THE NEW ZEALAND MEDICAL JOURNAL
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This Issue in the Journal

One-year follow-up of the 2011 Christchurch Earthquake stress cardiomyopathy cases
Christina Chan, Richard Troughton, John Elliott, Julie Zarifeh, Paul Bridgman

Within 4 days of the 22 February 2011 Christchurch Earthquake, 21 postmenopausal women presented to Christchurch Hospital with stress (takotsubo) cardiomyopathy. We closely examined these patients at presentation and at 12 months when telephone interviews were conducted. Patients answered a structured questionnaire to assess their cardiac and general health concerns as well as three psychometric questionnaires to assess psychological wellbeing. The majority of patients initially had classic features of stress cardiomyopathy. Recovery was prompt with low complication rate. At 12 months, survival rate was 100%. The psychometric questionnaires showed that none had a high level of health anxiety, general anxiety or depression. Only four patients endorsed symptoms suggestive of borderline post-traumatic stress disorder so this group had good short-term and medium-term outcomes without significant cardiac or psychological effects.

Adalimumab for Crohn's disease in New Zealand—a prospective multicentre experience
Gareth R Thomas, Timothy Lewis-Morris, David Rowbotham, Cathryn Whiteside, Stephne Joyce, Stephen Inns, Michael Schultz, Richard B Gearry

Crohn's disease causes inflammation of the gut leading to disabling symptoms and disability. Medical treatments are effective for many but not all patients. This study shows that in a New Zealand Crohn's disease population, the drug is mostly safe and effective.

The impact of oral antiviral therapy on long-term survival of hepatitis B surface antigen-positive patients on haemodialysis
Maggie M G Ow, Janak R de Zoysa, Edward J Gane

Hepatitis B infection is an important cause of mortality in kidney failure patients. The impact of antiviral therapy in this population is not known. This study found that haemodialysis patients with hepatitis B, when treated with antivirals if indicated, had equivalent survival to those on haemodialysis without hepatitis B. Hence, there was no increased risk of death with having hepatitis B infection if treated appropriately with antivirals. For those on medication, compliance is crucial as incomplete suppression of the virus was associated with a higher risk of liver-related death.

Exploring the potential for the drift of secondhand smoke from outdoor to indoor dining areas of restaurants in New Zealand
Frederieke S van der Deen, Amber L Pearson, Darko Petrović, Lucie Collinson

In this study, we examined the potential for secondhand smoke (SHS) to drift from outdoor restaurant dining areas to the nearby indoor areas via open windows and doors. To do this, we measured air particles of a specific size (PM2.5) known to relate to tobacco smoke and known to cause health problems. Although SHS has been studied in other settings in New Zealand such as bars and cafés, we believe it is important to study SHS in restaurants for the following reasons: 1) more children may be exposed in restaurant settings, and 2) there is the potential for a longer duration of SHS exposure throughout the course of a meal, rather than while just having a beverage. We measured $PM_{2.5}$ (small particulate matter in the air) in the outdoor dining areas (where smoking is permitted), and in the indoor areas (where smoking is banned), and (where possible) as far indoors away from the outdoor area in a total of eight restaurants in Wellington City to make comparisons.

New Zealand tobacco retailers' attitudes to selling tobacco, point-of-sale display bans and other tobacco control measures: a qualitative analysis
Richard Jaine, Marie Russell, Richard Edwards, George Thomson

All but four of the 18 retailers we interviewed were ambivalent about selling tobacco, would rather not sell it, or fell back on a business imperative for justification. Only one retailer was explicitly unconcerned about selling tobacco products. Most participants had few or no concerns about the removal of point-of-sale displays. Issues which were raised were mainly practical and logistical issues with the removal of displays. Only three thought sales would definitely be reduced. The majority of the retailers were not opposed to a possible requirement that nicotine replacement therapy products be made available wherever tobacco products are sold. Ten supported a licensing or registration scheme for tobacco retailers, and only three were opposed.

Variation in benzodiazepine and antipsychotic use in people aged 65 years and over in New Zealand
Gary Jackson, Catherine Gerard, Nikolai Minko, Nirasha Parsotam

The New Zealand Atlas of Healthcare Variation describes variation by geographic area in the provision and use of specific health services and health outcomes (http://www.hqsc.govt.nz/atlas). This paper examined the dispensing of antipsychotic and benzodiazepine medicines across DHBs in those aged 65+ in more detail. These medications have significant side effects, and are suggested to only be given in short courses for specified symptoms in selected cases. Rates of antipsychotic and benzodiazepine use in the elderly were found to remain high, and to vary significantly by DHB area around New Zealand.

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Takotsubo (stress) cardiomyopathy: insights gleaned from the Christchurch Earthquake experience

Cheuk-Kit Wong

On 12 June 2014, a search on medical literature website PubMed using the word "takotsubo" yielded 2058 articles. "Takotsubo" is a pot with a round bottom and narrow neck used for trapping octopuses in Japan.

Originally described in the 1980s by the Japanese, the typical patient with takotsubo cardiomyopathy has during systole ballooning of the left ventricular apex resembling a "takotsubo"[1]—a disease also commonly known as apical ballooning syndrome. Today, two other less common variants are described: the mid-ventricular ballooning pattern (20–30% of patients) and the inverted ballooning pattern involving the basal part of the left ventricle (1–2%).[2]

In a series of 136 consecutive patients with takotsubo cardiomyopathy from Minneapolis, USA (6 men and 130 women), 15 (11%) had no identifiable trigger, 64 (48%) had the syndrome precipitated by intensely stressful emotional events (hence its other name stress cardiomyopathy or "broken heart" syndrome) and 57 had syndrome precipitated by stressful medical events ranging from acute respiratory failure, neurological emergencies, medical procedures (often surgery with anaesthesia), infections and the use or withdrawal of medications or drugs.[3]

Excitation of the sympathetic nervous system or excess of catecholamines (including iatrogenic situations such as dobutamine cardiac stress tests) are thought to be the common pathway that precipitates an attack.[1–4]

The area of left ventricular involvement (occasionally right ventricle also involved) does not correspond at all to any single coronary artery perfusion territory arguing against a primary coronary problem in its pathophysiology. Despite having a left ventricular ejection fraction substantially lower than that in ST elevation acute myocardial infarction,[2] takotsubo syndrome is often considered more benign with reversible ventricular dysfunction.

This idea of having a more benign course was challenged by a recent meta-analysis including 2120 patients with takotsubo cardiomyopathy (87% women, mean age 68, and 40% with preceding acute medical illnesses—"secondary takotsubo") which found an in-hospital mortality of 4.5%.[5]

Male gender and "secondary takotsubo" predicted mortality, about 40% of which were from direct cardiac complications including heart failure/shock, ventricular arrhythmia, ventricular rupture and thromboembolism (mainly from left ventricular mural thrombus over the akinetic area).

The left ventricular dysfunction in the classical form of takotsubo (i.e. ballooning of the left ventricular apex) is often worsened by left ventricular outflow tract obstruction from hyper-contractility of the left ventricular basal segments causing systolic anterior motion of the mitral valve and mitral regurgitation.[1,2]

The annual recurrence rate for takotsubo cardiomyopathy, as reviewed by another recent meta-analysis, was 1–2% with another 10–15% of patients having persistent or recurrent symptoms.[6] Obviously, any clinical criteria for diagnosing takotsubo cardiomyopathy are a compromise of sensitivity and specificity, and it is well possible that the syndrome exists in milder forms which may even escape clinical attention.

In this issue of the *Journal*, Chan et al reported the Christchurch experience of 21 patients (all women, mean age of 68 years) who had takotsubo cardiomyopathy after the 2011 February earthquake.[7]

Table 1 highlights some reported patient characteristics from their study with general comments.

Table 1. Patients' characteristics in Chan et al's *NZMJ* article[7]

Findings	Comments
ECG changes (often ST elevation or deep T inversion) without epicardial coronary disease	Takotsubo is not an uncommon "STEMI misdiagnosis" causing cath lab activation for an intended primary angioplasty[8]
Prolonged QT interval, more prolongation at discharge	Typical progressive QT lengthening, often with deep T inversion, during the in-hospital course of the disease. While it can precipitate torsades de pointe, a polymorphic ventricular tachycardia, and cause sudden death, this is generally rare[1,2]
Typical apical ballooning in 19 of 21 patients and 2 had the mid wall variant sparing the apex	Consistent with literature[2]
Left ventricular ejection fraction of 39% (IQR 30–45%) with short hospitalisation, rapid recovery of ejection fraction on follow-up (67%) and zero 1-year mortality	This ejection fraction is ~10% higher than that from 259 takatsubo patients from the Minneapolis Heart Institute[2] and may explain the better outcome of the Christchurch cohort
Only moderately elevated cardiac biomarkers such as troponins level suggesting only modest myocardial damage	Takotsubo is characteristically not associated with late enhancement (evidence of fibrosis or infarction) despite being edematous on cardiac MRI studies.[1,2,9]
Two patients had history of takotsubo before 2011; whereas after discharge three patients required re-hospitalisation for cardiac causes.	Consistent with literature for recurrent takotsubo and recurrent cardiac symptoms.[6]
The patient with apical variant in the 2010 September earthquake presented with the mid-wall variant in 2011	Consistent with the literature that recurrence of takotsubo in the same patient can be with a different variant.[1,2]

Chan et al provided new information, assessing psychological wellbeing. Their psychometric questionnaires showed that none had a high level of health anxiety, general anxiety or depression. Four patients had symptoms suggestive of borderline post-traumatic stress disorder.[7] These findings have obvious practical value in health care. However, there could be deeper implications from studying the psychology of takotsubo patients.

As the authors pointed out, their series is unique because the stress cardiomyopathy in all 21 patients was provoked by the relatively similar emotional stressor arising from the earthquake. The better ejection fraction and clinical outcomes in their cohort[7] may suggest a milder form of Takotsubo syndrome, unlike the more severe forms secondary to physical illnesses or affecting males.[5]

Their patients represented those who had "broken hearts" from the (Christchurch) earthquake. It may be logical to speculate that each individual has a risk to develop takotsubo syndrome given the appropriate emotional stressor, with higher risks in those who are more psychological predisposed.

Some very predisposed subjects (perhaps including some with extreme anxiety) may develop the syndrome with minimal stress. This hypothesis is well consistent with the Mineapolis series[3] and other reports[1,2] that a minority of takatsubo patients did not even have any identifiable preceding stress events.

There are some interesting recent findings from studies in rats,[10] where either immobilisation (a form of severe "emotional" stress for rats) or exogeneous catecholamine can induce the equivalent of takotsubo cardiomyopathy. In a series of rat experiments, blood pressure was monitored through a catheter in the right carotid artery and cardiac morphology and function studied by echocardiography.[10]

Catecholamines were introduced intraperitoneally, testing isoprenaline (β_1/β_2-adrenoceptor agonist), epinephrine ($\beta_1/\beta_2/\alpha$-adrenoceptor agonist), norepinephrine (β_1/α-adrenoceptor agonist), dopamine ($\alpha/\beta_1/\beta_2$-adrenoceptor agonist) and phenylephrine (α-adrenoceptor agonist).

While all catecholamines induced takotsubo-like cardiac dysfunction, isoprenaline induced low blood pressure and predominantly apical dysfunction whereas the other catecholamines induced high blood pressure and basal dysfunction. In another set of experiments additionally infusing hydralazine or nitroprusside to rats that received epinephrine or norepinephrine (thus maintaining lower systolic blood pressure), the rats developed apical instead of basal dysfunction.

Conversely, infusion of phenylephrine (thus maintaining higher systolic blood pressure) after isoprenaline administration prevented apical ballooning. The authors concluded that different catecholamines induced different patterns of takotsubo-like cardiac dysfunction which also depended on afterload.[10]

These interesting animal findings somewhat echo with the clinical observation that the same patient can develop the different variants (apical versus mid-segment versus basal) of takotsubo cardiomyopathy over different period of time, as shown in the Christchurch report.[7]

One may speculate that an outpour of catecholamine (such as in patients with phaeochromocytoma) may induce a takotsubo cardiomyopathy. The Christchurch study[7] used diagnostic criteria similar to the modified Mayo criteria in diagnosing takotsubo cardiomyopathy. It is noteworthy that the full modified Mayo criteria also require the exclusion of phaeochromocytoma.[1]

Y-Hassan recently suggested the role of an acute cardiac sympathetic over-activation followed by disruption as the pathophysiology in takotsubo cardiomyopathy.[4] Cardiac sympathetic denervation had been noted for years in studies using ^{123}I-MIBG scans demonstrating cold spots in the myocardium with regional wall dysfunction.[1,2] Y-Hassan suggested that the cardiac sympathetic denervation may be due to excessive release of norepinephrine from myocardial sympathetic nerve terminals damaging both myocytes and nerve terminals.

The damage to the myocytes will be consistent with the evidence acutely of myocardial oedema in the involved myocardium demonstrated on cardiac MRI scan[9] and slow coronary flow to the involved myocardial region on angiography.[1,2]

The interesting theories aside, what can we take home from the Christchurch report? First and foremost, the report supports their practice in that it is (relatively) safe for early discharge for takotsubo cardiomyopathy triggered by earthquake, providing that patients are stable.

This is no minor issue given that any hospital system will be stretched much beyond its limits in the situation of a major earthquake. Secondly, patients have good outcomes without significant cardiac or psychological sequelae at least for the first year. This is so despite that patients were being exposed to significant aftershocks in Christchurch following February 2011.

One may speculate that beta-blockers would be particularly protective in these patients but a recent meta-analysis suggests that ACE-inhibitors/angiotensin receptor blockers rather than beta-blockers reduce risks for recurrence.[6] Among the 21 Christchurch patients, 9 were taking the former and 10 the latter at 1-year follow-up.[7] Lastly, Chan et al[7] are astute in highlighting that their patient cohort was unique with an identical single stressor.

The interested reader is welcome to search on the PubMed website the myriad of different clinical conditions that can precipitate takotsubo cardiomyopathy.

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Monoclonals against TNF are a major advance in the treatment of Crohn's disease

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract that results from a dysregulated immune response to commensal gut bacteria. In health there is a state of mucosal immune tolerance to our gut bacteria. There is a complex interaction between the epithelial cell and the T lymphocyte in the lamina propria. This "cross-talk" is medicated by cytokines such as TNF-alpha (TNF-α), IL12 and IL23.

TNF-alpha is central to the inflammatory response in Crohn's disease promoting other inflammatory cytokines and upregulating the expression of adhesion molecules on vascular endothelial cells.[1]

Monoclonal antibodies that target specific molecules (often called biologicals) have been a major advance in the treatment of Crohn's disease. The first target proposed was TNF-alpha (tumour necrosis factor) and this has proven to be a major success story. Monoclonal antibodies bind to TNF receptors on activated T cells and monocyte/macrophages causing blockade of activity but more importantly cause apoptosis and cell cycle arrest. The details of the inflammatory response in Crohn's disease have become much more important in the biological era in the search for other potential targets for inhibitory antibodies.

Infliximab was the first anti-TNF agent and continues to be widely used for Crohn's disease and many other inflammatory conditions. This drug needs to be given by infusion every 8 weeks—this limits acceptability but does ensure compliance.

Adalimimab is a humanised monoclonal to TNF-alpha that is given subcutaneously every 2 weeks. The review of adalimumab use in New Zealand (NZ) by Thomas et al, in this issue of the *Journal*, adds to the literature confirming effectiveness of these agents for moderate to severe Crohn's disease.[2]

Treatment options before the advent of anti-TNF monoclonal were limited. Corticosteroids have an initial effect but lose effect partly because these drugs do not lead to mucosal healing. Crohn's disease is a transmural inflammation that will lead to complications such as structuring, perforation and fistula if left unchecked.

Immunosuppressant treatment has been helpful, particularly azathioprine, which has been the favoured drug in NZ and in many parts of the world. It is an old drug that is being used as well as possible with new data on appropriate dosing determined by monitoring of blood levels of metabolites.

Surgery is required to deal with complicated disease but Crohn's disease will often reoccur and repeated operations quickly lead to major issues with nutrition and reduced quality of life.

Adalimumab and infliximab are approved and funded in NZ for use in moderate to severe Crohn's disease. Most clinical trials and the current PHARMAC criteria use

the Crohn's disease activity index (CDAI) to define severity of the disease. This is a somewhat cumbersome tool that is not used routinely in clinical practice.

The current criteria in NZ for adalimumab use a relatively high CDAI of 300 (compared to the enrolment criteria of CDAI of 220 for many of the pivotal clinical trials). It is often apparent that "real world" experience is different from clinical trials. The continuation rates in this NZ review (87.3% and 76.6% at 1 and 2 years respectively) are higher than would be expected from clinical trial data. However it should be emphasised that high rates of continuation do not equate directly with response or remission as defined in clinical trials.

Data from the CHARM study showed that complete remission (defined as a CDAI less than 150) occurred in only 36% at 52 weeks and response (defined as a >100 points fall in CDAI) occurred in 41% of patients.[4] Open label and single centre retrospective studies have shown response rates between 60–75% at 1 year. There are several possible reasons for the high rates of continuation in this study.

Firstly, patients that are naïve to previous anti-TNF treatment have higher response rates. The CARE study showed 61% in remission at 20 weeks for infliximab naïve patients compared with 52% for those previously exposed to anti-TNF treatment.[3] It is likely, as the authors suggest, that the rate of previous infliximab use was low in this NZ audit but this data is not presented apart from stating that 7% had "grandfathering", that is, transferring from infliximab to adalimumab, mainly for the convenience of subcutaneous dosing, expecting to maintain remission.[7]

Secondly, patients with objective signs of inflammation (mucosal lesions and raised CRP) may do better with anti-TNF treatment.[8] Patients in this review may have been treated earlier with more inflammatory disease and less complicated disease. Thirdly, there are several indications for starting treatment in NZ where the continuation rules are not based on CDAI (40% in this study) and therefore patients may continue treatment without achieving a strict definition of response.

This study shows a higher use of adalimumab in Canterbury. This is probably due to early enthusiasm and early uptake of treatment in this region but this variation between different centres may change over time with increasing use in centres outside of Canterbury. Community funding of adalimumab is a much better model then prescribing through gastroenterology departments which resulted in major regional differences in prescribing rates.

There is a gradual loss of response to anti-TNF monoclonal treatment that is approximately 15% per year (17% in this study over mean follow-up of 1.3 years). The falling continuation rates over 3 years in this study are consistent with this trial data.

Many clinical trials allowed an increase to weekly dosing if there was non-response or loss of response. Clinical trials and open label experience for first year show that approximately15–20% require a dose increase to 40 mg weekly but this option is not available in NZ at present.[3–6]

There is another anti-TNF monoclonal antibody called certolizumab which can offer another choice if there is loss of response to the other two agents but this is not available in NZ.

The cost of adalimumab in 2013 for the treatment of Crohn's disease was $11 million. This represents a significant increase in treatment costs for Crohn's disease. It is legitimate to ask what is the benefit over standard treatment?

Gastroenterologists who treat these patients have no doubt that lives have been transformed by this medication but accurate data is required to answer critics of the increasing drug costs. This benefit may be less quantifiable than increased months of survival for cancer treatment but may be more valuable for our community. This study has shown that days spent in hospital after 1 year of treatment is reduced. This is a crude indicator but it is very encouraging to find a significant difference in hospital stay over a relatively short period of treatment. Improved quality of life, return to employment and long-term avoidance of significant surgery are other important goals of treatment.[9]

The costs of treatment will decrease over time although it is likely that the proportion of patients treated with biologicals will gradually increase over time. There were 31 patients (16%) in this NZ audit who were 16 years or less. Children and adolescents do well with this treatment. The resulting improvement in overall wellbeing gives these young people hope to face the future, to complete studies, gain employment and start relationships with confidence.[6]

There are many debates in the field of anti-TNF treatment. The most difficult question is the use, in combination, of immunomodulators such as azathioprine. There is good evidence of better response rates for combination treatment, higher rates of mucosal healing and probably less problems with loss of response over time.[10]

The concern with combination treatment is with regards to long-term safety. The risk of infection is increased and there is an increased risk of lymphoma with long-term use of thiopurines—this may be a 3-fold increased risk of this rare cancer.[11] Combination treatment is favoured in NZ (data not presented in this study) but the potential risks need addressed with our patients.

When to stop anti-TNF treatment is another difficult question. Some patients achieve "deep remission" with no discernible disease activity, normal inflammatory markers and complete mucosal healing. It is likely that some of these patients will have a sustained response after stopping treatment.[12] Preventing postoperative recurrence is another potential use for adalimumab that is not yet funded. Under the current criteria patients need to have a significant clinical relapse and the opportunity to prevent further surgery may have been missed.

Monitoring of response with faecal calprotectin and serum levels of infliximab or adalimiumab with appropriate changes in dose or dosing interval is likely to become part of routine management.[13] There will be a trend to earlier prescribing in the course of the disease to prevent irreversible gut damage. There is good data showing a better response with early treatment.[14]

Biologicals should be started early with an aggressive disease phenotype—this is onset at a young age, poor response to corticosteroids (or early relapse after stopping) and early onset of complicated disease such as fistula (including perianal fistula).

The use of biologicals for ulcerative colitis (UC) has not been the same success story. There is some activity of anti-TNF treatment for UC but this is not considered cost-

effective in NZ at present. Infliximab can be used for severe ulcerative colitis. Other biologicals in development may be more effective for UC.

The future involves optimising the dosing of existing agents and looking to having more options available when there is loss of response. Crohn's disease affects young people and the real test will be the long-term success of biologicals over 10–15 years not just the first 12 months.

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One-year follow-up of the 2011 Christchurch Earthquake stress cardiomyopathy cases

Christina Chan, Richard Troughton, John Elliott, Julie Zarifeh, Paul Bridgman

Abstract

Introduction A major earthquake struck Christchurch on 22 February 2011 causing extensive damage to the city and 185 direct fatalities. Within 4 days 21 postmenopausal women presented to Christchurch Hospital with stress cardiomyopathy. We were able to closely examine these patients in the immediate phase of presentation and at 12 months.

Methods Patients were prospectively identified. Clinical details at presentation were recorded including basic characteristics, symptoms, investigations, results, treatments and complications. At 12 months, telephone interviews were conducted. Patients answered a structured questionnaire to assess their cardiac and general health concerns. Consenting patients also received three psychometric questionnaires to assess psychological wellbeing.

Results The majority of patients had classic features of stress cardiomyopathy. Recovery was prompt with low complication rate. At 12 months, survival rate was 100%. Five patients had hospital readmissions early on—three of which were cardiac related. None had ongoing symptoms or stress cardiomyopathy recurrence. Seven patients had non-cardiac related medical problems. The psychometric questionnaires showed that none had a high level of health anxiety, general anxiety or depression. Four patients endorsed symptoms suggestive of borderline post-traumatic stress disorder.

Conclusion The Christchurch Earthquake stress cardiomyopathy cohort has had good short-term and medium-term outcomes without significant cardiac or psychological sequelae.

Stress cardiomyopathy (SCM) is a fascinating condition that is triggered by emotional stress and may mimic acute myocardial infarction in presentation.[1] Over the past decade, there has been an increase in frequency of publications on SCM as it has gained broad attention in the field of cardiology around the world. However, given the rarity of SCM, the majority of the publications are individual case reports or small case series.

