38% (See Chart 1 and Table 3).



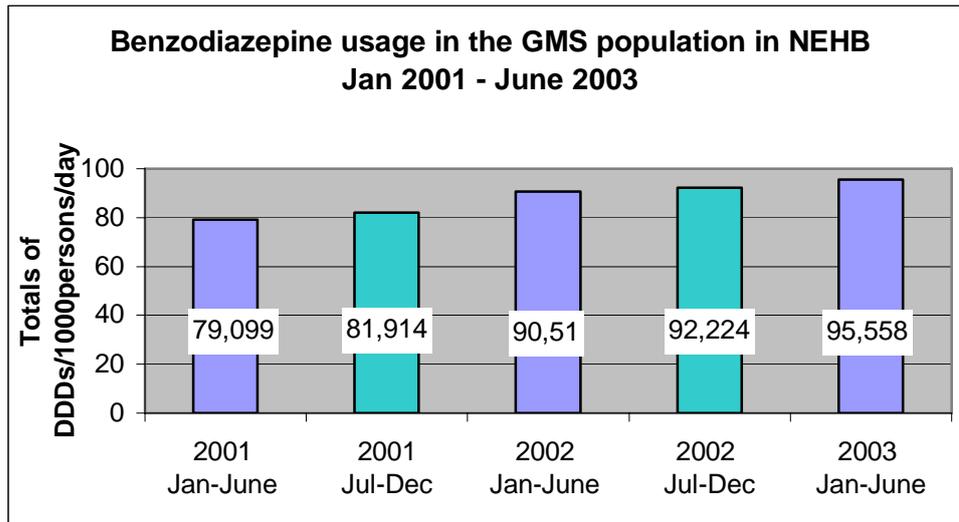
*Chart 1. Benzodiazepine and Related Drug Usage 2001 and 2002.*

	<b>2001</b>	<b>2002</b>
<b>No. of DDDs/1000 patients/Day</b>	80.518	91.379
<b>No. of Prescription Items</b>	140,757	160,985
<b>No. of Claims</b>	115,599	143,171

*Table 2. Yearly Benzodiazepine and Related Drug Usage Six-Month Data*

The prescribing of benzodiazepines and related drugs in the GMS population NEHB gradually increased during the study period January 2001 to June 2003. The dispensed quantity, expressed in terms as the total number of DDDs/1000 GMS Patients/Day was for the first six-month period 2001 was 79.1. For the same period in

2002 this figure increased by 14.4% to 90.51 and in 2003 by 6% to 95.6 (see Table 3 and Chart 2). For the second six month period of 2001 the total number of DDDs/1000 patients/Day was 81.9 and had increased by 12.6% to 92.2 in 2002. There was no data available for the second six month period of 2003 (see Table 4 and Chart 2). The dispensed amount increased by almost 21% over the whole study period.



*Chart 2. Benzodiazepine and Related Drug Usage January 2001-June 2003*

<b>1<sup>st</sup> Six-Month period of Each Year</b>			
<b>Jan-Jun</b>	<b>2001</b>	<b>2002</b>	<b>2003</b>
<b>No. of DDDs/1000 patients/Day</b>	79.099	90.510	95.558
<b>No. of Prescription Items</b>	67,967	78,747	83,227
<b>No. of Claims</b>	50,424	69,958	73,855

*Table 3. Jan-Jun Benzodiazepine and Related Drug Usage*

<b>2<sup>nd</sup> Six-Month period of Each Year</b>		
<b>July-Dec</b>	<b>2001</b>	<b>2002</b>
<b>No. of DDDs/1000 patients/Day</b>	81,914	92,224
<b>No. of Prescription Items</b>	72,790	72,240
<b>No. of Claims</b>	65,176	73,213

*Table 4. Jul-Dec Benzodiazepine and Related Drug Usage*

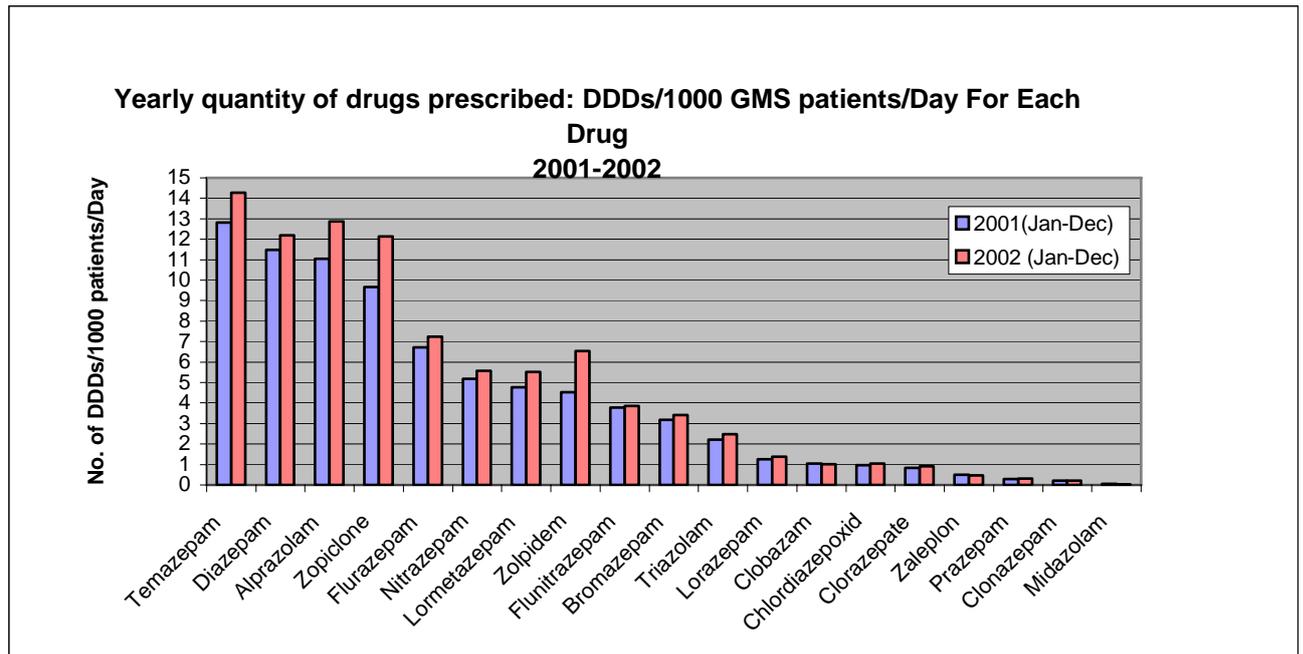
## 5.2 Breakdown by Drug Analysis

### Yearly Data

When comparing the total number of DDDs/1000/Day for each drug separately, all the typical anxiolytics and hypnotics increased in 2002 compared to 2001. The highest increase was seen for Alprazolam (anxiolytics), Temazepam (hypnotic), Zolpidem (non-benzodiazepine hypnotic) and Zopiclone (non-benzodiazepine hypnotic). The total number of DDDs/1000/Day fell slightly for four of the drugs; Zaleplon (non-benzodiazepine hypnotics), Clobazam (antiepileptic,) Midazolam (premedication) and clonazepam (antiepileptic). When the percentage of the total number of DDDs for each drug is compared, only Zolpidem and Zopiclone increased. Tablets and capsules were the main dose forms prescribed, which explains why the total number of DDDs/1000/Day was almost the same when just including these dose forms (See Table 5 and Chart 3).

International Non-Proprietary Name	No. of DDDs /1000 Patients/Day (All Dosage Forms)		
	ATC code	2001	2002
<i>Alprazolam</i>	N05BA12	<b>11.048</b> (13.72%)	<b>12.865</b> (14.08%)
<i>Bromazepam</i>	N05BA08	<b>3.172</b> (3.94%)	<b>3.421</b> (3.74%)
<i>Chlordiazepoxide</i>	N05BA02	<b>0.960</b> (1.19%)	<b>1.039</b> (1.14%)
<i>Clobazam</i>	N05BA09	<b>1.046</b> (1.30%)	<b>1.003</b> (1.10%)
<i>Clonazepam</i>	N03AE01	<b>0.209</b> (0.26%)	<b>0.205</b> (0.22%)
<i>Clorazepate</i>	N05BA05	<b>0.842</b> (1.05%)	<b>0.908</b> (0.99%)
<i>Diazepam</i>	N05BA01	<b>11.476</b> (14.25%)	<b>12.192</b> (13.34%)
<i>Flunitrazepam</i>	N05CD03	<b>3.782</b> (4.70%)	<b>3.845</b> (4.20%)
<i>Flurazepam</i>	N05CD01	<b>6.720</b> (8.34%)	<b>7.234</b> (7.92%)
<i>Lorazepam</i>	N05BA06	<b>1.256</b> (1.56%)	<b>1.372</b> (1.50%)
<i>Lormetazepam</i>	N05CD06	<b>4.769</b> (5.92%)	<b>5.522</b> (6.04%)
<i>Midazolam</i>	N05CD08	<b>0.045</b> (0.06%)	<b>0.038</b> (0.04%)
<i>Nitrazepam</i>	N05CD02	<b>5.191</b> (6.44%)	<b>5.560</b> (6.08%)
<i>Prazepam</i>	N05BA11	<b>0.295</b> (0.36%)	<b>0.314</b> (0.34%)
<i>Temazepam</i>	N05CD07	<b>12.801</b> (15.90%)	<b>14.268</b> (15.60%)
<i>Triazolam</i>	N05CD05	<b>2.226</b> (2.76%)	<b>2.461</b> (2.69%)
<i>Zaleplon</i>	N05CF03	<b>0.498</b> (0.62%)	<b>0.463</b> (0.51%)
<i>Zolpidem</i>	N05CF02	<b>4.529</b> (5.62%)	<b>6.539</b> (7.16%)
<i>Zopiclone</i>	N05CF01	<b>9.673</b> (12.01%)	<b>12.124</b> (13.27%)
<b>Total No. of DDDs/1000/Day</b>		<b>80.518</b> (100%)	<b>91.374</b> (100%)
<b>Total DDDs/1000/Day (Tabs &amp; Caps)</b>		<b>80.414</b>	<b>91.283</b>

Table 5. Yearly Total GMS Population Usage of Benzodiazepine and Related Drugs



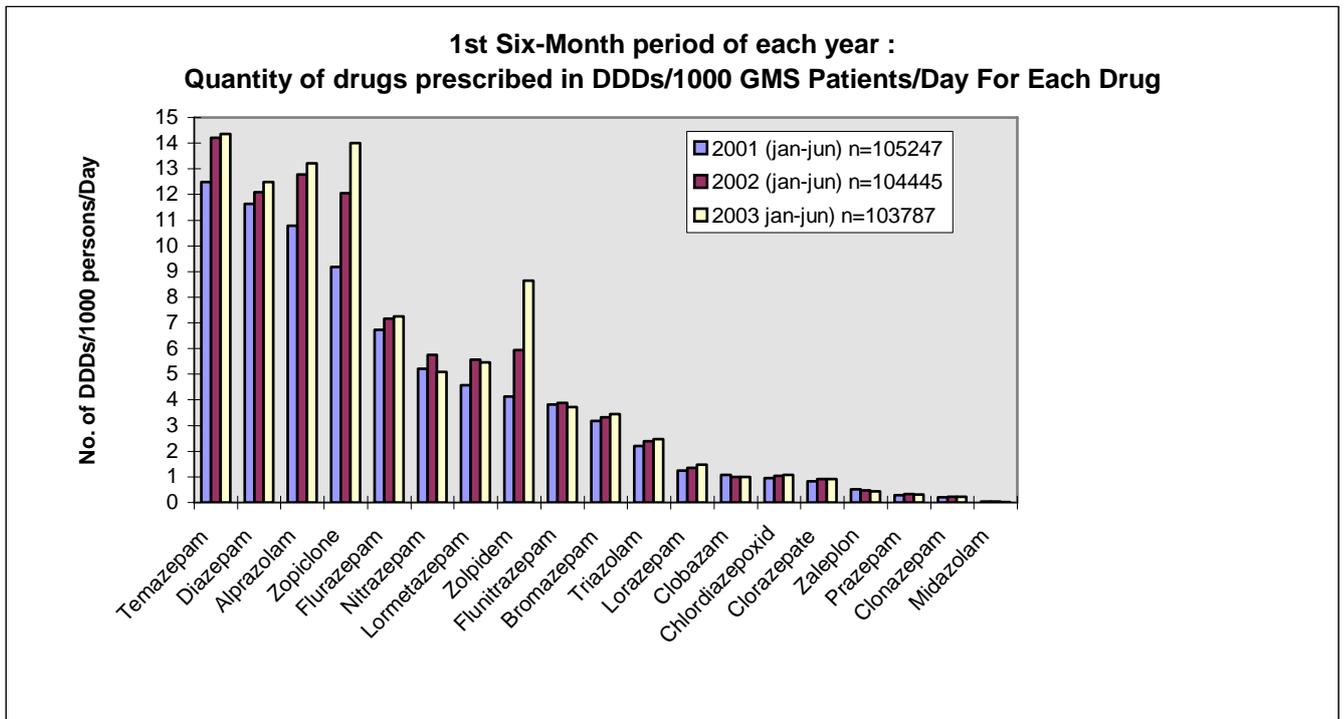
**Chart 3.** Yearly No. of DDDs/1000 GMS patients/Day For Each Drug

