

Multiple sclerosis disease modifying drug utilisation in Australia

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Main points:

- 1) Overall RRMS DMD use increased progressively from 0.02 to 2.10 DDD/ 1000 population/day between 1996 and 2011.
- 2) From 1996 to 1999 interferon β 1B was the only such agent available, and until 2007 was the most widely used RRMS DMD used despite the introduction of interferon β 1A in the interval.
- 3) Glatiramer acetate became available in 2004 and in 2008 it superseded interferon β 1B as the most widely prescribed agent.
- 4) The increased use of RRMS DMDs probably relates to growing medical and patient confidence in the benefits obtained from using such drugs, longer survival in MS patients (partly related to use of drug treatments), and easier recognition of MS with the wider availability of magnetic resonance imaging.
- 5) Overall RRMS drug use was higher in more southern states as compared with northern states.

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ABSTRACT

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Purpose:

To examine trends in dispensed use of disease modifying drugs (DMD) for relapsing remitting multiple sclerosis (RRMS) in Australia from 1996 to 2011.

Methods:

We analysed data from Medicare Australia for Pharmaceutical Benefits Schedule item statistics of RRMS drugs and by administrative area (state/territory). Prescription data were converted to defined daily doses (DDD)/1000 population/day using Australian population data.

Results:

Overall RRMS DMD use increased progressively from 0.02 to 2.10 DDD/ 1000 population/day between 1996 and 2011. From 1996 to 1999 interferon β 1B was the only such agent available, and until 2007 was the most widely used RRMS DMD despite the introduction of interferon β 1A in the interval. Glatiramer acetate became available in 2004 and superseded interferon β 1B as the most widely prescribed agent in 2008. Natalizumab was introduced in 2008 but its use appears to have been very small. Overall RRMS drug use was higher in more southern states than in northern states. Patterns of preferred agent varied between different Australian states and territories.

Conclusions:

RRMS DMDs use in Australia has grown progressively since 1996 Knowledge of the current patterns of use of these agents may help in assessing the effects on patterns of such drug use with the expected introduction into Australia of orally administered RRMS DMDs.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory, primary demyelinating disease of the central nervous system and is the most common cause of continuing neurological disability in young adults in western societies.¹ In most people, MS follows a relapsing-remitting course (relapsing remitting MS (RRMS)) at least in its earlier stages. In these stages there is often complete clinical recovery between attacks but over time recovery between attacks becomes incomplete and most patients ultimately enter a secondary progressive phase.¹ In about 10% of people the disease runs a primary progressive course, with continuing deterioration in neurological function from the outset, without relapses and remissions.^{2,3} The overall progressive nature of the disorder, the eventual debilitation, and the peak age of onset of 30-49 years¹, result in high levels of support and medical care being required and significant loss of productivity in the workforce.⁴ Half the people living with MS in Australia are unemployed. It is estimated that, in 2005, MS cost AUD\$600 million: lost productivity and informal community care being the two largest cost components.⁵

MS treatment was essentially symptomatic until new disease modifying drugs (DMD) became available in Australia after 1995, including interferon beta(β)1B, interferon beta(β)1A, glatiramer acetate and natalizumab.⁶ These drugs are approved for use in the relapsing-remitting phase of the disease and appear capable of favourably altering its natural history.⁷ In Australia they are publically subsidised on the Pharmaceutical Benefits Schedule (PBS) under the 'Authority Required' prescription mechanism⁸ for patients who i) have had at least two attacks in the preceding two years with partial or complete recovery and remain ambulant, and ii) have their diagnosis confirmed by magnetic resonance imaging (MRI) of the brain or spinal cord. Until recently, public rebates were available only on MRI studies ordered by a specialist. As a result, prescriptions of these agents are generally initiated by specialists (specifically neurologists) but may be continued by general practitioners in the community. These drugs are too expensive to be routinely obtained by private prescription (i.e. where the consumer pays the total cost) and the PBS has mechanisms to ensure that individuals do not receive more than one such agent simultaneously.⁹