Most of the case series in the literature list individuals with SCM triggered by a wide range of poorly characterised stressors occurring over a period of time. The exception was the work done by Watanabe's group, presenting 25 patients with SCM triggered by a single stressor, the 2004 Niigata earthquake.[2] However, their study lacked in detailed information such as patient characteristics or clinical outcomes.

On 22 February 2011, Christchurch, the second largest city in New Zealand with an urban population of 400,000, was struck by a 6.3 magnitude earthquake at 12:51pm.

The city suffered great damage and 185 lives were lost. As expected, cardiovascular complications increased.[3]

Within 4 days of the event, 21 patients presented to Christchurch Hospital with SCM.[4] This was an exceptionally high number given that annually, approximately six patients would be diagnosed with this condition only. After the September 2010 earthquake, nine patients presented with SCM within 1 week.

As Christchurch Hospital was the region's only acute cardiac service provider, an opportunity arose to further study these 21 SCM patients. The aim was to provide a better understanding of this unique condition, not only in the acute phase, but also in the intermediate period, especially when patients were exposed to similar stressors (aftershocks) after their initial presentations.

A follow-up study at 12 months after the February 2011 earthquake was therefore launched.

Method

The 21 patients with earthquake induced SCM were prospectively identified by Cardiology Department staff in the days following the earthquake. Systematic review of the clinical files, electronic discharge summaries, coronary angiograms and echocardiograms were undertaken for each patient. Data collected included basic patient characteristics, date of admission and discharge, investigations performed and results.

The diagnosis of stress cardiomyopathy was defined similar to the modified Mayo criteria.[5] All patients were admitted with chest pain and evolving ECG changes, a troponin I rise >0.03mcg/l, a recognised transient echocardiographic regional wall motion abnormality (apical ballooning pattern, mid wall variant or basal segment variant), and no culprit lesion on coronary angiography. Once the SCM patients were identified, a record of their clinic follow-up, medications and hospital readmissions were kept.

In March 2012, telephone interviews were conducted by an investigator. A structured questionnaire was used to assess patients' self-reported cardiac and general health status. Patients answered questions enquiring about their cardiac symptoms, especially in relation to major aftershocks, hospital admissions, other non-cardiac medical conditions and treatment.

After the initial telephone interview, three validated psychometric questionnaires were also posted out for consenting patients to complete. The Health and Anxiety Questionnaire (HAQ), the Hospital Anxiety and Depression Scale (HADS) and the Impact of Event Scale-Revised (IES-R) were used to assess the psychological well-being of this cohort of patients.

The HAQ was developed to identify individuals with high levels of concern about their health.[6] Total scores of 0–8 have been classified as representing low, 9–13 as medium, and 14 and above as high health anxiety.[7] The HADS has been shown to accurately diagnose generalized anxiety disorders and major depressive episodes in an outpatient setting.[8] Anxiety disorders and depression are defined by the use of a score ≥8 as cut-off.

The IES-R was developed to reflect the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) criteria of post-traumatic stress disorder (PTSD) in 1997.[9] It aims to assess levels of intrusion, avoidance and hyperarousal. Patients who score ≥33 may have post-traumatic stress disorder.

Results

All 21 SCM patients were postmenopausal females with median age of 68 years (52–85 years). As a whole, the group had few conventional cardiovascular risk factors (Table 1). One patient had a history of ischaemic heart disease requiring stenting to right coronary artery and left circumflex artery in September 2010. She actually presented shortly after the September 2010 earthquake with the typical apical balloon

pattern of SCM. Her left ventricular regional wall motion abnormality on echocardiography study extended beyond the area supplied by her diseased coronary arteries. Another woman also had a history of SCM. She had previously presented in August 2009 with apical ballooning triggered by an emotional stressor.

Table 1. Basic patient characteristics of the 21 SCM patients

Variables	Total cases=21
Age	68 years, median (52–85 years, range)
Females	21 (100%)
NZ European	20 (95.2%)
Ischaemic heart disease	1 (4.8%)
Hypertension	5 (23.8%)
Diabetes	0 (0%)
Dyslipidaemia	8 (38%)
Atrial fibrillation / atrial flutter	2 (9.5%)
CVA / TIA	1 (4.8%)
Current or ex smoker	5 (23.8%)
Previous SCM	2 (9.5%)
Psychiatric illness	2 (9.5%)

All patients had chest pain on admission. The median troponin I level was 1.6 mcg/l (IQR1.2–5.5 mcg/l). Everyone had ECG changes including ST elevation (12 patients), ST depression (two patients) and deep T wave inversion (seven patients). Median QTc interval prolongation was prolonged at discharge (493ms IQR 375ms to 560ms) compared to QTc on admission (437ms IQR 360ms to 480ms).

All patients had echocardiography studies within 24 hours of initial presentation. The typical pattern of mid wall and apical hypokinesis or akinesis was documented in 19 patients. The other two women had the mid wall variant of SCM with sparing of the apex. The median left ventricular ejection fraction was 39% (IQR 30–45%).

The patient who presented with the typical apical ballooning form of SCM after the September earthquake had a different regional wall motion abnormality on this occasion. She had the mid wall variant of SCM.[10]

Coronary angiography was performed in 20 women. The patient with previous history of SCM in August 2009 had a completely normal study then, therefore it was not repeated. Only one patient had severe circumflex disease that required treatment. Her left ventricular regional wall motion abnormality extended beyond the diseased single coronary vascular bed and involved the whole of apex and mid wall region. The rest of the group had either normal coronary arteries (nine patients), mild atheroma only (nine patients) or patent stents with no new lesions (one patient).

The average length of hospital admission was 37 hours (IQR 7–51 hours). Two patients developed mild left ventricular failure and were successfully managed with oral frusemide treatment. None required inotropic support or intra-aortic balloon pump insertion. There were no deaths in this SCM group during the study period.

The follow-up rate post discharge was good with 19 patients attending Cardiology Outpatient Clinic review. The median time to clinic follow-up was 56 days (IQR 54–

70 days). Echocardiography studies were repeated a few days prior to or on the day of the clinic appointments. All 19 patients had normal left ventricular systolic function with a median left ventricular ejection fraction of 67% (IQR 64–72%). Only two patients had residual mild apical hypokinesis whereas 17 had no left ventricular regional wall motion abnormality.

At 12 months, all 21 SCM patients were successfully interviewed. Two patients left Christchurch shortly after the 2011 earthquake. One had taken permanent residence in the North Island and the other had returned to live in Christchurch 13 months after the event. The remaining 19 patients stayed in Christchurch.

Initially, six women still had chest pain after discharge. Five patients reported that they have experienced a few episodes of chest pain with aftershocks. One patient experienced chest pain on exertion. She had normal coronary arteries on coronary angiography in February. All reported their symptoms settled by May 2012. There was no recurrence of SCM in the 12 months follow-up period.

There were a total of six hospital admissions—five patients were admitted to hospital and one patient had two admissions in the follow-up period. There were three cardiac related admissions in March 2011. One patient re-presented 1 day after discharge with heart failure symptoms. She stayed in hospital for another 24 hours and received treatment for heart failure.

A patient presented 9 days after she was discharged with chest pain. She did not have new ECG changes or significant troponin rise and was managed conservatively. Another patient presented 28 days after initial discharge with atrial fibrillation requiring rate control treatment. There were three non-cardiac related admissions that occurred later on which included exacerbation of chronic airway disease, pain due to compression fractures and renal colic.

Seven out of 21 patients reported ongoing active medical problems. Musculoskeletal disorder was the commonest concern with five patients suffering from conditions such as compression fracture, fracture of wrist, osteoporosis, sciatica, rheumatoid arthritis and osteoarthritis. A patient was diagnosed with hyperthyroidism and borderline type 2 diabetes mellitus. Another patient suffered from chronic obstructive airway disease. The majority of patients remained healthy with no ongoing medical issues.

Prior to developing SCM, not many patients were on cardiovascular related medications (Table 2). Most patients were treated with aspirin and beta blockers during and after their admission with 43% receiving angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB).

At follow-up clinic appointments most patients had the beta blockers discontinued. Our 12-month follow-up interview found that beta blockers and ACEI/ARB were restarted in a number of cases; the patients reported that hypertension was the most common reason for this.

Table 2. Medication changes for the 21 SCM patients

Medication	Prior to SCM N=21	During admission N=21	Post clinic follow-up N=19	At 12 months N=21
Aspirin	7 (33.3%)	16 (76.2%)	7 (36.8%)	7 (33.3%)
Clopidogrel	1 (4.8%)	2 (9.5%)	1 (5.3%)	0 (0%)
Beta-blocker	3 (14.2%)	19 (90.5%)	6 (31.6%)	10 (47.6%)
ACEI/ARB	4 (19%)	9 (42.9%)	6 (31.6%)	9 (42.9%)
Statin	6 (28.6%)	7 (33.3%)	6 (31.6%)	6 (28.6%)
Long-acting nitrate	0 (0%)	0 (0%)	1 (5.3%)	1 (4.8%)
Calcium channel blocker	1 (4.8%)	1 (4.8%)	1 (5.3%)	3 (14.3%)
Anxiolytics	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Seventeen patients completed the HAQ. Overall, 9 patients had normal health anxiety levels (score 0 to 8) and 8 patients had a medium level of health anxiety (score 9 to 13). No one had a high level of health anxiety according to the questionnaire. Eighteen patients completed the HADS. The test indicated that only 5 patients had borderline anxiety (score 9 to 13) and 1 had borderline depression (score 10). The rest of the group did not have an abnormal level of anxiety or depression. Sixteen patients completed the IES-R questionnaires. Twelve patients were thought not to have PTSD as they had a normal score (score 2 to 26). Four patients might have borderline PTSD as they had a score greater than 33 (score 39 to 45).

Discussion

This earthquake study provides detailed initial and follow-up data on 21 cases of SCM triggered by the February 2011 Christchurch earthquake. It is a unique case series, in that all cases had the same single emotional stressor.

The clinical features of the 21 SCM at initial presentations detailed in this study were very similar to previous case series. This includes chest pain on presentation, ECG changes of ST elevation followed by T wave inversion and QTc prolongation,[11-13] modest elevation of myocardial injury markers,[14,15] transient and reversible apical ballooning on echocardiography,[14] and the lack of significant coronary disease on angiography.[13] The time course of disease recovery was also in accordance with literature.

Most patients had complete normalisation of left ventricular function and regional wall motion within a few weeks.[12] Our data shows that the patients could do well with a very short hospital admission. The Cardiology Department staff had previous experience of managing a cluster of SCM following the September 2010 earthquake.[16] This led to a high index of suspicion and rapid investigation and treatment.

In the days following the earthquake the hospital was under significant strain and there was pressure to discharge patients as soon as they were safe to leave. Patients who were stratified by their clinicians to be low risk had very short hospital stays, as short as 3 hours.

At 12 months, a telephone interview showed 100% survival rate with no ongoing cardiac sequelae. One-third of the patients suffered from medical issues such as musculoskeletal problems, chronic airway disease, hyperthyroidism and renal colic.

This was not unexpected given the median age of this cohort of patient was 72 years. At 12 months, there was no SCM recurrence. The rate of recurrence was low compared to previous case series.[17]

The favourable 12 month outcome data of this cohort of patients was comparable to Parodi's findings at 6 months.[18] This was in contrast to Sharkey's findings with 15% of mortality rate from four months to 4.7 years from SCM onset.[14] Obviously, a longer study period for our cohort of SCM would be ideal to further assess prognosis of this condition, but it is notable how good the cardiovascular outcomes were for the period we studied.

In terms of psychological outcomes, psychometric questionnaires showed that none had a high level of health anxiety level and the majority was not depressed or anxious. Only four patients had possible borderline PTSD. The three psychometric questionnaires showed that the majority of the SCM patients were not particularly anxious or depressed nor did they have PTSD at 12 months after the February 2011 earthquake.

The strength of this study is that this is a single centre experience. Given that Christchurch Hospital was the only acute hospital in the region and that the 21 patients with SCM were all residents of the city, we had complete capture of data. This also ensured good follow-up attendance which was of utmost importance to monitor recovery.

The weakness of this study is the lack of a matched control group and baseline psychometric testing on our study group. Ideally, they should all have similar tests during hospital admission immediately post event to establish baseline levels of health anxiety, generalised anxiety, depression and tendency for PTSD. Given their SCM were triggered by a clear emotional stressor, it would be easy to assume that this group of women were more emotionally vulnerable.

However, a study done after the September 2010 earthquake, Zarifeh et al successfully obtained complete psychometric data from six SCM patients as well as from five patients with AMI and six with non-cardiac chest pain presentations.[16] Within 6 weeks of the earthquake, these women underwent a semi-structured interview with a senior clinical psychologist who was blinded to the patients' cardiac diagnosis. They found that SCM following an earthquake was not specific to psychologically vulnerable women.

In fact, women who presented with non-cardiac chest pain following an earthquake had higher anxiety and neuroticism scores than women with either AMI or SCM. There was no excess of depression or depressive symptoms in any of the three groups. The medium-term data from the February 2011 earthquake adds to a picture of SCM occurring in otherwise psychologically robust women and carrying no medium-term psychological risk.

Conclusion

The 22 February 2011 earthquake triggered 21 cases of SCM within 4 days of the event. All 21 patients were postmenopausal women with few cardiovascular risk factors. The short-term clinical outcome was excellent, with no mortality or significant morbidities.

The follow-up study was launched at 12 months in order to gain better understanding of longer-term outcome of earthquake induced SCM patients, as it has not been previously studied. Again, patient outcome was favourable with 100% survival without SCM recurrence. Most patients remained healthy both physically and psychologically despite being exposed to incessant aftershocks following February 2011.

Competing interests: Nil.

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Adalimumab for Crohn's disease in New Zealand—a prospective multicentre experience

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Abstract

Aim Adalimumab is an effective treatment for Crohn's disease (CD). We aimed to describe the early patterns of use, efficacy and response to adalimumab in four regions of New Zealand.

Methods Prospectively collected CDAI data were used to examine adalimumab continuation rates in CD patients. Reasons for adalimumab cessation were determined and phenotypic characteristics of those remaining on adalimumab were examined.

Results 194 patients (100 female) from four centres were included. Indications for adalimumab included CDAI>300 (59.8%), extensive small intestinal disease (21.1%), stoma with active disease (4.6%), risk of short gut syndrome (7.7%) and other (6.7%). The mean follow-up was 20 months (252.8 patient years of data). Adalimumab continuation rates at 6, 12, 24 and 30 months were 92.7%, 87.3%, 76.6% and 67.4%, respectively. Patients with penetrating disease behaviour were more likely to continue on adalimumab ($p<0.005$). There was a significant reduction in mean CDAI from 357 to 110 ($p<0.0001$) over a 6-month period. The mean (range) number of days spent in hospital per patient in the year prior and after adalimumab initiation were 3.5 (0–38) days and 1.9 (0–67) days, respectively ($p<0.0001$).

Conclusions Adalimumab continuation rate in this multicentre CD population was higher than other populations. This may be due to adalimumab being used more commonly as the initial biologic drug in New Zealand.

Crohn's disease (CD) is an incurable chronic relapsing inflammatory enteropathy that leads to significant symptoms, morbidity and disability amongst those affected.[1] CD incidence is rising rapidly with high rates described in New Zealand and Australia and increasing rates in Asia.[2–5] The treatment aims in CD are to induce and maintain clinical remission and subsequently prevent complications such as strictures, fistulising disease and surgery.

The treatment of CD includes a wide range of anti-inflammatory and immunosuppressive drugs, nutritional therapy and surgery. Over the last decade, biological drugs such as infliximab and adalimumab have been developed and shown to be effective at inducing and maintaining remission in patients with moderate to severe CD.[6,7]

Adalimumab was first approved for use for moderate to severe CD in New Zealand in April 2007 while it became fully funded in September 2009 with specific criteria governing its use (Figure 1). These criteria were similar to those adopted in Australia,

although are more restrictive than the inclusion criteria used in clinical trials and in other jurisdictions.

Figure 1. Pharmac criteria used to approve adalimumab use in New Zealand

INITIAL APPLICATION

Applications only from a Gastroenterologist. Approvals valid for 3 months.

Patient has severe active Crohn's disease,

AND

Patient has a Crohn's disease Activity Index (CDAI) score of greater than or equal to 300

OR

Patient has extensive small intestinal disease affecting more than 50 cm of the small intestine

OR

Patient has evidence of short gut syndrome or would be at risk of short gut syndrome with further bowel resection

OR

Patient has an ileostomy or colostomy, and has intestinal inflammation

AND

Patient has tried but has had an inadequate response to, or has experienced intolerable side effects from, prior systemic therapy with immunomodulators at maximal tolerated doses (unless contraindicated) and corticosteroids

AND

Surgery (or further surgery) is considered clinically inappropriate

RENEWAL

Applicant is a Gastroenterologist

OR

Applicant is a Practitioner and confirms that a Gastroenterologist has provided a letter, email or fax recommendation that the patient continues with adalimumab treatment

AND

The CDAI score has reduced by 100 points from the CDAI score when the patient was initiated on adalimumab

OR

The CDAI score is 150 or less

OR

The patient has demonstrated an adequate response to treatment but CDAI score cannot be assessed

AND

Applicant to indicate the reason that CDAI score cannot be assessed

AND

Adalimumab to be administered at doses no greater than 40mg every 14 days

Adalimumab is a fully humanised immunoglobulin G Class 1 molecule targeting tumour necrosis factor-α (TNF-α). It is licensed for use in a number of inflammatory diseases including Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis. While clinical trials provide essential endpoints for drug registration, the real life experience of using these drugs is often different, particularly with regard to patient selection and efficacy.

Exploring the efficacy and toxicity of adalimumab for CD patients in New Zealand provides a unique opportunity. Unlike most countries where both anti-TNF-α drugs (adalimumab and infliximab) are available equally for the treatment of luminal CD, this has not been the case in New Zealand.

The government drug-buying agency (Pharmac) negotiated a single supply deal with AbbVie (formerly Abbott Laboratories) to reimburse the cost of adalimumab for the treatment of severe CD with specific criteria (Figure 1).

While infliximab has remained available for the treatment of luminal CD, the use of infliximab for this indication has been very limited and at the financial discretion of individual hospitals.

Adalimumab, therefore, has become the first choice anti-TNF-α for the treatment of luminal CD in New Zealand. Furthermore, the use of this drug requires strict criteria to be met (Figure 1) with patients who are able to (i.e. those without a stoma) being required to complete a CDAI prospectively prior to the initiation of adalimumab and at six monthly intervals thereafter to confirm remission (CDAI<150) or CDAI 100 response.

In this uniquely controlled environment, we aimed to describe the early patterns of use, efficacy and response to adalimumab in four regions of New Zealand.

Materials and Methods

IBD services in four regions of New Zealand provided data on patients receiving adalimumab for CD. Each of these services supervised the application and renewal process for all CD patients receiving adalimumab for CD in their region. The regions were Canterbury (population 490,000), Otago (population 210,000), Auckland City (population 468,000) and Hutt Valley/Wairarapa (population 186,000).

Data were collected on each patient prospectively including date of birth, date of diagnosis, date of adalimumab commencement and date of cessation (and indication) or last follow up, sex, disease phenotype using Montreal classification,[8] indication for adalimumab commencement (Figure 1), CDAI at adalimumab commencement, adverse drug reactions, days in hospital in the year before and the year after adalimumab commenced.

Data were analysed descriptively using SPSS Statistics Version 20 (IBM). Discrete variables were analysed using the Chi-squared test with the level of significance at $p<0.05$. Kaplan Meier survival curves were constructed to show time to loss of response to adalimumab. A Mantel-Cox log rank test was used to compare the survival of phenotypic and other subgroups.

This study fulfilled the New Zealand Health and Disability Human Ethics Criteria for audit activity.

Results

The characteristics of the study population can be seen in Table 1. Most patients were from the Canterbury region and there were significant differences between the study groups with regard to age of diagnosis, disease location and behaviour and mean duration receiving adalimumab.

Table 1. Characteristics of the study population

Variables	Canterbury	Auckland City	Otago	Hutt/Wairarapa	Total population
Total	117	30	19	28	194
Female	59 (50.4)	15 (50)	8 (42.1)	18 (64.3)	100 (51.5)
Age*					
<17	16 (13.9)	11 (36.7)	0 (0)	4 (14.3)	31 (16.1)
17–40	83 (62.4)	18 (60)	15 (78.9)	17 (60.7)	133 (69.3)
>40	16 (13.9)	1 (3.3)	4 (21.1)	7 (25)	28 (14.6)
Location**					
Ileal	24 (20.9)	8 (26.7)	13 (68.4)	5 (17.9)	50 (26)
Colonic	36 (31.3)	15 (50)	3 (15.8)	5(17.9)	59 (30.7)
Ileocolonic	55 (47.8)	7 (23.3)	3 (15.8)	18 (64.3)	83 (43.2)
Behaviour#					
Inflammatory	68 (61.3)	12 (40)	13 (68.4)	11 (39.3)	104 (55.3)
Stricturing	30 (27)	12 (40)	1 (5.3)	8 (28.6)	51 (27.1)
Penetrating	13 (11.7)	6 (20)	5 (26.3)	9 (32.1)	33 (17.6)
Perianal disease	32 (27.4)	15 (50)	5 (26.3)	10 (35.7)	62 (32)
Disease duration (mean)	8.5 years	8.4 years	8.3 years	11.5 years	8.9 years
ADA indication					
Elevated CDAI	68 (58.1)	19 (63.3)	10 (52.6)	19 (67.9)	116 (59.8)
Extensive small bowel disease	26 (22.2)	6 (20)	5 (26.3)	4 (14.3)	41 (21.1)
Stoma	5 (4.3)	1 (3.3)	0 (0)	3 (10.7)	9 (4.6)
Grandfathered	9 (7.7)	0 (0)	2 (10.5)	2 (7.1)	13 (6.7)
Short gut	9 (7.7)	4 (13.3)	2 (10.5)	0 (0)	15 (7.7)
Duration of disease prior to ADA (mean)**	19.3 months	22.5 months	15.1 months	25.5 months	20.3 months
Duration on ADA (mean)#	1.2 years	1.4 years	1.1 years	1.9 years	1.3 years
Cessation due to ADR	5 (4.3)	2 (6.6)	0 (0)	1 (3.6)	8 (4.1)
Cessation due to loss of response	24 (20.9)	3 (9.9)	4 (21)	2 (7.1)	33 (17.1)
Cessation due to pregnancy	1 (0.8)	0 (0)	2 (10.5)	0 (0)	3 (1.5)
Cessation during the study period	30 (26)	5 (16.5)	6 (31.5)	3 (10.7)	44 (23.7)

*P<0.005, **P<0.01, #P<0.05.

The most common cause for cessation was loss of response followed by adverse drug reactions and voluntary cessation due to pregnancy. Adverse drug reactions leading to cessation included neurological symptoms [paraesthesia (1), pins and needles (1)], tiredness (1), allergic reaction (1), cardiomyopathy (1), neutropaenia (1) and psoriaform reaction (2). These adverse effects occurred over 252.7 years of patient follow-up.

