Making new choices about antidepressants in Australia: the long view 1975–2002

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ABSTRACT

Objective: To examine trends in types of antidepressant medications prescribed in Australia between 1975 and 2002.

Design: Sales data from the Australian pharmaceutical industry were used to examine trends in overall antidepressant prescribing and changes in the types of antidepressants prescribed between 1975 and 2002.

Main outcome measures: Antidepressant sales were expressed as defined daily doses (DDDs) per 1000 people per day, using the estimated Australian population for each year obtained from the Australian Bureau of Statistics.

Results: Average annual growth in the sales of antidepressants was 1.1% per year from 1975 to 1990, after which growth rose steeply to reach 29% in 1995. By 2002 the rate of growth had slowed to 6.6%. Eighty per cent of total sales were accounted for by four drugs in 1975, 1980 and 1985; five in 1990; seven drugs in 1995 and 2000; and six drugs in 2001 and 2002.

Conclusions: The rapid growth in antidepressant prescribing that was characteristic of the early 1990s, and reflected the emergence of new classes of agents, did not continue into the late 1990s. Selective serotonin reuptake inhibitors now dominate antidepressant prescribing in Australia.

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Most episodes of depression in Australians are diagnosed and treated by general practitioners, who prescribe 85% of the antidepressants subsidised by the Pharmaceutical Benefits Scheme (PBS).[1,2] When a patient presents, the doctor has to decide whether the individual has clinical depression and, if so, whether to embark on antidepressant drug therapy or a non-pharmacological therapy. Contrary to much media reporting, GPs do not inevitably prescribe antidepressants when dealing with depression and anxiety.[3,4] However, if a drug is to be prescribed, a decision must be made about which drug to use, or what other drug change to make if there has been a lack of response or adverse effects.

The uptake of new drugs by medical practitioners is mediated by a complex set of doctor, patient, regulatory and commercial influences.[5-8] Major influences include the doctors' experiences with their patients, the opinions and practices of colleagues, the availability of the drug on the PBS, whether prescribing of the drug is restricted by the authority system, and the marketing and promotional activities of pharmaceutical companies.

We have previously reported on a sharp increase in antidepressant prescriptions dispensed in the community that occurred in the 1990s in Australia (from 5.1 million in 1990 to 8.2 million in 1998) with the introduction of the selective serotonin reuptake inhibitors and other new antidepressants.[1] Here we analyse antidepressant sales data to describe changes in choices of antidepressants prescribed by Australian doctors between 1975 and 2002.

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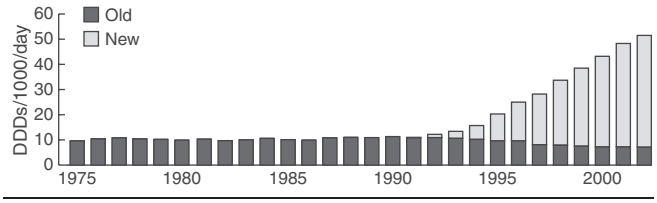
METHODS

Total Australian sales of proprietary antidepressants for the period 1975 to 2002 were obtained from IMS Health Australia Pty Ltd, the leading international provider of information on drug use for the pharmaceutical and healthcare industries. Sales of antidepressants in kilograms were converted into defined daily doses (DDDs).[9] The DDD is the internationally agreed average daily dose of a drug when used for its main indication and is the approved unit for drug utilisation studies. Its use allows the comparison of drug use independent of differences in price, preparation and quantity per prescription. The DDD for an antidepressant may not reflect Australian prescribing practice; however, it provides a stable system of drug consumption measurement and so can be used to follow trends in the use of drugs. To compare antidepressant use per head of population over the period, antidepressant sales were calculated as DDDs per 1000 people per day (DDDs/1000/day) using the estimated Australian population as at 30 June in each year (provided by the Australian Bureau of Statistics). Antidepressants were categorised as old or new according to year of marketing (new antidepressants being those first marketed from 1990 onwards).