**Six-Month Data**

As for the 12 month data, the dispensed quantity of the most frequently prescribed anxiolytics and hypnotics were greater for Jan-June 2002 compared to the same period in 2001. The increase between the six month period in 2002 and 2003 was smaller than between 2001 and 2002 and was mainly due to an increase for the benzodiazepine-related drugs Zolpidem and Zopiclone. Although there was a small increase for the benzodiazepine drugs Temazepam (hypnotic), Diazepam (anxiolytic, anticonvulsant), Alprazolam (anxiolytic), Flurazepam (hypnotic) and Lorazepam (anxiolytics, anticonvulsant). The number of DDDs/1000/Day was lower in 2003 compared to 2001 and 2002 for the drugs Zaleplon (non-benzodiazepine hypnotic), Clobazam (antiepileptic), Flunitrazepam (hypnotic) and Midazolam (premedication). When the percentage of the total number of DDDs for the individual drugs was compared, only Zolpidem and Zopiclone showed an increase. Zolpidem constituted 5.2% of the total number of DDDs in 2001 and increased to 9.0% in 2003. Zopiclone increased from 11.65% in 2001 to 14.65% in 2003. As for the 12 month data the main dose forms were tablets and capsules so the difference between the total numbers of DDDs/1000/Day for all dose forms and for just tablets and capsules was minimal (see Table 6 and Chart 4).

<b>1<sup>st</sup> Six-Month period of Each Year (Jan-Jun)</b>				
<b>International Non-Proprietary Name</b>	<b>No. of DDDs/1000 GMS Patients/Day</b>			
	<b>ATC code</b>	<b>2001</b>	<b>2002</b>	<b>2003</b>
<i>Alprazolam</i>	N05BA12	<b>10.778</b> (13.63%)	<b>12.78</b> (14.12%)	<b>13.207</b> (13.82%)
<i>Bromazepam</i>	N05BA08	<b>3.170</b> (4.00%)	<b>3.319</b> (3.67%)	<b>3.439</b> (3.60%)
<i>Chlordiazepoxide</i>	N05BA02	<b>0.949</b> (1.20%)	<b>1.031</b> (1.14%)	<b>1.089</b> (1.14%)
<i>Clobazam</i>	N05BA09	<b>1.079</b> (1.36%)	<b>1.007</b> (1.11%)	<b>0.988</b> (1.03%)
<i>Clonazepam</i>	N03AE01	<b>0.209</b> (0.26%)	<b>0.225</b> (0.25%)	<b>0.237</b> (0.25%)
<i>Clorazepate</i>	N05BA05	<b>0.840</b> (1.06%)	<b>0.910</b> (1.01%)	<b>0.914</b> (0.96%)
<i>Diazepam</i>	N05BA01	<b>11.639</b> (14.71%)	<b>12.099</b> (13.37%)	<b>12.476</b> (13.05%)
<i>Flunitrazepam</i>	N05CD03	<b>3.820</b> (4.83%)	<b>3.879</b> (4.29%)	<b>3.718</b> (3.89%)
<i>Flurazepam</i>	N05CD01	<b>6.735</b> (8.51%)	<b>7.174</b> (7.93%)	<b>7.241</b> (7.58%)
<i>Lorazepam</i>	N05BA06	<b>1.250</b> (1.58%)	<b>1.346</b> (1.49%)	<b>1.466</b> (1.53%)
<i>Lormetazepam</i>	N05CD06	<b>4.562</b> (5.77%)	<b>5.572</b> (6.16%)	<b>5.463</b> (5.72%)
<i>Midazolam</i>	N05CD08	<b>0.041</b> (0.05%)	<b>0.042</b> (0.05%)	<b>0.027</b> (0.03%)
<i>Nitrazepam</i>	N05CD02	<b>5.218</b> (6.60%)	<b>5.745</b> (6.35%)	<b>5.094</b> (5.33%)
<i>Prazepam</i>	N05BA11	<b>0.295</b> (0.37%)	<b>0.325</b> (0.36%)	<b>0.319</b> (0.33%)
<i>Temazepam</i>	N05CD07	<b>12.488</b> (15.79%)	<b>14.202</b> (15.69%)	<b>14.356</b> (15.02%)
<i>Triazolam</i>	N05CD05	<b>2.196</b> (2.78%)	<b>2.382</b> (2.30%)	<b>2.464</b> (2.58%)
<i>Zaleplon</i>	N05CF03	<b>0.521</b> (0.66%)	<b>0.470</b> (0.52%)	<b>0.427</b> (0.45%)
<i>Zolpidem</i>	N05CF02	<b>4.128</b> (5.22%)	<b>5.939</b> (6.56%)	<b>8.636</b> (9.04%)
<i>Zopiclone</i>	N05CF01	<b>9.181</b> (11.61%)	<b>12.058</b> (13.32)	<b>13.998</b> (14.65%)
<b>Total No. of DDDs/1000/Day</b>		<b>79.100</b> (100%)	<b>90.510</b> (100%)	<b>95.559</b> (100%)
<b>Total No. of DDDs/1000/Day (Tabs &amp; Caps)</b>		<b>78.993</b>	<b>90.419</b>	<b>95.474</b>

**Table 6.** Total GMS Population Usage of Benzodiazepine and Related Drugs for the 1<sup>st</sup> six-month periods in 2001, 2002 and 2003.



**Chart 4.1<sup>st</sup>** Six-Month of each year: No. of DDDs/1000 GMS patients/Day for Each Drug

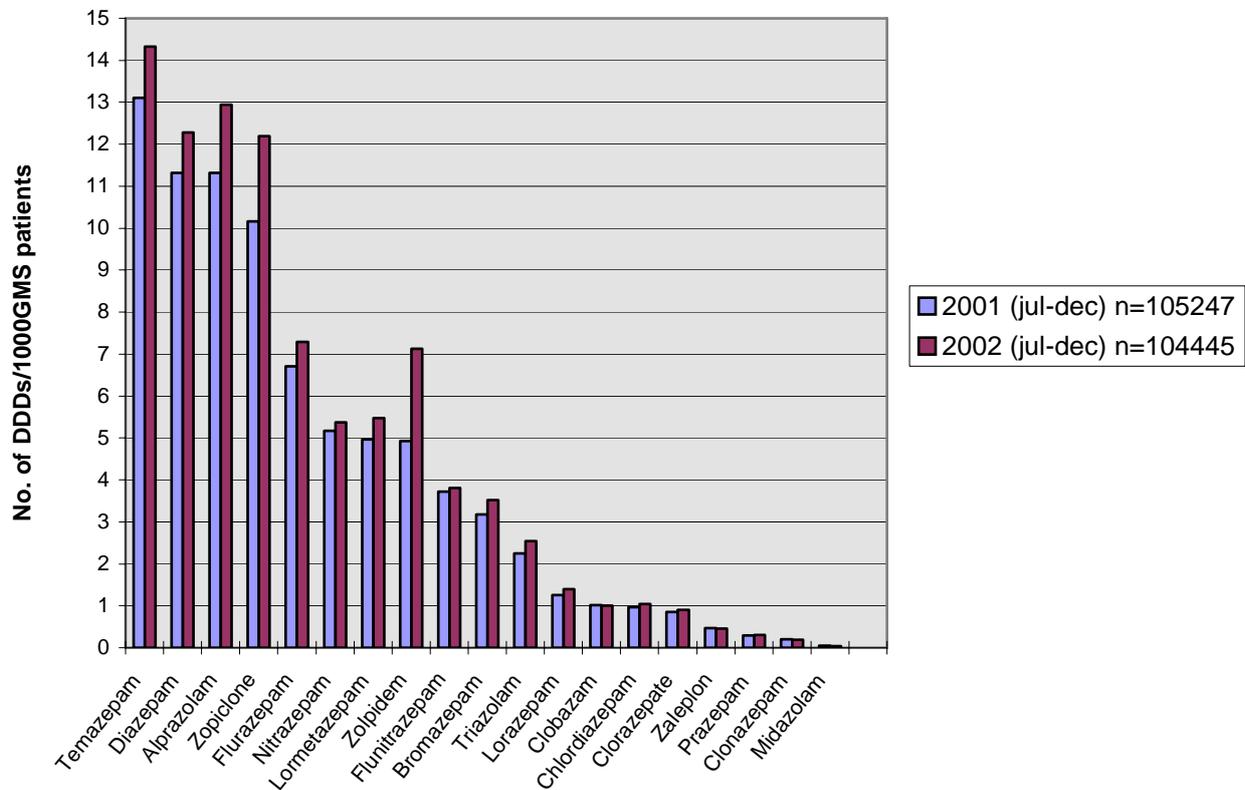
**2<sup>nd</sup> Six Month Period**

The trend for the period Jul-Dec was the same as for the entire year data: the dispensed quantity, expressed as the total number of DDDs/1000 GMS Patients/Day for all the included drugs and all dose forms was higher 2002 than for the same period in 2001. In 2001 the total number of DDDs/1000 GMS Patients/Day was 81.9 and increased by 12.6% to 92.2 in 2002. The quantities prescribed for all the typical anxiolytics and hypnotics were greater for the period in 2002 compared to 2001. The greatest increase was seen for the drugs Alprazolam (anxiolytic), Temazepam (hypnotic), Zolpidem (non-benzodiazepine hypnotic) and Zopiclone (non-benzodiazepine hypnotic) (See Table 7 and Chart 5). The numbers were also higher for the 2<sup>nd</sup> six-month period compared to the 1<sup>st</sup> six-month period of 2001 and 2002.

