Patterns of Antidepressant Drug Prescribing and Intentional Self-harm Outcomes in New Zealand: An ecological study

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Executive Summary

Depression is a common and treatable condition. If not appropriately treated, depression and other psychiatric disorders can have significant consequences. Antidepressant medications benefit many patients, but it is important that doctors and patients are aware of the benefits and risks.

This report presents the findings of an observational pharmacoepidemiological study that has been undertaken by Public Health Intelligence (PHI) to investigate whether a relationship can be observed between antidepressant prescribing (particularly selective serotonin reuptake inhibitors) in New Zealand and suicide-related outcomes. A secondary objective of the study was to examine the usefulness of the national data sets – in particular the Pharmhouse data – to inform research into questions about the safety and efficacy of drug use in New Zealand. A Pharmacoepidemiological study is population level observational research on the use of drugs and their effects in the population. The study uses data from national data sets, and internationally accepted drug utilisation methods. It provides information describing the patterns of antidepressant prescribing in New Zealand over time, examines whether a relationship can be observed between the patterns of prescribing and suicide-related harm – in particular, hospitalisations for intentional self-harm, and a review of the international literature on the issue.

Given the new mental health policy related initiatives in New Zealand, it is timely to examine whether there is any observed association in New Zealand between antidepressant use and suicide related outcomes.

This study has found significant regional differences in the numbers of people prescribed antidepressants in the population, and found a statistically significant observed association between increased prescribing in the population of nortriptyline, paroxetine and fluoxetine and increased hospitalisations for deliberate self-harm events. However the risk is very small (Odds Ratio ranging from 1.25 to 1.63). The findings are generally comparable with similar studies reported in the international literature. A number of explanations for the findings are examined.

On the evidence reviewed and presented in this study, it seems prudent to remind clinicians that when prescribing antidepressants to patients diagnosed with a condition associated with increased risk of suicidal behaviour – such as depression – it is important that they make regular contact with the patient in the early period following initial prescribing.

This study is unable to resolve the debate about the risks and benefits of using antidepressants because of the study design and limitations in the data sets used. Given the complexity of the issue and the relative rarity of the health outcome of interest, undertaking the ideal of a randomised control studies to resolve the debate is not feasible in New Zealand because of the size of the study that would be required. One alternative is to undertake a more detailed observational study in approximately three to five years time using the national datasets and methods trialled in this report.

Introduction

Background

Improved antidepressant drug utilisation is often held to be an important intervention for both suicide prevention and improved mental health. Promoting effective and efficient drug use is an ongoing issue of interest to the government, the health sector, health consumers and pharmaceutical companies.

However, for some time there has been concern, and much debate, about the safety and efficacy of antidepressants, and recently selective serotonin reuptake inhibitors (SSRIs) in particular (see Bridge et al 2007; Ellis 2002; Fergusson et al 2005; Hall 2006; Healy 2000, 2002, 2003, 2006a, 2006b; Healy and Aldred 2004; Healy et al 1999; Juredini et al 2004; Khan et al 2003; Kirsch et al 2002; Martin et al 2003; Moncrieff 2001, 2002, 2003; Moncrieff and Kirsch 2005; Rubino et al 2007; Safer and Zito 2007; Simon 2006; Simon et al 2006).

In the past, concern focused on the risk of overdose from tricyclic antidepressants (TCAs). Recently, attention has shifted to whether there is an increased risk of suicide and/or suicidal ideation and intentional self-harm among those prescribed an SSRI, particular among children and adolescents (Federal Drug Administration 2005a, 2005b). In October 2004, on the advice of the Medicines Adverse Reactions Committee, Medsafe sent out new advice to New Zealand prescribers, noting that the risk:benefit ratio of prescribing SSRIs (except fluoxetine) to children and adolescents was not favourable (Medsafe 2004).

In July 2005 Pharmac noted in their annual report the substantial growth in the prescribing of antidepressants in New Zealand in recent years, yet only one New Zealand-based study has investigated whether there is a relationship between prescribing SSRIs and suicide-related outcomes (Didham et al 2005). In their study, Didham et al explored the incidence and risk of suicide-related outcomes among patients prescribed an antidepressant by a general practitioner from 1996 to 2001. Over this period, a total of 57, 361 patients were identified, among whom 26 completed suicide and 330 episodes of self-harm occurred within 120 days of prescribing for an antidepressant. After adjusting for age, gender and pre-existing depression and/or suicidal ideation, the authors found a diminished but persisting increased risk of self-harm hospitalisations (OR[1] 2.26 (1.27–4.76)), but not suicide (OR 1.92 (0.77–4.83)), for patients prescribed an SSRI. Didham et al concluded that age, gender and pre-existing depression or suicidal ideation are important confounders in observational studies of the association between antidepressants and suicide-related outcomes.

[1] OR = odds ratio.

Analysis by the Ministry of Health has shown a significant variation between District Health Boards (DHBs) in the trends of suicide mortality and morbidity rates over time, and that suicide mortality and morbidity are related to deprivation (Ministry of Health 2006a, 2006b). Comparison of DHB age-standardised rates of suicide-related mortality and morbidity over a 20-year period (1983–2003) indicates that there may be a relationship between high suicide rates and low hospitalisation rates, and vice versa. Where suicide rates have clearly declined in some DHBs, hospitalisation rates in those DHBs increased in the same period (Ministry of Health 2006a).

Over the same period (1983–2003), suicide rates have been consistently higher in the more deprived areas of New Zealand, and the most deprived areas have shown relatively larger rises and, more recently, falls. In contrast, the least deprived areas of New Zealand have shown relatively little variation in rates over time. Similarly, higher hospitalisation rates for intentional self-harm in the more deprived areas of New Zealand have been a consistent feature over the period, with the most deprived areas of New Zealand recording more than twice the number of hospitalisations for intentional self-harm than the least deprived areas (Ministry of Health 2006a).

There are a number of possible explanations for these variations, including differences in the underlying rate of depression in the population; structural factors of the population such as age, sex, ethnicity and deprivation; differences in treatment and prescribing practice by clinicians in each area; and differential admission and data recording policies for intentional self-harm by the DHBs.

Aims and intended audience

Given the debate in the literature about the safety and efficacy of antidepressants and recent mental health policy initiatives in New Zealand,[2] this is a good time to examine whether there is any observed association in New Zealand between antidepressant use and suicide-related outcomes.

This report presents the findings of an observational pharmaco-epidemiological study undertaken by Public Health Intelligence to investigate whether a relationship can be observed between antidepressant prescribing (particularly SSRIs) in New Zealand and suicide-related outcomes, using data from national data sets and internationally accepted drug utilisation measures. A secondary objective of the study was to examine the usefulness of the national data sets – in particular the Pharmhouse data – for informing research into questions about the safety and efficacy of drug use in New Zealand.

The report aims, firstly, to inform policy makers, clinicians and researchers about antidepressant use in New Zealand and any observed relationship to suicide-related outcomes, and, secondly, to outline the utility of the methods used for exploring similar questions in any future studies.

[2] See Associate Minister of Health 2006a and 2006b; Minister of Health 2006.

Methods

The research 'gold standard' for answering the types of questions that have been raised in the literature is to undertake a randomised control trial. However, because of a range of methodological issues, such a study is not feasible for antidepressant use and suicide-related outcomes for even large countries such as the United States (Simon 2006). An alternative method is to undertake a pharmaco-epidemiology study. These are population-level observational studies that research the use of drugs and their effects in the population (University of Portsmouth 2007; WHO Collaborating Centre for International Drug Monitoring 2006). By combining information from a number of New Zealand Health Information Service (NZHIS) national data sets, and using internationally accepted statistical methods and classification systems such as the defined daily dose (DDD) and the prescribed daily dose (PDD), it is possible to describe and compare the patterns of prescribing pharmaceuticals for the treatment of the health outcomes of interest within the New Zealand population.

Questions that may be examined include:

- What proportion of a given population is being prescribed a pharmaceutical?
- Which population groups are being prescribed a pharmaceutical?
- Which drugs are being used to treat a diagnosed condition?
- What doses are being used to treat the diagnosed condition?
- What health outcomes have been experienced from the use of the drugs?
- Do prescribing practices differ from recommended prescribing guidelines, and between geographical regions?
- Can patterns be observed between drug prescribing practice and the health outcome of interest?

In order to answer these questions in the context of antidepressant prescribing and suicide-related outcomes, a pharmaco-epidemiology ecological[3] study was devised consisting of three parts, as outlined in Table 1.

[3] Ecological studies use aggregated population-level data rather than individual-level data. They allow for the consideration of population-level explanatory factors such as age, sex, ethnicity, deprivation and regional prescribing differences to be considered in statistical modelling.

Table 1: Summary of research methods used in study

Research questions and methodological approach	Analysis	Information and data sources
Pharmaco-epidemiological study describing patterns and trends in antidepressant prescribing in New Zealand and by DHB between 1997 and 2005, and pattern of mental health diagnosis and drug treatment in 2005	Calculation of: • defined daily doses (DDD) by antidepressant, age group and DHB • prescribed daily doses (PDD) for each antidepressant Construction of: • graphs illustrating New Zealand's pattern of antidepressant prescribing and suicide-related outcomes over time • a table illustrating the pattern of mental health diagnosis and antidepressant treatment in 2005	NZHIS: • Pharmhouse warehouse • National Minimum Data Set – Mortality • National Minimum Data Set – Morbidity • Mental Health Information National Collection • National Health Index database Statistics NZ – census and population estimates World Health Organization – DDD and PDD methodology, and ATC[4] (WHO 2006) classification British National Formulary No. 52 (BNF 2006) – Drug class classification, indication and treatment guidelines Medsafe – NZ Prescribing Guidelines
Statistical modelling of interactions between intensity of antidepressant drug prescribing (DDD and PDD), population-level variables (eg, age group, sex, deprivation, DHB), and hospitalisation for intentional self-harm outcomes as a proxy for suicide attempt in 2005	Use of the Poisson regression model to explore the interaction between a range of population-level factors and hospitalisation for intentional self-harm outcomes in 2005	
Literature review of the debate about whether there is an increased risk of suicide-related outcomes from the prescribing of antidepressants, particularly SSRIs	Discussion of methods used, results reported, possible explanations and implications of findings for research and policy	Ministry of Health library for supply of literature Medsafe – NZ Prescribing Guidelines British National Formulary Guidelines (2006)

[4] Anatomical Therapeutic Chemical (ATC) classification system (WHO 2006).