Previous studies have suggested an increasing MS prevalence with increasing southerly latitude in Australia, however differences in diagnostic criteria and acquirement of MS prevalence data has caused difficulties in comparison between studies.¹⁰⁻¹⁵ Despite these epidemiological studies, to our knowledge, no one has profiled the growth in the use of RRMS drugs in Australia. Newer agents are soon expected on the market so we wanted to capture the current situation regarding the use of these drugs. We examined the patterns of

dispensed use of RRMS drugs between 1996 and 2011 in Australia and differences at various times in dispensed use among the nation's states and territories.

METHODS

All the drugs were available under the Australian Government's subsidised drug formulary – the PBS. The PBS provides a broad range of Australian registered drugs to Australian citizens with two levels of patient co-payments: general (AUD\$35.40, 2012) and concessional (AUD\$5.80, 2012).¹⁷ Concessional beneficiaries are those who receive social security benefits because they hold a Pensioner card, a Health Care card, or a Commonwealth Seniors Health card. The drugs considered in this study are listed only for use in patients with diagnosed RRMS that meets the criteria mentioned above, are used in a monotherapy format (i.e. only one of these drugs is prescribed to an individual patient at any given time) and are all priced substantially above the level of copayment. Patients who have progression of disease despite treatment are not eligible for repeat prescriptions of subsidised drugs.⁷ None of these drugs has any other subsidised therapeutic use and they are almost invariably used in the same standard dose without individual variation. A single prescription (initial plus five repeats) supplies one person for 24 weeks. The drug cost for all the agents (except natalizumab) for one person with RRMS is approximately AUD\$1055 per 28 day period – more than AUD\$13,000 per annum. There would likely be very little prescription of these agents in public hospitals due to costs and because patients with RRMS are mostly managed on an outpatient basis. Natalizumab, a monoclonal antibody, has been available since July 2008 (under PBS Section 100 Public from August 2010) for use in approved hospitals for monthly intravenous infusion in day procedures for the treatment of RRMS. It costs over AUD\$2000 for a month's supply.

The number of dispensed prescriptions for RRMS drugs was obtained from public domain Medicare Australia PBS drug use statistics provided by the Australian Government Department of Health and Ageing.⁶ Data were collected for the period between January 1996 and December 2011 and stratified by administrative areas - state or territory - for each formulation of each drug. The amount of drug dispensed (as prescriptions) was standardised to drug utilisation using the defined daily dose (DDD) per 1000 population per day. The DDD, as established by the World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology, is the assumed average maintenance dose per day (expressed in terms of the dose contained in marketed dosage forms) for a drug used for its main indication in adults.¹⁸ For DDD calculations we used the midyear population for each state or territory and Australia.¹⁹ Yearly totals of DDDs were summed for each administrative region

and for the whole nation. The utilisation of 10 DDD/1000 population /day would correspond to about 1% of the population taking a standard dose (DDD) each day. The midyear population in 2011 was 22.3 million people.

The drugs in alphabetical order by generic name (with the trade name and DDD) are: glatiramer acetate (Copaxone®, 20mg); interferon β_{1A} - Avonex® (4.3mcg); interferon β_{1A} - Rebif® (4.3mcg); interferon β_{1B} (Betaferon®, 4mU); and natalizumab (Tysabri®, 10mg). Interferon β_{1B} was listed on the PBS in November 1996 followed by interferon β_{1A} -Avonex® preparations in February 1999 and interferon β_{1A} -Rebif® preparations in May 2000. Glatiramer acetate was listed in May 2004 and natalizumab in July 2008.