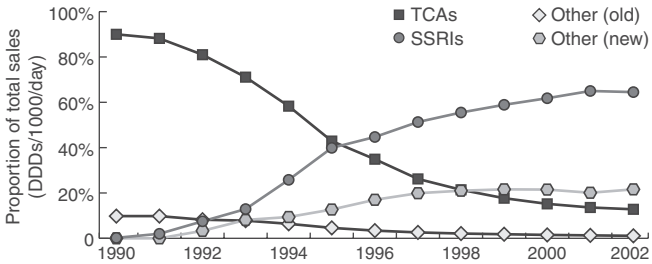
Individual antidepressant sales for each year are enumerated by chemical (generic drug) name. The number of drugs contributing 80% of sales as a proportion of the total number of drugs available was calculated for 1975 and every fifth year to 2000, as well as for 2001 and 2002, as an indicator of the extent to which doctors

1 Use of antidepressants in the Australian population, 1975–2002



New = selective serotonin reuptake inhibitors, moclobemide, venlafaxine, nefazodone, mirtazapine, and reboxetine. Old = tricyclic antidepressants, monoamine oxidase inhibitors, mianserin, and nomifensine.

2 Classes of antidepressant as proportion of total sales of antidepressants in the Australian population, 1990–2002



Other (new) = moclobemide, venlafaxine, nefazodone, mirtazapine and reboxetine. Other (old) = monoamine oxidase inhibitors, mianserin and nomifensine. SSRI = selective serotonin reuptake inhibitor. TCA = tricyclic antidepressant.

restrict the number of different drugs prescribed. We also calculated rankings for the 10 top-selling antidepressant agents retrospectively from 2002.

RESULTS

Overall trends in antidepressant prescribing

From 1975 to 1990, the market was extremely stable (only a 19% overall increase) at about 10 DDDs/1000/day, with an average growth rate of 1.1% per year (range, −5.7% to 9.1%) (Box 1).

From 1990 to 2002, antidepressant use increased by 352%, to reach 51.5 DDDs/1000/day. Over this period the average annual growth rate was 13.4% (range, −2.6% in the first year of selective serotonin reuptake inhibitor [SSRI] sales to 29% in 1995). After 1995, the annual rate of growth declined to 6.6% in 2002.

Trends in type of antidepressant prescribed

In 1990, a major new market opened for antidepressants with the introduction of the SSRIs and other new agents (Box 2). Fluoxetine, the first SSRI, was marketed in 1990. This was followed by moclobemide (a reversible monoamine oxidase inhibitor [MAOI]) in 1992 and by other SSRIs (eg, sertraline and paroxetine in 1994). Venlafaxine — an inhibitor of both serotonin and noradrenaline reuptake — reached the market in 1996.

By 2002, the SSRIs and other new antidepressants represented 64.5% and 21.6% of sales (DDDs/1000/day), respectively. Although the proportion of antidepressant use represented by tricyclic antidepressants (TCAs) dropped from 90% in 1990 to 12.8% in 2002, because of the substantial increase in total antidepressant prescribing, sales of TCAs (DDDs/1000/day) only dropped to 65% of the 1990 value.

Utilisation within drug class: preferred choices

In each year for which the summary indicators are presented in Box 3, doctors have been able to select from a large number of different antidepressant drugs (14 in 1975 and 21 in 2002). In any one year, however, relatively few drugs were responsible for most prescribing.

Box 4 ranks the 10 top-selling antidepressant agents in terms of sales (DDDs/1000/day) for 2002, and retrospectively at 5-, 5- and 10-year intervals. In the past 5 years, the market share for each of the top-selling TCAs has been below 7% of total sales, all of them sharply affected by the advent of the newer antidepressants.