Data sources and limitations found in the data sets

Estimation of antidepressant prescribing levels

There are 20 antidepressant drugs approved/available for use in New Zealand, and there are two substantial pharmaceutical databases that monitor different aspects of prescribing practice in New Zealand. One database is maintained by the Intensive Medicines Monitoring Programme (IMMP) at the University of Otago, which collects prescription data for monitored medicines from over 90% of pharmacies, including community and hospital pharmacies. However, many of the drugs of interest in this study are not monitored by IMMP.

The second database is the Pharmhouse data set maintained by the NZHIS. This data set contains claim and payment information for subsidised drugs dispensed by pharmacists, but not hospitals. The data available includes information about each subsidised drug and formulation dispensed, date dispensed, daily dose, dose, frequency, days supply dispensed, and quantity of the drug dispensed. Patient information available includes the unique identifier, health care user (HCU), age group, ethnicity, gender, residence/address (health domicile – HD), address of dispensing pharmacy, and address of prescribing clinician. The patient is allocated to one of three age groups: under 6, 6–18 (juvenile), 19+ (adult).

Pharmhouse data on all prescriptions for the following therapeutic groups of antidepressants for the period 1997 to 2005 was obtained from the NZHIS. Complete data was only available as far back as 1997. The extract contained the following antidepressant drug classes, as defined by the World Health Organization (WHO):

- selective serotonin reuptake inhibitors (SSRIs)
- tricyclics (TCAs) and related agents
- monoamine-oxidase inhibitors (MAOIs) – non selective
- monoamine-oxidase type A inhibitors
- other antidepressants.

There are three important limitations to the Pharmhouse data set that can lead to an underestimation of the level of exposure in the population to the drug of interest, and of the associated health outcomes. First, the data set does not include prescriptions that have been written by clinicians but not presented by the patient. It does, however, include prescriptions filled by the pharmacist (ie, dispensed) but not collected by the patient. Limited research conducted in New Zealand during the early 1990s shows that the number of patients not presenting a prescription is likely to be less than 5% (Dixon et al 1994; Jones and Purdie 1993).

A second limitation is that because only information on subsidised drugs is collected, the full extent to which a population is exposed to a drug is unknown. The level of exposure can also be affected by the level of subsidy available over time for a drug. For example, when a drug is new it may not receive a subsidy and its use will not be recorded in Pharmhouse, although it may be used by a segment of the population. However, later on the drug may become subsidised, at which point the level of prescribing is monitored. A drug may also only be subsidised once its level of use passes a particular threshold for a patient, which means its use is only recorded when the patient receives a subsidy.

The third limitation is that while medicines prescribed in a general practice setting are counted, those prescribed and dispensed in hospitals are not recorded in the data set. This limitation may result in an underestimation of the health effects of a drug in the treatment of more seriously ill patients, and underestimate the level of exposure to a drug in a particular geographic region.

Estimation of mental health conditions and use of antidepressants

The Mental Health Information National Collection (MHINC) contains information on the provision of secondary mental health and alcohol and drug services purchased by the government. This includes secondary inpatient, outpatient and community care provided by hospitals and non-government organisations (NGOs), but excludes primary care. Data available includes diagnosis and patient HCU.

Using the patient HCU unique identifier, patients in the MHINC were linked to the Pharmhouse prescribing data extract. This made it possible to examine the prescribing of antidepressants by mental health diagnosis (ICD-10 Mental Health and Behavioural disorder F00–F99) for the years 2001 to 2005. This time span was selected because these are the years for which the two data sets overlap. To be included in the analysis a patient had to have received a diagnosis and a prescription for an antidepressant in the same year. For inclusion in the Poisson regression analytical model a patient had to have received a diagnosis and a prescription for an antidepressant in 2005 and to have been hospitalised for an intentional self-harm event in the same year. Because this data set excludes primary care, the count of the mental health conditions and associated type of drug prescribing reported for the period will undercount the number of mental health conditions at the low end of severity and associated prescribing.

Population-level exposures to antidepressants in New Zealand 1997–2005 (prescribed daily dose and defined daily dose)

The prescribed daily dose (mg) (PDD) and defined daily dose (DDD) were calculated for each antidepressant for the years 1997 to 2005 using the WHO methodology for these measures (WHO Collaborating Centre for Drug Statistics Methodology 2006). The PDD was compared with the recommended adult daily maintenance dose according to Medsafe data sheets for the drug's treatment of depression, the WHO DDD for an adult on a maintenance dose and the British National Formulary (2006) recommendations for the treatment of depression.

Patterns of prescribing by DHB for the year 2005 were examined using the Pharmhouse data for that year. Prescribing data was assigned to a DHB using the patient's HCU to match them to the National Health Index database.[5] Where this was not possible, the assignment to a particular DHB was based on the pharmacist's address. For each DHB, the number of DDDs dispensed to the population per 1000 people was calculated for each antidepressant formulation prescribed, and by each class of antidepressant. Statistics New Zealand population data from the 2001 census was used to project DHB population denominators for 2005.

The DDD in the population is calculated by totalling the amount of each antidepressant formulation dispensed for the year in milligrams, and dividing this by the WHO DDD (mg) for that drug (WHO Collaborating Centre for Drug Statistics Methodology 2006). This gives a figure of how many DDDs are dispensed each year. To calculate the proportion of the population receiving this dose on a daily basis, this figure is divided by 365 days and expressed as a rate per 1000 people of the DHB population. This provides an estimate of the number of people per 1000 in the DHB that were prescribed a daily (maintenance) dose (mg) of antidepressant.

A DHB's DDD per 1000 people was compared to the national mean DHB DDD per 1000 people. Those DHBs with a DDD rate above or below the 95% confidence of the national mean DHB DDD rate were deemed to be statistically significantly different from the national average. This DHB comparison was done for each drug formulation and drug class.

For each DHB, the DDD per 1000 children and adolescents for each antidepressant drug formulation prescribed to children and adolescents was calculated and compared. The age ranges 0–5 years and 6–18 years were used, as these are the age groups available in the prescribing data.

Indicators of suicide-related outcomes

A suicide-related outcome or behaviour can be defined as any act of self-injury undertaken with the intent of harming oneself (Beautrais et al 2005). This definition includes a continuum of outcomes, ranging from suicide (completed), suicide attempts that do not result in death, intentional self-harm, and suicidal ideation. Not all intentional self-harm is necessarily a suicide attempt, and it can be defined as an act of intentional self-poisoning or self-injury, irrespective of the apparent purpose of the act.

[5] The National Health Index database contains details of a patient's address, sex, ethnicity, date of birth, etc.

1. Hospitalised intentional self-harm events

Hospitalisation for suicide and intentional self-harm is an internationally accepted proxy measure for attempted suicide. Hospitalisation data was obtained from the National Minimum Data Set (NMDS) maintained by the NZHIS. The number of hospitalised intentional self-harm events was defined as the number of publicly funded first in-patient (excludes day-patient) admissions to public hospitals for an injury event. In 2000/01 psychiatric hospital discharges for intentional self-harm began to be included in hospitalisation data, resulting in double counting of the same injury event in some cases. To account for this, the unique injury event was determined by the patient's health care user (HCU) identifier and the date of injury. As a result, people who are hospitalised several times (either re-admitted for the same injury event or moved between parts of the hospital) for the same intentional self-harm event are only counted once. Admissions that resulted in a death in hospital were included (about 30 deaths per year).

Due to potential differences in the reporting of emergency department events and the definition of day patient and inpatient cases between DHBs, where only the zero day stay was used to identify intentional self-harm hospitalisations these discharges were excluded. These were found to be particularly common in Taupo hospital, Auckland facilities and a few other small facilities.

One limitation of this data source is that only a proportion – possibly the most severe – of intentional self-harm events result in hospitalisation. Many are treated in emergency departments, in general practice or receive no treatment at all. Different hospitals/ DHBs may have different policies on which patients are admitted following a self-harm event, and some have different reporting practices. Nonetheless, this data is the only readily available and comprehensive source of information on intentional self-harm events for the entire New Zealand population.

2. Suicide deaths / completed suicide

Details of suicide deaths were obtained from the NMDS and are only available up to the year 2003. Classification of a death as suicide requires the completion of a coronial inquiry and inquest. This can result in delays in completing mortality data. Mortality data for 2003 is only provisional. A small number of deaths (18) were still subject to coroner's investigations and had not been assigned an official cause of death at the time of this study.

Trends in antidepressant use and suicide-related outcomes

Suicides deaths for the period 1984–2002 and hospitalisations for intentional self-harm over 1984-2003 were compared with the annual number of (dispensed) prescriptions for any antidepressant, and for SSRIs for the period 1997–2005. Although only the pattern for SSRIs is presented in Figures 2 and 3, the same pattern existed for antidepressants overall.

A prescription is defined as an authorised request (a script) for the dispensing of a prescribed course of antidepressants for the treatment of a diagnosed condition. A script may contain multiple drug prescriptions and/or formulations for an individual patient. From 1983 to 1999 the ICD-9 codes were E950–E959 and from 2000 they have been the ICD-10 codes X60–X84.[6] Other influences on the reporting of hospitalisation data over time and between DHBs are changes in admission or treatment practices, and the coding and reporting of such information. Both types of influence have resulted in more outpatient or emergency department treatments, reducing the number of people treated as inpatients.

Use of the Poisson regression model to predict the relationship between antidepressant prescribing and intentional self-harm

In order to explore the association between antidepressant use, population-level confounders such as those identified by (Didham et al 2005) and suicide-related outcomes, an ecological Poisson regression model using antidepressant prescribing and hospitalisation for intentional self-harm data was constructed. The model adjusted for differences in age, ethnicity, gender, deprivation and DHB antidepressant prescribing. The analysis was restricted to the year 2005, because this year has the highest coverage of National Health Index information. Consequently, suicide mortality data was not included in the model because of the unavailability of complete data for 2005.

Hospitalisation for intentional self-harm was used as a proxy measure for suicide attempt. The dependent variable was the number of intentional self-harm hospitalisation events. The independent variables were:

- age (five-year age-groups: 10–14, 15–19, ..., 85+ years)
- gender
- prioritised ethnic group (Māori, Pacific and non-Māori/non-Pacific)
- year of self-harm event
- area New Zealand deprivation (NZDep) quintile
- mean rate of prescribing of each antidepressant drug
- mean daily dose of prescribing of each antidepressant drug
- DHB.