<b>2<sup>nd</sup> Six-Month period of each year (Jul-Dec)</b>				
<b>International Proprietary Name</b>	<b>Non-</b>	<b>No. of DDDs/1000 GMS Patients/Day</b>		
		<b>ATC code</b>	<b>2001 (July-Dec)</b>	<b>2002 (July-Dec)</b>
<i>Alprazolam</i>		N05BA12	<b>11.313</b> (13,81%)	<b>12.947</b> (14,04%)
<i>Bromazepam</i>		N05BA08	<b>3.174</b> (3,87%)	<b>3.521</b> (3,82%)
<i>Chlordiazepoxide</i>		N05BA02	<b>0.970</b> (1,18%)	<b>1.047</b> (1,14%)
<i>Clobazam</i>		N05BA09	<b>1.014</b> (1,24%)	<b>0.998</b> (1,08%)
<i>Clonazepam</i>		N03AE01	<b>0.208</b> (0,25%)	<b>0.185</b> (0,2%)
<i>Clorazepate</i>		N05BA05	<b>0.845</b> (1,03%)	<b>0.907</b> (0,98%)
<i>Diazepam</i>		N05BA01	<b>11.316</b> (13,81%)	<b>12.283</b> (13,32%)
<i>Flunitrazepam</i>		N05CD03	<b>3.723</b> (4,55%)	<b>3.812</b> (4,13%)
<i>Flurazepam</i>		N05CD01	<b>6.705</b> (8,19%)	<b>7.292</b> (7,91%)
<i>Lorazepam</i>		N05BA06	<b>1.262</b> (1,54%)	<b>1.397</b> (1,51%)
<i>Lormetazepam</i>		N05CD06	<b>4.972</b> (6,07%)	<b>5.473</b> (5,93%)
<i>Midazolam</i>		N05CD08	<b>0.049</b> (0,06%)	<b>0.034</b> (0,037%)
<i>Nitrazepam</i>		N05CD02	<b>5.164</b> (6,3%)	<b>5.378</b> (5,83%)
<i>Prazepam</i>		N05BA11	<b>0.295</b> (0,36%)	<b>0.304</b> (0,33%)
<i>Temazepam</i>		N05CD07	<b>13108</b> (16,0%)	<b>14.333</b> (15,54%)
<i>Triazolam</i>		N05CD05	<b>2.243</b> (2,74%)	<b>2.539</b> (2,75%)
<i>Zaleplon</i>		N05CF03	<b>0.472</b> (0,58%)	<b>0.456</b> (0,49%)
<i>Zolpidem</i>		N05CF02	<b>4.923</b> (6,01%)	<b>7.130</b> (7,73%)
<i>Zopiclone</i>		N05CF01	<b>10.157</b> (12,40%)	<b>12.190</b> (13,22%)
<b>Total No of DDDs/1000/Day</b>			<b>81.914</b> (100%)	<b>92.224</b> (100%)
<b>Total No. of DDDs/1000/Day (Tabs &amp; Caps)</b>			<b>81.811</b>	<b>92.132</b>

*Table 7. Total GMS Population Usage of Benzodiazepine and Related Drugs for the 2<sup>nd</sup> six-month period in 2001 and 2002.*

**2nd Six-Month period of each year: Quantity of drugs prescribed in DDDs/1000  
GMS Patients/Day For Each Drug**



**Chart 5.** 2nd Six-Month period of each year: Quantity prescribed in DDDs/1000 GMS Patients/Day for Each Drug

**5.3 Adult GMS Population Benzodiazepine and Related Drug Usage**

**Yearly Data**

The use of benzodiazepines or related drugs in the adult GMS population NEHB, in terms as number of DDDs/1000 GMS Adults/Day dispensed was 103.48 for the year 2001 and increased by 13.6% to 117.56 during 2002. The prescribed quantities for both the hypnotics and anxiolytics were higher in 2002 compared to 2001.

The highest increasing is seen for Alprazolam (anxiolytic), Temazepam (hypnotic), Zolpidem (non-benzodiazepine hypnotics) and Zopiclone (non-benzodiazepine hypnotics). The total number of DDDs/1000/Day prescribed decreased for Zaleplon

(non-benzodiazepine hypnotics), Clobazam (antiepileptic), Midazolam (premedication) and Clonazepam (antiepileptic) (see Table 8 and Chart 6, 7).

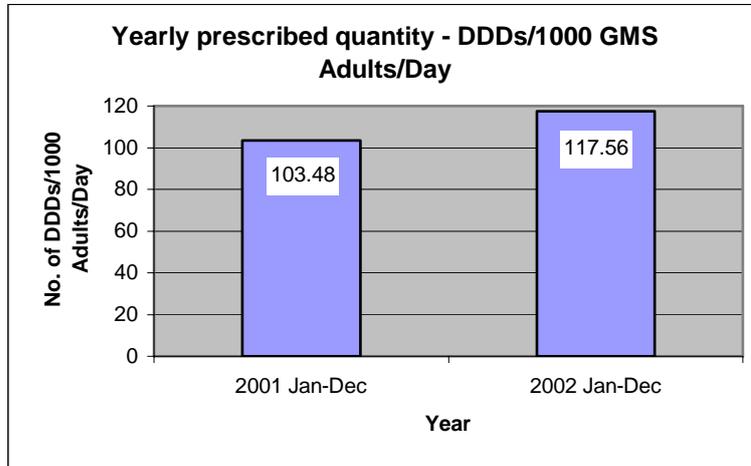


Chart 6. Yearly No. of DDDs/1000 GMS Adults/Day, 2001 and 2002.

Prescribed quantity - DDD/1000 GMS Adults/Day			
International Non-Proprietary Name (All dosage forms)	ATC code	2001 (n=81802)	2002 (n=81061)
<i>Diazepam</i>	N05BA01	14.731 (14.24%)	15.662 (13.32%)
<i>Chlordiazepoxide</i>	N05BA02	1.234 (1.19%)	1.338 (1.14%)
<i>Clorazepate</i>	N05BA05	0.641 (0.61%)	1.169 (0.99%)
<i>Lorazepam</i>	N05BA06	1.616 (1.56%)	1.765 (1.5%)
<i>Bromazepam</i>	N05BA08	4.078 (3.94%)	4.403 (3.75%)
<i>Clobazam</i>	N05BA09	1.341 (1.30%)	1.288 (1.10%)
<i>Prazepam</i>	N05BA11	0.379 (0.37%)	0.405 (0.34%)
<i>Alprazolam</i>	N05BA12	14.184 (13.71%)	16.528 (14.06%)
<i>Flurazepam</i>	N05CD01	8.644 (8.35%)	9.316 (7.92%)
<i>Nitrazepam</i>	N05CD02	6.678 (6.45%)	7.164 (6.09%)
<i>Flunitrazepam</i>	N05CD03	4.850 (4.69%)	4.955 (4.21%)
<i>Triazolam</i>	N05CD05	2.855 (2.76%)	3.167 (2.7%)
<i>Lormetazepam</i>	N05CD06	6.133 (5.93%)	7.113 (6.05%)
<i>Temazepam</i>	N05CD07	16.462 (15.91%)	18.372 (15.63%)
<i>Midazolam</i>	N05CD08	0.057 (0.06%)	0.048 (0.04%)
<i>Zopiclone</i>	N05CF01	12.431 (12.01%)	15.606 (13.28%)
<i>Zolpidem</i>	N05CF02	5.817 (5.62%)	8.400 (7.15%)
<i>Zaleplon</i>	N05CF03	0.638 (0.62%)	0.595 (0.51%)
<i>Clonazepam</i>	N03AE01	0.268 (0.26%)	0.264 (0.22%)
<b>Total No of DDDs/1000/Day</b>		<b>103.477 (100%)</b>	<b>117.559 (100%)</b>
<b>Total No. of DDDs/1000/Day (Tabs &amp; Caps)</b>		<b>103.349</b>	<b>117.447</b>

Table 8. Yearly Adult GMS Population Usage of Benzodiazepine and Related Drugs

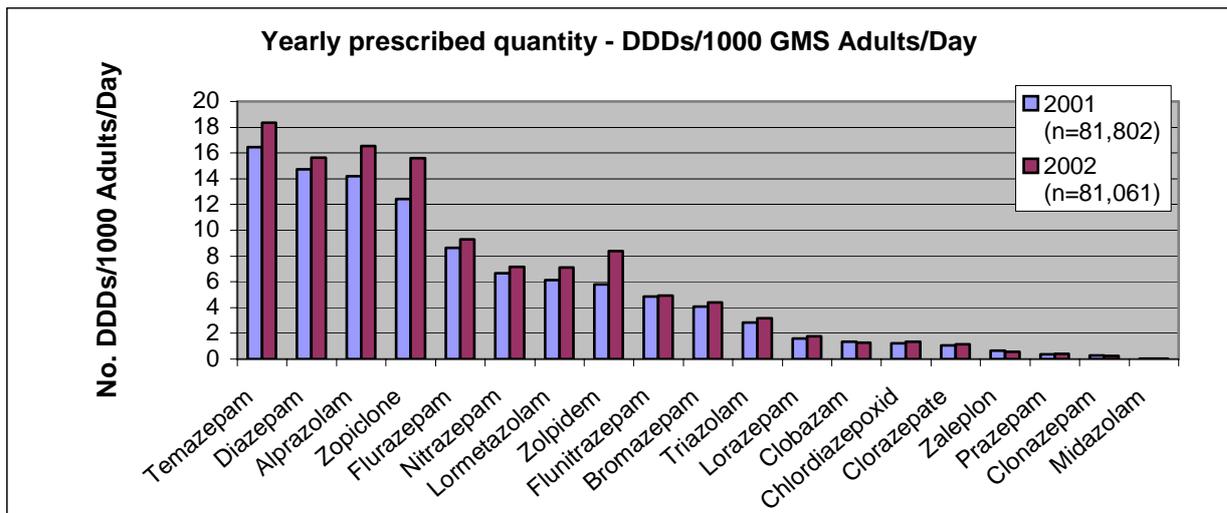
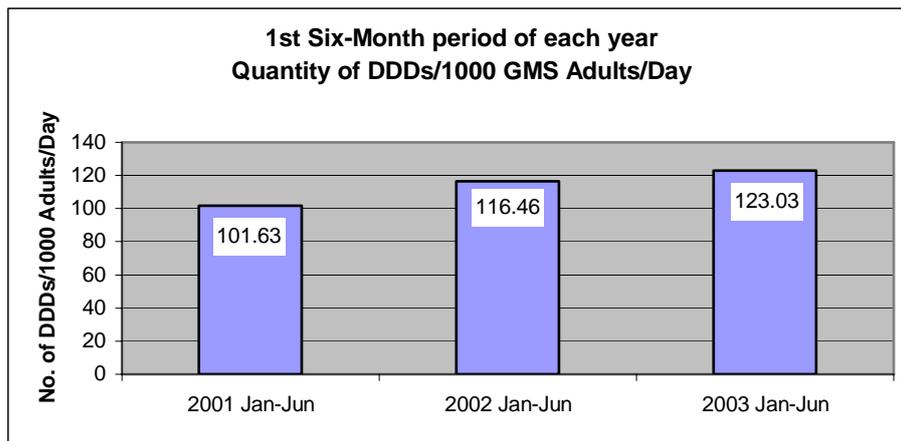


Chart 7. Yearly prescribed quantity: DDDs/1000 GMS Adults/Day for Each Drug

### **Six-Month Data – 1<sup>st</sup> Six-Month Period**

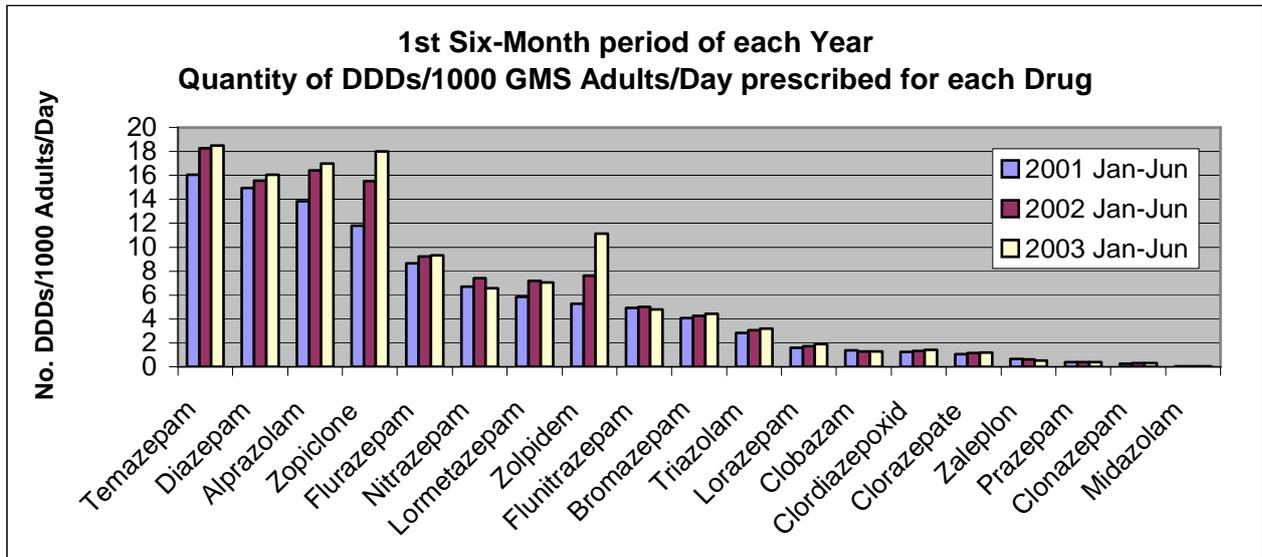
The overall prescribing of benzodiazepines and related drugs gradually increased during the 1<sup>st</sup> six month periods of 2002 and of 2003 compared to 2001. The total number of DDDs/1000 GMS Adults/Day for all the included drugs increased from 101.6 in the 1<sup>st</sup> six month period of 2001 by 14.7% to 116.5 in Jan-June 2002 and by 5.6% to 123.0 for the same period in 2003. The increase was greater between 2001 and 2002 than between 2002 and 2003. All of the most frequently prescribed anxiolytics and hypnotics increased in usage during Jan-Jun in 2001 compared to the same period in 2002. But the increase between the six month period in 2002 and 2003 was mainly due to an increase in the benzodiazepine-related drugs Zolpidem and Zopiclone. If the figures for the total number of DDDs per drug are compared, Zolpidem and Zopiclone were the only drugs that are increased. Zolpidem constituted 5.2% of the total number of DDDs in 2001 and increased to 9.0% in 2003. Zopiclone increased from 11.60% in 2001 to 14.7% in 2003.