Box 5 plots the trends for each year from 1990 to 2002 for the top-selling agents (those that constituted 80% of total antidepressant sales) in 2002. Amitriptyline was the only older agent to remain in the top-selling group. Fluoxetine was the first of the newer antidepressants and the first choice of all antidepressants in 1994 and 1995, after which sertraline has been consistently preferred.

DISCUSSION

Antidepressant use was stable from 1975 to 1990, a pattern that is typical of a mature market. From 1991 to 2002, the data show an early period of substantial growth in the market, coinciding with the entry of a major new class of compounds, namely the SSRIs, and later the serotonin–noradrenaline reuptake inhibitors and other new antidepressants. Prescribers quickly favoured the newer agents over the older ones. This preference may have reflected the importance that GPs place on the better tolerability of the newer antidepressants.[10] A major advantage of the newer antidepressants

3 Indicators of market concentration for antidepressant sales for index years (5-year intervals 1975–2000, 2001, 2002)

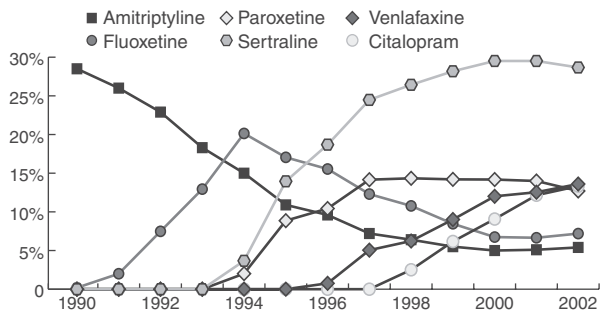
	1975	1980	1985	1990	1995	2000	2001	2002
Total number of antidepressants marketed	14	15	16	14	15	19	20	21
Number of antidepressants constituting 80% total sales	4	4	4	5	7	7	6	6
Antidepressants constituting 80% of sales as a proportion of the total	0.29	0.27	0.25	0.36	0.47	0.37	0.30	0.29
Percentage volume of sales for leading antidepressant	50.5%	46.0%	38.1%	28.5%	17.0%	29.5%	29.5%	28.7%
Percentage volume of sales for top six antidepressants	95.1%	96.9%	92.8%	88.1%	76.5%	79.8%	81.0%	80.8%

4 Ranking of the 10 top-selling antidepressant agents in terms of sales (DDDs/1000/day)

Rank	1982	1992	1997	2002
1	amitriptyline (42.8%)	amitriptyline (22.9%)	sertraline (24.5%)	sertraline (28.7%)
2	doxepin (23.5%)	dothiepin (20.1%)	paroxetine (14.2%)	venlafaxine (13.6%)
3	imipramine (12.7%)	doxepin (18.1%)	moclobemide (13.7%)	citalopram (13.3%)
4	nortriptyline (8.0%)	imipramine (9.7%)	fluoxetine (12.3%)	paroxetine (12.7%)
5	trimipramine (4.4%)	fluoxetine (7.5%)	dothiepin (7.6%)	fluoxetine (7.2%)
6	tranylcypromine (4.3%)	mianserin (4.0%)	amitriptyline (7.2%)	amitriptyline (5.4%)
7	mianserin (1.2%)	tranylcypromine (3.6%)	doxepin (5.4%)	moclobemide (4.7%)
8	desipramine (1.0%)	nortriptyline (3.5%)	venlafaxine (5.0%)	dothiepin (3.1%)
9	protriptyline (0.8%)	moclobemide (3.3%)	imipramine (2.9%)	fluvoxamine (2.6%)
10	phenelzine (0.6%)	clomipramine (3.1%)	mianserin (1.3%)	mirtazapine (2.6%)

Figures in parentheses are the percentages of total sales (DDDs/1000 per day) represented by each agent.