For inclusion in the model a patient had to have received a diagnosis and a prescription for an antidepressant in 2005, and to have been hospitalised for an intentional self-harm event in the same year. The modelling was undertaken using an SAS (v 9.1) Poisson regression Procedure GENMOD so as to include the fact that some people had more than one intentional self-harm event in that year. The logarithm of projected population (denominators) was used as the model offset.

[6] In 1999/2000 the ICD-10-AM coding system was introduced, which changed the classification criteria for the coding of the diagnosis of intentional self-harm. This coding change is not thought to have significantly changed the number of hospitalisations reported (NZHIS 2006, personal communication).

Denominator data

Population projections for the 2005 year were based on projections from the 2001 census. The projections were straight-line interpolations of medium levels of mortality, fertility and migration for each population group, by five-year age group, gender, prioritised ethnic group (Māori, Pacific and non-Māori/non-Pacific) and DHB. NZDep quintiles were added by assigning the projected populations to groups proportionally the same size as those deprivation quintile groups for 2001.

Prescribing data

Prescribing data for 2005 from the Pharmhouse extract was used. For 12% of the dispensing/prescribing data, an ethnic group and gender had to be imputed because only 88% of the data had an HCU identifier. The data has a variable called patient category, which assigns pharmaceutical users to three age categories (under 6 years, 6–18, 19+), and this was used to assign dispensing data to the model's age groups. Where the patient's domicile was available, this was found to have a higher concordance with the health domicile (HD) of the dispensing pharmacy than the HD of the prescribing provider. This information was used to decide the order of allocation of patient HD when their HD was missing. The HD of the patient was used to assign the NZDep quintile (Statistics New Zealand area unit level, NZDep 2001). Individual antidepressant drugs were identified by the chemical name of the active ingredient in the data set.

Antidepressant prescribing was represented in the model by the DDD and PDD for each antidepressant drug, and the WHO DDD level was used to represent the recommended efficacious dose for each drug.

Hospitalisation data

Hospitalisation data for intentional self-harm (ICD-10 X60–84) in the year 2005 was obtained from the NZHIS.

Ethnic definition

A prioritised ever-ethnic definition has been used. This is a process whereby recorded ethnicities for all individuals are pooled across all data sets, matched against HCUs for that individual and then prioritised as per usual for that individual (Māori, then Pacific, then Asian, and then other).

Constructing the model

The first stage of the analysis was to identify the best-fitting model (including explanatory variable interactions) for each individual antidepressant drug. Starting with the most complex model for which the Hessian was invertible, and in a stepwise process using the Type III deviance and the AIC[7] criteria, interactions and main effects were excluded where necessary. A composite chemical/antidepressant model was then created using what had been learnt about the possible explanatory effects for each of the antidepressant drugs and explanatory variables in the marginal models on intentional self-harm hospitalisations. Then a second stepwise process was undertaken, using the Type III deviance and the AIC criteria to exclude interactions and main effects where necessary.

As a final check, all interactions and main effects that had been excluded were included one at a time in the candidate composite model to see if they significantly affected the fit of the model. None were found in this process that needed to be included in the final composite model. The need to include a factor to account for correlated data (over-dispersion) was tested (Proc GENMOD MODEL options DSCALE) and found to be unnecessary.

The inclusion of the Asian ethnic group, an NZDep score of 0 (no estimate of deprivation), age groups under 10 years and the unknown DHBs were found to produce instability in the final model estimates and were excluded from the analysis (Asian people were included in the non-Māori/non-Pacific ethnic group).

The final composite model included categorial terms for NZDep quintile, DHB, age group, gender, ethnic group and the interaction terms gender*ethnic group and age group*gender. The covariate terms included in the model were the PDD and DDD for each drug formulation. Used in this way, the model acts as a predictor of a level of intentional self-harm outcome that can be expected from the level of prescribing of a given antidepressant in the population.

[7] Akaike information criterion.

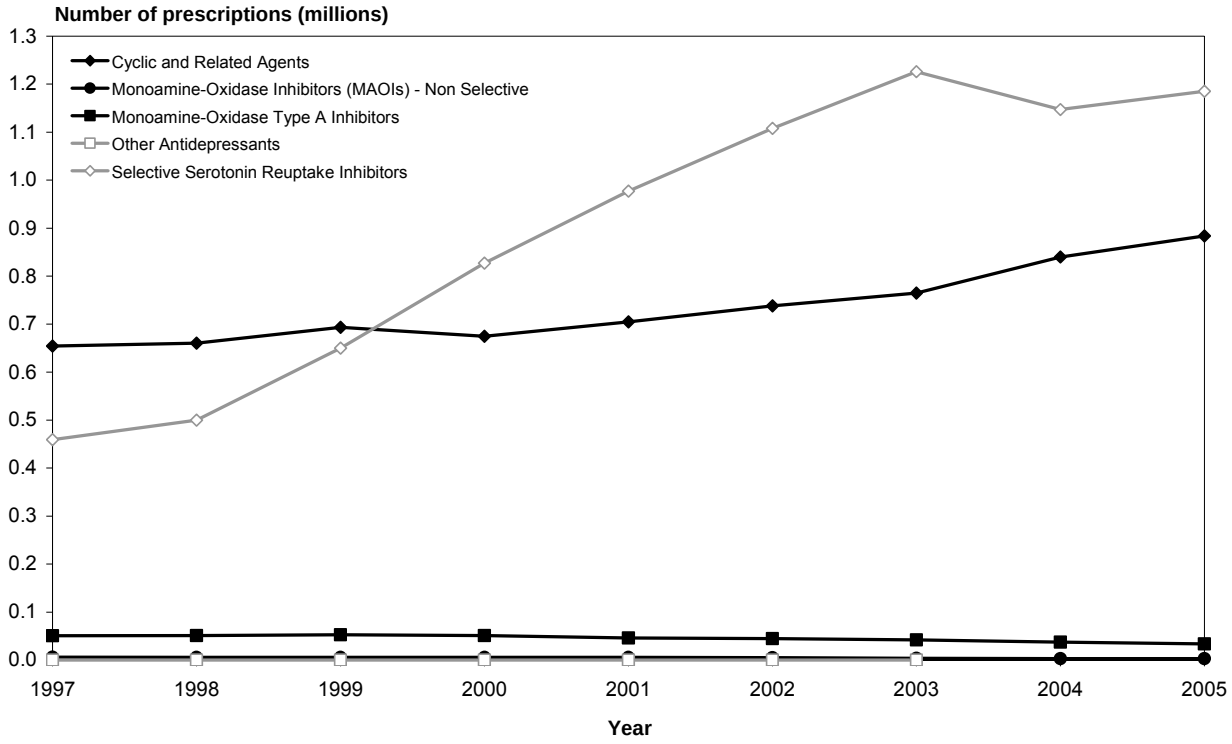
Results

Antidepressant prescribing in New Zealand, 1997–2005

Quantity and types of antidepressants prescribed in New Zealand, 1997–2005

In the period from 1997 to 2005 the number of prescriptions for a course of antidepressants doubled from 1.1 million in 1997 to 2.1 million in 2005. The increase in prescribing is almost entirely due to the new prescribing of SSRIs (Figure 1). Although there has been a small increase in the prescribing of tricyclic antidepressants (TCAs) in recent years, this is insignificant in comparison to the growth in prescribing SSRIs. In 1997, TCAs and SSRIs represented 55.9% and 39.4% respectively of all antidepressants prescribed in that year. By 2005 this pattern had reversed, and SSRIs represented 56.3% of all antidepressants prescribed in that year compared to 41.9% for TCAs (Figure 1).

Figure 1: Number of antidepressant prescriptions (millions) dispensed, by major drug class, 1997–2005



Note: A prescription is defined as a script for a course or courses of antidepressant.

Types of mental health conditions treated by antidepressants, 2001–2005

In the five-year period 2001–2005, 50,210 people accessing secondary and tertiary treatment services (both inpatient and outpatient – but excluding primary care) were recorded as being diagnosed with an ICD-10 Mental Health and Behavioural disorder (F00–F99) and prescribed an antidepressant (see Table 2). The most commonly recorded condition among those taking antidepressants was 'current depressive episode' at 19.3% (9696/50,210). Another 6.5% (3239/50,210) were recorded with a 'recurrent depressive episode', and 8.5% were being treated for a 'depressive episode and co-morbidity' (4310/50,210).

Table 2: Percent people recorded with a recorded ICD-10 mental health condition and prescribed an antidepressant, 2001–2005

Diagnosis (ICD-10: F00–F99)	Cyclic and other	Cyclic and related agents	Cyclic, SSRI and/or other	Monoamine-oxidase inhibitors (MAOIs) – non-selective	Monoamine-oxidase type A inhibitors	Other	Selective serotonin reuptake inhibitors	SSRI and other	Total (n)	Total (%)
F03 Unspecified dementia	0.3%	28.6%	8.5%	0.0%	2.4%	0.0%	59.8%	0.3%	2626	100.0%
F03 Unspecified dementia + comorbidity	1.0%	19.2%	15.4%	2.9%	5.8%	0.0%	54.8%	1.0%	104	100.0%
F10 Mental and behavioural disorders due to use of alcohol	0.1%	24.2%	12.7%	0.0%	0.8%	0.0%	62.0%	0.2%	3215	100.0%
F10 Mental and behavioural disorders due to use of alcohol + comorbidity	0.2%	12.0%	16.1%	0.1%	1.0%	0.0%	70.1%	0.6%	3427	100.0%
F12 Mental and behavioural disorders due to use of cannabinoids	0.0%	20.9%	10.0%	0.0%	1.1%	0.0%	67.8%	0.2%	522	100.0%
F12 Mental and behavioural disorders due to use of cannabinoids + comorbidity	0.0%	10.3%	20.7%	0.0%	1.7%	0.0%	65.5%	1.7%	58	100.0%
F20 Schizophrenia	0.1%	17.0%	6.8%	0.1%	1.5%	0.0%	74.5%	0.1%	1856	100.0%
F20 Schizophrenia + comorbidity	0.3%	17.8%	7.0%	0.0%	1.6%	0.0%	73.0%	0.3%	315	100.0%
F31 Bipolar affective disorder	0.7%	16.3%	12.3%	0.6%	2.6%	0.0%	66.6%	0.9%	2289	100.0%
F31 Bipolar affective disorder + comorbidity	0.6%	15.6%	14.5%	0.0%	2.2%	0.0%	66.5%	0.6%	179	100.0%
F32 Depressive episode	0.5%	13.0%	17.4%	0.3%	1.8%	0.0%	66.0%	1.0%	9696	100.0%
F32 Depressive episode + comorbidity	0.6%	11.5%	21.1%	0.6%	2.8%	0.1%	61.8%	1.6%	4310	100.0%
F33 Recurrent depressive disorder	0.9%	14.8%	19.7%	0.6%	2.0%	0.0%	60.9%	1.1%	3239	100.0%
F41 Other anxiety disorders	0.3%	24.1%	17.3%	0.1%	1.9%	0.0%	55.4%	0.9%	4199	100.0%
F41 Other anxiety disorders + comorbidity	1.2%	16.8%	19.4%	0.4%	2.5%	0.1%	58.5%	1.2%	856	100.0%
F43 Reaction to severe stress, and adjustment disorders	0.2%	17.1%	13.6%	0.1%	1.4%	0.0%	67.1%	0.5%	2331	100.0%
F43 Reaction to severe stress, and adjustment disorders + comorbidity	0.0%	11.1%	18.1%	0.0%	2.5%	0.0%	67.4%	0.8%	476	100.0%
Other	0.2%	26.2%	11.1%	0.1%	1.4%	0.0%	60.6%	0.4%	8900	100.0%
Other comorbidity	0.3%	20.0%	12.3%	0.1%	1.4%	0.0%	65.4%	0.5%	1612	100.0%
Total (n)	195	9339	7439	115	883	9	31865	365	50210	
Total (%)	0.4%	18.6%	14.8%	0.2%	1.8%	0.0%	63.5%	0.7%	100.0%	