RESULTS

Dispensed use over time

Overall use of RRMS drugs increased 15.5-fold between 1996 and 2011 (from 0.012 to 0.188 DDD/1000 population/day; Table 1). The most commonly prescribed drug until 2008 was interferon β_{1B} , with a peak dispensed use of 0.067 DDD/1000 population/day in 2005. Glatiramer acetate use exceeded interferon β_{1B} use in 2008 (0.061 and 0.067 DDD/1000 population/day respectively; Figure 1) and had 51% share of the market in 2011. Interferon β_{1B} use, as a proportion of all MS drug use decreased from its initial monopoly to 30% in 2011. Natalizumab use has been low since its introduction in 2008. There was a relative plateau in overall RRMS drug use between 2005 and 2007 with further increasing use in 2009 and subsequently - the increase being largely accounted for by growth in use of glatiramer acetate (Figure 1).

Dispensed use by state or territory

The total Australian RRMS drug use was 0.201 DDD/1000 population/day in 2011. Australian Capital Territory (ACT) had the highest dispensed use of RRMS drugs with 0.411 DDD/1000 population/day in 2011 (Figure 2) and Northern Territory (NT) the lowest with 0.053 DDD/1000 population/day, about one eighth that of ACT. Interferon β_{1A} use was low and fairly consistent across all states and territories. In all jurisdictions, except Tasmania, glatiramer acetate became the most used RRMS drug. Although there was increasing use along a general north-south gradient of states, there was a major exception in that its use in the ACT (0.322 DDD/1000 population/day) was considerably greater than in the geographically surrounding state of New South Wales (NSW; 0.088 DDD/1000 population/day). The population in the ACT is about 5% that in NSW. There was an increasing north-south gradient of interferon β_{1B} use across the states and territories, being

highest in Tasmania (0.141 DDD/1000 population/day) where it was more than double that of Queensland (0.056 DDD/1000 population/day).

Dispensed use with time in different administrative areas

The introduction of each new RRMS DMD to the PBS was associated with changes in the proportion of overall drug use for which each agent was responsible, both nationally and in the individual states and territories. The proportions for each drug in each administrative area for the years 2003 (immediately before glatiramer acetate became available), 2007 and 2011 are shown in Figure 3. Overall in Australia and in each administrative area, as glatiramer acetate use grew use of β -interferons showed a relative decline to values which ranged between 62% of overall MS drug use for Tasmania and 21% for the ACT. However, in the states where use of interferon β_{1A} was lowest initially (Queensland 17% and Tasmania 16%), there was little relative change in its use. Where its initial use was higher, that use declined to a fairly consistent figure of around 20% of overall use, except in ACT, where use fell from 40% to 11% over the nine year period considered. Interferon β_{1B} use declined progressively in all states and territories as glatiramer acetate use grew, the decrease being greatest in the ACT (from 60% to 10%). The ratio of interferon β_{1A} to interferon β_{1B} use never exceeded unity (except in the ACT) across the study period (Table 2). In 2011 the ratio of use ranged from 0.22 in the Northern Territory to 1.04 in the ACT.

DISCUSSION

Over the period between 1996 and 1999, when interferon β_{1B} was the only RRMS DMD available in Australia, its use in the whole country increased nearly five-fold. This growth may have mainly been a result of prescribers becoming increasingly familiar with the idea of a new type of therapy being available, and people with MS becoming aware of its existence. As more treatment options became possible, total RRMS DMD use continued to increase. Use of interferon β_{1B} , which accounted for all dispensed prescriptions of RRMS therapy before 1999, provided less than one third of total RRMS drug use by 2011, despite interferon β_{1B} use being relatively steady from 2002 to 2007, and thereafter declining only slightly. The availability of various dosage forms of interferon β_{1A} from 1999 onwards may have slowed the growth of interferon β_{1B} use, though the total national use of the various interferon β_{1A} preparations did not achieve more than the use of interferon β_{1B} at any stage. Disease-modifying drugs more recently listed on the PBS, viz. glatiramer acetate and natalizumab, particularly the former, are becoming more widely used and largely account for the overall increase in use of RRMS DMDs from 2009 onwards.