5 Utilisation of top-selling* antidepressants in the Australian population, 1990–2002



* Defined as agents that constituted 80% of total antidepressant sales in 2002.

is the lack of anticholinergic, cardiovascular and other adverse effects, which were a major limitation of the TCAs.[11]

It should be recognised that sales data overestimate actual use, as not all drugs sold to pharmacies are dispensed or taken by patients. In addition, doctors usually prescribe SSRIs in doses corresponding to the DDD, whereas TCAs are often prescribed in doses lower than the assigned DDD, and this is likely to contribute to the observed differences in use of older and newer agents.[1,2]

Nevertheless, it is evident that the availability of and the subsidised access to these new pharmacological agents encouraged more doctors to diagnose and treat depression over the period.[2] The rapid uptake of newer antidepressants during the early 1990s was accompanied by a decrease of only 35% in the use of the TCAs. This supports the view that the major users of the newer antidepressants were patients previously untreated with any antidepressant rather than those changing from the older drugs. However, these data cannot inform us as to whether the appropriate patients are being treated with antidepressants.

Another factor influencing GP preference may be the most clear-cut advantage of the new antidepressants — their lower toxicity in overdose compared with the TCAs. Recent observational studies suggest that the increased use by the population of SSRIs has been associated with a decline in suicide rates in Australia and the Nordic countries.[12-14] In Australia, older adults had the highest growth in antidepressant use and the greatest decline in suicide.[12] Thus, even if some antidepressant prescribing is unnecessary or ineffective, increased exposure to these agents through prescribing in general practice may have produced a measurable reduction in the burden of depression in the population.

The pace of growth for the antidepressants has slowed, although a longer period is required for more confidence in the trend. A plateauing of growth ("steady state") has been observed previously for individual drugs.[15] In part, it may have been associated with the greater public effort made to increase community awareness of depression and the importance of psychological management in its treatment.[16,17] The observed trend may indicate that the market for prescribing *existing* forms of antidepressant is approaching saturation. There could be further growth in prescribing if a significant new type of antidepressant were to be registered and marketed. Alternatively, there could be a significant decline if epidemiological evidence of harm emerged (eg, increased suicide rates), or there was an increased perception in the community that the use of these drugs caused harm, as occurred with the benzodiazepines in the mid 1980s.[5]

Australian doctors have made sertraline their first-choice antidepressant agent since 1996. It is interesting to note that the first choice of antidepressant since the introduction of the SSRIs has not reached the market dominance attained by amitriptyline in 1975 (50% of market share). The "age" of the overall market may be a factor influencing uptake of new drugs;[15] doxepin and dothiepin took much longer to reach their maximum popularity within the low-growth TCA market than did successive new antidepressants entering the expanding market after 1990.

Trends in the proportion of the number of antidepressants that account for 80% of sales to the total number of agents available (Box 3) indicate that doctors prescribe a restricted number of different antidepressants. This proportion was as high as 0.5 in 1995 when the market was unstable and expanding rapidly. By 2002, the proportion was the same as in 1975 (0.3), indicating that, in the long run, doctors prefer to prescribe a limited number of antidepressant drugs. This is in line with accepted pharmacological advice that prescribers should get to know a few drugs well.

CONCLUSION

Antidepressant prescribing increased substantially following the introduction of the SSRIs. The SSRIs dominated antidepressant prescribing in Australia by the end of the 1990s, with a small number of these drugs accounting for most prescriptions.

General practice has a major responsibility in addressing the burden of depression.[10] It appears that Australian GPs have responded to unmet needs in the treatment of depression by being more ready to diagnose and prescribe for depression, and by switching to the newer antidepressants. This change is likely to have been due to a combination of commercial pressures,[7,8]

professional opinion[10,16] and greater readiness on the part of patients to discuss their symptoms.[17]

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COMPETING INTERESTS

William S Montgomery is an employee of and owns stock in Eli Lilly, manufacturer of fluoxetine (Prozac). Ian Hickie has received honoraria for participation in industry-sponsored scientific meetings, and has participated in educational programs sponsored by Bristol-Myers Squibb, Pfizer and Wyeth.

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