Notes: 'Comorbidity' refers to another diagnosis of any other mental illness apart from those listed in the table. 'Other' refers to all those patients with a single diagnosis that was not one of those listed in the table. 'Other comorbidity' refers to patients with more than one diagnosis that was not one of those listed in the table.

Of those recorded with a current or recurrent depressive episode and prescribed an antidepressant, 66.0% (6404/9696) and 60.9% (1972/3239) respectively were treated with an SSRI (Table 2). Another 17.4% and 19.7% of those with a current or recurrent depressive episode respectively were prescribed a combination of TCA, SSRI and/or other drugs. An additional 13.0% and 14.8% respectively were prescribed a TCA and related agent.

In the five-year period, 1856 and 315 people were recorded with schizophrenia or schizophrenia and co-morbidity respectively. Of those recorded with schizophrenia, 74.5% were prescribed a course of SSRIs, and 17.0% a course of TCAs and related agents. This pattern of prescribing was very similar for those recorded with schizophrenia and a co-morbidity (Table 2).

Treatment intensity: prescribed daily dose (PDD) 1997–2005

The prescribed daily dose (PDD) gives the average daily amount of a drug that is actually prescribed, and provides an indicator of the actual quantity of the identified drug or class of drug used per day over a given time period per pharmaceutical user. The PDD for each antidepressant drug prescribed in each year in the period 1997–2005 is presented in Table 3. The table shows that over the period there has been no significant change in the dose levels prescribed for each drug.

Although the PDD dose levels have not changed over time, of the 20 antidepressants in Table 3, three drugs are being prescribed at levels lower than the recommended Medsafe adult maintenance treatment range for the drug (imipramine hydrochloride, nortriptyline hydrochloride, trimipramine maleate); another 11 are at the low end of the recommended range; and two (sertraline hydrochloride and tranylcypromine sulphate) are significantly above that recommended (Table 3). Three drugs (doxepin hydrochloride, mianserin hydrochloride and moclobemide) were prescribed at dose levels in the middle of the recommended Medsafe range.

Table 3: Prescribed daily dose (mg) of antidepressants and recommended dose ranges, 1997–2005

Drug name	Prescribed daily dose (PDD) in mg for year										Recommended adult PDD mg (MedSafe data sheets) (*=BNF recommendation)	WHO DDD (mg)	Class*
	1997	1998	1999	2000	2001	2002	2003	2004	2005	PDD mg for period 1997–2005			
Amitriptyline	73	81	65	59	56	60	56	55	55	64	50–100	75	TCA
Amoxapine (no longer supplied)	114	117	127	129	129	144	74			121	200–300	150	MAOI
Citalopram hydrobromide			24	26	27	28	28	28	28	27	20–60		SSRI
Clomipramine hydrochloride	53	55	59	59	60	61	61	59	59	58	50–100	100	TCA
Desipramine hydrochloride	93	96	99	93	94	86	90	85	93	92	100–150	100	TCA
Dothiepin hydrochloride	81	83	92	89	87	88	88	86	85	86	75–150	150	TCA
Doxepin hydrochloride	69	70	75	73	72	74	74	72	71	72	30–100	100	TCA
Fluoxetine hydrochloride	23	24	25	25	18	19	19	19	18	21	20–80	20	SSRI
Imipramine hydrochloride	47	48	49	49	49	48	49	48	48	48	50–100	100	TCA
Maprotiline hydrochloride	78	77	81	78	79	79	81	80	83	79	75–150	100	TCA related
Mianserin hydrochloride	68	74	68	59	61	61	61	56	54	62	30–90	60	TCA related
Moclobemide	337	531	563	533	500	497	505	500	508	499	300–600	300	MAOI – Type A
Nefazodone		355	385	377	363	364	364	364		367	300–600	400	Other
Nortriptyline hydrochloride	68	76	68	62	44	43	43	42	43	57	75–100	75	TCA
Paroxetine hydrochloride	24	25	25	24	24	24	25	25	25	25	20–50	20	SSRI
Phenelzine sulphate	50	51	53	53	53	53	54			52	45–60	60	MAOI
Sertraline hydrochloride	75	149	150	166	166	175	175			157	50 (* up to 200)	50	Other
Tranylcypromine sulphate	37	35	34	34	35	35	33	34	34	35	10–20 (* up to 30)	10	MAOI – non-selective
Trimipramine maleate	56	59	60	70	67	68	68	79	79	66	75–150	150	TCA
Venlafaxine			113	200	215	199	150			179	75–375	100	Other

* Source: British National Formulary No 52 (2006). (Some drugs may be used as treatment for other indications.)

Treatment intensity: defined daily dose (DDD)

Defined daily dose, by DHB

Although the PDDs are largely consistent across time and drug formulation, in 2005 there was considerable variation in the rate of prescribing a DDD of antidepressants between DHBs. Canterbury DHB in particular has significantly higher rates of prescribing across all classes of antidepressants compared to the other DHBs. In contrast, Auckland, Waitemata, Counties Manukau, Tairawhiti and Capital and Coast consistently have the lowest rates (see Table 4 and Appendix 1, Table A1). The pattern is dominated by the rate of prescribing for SSRIs, and the rate of prescribing in Canterbury and South Canterbury is typically double that of the lowest rate (Table 4 and Appendix 1, Table A1). For example, in 2005 in Canterbury DHB, 89 people per 1000 in the population (equivalent to 8.9% of the population) were prescribed a DDD of an antidepressant compared to 37.7 people per 1000 population (3.7% of the population) in Counties Manukau DHB (Table 4).

Table 4: Total DDD per 1000 population, by antidepressant class and DHB, 2005

DHB	Class of antidepressant			
	All	SSRIs	TCAs	MAOIs
Canterbury	89.3	71.00	15.10	3.20
South Canterbury	77.7	57.90	15.60	4.20
Otago	71.1	53.90	15.20	2.00
Wairarapa	69.5	53.70	14.10	1.70
Taranaki	68.2	55.20	11.60	1.40
Nelson–Marlborough	64.4	50.30	13.30	0.80
Hutt Valley	62.5	48.30	13.30	0.90
West Coast	60.1	46.00	12.60	1.50
Whanganui	59.7	44.80	13.00	1.90
Lakes	59.4	47.90	9.80	1.70
Bay of Plenty	57.0	43.50	11.90	1.60
Waikato	56.5	45.50	9.80	1.20
Northland	56.2	43.20	11.90	1.10
Hawke's Bay	55.7	43.10	11.60	1.00
MidCentral	55.5	43.20	10.20	2.10
Capital and Coast	52.6	41.30	10.20	1.10
Southland	49.6	37.80	11.00	0.80
Auckland	45.4	37.30	7.10	1.00
Waitemata	44.7	35.70	8.30	0.70
Tairawhiti	40.9	30.20	9.90	0.80
Counties Manukau	37.7	29.90	7.30	0.50
Mean DHB DDD per 1000 people	58.75	45.70	11.56	1.49
95% CI (upper range)	82.21	64.73	16.45	3.24
95% CI (lower range)	34.28	26.67	6.67	-0.27
Significantly over		Significantly under		

Defined daily dose in people under 18 years, by DHB

In 2005, in all 21 DHBs a DDD of SSRIs was prescribed to children and adolescents aged 6 to 18 years, in 13 DHBS a TCA was being prescribed and in three DHBs an MAOI (see Table 5). In addition, in four DHBs an SSRI and/or a TCA was being prescribed to children less than five years of age (Table 6). The rate of prescribing citalopram hydrobromide (20 mg tablets) and fluoxetine hydrochloride (20 mg capsules) to adolescents in Canterbury is significantly higher compared to the other DHBs (Table 5).