*Chart 8. 1<sup>st</sup> Six-Month period of each year prescribed quantity: DDDs/1000 GMS Adults/Day during 2001, 2002 and 2003.*

International Non-Proprietary Name (All dosage forms)	ATC code	No. of DDDs/1000 GMS Adults/Day		
		2001 Jan-Jun	2002 Jan-Jun	2003 Jan-Jun
<i>Diazepam</i>	N05BA01	<b>14.938</b> (14.70%)	<b>15.554</b> (13.36%)	<b>16.040</b> (13.04%)
<i>Chlordiazepoxide</i>	N05BA02	<b>1.221</b> (1.20%)	<b>1.328</b> (1.14%)	<b>1.404</b> (1.14%)
<i>Clorazepate</i>	N05BA05	<b>1.081</b> (1.06%)	<b>1.170</b> (1.00%)	<b>1.178</b> (0.96%)
<i>Lorazepam</i>	N05BA06	<b>1.608</b> (1.58%)	<b>1.732</b> (1.49%)	<b>1.890</b> (1.54%)
<i>Bromazepam</i>	N05BA08	<b>4.075</b> (4.00%)	<b>4.273</b> (3.67%)	<b>4.431</b> (3.60%)
<i>Clobazam</i>	N05BA09	<b>1.384</b> (1.36%)	<b>1.290</b> (1.11%)	<b>1.273</b> (1.03%)
<i>Prazepam</i>	N05BA11	<b>0.379</b> (0.37%)	<b>0.419</b> (0.36%)	<b>0.410</b> (0.33%)
<i>Alprazolam</i>	N05BA12	<b>13.831</b> (13.61%)	<b>16.426</b> (14.10%)	<b>16.981</b> (13.8%)
<i>Flurazepam</i>	N05CD01	<b>8.661</b> (8.52%)	<b>9.238</b> (7.93%)	<b>9.329</b> (7.58%)
<i>Nitrazepam</i>	N05CD02	<b>6.712</b> (6.60%)	<b>7.401</b> (6.35%)	<b>6.557</b> (5.33%)
<i>Flunitrazepam</i>	N05CD03	<b>4.911</b> (4.83%)	<b>4.998</b> (4.29%)	<b>4.793</b> (3.90%)
<i>Triazolam</i>	N05CD05	<b>2.823</b> (2.78%)	<b>3.067</b> (2.63%)	<b>3.176</b> (2.58%)
<i>Lormetazepam</i>	N05CD06	<b>5.865</b> (5.77%)	<b>7.176</b> (6.16%)	<b>7.040</b> (5.72%)
<i>Temazepam</i>	N05CD07	<b>16.053</b> (15.80%)	<b>18.288</b> (15.70%)	<b>18.498</b> (15.03%)
<i>Midazolam</i>	N05CD08	<b>0.053</b> (0.05%)	<b>0.054</b> (0.046%)	<b>0.035</b> (0.03%)
<i>Zopiclone</i>	N05CF01	<b>11.793</b> (11.60%)	<b>15.529</b> (13.33%)	<b>18.025</b> (14.65%)
<i>Zolpidem</i>	N05CF02	<b>5.299</b> (5.21%)	<b>7.627</b> (6.55%)	<b>11.116</b> (9.03%)
<i>Zaleplon</i>	N05CF03	<b>0.670</b> (0.66%)	<b>0.603</b> (0.52%)	<b>0.551</b> (0.45%)
<i>Clonazepam</i>	N03AE01	<b>0.269</b> (0.26%)	<b>0.290</b> (0.25%)	<b>0.305</b> (0.24%)
<b>Total No. of DDDs/1000/Day</b>		<b>101.626</b> (100%)	<b>116.463</b> (100%)	<b>123.033</b> (100%)
<b>Total No. of DDDs/1000/Day (Tabs &amp; Caps)</b>		<b>101.496</b>	<b>116.352</b>	<b>122.931</b>

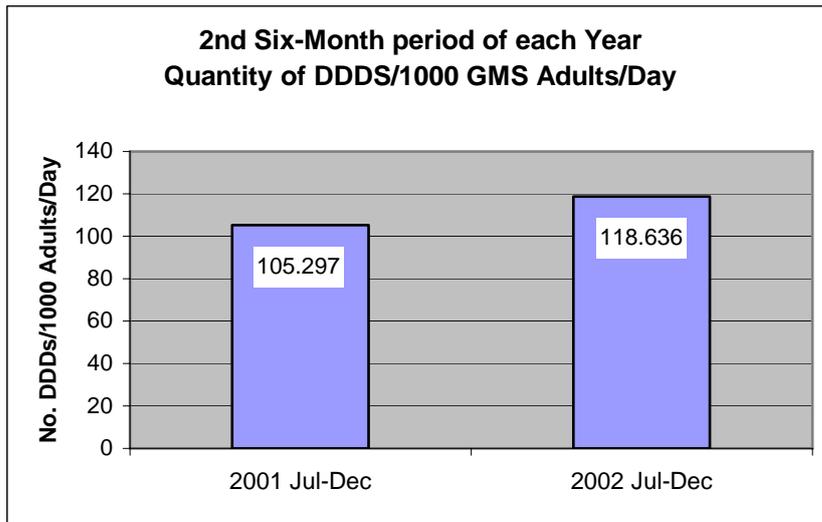
*Table 10. 1<sup>st</sup> Six-Month period of each year: quantity of DDDs/1000 GMS Adults/Day prescribed for each Drug during 2001, 2002 and 2003.*



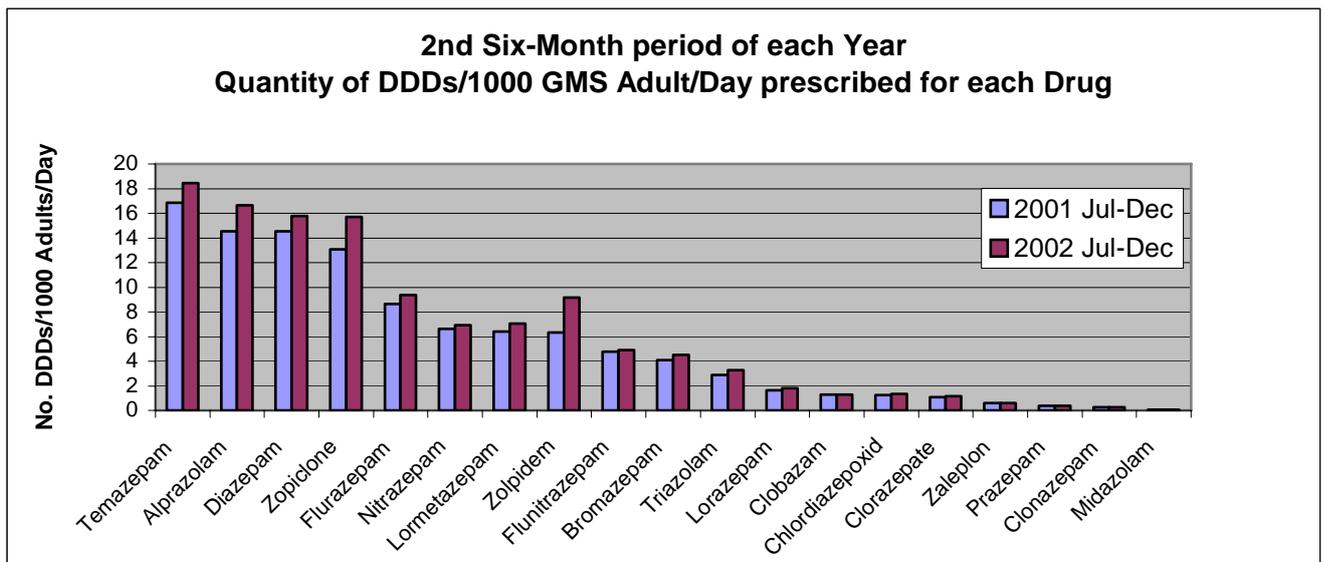
*Chart 9. 1<sup>st</sup> Six-Month period of each year: Quantity prescribed in DDDs/1000 GMS Adults/Day for each Drug*

### **2<sup>nd</sup> Six-Month Period**

The total number of DDDs/1000 GMS Adults/Day for all the included drugs and all dose forms were higher for the period Jul-Dec 2002 than for the same period in 2001, (105.3 compared to 118.6). The numbers were also higher for the 2<sup>nd</sup> six-month periods compared to the 1<sup>st</sup> six-month periods of 2001 and 2002. The number of DDDs/1000/Day of the most frequently prescribed anxiolytics and hypnotics were greater the period in 2002 compared to 2001. (see Table 10 and Chart 10,11 ). The greatest increase was seen for the drugs Alprazolam (anxiolytic), Temazepam (hypnotic), Zolpidem (non-benzodiazepine hypnotic) and Zopiclone (non-benzodiazepine hypnotic).



**Chart 10.** 2<sup>nd</sup> Six-Month period of each year: Quantity of DDDs/1000 GMS Adults/Day prescribed for each Drug



**Chart 11.** 2<sup>nd</sup> Six-Month period of each year: Quantity of DDDs/1000 GMS Adults/Day prescribed for each Drug

International Non-Proprietary Name (All dosage forms)	ATC code	No. of DDDs/1000 GMS Adults/Day	
		2001 Jul-Dec	2002 Jul-Dec
<i>Diazepam</i>	N05BA01	<b>14.527</b> (13.8%)	<b>15.768</b> (13.29%)
<i>Chlordiazepoxide</i>	N05BA02	<b>1.247</b> (1.18%)	<b>1.349</b> (1.14%)
<i>Clorazepate</i>	N05BA05	<b>1.084</b> (1.03%)	<b>1.168</b> (0.98%)
<i>Lorazepam</i>	N05BA06	<b>1.624</b> (1.54%)	<b>1.798</b> (1.52%)
<i>Bromazepam</i>	N05BA08	<b>4.081</b> (3.88%)	<b>4.531</b> (3.82%)
<i>Clobazam</i>	N05BA09	<b>1.298</b> (1.23%)	<b>1.286</b> (1.08%)
<i>Prazepam</i>	N05BA11	<b>0.379</b> (0.36%)	<b>0.391</b> (0.33%)
<i>Alprazolam</i>	N05BA12	<b>14.530</b> (13.8%)	<b>16.629</b> (14.02%)
<i>Flurazepam</i>	N05CD01	<b>8.627</b> (8.19%)	<b>9.394</b> (7.92%)
<i>Nitrazepam</i>	N05CD02	<b>6.644</b> (6.31%)	<b>6.929</b> (5.84%)
<i>Flunitrazepam</i>	N05CD03	<b>4.789</b> (4.55%)	<b>4.912</b> (4.14%)
<i>Triazolam</i>	N05CD05	<b>2.886</b> (2.74%)	<b>3.266</b> (2.75%)
<i>Lormetazepam</i>	N05CD06	<b>6.397</b> (6.08%)	<b>7.052</b> (5.94%)
<i>Temazepam</i>	N05CD07	<b>16.863</b> (16.01%)	<b>18.454</b> (15.56%)
<i>Midazolam</i>	N05CD08	<b>0.061</b> (0.06%)	<b>0.043</b> (0.04%)
<i>Zopiclone</i>	N05CF01	<b>13.058</b> (12.40%)	<b>15.681</b> (13.22%)
<i>Zolpidem</i>	N05CF02	<b>6.326</b> (6.00%)	<b>9.161</b> (7.72%)
<i>Zaleplon</i>	N05CF03	<b>0.606</b> (0.57%)	<b>0.587</b> (0.50%)
<i>Clonazepam</i>	N03AE01	<b>0.268</b> (0.25%)	<b>0.239</b> (0.20%)
<b>Total No. of DDDs/1000/Day</b>		<b>105.297</b> (100%)	<b>118.636</b> (100%)
<b>Total No. of DDDs/1000/Day</b> (Tabs & Caps)		<b>105.170</b>	<b>118.525</b>

*Table 10. 2<sup>nd</sup> six-month period of each Year: Quantity of DDDs/1000 GMS Adults/Day prescribed for each Drug*

#### **5.4 Prescription Item Analysis**

##### **Yearly Data**

Year	Total No. of Claims	Total No. of Prescribed Items	Total No. of DDDs	Ave. No. of DDDs/Item	Ave. No. of Items /GMS Patient	Ave. No. of Items /Benzodiazepine patient*	Ave. No. Claims/ Benzodiazepine patient*
2001	115,599	140,757	3,093,120.71	21.97 (3093120.71/140757)	1.34 (140757/105247)	7.00 (140757/20114)	5.75 (115599/20114)
2002	143,171	160,985	3,483,402.96	21.64 (3483402.96/160985)	1.54 (160985/104445)	7.48 (160985/21513)	6.66 (143171/21513)

\*Benzo population includes all patients prescribed benzodiazepine and related drugs (ATC code: N05BA, N05CD, N05CF and N03AE01) in the NEHB GMS population.