There was no statistically significant difference between centres with regard to continuation rates. Combined adalimumab continuation rates at 6, 12, 24 and 30 months after initial prescription were 92.7%, 87.3%, 76.6% and 67.4%, respectively.

There were no significant differences in adalimumab continuation rates between sexes, disease locations, the presence of perianal disease, disease duration and indication for commencing adalimumab (Figures 2–4). Patients with penetrating disease behaviour were more likely than those with stricturing or inflammatory behaviour to continue on adalimumab (Figure 5, $p<0.005$).

In those patients who were prescribed adalimumab for severe active Crohn's disease with a CDAI>300, there was a significant reduction in mean CDAI from 357 to 110 (Figure 6, $p<0.0001$).

Admission rates in patients prescribed adalimumab were compared before and after the commencement of adalimumab. The mean (range) number of days spent in hospital per patient in the year prior and the year after the initiation of adalimumab was 3.5 (0–38) days and 1.9 (0–67) days, respectively ($p<0.0001$).

Figure 2. Cumulative probability of remaining on adalimumab treatment for Crohn's disease between disease location

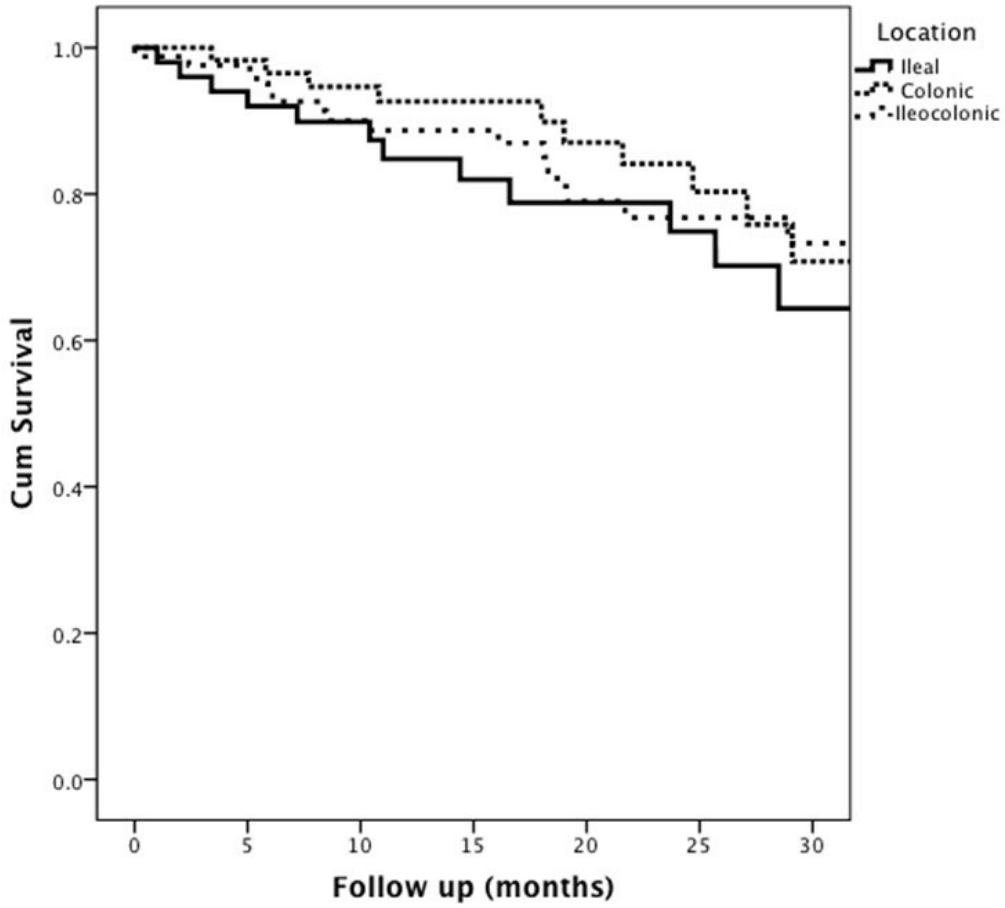


Figure 3. Cumulative probability of remaining on adalimumab treatment for Crohn's disease in those with and without perianal disease

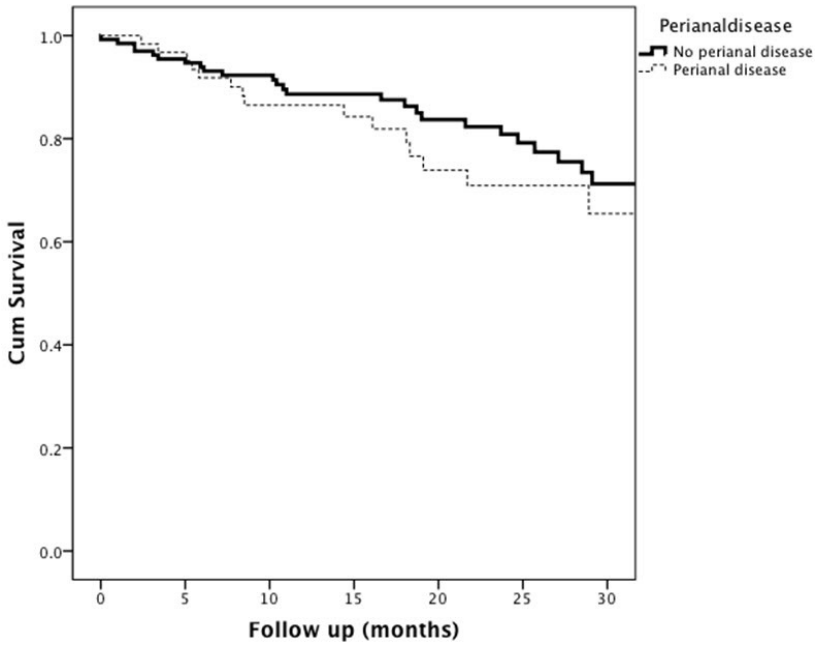


Figure 4. Cumulative probability of remaining on adalimumab treatment for Crohn's disease in those with different indications for adalimumab therapy

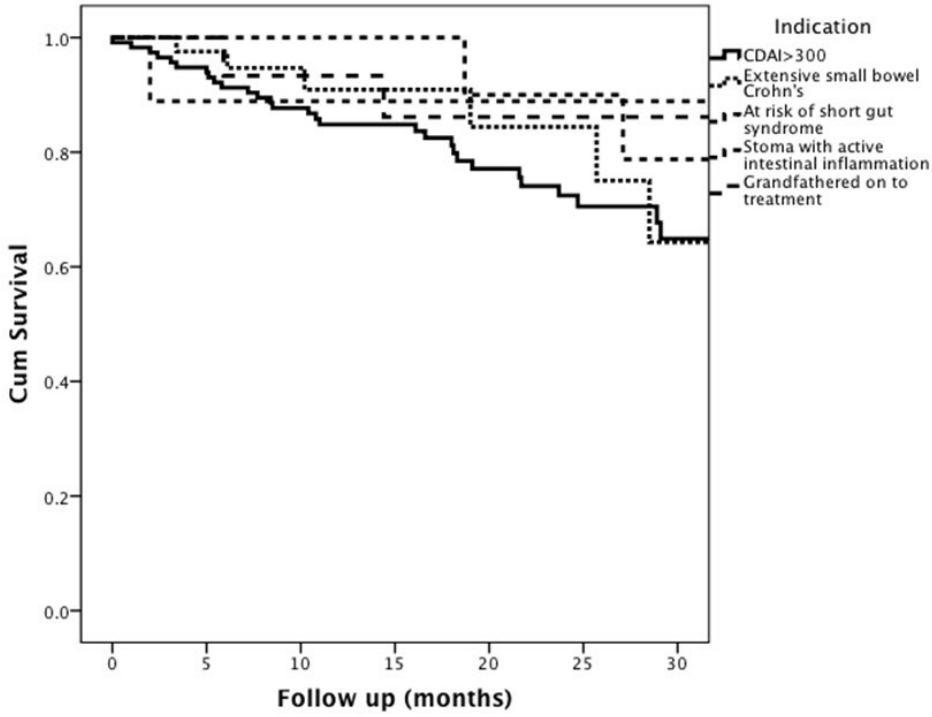


Figure 5. Cumulative probability of remaining on adalimumab treatment for Crohn's disease in those with different disease behaviour

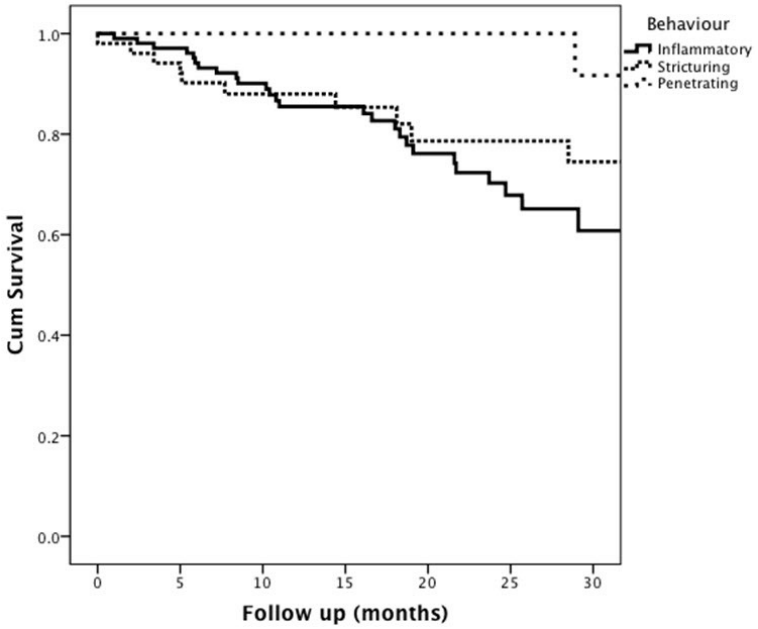
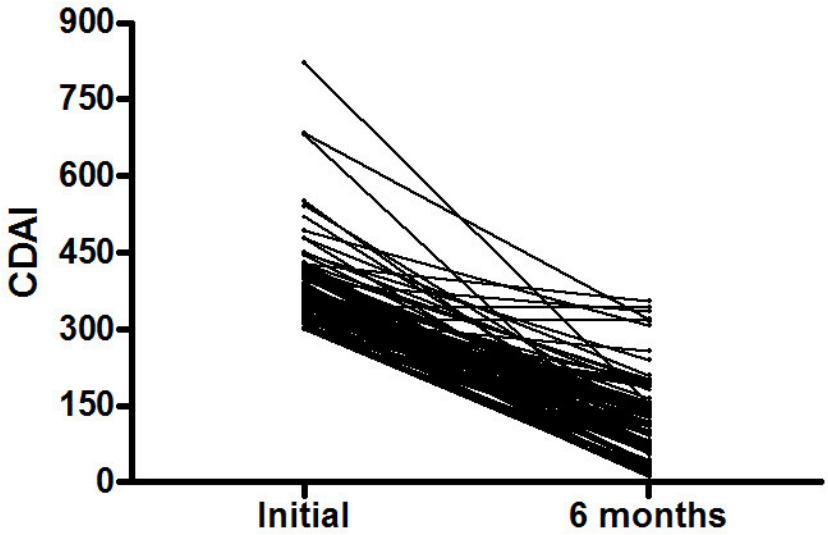


Figure 6. Changes in CDAI in patients with severe active Crohn's disease following initiation of adalimumab



Discussion

Adalimumab has been shown to be effective for the treatment of moderate to severe Crohn's disease in clinical trials.[7,9] However, the experience of efficacy and toxicity of a drug in the real world may differ from clinical trials where many patients are

excluded.[10] Furthermore, some patients who received adalimumab in clinical trials would not be eligible to receive it in some jurisdictions. The present study demonstrates high rates of adalimumab continuation compared with clinical trials. At 30 months after initiation of adalimumab, over three-quarters of all patients remained on the drug. Furthermore, the rates of adverse reactions leading to cessation of the drug were low (4.1%) and a small number of patients voluntarily stopped the drug after finding that they were pregnant (1.5%).

Compared with other published case series of adalimumab continuation rates, the present study suggests high rates of efficacy. Data from a multicentre retrospective study from Madrid of 174 CD patients with luminal disease followed for a mean of 40 weeks showed a response rate of 70% at 6-month follow up. However, 59% of the cohort had previously been treated with infliximab.[11]

A retrospective study from the Mayo Clinic (Rochester) of 118 CD patients revealed a cumulative probability of complete or partial response at one year of 81.3%. However, 96% of the patients had received prior infliximab and almost half were receiving systemic corticosteroids at the commencement of adalimumab. Furthermore, dose escalation to weekly adalimumab was required in 54% of patients by 1 year.[12]

A further retrospective study of 55 Swiss patients revealed a remission rate at 12 months of 44.7%.[13] An early series prospectively describing 38 CD patients using adalimumab from Western Australia demonstrated response and remission rates of 81.8% and 63.6% at 12 weeks.[14]

Unlike the present study, 15 of these patients were secondary non-responders to infliximab. Finally, a Scottish nationwide retrospective study of 98 CD patients receiving adalimumab with 100.5 patient follow-up years revealed a clinical remission rate of 60% at 1 year but dose escalation in 30% by this time.[15]

A large database study using US Medicare data from 2006–2010 revealed that 47% of patients commenced on adalimumab continued on the drug at 26 weeks. Similar rates were found for infliximab continuation with no significant difference between the two drugs with regard to need for surgery or hospitalisation.[16]

The present study differs from other published studies that used retrospective assessments of disease activity, included high rates of infliximab experienced patients and included frequent dose escalations.[14,15,17–20]

The present study is one of the only prospective studies where adalimumab is used as a first line biologic drug. These differences may be the major reasons for the high rate of continuation in the present study compared with other published studies. It is clear from a number of studies that the rate of response and remission to a second biologic drug is less than that for the first biologic drug,[21] an observation that may reflect more severe disease in those who fail a biologic, or increased drug clearance.

The cohort of patients included in this study represents those with the most severe Crohn's disease from the centres that provided data. In addition to the continuation rates being high, there is a significant CDAI reduction in those prescribed adalimumab for active luminal disease. These data were recorded prospectively and show a significant reduction in CDAI from a mean of 357 to 110.

Crohn's disease patients in New Zealand must have a CDAI greater than 300 and have failed imunomodulators to access adalimumab. To remain on adalimumab they must either enter remission (CDAI <150) or have a 100-point reduction in CDAI from baseline. These criteria for commencing adalimumab represent patients with more severe disease than the clinical trials where a CDAI of greater than 220 was required and many patients did not receive immunomodulators.[7,9]

The reduction in CDAI has also translated into a reduction in Crohn's disease related hospitalisation which, in this group of patients, reduced in the year after commencing adalimumab from a mean of 3.5 to 1.9 days in hospital per patient. Reductions in hospitalisation have been seen in randomised controlled trials where patients receiving adalimumab are hospitalised significantly less than those receiving placebo.[22] Long-term effects on hospitalisation and surgery have also been seen in open label studies.[23]

There is heterogeneity between the populations from each of the study centres. Canterbury patients comprise the majority of patients but also represent the largest population with a high prevalence and incidence of Crohn's disease.[2,24] It is known that some patients from the Auckland City region were not recruited, particularly those who are cared for in the private sector. The phenotype of patients receiving adalimumab in each of the centres was also different, with Canterbury and Otago having higher proportions of patients with inflammatory disease behaviour while Auckland City and Hutt Valley/Wairarapa having higher proportions of patients with complicated disease behaviour.

There were no significant differences in adalimumab continuation rates between other disease phenotypic or drug indication characteristics except for higher rates of drug continuation amongst those who had penetrating disease behaviour. This observation is somewhat surprising given that patients with penetrating disease have a higher risk of requiring surgery and failing medical therapy than patients with inflammatory disease.[25,26] One explanation for this observation may be that these patients were more likely to have already undergone surgery prior to commencing adalimumab, or that they were more likely to have been prescribed adalimumab for non-CDAI indications such as active disease in a patient with a stoma, or active disease in those with a high risk of developing short gut syndrome.

The adverse events noted in this study are consistent with the published literature. Interestingly infections did not comprise a significant number of adverse reactions leading to adalimumab cessation. Other centres in Australasia have also reported relatively low rates of infections in patients receiving biological drugs[27] although one must always be vigilant for infections in this group of patients.[28]

In summary, we report high continuation rates of adalimumab therapy in a large prospectively recruited cohort of CD patients. Unlike other studies, these patients received adalimumab as a first line biologic drug for CD after failing standard immunomodulator therapy. These high rates of continuation are likely to reflect the use of adalimumab as the first biologic drug in these patients. Furthermore, the prospective collection of data confirms the efficacy of adalimumab for severe Crohn's disease and demonstrates a significant impact on short-term hospitalisation. No new or unexpected adverse events have been identified.

Competing interests: Nil.

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The impact of oral antiviral therapy on long-term survival of hepatitis B surface antigen-positive patients on haemodialysis

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Abstract

Aims Hepatitis B (HBV) is an important cause of morbidity and mortality in end-stage renal disease patients. The effect of oral antiviral therapy on survival in this population is not known. We evaluated the impact of oral antivirals on survival of HBV-infected haemodialysis patients.

Method This retrospective study included 52 HBsAg-positive haemodialysis patients and 156 non-infected haemodialysis controls. Criteria adopted for starting lamivudine were the 2001 American Association for the Study of Liver Diseases guidelines. Lamivudine was commenced in 21 (40.4%) patients, with median treatment duration of 58 months. The primary endpoint was transplant-free survival.

Results Survival of HBsAg-positive patients was equivalent to that of age- and sex-matched HBsAg-negative controls (39.1% vs 33.2% at 10 years, respectively; P=0.12). In treated patients, complete viral suppression was associated with improved survival (serial HBV DNA $\leq$2 $\log_{10}$ IU/mL, 90.9% vs HBV DNA >2 $\log_{10}$ IU/mL on at least one occasion, 74.1% at 5 years; P=0.049). Out of 20 deaths, three were liver-related.

Conclusion Haemodialysis patients with chronic HBV, when given oral antiviral therapy if indicated, had equivalent long-term survival to that of non-infected controls. In those with active viral hepatitis, viral suppression was associated with reduced liver-related mortality.

Hepatitis B (HBV) is an important cause of morbidity and mortality in patients with end-stage renal disease (ESRD). In recent decades, its prevalence has fallen due to various preventative measures, including infection control, universal screening of blood donors, HBV vaccination, and availability of recombinant erythropoietin.[1,2] However, HBV remains a major problem in the Asia-Pacific, where its prevalence in dialysis patients directly reflects that of the local population[3] and can be up to 15%.[4]

The impact of HBV on survival of patients on dialysis remains controversial. The data on survival of hepatitis B surface antigen (HBsAg)-positive dialysis patients are mostly historical. One study showed an increase in mortality in haemodialysis (HD) patients with HBV compared to those without,[5] but two other studies showed no survival difference.[6,7]

Prior to the era of oral nucleos(t)ide analogues (NAs), antiviral therapy in ESRD patients was challenging and limited to interferon, which remains poorly tolerated in dialysis patients. Conversely, experience with NAs in this population has found them to be better tolerated. Lamivudine was the first NA available and has proven efficacy

in patients with normal renal function, achieving profound viral suppression, normalisation of aminotransferases, and prevention of fibrosis progression.[8]

Due to its poor resistance profile, it has been superseded by newer generations of NAs with greater potency and high genetic barrier to resistance, such as entecavir and tenofovir. In the dialysis population, data on NAs are limited to case series reporting on virologic response rates.[9,10] There are no published data on the effect of NAs on survival of dialysis patients with HBV. Although NAs are used to treat dialysis patients, any potential benefit in outcomes has been inferred from studies on patients with normal renal function.

We report on the long-term survival of HD patients with chronic HBV treated at Auckland City Hospital and assess the impact of NA therapy in this population.

Method

Study design—Between June 2000 and June 2008, ESRD patients on maintenance HD with chronic HBV (HBsAg-positive ≥6 months) were included in this retrospective study. Patients with hepatitis C or delta co-infection were excluded. Patients were followed up until transplant or end of study, whichever occurred first.

The following were measured at baseline and 3- to 6-monthly—liver enzymes, HBsAg, hepatitis B e antigen (HBeAg), hepatitis B e antibody, and quantitative HBV DNA.

Liver ultrasonography was performed at baseline. Liver biopsy was used to stage the level of fibrosis where clinically indicated. Staging was according to the Metavir scoring system (F0–F4). Advanced liver disease was defined as histological F3–F4 or clinical evidence of cirrhosis. The presence of thrombocytopaenia, hypoalbuminaemia, increased prothrombin time, or endoscopic/radiographic portal hypertension was accepted as evidence of cirrhosis. Liver elastography was not routinely performed and thus has not been included in this study.

Lamivudine was commenced according to the 2001 American Association for the Study of Liver Diseases guidelines.[11] Criteria for initiation were: (i) HBeAg-positive or HBV DNA >20,000 IU/mL; with (ii) elevated alanine aminotransferase (ALT) or advanced liver disease. Lamivudine dosage was adjusted for creatinine clearance as per manufacturer's recommendations—first dose 35 mg, then 10 mg once daily.

Virologic breakthrough was defined as an increase in HBV DNA by ≥1 $\log_{10}$ IU/mL above nadir, or, reappearance of HBV DNA after having been undetectable. Genotypic resistance was confirmed by direct sequencing of the polymerase gene. In patients with lamivudine resistance, those without cirrhosis were switched from lamivudine to adefovir and those with cirrhosis had adefovir added to lamivudine. Adefovir dosage was 10 mg once weekly post-dialysis, as per manufacturer's recommendations.

Primary endpoint—The primary endpoint was transplant-free survival, taken from start of HD until transplant, death or end of study, whichever occurred first.

Statistics—Categorical data were analysed using the Fisher's exact test. Patient survival was analysed according to the Kaplan-Meier method and compared using the log-rank test. A univariate Cox proportional hazards model was used to identify potential predictors of mortality. Statistical significance levels were determined by two-tailed tests (P <0.05).

Results

A total of 52 HBsAg-positive HD patients met criteria for inclusion into the study. All patients had chronic HBV diagnosed prior to starting HD. There were 36 males and 16 females, with a median age of 51 years.

The most common cause of kidney disease was glomerulonephritis (GN) in 20 patients; 6 were HBV-related. All patients started HD between 1995 and 2008.

Median follow up was 5.4 (interquartile range 2.7–9.7) years. By the end of the study, 13 patients had received a renal transplant.

Patient survival of HBsAg-positive vs HBsAg-negative HD patients—The survival of 52 HBsAg-positive HD patients was compared with an age-, sex-, and ethnically matched non-infected control group of 156 ESRD patients started on HD in the same period. Baseline characteristics of the two groups are shown in Table 1.