Table 5: DDD per 1000 children and adolescents aged 6–18 years, 2005

DHB	SSRIs				TCAs			MAOI
	Citalopram hydrobromide, Tab 20 mg	Fluoxetine hydrochloride, Cap 20 mg	Fluoxetine hydrochloride, Tab dispersible 20 mg, scored	Paroxetine hydrochloride, Tab 20 mg	Amitriptyline, Tab 10 mg	Amitriptyline, Tab 25 mg	Amitriptyline, Tab 50 mg	Moclobemide, Tab 150 mg
Canterbury	2.10	3.40	0.30	0.30	0.10	0.10		
South Canterbury	1.50	2.70	0.30	0.10	0.10	0.10		
Nelson–Marlborough	1.40	2.20	0.20	0.60				
Bay of Plenty	1.20	1.00	0.20	0.30				
Otago	1.20	2.00	0.10	0.20	0.10		0.10	
West Coast	1.10	1.60	0.00	0.30	0.10	0.00		
Southland	1.00	1.80	0.20	0.40	0.10	0.10		
Wairarapa	1.00	3.20	0.60	0.40	0.10	0.20	0.10	0.30
Hawke's Bay	0.90	1.40	0.10	0.50		0.10		
Taranaki	0.90	1.00	0.30	0.10				
Waikato	0.90	1.30	0.20	0.20	0.10	0.10		
Hutt Valley	0.80	2.30	0.30	0.30	0.10	0.50	0.60	
MidCentral	0.80	1.30	0.10	0.30	0.10	0.10		
Capital and Coast	0.60	2.00	0.30	0.20	0.10	0.10	0.10	0.10
Waitemata	0.50	1.10	0.10	0.30				
Lakes	0.40	0.50	0.10	0.20				
Northland	0.40	0.90	0.10	0.00				
Auckland	0.30	0.80	0.10	0.20				
Counties Manukau	0.30	0.60	0.10	0.30				
Tairawhiti	0.30	0.30	0.10	0.30	0.10			
Whanganui	0.20	1.30	0.10	0.40	0.10	0.10		0.10
Mean DHB DDD per 1000 children and adolescents	0.85	1.56	0.19	0.28	0.10	0.14	0.23	0.17
95% CI (upper range)	1.8	3.26	0.45	0.55	0.10	0.41	0.73	0.40
95% CI (lower range)	-0.11	-0.15	-0.08	0.01	0.10	-0.13	-0.28	-0.06
Significantly over		Significantly under						

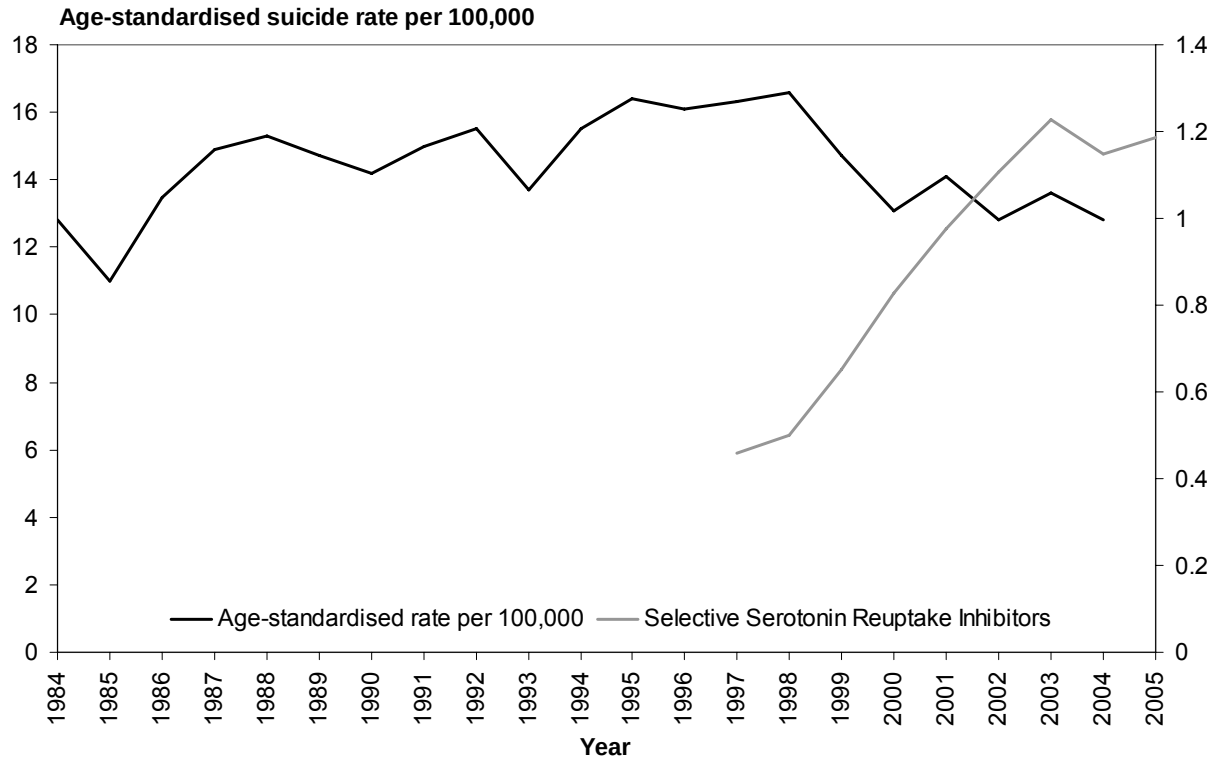
Table 6: DDD per 1000 people aged 0–5 years, 2005

DHB	SSRIs		TCAs		
	Citalopram hydrobromide, Tab 20 mg	Paroxetine hydrochloride, Tab 20 mg	Amitriptyline, Tab 25 mg	Amitriptyline, Tab 50 mg	Nortriptyline Hydrochloride, Tab 25 mg
Canterbury	0.10				
South Canterbury	0.20	0.10			0.10
Wairarapa			0.10		
Hutt Valley			0.20	0.10	

Observed trends in suicide-related outcomes and SSRI prescribing

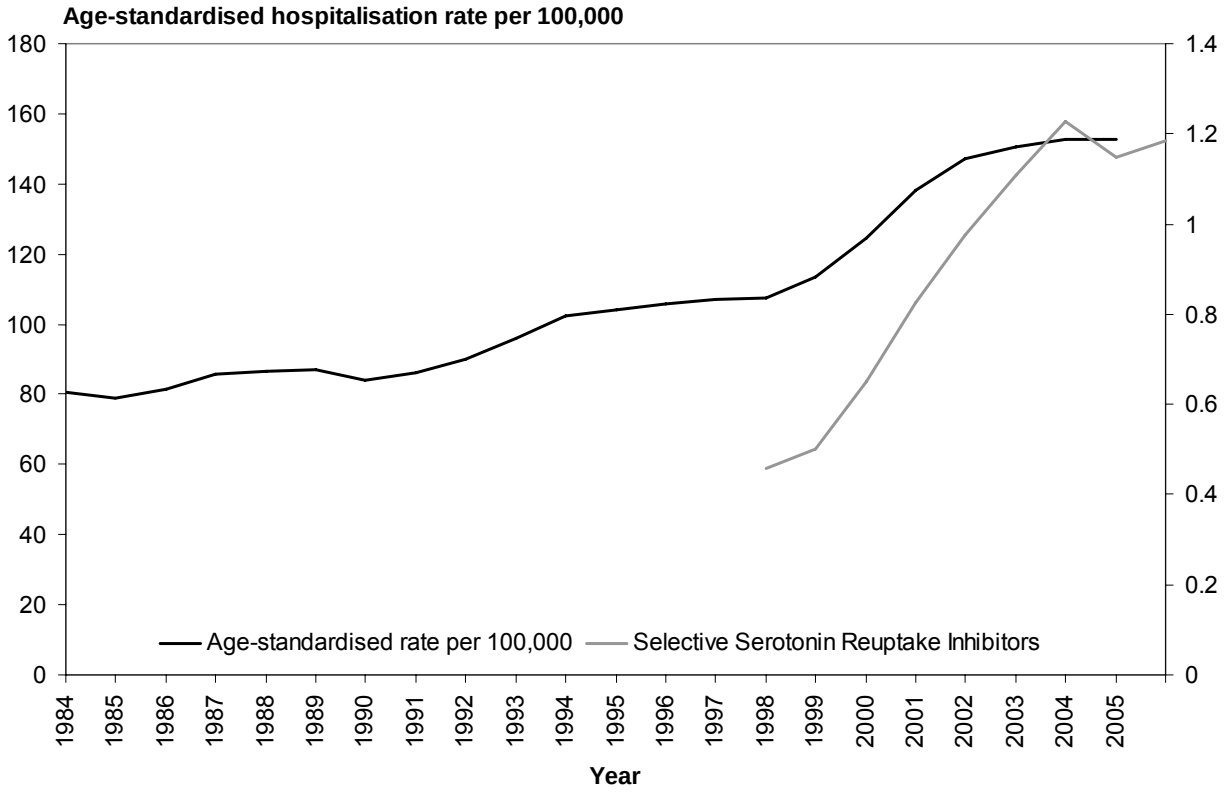
In the period between 1996/97 and 2005 the prescribing of antidepressants in the population, and SSRIs in particular, increased significantly (see Figure 2). Over the same period, New Zealand's suicide rates have significantly declined, although hospitalisations for intentional self-harm have significantly increased (Ministry of Health 2006a). The observed pattern between the prescribing of SSRIs and the changes in suicide-related outcomes is depicted in Figures 2 and 3 below.

Figure 2: Age-standardised suicide rate and number of SSRI prescriptions (millions)



Notes: Age standardised to WHO population. Rates shown are the mid-points of three-year moving averages.

Figure 3: Age-standardised intentional self-harm hospitalisation rates (per 100 000) and number of SSRI prescriptions (millions)



Note: Age standardised to WHO population. Rates shown are the mid-points of three-year moving averages.

Modelling antidepressant utilisation and intentional self-harm outcomes adjusting for age, ethnicity, gender, DHB prescribing and NZDep

Of the 21 different antidepressants prescribed in 2005 that were examined for increased risk of intentional self-harm hospitalisation using the Poisson regression composite ecological model, nortriptyline, paroxetine and fluoxetine were significantly associated ($p < 0.002$), with an increased odds ratio (OR) of hospitalisation for intentional self-harm as the intensity of prescribing in the population increased, particularly fluoxetine (Table 7, Figure 4). The model adjusted for age, ethnicity, gender, DHB prescribing and NZDep as possible social explanations for the observed variation in the patterns of prescribing between DHBs and increased risk of intentional self-harm. Table 8 presents the cell counts used in construction of the model.

The model shows there is an observable statistically significant small risk of increased suicide-related outcomes associated with increased levels of prescribing in the population of the antidepressants nortriptyline, paroxetine and fluoxetine.