*Table 11. Yearly prescribing frequency and average number of DDDs dispensed per prescription item for benzodiazepine and related drugs*

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In 2001, 19.1% (20114/105247) of the total GMS population in the NEHB were prescribed a benzodiazepine derivate or related drug at least once. In 2002 this figure increased to 20.6% (21513/104445), (for population data see Chart1). On average, each GMS patient received 1.34 and 1.54 prescription items per year for 2001 and 2002 respectively. Taking only those GMS patients prescribed a benzodiazepine or related drug (benzodiazepine patient) into account, the average number of prescription items per patient was 7 and 7.5 per year respectively. The average number of claims per benzodiazepine patient increased from 5.75 in 2001, to 6.66 in 2002. (See Table 11). The average number of DDDs per prescription items was the total number of DDDs for the whole year divided by the total number of prescription items for benzodiazepines each year. In 2001 the average number of DDDs per prescription items was 21.97 and it was 21.64 in 2002. On average therefore, each prescription item was for 22 days supply both 2001 and 2002.

The number of DDDs per prescription items for each drug separately was about the same in 2001 and 2002 (See Table 12 and 13). All the typical hypnotics had average quantity of DDDs per prescription higher than the recommended, for 14 days supply. As an example, Flunitrazepam, which is classified as a Schedule 3 controlled drug, the average amount prescribed was equivalent to 33 days supply (average of 33 DDDs per prescription) while the figure for Nitrazepam was 36. The typical anxiolytics were also prescribed average from 13 days supply and greater as measured by the number of DDDs per prescription. On average each benzodiazepine patient had 7 prescriptions for benzodiazepines or related drugs during the year 2001 and had on average 6 prescriptions for just benzodiazepine drugs. The lowest number of DDDs per prescription was seen for Clonazepam (antiepileptic indication) and Midazolam (premedication). The average total of DDDs per prescription item in 2002 for all included drugs was 22. For just benzodiazepines this figure was 21. When comparing the amount of DDDs per prescription item for each drug separately, the trend was the same as for 2001: the average number of DDDs per prescription was higher than the recommended guideline amount of 14 days supply. As an example, Flunitrazepam, which is classified as a Schedule 3 controlled drug, was on average prescribed for 33 days supply (i.e. average no. of DDDs per prescription was 33) and for Nitrazepam

this figure was 36. The typical anxiolytics had average number of DDDs per prescription that ranged from 13 days supply and higher. The lowest average quantity of DDDs per prescription was seen for Clonazepam (antiepileptic indication) and Midazolam (premedication).

<b>Year 2001</b> (n=20,114)					
<b>International Non-Proprietary Name</b> (All dosage forms)	<b>ATC code</b>	<b>Total No. of Prescription Items</b>	<b>Number of DDDs</b>	<b>Number of DDDs /Item</b>	<b>Ave No. of Items /Benzo* Patient</b>
<i>Diazepam</i>	N05BA01	20,607	440,854.10	21.39	1.025
<i>Chlordiazepoxide</i>	N05BA02	2,695	36,869.33	13.68	0.134
<i>Clorazepate</i>	N05BA05	1,772	32,355.75	18.26	0.088
<i>Lorazepam</i>	N05BA06	1,776	48,256.00	27.17	0.088
<i>Bromazepam</i>	N05BA08	9,649	121,845.30	12.63	0.480
<i>Clobazam</i>	N05BA09	1,358	40,191.50	29.60	0.068
<i>Prazepam</i>	N05BA11	783	11,326.33	14.47	0.039
<i>Alprazolam</i>	N05BA12	25,724	424,407.00	16.50	1.279
<i>Flurazepam</i>	N05CD01	11,045	258,155.00	23.37	0.549
<i>Nitrazepam</i>	N05CD02	5,492	199,400.00	36.31	0.273
<i>Flunitrazepam</i>	N05CD03	4,386	144,873.00	33.03	0.218
<i>Triazolam</i>	N05CD05	2,742	85,271.50	31.10	0.136
<i>Lormetazepam</i>	N05CD06	7,309	183,192.00	25.06	0.363
<i>Temazepam</i>	N05CD07	22,034	491,734.00	22.32	1.095
<i>Midazolam</i>	N05CD08	187	1,729.33	9.25	0.009
<i>Zopiclone</i>	N05CF01	12,666	371,581.50	29.34	0.630
<i>Zolpidem</i>	N05CF02	7,886	173,985.00	22.06	0.392
<i>Zaleplon</i>	N05CF03	1,041	19,076.00	18.32	0.052
<i>Clonazepam</i>	N03AE01	1,605	8,018.06	5.00	0.080
<b>Total</b>		<b>140,757</b>	<b>3,093,120.71</b>	<b>21.97</b>	<b>6.998</b>
<b>Total without N03AE01</b>		<b>139,152</b>	<b>3,085,103.00</b>	<b>22.17</b>	<b>6.918</b>
<b>Total without N03AE01 and N05CF</b>		<b>117,559</b>	<b>2,520,460.50</b>	<b>21.44</b>	<b>5.844</b>

\*Benzo population includes all patients prescribed benzodiazepine and related drugs (ATC code: N05BA, N05CD, N05CF and N03AE01) in the NEHB GMS population.

*Table 12. Year 2001 (Jan-Dec) broken down by drug: Prescribing frequency of benzodiazepines and related drugs and the average number of DDDs dispensed per prescription item.*

**Year 2002**  
(n=21,513)

International Non-Proprietary Name (All dosage forms)	ATC code	Total No. of Prescription Items	Total No. of DDDs	No. of DDDs/Item	Ave. No. of Items/Benzo* Patients
<i>Diazepam</i>	N05BA01	22,697	464,777.90	20.48	1.055
<i>Chlordiazepoxide</i>	N05BA02	3,011	39,618.00	13.16	0.140
<i>Clorazepate</i>	N05BA05	1,831	34,620.00	18.91	0.085
<i>Lorazepam</i>	N05BA06	2,147	52,298.40	24.36	0.100
<i>Bromazepam</i>	N05BA08	10,451	130,422.45	12.48	0.486
<i>Clobazam</i>	N05BA09	1,300	38,223.50	29.40	0.060
<i>Prazepam</i>	N05BA11	836	11,985.33	14.34	0.039
<i>Alprazolam</i>	N05BA12	30,429	490,436.25	16.12	1.414
<i>Flurazepam</i>	N05CD01	12,062	275,763.00	22.86	0.561
<i>Nitrazepam</i>	N05CD02	5,853	211,966.00	36.21	0.272
<i>Flunitrazepam</i>	N05CD03	4,383	146,595.00	33.45	0.204
<i>Triazolam</i>	N05CD05	2,984	93,832.50	31.45	0.139
<i>Lormetazepam</i>	N05CD06	8,417	210,528.00	25.01	0.391
<i>Temazepam</i>	N05CD07	24,678	543,936.50	22.04	1.147
<i>Midazolam</i>	N05CD08	186	1,444.00	7.76	0.009
<i>Zopiclone</i>	N05CF01	15,696	462,212.00	29.45	0.730
<i>Zolpidem</i>	N05CF02	11,353	249,294.50	21.96	0.528
<i>Zaleplon</i>	N05CF03	1,015	17,637.00	17.38	0.047
<i>Clonazepam</i>	N03AE01	1,656	7,812.63	4.72	0.077
<b>Total</b>		<b>160,985</b>	<b>3483,402.96</b>	<b>21.64</b>	<b>7.484</b>
<b>Total without N03AE01</b>		<b>159,329</b>	<b>3475,590.33</b>	<b>21.81</b>	<b>7.410</b>
<b>Total without N03AE01 and N05CF</b>		<b>131,265</b>	<b>2746,446.83</b>	<b>20.90</b>	<b>6.100</b>

\*Benzo population includes all patients prescribed benzodiazepine and related drugs (ATC code: N05BA, N05CD, N05CF and N03AE01) in the NEHB GMS population.

*Table 13. Year 2002 broken down by drug: Prescribing frequency of benzodiazepines and related drugs and the average number of DDDs dispensed per prescription item.*

### **Six-Month Data**

<b>1<sup>st</sup> 6-Month periods (Jan-Jun) for 2001-2003</b>							
<b>Jan-June</b>	<b>Total No of Claims</b>	<b>Total No. of Prescription Items</b>	<b>Total No. of DDDs</b>	<b>No. of DDDs /Item</b>	<b>Ave. No. of Items /GMS Patient</b>	<b>Ave. No. of Items /Benzodiazepine patient*</b>	<b>Ave. No. of Claims /Benzodiazepine patient*</b>
<b>2001</b>	<b>50,424</b>	<b>67,967</b>	<b>1,506,820.20</b>	<b>22.17</b>	<b>0.65</b> (67967/105247)	<b>4.83</b> (67967/14081)	<b>3.58</b> (50424/14081)
<b>2002</b>	<b>69,958</b>	<b>78,745</b>	<b>1,711,049.37</b>	<b>21.73</b>	<b>0.75</b> (78745/104445)	<b>4.76</b> (78745/16527)	<b>4.23</b> (69958/16527)
<b>2003</b>	<b>73,855</b>	<b>83,227</b>	<b>1,795,104.64</b>	<b>21.57</b>	<b>0.80</b> (83227/103787)	<b>4.95</b> (83227/16815)	<b>4.39</b> (73855/16815)

*Table 14. Six-Month (Jan-Jun) period data; prescribing frequency and average number of DDDs dispensed per prescription item for benzodiazepine and related drugs.*

During the first six months period 2001, 13.4% (14081/105247) of the total GMS population in the NEHB were prescribed a benzodiazepine derivate or related drug at least once. For the same period in 2002 and 2003 this figure had increased slightly to 15.8% (16527/104445) and 16.2% (16815/103787) respectively - (for population data see Chart1).

On average, each GMS patient received 0.65, 0.75 and 0.8 prescription items during jan-jun in 2001, 2002 and 2003 respectively. Taking only those GMS patients prescribed a benzodiazepine or related drug (benzodiazepine patient) into account, the average number of prescription items per patient was 4.83, 4.76 and 4.95 for each respective period. The average number of claims per benzodiazepine patient increased from 3.58 the first period of 2001, to 4.23 in 2002 and 4.39 in 2003. (See Table 14.)

During the period the average number of DDDs per prescription items was 22, or 22 days supply. The number of DDDs per prescription items for each drug separately for the period Jan-Jun 2003 was about the same as in 2001 and 2002. For details see Table 12, 13 and 15.