Table 1. Baseline characteristics of 52 HBsAg-positive and 156 matched HBsAg-negative patients

Characteristic	HBsAg-positive	HBsAg-negative	*P* value*
Age, median (interquartile range) – yrs	51 (43–59)	52 (45–59)	–
Male sex – no. (%)	36 (69.2%)	108 (69.2%)	–
Ethnicity – no. (%)			
Māori	20 (38.5%)	60 (38.5%)	–
Pacific people	21 (40.4%)	63 (40.4%)	–
European	6 (11.5%)	18 (11.5%)	–
Asian	5 (9.6%)	15 (9.6%)	–
Underlying kidney disease – no. (%)			
Glomerulonephritis	20 (38.5%)	29 (18.6%)	<0.01
Diabetes	19 (36.5%)	59 (37.8%)	1.00
Hypertensive	5 (9.6%)	17 (10.9%)	1.00
Reflux	3 (5.8%)	13 (8.3%)	0.77
Idiopathic	3 (5.8%)	19 (12.2%)	0.30
Other	2 (3.8%)	19 (12.2%)	0.11

* Calculated for non-matched parameters

There was a higher proportion of GN in the HBsAg-positive group than in the HBsAg-negative group (38.5% vs 18.6%, respectively; P <0.01).

There was no difference in transplant-free survival between HBsAg-positive patients and non-infected controls (77.0% vs 63.6% at 5 years and 39.1% vs 33.2% at 10 years, respectively; P=0.12; Figure 1).

The transplantation rate during follow-up was similar between the 2 groups—13 (25%) patients were transplanted in the HBsAg-positive group and 35 (22%) patients in the non-infected group.

Baseline predictors of transplant-free survival in HBsAg-positive HD patients— Liver biopsy was performed in 38 (73.1%) patients—29 had F0-F2 fibrosis; 9 had F3–F4. One other patient had radiological cirrhosis with portal hypertension. Thirteen patients did not have clinical, biochemical, or radiological evidence of advanced liver disease and did not have a liver biopsy.

The effect of liver fibrosis on survival was examined by comparing 29 patients with histological mild (F0–F2) fibrosis vs 10 patients with advanced fibrosis (histological F3–F4 or clinical cirrhosis).

Cumulative survival was somewhat lower in patients with advanced fibrosis than those with mild fibrosis at 5 years (68.6% vs 81.9%, respectively), although this was not statistically significant (P=0.46; Figure 2).

Figure 1. Transplant-free survival of 52 HBsAg-positive vs 156 HBsAg-negative HD patients

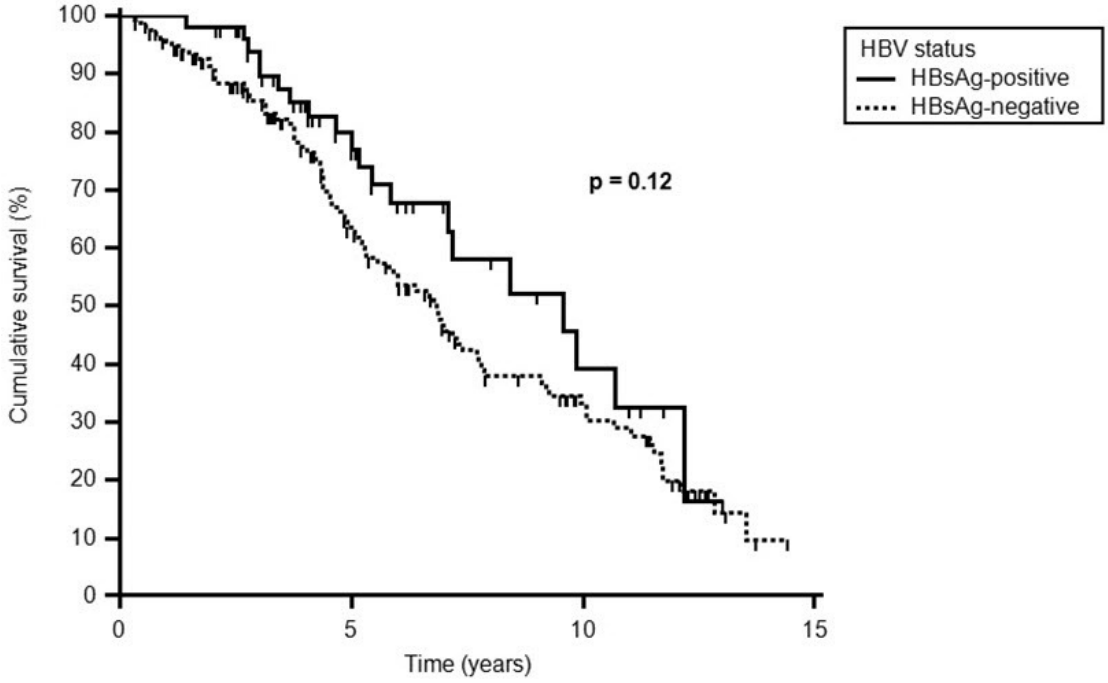
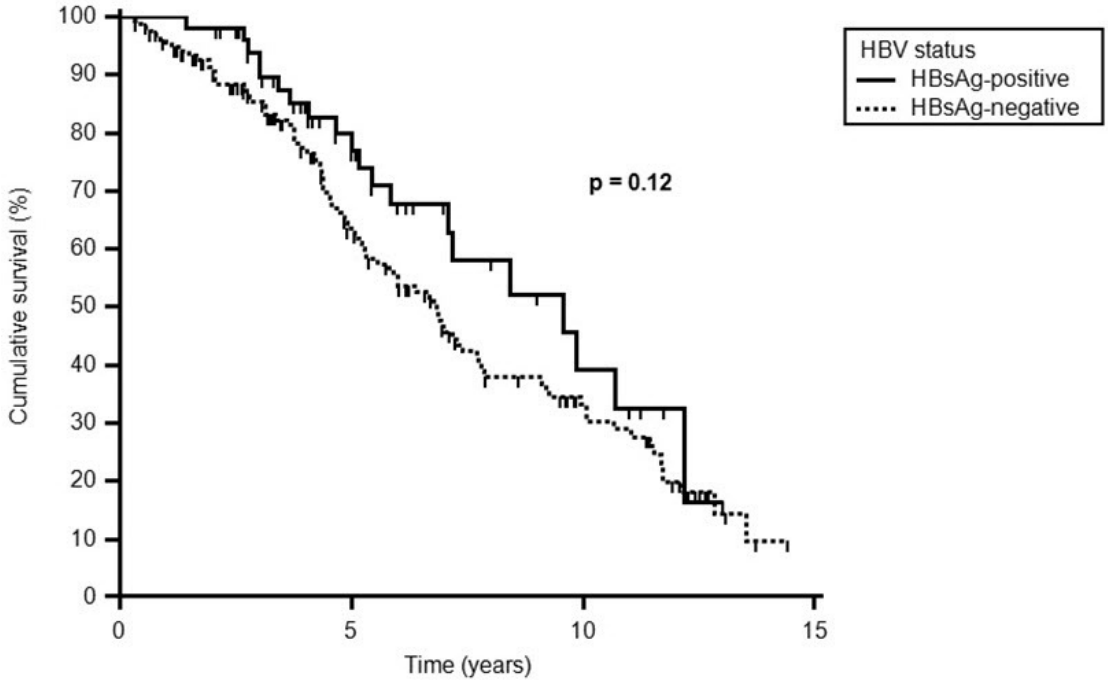


Figure 2. Transplant-free survival of 29 HBsAg-positive HD patients with mild (F0-F2) fibrosis vs 10 HBsAg-positive HD patients with advanced (F3–F4) fibrosis/clinical cirrhosis



A univariate Cox proportional hazards analysis was performed to identify baseline variables that may predict survival of HBsAg-positive patients (Table 2). None of the variables, including baseline HBV DNA, were significant.

Table 2. Univariate Cox proportional hazards analysis for transplant-free survival of 52 HBsAg-positive HD patients

Parameter	Hazard ratio	95% CI	*P* value
Age	1.043	0.996–1.092	0.06
Sex (Male=0, Female=1)	0.738	0.283–1.927	0.54
Ethnicity			
Māori=0	Ref		
Pacific people=1	0.474	0.096–2.339	0.36
European=1	0.504	0.106–2.390	0.39
Asian=1	0.549	0.048–6.227	0.63
Elevated baseline ALT			
(No=0, Yes=1)	1.159	0.442–3.038	0.76
HBeAg positive (No=0, Yes=1)	0.735	0.239–2.265	0.59
Baseline HBV DNA (IU/mL)			
Undetectable – 9.9×10^{1}=0	Ref		
1.0×10^{2} – 9.9×10^{3}=1	1.489	0.457–4.852	0.51
$\geq1.0\times10^{4}$=1	1.347	0.448–4.052	0.60
Advanced liver disease			
(No=0, Yes=1)	0.735	0.262–2.063	0.56
Met criteria for antiviral therapy			
(No=0, Yes=1)	1.680	0.635–4.444	0.30

Antiviral therapy—All patients were treatment-naïve. On study entry, 43 (82.7%) patients were HBeAg-negative; 34 (65.4%) had normal ALT. During follow-up, 21 (40.4%) patients met criteria for antiviral treatment and 31 (59.6%) did not. The allocation of antiviral therapy based on treatment criteria did not predict survival (Table 2), suggesting that patients who did not meet criteria for antivirals were not at a survival disadvantage.

In the treated group, median duration of lamivudine monotherapy was 58.2 (interquartile range 37.3–80.8) months. Lamivudine resistance developed in five patients—two were switched to adefovir; three were changed to combination lamivudine and adefovir.

Resistance rates were 9.5% and 14.3% at 1 and 2 years of treatment, respectively. There were no cases of HBeAg seroconversion and no HBsAg loss was observed. Lamivudine was withdrawn in only one patient, after 38.8 months of treatment. This patient had HBeAg-negative active hepatitis and stage 0 fibrosis pre-treatment. There was no virologic rebound off treatment up to end of follow-up at 122.4 months post-cessation.

HBV DNA levels of treated patients are shown in Table 3. At the end of the study, there were three patients with high viral load (4-6 $\log_{10}$ IU/mL). All three had an initial virologic response and tested negative for lamivudine resistance. On reviewing their clinical notes, compliance was documented to be erratic.

Table 3. HBV DNA of 21 HBsAg-positive patients treated with NAs

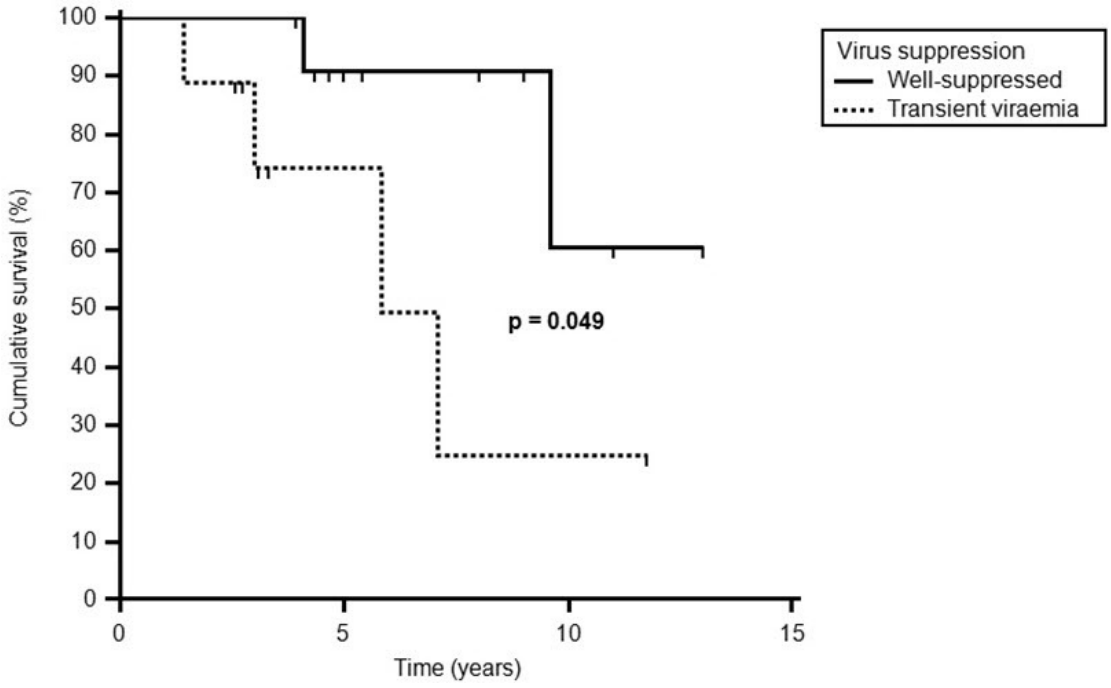
HBV DNA (IU/mL)	Baseline	End of study
Undetected (<12)	0 (0%)	10 (47.6%)
$1.2 – 9.9\times10^{1}$	0 (0%)	2 (9.5%)*
$1.0\times10^{2} – 9.9\times10^{3}$	2 (9.5%)	6 (28.6%)
$1.0\times10^{4} – 9.9\times10^{6}$	14 (66.7%)	3 (14.3%)
$\geq1.0\times10^{7}$	5 (23.8%)	0 (0%)

* One patient withdrawn from antiviral treatment

On-treatment viral suppression was examined to determine its impact on survival. Following initial virologic response, there were 12 patients with on-treatment viral loads persistently $\leq$2 $\log_{10}$ IU/mL ("complete" suppression) and nine patients with at least one on-treatment viral load >2 $\log_{10}$ IU/mL ("incomplete" suppression).

Survival of treated patients with complete suppression was higher than those with incomplete suppression (90.9% vs 74.1% at 5 years and 60.6% vs 24.7% at 10 years, respectively; *P*=0.049; Figure 3).

Figure 3. Transplant-free survival of 12 HBsAg-positive HD patients well suppressed on treatment (HBV DNA persistently $\leq$2 $\log_{10}$ IU/mL) vs 9 HBsAg-positive HD patients with transient viraemia on treatment (HBV DNA >2 $\log_{10}$ IU/mL on at least one occasion)



Causes of death—At the end of the study, 20 patients had died. In the untreated group (n=31), there were 14 deaths. Causes of death were sepsis (five cases), dialysis withdrawal (four cases), cardiac (two cases), non-hepatic malignancy (two cases) and hepatocellular carcinoma (HCC; one case).

In the treated group (n=21), there were six deaths. In patients with complete suppression, two deaths occurred due to non-hepatic causes (one dialysis withdrawal, one sepsis). In patients with incomplete suppression, there were two liver-related deaths (HCC, spontaneous bacterial peritonitis) and two deaths due to dialysis withdrawal.

Discussion

This study examined the long-term survival of HD patients with chronic HBV, treated with NAs when indicated as per general guidelines, and found the survival of HBsAg-positive HD patients to be equivalent to non-infected HD patients. In treated patients, those with continuous viral suppression had improved survival compared to those with transient viraemia.

Reduced survival in patients with inadequate suppression was mainly due to a difference in liver-related mortality. In treated patients with incomplete suppression, half of the deaths were liver-related, compared to no liver-related deaths in treated patients with complete suppression. Additionally, patients who did not require antivirals (those with inactive hepatitis) also had a low liver-related mortality rate of 7%. These findings support the importance of effective viral suppression in patients with active viral hepatitis to prevent liver-related complications.

Liver cirrhosis in dialysis patients carries an increased mortality risk of 35% compared to non-cirrhotic patients.[12] We did not find a significant difference in survival between patients with mild and advanced fibrosis. Furthermore, no patient with cirrhosis died from liver failure. These findings support the importance of antiviral suppression in reducing risk of hepatic decompensation and preserving synthetic function in patients with advanced fibrosis.[13,14]

HCC remains an important cause of death in dialysis patients with HBV. The risk of HCC is strongly correlated with HBV DNA.[15] Antiviral therapy is associated with reduced risk of HCC and patients who maintain undetectable HBV DNA levels have a lower HCC rate than those with virologic non-response or breakthrough. [16] However, even in patients who achieve complete viral suppression, there is still a small risk of developing HCC. There were two deaths from HCC in our cohort – one in a patient with incomplete viral suppression and another with inactive viral hepatitis.

To ensure early detection, dialysis patients with chronic HBV should be considered for HCC surveillance with 6-monthly alpha-fetoprotein and liver ultrasound. If detected early, most HCCs will be amenable to curative resection or ablation. In selected patients, combined liver-kidney transplantation may be considered.

In this study, antiviral therapy was initiated in patients with active viral replication and biochemical inflammation, except in those with advanced liver disease where active replication alone warranted treatment. These criteria for antiviral treatment have not been specifically validated in dialysis patients. We observed similar survival in patients who received antiviral therapy and those who did not have an indication,

which suggests that current treatment guidelines can be safely applied to HD patients without disadvantaging those that do not meet criteria.

There are some limitations to our study. This is a retrospective single centre study with a small number of patients. This limits the power of the study and increases the risk of a type II error (i.e. not rejecting the null hypothesis when there is a true difference). Both positive and negative findings have to be interpreted with caution, especially in the case of the sub-analyses where the sample size is even more limited.

Lamivudine is the oldest analogue available and has been replaced by newer analogues, like entecavir and tenofovir, as first-line monotherapy. In this study, the aim was to determine long-term survival and so it was important to obtain data with sufficiently long follow-up but consequently, the older analogues were the only antivirals available to patients from that era. Notwithstanding this, the benefits of viral suppression were evident in this population, even with an older generation drug.

In conclusion, HD patients with chronic HBV, when treated with oral antiviral therapy if indicated, had equivalent long-term survival to that of non-infected HD patients. There was no survival disadvantage in those that did not meet treatment criteria. Hence, NAs should only be started in the presence of active viral hepatitis. In treated patients, continuous viral suppression is a strong predictor of survival, with transient viraemia associated with poorer long-term outcomes due to an increase in liver-related mortality.

Regular HBV DNA monitoring for those on treatment and emphasis on compliance are crucial. There remains a small risk of HCC. Ongoing surveillance remains an important aspect of management, particularly in patients considered for transplantation.

Competing interests: Nil.

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Exploring the potential for the drift of secondhand smoke from outdoor to indoor dining areas of restaurants in New Zealand

Frederieke S van der Deen, Amber L Pearson, Darko Petrović, Lucie Collinson

Abstract

Aim To examine levels of fine particulates of secondhand smoke (SHS) in outdoor dining/smoking areas and the adjacent indoor dining areas of restaurants to assess possible drift via open windows/doors.

Method We measured fine particulates ($PM_{2.5}$ mcg/m^3) with real-time aerosol monitors as a marker of SHS inside where smoking is banned and outside dining areas (which permit smoking) of eight restaurants in Wellington. We also collected related background data (e.g. number of smokers, time windows/doors were open, etc.).

Results Highest overall mean $PM_{2.5}$ levels were observed in the outdoor dining areas (38 µg/m^3), followed by the adjacent indoor areas (34 mcg/m^3), the outdoor ambient air (22 mcg/m^3) and the indoor areas at the back of the restaurant (21 mcg/m^3). We found significantly higher $PM_{2.5}$ levels indoor near the entrance compared to indoor near the back of the restaurant ($p=0.006$) and in the outdoor smoking area compared to outdoor ambient levels ($p<0.001$). Importantly, we did not detect a significant difference in mean $PM_{2.5}$ levels in outdoor smoking areas and adjacent indoor areas ($p=0.149$).

Conclusion Similar $PM_{2.5}$ concentrations in the outdoor and adjacent indoor dining areas of restaurants might indicate SHS drifting through open doors/windows. This may especially be a problem when smoking patronage is high, the outdoor dining area is enclosed, and during peak summer season when restaurants generally have all doors and windows opened. Tighter restrictions around outdoor smoking at restaurants, to protect the health of both patrons and staff members, may be needed.

New Zealand has made significant progress over recent decades with reducing air pollution from tobacco smoke, especially in indoor environments[1] and the Government recently announced the ambition to become a 'smoke-free' nation by 2025 (frequently defined as a smoking prevalence below 5%).[2] Nevertheless, a number of New Zealand studies on urban pubs[1,3,4] and rural pubs[5] have found evidence for secondhand smoke (SHS) drift from outdoor smoking areas to indoor areas (via open windows and doors).

Studies in other countries have found that the particulate[6] and nicotine[7] air quality of indoor areas adjacent to outdoor smoking areas was compromised. Similar levels of SHS have been detected in hallways and near outdoor main entrances where smoking is permitted,[8] such as entrances to office buildings.[9] Likewise, a study measuring airborne nicotine concentrations to monitor SHS in different locations of a hospital, before and after a smoking ban, found the smallest reduction at the hospital main entrance and hallway when compared with all other areas.[10]

Drifting SHS can be a public health concern for both patrons and workers in settings where outdoor smoking is permitted, particularly when levels of smoking are high. Indeed, a study from the United States indicated significant increases in markers for tobacco smoke absorption by non-smokers (salivary cotinine and a urinary marker [NNAL]) following outdoor SHS exposure in the outdoor areas of bar and restaurant settings.[11] This is of concern as exposure to SHS has been linked to a number of health consequences such as lung cancer, coronary heart disease, sudden infant death syndrome and stroke.[12]

A recent review of studies on the SHS drift in outdoor areas denotes that most studies reported similar mean $PM_{2.5}$ concentrations between outdoor areas where smoking was permitted and the nearest smokefree indoor areas.[13] Measured levels of SHS were higher where smoker density was high, smokers were in the vicinity of the area being measured, and where the outdoor smoking area was more enclosed.

To date, there has been no investigation into the issue of possible SHS drift in restaurant settings in New Zealand, even though it has been found to be a problem in New Zealand pubs[1,3,5,14] or in restaurants in other countries where indoor smoking is banned as well.[15] Most international studies have looked into this potential drift issue in a number of hospitality settings (e.g. night bars, pubs and restaurants) together.

Different hospitality venues might, however, have different background determinants influencing measured $PM_{2.5}$ concentrations such as cooking smoke in venues where dinner is served.[13] Moreover, we believe it is important to study the potential for SHS drift in restaurant settings separately as a higher number of children might be exposed (as compared to pubs or night bars) and the potential for longer duration of exposure (e.g. throughout a meal, rather than while having a beverage).

This study therefore aimed to examine the levels of fine particulates ($PM_{2.5}$) of SHS in outdoor smoking areas and in the adjacent indoor areas to assess possible drift via open windows and doors in a selected sample of restaurants in the urban centre of New Zealand's capital, Wellington.

In this study we aimed to:

(i) Evaluate evidence of possible drift of fine particulates of SHS from: (a) outside selected restaurants (at the "outdoor" dining area), when compared to (b) the nearest tables indoors to the outdoor area; and (c) as far indoors as possible from the outdoor dining area; and

(ii) Collect additional background data (e.g. presence of potential other sources of fine particulates from cooking and lit candles, number of smokers in the outdoor dining/smoking area, time windows/doors were open, wind speed, distance of indoor and outdoor seat to connecting doors/windows, and the extent of enclosure of the outside dining/smoking area (e.g. roofing, walls etc.).

Methods

Restaurant selection—We took a purposeful sample of eight restaurants in different areas of the Wellington urban core (e.g. Courtenay place area, Cuba street area, Central Business District and along the waterfront). Restaurants were selected if they were: (i) located in the Wellington urban core; (ii) had outdoor tables within five metres of door(s) or window(s) that connected to the restaurant interior;

and (iii) were relatively popular among smokers (at least one person smoking upon onset of data collection period). All restaurants were located on streets with car and bus traffic. Traffic levels may have varied slightly. However, restaurants were purposefully selected in the downtown urban area to minimise this variation and ambient measurements were taken while walking between venues.