Table 7: Odds ratio for hospitalisation for intentional self-harm and rate of prescribing a DDD in the population (adjusted for age, ethnicity, gender, DHB prescribing and NZDep)

Parameter	OR (increasing with proportion of prescribing in population)	DF*	Estimate	Standard error	Wald 95% confidence limits		Chi-square	Pr > Chi-Sq**
Intercept		1	-8.3184	0.4097	-9.1213	-7.5154	412.3	< 0.0001
Fluoxetine (20 mg WHO DDD)	1.00–1.62	1	4.8166	0.6999	3.4448	6.1885	47.35	< 0.0001
Paroxetine (20 mg WHO DDD)	1.00–1.25	1	2.7834	0.8857	1.0475	4.5194	9.88	0.0017
Nortriptyline (75 mg WHO DDD)	1.25–1.63	1	5.245	1.7141	1.8855	8.6046	9.36	0.0022
Nortriptyline (42 mg MPDD)	1.13–1.47	1	0.003	0.0008	0.0013	0.0046	12.43	0.0004

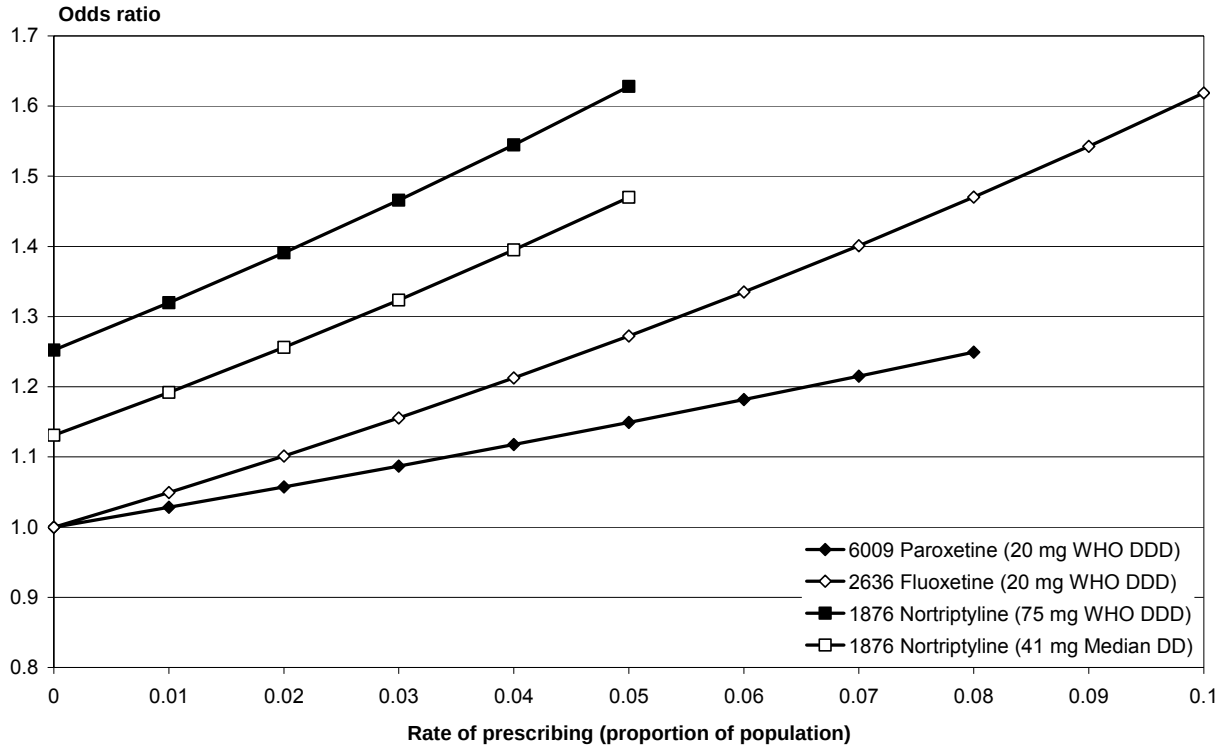
* DF = Degree of freedom
** PR = Probability

Table 8: Counts of deliberate self-harm hospitalisations for population groups (ecological analysis) exposed to particular antidepressants, by chemical type, 2005

Drug name	Number patients prescribed*	Number of hospitalisations for deliberate self-harm events
Amitriptyline	76,687	2999
Citalopram hydrobromide	62,352	3024
Clomipramine hydrochloride	3192	1456
Desipramine hydrochloride	363	258
Dothiepin hydrochloride	17,550	2356
Doxepin hydrochloride	15,627	2095
Fluoxetine hydrochloride	80,829	3113
Imipramine hydrochloride	5064	1566
Maprotiline hydrochloride	260	125
Mianserin hydrochloride	152	38
Moclobemide	4672	1607
Nortriptyline hydrochloride	26,441	2709
Paroxetine hydrochloride	68,432	3006
Tranylcypromine sulphate	349	275
Trimipramine maleate	3181	906

* These are total counts by chemical, so some patients prescribed more than one drug are counted twice.

Figure 4: Association (OR) between drug utilisation in the population and intentional self-harm hospitalisations, 2005 (adjusted for age, ethnicity, gender, DHB prescribing, NZDep)



Discussion

Key findings

This study describes the patterns of antidepressant prescribing in the New Zealand population between 1997 and 2005, investigates whether there is a relationship between the prescribing of antidepressants (in particular SSRIs) and suicide-related outcomes, and examines the utility of a number of national data sets and drug utilisation methods to undertake pharmaco-epidemiological studies.

The research clearly shows that the prescribing of antidepressants in New Zealand has significantly increased since 1997, the proportion of the population prescribed an antidepressant varies significantly between DHB regions, the intensity of prescribing is at levels at the low end of the adult treatment range recommended by Medsafe, and there is an observed small increased risk of hospitalisation for intentional self-harm and the prescribing of nortriptyline, paroxetine and fluoxetine after adjusting for a range of population-level confounders.

Methodologically, the study has shown that it is possible to undertake pharmaco-epidemiological studies in New Zealand using national data sets and internationally accepted drug utilisation methods. However, there are a number of problems with the data sets, outlined earlier, that limit their usefulness. These limitations, along with the others outlined below, mean that ecological studies such as this one cannot definitively answer complex research and clinical questions such as those at the centre of the debate about the safety and efficacy of antidepressants in relation to suicide-related outcomes.

Limitations of the study

Drug utilisation studies such as this one are not suitable for assessing the appropriateness of drug treatment at the individual level of treatment (the ecological fallacy issue). This study has shown that although useful pharmaco-epidemiology can be undertaken using the identified national data sets, the analysis and interpretation are significantly limited by:

- lack of detailed information about the:
  - diagnosis and severity of condition, which is necessary to rule out confounding by indication
  - duration of treatment
  - actual course of treatment prescribed, where multiple indications are involved and multiple classes of drugs are prescribed
  - length of time from initiation or completion of treatment to the health outcome of interest
  - change in individual drug prescribing for a diagnosed condition during the course of a treatment
- the relative rarity of some health outcomes and medical conditions of interest – in this case, suicide, which results in small numbers
- change in regulatory prescribing advice over time

- change in coding practices in the data sets over time
- lack of information about compliance with the prescribing regime
- lack of information about the prescribing setting (primary versus secondary)
- non-collection of hospital-based prescribing.

Other issues for this study are the lack of detailed information about the prevalence of mental illness (particularly depression) in the population and the condition for which the drug was prescribed, the level of compliance with the prescribed treatment, the actual drug treatment followed where multiple classes of drugs were prescribed, and the length of time between treatment initiation or completion and the health outcome of interest. All these factors influence the effectiveness of the treatment and therefore suicide-related outcomes, and ascribing a health outcome to a particular drug is problematic when the above information is incomplete, as in this study.

These limitations make undertaking disaggregated analysis of complex medical events involving relatively rare health outcomes particularly problematic, because the numbers involved are often too small to allow for statistical analysis of sufficient power to be able to identify significant differences between population groups, treatment practices, and the health outcome of interest. Even at the DHB level, one year's data is not enough: pooled data over several years is required in order to provide statistically stable analyses. Finally, this study is ecological in that it is based on aggregate data from the population and as such can identify significant associations, but without longitudinal and individual data it can only point to potential causal relationships.

Comparability of results with other studies

Significant increases in the prescribing of antidepressants since the 1990s have been reported in the United Kingdom (UK), Italy and a range of Scandinavian countries, with the increases ranging from 50% to 400% over different time periods (Barbui et al 1999; Gunnell and Ashby 2004; Helgason et al 2004; Isacsson 2000; Isacsson et al 2005; Reseland et al 2006). In the UK the increase in the prescribing of SSRIs has not seen a decrease in the prescribing of TCAs, and the prescribing of SSRIs and TCAs account for the majority of the prescriptions (Gunnell and Ashby 2004).

In terms of comparing the intensity of prescribing in the New Zealand population using the national DHB mean of 58.75 DDD per 1000 people as the comparison, Helgason et al (2004) reported that the use of antidepressants in Iceland reached 72.7 DDD per 1000 people in 2000, and levels of between 10 to 17 DDD per 1000 people have been reported for Norway, Sweden, Denmark and Finland between 1989 and 2001 (Reseland et al 2006). The prescribing of daily doses under or at the low end of the recommended efficacious range for antidepressants, particularly for TCAs, is consistent with studies in a range of OECD countries (Donoghue and Hylan 2001). Average daily doses for TCAs of under 100 mg have been found in Denmark, Italy and Sweden. In the UK, 85% of patients have been found to have received doses less than that recommended by regulators, with the most commonly prescribed TCAs (amitriptyline and dothiepin) being prescribed at sub-therapeutic levels of 10 and 25 mg respectively (Donoghue and Hylan 2001; Nutt 2005).

The potential for a small increased risk of suicide-related outcomes to the extent found in this study from the use of SSRIs, in particular fluoxetine and paroxetine, has been found in other studies using a range of methodologies, but there is considerable debate in the literature about the significance of and explanations for the association (Bridge et al 2007; Cheung 2007; Cipriani et al 2005; Courtney 2004; Didham et al 2005; Donoghue and Hylan 2001; Donoghue and Tylee 1996; Donovan et al 2000; Fergusson et al 2005; Goldney 2006; Gunnell and Ashby 2004; Gunnell et al 2005; Hall 2006; Hawton et al 1998; Healy 2000, 2002, 2003, 2006a, 2006b; Healy and Aldred 2004; Healy et al 1999; Hotopf 1998; Isacsson 2000; Isacsson et al 2005; Isacsson and Rich 2005; Jick et al 2004; Jureidini et al 2004; Khan et al 2003; Kirsch et al 2002; Lancet 2003; Mahendran 2006; March et al 2004; Markowitz 2001; Martinez et al 2005; Moncrieff 2001, 2002, 2003; Moncrieff and Kirsch 2005; Nutt 2003, 2005; Rihmer and Akiskal 2006; Rubino et al 2007; Safer and Zito 2007; Simon 2006; Simon et al 2006; Wallace et al 2006; Wee 2005; Wessely and Kerwin 2004).