The increase in overall RRMS drug use over the 15 years likely reflects the influences of several factors. Though no cure has yet been found for MS, advances in the available DMDs and advances in symptomatic therapy have resulted in increased life expectancy for people with MS.³ As a consequence, there has been an increase in disease prevalence. As well, aided by the growing availability and diagnostic capability of MRI, there has been an increasing recognition of cases of RRMS in the Australian community, further increasing the number of people with MS available for treatment. Following the earlier growing prescriber awareness of the availability of RRMS DMDs, there has been a subsequent growing consciousness among prescribers of the benefit to people with RRMS of using such therapies and these people have more or less simultaneously become aware of the benefit.

There was generally higher use of RRMS drugs in the more southerly Australian administrative areas than in the more northerly ones, consistent with the known higher prevalence of the disease with increasing distance from the equator in both hemispheres,^{10-13 20} for reasons which remain unclear.¹⁵ There was, however, an exception to this relationship in the unusually high use of RRMS drugs in ACT, compared with their use in the surrounding state of New South Wales - a usage pattern driven by heavy prescribing of glatiramer acetate in the ACT.

During the period between 2003 and 2011 there were changes in the proportions of overall RRMS DMD use attributable to the various individual drugs, both nationwide and between states and territories. It is interesting that, in states and territories where interferon β 1A was not heavily used in 2003, its use remained relatively constant as time passed, whereas in those where its early use was greater, its use fell towards the value that applied for areas where it had never been widely used. This perhaps suggests that prescribers came to identify a section of the RRMS population for which interferon β 1A appeared to be the most advantageous agent among those available. However, the influences of the effectiveness of pharmaceutical marketing in different administrative areas cannot be discounted in this regard. It is also noticeable that the two administrative areas with patterns of prescribing that differ most from the norm (Tasmania and ACT) have relatively small populations and relatively few neurologists practising. Unusual patterns of prescribing by a single practitioner (with or without any clinicians that practitioner has trained) are likely to have more obvious effects in such areas than in areas with larger populations and more neurologists. It cannot be determined from the available data that this has happened, but if it has, after allowing for the expected differences in MS prevalence with latitude, the national distribution of

proportions of RRMS DMD use may represent the pattern of preferred use of these agents by the great majority of prescribers in Australia in recent times.

Dispensed use of natalizumab through the PBS, introduced in 2008, probably was greater than appears in the data. Confidential sales figures provided by the marketing company suggest that there may be delayed reporting of its use to the Australian Government by hospital pharmacies in contrast to community pharmacies who report dispensing other RRMS drugs quickly to receive government payments. We suggest that this delay would likely be less than a year. This possible discrepancy confounds the interpretation of natalizumab data from 2008 to 2011. Furthermore, natalizumab use may have been slow to increase due to progressive multifocal leucoencephalopathy.²¹

The strength of this study is that it presents national data on all subsidised prescribing, and likely approximately all prescribing, of RRMS DMDs over a 15 year period in Australia. This is the case because, with the high cost of these drugs, it is highly unlikely that they would be purchased privately (i.e. without government subsidy). These data may serve as a useful baseline for comparisons with probable changes in drug use which are likely to occur when disease-modifying drugs for MS that can be taken by mouth come on the Australian market, probably within a few years, if not sooner.

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Figure 1: Individual and total RRMS drug utilisation (DDD/1000 population/day between 1996 and 2011 for all of Australia