<b>1<sup>st</sup> six-month period: Jan-June 2003</b> (n=16,815)
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International-Non Proprietary Name (All dosage forms)	ATC code	Total No. of Prescription Items	Total No. of DDDs	Ave No. of DDDs /Item	Ave. No. of Items /Benzodiazepine patient*
<i>Diazepam</i>	N05BA01	11,437	234,369.90	20.49	0.680
<i>Chlordiazepoxide</i>	N05BA02	1,533	20,450.50	13.34	0.091
<i>Clorazepate</i>	N05BA05	892	17,162.63	19.24	0.053
<i>Lorazepam</i>	N05BA06	1,138	27,537.00	24.20	0.068
<i>Bromazepam</i>	N05BA08	5,268	64,611.45	12.26	0.313
<i>Clobazam</i>	N05BA09	650	18,555.00	28.55	0.039
<i>Prazepam</i>	N05BA11	395	6,000.33	15.19	0.023
<i>Alprazolam</i>	N05BA12	15,438	248,092.25	16.07	0.918
<i>Flurazepam</i>	N05CD01	6,152	136,028.00	22.11	0.366
<i>Nitrazepam</i>	N05CD02	2,627	95,692.00	36.43	0.156
<i>Flunitrazepam</i>	N05CD03	2,137	69,836.00	32.68	0.127
<i>Triazolam</i>	N05CD05	1,474	46,281.50	31.40	0.088
<i>Lormetazepam</i>	N05CD06	4,090	102,618.50	25.09	0.243
<i>Temazepam</i>	N05CD07	12,206	269,687.50	22.09	0.726
<i>Midazolam</i>	N05CD08	81	515.33	6.36	0.005
<i>Zopiclone</i>	N05CF01	9,027	262,950.50	29.13	0.537
<i>Zolpidem</i>	N05CF02	7,261	162,238.00	22.34	0.432
<i>Zaleplon</i>	N05CF03	434	8,029.00	18.50	0.026
<i>Clonazepam</i>	N03AE01	987	4,449.25	4.51	0.059
<b>Total</b>		<b>83,227</b>	<b>1,795,104.64</b>	<b>21.57</b>	<b>4.950</b>
<b>Total without N03AE01</b>		<b>82,240</b>	<b>1,790,655.39</b>	<b>21.77</b>	<b>4.891</b>
<b>Total without N03AE01 and N05CF</b>		<b>65,518</b>	<b>1,357,437.89</b>	<b>20.72</b>	<b>3.896</b>

*Table 15. Six-Month (Jan-Jun) 2003 broken down by drug: Prescribing frequency of benzodiazepines and related drugs and the average number of DDDs dispensed per prescription item.*

<b>2<sup>nd</sup> six-month period (Jul-Dec), 2001-2002</b>							
Jul-Dec	Total No. of Claims	Total No. of Prescription Items	Total No. of DDDs	No. of DDDs /Item	Ave. No. of Items /GMS Patients	Ave. No. of Items /Benzodiazepine patient*	Ave. No. of Claims /Benzodiazepine patient*
<b>2001</b>	<b>65176</b>	<b>72790</b>	<b>1,586,300.51</b>	<b>21.79</b>	<b>0.69</b> (72790/105247)	<b>4.51</b> (72790/16149)	<b>4.04</b> (65176/116149)
<b>2002</b>	<b>73213</b>	<b>82240</b>	<b>177,235,3.59</b>	<b>21.5</b>	<b>0.79</b> (82240/104445)	<b>4.92</b> (82240/16724)	<b>4.38</b> (73213/16724)

\* 2003 Data (July-Dec) was not available for this period

*Table 16. Six-month (Jul-Dec) prescribing frequency of benzodiazepine and related drugs and average number of DDDs dispensed per prescription item.*

During the period Jul-Dec in 2001, 15.5% (16149/105247) of the total GMS population in the NEHB were prescribed a benzodiazepine derivative at least once. For the same

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period in 2002 this figure had increased to 15.8% (16724/104445) - (for population data see Chart 1).

On average, each GMS patient received 0.69 prescription items during Jul-Dec 2001 and 0.79 for the same period in 2002. The average number of prescription items per benzodiazepine patient was 4.51 and 4.92 for the respective period. The average number of claims per benzodiazepine patient increased from 4.04 the second period in 2001, to 4.38 in 2002. (See Table 16.)

The average number of DDDs per prescription item was 22.79 in 2001 and 21.5 in 2002. On average it is estimated that each prescription item was for 22 days supply in every period as for the whole year periods.

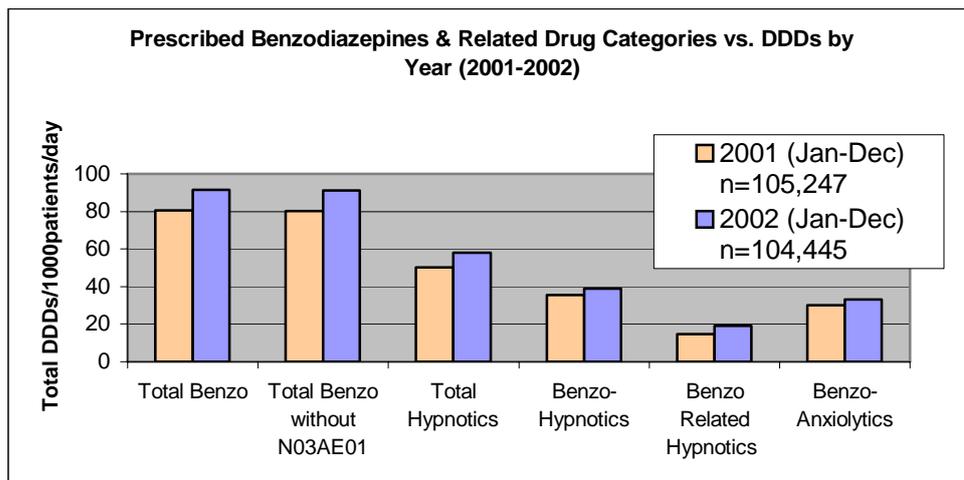
### **5.5 Analysis of GMS Prescribed Quantities of Benzodiazepine and Related Drugs** **Yearly Data**

There was an increase in the overall prescribing of benzodiazepines and related drugs in 2002 compared to 2001. Both the hypnotics and anxiolytics were prescribed in greater quantities as measured by DDD/1000 GMS Patients/Day in 2002 than in 2001, though the increase was higher for the hypnotic drugs. The increase among the hypnotics was greater for the benzodiazepine-related hypnotics than for the benzodiazepines (See Table 17 and Chart 12, 13).

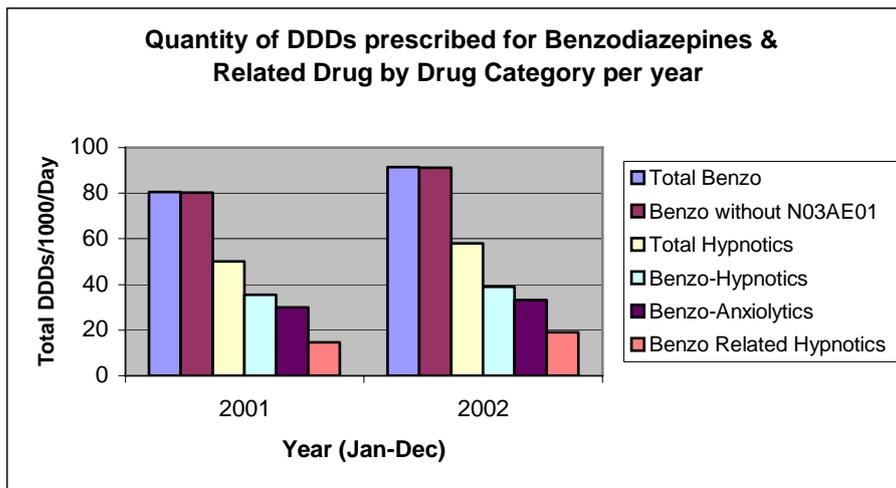
No. of DDDs/1000 GMS Patients/Day
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ATC Categories	2001 (n=105,247)	2002 (n=104,445)
<b>Benzo &amp; Related</b> (N05BA, N05CD, N05CF and N03AE01)	<b>80.518</b>	<b>91.374</b>
<b>Benzo &amp; Related</b> <i>without</i> N03AE01	<b>80.310</b>	<b>91.169</b>
<b>HYPNOTICS</b>		
<b>Benzodiazepine</b> (N05CD)	<b>35.517</b>	<b>38.928</b>
<b>Benzodiazepine-related</b> (N05CF)	<b>14.699</b>	<b>19.126</b>
<b>Total</b> (N05CD & N05CF)	<b>50.216</b>	<b>58.054</b>
<b>ANXIOLYTICS</b>		
<b>Benzodiazepine</b> (N05BA)	<b>30.010</b>	<b>33.115</b>

*Table 17. 2001-2002 GMS Prescribed Benzodiazepines & Related Drug DDDs by Category*



*Chart 12. 2001-2002 GMS Prescribed Benzodiazepines & Related Drug DDDs by Category*



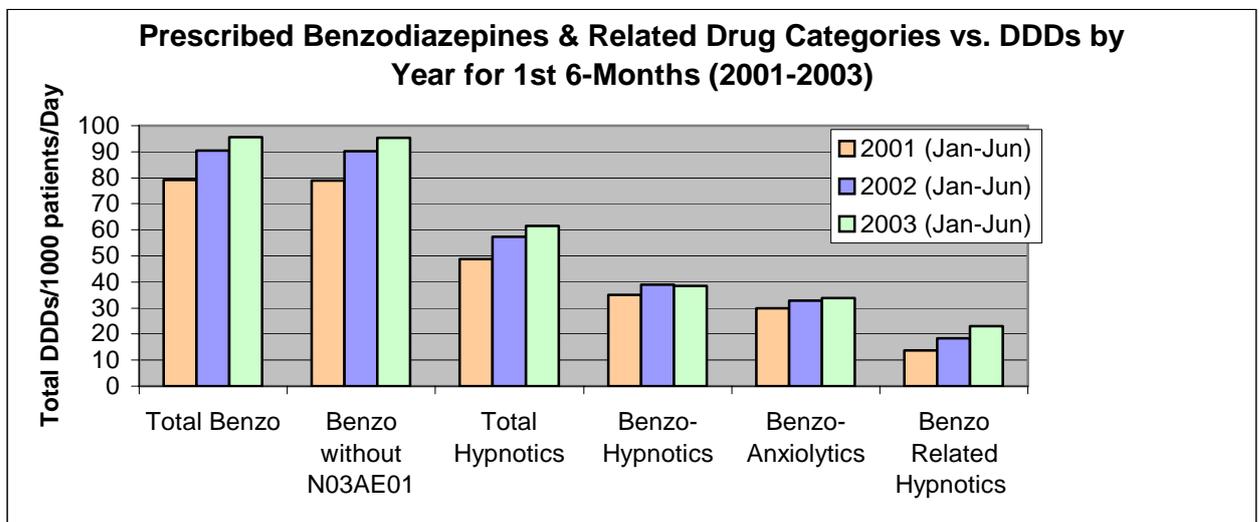
*Chart 13. 2001-2002 GMS Prescribed Benzodiazepines & Related Drug DDDs by Category*

### **Six-Month Data – 1st Six-Month Period**

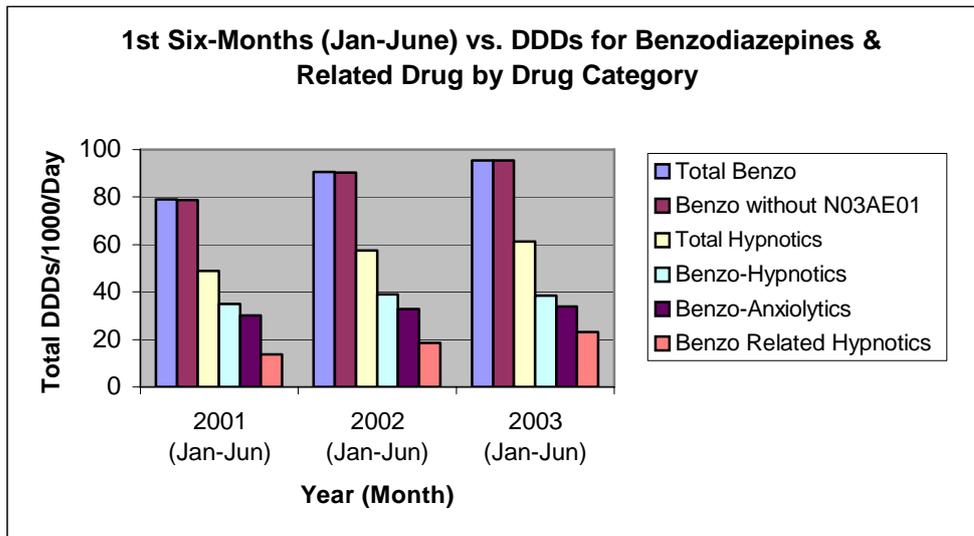
The overall prescribing of benzodiazepines and related drugs gradually increased during the 1<sup>st</sup> six month period of 2002 and of 2003 compared to 2001. There was a slight increase in the amount of DDD/1000 GMS Patients/Day for the anxiolytics, while a greater increase was seen for the hypnotic drugs. Among the hypnotics both the benzodiazepines and the benzodiazepine-related drugs increased during Jan-Jun in 2002 compared to 2001. But between 2002 and 2003 only the benzodiazepine-related drugs increased while the benzodiazepines marginally decreased. (See Table 18 and Chart 14,15).