Study period—The study was conducted between February and April (late summer) in 2013 on Wednesday and Thursday evenings between 1800 and 2200h.

Sampling locations—Data were obtained from three different positions inside and outside restaurants simultaneously: (i) the outdoor dining areas (in the most central table available) where smoking was permitted; (ii) within the restaurant (at the table closest to the window or doors connecting with the outdoor dining area); and in a subset of restaurants (n=4) (iii) as far as possible within the restaurant away from the window(s) or door(s). The latter measurement was achieved (where feasible) by standing at the bar or most distant table from the window(s) or door(s) connecting the indoor area to the outdoor smoking area. A minimum of 10 minutes of sampling in each restaurant at each position was established, with a goal of thirty minutes of sampling per restaurant at the indoor and outdoor dining area. A team of two researchers stayed in the outdoor area and another such team spent time in both indoor locations (where feasible). Nevertheless, to avoid affecting occupants' behaviour, the researchers behaved discretely and as typical customers (i.e. consumed drinks and meals).

Air quality monitors—The use of the two air quality monitors followed a protocol modified from and developed for a global air quality monitoring project[16] and which has been used in other studies measuring exposure to SHS.[1,3–5] In the sampling, fine particulates were measured ($PM_{2.5}$) using portable real-time airborne particle monitors (i.e. the TSI *SidePak* AM510 Personal Aerosol Monitor, TSI Inc, St Paul, USA). The air monitors were carried hidden in a bag on the shoulder of one of the observers in each two-person team to sample the ambient air close to the breathing zone. During meals, the bags containing the air monitor were placed on the table or nearest empty seat and faced upward so as to simulate a realistic restaurant experience. A recent review of studies on the SHS drift in outdoor areas denotes that most studies have used fine smoking particulates measurements ($PM_{2.5}$) as an indicator of SHS.[13]

A calibration factor (0.32) for SHS based on empirical validation studies with the *SidePak* monitor was applied (i.e. adjusted in each monitor's internal settings).[17] The monitors were zero-calibrated routinely and internal components were set up as directed by the manufacturer prior to each day of data collection. Monitors were fitted with a 2.5 mcg impactor, had air flow rates of 1.7 L/min and had logging periods of 60 seconds. A length of Tygon™ tubing was attached to the inlet of each monitor, with the other end left protruding slightly outside of the shoulder carry bag. Air quality data were then downloaded from the monitor to a computer, using TrakPro software (Shoreview, MN, USA).

Other data collected—The number of cigarettes smoked in the outdoor dining area was noted using a 30-second scan every 10-minutes during air quality data collection and reported as total number of patrons seen smoking outside per venue throughout data collection. Additional observational data were collected on the extent to which the outdoor dining area was 'enclosed' (walls and roofing), wind speed (using a pocket air speed and temperature meter), distance in metres to the nearest connecting window/doors to the indoor dining area (using a laser distance meter), the percentage of time that the window/doors were open, and the number of tables in the indoor and outdoor dining area. In all the indoor settings, non-cigarette sources of fine particulates (e.g. burning candles, smoke from cooking areas) were noted. These data were discretely recorded on paper before being compiled in Microsoft Excel 2010 and used as background information when interpreting our results.

Analyses—Observational data about the restaurant facilities and other potential sources of $PM_{2.5}$ were analysed in Microsoft Excel and frequencies and percentages for these features were reported. Air monitor data were exported from TrakPro software into Microsoft Excel for compilation. Next, data were exported for analyses in Stata v.12 (College Station, TX, USA). Descriptive statistics for $PM_{2.5}$ measurements for indoor near entrance, indoor near back of restaurant, and outdoor locations were calculated for each venue and overall. We also ran paired t-tests to test for significant differences between mean $PM_{2.5}$ measurements between the outdoor versus indoor near the entrance, where we had measurements taken at identical time points. We conducted ANOVAs to test for significant differences between the indoor location near the entrance and the indoor area at the back of the restaurant and between the outdoor dining area versus outdoor ambient air.

Ethical approval—We obtained approval through the University of Otago (Category B ethics approval process) and were cognisant of the ethical issues involved in this type of research.[18]

Results

Background information—Of the eight restaurants included in this study, we observed the presence of non-cigarette sources of fine particulates (e.g. burning candles, smoke from cooking area) in the indoor dining areas of six venues (see Table 1).

Across all restaurants, we observed an average of nine patrons smoking in the outdoor dining area per venue throughout the air pollution sampling. There were on average 14 tables (range: 6–22) available in the indoor areas and 10 tables (range: 3–25) in the outdoor areas.

The majority of outdoor dining areas (67%) were enclosed by either roofing and/or walls (with an average of three sides enclosed). Five of the selected restaurants had doors connecting the indoor and outdoor areas of the restaurants open 100% of the time.

Three restaurants only had the doors open for movement of patrons and staff between the inside and outside of the restaurant and were opened between 10–50% of the time. None of the selected venues had windows opened between the indoor and outdoor areas. We also measured the wind speed at outdoor areas for all venues which ranged from calm to a light breeze (0.0–10.0 km/h).

Table 1. Observational data by restaurant

Item	Restaurant							
	I	II	III	IV	V	VI	VII	VIII
No. of tables in the outdoor area	3	5	25	6	21	9	4	15
Total no. of patrons seen smoking in outdoor dining/smoking area during data collection	5	1	14	8	6	23	3	11
Distance in metres from indoor area to entrance to outdoor dining/smoking area	1.78	2.03	0.96	0.05	2.00	3.50	4.80	1.30
% of time connecting door(s) was/were open (and number of doors)	80 (1)	100 (1)	100 (4)	100 (1)	50 (1)	100 (1)	10 (1)	20 (1)
% of time connecting window(s) was/were open	0	0	0	0	0	0	0	0
% of outdoor dining/smoking area 'enclosed'	50%	0%	80%	70%	50%	90%	20%	0%
Wind speed (km/h)	0.30	2.80	2.60	0.30	0.00	0.00	0.00	0.00
Burning candles observed in the indoor dining area (yes/no)	yes	no	yes	no	yes	yes	no	yes
Cooking smoke observed in the indoor dining area (yes/no)	no	yes	yes	no	yes	no	no	no

$PM_{2.5}$ measurements—We collected fine particulate ($PM_{2.5}$) measurements at eight restaurants in the indoor and outdoor dining area for a total of 393 minutes (an average of 49 minutes per restaurant). We also collected $PM_{2.5}$ measurements indoors in the restaurants as far away as possible from the doors/windows connecting the indoor with the outdoor area for a total of 67 minutes and ambient outdoor measurements for a total of 72 minutes.

The results indicate a wide range of $PM_{2.5}$ levels in the different restaurants. When examining results by each venue, very similar $PM_{2.5}$ levels were observed between the

outdoor and adjacent indoor dining area of venue III, where the mean $PM_{2.5}$ level in the outdoor dining area was 38 mcg/m^3, and in the indoor area 41 mcg/m^3 (see Table 2).

Table 2. Results of air quality monitoring (fine particulates, $PM_{2.5}$) in different areas of restaurants and ambient air measurements in Wellington

Restaurant	Minutes measured (n)	Mean $PM_{2.5}$ (mcg/m^3)	Min $PM_{2.5}$ (mcg/m^3)	Max $PM_{2.5}$ (mcg/m^3)
Outdoor dining/smoking areas				
I	79	35	24	64
II	31	37	23	178
III	44	38	10	264
IV	71	32	18	276
V	82	28	8	134
VI	52	74	13	321
VII	13	41	13	170
VIII	21	20	10	59
Mean	49	38	15	183
Indoor dining areas (at the closest table possible to the door/window connecting to the outdoor dining area)				
I	79	29	18	55
II	31	46	24	106
III	44	41	12	165
IV	71	17	7	43
V	82	56	5	208
VI	52	26	5	154
VII	13	12	6	20
VIII	21	15	11	23
Mean	49	34*	11	97
Indoor dining area (as far away as possible from the door/window connecting to the outdoor dining area)				
III	19	24	13	37
V	8	51	11	115
VII	30	14	8	27
VIII	10	18	8	40
Mean	17	21†	10	55
Outdoor ambient air				
I & II	10	33	25	42
II & III	30	21	17	43
VII & VIII	32	19	13	108
Mean	24	22‡	18	64

* We did not detect a significant difference in mean $PM_{2.5}$ levels between the outdoor dining/smoking areas and the adjacent indoor areas (p=0.149).

† We found significantly higher $PM_{2.5}$ levels at indoor areas near the entrance compared to indoor areas near the back of the restaurant (p=0.006).

‡ We found significantly higher $PM_{2.5}$ levels in the outdoor areas of restaurants where smoking was permitted compared to outdoor ambient levels while walking between venues (p <0.001).

Although we observed lit candles and cooking smoke in the indoor area of this venue, the mean fine particulate measurement at the back of the restaurant (24 mcg/m^3), as

far away as possible from tobacco sources, was considerably lower. The highest mean (74 mcg/m^3) and maximum $PM_{2.5}$ concentration (321 mcg/m^3) were observed in the outdoor dining/smoking area of restaurant VI, with a total of 23 patrons seen smoking throughout the data collection period (thus not at a single time point, but total during the course of the meal). The outdoor dining area of this venue was almost entirely enclosed. Although we did observe lit candles in the indoor dining area of this venue, the average indoor dining area measurement was considerably lower (26 mcg/m^3), possibly due to a larger distance from the indoor dining area seat to the outdoor tobacco source and only one small door opened between the indoor and outdoor area.

We noticed a wide range in the values of the outdoor $PM_{2.5}$ measurements of the three venues where the highest total number of smokers were counted throughout data collection (restaurant III: 38 mcg/m^3 (14 smokers), restaurant VI: 74 mcg/m^3 (23 smokers), and restaurant VIII: 20 mcg/m^3 (11 smokers). The same pattern was found in the fine particulate levels in the adjacent indoor dining areas near the connecting doors of restaurant III: 41 mcg/m^3, restaurant VI: 26 mcg/m^3, and restaurant VIII: 15 mcg/m^3.

Overall results indicate that the highest $PM_{2.5}$ concentrations were observed in the outdoor dining areas (mean: 38 mcg/m^3; range of maximum values: 59–321 mcg/m^3) with highest levels being recorded in outdoor areas containing the largest number of smokers throughout data collection. Higher fine particulate matter levels were, however, also observed in the indoor dining areas adjacent to the outdoor dining/smoking area (mean: 34 mcg/m^3; range of maximum values: 20–208 mcg/m^3).

Lowest overall mean levels were measured both at the indoor areas at the back of the restaurant (mean: 21 mcg/m^3; range of maximum values: 40–115 mcg/m^3) and in the outdoor ambient air (mean: 22 mcg/m^3; range of maximum values: 42–108 mcg/m^3).

The results of the means comparisons indicate significantly higher $PM_{2.5}$ levels at indoor areas near the entrance compared to indoor near the back of the restaurant ($p=0.006$) and in the outdoor smoking areas compared to outdoor ambient levels ($p<0.001$). We did not detect a significant difference in mean $PM_{2.5}$ levels in outdoor smoking areas and indoor areas near the entrance ($p=0.149$).

Discussion

To our knowledge this is the first study that examines and compares fine particulates of SHS between outdoor smoking areas and the indoor areas in restaurant settings in New Zealand. Three main conclusions can be drawn from our findings. First, we observed similar concentrations of $PM_{2.5}$ between the outdoor smoking areas and adjacent indoor areas of restaurants.

A recent review of studies on the SHS drift from outdoor to indoor areas also reported that most studies found comparable mean $PM_{2.5}$ concentrations between outdoor areas where smoking was permitted and the nearest smokefree indoor areas.[13] However, in addition to most other studies, we also ran paired t-tests to test for a significant difference between mean $PM_{2.5}$ measurements between the outdoor versus indoor area near the entrance, where we had measurements taken at identical time points. We did not detect a significant difference in the overall mean levels between these areas.

We found significantly higher levels in the front areas of restaurants (near the outdoor smoking/dining area) compared to the back sections and significantly higher levels in the outdoor smoking areas of restaurants compared to ambient air levels. These results at least suggest the potential for SHS drifting through open windows/doors into adjacent indoor areas of restaurants, at levels higher than ambient pollutant levels.

Secondly, $PM_{2.5}$ measurements of the outdoor dining areas in the restaurant varied considerably due to different number of patrons who were smoking, but possibly also due to different design of the outdoor dining areas. Measurements were particularly high when we observed both a large number of smokers and if the outdoor area was enclosed, whereas we found lower measurements with large number of smokers when the outdoor area was designed to be more open (e.g. no roofing, no high walls). Sureda and colleagues (2013) also found measured levels of SHS to be generally higher where smoker density was high, smokers were nearby and where the outdoor smoking area was more enclosed.[13] Lower wind speeds are generally associated with higher $PM_{2.5}$ concentrations in urban settings.[19] The low wind speed measurements in our study might have contributed to elevated fine particulate concentrations in the outdoor smoking areas in the places where a large number of smoking patrons were observed.

Thirdly, in the case of high $PM_{2.5}$ measurements in the outdoor dining area, we only found similarly high levels in the adjacent indoor areas if multiple doors were open at all time (but not if only one door was opened or if doors were open only some of the time) and if smokers were seated nearby the door connecting the outdoor with the indoor area. Research has shown that the distance from the source of tobacco smoke plays an important role in SHS exposure, with $PM_{2.5}$ concentrations decreasing considerably with increasing distance from the tobacco source.[20]

Comparing the mean $PM_{2.5}$ levels found in our study to other similar studies, showed that the overall mean indoor restaurant $PM_{2.5}$ measurement (34 mcg/m^3) found in the present study was much higher than the average level that was found indoors in Irish pubs in Wellington (9.7 mcg/m^3—also collected during late summer).[4] This might be explained by other possible determinants that influence fine particulate levels in restaurants such as cooking smoke.[13] Our findings of the adjacent indoor dining areas were more similar to the average level found in the indoor areas of bars/cafes collected in Wellington during a similar time period in 2011 (41 mcg/m^3).[3]

Our overall mean outdoor measurement (38 mcg/m^3) was, however, much lower than the average level found for the outdoor areas of pubs and cafes in this same study (74 mcg/m^3).[3] However, the latter study selected a purposeful sample of semi-closed outdoor areas, which may explain higher $PM_{2.5}$ concentrations, whereas the outdoor dining areas of our sample vary from open to completely enclosed outdoor areas with accompanying lower to higher $PM_{2.5}$ levels resulting in a lower overall average in our study.

This study has some methodological limitations, particularly the purposeful sample, and the small sample size. Two restaurants had visible cooking areas with open connection to the dining areas, and in three restaurants cooking smoke smells were reported, so there is the potential for indoor measurements being elevated by this or other non-cigarette sources such as lit candles.[21] Despite this we found significantly lower mean measurements deeper inside the restaurants compared to areas near the

front of the restaurant, suggesting that cook smoke or lit candles could not be the sole explanation for higher $PM_{2.5}$ measurements near the front of restaurants (i.e. indoor area near the outdoor smoking/dining area).

Although we showed that the overall levels of measured fine particulates were significantly lower while walking between venues compared to outdoor smoking areas of restaurants, indicating that traffic cannot be a sole explanation for fine particulates drifting from outside to indoor dining areas, we did not obtain ambient measurements outdoors directly adjacent to the smoking areas or at the exact same time points as the outdoor smoking measurements.

Future studies could collect data during the peak of warm weather, from a wider range of restaurants that have outdoor dining areas (and also more of each type ranging from open to completely enclosed outdoor areas) – including from multiple New Zealand cities, during busier times with more smoking patronage such as in the weekends and for longer sampling time periods.

In conclusion, although a future study with a larger sample of restaurants is warranted, our analyses at least suggest that SHS possibly drifts into the indoor dining areas of restaurants through the connecting open doors and windows. This might especially be a problem with high smoking patronage (e.g. during weekends), during peak summer season when generally most restaurants have all doors and windows opened, and when the outdoor dining/smoking area is partially to completely enclosed.

To maximise the health protection of both patrons and restaurant staff members (given there is no risk-free level of exposure to SHS[12]), completely or partially restricting outdoor smoking at restaurants may be needed, as recently recommended for other outdoor areas including streets.[22,23]

In addition, it may also be important to increase awareness among smokers of the health risks associated with SHS for exposed non-smokers (e.g. as an addition to the current range of health warnings on cigarette packs: "secondhand smoke can cause stroke in non-smokers")[24] and non-smokers of the extent to which they are exposed to SHS (and the involved health risks) when sitting near an outdoor area where smoking is permitted.

Competing interests: Although we do not consider it a competing interest, for the sake of full transparency we note that some of the authors have had previous funding support from health sector organisations working for tobacco control.

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New Zealand tobacco retailers' attitudes to selling tobacco, point-of-sale display bans and other tobacco control measures: a qualitative analysis

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Abstract

Aims We aimed to explore New Zealand tobacco retailers' views on selling tobacco, the forthcoming 2012 point of sale display ban and two other potential tobacco control interventions in the retail setting: compulsory sales of nicotine replacement therapy and licensing of tobacco retailers.

Methods We carried out in-depth interviews with 18 retailers from a variety of store types where tobacco was sold. Stores were selected from a range of locations with varying levels of deprivation. We used thematic analysis to analyse the data.

Results All but four of the retailers were ambivalent about selling tobacco, would rather not sell it, or fell back on a business imperative for justification. Only one retailer was explicitly unconcerned about selling tobacco products.

Most participants had few or no concerns about the removal of point-of-sale displays. Issues which were raised were mainly practical and logistical issues with the removal of displays. Only three thought sales would definitely be reduced.

The majority of the retailers were not opposed to a possible requirement that nicotine replacement therapy products be made available wherever tobacco products are sold. Ten supported a licensing or registration scheme for tobacco retailers, and only three were opposed.

Conclusions We found widespread ambivalence about selling tobacco. There was considerable support for the licensing of tobacco retailers and other potential tobacco control measures. The retailers' attitudes about potential financial costs and security issues from a tobacco display ban were at odds with the tobacco industry predictions and the views of retailers' organisations. Some retailers appear to be potential allies for tobacco control. This is in contrast to retailer organisations, which may be out of step with many of their members in their strong opposition to retail tobacco control interventions.

The New Zealand Government has committed itself to the goal of making New Zealand smokefree by 2025.[1] To achieve this outcome, a range of tobacco control measures has been suggested.[2]

The *Smoke-free Environments (Controls and Enforcement) Amendment Act 2011* (SFEA Act) was developed as a step towards this goal and included provisions that addressed the retail environment, including the requirement to remove point-of-sale (PoS) tobacco displays by July 2012.

This policy reduces a tobacco marketing activity by removing the colourful reminder of tobacco availability, which can be a cue for purchases, and may promote smoking uptake among children.[3-6] Removing displays may reduce tobacco purchases by youths.[7, 8] Surveys across countries with and without display bans have found that where there were bans smokers reported reduced exposure to tobacco marketing, and lower impulse purchasing.[9]

During the development of these laws the tobacco industry and some retailer groups campaigned against the changes. Arguments presented in opposition to the removal of PoS displays included that there was a lack of evidence that removing them would be effective. There were predictions that retailers would experience financial losses (including reduced sales and the cost of removing and replacing store furniture) and increased thefts and safety risks.[10,11] The 'Association of Community Retailers' claimed that there was 'huge opposition' amongst retailers to the changes.[12]

The law change provided a good opportunity to examine New Zealand tobacco retailers' attitudes to tobacco and tobacco control measures in the retail setting. New Zealand-specific research on retailers' attitudes to tobacco is limited, with only a few published articles in this area.[13–18] One exploratory qualitative study assessed retailers' views on the tobacco industry and explored possible tobacco control interventions in the retail environment, particularly removal of PoS displays.[17] The study, conducted before there had been any significant public debate about the issue, found mixed views about removing PoS displays, with many of the retailers unconcerned about or even in favour of removing them. Another qualitative study investigated the views and experiences of retailers who had voluntarily removed PoS displays.[18] This study found that their experience was overwhelmingly positive, and at odds with the predictions of the tobacco industry and retailer groups campaigning against the removal of PoS displays.

International evidence specific to retailers' attitudes to tobacco is also limited. A few studies from North America[19-22] have found retailers support tobacco control measures in certain circumstances (e.g. on sales to minors).

Besides the recent changes on PoS displays in New Zealand, other possible tobacco retail interventions include requiring that nicotine replacement therapy (NRT) products (and other cessation support) are available wherever tobacco products are sold, and the licensing of tobacco retailers. Again, research on retailer attitudes in this area is limited. One small New Zealand study of retail staff found mixed support for the licensing of tobacco retailers.[17]

Reasons for support included making tobacco less available, reducing underage smoking and that it was logical given that a licence was needed to sell alcohol. Reasons for opposing licensing tended to focus on the business aspect; it would disadvantage small independent stores, and specialist tobacconists would dominate.

Licensing of tobacco retailers provides the opportunity for health authorities to better communicate with retailers and to regulate the retail sales of tobacco products. For example, it could facilitate introducing and enforcing requirements for retailer training and conduct, and the ability to limit the number and locations of the tobacco retailers.[23]

With such limited research about the views of tobacco retailers, the aims of this study were to:

- Explore the views of New Zealand tobacco retailers about changes to the SFEA Act, in particular the removal of PoS tobacco product displays, and whether this would result in the adverse effects predicted by the tobacco industry
- Explore retailers' views about their experiences of selling tobacco, and their thoughts on other potential tobacco control retail interventions, particularly selling NRT and the licensing of tobacco retailers.

In New Zealand, the main places where tobacco products are sold are: large supermarkets (run by two supermarket groups Foodstuffs and Progressive Enterprises), service stations (dominated by the four main groups—BP, Mobil, Z and Caltex), convenience stores and dairies (the latter mostly independently owned) and some bars and cafes.

The importance of tobacco sales for retailers' turnover and profit varies between different store types. A 2007 report found that the limited evidence available then indicated that the proportion of store turnover that was due to tobacco products varied from an average 37% for convenience stores to 3–4% of sales for supermarkets.[14]

Convenience stores reported a 14% gross profit margin on tobacco products (lower than the 24% average margin for all sales in those stores). However, tobacco sales may give higher profits per shop floor area unit or display area unit.[14]

Methods

We anticipated that 15-20 semi-structured face-to-face interviews with tobacco retailers in the greater Wellington region would be required to achieve a saturation of themes. This was in the light of the study aims, the deductive, question-driven thematic analysis, and the possible differing opinions of staff in large and small shops.[24, 25]

Participants were purposively selected (with an element of random selection) to ensure a diverse range of participants from different store types and areas. It was not possible to anticipate which particular retailers would be information rich, articulate and experienced, except to recruit store managers or owners. We did not consider that snowball recruitment would be sufficiently productive.