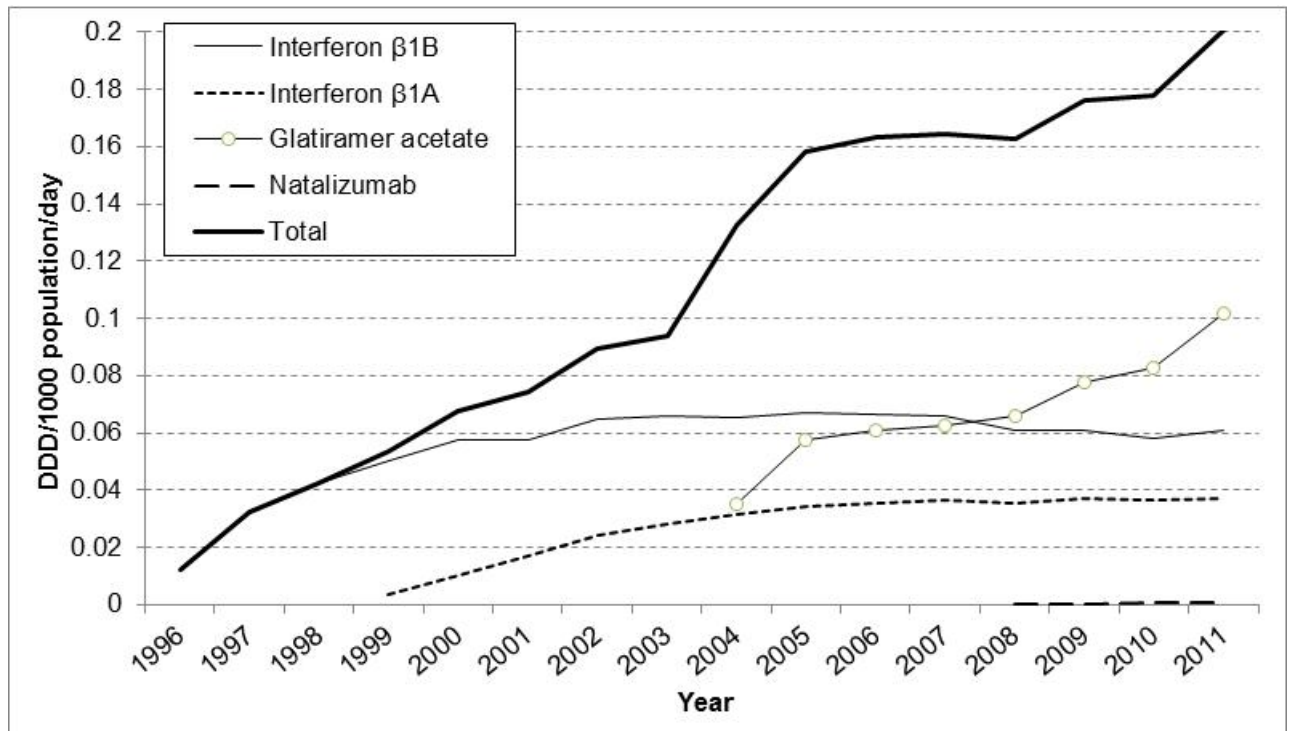


Table 1: Utilisation (DDD/1000 population/day) and proportion of all use (%) for all RRMS drugs between 1996 and 2011 in all of Australia

	Interferon β 1B		Interferon β 1A		Glatiramer acetate		Natalizumab		All drugs	
	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
1996	0.0122	100%		0%		0%		0%	0.0122	100%
1997	0.0325	100%		0%		0%		0%	0.0325	100%
1998	0.0423	100%		0%		0%		0%	0.0423	100%
1999	0.0500	93%	0.0036	7%		0%		0%	0.0536	100%
2000	0.0576	85%	0.0101	15%		0%		0%	0.0677	100%
2001	0.0576	77%	0.0168	23%		0%		0%	0.0744	100%
2002	0.0650	73%	0.0244	27%		0%		0%	0.0894	100%
2003	0.0661	70%	0.0279	30%		0%		0%	0.0939	100%
2004	0.0656	50%	0.0315	24%	0.0353	27%		0%	0.1323	100%
2005	0.0671	42%	0.0341	22%	0.0573	36%		0%	0.1585	100%
2006	0.0667	41%	0.0356	22%	0.0610	37%		0%	0.1634	100%
2007	0.0657	40%	0.0366	22%	0.0623	38%		0%	0.1647	100%
2008	0.0610	37%	0.0355	22%	0.0661	41%	0.0002	0%	0.1628	100%
2009	0.0609	35%	0.0372	21%	0.0777	44%	0.0004	0%	0.1761	100%
2010	0.0581	33%	0.0368	21%	0.0828	46%	0.0005	0%	0.1781	100%
2011	0.0609	30%	0.0373	19%	0.1016	51%	0.0007	0%	0.2006	100%