Similarly, there is considerable debate about whether downward trends in national suicide rates in a range of countries are related to the increased prescribing of SSRIs. A range of divergent patterns has been reported in the literature, some of which indicate a positive relationship, while others do not (Gibbons et al 2006; Hall 2006; Healy and Aldred 2004; Helgason et al 2004; Isacsson 2000; Isacsson and Rich 2005; Reseland et al 2006; Rihmer and Akiskal 2006).

Explanations

Increase in antidepressant prescribing

The significant increase in the prescribing of SSRIs in New Zealand since the mid-1990s probably reflects the increased availability of these new types of antidepressants in Australasia in that decade. SSRIs have been promoted on the basis that they are thought to offer increased benefits compared to the older antidepressants. SSRIs differ from the older TCAs and MAOIs in their chemical structure, method of action and decreased toxicity in overdose, and the side-effects are thought to be more tolerable (Norman 1999, 2006).

A change in the use of particular drugs may reflect funding/subsidy changes. The use of different classes of antidepressants to treat may be explained as appropriate clinical treatment to produce different effects and manage risks; for example, TCA in dementia for sedation, and SSRI use in schizophrenia to decrease the likelihood of overdose with TCA.

Regional differences in the density of prescribing antidepressants in the population

There are a number of possible explanations for the significant variation found between DHBs in the intensity of prescribing in the population, as defined by the defined daily dose. These range from differences in the underlying rate of depression in the population; to structural factors such as age, gender, ethnicity and socioeconomic deprivation; to differential admission policies for intentional self-harm, differential recording of hospitalisation data by the DHBs, changes in ICD coding, and differences in prescribing practice by clinicians in each area.

The findings of the national New Zealand Mental Health Survey found evidence for significant differences in the prevalence in any mental health disorder based on individual socioeconomic variables (sex, age group, education, household income (Oakley-Browne et al 2006). Females, younger people, those on low incomes, and low educational outcomes all had higher prevalence's of any mental health disorder than other groups. Māori and Pacific peoples have higher prevalences than other ethnic groups, although the size of the difference is reduced after adjusting for socioeconomic variables. In terms of area-level characteristics (urbanicity, deprivation, region), those in more deprived and urban areas had higher prevalence's than those in other areas.

Regionally, the Central region (comprising Hawke's Bay, MidCentral, Whanganui, Wairarapa, Hutt and Capital Coast DHBs) had a lower prevalence of disorder when compared to the three other regions combined. However, after adjusting for severity of the disorder, these differences in the prevalence of any mental health disorder disappear when considering the percentage with a visit to a mental health service (Table 9), except for sex differences, where females were more likely than males to make a mental health visit (Oakley-Browne et al 2006).

Table 9: Prevalence of any mental health disorder, severity and mental health service visits, by region

Region (DHB)	12-month prevalence of any disorder % (95% CI)	Prevalence of serious disorder % (95% CI)	Percentage with a mental health visit, adjusted for severity % (95% CI)
North	21.5 (19.5–23.7)	4.8 (4.1–5.7)	11.6 (10.1–13.1)
Midland	21.8 (19.5–24.4)	5.3 (4.3–6.5)	11.2 (9.6–12.9)
Central	17.2 (15.2–19.5)	3.5 (2.7–4.5)	11.5 (9.7–13.2)
South	21.5 (19.1–24.1)	5.0 (4.0–6.2)	13.3 (11.4–15.3)

Source: Adapted from Table 2.3 in Oakley-Brown et al 2006.

In summary, the finding of significant differences in the intensity of prescribing of antidepressants in the population between DHBs may be explained in part by the underlying prevalence of mental disorder related to socioeconomic correlates of the population being served. However, given there is no statistically significant difference regionally between the percentages visiting mental health services, the most likely explanation for the observed differences is that they reflect actual differences in clinical treatment practices between DHBs.

The increase in prescribing of antidepressants and the density of prescribing observed raise a number of important policy and clinical questions about how people are either diagnosed and/or treated for a mental illness such as depression. For example, given the underlying 12-month prevalence of 5.7% for a major depressive disorder in the New Zealand population reported by Oakley-Browne et al (2006), is the level of national prescribing a defined daily dose of an antidepressant of 5.8% (58.7 per 1000 people) appropriate, and are the regional differences observed appropriate?

Prescribed daily dose levels

Interpretation of what the observed levels of PDD mean in terms of whether they represent appropriate clinical practice requires considerable caution. For example, with regard to the three drugs being prescribed at levels lower than that recommended by Medsafe, these drugs are TCAs and can have significant side-effects and are dangerous in overdose. Consequently to manage these risks, a normal course of treatment may last from a few weeks to a few months, with treatment with a TCA beginning at an initial dose of 25 or 50 mg, depending on age, then increasing every few nights up to 75 mg if tolerated by the patient. At this level a full therapeutic effect may be observed. However, in some circumstances dosage may be steadily increased up to 150 mg daily, and then reduced over time towards a maintenance level of 75 mg, depending on the severity of the condition and the indication.

Similarly, two drugs prescribed at levels significantly higher than that recommended by Medsafe may be being prescribed appropriately if practitioners are following the widely used British National Formulary (2006) recommendations, where such dose levels are appropriate for severe depression and the patient is under close supervision.

Observed association between prescribing some antidepressants and suicide-related outcomes

The finding of an association between intentional self-harm and the prescribing of SSRIs in the population is subject to much debate about its meaning and importance for individual clinical treatment, and as a public health measure to reduce the burden of suicide and depression in society (Cipriani et al 2005; Goldney 1997, 2005, 2006; Gunnell and Ashby 2004; Hall 2006; Healy and Aldred 2004; Jick et al 2004; Moncrieff 2002; Moncrieff and Kirsch 2005; Nutt 2005; Rihmer and Akiskal 2006; Simon 2006; Simon et al 2006; Wessely and Kerwin 2004).

On the one hand, it has been argued that SSRIs as an antidepression treatment is not particularly effective and that:

- they provoke suicidal ideation[8] in both depressed patients and other patients prescribed SSRIs for other indications
- the effects persist beyond treatment
- in rare and extreme cases they may cause externally directed aggression resulting in homicide
- they may result in drug dependence/addiction

(Healy 2000, 2002, 2003, Healy 2006b; Healy and Aldred 2004; Healy et al 1999; Medawar and Hardon 2004; Nutt 2003; Wallace et al 2006).

On the other hand, while there may be a very small risk, and the method of action is relatively unknown, there remains a positive risk:benefit ratio to antidepressant use, in particular for SSRIs compared to TCAs when coupled with appropriate monitoring for suicidal ideation in the first few weeks of prescribing and cognitive behaviour therapies, and when considering other positive health outcomes such as improved mental health in the population (Hall 2006; Gibbons et al 2005; Gibbons et al 2006; March et al 2004; Nutt 2003; Rihmer and Akiskal 2006; Rubino et al 2007; Simon et al 2006).

However, the debate over the safety and efficacy of SSRIs does not account for the nortriptyline finding, which is the strongest one and unexpected. One explanation for the result is that the PDD for nortriptyline (68 mg) is less than the recommended dose (75–100 mg), and as prescribed may not be efficacious to reduce the risk of harm. However, the low doses may simply reflect that nortriptyline is being prescribed more often in low doses for the mildly depressed because, and of the TCAs available to non-specialist prescribers it is the least likely to cause adverse effects. Another explanation is that as a TCA, the association of increased risk of intentional self-harm/attempted suicide may be related to the increased risk of harm from overdose. Also, those hospitalised may be at the most severe of a mental health disorder diagnosis and may not have complied with the prescribed regime. Finally, the finding of an association for nortriptyline but not citalopram, doxepin and dothiepin may reflect a type A statistical error in the data for these other drugs.

[8] Suicidal ideation, and consequently risk of intentional self-harm, may increase through 'energisation' via 'agitation' (akathisia) and 'activation' of the patient during the early recovery phase.

Conclusions and recommendations

Conclusions

Depression is a common and treatable condition. If not appropriately treated, depression and other psychiatric disorders can have significant consequences. Antidepressant medications benefit many patients, but it is important that doctors and patients are aware of the risks.

This study has found significant regional differences in the number of people prescribed an antidepressant in the population, and a statistically significant observed association between increased prescribing in the population of nortriptyline, paroxetine and fluoxetine and increased hospitalisations for deliberate self-harm events. However, the risk is very small (odds ratio ranging from 1.25 to 1.63), and although the results are statistically significant this does not necessarily mean they are clinically significant at the individual treatment level because of limitations in the study design. The findings are comparable with similar studies reported in the international literature that indicate a slight increase in suicidality for patients taking antidepressants in early treatment for most of the medications, particular for children and adolescents. However, we emphasize that depression and certain other serious psychiatric disorders are themselves the most important causes of suicide – not the drug treatments.

People currently prescribed antidepressant medications should not stop taking them. Those who have concerns should notify their health care providers.

Recommendations

On the evidence reviewed and presented in this study, it seems prudent to remind clinicians that when prescribing antidepressants to patients diagnosed with a condition associated with increased risk of suicidal behaviour, such as depression, it is important they make regular contact with the patient in the early period following initial prescribing.

Continuous monitoring and evaluation of this issue by policy makers and clinicians is also recommended in light of an anticipated increase in the prescribing/use of antidepressants resulting from the recent government policy initiatives in the areas of mental health, depression awareness and suicide prevention.

Given the complexity of the issue and the relative rarity of the health outcome of interest, undertaking the ideal of a randomised control study to resolve the debate is not feasible in New Zealand because of the size of the study that would be required. One alternative is to undertake a more detailed observational study in approximately three to five years time using the national data sets and methods trialled in this report. Such a study would have to undertake further disaggregation of the prescribing data in conjunction with the diagnostic data to obtain a better insight into who and what was being treated by the antidepressants, and to consider the effects of other possible confounders and effect modifiers not included in this study, such as:

- level of PDD versus the seriousness of the health status diagnosed
- interactive effects between classes of drug prescribed
- underlying incidence of causal factors in a particular populations, such as depression in a region or severity of illness in those prescribed
- access to services
- time from onset of prescribing to health outcome of interest
- levels of compliance with the prescribing regime.