As a sampling frame we used a tobacco retailer list for the greater Wellington region from the public health authority, Regional Public Health. The region covers the local authorities of Wellington, Lower Hutt, Upper Hutt, Kapiti Coast District, Masterton, Carterton, South Wairarapa District and Porirua. The list of 496 retailers was divided into type of store (i.e. supermarket, service station, dairy/mini-market/convenience store) and local council area. From these lists, one or two retailers were randomly selected (through random number generation) for each store type and council area (see Table 1 in Results section).

To ensure that retailers from areas of higher socio-economic deprivation and varied ethnic composition were included, we sampled dairies and services stations from high deprivation areas of two cities (three sites in total). These were areas in the highest deprivation quintile, as shown in an atlas of deprivation that used the standard New Zealand area-based measure of socio-economic status (NZDep) from 2006 census data.[26] Participants were eligible for interviews if they were owner/operators, or site or operations managers.

Supermarkets were defined as large, branded supermarkets. Service stations were defined as branded and independent service stations. All other retailers fell into the dairy/mini-market/convenience store type (generally referred to as dairies or dairy from here on).

The researchers attempted to contact each potential participant by phone (most commonly) or occasionally face-to-face. Up to four attempts were made to contact each potential participant. Retailers

were not recruited if they refused to participate, if contact details for outlet were unavailable, or if no contact was made after four attempts.

Ethics approval for anonymous interviews was granted through the Department of Public Health, University of Otago, Wellington through the University's procedure for approval of low risk studies.

The interview schedule included questions on attitudes to selling tobacco and NRT, the possible impacts of the PoS display ban for business and for smokers, and attitudes to two other potential interventions in the retail setting: retailer licensing and making the sale of nicotine replacement products compulsory where tobacco is sold. The interview schedule was piloted with several trial retailer interviewees. The main interviews were carried out in April and May 2012. Each interview was face-to-face, audio recorded and then transcribed verbatim.

The transcripts and recordings were then checked for accuracy by one of the authors and analysed to identify the main themes of the interviews that were related to the research questions. These were: retailer attitudes to and views on the removal of PoS tobacco product displays, possible adverse effects, selling tobacco, and potential tobacco control retail interventions. Where material was found across some interviews that was not related to the research questions, this was noted and explored.

Themes were discussed and agreed with the other authors. This largely deductive, question-driven thematic analysis was carried out as generally outlined by Braun and Clarke for deductive analysis.[27] That is, by manually assigning codes to data areas, forming themes from the coded data, and refining and reviewing the themes.

Idea elements were identified while reading written transcripts and then one researcher (MR) grouped material into the themes. The themes were then rechecked against the transcripts. A second researcher (RJ) then read all the transcripts and allocated further material to the themes. A third researcher (GT) read all the transcripts, checked the material allocated to the themes, and suggested a number of changes. Differences in allocation were discussed and resolved.

Results

Participants and saturation—We attempted to contact 55 different businesses. Of these, 11 were no longer in service or contact details were unavailable. Of the remaining 44 contacts who were eligible, 18 agreed to participate (a response rate of 41%).

Of the 26 that were not recruited, 14 stated that they needed approval from their respective head offices to participate, and this was not provided (these were mostly supermarkets and one brand of service stations), eight refused to participate, and for the remaining four no contact was made after multiple attempts.

We completed 18 interviews from a variety of store types and locations, and from different deprivation-level areas (see Table 1).

Table 1. Numbers of retailers recruited from each category

Area	Supermarkets	Dairies, etc.*	Service stations	Total
Wellington	1	2	1	4
Hutt Valley#	1	2	1	4
Porirua#	1	2	1	4
Kapiti Coast	1	1	1	3
Wairarapa	1	1	1	3
Total	**5**	**8**	**5**	**18**

* Includes convenience stores and mini-markets

This included high deprivation areas

Most interviewees had been in the retail business for more than 10 years (range 3 to 35 years) and the majority had been involved with their current outlet for most of that time.

Except for one of 10 minutes and one of 49 minutes, the duration of the interviews ranged from 17 to 33 minutes, with an average for the 18 interviews of 25 minutes.

In the supermarkets and petrol stations the interviews were held in a separate office, but for the convenience stores, dairies and mini-markets the interviews were with retailers at the counter. These retailers sometimes stopped to serve customers, so the total interview times do not always represent actual speaking times.

It was clear during the analysis that a saturation of themes had been achieved with the 18 interviews. There were very few new themes or opinions emerging during the last few interviews.

Attitudes to selling tobacco—When asked 'how do you feel about selling tobacco' all but four of the retailers were either ambivalent about selling tobacco, would rather not sell it, or fell back on a business- or job-related imperative for their involvement. Of these four, three appeared to be relatively neutral:

> I'm not really interested in cigarettes. If they take it away tomorrow so be it.
> *(Service station retailer, Interview 9)*

Only one retailer was explicitly unconcerned about selling tobacco (he was an ex-smoker who had given up smoking while still at high school):

> I've got no problems with it because I used to be a smoker… when you need one, you need one that's it. Irrespective of the harm.
> *(Dairy retailer, Interview 17)*

Of the 14 who were *not* neutral or positive about smoking, nine had concerns of some sort, for instance:

> I feel that it's really bad [for the] whole society. Because [when] you start smoking your siblings and your children automatically try to copy you and start smoking too. Because it goes on and on.
> *(Supermarket retailer, Interview 1)*
>
> It would be good if we didn't sell them… I would rather not sell them.
> *(Supermarket retailer, Interview 13)*
>
> [It] should be completely stopped by Government, smokefree should be 2015 not 2025.
> *(Dairy retailer, Interview 12)*

Four of those with concerns about selling tobacco noted that their concerns were in conflict with the requirements of the job or business, e.g.:

> I don't want to sell smokes to any people [but] you have to follow the company rules, if there is a smoker, you have to sell smokes.
> *(Service station retailer, Interview 2)*

For two others, their concerns were about young people:

> Don't like selling it to people that are just of age, I don't really think people are old enough to actually realise, but if it's an older person,… it's up to them.
> *(Supermarket retailer, Interview 16)*

Of the 14 who were *not* neutral or positive, a further four indicated that it was part of the job or a business necessity to stock tobacco products, but did not express concerns:

> We have it because our competitors do, because everyone else does.
> *(Supermarket retailer, Interview 10)*

Another was aware of the harm, but any concern appears to have been pushed away:

> I'm selling them something that's going to harm them but I don't really think about it.
> *(Service station retailer, Interview 4)*

Profit from tobacco sales—When asked about the profit from tobacco sales, the majority implied that the profit margin was low, and/or that the contribution to overall profits or turnover was modest. Twelve of the retailers indicated that the profit was 'very little/very small/very low' (n=6), 'low', 'not much', 'small margin' or 'not very profitable'. Another indicated it was only 2.5% of store profit (Service station retailer, Interview 6).

One said a quarter of their turnover was from tobacco (Service station retailer, Interview 15) and one gave a figure of 12–18%, which appeared to be store turnover rather than profit (Dairy retailer, Interview 14).

One pointed out that the profit partly came from the payment by the tobacco company for store space (Supermarket retailer, Interview 16). Two interviewees didn't know or were unsure of their profits from tobacco sales.

Retailers pointed out that though it could be a relatively high turnover product, the profit margin was low.

> There's not much profit involved anyway.
> *(Dairy retailer, Interview 18)*

For supermarkets, tobacco was a small part of their turnover and profit. A supermarket retailer indicated that tobacco was not very important for them:

> It is such a small contributor, of course it [the display ban] will affect but to us not a great deal.
> *(Supermarket retailer, Interview 13)*

Anticipated impact of PoS display bans on business operations—Opinion was mixed as to whether PoS display bans would affect sales: 10 retailers thought it would not affect sales at all or very little, while three thought sales would definitely reduce. The other five did not mention sales when responding to the question about the impact of the ban.

Of those 10 who thought the impact would be nil or limited, three indicated that price was a much more important factor:

> Sales are already down from recent price rises. New changes won't affect profit much…. Not much impact. More people will give up.
> *(Dairy retailer, Interview 12)*

Others from those 10 focused on impacts other than sales. One mentioned a possible move by 'starter' smokers to brands that are most widely known. Because 'starters' would not be able see the brands displayed and thus be able to choose a brand so easily, after the change the most well-known brands will be more likely to be asked for:

> I have heard the reps talking about that in Australia, that the popular lines will stay and the little ones will phase out. It will be hard for the starters to choose their brand, makes it more difficult to start.
> *(Dairy retailer, Interview 11)*

A further three from those 10 thought the effect on sales of removing PoS displays would be limited because it would only affect smoking uptake, not current smokers:

> I don't think it's going to stop the smokers now. I guess it's not about that, it's stopping the ones that aren't smoking, it's the uptake.
> *(Supermarket retailer, Interview 16)*

Others, who acknowledged there might be an impact on sales, downplayed the effect it would have on their business. For example, one retailer suggested there would be a substitution effect if smokers quit:

> If a customer gives up on smoking, they might buy other grocery lines or they might buy a pie and a drink instead of a pack of smokes.
> *(Dairy retailer, Interview 3)*

Another believed any impact on sales would be temporary:

> [Sales will] probably drop off for the first couple of months, and then come back to its normal [rate].
> *(Service station retailer, Interview 4)*

Of the three who thought sales would definitely reduce, one mentioned the 'reminder' effect of displays:

> People won't see that continual reminder.
> *(Supermarket retailer, Interview 8)*

Other anticipated adverse impacts tended to be practical issues: re-stocking shelves; issues of opening and closing cabinets; speed of service; and security. Some retailers were aware that the way they re-stock would require some changes, as, legally, the public should not be able to see tobacco products during re-stocking. As a high turnover product, re-stocking sometimes had to take place daily and may have to be done out of opening hours to prevent customers seeing tobacco. Five retailers mentioned one or both of re-stocking or speed of service:

> It will reduce the space,… efficiency when you are trying to serve other customers.
> *(Dairy retailer, Interview 5)*

However, for one supermarket, re-stocking would be easier:

> Filling [cupboards] will be easier… if it's not visible we can fill it at any time of day, now it has to be done before we open which is 6am.
> *(Supermarket retailer, Interview 10)*

One retailer anticipated disgruntled customers:

> I think they will probably get grumpy at us because they can't see what they want to buy. I know we will probably cop a lot of flak like that.
> *(Service station retailer, Interview 15)*

None of the retailers indicated that there would be significant financial cost to their store in terms of changing cabinets, and this included a supermarket that was building new modular units itself. Six retailers said that the tobacco companies owned the cabinet stand, would be paying to change it and would ensure it complied with the legislation.

Security and theft—Eight retailers raised concerns about security and theft. Six stated they were not concerned about thefts, with or without the display ban. Four did not comment on security or theft. Of the eight with concerns about tobacco-related security of staff and theft, for seven this was not because of the display ban. Only one indirectly related the change with security. Three of these eight retailers with concerns stated that closed cabinets would result in reduced risk of theft:

> If people don't see the smokes there would probably be less robbery.
> *(Dairy retailer, Interview 18)*

When asked about the impact of the display changes on their business, one dairy retailer appeared to be more concerned about security than sales impact:

> I feel more safe because I don't have my smokes open and people coming in and just grab them, and probably the turnover would be lower.
> *(Dairy retailer, Interview 18)*

For one dairy retailer, closed doors were already used as a means to *increase* security and deter theft:

> We've always had the practice of closing the cabinet door, for security as well, we don't need everybody seeing all the cigarettes all day every day.
> *(Dairy retailer, Interview 14)*

One supermarket had taken the opportunity of the change to address security:

> For the security side of it, we will build a modular unit [with drawers] and then at night we will just wheel those drawers/cabinets to another area.
> *(Supermarket retailer, Interview 16)*

Only one retailer mentioned security concerns, when asked about the likely impact of the change:

> Don't like turning [my] back on customers. A few little incidents where people run off without paying.
> *(Dairy retailer, Interview 11)*

For at least three of those concerned about security, the potential theft of valuable, transportable stock was a worry, but these concerns did not seem to relate to any obvious effect from the removal of point of sale displays. Rather they were concerned that the amount and value of tobacco products that were in stock may promote theft:

> The more stock we hold, the more risk we are of being a target.
> *(Dairy retailer, Interview 3)*

Attitudes towards selling nicotine replacement therapy—Retailers were asked if they currently sold or would consider selling NRT products, as well as how they would feel if stores that sold tobacco products were required to sell NRT. Only four retailers currently sold NRT products.

Common reasons for not selling NRT included that it did not sell well, and that it could be obtained elsewhere at highly subsidised prices:

> People that want to give up usually tend to go to a chemist for stuff like that.
> *(Service station retailer, Interview 9)*

> We have the gum only. It's in the health and beauty aisle with the panadols. Doesn't sell very well, as they can ring Quitline and get it cheaper or free in a lot of cases.
> *(Supermarket retailer, Interview 10)*

Up-front price was important, with one retailer wanting a pack of NRT to be the same or less than a pack of cigarettes:

> What I'd like to see, and that would be the biggest difficulty, is that the two [NRT and tobacco] are equal [in price].
> *(Service station retailer, Interview 6)*

For one chain of service stations, the wholesale supplier had stopped stocking NRT:

> [We used to sell NRT but we] can't access them anymore… not through the suppliers that we have. We've just started putting in the electronic cigarettes… we used to get the gum and that through [the supplier], they now don't stock it anymore.
> *(Service station retailer, Interview 6)*

Despite most retailers not stocking NRT, all but one had no objection to compulsory stocking of NRT alongside tobacco products and two explicitly supported this measure:

> I think it would be good if every retail supermarket selling tobacco would have to have nicotine gum too.
> *(Supermarket retailer, Interview 1)*

> Yes, I'm happy with [compulsory stocking of NRT], because sometimes people say 'I want to quit' and you [say] 'good luck', what else can you do. But if you have this product here, I [could] say, look, take some of these, try and see if it works.
> *(Dairy retailer, Interview 18)*

The one that disagreed expressed this as more of a general objection to excessive regulation:

> Generally I believe we are over legislated in New Zealand, I wouldn't be comfortable with [the government] introducing that [requirement to sell NRT].
> *(Supermarket retailer, Interview 8)*

Attitudes towards tobacco retailer licensing—Retailers were then asked how they would feel if those who sold tobacco were required to be licensed (in a similar way to alcohol outlets). Ten of the 18 interviewees would support tobacco licensing in the same way that alcohol is licensed. One said:

> Maybe [a tobacco licensing scheme] might be helpful to learn… if people say I don't want to smoke… some knowledge about how to advise them not to smoke.
> *(Dairy retailer, Interview 18)*

One pointed out that alcohol licence training was considered a hassle at first, but:

> With change you get used to it, it just becomes part of the equation.
> *(Supermarket retailer, Interview 16)*

Of the remaining eight retailers, three were opposed and five were unsure or undecided. Of those eight retailers who had some reservations about licensing, at least three were concerned about resource costs, including the financial cost of a licence and the time cost of applying and training for the licence.

Some suggested that introducing licensing may result in them reappraising whether it was worth their while to sell tobacco products:

> We would have to get all the paperwork and everything…and then they maybe might give an exam or test or something for that.
> *(Dairy retailer, Interview 7)*

One retailer who was opposed to licensing suggested that better enforcement of the current laws was needed, in particular, ensuring that retailers were not selling tobacco to people under 18 years of age.

> I don't believe it's necessary… [It's] unnecessary when all we've got to do is actually enforce the Act and if we enforce the Act then the bad retailers don't exist.
> *(Supermarket retailer, Interview 8)*

Another was concerned about extra 'pressures' on staff from licensing:

> The staff sort of begrudge having to do what they do now, so having to have their names on a register and things like that, and again because we have young ones here like school age kids, we don't employ anybody under 15 but they have to be 15, it puts a lot of pressure on those types of people, to decide whether somebody is 18 or not.
> *(Service station retailer, Interview 15)*

Providing support for customers—While it was not an explicit topic of the interview schedule, a few retailers made unprompted comments that they would appreciate having further ways to support customers who are making quit attempts. These retailers felt that they would like to offer further cessation support to customers.

One retailer had provided Quitline information for customers, and had offered to no longer stock the attempting quitters' brands of cigarettes. One suggested that with the tobacco out of sight, they could refuse to sell tobacco to those trying to give up:

> Basically we'll be able to say to the customer no. If they see stock on the shelf, they'll request it, they'll ask for it and we can't really say no straight off… But not having it on display we can just say no.
> *(Dairy retailer, Interview 3)*

Other findings—The retailers' views did not systematically differ between store types. There was no difference in attitudes to compulsory NRT availability with tobacco products by retailer type; small, independent retailers were as likely as large chain retailers to support this. We did not detect any difference in attitudes by geographical area or deprivation level of store location.

Discussion

Our findings contrasted markedly with the picture that is often portrayed of retailers being overwhelmingly opposed to tobacco control interventions in the retail setting. For example, there was little enthusiasm for and widespread ambivalence about selling tobacco. This was consistent with previous New Zealand research.[17, 18]

Our study indicated that the profit from tobacco was generally seen as a small part of their businesses, although there may be some effect of secondary purchases by customers who come into the store to buy tobacco products. Profit may also come from tobacco distributors paying retailers for store space (although the extent of this profit is unknown).

Security and theft were significant issues for some retailers, because of the high value and transportability of tobacco products. However, only one retailer indicated that the

display ban could increase risk, and this appeared questionable as they already had to turn their backs to get tobacco products. Several others either considered that security would be enhanced by the PoS display bans or had used the legislation changes to improve security in their stores.

There were mixed, but mostly supportive reactions to other tobacco control interventions in the retail setting. There was majority support for making it compulsory to have NRT products available wherever tobacco is sold and for a tobacco retailer licensing scheme. This support for compulsory NRT sales with tobacco products strengthens New Zealand evidence from Williman et al.[7] which found half the retailers in that study supported the idea.

Several retailers were aware that NRT is subsidised and could be obtained far cheaper than at retail outlets. This was seen as a barrier to stocking NRT. For such a scheme to succeed, NRT in the retail environment would need to be subsidised to a similar level to NRT products available elsewhere.

There was some support for requiring tobacco retailers to be licensed, but there were frequent reservations. In particular, there was concern about the likely cost and time involved in applying for a licence. This finding is consistent with a previous New Zealand study.[17] Some retailers in our study suggested they would not stock tobacco if licensing introduced these extra costs. As such, a licence fee may be a way to decrease the number of outlets. In South Australia the number of outlets dropped by over 20% after a licence fee increase in 2007.[28]

The level of concern about the PoS display ban was generally low. It is clear from this study that the retailers' attitudes to tobacco control measures were at odds with the predictions of the tobacco industry and retailer organisations.

While the tobacco industry and retailer groups have argued that removing PoS displays would be a financial burden on retailers (in terms of shelving and cabinetry), this study found that retailers generally did not hold these concerns. A number of the retailers believed that this cost would be borne by the tobacco industry. Concerns raised by the industry about security issues and increased thefts due to the display ban were also not supported by the retailers in this study.

Interestingly, a number of the retailers expressed unprompted interest in encouraging their customers' cessation attempts. It is possible that these views could be more widely held in the retail sector. These positive views on customer support may be because retailers (especially small retailers) are closely linked to their communities and often know their customers on a personal level. These retailers, therefore, have empathy for their customers' and community's wellbeing.

Our findings suggest that retailers may be supportive of tobacco control measures as part of their service to the community. These findings contrast with the views of organisations purporting to represent retailers, and suggest that retailers could be enlisted as supporters of tobacco control measures rather than being assumed to be opposed. Measures such as a tobacco retailer licensing programme could provide them with further assistance and knowledge to support their customers who wish to quit smoking.

A strength of this study is that it canvassed a range of interviewees based on retailer type, geographical area and deprivation level of store location. A saturation of themes was achieved during the 18 interviews, suggesting it was a sufficient number to identify the major themes. The range of stores from which the interviewees came (including some rural retailers) helped ensure that the study gained a variety of opinions.

A limitation is that this study took place in the greater Wellington region, and may not be representative of all New Zealand retailers. Furthermore, the interviewees were at the retailer level, and policy for supermarket and service station chains will generally be made at their head offices. However, a previous New Zealand study that included senior managers from national retail chains also found support for retail tobacco control measures at that level.[17]

This study identified further areas for research. Follow up research could identify how retailers were impacted by the removal of PoS displays and whether their concerns were realised. It may also identify any unexpected outcomes from the legislation at the retail level. Future research could also explore retailers' attitudes to other tobacco control measures that we did not mention, and explore further their relations with tobacco suppliers and retailer organisations.

In conclusion, this study found that the views of most of the retailers interviewed did not align with views about the new PoS regulations attributed to them by the tobacco industry and some retailer organisations. Many of them also supported further tobacco control measures in retail settings.

Tobacco control policy interventions, including the PoS display bans, are a positive step towards achieving the Government's 2025 smokefree goal, and it is encouraging to find that these retailers generally supported interventions aimed at achieving this goal.

Competing interests: Nil.

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Variation in benzodiazepine and antipsychotic use in people aged 65 years and over in New Zealand

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Abstract

Aims To examine the variation in the dispensing of antipsychotic and benzodiazepine medicines in the elderly (aged 65+) across New Zealand.

Methods Data drawn from the New Zealand Pharmaceutical Collection for the New Zealand Atlas of Healthcare Variation was used to establish a regression model to examine dispensing rates by age, gender, district health board (DHB) of domicile and aged residential care usage rates over a 4 year period 2008/09 to 2011/12.

Results On average 24 per 1000 people aged 65+ in New Zealand were dispensed an antipsychotic in any given quarter. Benzodiazepine dispensing rates were even higher, at 109 per 1000 aged 65+. Both rates climbed steeply with age, were higher in females, and had a 1.6 to 1.8 fold variation across DHBs. Rates did not vary significantly with rest home and private hospital residential care usage, but antipsychotic rates appeared related to the use of psychogeriatric and dementia beds.

Conclusion Given the evident harms associated with the use of antipsychotic and benzodiazepine medicines in the elderly, and the relatively poor efficacy of antipsychotics in dementia care, prescribing of these medicines should be reassessed. DHBs should examine the causes of the high rates in their area and design interventions to reduce the rates.

The New Zealand Atlas of Healthcare Variation describes variation by geographic area in the provision and use of specific health services and health outcomes (http://www.hqsc.govt.nz/atlas). It is designed to prompt debate and raise questions on why differences exist and to stimulate improvement through this debate.

One of the domains investigated is polypharmacy in older people, defined for the Atlas as dispensing of 5 or more medicines concurrently in those aged 65 years and over. In addition, the Atlas examined the use of specific medications in the elderly, including antipsychotics and benzodiazepines.

Polypharmacy is associated with negative health outcomes including adverse drug reactions, poor adherence and geriatric syndromes, for example, urinary incontinence, cognitive impairment and impaired balance leading to falls.[1]

In older people certain classes of medicines carry a substantially higher risk of adverse effects, including antipsychotics, benzodiazepines and zopiclone. New initiation of a benzodiazepine in persons aged 65 and over is associated with an approximately 50% increase in the risk of dementia.[2]

Antipsychotic and benzodiazepine use is also associated with an increased risk of death.[3,4] Both are strongly recommended for avoidance in the American Geriatrics Society updated Beers Criteria and STOPP/START criteria.[5,6]

The Atlas showed variation in the dispensing of antipsychotic and benzodiazepine medicines across New Zealand. We examined this variation in more detail by district health board (DHB) of domicile, age, and gender over a four year period by quarter.