Table 2: Interferon β 1A use as a percentage of Interferon β 1B use in 2003, 2007 and 2011 in Australian state and territories plus population in 2011 (M – millions)

Administrative area	2003	2007	2011	Population (2011)
Northern Territory (NT)	35.4%	59.6%	21.9%	0.23 M
Queensland (QLD)	20.1%	28.6%	42.4%	4.47 M
New South Wales (NSW)	53.9%	68.1%	70.4%	7.21 M
Western Australia (WA)	36.6%	53.6%	60.4%	2.35 M
South Australia (SA)	48.9%	67.4%	73.6%	1.64 M
Australian Capital Territory (ACT)	67.3%	132.7% ^a	104.4% ^a	0.37 M
Victoria (VIC)	48.4%	64.3%	67.6%	5.53 M
Tasmania (TAS)	19.7%	24.4%	25.9%	0.51 M
Australia	42.2%	55.8%	61.3%	

^a Percentage exceeds unity as use of Interferon β 1A was greater than use of Interferon β 1B.

Figure 2: Utilisation (DDD/1000 population/ day) the two β interferons and glatiramer acetate, and the three agents combined in Australian state and territories (by latitude of capital city) for 2011

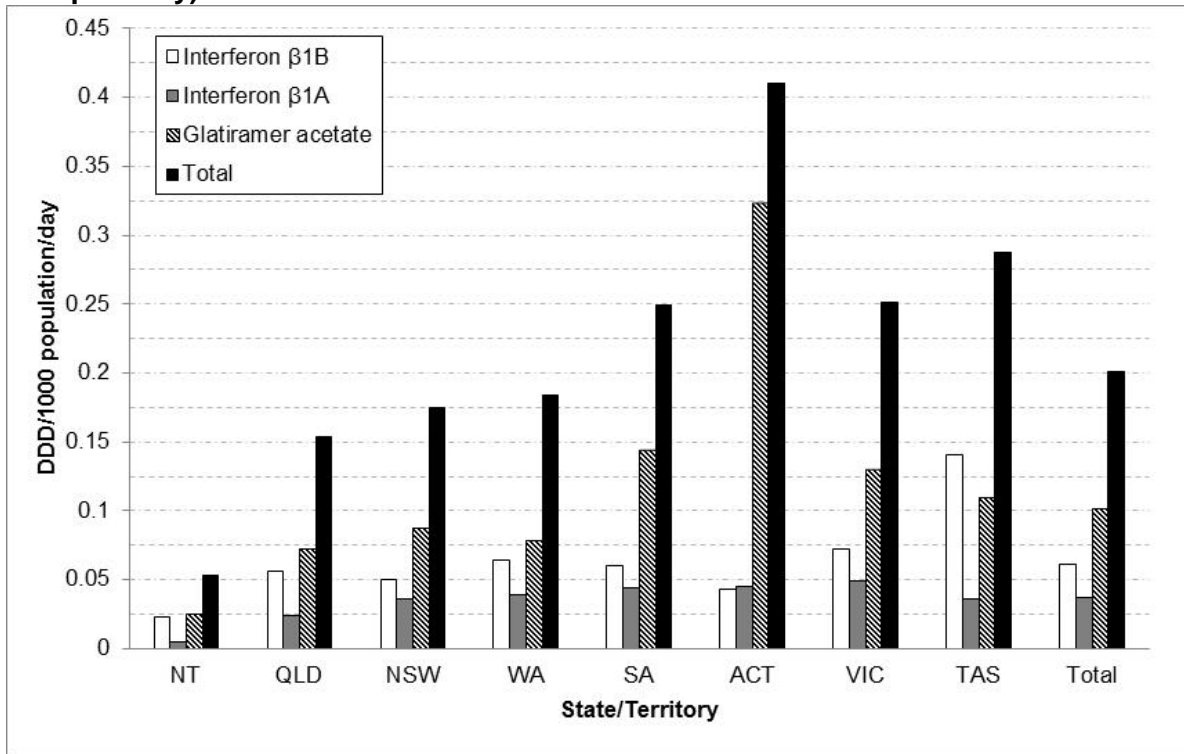
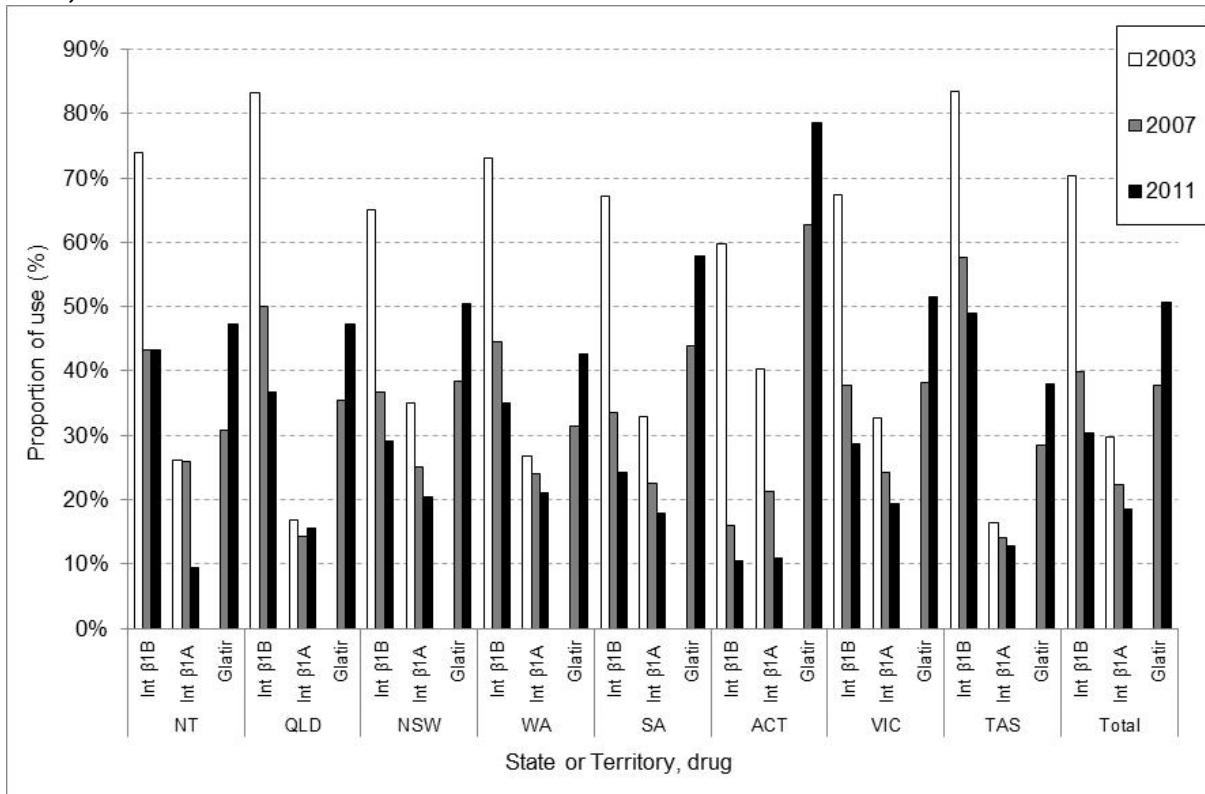


Figure 3: Proportion of use (%) of RRMS drugs (natalizumab data not shown because of uncertainty about its completeness) within Australian states and territories for 2003, 2007 and 2011.



Glatiramer acetate was not available until 2004.