<b>No. of DDDs/1000 GMS Patients/Day</b>			
	<b>2001 (Jan-Jun)</b> n=105247	<b>2002 (Jan-Jun)</b> n=104445	<b>2003 (Jan-Jun)</b> n=103787
<b>Total Benzo</b> (N05BA, N05CD, N05CF, N03AE01)	<b>79.099</b>	<b>90.510</b>	<b>95.558</b>
<b>Benzo without</b> N03AE01	<b>78.89</b>	<b>90.283</b>	<b>95.321</b>
<b>HYPNOTICS</b>			
<b>Total</b> (N05CD and N05CF)	<b>48.885</b>	<b>57.463</b>	<b>61.421</b>
<b>Benzodiazepine</b> (N05CD)	<b>35.06</b>	<b>38.996</b>	<b>38.362</b>
<b>Benzodiazepine-related</b> (N05CF)	<b>13.825</b>	<b>18.467</b>	<b>23.06</b>
<b>ANXIOLYTICS</b>			
<b>Benzodiazepine</b> (N05BA)	<b>29.999</b>	<b>32.819</b>	<b>33.9</b>

**Table 18.** 1<sup>st</sup> six month period (Jan-Jun) of 2001-2003 GMS Prescribing of Benzodiazepines & Related Drug by DDDS by Category



**Chart 14.** 1<sup>st</sup> six month (Jan-Jun) period of 2001-2003, GMS Prescribed Benzodiazepines & Related Drug DDDS by Category



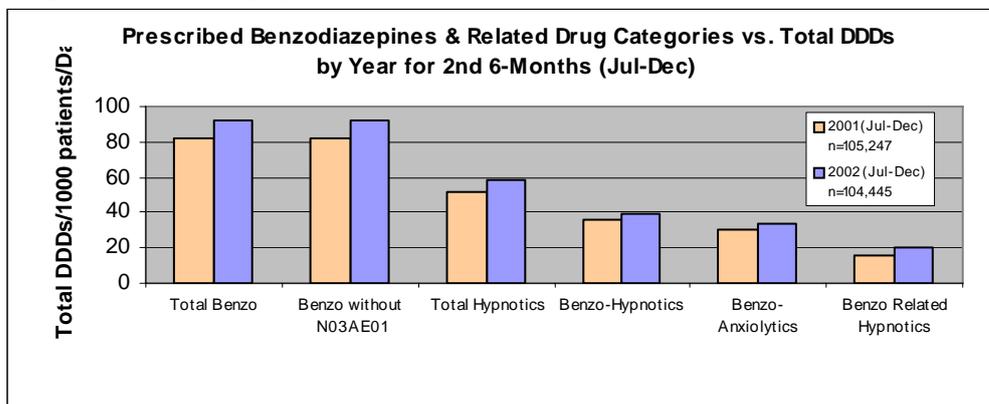
*Chart 15. 1<sup>st</sup> six month (Jan-Jun) period of 2001-2003, GMS Prescribed Benzodiazepines & Related Drug DDDs by Category*

### 2<sup>nd</sup> Six-Month Period

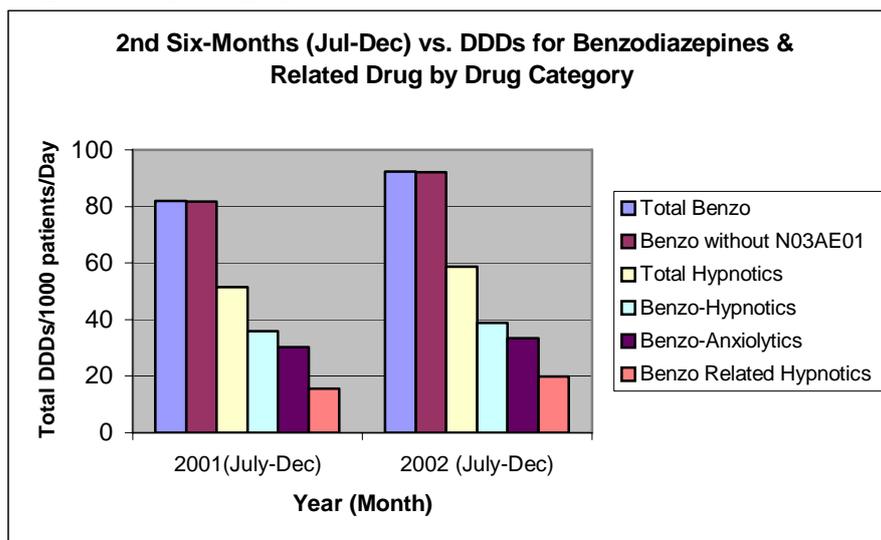
The overall prescribing of benzodiazepines and related drugs was higher in Jul-Dec 2002 compared to the same period in 2001. The amount of DDDs/1000 GMS Patients/Day increased from 81.9 to 92.2 and both figures were higher than the data from the 1<sup>st</sup> six month period of 2001 and of 2002. There was a slight increase in the quantities prescribed for the anxiolytics, while a greater increase was seen for the hypnotic drugs. Among the hypnotics both the benzodiazepines and the benzodiazepine-related drugs increased during Jul-Dec in 2002 compared to 2001, though the increase was higher for the benzodiazepine-related hypnotics than for the benzodiazepines (See Table 19 and Chart 17, 18).

No. of DDDs/1000 GMS Patients/Day		
	2001 (Jul-Dec) n=105,247	2002 (Jul-Dec) n=104,445
<b>Total Benzo</b> (N05BA, N05CD, N05CF and N03AE01)	<b>81.914</b>	<b>92.224</b>
<b>Benzo without N03AE01</b>	<b>81.706</b>	<b>92.039</b>
<b>HYPNOTICS</b>		
<b>Total</b> (N05CD and N05CF)	<b>51.516</b>	<b>58.637</b>
<b>Benzodiazepine</b> (N05CD)	<b>35.964</b>	<b>38.861</b>
<b>Benzodiazepine-related</b> (N05CF)	<b>15.552</b>	<b>19.776</b>
<b>ANXIOLYTICS</b>		
<b>Benzodiazepine</b> (N05BA)	<b>30.188</b>	<b>33.403</b>

*Table 19. 2nd Six-Months (Jul-Dec) 2001-2002 GMS Prescribed Benzodiazepines & Related Drug DDDS by Category.*



*Chart 17. 2nd Six-Months (Jul-Dec) 2001-2002 GMS Prescribed Benzodiazepines & Related Drug DDDS by Category*



*Chart 18. 2nd Six-Months (Jul-Dec) 2001-2002 GMS Prescribed Benzodiazepines & Related Drug DDDS by Category*

### **5.6 Long-Term Use Analysis**

#### **Yearly Data 2001:**

Of the 20114 benzodiazepine patients in the GMS population, NEHB, 7429 or 36.9% (7429/20114) had six or more prescription items for benzodiazepines or related drugs in either or both of the two six month periods. There were 3544 benzodiazepine patients, or 17.6% (3544/20114) who had six or more prescription items in just one of the six-month periods and 3885 patients, or 19.3% (3885/20114) who had six or more prescriptions in both of the six month periods (or in other words, had 12 or more prescriptions per year). (See Table 20).

#### **Yearly data 2002:**

During 2002, 8548 of the 21513 benzodiazepine patients, or 39.7% (8548/21513) had 6 or more prescription items in either or both of the two six month periods. There were 3601 benzodiazepine patients, or 16.7% (3601/21513) who had six or more prescription items in just one of the six-month periods and 4947 patients, or 23.0% (4947/21513) who had six or more prescriptions in both of the six month periods (or in other words, had 12 or more prescriptions per year). The number of long-term users (based on prescription items) was higher in 2002 than 2001. (See Table 20).

<b>Long-term Use During Jan-Jun and Jul-Dec Based on No. of Prescription Items/6-Month Period*</b>		
	<b>2001 (n=20,114)</b>	<b>2002 (n=21,513)</b>
<b>% of Patients Receiving <math>\geq 6</math> Items in <i>Either one</i> 6-Month Periods</b>	17.6%(3544)	16.7% (3601)
<b>% of Patients Receiving <math>\geq 6</math> Items in <i>Both</i> 6-Month Periods</b>	19.3% (3885)	23.0% (4947)
<b>% of Patients Receiving <math>\geq 6</math> Items in <i>Either or Both</i> 6-Month Periods</b>	36.9% (7429)	39.7% (8548)

\*Items may not have been dispensed in consecutive months, and patients may have received more than one item per month.

**Table 20.** Long-term Use During Jan-Jun and Jul-Dec based on No. of Prescription Items/6-Month Period

It was only possible to look at long term dispensing in consecutive months for the whole year 2002. The data available for 2001 composed of two six month periods

(Jan-June) and (July-Dec) and was not broken down by month as the 2002 and there was no data available for the 2<sup>nd</sup> six month period in 2003 at the time for the study.

Of the 21513 benzodiazepine patients in the GMS population, NEHB 10509 or 48.9% (10509/21513) had prescription items in three or more consecutive months. Accordingly 11004 or 51.1% of the patients did not prescription items in three or more consecutive months. 6522 patients, or 30.3% had prescription items in six or more consecutive months and 2097, or 9.7% had prescriptions in every month over the year 2002. (See Table 21).

Of the whole GMS population, NEHB, 10.1% (10509/104445) had prescription items in three or more consecutive months, 6.4% had prescriptions in six or more consecutive months and 2.0% had prescriptions in every month during the year 2002 (See Table 21).

<b>Long-term Dispensing in Consecutive Months</b>		
Jan-Dec 2002		
<b>Consecutive Dispensing Period</b>	<b>% of Benzodiazepine patients</b> (n=21,513)	<b>% of GMS Patients</b> (n=104445)
<b>Prescription items in <math>\geq 3</math>-consecutive months</b>	48.9% (10509)	10.1% (10509)
<b>Prescription items in <math>\geq 6</math>-consecutive months</b>	30.3% (6522)	6.2% (6522)
<b>Prescription items in all 12-months</b>	9.7% (2097)	2.0% (2097)

Table 21. Long-term Dispensing in Consecutive Months during 2002

### **Six-Month Data**

#### **2001**

During Jan-Jun 38.6% (5442/14081) of the benzodiazepine patients had  $\geq$  six prescription items. For the period Jul-Dec this figure was 36.4% (5872/16149). (See Table 22).

#### **2002**

For the period Jan-Jun 39.8% (6584/16527) of the benzodiazepine patients had six prescription items or more. For the second six month period the same figure was 41.3% (6911/16724). (See Table 22).

#### **2003**

In Jan-Jun there were 6966, or 41.4% (6966/16149) patients with six or more prescription items during this six month period. (See Table 22).

<b>Yearly long-term use within a 6-month period*</b>			
	<b>Patients with <math>\geq 6</math> prescription items in either or both 6-month period</b>		
<b>6-Month Period</b>	<b>2001</b>	<b>2002</b>	<b>2003</b>
<b>Jan-Jun</b>	38.6% (5442/14081)	39.8% (6584/16527)	41.4% (6966/16815)
<b>Jul-Dec</b>	36.4% (5872/16149)	41.3% (6911/16724)	N/A

\*Items may not have been dispensed in consecutive months, and patients may have received more than one item per month. There was no data available for the period Jul-Dec in 2003 at the time for the study.