We also investigated factors that might be associated with this variation, including the supply of prescribing clinicians (general practitioners, psychiatrists, geriatricians), use of primary care (general practice visits) and residential care bed use by category.

Methods

Data were drawn from the New Zealand Pharmaceutical Collection, which contains claim and payment information from community pharmacists for all prescription dispensing of patients living in the community and residential care.

All the medicines examined (Table 1) are prescription-only in New Zealand, so we would expect near 100% capture in the pharmaceutical collection. These are referred to as "antipsychotics" or APs and "benzodiazepines" or BZs in the text and tables. Four years data from 2008/09 to 2011/12 were examined.

For each quarter, at least one dispensing of a noted medicine was considered to be a positive finding (i.e. multiple dispensings in a quarter were only counted as one). The available quarters in each year were then averaged. We interpreted rates derived from this, e.g. 20/1000, as meaning that during that year, 20 out of every 1000 people would have had at least one dispensing in any given 3-month period.

Table 1. Funded medicines on the New Zealand Pharmaceutical Schedule between 2008/09 to 2011/12 examined

Antipsychotics (AP)	amisulpride, aripiprazole, clozapine, chlorpromazine hydrochloride, haloperidol, levomepromazine, olanzapine, olanzapine pamoate monohydrate, pericyazine, quetiapine, quetiapine fumarate, risperidone, trifluoperazine hydrochloride, ziprasidone, zuclopenthixol decanoate, zuclopenthixol dihydrochloride and zuclopenthixol hydrochloride.
Benzodiazepines and zopiclone (BZ)	alprazolam, diazepam, lorazepam, lormetazepam, midazolam, nitrazepam, oxazepam, temazepam, triazolam and zopiclone

New Zealand residents' age specific population data were taken from the population projection developed by Statistics New Zealand for the Ministry of Health (MOH) in 2012. General practitioner (GP) visits were taken from the MOH's national Primary Health Organisation (PHO) Enrolment Collection.

Aged residential care (ARC) usage rates were calculated from the DHB Shared Services ARC Demand Planner (http://www.dhbsharedservices.health.nz/Site/Health-of-Older-People-/ARC-Demand-Planner-.aspx). This covered all DHB or MOH subsidised residential care beds in New Zealand, by age, gender and DHB.

We used data for the 2008/09 to 2011/12 years to match the pharmaceutical data in hand. The bed types were grouped for analysis into rest home and hospital bed days as one group, and psychogeriatric and dementia care bed days as the other. Self-paying rest home residents were not included.

We obtained full-time equivalent general practitioner, psychiatrist, and geriatrician numbers from the Medical Council of New Zealand for the calendar year 2012. They were assigned to DHB based on worksite information.

We sought to compare the rate of dispensing with the rate of use of general practice. General practitioner consultation rates by age, gender and DHB were obtained from the MOH PHO enrolment data.

The enrolment data records whether a person has had a visit in the last quarter, leading to the slightly odd metric of "the number of GP visits per year, but counting a maximum of one per quarter". This allowed comparison across the DHBs, the ability to analyse same age-gender-DHB grouping, and was proportional to the total number of consultations made.

We assumed that benzodiazepines or antipsychotics would be prescribed based on a patient's clinical conditions, and these conditions would be expected to have similar prevalence throughout New Zealand. Thus the number of patients with such conditions should follow the population and only a small variation is expected between DHBs.

All collected data were linked together by DHB, age and gender by financial year. Means and standard deviations were determined for each variable. We performed canonical correlation and linear regression analysis between the number of people dispensed medicines of interest (benzodiazepines, antipsychotics and both) with each DHB's population by age and gender, by financial year. Workforce figures, general practice consultation rates and hospital and residential care bed days and psychogeriatric and dementia bed days were separately tested, then combined.

Non-significant variables were removed from the regression in step-wise fashion until the most parsimonious model was obtained. Crude rates, standardised ratios (SRs) with 95% confidence intervals, and linear regression between predictor and dependent variables of interest were performed in Statistical Analysis System (SAS) v9.3 software.

Results

On average, 24/1000 people aged 65+ in New Zealand in 2008/09 to 2011/12 were dispensed an antipsychotic in any quarter (detailed results shown in Table 2). The rate of dispensing increased significantly with age, from 15/1000 in the 65–74 year olds to 56/1000 in those aged 85+.

Table 2. Dispensing rates and standardised ratios per 1000 population, 2011/12

Variables	*Rate/1000 population*			*Standardised ratios (SRs)*			
	APs	**BZs**	***Both***	***APs***	***BZs***	***Both***	
All	23.8	108.5	*8.8*	*1*	*1*	*1*	*(reference)*
Female	27.8	137.8	*10.7*	*1.08 (1.05–1.10)*	*1.21 (1.20–1.22)*	*1.12 (1.08–1.16)*	
Male	19.0	73.9	*6.6*	*0.89 (0.87–0.91)*	*0.72 (0.71–0.73)*	*0.84 (0.81–0.88)*	
65-74y	15.0	82.1	*5.3*	*0.65 (0.63–0.67)*	*0.78 (0.77–0.79)*	*0.62 (0.59–0.65)*	
75-84y	26.8	125.8	*10.2*	*1.12 (1.09–1.15)*	*1.15 (1.14–1.17)*	*1.15 (1.09–1.20)*	*DHB*
85y+	55.6	183.7	*21.3*	*2.10 (2.04–2.17)*	*1.49 (1.46–1.51)*	*2.13 (2.02–2.24)*	*coding on graphs*
Northland	18.9	109.1	*8.4*	*0.88 (0.81–0.95)*	*1.08 (1.05–1.12)*	*1.06 (0.93–1.19)*	*1*
Waitemata	17.7	112.2	*7.5*	*0.74 (0.69–0.78)*	*1.03 (1.01–1.05)*	*0.84 (0.77–0.92)*	*2*
Auckland	28.8	130.6	*12.1*	*1.17 (1.10–1.23)*	*1.18 (1.16–1.21)*	*1.32 (1.21–1.44)*	*3*
Counties Manukau	18.7	96.4	*6.9*	*0.89 (0.83–0.94)*	*0.95 (0.93–0.98)*	*0.88 (0.79–0.97)*	*4*
Waikato	19.8	103.6	*7.2*	*0.85 (0.80–0.90)*	*0.97 (0.94–0.99)*	*0.84 (0.75–0.92)*	*5*
Lakes	22.7	107.6	*7.9*	*1.03 (0.92–1.14)*	*1.04 (0.99–1.09)*	*0.98 (0.80–1.15)*	*6*
Bay of Plenty	20.5	122.1	*8.3*	*0.85 (0.79–0.91)*	*1.12 (1.09–1.15)*	*0.93 (0.83–1.04)*	*7*
Tairawhiti	21.2	79.6	*3.4*	*0.94 (0.78–1.11)*	*0.75 (0.68–0.81)*	*0.41 (0.22–0.59)*	*8*
Taranaki	20.3	98.4	*7.1*	*0.82 (0.73–0.90)*	*0.88 (0.84–0.92)*	*0.76 (0.62–0.90)*	*9*
Hawke's Bay	25.1	116.3	*8.3*	*1.05 (0.96–1.13)*	*1.06 (1.03–1.10)*	*0.92 (0.79–1.05)*	*10*
MidCentral	25.4	119.1	*9.7*	*1.05 (0.97–1.13)*	*1.09 (1.05–1.12)*	*1.08 (0.94–1.21)*	*11*
Whanganui	23.3	129.4	*9.6*	*0.95 (0.83–1.07)*	*1.15 (1.10–1.21)*	*1.04 (0.84–1.25)*	*12*
Capital & Coast	24.7	98.2	*8.3*	*1.01 (0.94–1.08)*	*0.89 (0.86–0.92)*	*0.92 (0.81–1.03)*	*13*
Hutt	24.9	111.2	*8.6*	*1.05 (0.95–1.14)*	*1.02 (0.98–1.06)*	*0.98 (0.82–1.13)*	*14*
Wairarapa	22.6	118.7	*8.7*	*0.96 (0.81–1.10)*	*1.10 (1.03–1.17)*	*0.99 (0.74–1.23)*	*15*
Nelson Marlborough	27.8	96.0	*11.4*	*1.16 (1.07–1.25)*	*0.89 (0.86–0.92)*	*1.28 (1.13–1.43)*	*16*
West Coast	26.2	79.3	*5.5*	*1.21 (1.02–1.41)*	*0.79 (0.72–0.86)*	*0.69 (0.44–0.94)*	*17*
Canterbury	31.5	113.9	*11.7*	*1.25 (1.20–1.30)*	*1.01 (0.99–1.03)*	*1.24 (1.16–1.33)*	*18*
Sth Canterbury	24.7	92.7	*7.9*	*0.97 (0.85–1.09)*	*0.82 (0.77–0.87)*	*0.83 (0.64–1.01)*	*19*
Southern	27.8	92.1	*8.7*	*1.14 (1.08–1.20)*	*0.84 (0.81–0.86)*	*0.96 (0.86–1.05)*	*20*

Note: All rates are for the 65+ population apart from the age-specific rates. Standardised ratios (SRs) are standardised for each other variable listed. AP=antipsychotic, BZ=benzodiazepine and zopiclone. Shaded values in DHB section have a SR over 1 and 95% confidence intervals clearly not overlapping 1.

Benzodiazepine dispensing rates were even higher, at 109/1000 aged 65+, increasing from 82/1000 for 65–74 year olds to 184/1000 in those aged 85+. Nearly 1 in 5 New Zealanders aged 85+ had a benzodiazepine dispensed in any given quarter of 2011/12.

The combination of any one individual getting dispensed both antipsychotics and benzodiazepines in the same quarter was present in 8.8/1000 65 year olds and over. This also rose with age to reach 21/1000 85 year olds and over, just over 2%.

Those aged 85 and over were nearly four times more likely to be dispensed antipsychotics than those aged 65–74 (standardised ratio (SR) 2.1, 95% CI 2.04–2.17).

Males aged 65 and over had a lower rate of antipsychotic dispensing than females, 19/1000 aged 65 and over compared with 28/1000 (SR 0.89 compared with 1.08).

The benzodiazepines rate difference was even higher at 74/1000 for males 65 and over compared with 138/1000 for females (SR 0.72 compared with 1.21). Males were also less likely than females to have dispensed both medicines in the same quarter – SR 0.84 compared with 1.12.

Female rates showed more variation across the DHBs. No particular trend was noted over the relatively short timeframes examined, though rates were slightly higher in more recent years.

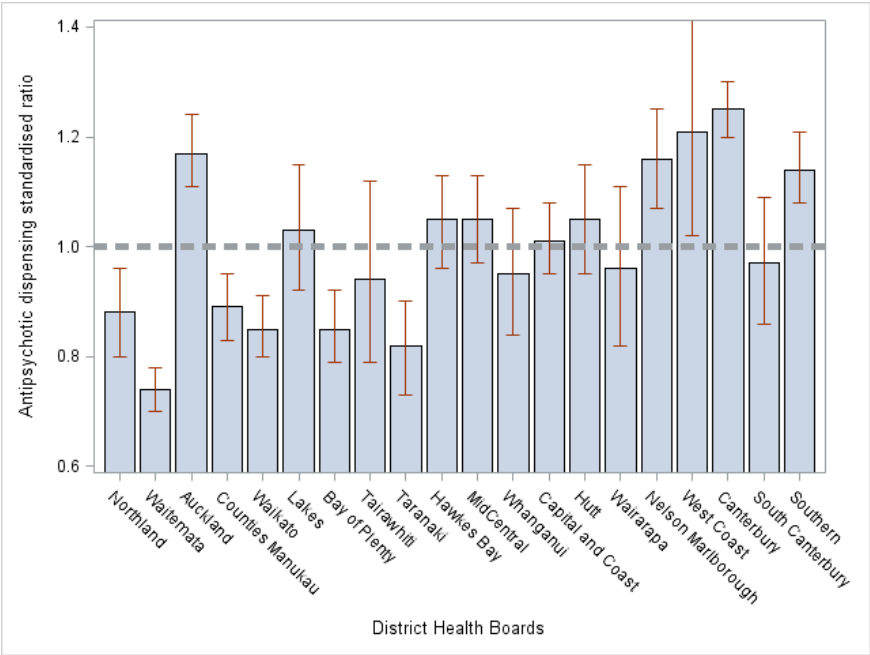
Antipsychotic dispensing rates by DHB varied from 17.7/1000 in those aged 65 and over at Waitemata DHB to 31.5 at Canterbury DHB, a 1.8-fold difference (Figure 1).

Canterbury showed a significantly higher rate of dispensing (SR 1.25, 1.20–1.30), along with Auckland, Nelson Marlborough and Southern. Waitemata had a significantly lower rate of antipsychotic dispensing (SR 0.74, 0.69–0.78), as to a lesser extent did Taranaki, Northland, Counties Manukau, Waikato, and Bay of Plenty.

Benzodiazepine dispensing rates by DHB ranged from 79.3/1000 for those aged 65+ in West Coast DHB to 130.6 at Auckland DHB (Figure 2), a 1.6-fold difference. Auckland, Whanganui and Bay of Plenty DHBs had significantly higher rates of dispensing, while a number of DHBs including Tairawhiti, West Coast, Southern and South Canterbury had lower rates.

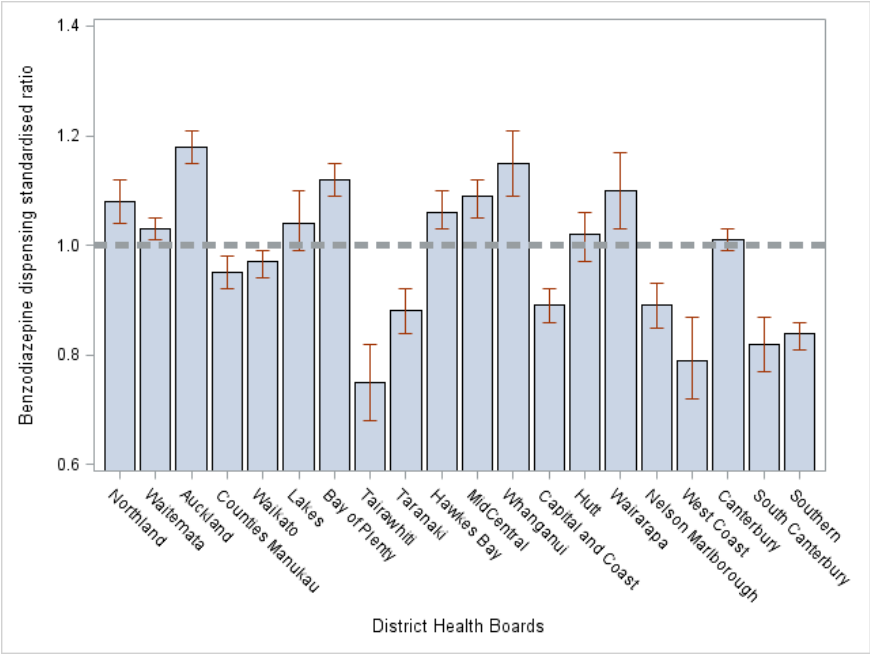
The pattern for people dispensed both benzodiazepines and antipsychotics was similar to that for antipsychotics alone, with Auckland, Nelson Marlborough and Canterbury DHBs reaching significance with high co-dispensing rates (Figure 3).

Figure 1. Antipsychotic dispensing for aged 65+, years 2008–12, standardised rates by DHB



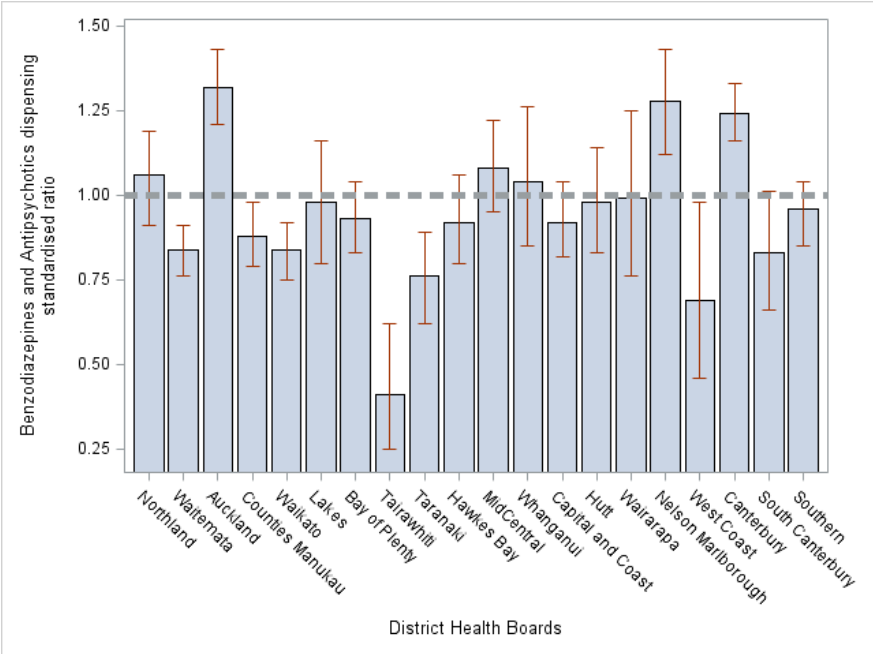
Note: No more than 1 dispensing counted per person per quarter. Standardised for age and sex – a ratio of 1 means the DHB has the same dispensing rate as the New Zealand average.

Figure 2. Benzodiazepine dispensing for aged 65+, years 2008–12, standardised rates by DHB



Note: As per Figure 1.

Figure 3. Combined antipsychotic and benzodiazepine dispensing in same quarter for aged 65+, years 2008–12, standardised rates by DHB



Note: As per Figure 1.

Dispensing rates increased across the four year study period. Antipsychotics went from 22.4 to 23.8 per 1000 aged 65 and over from 2008/09 to 2011/12 (linear trend by quarter r^2=0.71). Benzodiazepines went from 106 to 109 per 1000 aged 65 and over in the same time period (r^2=0.72), while those dispensed both in the same quarter increased from 8.0 to 8.8 per 1000 aged 65 and over (r^2=0.91).

When compared with occupied bed days in the aged residential care sector, there was no effect in removing rest home and hospital facilities from either antipsychotic or benzodiazepine dispensing. However the occupied psychogeriatric and dementia bed days (PGDM) did show a clear relationship with antipsychotic dispensing, giving a better fit particularly for Canterbury and the South Island DHBs than a straight population count. The Northern Region's DHBs had relatively less PGDM beds per person aged 65 year and over, and showed a lesser fit on this measure.

The workforce supply figures per DHB (general practitioner, psychiatrist, and geriatricians) did not add anything to the analysis and were not used in the final regression work. Likewise, GP consultation numbers largely varied with population counts, so did not add any explanatory power.

Discussion

This study—Rates of antipsychotic and benzodiazepine dispensing rise with age, with females having a higher rate than males. There are variations in the dispensing of antipsychotics and benzodiazepines between DHBs, up to 1.8-fold, even after controlling for age and residential care bed numbers.

Disease rates do not vary by this magnitude by area, so health system factors are the likely driver for this variation.[7] Rates of dispensing do not appear to be related to the general practitioner, psychiatrist, and geriatrician full-time-equivalent (FTE) numbers in a DHB, or the number of GP consultations occurring in that DHB.

Dispensing rates did not vary based on the occupied bed days in residential care hospital and rest homes, but did vary for antipsychotics when psychogeriatric and dementia bed days were taken into account.

The high rate of antipsychotic dispensing in Canterbury appeared associated with the higher rate of psychogeriatric and dementia bed use in that DHB. We could find no reason as to why there are relatively more such beds in Canterbury.

Previous work in New Zealand—Previous work in New Zealand has shown high rates of use of these medicines in the elderly. A study in Hawke's Bay in 2005 showed stable rates of prescribing over a 15 year period, but still high rates of both benzodiazepine and antipsychotic prescribing.[8]

Rates of psychotropic prescribing varied greatly between facilities offering more or less the same level of care, with rates particularly high in dementia units – 60% compared with other residential care facilities (17%). The prescriber and environment factors appeared to be the main influences upon prescribing patterns suggested the editorial that accompanied that paper, leading to educative and care-resource interventions perhaps being able to be selectively applied to reduce medicine usage for outliers.[9]

Off-label use of antipsychotics has been noted to be very high in Canterbury, with a third of psychiatrists in the region prescribing off-label for the management of behavioural and psychological symptoms of dementia.[10]

The authors' conclusions are clear: *"Considering that even low dose [atypical antipsychotics] can have significant side-effects, are of unknown efficacy, and appear to have a potential for abuse, we recommend a more considered and measured approach to their use.*"

Recent analysis of Pharmac data for 2009/10 showed rates of antipsychotic prescribing in the 65 and over population for Canterbury and Bay of Plenty DHBs of 5.3% and 3.5% respectively.[11] These rates show as higher than the current study (Canterbury 3.2% and Bay of Plenty 2.1%) as they relate to any script in the course of the year, rather than per quarter.

Croucher et al also noted the rate of antipsychotic medication use amongst older people increasing with age, and the higher rate for older women than men.[11]

We add to this work to show these relatively high rates of prescribing continue today throughout New Zealand, are not falling, and may be associated with aged residential care use.

Limitations—Our study has limitations. It was not possible to assess the appropriateness or otherwise of prescribing as the pharmaceutical data collection used does not contain data on the patients' condition. It also does not indicate whether people took the medicine, only that it was dispensed. While it does not capture over-the-counter medicines, this does not feature in the medicine categories being examined.

All New Zealand residents, the population under study, are eligible for subsidy for pharmaceutical use so their claims will be submitted by the pharmacy and be included in the collection. If the cost of the pharmaceutical is less than the patient copayment ($3 at the time of the study), then a claim did not need to be submitted. This is unlikely for the medicines involved.

Public hospital-dispensed medicines are not included, nor any medicines not on the Pharmaceutical Schedule. Both will be very small volumes compared with the main medicines analysed.

The main limitation of this study is that it can only report an association at a population level between the different variables. Further work is recommended to link the individual patients through the national health data collections to more definitively establish the apparent link between psychogeriatric and dementia bed use and antipsychotic use, to check on the dose and quantities dispensed and the period of time over which each individual is dispensed medicines.

Local analysis including information of the patient's condition, the purpose for starting the medication and the reviews for continuation would be particularly valuable. The study had limited power to detect whether the supply of clinicians in the New Zealand context might influence the amount of medicine dispensed.

Given that rest home residence did not seem to be related to prescribing rates, the lack of inclusion of self-paying rest home residents is unlikely to have affected our results. They were not included as data is not collected on this group of people centrally as they receive no subsidy from DHBs.