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Appendix 1: Defined Daily Dose, Antidepressants per 1000 people, by DHB, 2005

Table A1: Defined daily dose, antidepressants per 1000 people, by DHB, 2005

DHB	Amitriptyline, Tab 10 mg	Amitriptyline, Tab 25 mg	Amitriptyline, Tab 50 mg	Citalopram hydrobromide, Tab 20 mg	Clomipramine hydrochloride, Tab 10 mg	Clomipramine hydrochloride, Tab 25 mg	Desipramine hydrochloride, Tab 25 mg	Dothiepin hydrochloride, Cap 25 mg	Dothiepin hydrochloride, Tab 75 mg	Doxepin hydrochloride, Cap 10 mg	Doxepin hydrochloride, Cap 25 mg	Doxepin hydrochloride, Cap 50 mg	Doxepin Hydrochloride, Cap 75 mg	Fluoxetine hydrochloride, Cap 20 mg	Fluoxetine hydrochloride, Tab dispersible 20 mg, scored	Imipramine hydrochloride, Tab 10 mg	Imipramine hydrochloride, Tab 25 mg	Maprotiline hydrochloride, Tab 25 mg	Maprotiline hydrochloride, Tab 75 mg	Mianserin hydrochloride, Tab 30 mg	Moclobemide, Tab 150 mg	Moclobemide, Tab 300 mg	Nortriptyline hydrochloride, Tab 10 mg	Nortriptyline hydrochloride, Tab 25 mg	Paroxetine hydrochloride, Tab 20 mg	Tranylcypromine sulphate, Tab 10 mg	Trimipramine maleate, Cap 25 mg	Trimipramine maleate, Cap 50 mg	Total DDD (all antidepressants) per 1000 people	Mean DDD (all antidepressants) per 1000 people
Canterbury	1.20	2.60	1.20	29.00		0.80	0.10	0.50	0.50	0.20	0.80	0.50	0.40	26.50	1.00		0.70			0.10	1.40	0.90	0.50	4.80	14.50	0.90	0.10	0.10	89.3	3.72
South Canterbury	1.70	3.20	1.60	17.60		0.40		1.00	0.90	0.50	1.80	0.80	0.40	23.80	0.70		0.50	0.20			1.20	2.70	0.20	2.00	15.80	0.30	0.20	0.20	77.7	3.38
Otago	1.90	3.10	1.40	17.70		0.50	0.10	0.50	0.40	0.60	1.40	1.00	0.50	18.50	1.20	0.10	1.00			0.10	1.00	0.50	0.20	1.90	16.50	0.50	0.30	0.20	71.1	2.84
Wairarapa	2.10	3.90	1.50	17.60		0.30		1.80	1.50	0.10	0.40	0.30	0.10	20.60	1.20		0.30				1.40	0.30	0.30	1.00	14.30		0.20	0.30	69.5	3.31
Taranaki	1.00	2.30	1.40	18.00		0.30		1.60	1.80	0.10	0.40	0.30	0.20	15.50	1.00	0.10	0.40			0.10	0.80	0.50	0.30	1.00	20.70	0.10	0.10	0.20	68.2	2.84
Nelson–Marlborough	1.20	3.40	1.50	15.50		0.40		0.60	0.60	0.30	1.30	0.50	0.40	17.00	1.00	0.10	0.80				0.40	0.20	0.20	1.80	16.80	0.20	0.10	0.10	64.4	2.80
Hutt Valley	1.50	3.50	2.10	13.50		0.20		1.30	1.00	0.30	0.80	0.40	0.50	18.50	1.10		0.50				0.60	0.20	0.30	0.70	15.20	0.10	0.10	0.10	62.5	2.84
West Coast	0.80	2.80	1.10	14.40		0.70		0.80	0.70	0.30	0.80	0.50	0.30	17.20	0.40		0.40	0.10		0.20	1.40		0.20	2.80	14.00	0.10	0.10		60.1	2.73
Whanganui	1.70	3.30	2.40	11.90	0.10	0.50		0.70	0.80	0.20	0.60	0.50	0.40	15.40	0.70	0.10	0.50	0.10			1.50	0.20	0.10	0.70	16.80	0.20	0.20	0.10	59.7	2.39
Lakes	1.50	2.00	1.10	15.10		0.30	0.20	0.80	0.80	0.10	0.30	0.20	0.10	17.60	0.70	0.10	0.30				0.90	0.70	0.30	1.30	14.50	0.10	0.20	0.20	59.4	2.48
Bay of Plenty	1.60	2.40	1.20	14.30		0.60	0.10	1.40	1.40	0.10	0.30	0.20	0.20	15.40	0.80	0.10	0.30			0.10	1.00	0.50	0.20	1.10	13.00	0.10	0.30	0.30	57.0	2.28
Waikato	1.60	2.20	1.00	13.60		0.40		0.90	1.20		0.20	0.10	0.20	14.80	0.70		0.30				0.80	0.30	0.30	1.10	16.40	0.10	0.10	0.20	56.5	2.69
Northland	1.60	2.60	1.60	12.40		0.50		0.80	0.90	0.10	0.40	0.30	0.20	15.10	0.70		0.20				0.80	0.20	0.30	1.90	15.00	0.10	0.20	0.30	56.2	2.55
Hawke's Bay	1.50	2.50	1.40	13.00		0.30		0.80	1.10	0.20	0.60	0.40	0.60	14.90	0.60	0.10	0.40				0.80	0.20	0.40	1.10	14.60		0.10	0.10	55.7	2.53
MidCentral	1.70	2.00	1.60	11.90		0.40		0.90	0.80	0.10	0.50	0.40	0.20	14.50	0.50		0.30				1.50	0.40	0.20	0.60	16.30	0.20	0.20	0.30	55.5	2.52
Capital and Coast	1.20	1.80	1.20	12.90		0.30	0.10	1.10	1.30	0.20	0.50	0.30	0.30	15.30	1.10		0.40				0.80	0.20	0.20	1.10	12.00	0.10	0.10	0.10	52.6	2.29
Southland	0.90	2.50	1.00	11.40		0.50	0.10	0.50	0.40	0.40	1.10	0.80	0.40	13.40	0.70		0.70				0.70	0.10	0.10	1.10	12.30		0.30	0.20	49.6	2.25
Auckland	1.00	1.40	0.60	11.50		0.30		0.40	0.40	0.10	0.20	0.20	0.10	10.10	0.70		0.30				0.50	0.20	0.30	1.60	15.00	0.30	0.10	0.10	45.4	2.06
Waitemata	1.10	1.50	0.80	10.60		0.40		0.50	0.60	0.10	0.30	0.20	0.10	10.50	0.60		0.30				0.40	0.10	0.30	1.90	14.00	0.20	0.10	0.10	44.7	2.03
Tairawhiti	1.80	2.50	0.90	9.60		0.30		0.30	0.60	0.30	0.70	0.50	0.40	11.40	0.60		0.40				0.60	0.10	0.10	0.70	8.60	0.10	0.20	0.20	40.9	1.86
Counties Manukau	1.10	1.50	0.80	7.40		0.20		0.40	0.30	0.10	0.20	0.10	0.10	9.00	0.30		0.20				0.30	0.10	0.40	1.70	13.20	0.10	0.10	0.10	37.7	1.71

DHB	Amitriptyline, Tab 10 mg	Amitriptyline, Tab 25 mg	Amitriptyline, Tab 50 mg	Citalopram hydrobromide, Tab 20 mg	Clomipramine hydrochloride, Tab 10 mg	Clomipramine hydrochloride, Tab 25 mg	Desipramine hydrochloride, Tab 25 mg	Dothiepin hydrochloride, Cap 25 mg	Dothiepin hydrochloride, Tab 75 mg	Doxepin hydrochloride, Cap 10 mg	Doxepin hydrochloride, Cap 25 mg	Doxepin hydrochloride, Cap 50 mg	Doxepin Hydrochloride, Cap 75 mg	Fluoxetine hydrochloride, Cap 20 mg	Fluoxetine hydrochloride, Tab dispersible 20 mg, scored	Imipramine hydrochloride, Tab 10 mg	Imipramine hydrochloride, Tab 25 mg	Maprotiline hydrochloride, Tab 25 mg	Maprotiline hydrochloride, Tab 75 mg	Mianserin hydrochloride, Tab 30 mg	Moclobemide, Tab 150 mg	Moclobemide, Tab 300 mg	Nortriptyline hydrochloride, Tab 10 mg	Nortriptyline hydrochloride, Tab 25 mg	Paroxetine hydrochloride, Tab 20 mg	Tranylcypromine sulphate, Tab 10 mg	Trimipramine maleate, Cap 25 mg	Trimipramine maleate, Cap 50 mg	Total DDD (all antidepressants) per 1000 people	Mean DDD (all antidepressants) per 1000 people
Mean DHB DDD per 1000 people	1.41	2.52	1.30	14.23	0.10	0.41	0.12	0.84	0.86	0.22	0.65	0.40	0.29	15.95	0.78	0.10	0.44	0.13	0.00	0.12	0.90	0.43	0.26	1.52	14.74	0.21	0.16	0.18	58.75	2.58
STD	0.36	0.70	0.43	4.39	0.00	0.15	0.04	0.41	0.41	0.15	0.44	0.24	0.15	4.24	0.25	0.00	0.21	0.06	0.00	0.04	0.38	0.58	0.10	0.94	2.36	0.20	0.07	0.08	12.23	0.50
95% CI	0.15	0.30	0.18	1.88	0.00	0.07	0.03	0.18	0.17	0.06	0.19	0.10	0.07	1.81	0.11	0.00	0.09	0.07	0.00	0.04	0.16	0.25	0.04	0.40	1.01	0.09	0.03	0.03	5.23	0.21
95% CI (upper range)	2.13	3.92	2.16	23.00	0.10	0.72	0.20	1.66	1.67	0.51	1.52	0.88	0.60	24.42	1.29	0.10	0.85	0.25	0.00	0.21	1.65	1.58	0.46	3.39	19.47	0.62	0.31	0.33	83.21	3.57
95% CI (lower range)	0.70	1.13	0.45	5.46	0.10	0.10	0.04	0.02	0.05	-0.07	-0.22	-0.07	-0.02	7.48	0.27	0.10	0.03	0.02	0.00	0.03	0.14	-0.72	0.05	-0.35	10.01	-0.19	0.01	0.02	34.28	1.58
Significantly over					Significantly under																									