*Table 22. Yearly long-term use within a 6-month period*

#### **Long-term use, Consecutive 6-month period dispensing 2002:**

During Jan-Jun 48.1% (7943/16527) of the benzodiazepine patients had prescription items in three or more consecutive months. In the period Jul-Dec this figure was 50.6% (8459/16724). 21.1% (3484/16527) of patients had prescriptions in every month during the period Jan-Jun and this figure increased in Jul-Dec to 25.1% (4204/16724). (See table 23).

#### **Long-term use, Consecutive 6-month period dispensing 2003**

For the period Jan-Jun 51.8% (8703/16815) of the patients have prescription items in three or more consecutive month and 25.4% (4274/16815) have prescription items in every month. (See table 23).

<b>Long-term use: Consecutive 6-month period dispensing</b>		
	<b>2002</b>	<b>2003</b>
<b>Prescription items in <math>\geq 3</math> consecutive months</b>		
<b>Jan-Jun</b>	48.1% (7943/16527)	51.8% (8703/16815)
<b>Jul-Dec</b>	50.6% (8459/16724)	N/A
<b>Prescription items in <math>\geq 6</math> consecutive months</b>		
<b>Jan-Jun</b>	21.1% (3484/16527)	25.4% (4274/16815)
<b>Jul-Dec</b>	25.1% (4204/16724)	N/A

*Table 23. Long-term use: Consecutive 6-month period dispensing 2002 and 2003.*

## **6. DISCUSSION**

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Since it became clear in the 1980's that extended benzodiazepine use may lead to dependence and withdraw reactions, many studies have been performed to evaluate their use. However it is difficult to compare many of these studies because they differ in many respects. As for example in their definitions of: study population (sex, age, social class), benzodiazepine use (long-term, short-term/ever), study period (days, weeks, month, years), and the method used to collect the data (interviews, using prescription records) [25]. Because this study only includes the GMS population in the NEHB, most of the comparisons are made with the two studies that on request of the Benzodiazepine Committee examined the use of benzodiazepines in the GMS population, Ireland, and there by used the same type of study population and in addition used the same type of study method [4] and with an earlier national utilization study [26].

The use of benzodiazepines or related drugs in the adult GMS population NEHB, in terms of the quantity of DDDs/1000 GMS Adults/Day dispensed was 103.48 for the year 2001 and increased to 117.56 during 2002. The prescribed quantities for both the hypnotics and anxiolytics were higher in 2002 compared to 2001, though the proportional increase was greater for the hypnotic drugs. Among the hypnotics, the increase was greater for the benzodiazepine-related hypnotics than for the benzodiazepines (See Table 17 and Chart 12, 13). The overall prescribing of benzodiazepines and related drugs gradually increased during the 1<sup>st</sup> six month period of 2002 and 2003 compared to 2001. The total number of DDDs/1000 GMS Adults/Day for all the included drugs increased from 101.6 in the 2001 to 116.5 respectively 123.0 for the same periods in 2002 and 2003.

Some of the increase may have been a result of the extension of the GMS scheme to all of those  $\geq 70$  years of age. Two factors suggest that the influence of this policy was limited; firstly, a steady increase in total benzodiazepine utilization nationally was reported for 1995-2000 [17], and between 1977 and 1987 [26]; secondly, the patients who became eligible in 2001 can be considered to be affluent and these patients are

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much less likely to receive benzodiazepines [28], a difference that has also been consistent over time [26].

The increased prescribing of long acting drugs was proportionally less than that of the intermediate-short acting agents resulting in a slight shift towards the prescribing of short acting benzodiazepines in both the anxiolytic and hypnotic sub-groups. However the most frequently prescribed of the long acting drugs maintained their utilization levels suggesting that there was little switching within each sub-group. The quantity of drugs prescribed per prescription fell by around 2-3% indicating a reduction in the duration of prescribing, but the number of items prescribed per patient rose, suggesting slightly smaller quantities prescribed more frequently. Increasing use of these drugs for indications other than anxiety and insomnia cannot be ruled out, however, the exclusion of those under 15 years of age and of the antiepileptic, clonazepam, and the parenteral sedative, midazolam, limited the number of confounding factors.

The GMS population serves all of the elderly, a group whose pharmacodynamic responses and pharmacokinetic handling of benzodiazepines is known to differ from that of young adults [6,23] and long-acting drugs are more likely to produce effects on cognitive function and upon motor co-ordination with a variety of adverse consequences[13,18]. Prescribing guidelines for the elderly recommend that long-acting benzodiazepines and high doses of short-intermediate acting drugs should not be used [6, 23, 29], but in this study, it was not possible to identify the elderly and so to examine the drugs and doses that were dispensed for them. Because the DDD is defined as an average recommended adult dose, this is often greater than the dose recommended for elderly patients BNF, so that at a given level of utilization, the exposure of the elderly to high doses is more likely. Taken together with the apparent stability of the utilization patterns for the long acting agents it is highly probable that some benzodiazepine prescribing for the elderly is sub-optimal as others have shown<sup>2</sup>.

Of the whole GMS population, NEHB, 10.1% (10509/104445) received prescription items in 3 or more consecutive months, 6.4% received prescriptions in 6 or more consecutive months and 2.0% received prescriptions in every month during the year

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2002. (See table 21). These findings are higher than the results from the Dutch study, described above, which reported that 2% of the NHA population in 1997 used benzodiazepines for more than 6 months and 0.6% used benzodiazepines in every month during a one year observation [25]. However it is difficult to draw firm conclusions from the comparison of these results because of differences in the population and study method.

As a rough estimation of the extended use of benzodiazepines and related drugs among the users, the average number of claims and prescription items were calculated (See Table 11, 14, 16). The average number of claims for benzodiazepines and related drugs increased from 3.6 in Jan-Jun 2001, to 4.2 in 2002 and to 4.4 in 2003 among the patients prescribed benzodiazepines in the GMS population of the NEHB. (See Table 14.) This is similar as for GMS population, ERHA, who received approximately 4.3 claims each for benzodiazepines during Jan-Jun 1999 and 2000 [4]. Although the ERHA study did not include the benzodiazepine-related drugs (with ATC code N05CF) which are included in this study. The average number of claims and prescription items for the whole year data in this study was 5.75 respectively 7 in 2001 and 6.66 respectively 7.48 in 2002. These findings may indicate that many users take benzodiazepines on a continuing basis.

As an effort to further evaluate the long-term use both the number of prescription items dispensed per six month period and prescription dispensing in consecutive months (See Table 20-23) were analysed. The results indicate that the prescribing of benzodiazepines and related drugs in this population were at a high level prescribed for long-term use which is against the advised guidelines (they should not be prescribed for more than 2-4 weeks [4, 6]). During 2002, 10509 benzodiazepine patients, or 48.9% had prescriptions in three or more consecutive months. Six thousand five hundred twenty two benzodiazepine patients or 30.3% received prescriptions in  $\geq$  six consecutive months and 2097 or 9.7% were dispensed prescriptions in every month during 2002.

In the 1980s GMS benzodiazepine utilisation was found to be 71.88 DDD/1000/day [26]. The population studied included those under 15 years of age since it was not

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possible to separate out patients in that age group who received prescriptions and it represents the total GMS population not just those receiving benzodiazepines. The composition of the anxiolytic benzodiazepine group (N05B) was slightly different since bromazepam and alprazolam had only recently been introduced. Among the hypnotic group flunitrazepam and lormetazepam were introduced in 1983 and 1982 respectively while Zopiclone was introduced in 1989 and Zaleplon and Zolpidem were introduced in 1999. The rank order of the main drugs in each group at different times suggests that the national figures reflect some shift towards prescribing shorter-acting sedative benzodiazepines and an increase in the prescribing of some of the non-benzodiazepine hypnotics [26]. While the increased use of short-term agents is welcome, there is still a high level of use of the longer acting drugs in the GMS population, many of whom are elderly and at greater risk of direct and indirect adverse effects associated with these drugs. However, the total prescribing measured in DDDs/1000/day has continued to rise from 1977 throughout the 1980s [26] and 1990s and this report shows that a steady increase is still occurring. This implies that at least some prescribers are prescribing additional shorter acting anxiolytics and non-benzodiazepine hypnotics rather than simply substituting for longer-acting anxiolytics and older benzodiazepine hypnotics.

The Benzodiazepine Committee Report in 2002 concluded that the utilization of benzodiazepine hypnotics had declined, but since triazolam, one of the benzodiazepine hypnotics, was omitted from their analysis, this conclusion was incorrect. Adjusting their figures shows that triazolam utilization increased by around 46% from 1995-2000 and that of the total benzodiazepine hypnotic sub-group increased by almost 11% [4]. In this study, growth in the prescribing of hypnotics increased considerably but non-benzodiazepine hypnotics increased to a greater extent than benzodiazepine drugs, a pattern that has also been noted nationally [4, 26]. The small increase in benzodiazepine utilization implies long term prescribing for a cohort of patients. Taken together with the two thirds increase in non-benzodiazepine hypnotic utilization and the increase in the number of claims for these drugs accompanied by a fall (1.25%) in the number of DDDs per item of zopiclone but an increase (1.5%) in the number of DDDs per item of zolpidem, this strongly suggests

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an increase in the population of patients prescribed a non-benzodiazepine drug. Overall therefore, there has been an increase in the utilization of hypnotic drugs.

The efficacy, value and safety of the non-benzodiazepine hypnotics compared to the benzodiazepine hypnotics continue to be debated [6, 11, 30-31]. Further analysis could provide information on the patterns of usage by patients and of prescribing by GPs and its costs, allow the monitoring of trends in areas of social disadvantage and in response to policy implementation affecting both the medical use and abuse of these drugs [32-33]. Such information is a pre-requisite for informed and coherent policy developments at all levels and was recommended by the Benzodiazepine Committee [4].

The prescribing and use of these drugs raise complex and contentious issues [3, 5, 21, 33-35]. The views and experiences of prescribers and patients appear to be discordant [3,21,35] and consequently, if a GP or Community Pharmacist raises the issue of dependence and withdrawal with a patient, there is the risk that the patient will transfer to another practitioner to maintain their supply. Use and abuse of benzodiazepines and the 'z' drugs, is reported to be high in drug/substance abusing patients and the widespread availability of the drugs contributes to this [11, 35-36]. GPs and Community Pharmacists recognize the problems of the drugs in patients and drug/substance misusers but see few alternatives to prescribing or opportunities to help with discontinuation via counselling and support services [37]. GPs' role as gatekeepers puts the onus on them to prescribe appropriately or to refer [4, 33], but Community Pharmacists have a 'duty of care' to the patients for whom they dispense, and contractual responsibilities to review a patient's medications, to monitor for the abuse of medicines, to promote cost-effective prescribing and to reduce waste in prescribing [38]. Since both practitioners are independent contractors of health services to the State, these roles provide potential for conflict between them, and act as a barrier to collaborative practice.

It is clear that additional policy measures are needed to tackle this problem. Both the public and members of the Primary Care Teams and Networks should be alerted to

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the level of sub-optimal prescribing of these drugs. Increased regulation to reduce the utilization of benzodiazepines may result in other, less suitable drugs being prescribed or no drug at all being provided, and have more effect on ‘non-problematic’ rather than ‘problematic’ patients [2, 32] and may reduce the access of patients with substantial clinical need for the drugs [39]. A multilevel regulatory approach has been suggested [33], but to be effective, it will have to ensure multi-disciplinary, collaborative practice and to be complementary to, a public health educational effort with community and ‘expert’ patient initiatives to promote public engagement.

This study has several limitations; no information about diagnosis is recorded in the database so it was not possible to differentiate the indications for which these drugs had been prescribed; although it was possible to separate out the use of benzodiazepines in those under 15 years of age, further details of age bands, and of gender were not available and hence the data could not be transformed into Standardised Prescribing Ratios as developed by Johnson and colleagues [27]; a sample of prescriptions would be required to calculate Prescribed Daily Doses to supplement the information about the dose and duration of treatment that has been inferred from DDDs per prescription; the study population used is not representative for the overall Irish population (eligible patients include the socially disadvantaged and persons  $\geq 70$  years old); only the dispensed amount of the included drugs were evaluated, and this may or may not indicate the actual consumption of the drugs by the patient; the data was not available for each month of each of the times periods studied and only Health Board-wide data rather than Community Care Area or District Electoral District (DED) data so that a Small Area analysis could not be carried out, and since Deprivation indices are based upon DEDs, the relationship with prescribing and deprivation could not be explored.

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