Context—The rate of antipsychotic dispensing in New Zealand noted in this study, 2.4% of those aged 65 and over per quarter, is likely to be below the rate estimated in the UK of 5.3% per year,[12] even allowing for the difference between the quarterly and annual measures. This UK overall proportion is similar to that reported for Manitoba, Canada (4.3% in men and 6.0% in women).[13]

The rates of antipsychotic medication use amongst older people increasing with age, and the higher rates for older women than men are consistent with Australian and Canadian figures.[13, 14] Higher rates of antipsychotic use amongst older women may reflect their over-representation in residential care, where rates of prescribing are higher.[15]

Overall population aged 65 and over rates of benzodiazepine dispensing were noted to be as high as 22.5% in Ontario, Canada, in 1998,[16] and noted rates of 16% in the UK,

20% in France and 23% in Quebec,[17] all likely to be higher than the quarterly rate noted here of 10.8%.

Variation by region in medication rates in the elderly shown here mirrors previous findings of variation in excess of what can be explained by variations in the characteristics of the population being considered.[18, 19]

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) and PHARMAC have developed recommendations for prescribing of antipsychotics for the treatment of elderly people in residential care with psychological and behavioural symptoms of mental disorders.[20] The Ministry of Health backed this up with their publication in 2011 *Medicines Care Guides for Residential Aged Care.*[21]

The New Zealand Ministry of Health guidelines for Mental Health and Addiction Services for Older People and Dementia Services2[22] are also clear on the need to manage prescribing of these agents "A preference for psychological before pharmacological approaches, and effective monitoring of practice to reduce risk of harmful outcomes, are recommended." (p25)

Guidelines emphasise the non-pharmacological management of troublesome behaviours, especially given the increased mortality rate and risk of stroke seen in people with dementia given antipsychotics.[4, 23-25] A range of non-pharmacological methods are available.[24-27]

Antipsychotics and benzodiazepines are recommended for avoidance in the American Geriatrics Society updated Beers Criteria [5] and for stopping in the STOPP/START criteria.[6, 28]

Over-prescription of antipsychotic drugs in aged residential care facilities has been noted in New Zealand,[24] mirroring findings in the United Kingdom.[29]

The Department of Health in England notes a reduction in antipsychotic prescribing more recently,[30] explaining it as a consequence of the new standards for dementia care set out in their National Dementia Strategy, published in 2009.[31] It is backed up by very clear and strong warnings by the Medicines and Healthcare Regulatory Authority (MHRA) in the UK regarding the "risk from serious and life-threatening side effects", and noting the medicines are useful only for short-term (up to 6 weeks) treatment of persistent aggression in Alzheimer's dementia, and are of limited effectiveness.[32]

For practitioners in the field, overprescribing of these drugs particularly in residential care facilities has been a concern for a number of years, and considerable educational effort has gone into promoting more rational prescribing habits. It is therefore disappointing that no improvement in rates was discernible across the 4-year study period, with the trend more towards an increase in dispensing.

Conclusion

Given the poor efficacy of antipsychotics in dementia care, and the evident harms associated, prescribing of these medicines should be reassessed.

Clinicians involved in the care of the elderly should document whenever these medicines are used as to the purpose for the treatment, and the length of time the medicine is to be trialled for – starting them seems easier than stopping them.

DHBs should examine the causes of the high rates of prescribing in their area and design interventions to reduce the high rates.[33] Work has been underway in Canterbury along these lines.[34]

Most older people taking antipsychotics can be successfully weaned off after a short course of low dose treatment without re-emergence of behavioural issues, although some people experience a reoccurrence of their dementia-related symptoms.[35-37]

Likewise the potential harms from benzodiazepines are well documented and habituation makes their long term use pointless.[2-3] Despite this evidence rates of use remain very high.

A strength of the New Zealand Atlas of Healthcare Variation is that the DHBs with lower rates can provide an initial target for other DHBs to aim for, realising that one is not expecting a target of zero. The Atlas provides a mechanism towards tracking progress in reducing the use of these medicines.

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Brain popcorn

Han Seng Chew, Sujit Nair

A previously fit and healthy 37-year-old gentleman presented to Casualty with left-sided weakness.

Figure 1

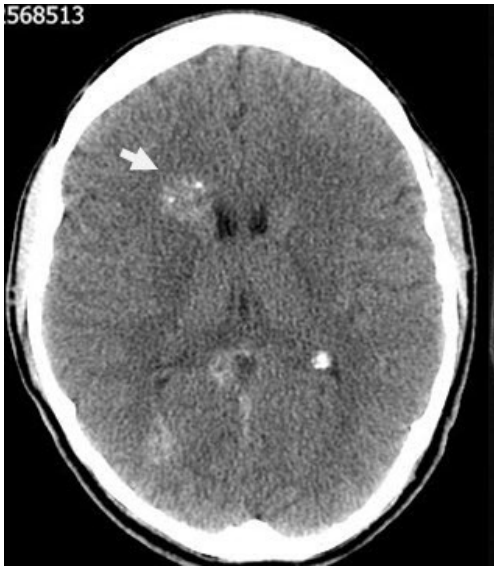

Figure 2

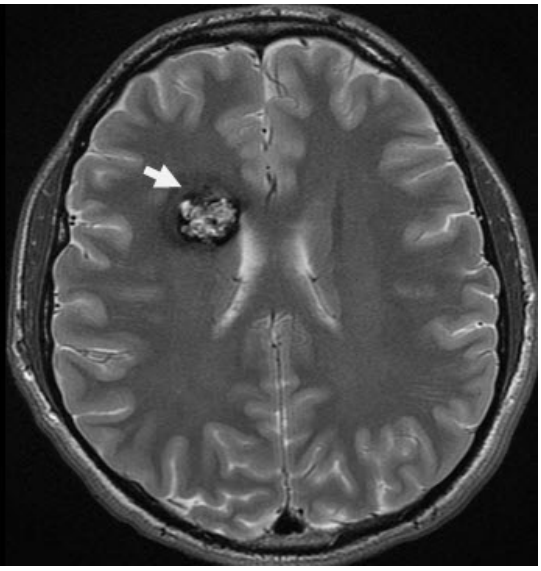

Figure 3

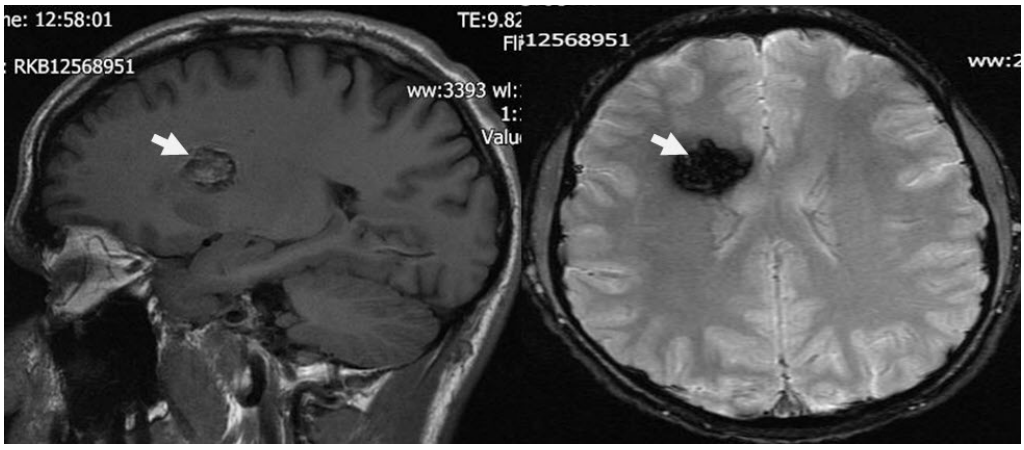

Figure 4

The noncontrast CT head scan (Figure 1) shows a high attenuation area (white arrow) with calcification within the right frontal lobe deep white matter.

MRI scan shows typical “popcorn ball” appearance with low signal intensity hemosiderin rim on T2W (Figure 2); bright locules of methemoglobin on T1W images (Figure 3); and low signal intensity blooming on Axial T2*GRE (Figure 4) due to paramagnetic effect of blood degradation product.

What is the diagnosis?

Answer: *Cavernoma*

A cavernous malformation is an abnormal cluster of thin-walled capillaries and venules which give rise to "popcorn" appearance in the brain or spinal cord. It has the tendency to bleed periodically and usually contains blood products of varying ages hence the typical appearance seen on the MRI scan.

The peak incidence occurs between 40–60 years of age. Most patients have a single lesion which remains clinically silent and usually presents as an incidental finding on neuroimaging. When symptomatic, cavernoma may cause seizure or focal neurological deficit. There is a 1% risk of haemorrhage per year for familial cases and much less for sporadic lesions. They tend to be supratentorial (in approximately 80% of cases) but can be found anywhere in the neural axis.

MRI is the investigation of choice which demonstrates characteristic “popcorn” appearance of cavernoma with a low signal rim due to haemosiderin deposit.

Incidental lesions are usually managed conservatively. Surgical intervention is rarely required unless they are causing significant mass effect, poorly controlled epileptic activities or recurrent haemorrhage. Complete resection is however usually curative.

Learning points

- Most common presentation is seizures. Cavernoma has typical popcorn appearance on MRI
- May progress, enlarge or regress with time (propensity to grow via repeated intralesional haemorrhages)
- Treatment and follow-up is not necessary. Surgical resection is only recommended in symptomatic haemorrhage

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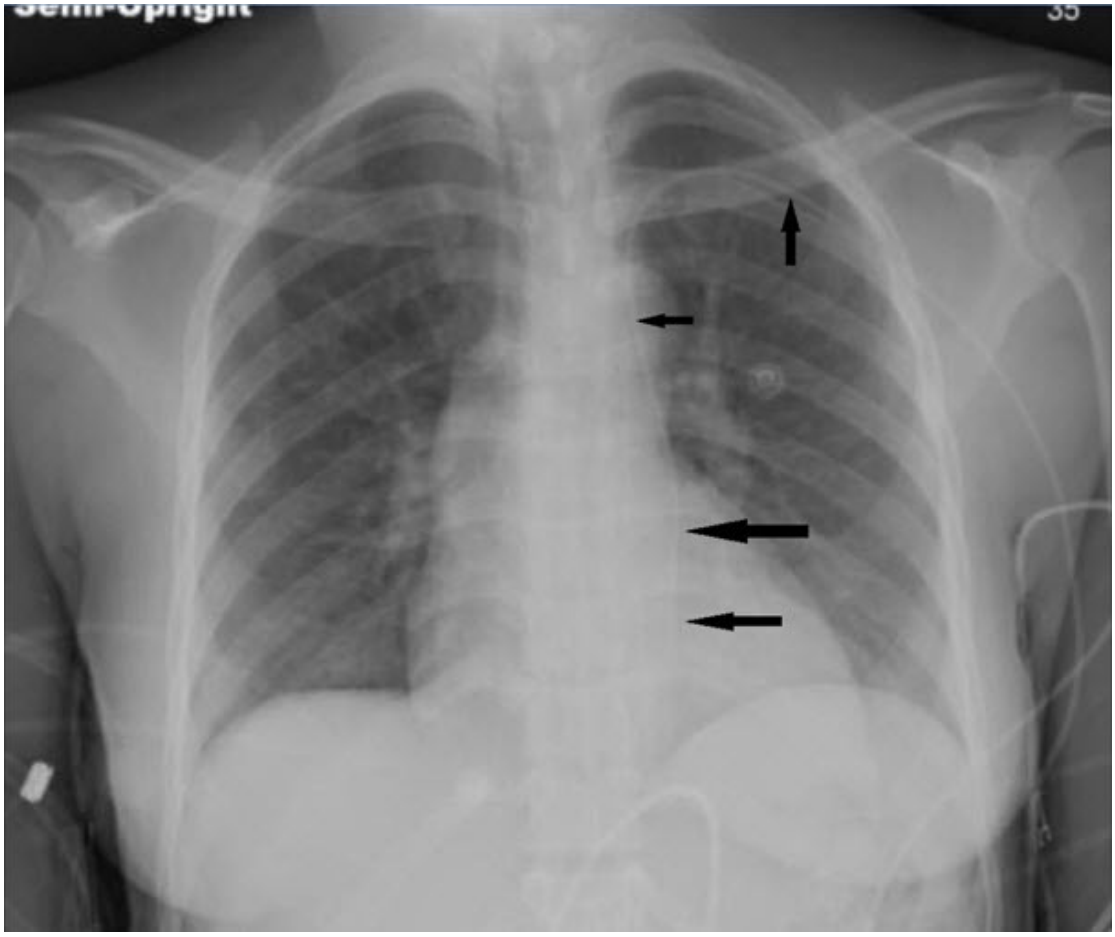
Can I use this central line?

Abdel Rahman Lataifeh, Khaled R Khasawneh

Clinical—A patient admitted to the ICU required a peripherally inserted central catheter (PICC).

Chest X-ray (CXR) demonstrated the PICC taking an unusual left parasternal course with the tip posterior to the left ventricle (Figure 1). Blood gas was consistent with venous blood.

Figure 1. CXR demonstrating the unusual left parasternal position of the PICC (black arrows)



Would you use this PICC line?

Answer—Review of previous CT scan confirmed the presence of bilateral superior vena cava with persistent left superior vena cava (PLSVC). See Figures 2 and 3.

Figure 2. CT chest scan with persistent left superior vena cava (top right arrow), right superior vena cava (left arrow) and aorta (lower right arrow)

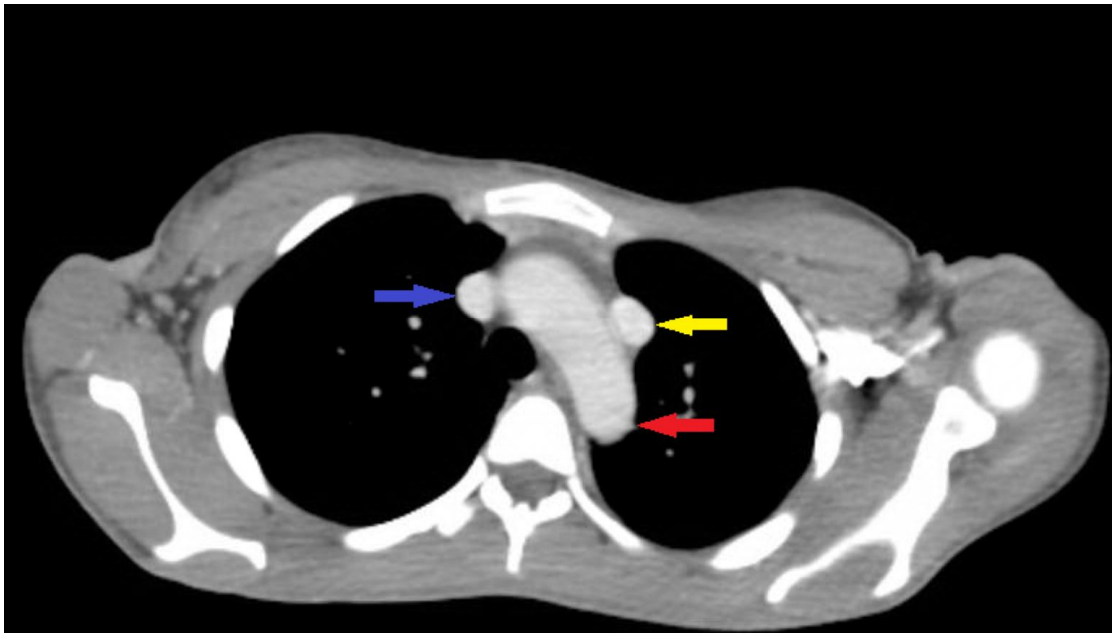
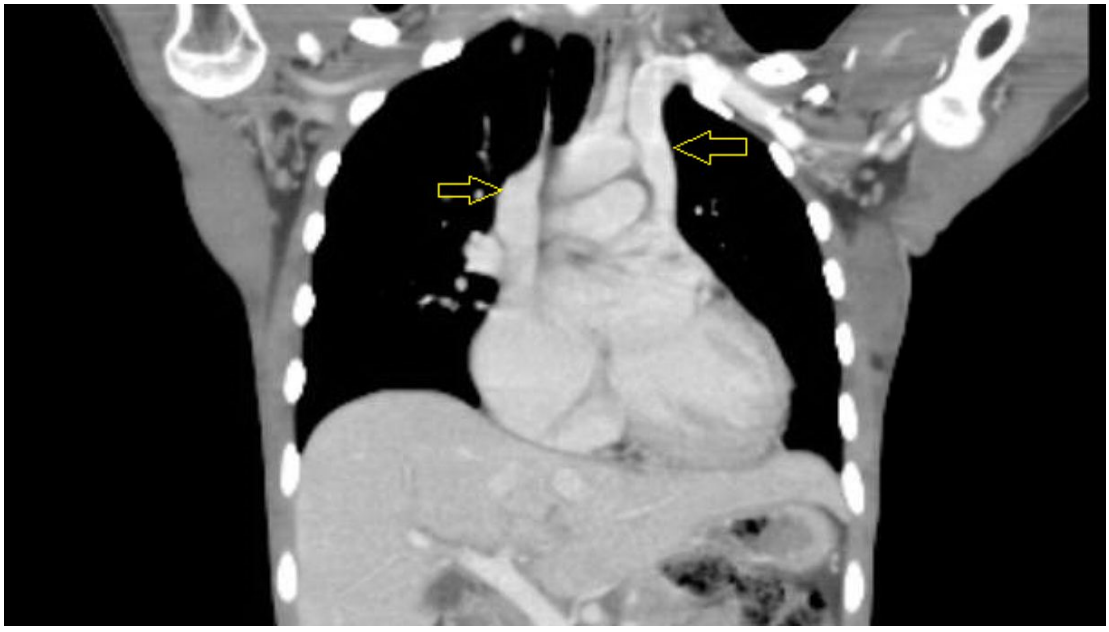


Figure 3. Left and right superior vena cava (arrows). PLSVC drains to the right atrium via the coronary sinus. The left subclavian and internal jugular veins drain directly to the PLSVC and the left brachiocephalic vein is absent



Discussion—PLSVC is a rare but clinically important anatomical variation. It affects 0.5% of the general population.[1] About 90% of PLSVC patients have a normal right-sided SVC and the PLSVC drain into the right atrium via the coronary sinus.[2]

In approximately 65% of the cases the left brachiocephalic vein is completely absent.[3]

PLSVC draining to the left atrium is associated with right to left shunt and higher incidence of cardiac arrhythmia.

PLSVC draining to right atrium is usually asymptomatic but it becomes clinically significant when patient has a central venous catheter (CVC), PICC line or pacemaker where it can be confused with intra-arterial, pericardial or pleural placement on CXR.

Blood gas analysis, waveform tracing, venography or chest CT should be used to confirm venous placement and to verify that the PLSVC is draining to the right atrium before using the central venous line.[3]

Learning objectives

- PLSVC is a rare anatomical variation with important clinical implications
- PLSVC drains to the right atrium via the coronary sinus in 90% of the cases
- CVC that are placed from the left side in patients with PLSVC have a misleading appearance on the CXR that mimics intra-arterial or extravascular position
- When PLSVC is suspected after CVC placement, further testing is needed to confirm venous placement and that the PLSVC drains to the right atrium before the CVC can be used

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Parenteral vitamin C for palliative care of terminal cancer patients

Two early studies in advanced/terminal cancer patients treated with high-dose vitamin C indicated subjective improvements in quality of life, including reduced pain and the need for analgesics.[1,2] No control groups were included in these studies making it difficult to exclude a placebo effect. However, the authors stated that "any agent which can make, or even appear to make, the burden of terminal cancer more tolerable, deserves further study".[1]

Subjective changes in quality of life are difficult to measure and quantify. The European Organisation for Research and Treatment of Cancer (EORTC) has developed a reliable and valid Quality of Life Questionnaire comprising 30 core items (QLQ-C30).[3] Multi-item scales include five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), and a global health and quality-of-life scale. Additional single item scales include symptoms commonly reported by cancer patients (e.g. dyspnoea, appetite loss, sleep disturbance, constipation and diarrhoea) as well as the financial impact of the disease and treatment.

In 2007, Yeom et al[4] used the EORTC QLQ-C30 to assess the quality of life of 39 terminal cancer patients before and after administration of IV vitamin C (10 g twice over three days) followed by oral vitamin C intake (4 g/d for one week). The patients reported significantly lower scores for fatigue, pain, nausea/vomiting, and appetite loss following administration of vitamin C. The patients also reported significantly higher scores for physical, role, emotional and cognitive function, as well as an overall improvement in their global health status (from a score of 36 to a score of 55) following vitamin C administration. In general, a difference of 4–10 points represents a small change, while a difference of 10–20 points represents a medium change in quality of life.[5] Similar results have been reported in another quality of life study of 60 patients with advanced cancer.[6]

Fatigue is one of the most common and debilitating symptoms reported by cancer patients, and can affect quality of life more than pain.[7] It is particularly common for patients undergoing chemotherapy, and may also persist for years after treatment completion.[7] Although cancer-related pain can be managed with opioids, no effective therapy for fatigue has yet been identified. Numerous measures of fatigue have been developed, however, because fatigue is multidimensional in nature, i.e. expresses on physical, emotional and mental levels, multidimensional measures, such as the Multidimensional Fatigue Symptom Inventory (MFSI), offer more comprehensive information.[8]

We carried out a case study of an 81-year-old male who had been diagnosed in 2004 with a rare sarcoma of the left pulmonary artery. He underwent a left pneumonectomy with resection of the left pulmonary artery in 2005.[9] He recovered from surgery and continued to have a good quality of life until a recurrent pulmonary angiosarcoma was diagnosed in 2013 and deemed inoperable by his oncologist. Intravenous vitamin C

(30 g/session, AscorL500, McCuff Pharmaceuticals, Santa Ana, USA) was initiated and quality of life (EORTC QLQ-C30)[3] and fatigue (MFSI-SF)[8] questionnaires were administered before and after seven days of vitamin C administration.

The quality of life questionnaire showed a 37% decrease in fatigue (from a score of 90 to a score of 57) and complete cessation of pain, nausea/vomiting and insomnia, as well as reduced loss of appetite, following vitamin C administration. Improvements in physical, emotional, cognitive and social functioning were also observed, as well as an enhancement of overall quality of life. With respect to the multidimensional aspects of fatigue, there were decreases in general, physical, emotional and mental fatigue, resulting in a 50% decrease in total fatigue following vitamin C administration.

Prior to vitamin C administration the patient was wheelchair bound, unable to walk unaided and totally dependent on physical assistance. Following vitamin C administration there was a complete reduction in pain (notably he no longer required analgesics), he was able to walk and do many other daily activities unaided, and he experienced a dramatic decrease in fatigue levels. The patient's primary carer also reported that the patient developed a more positive outlook on life. No adverse side effects of the vitamin C treatment were observed by the patient's primary carer and GP.

Placebo injections were not carried out as it was deemed by his GP to be unethical to withhold the intravenous vitamin C based on the severity of the patient's illness. As such, it is not possible to rule out a placebo effect, particularly as this effect tends to be more prevalent with measures of subjective symptoms such as pain.[10] However, based on the varied functions of vitamin C in the body, from its role as a cofactor in the biosynthesis of carnitine, neurotransmitters and neuropeptide hormones, to its regulation of epigenetics and gene transcription,[11] it is plausible that vitamin C contributed to some of the observed quality of life effects.

It has been stated that "in terminal cancer patients the quality of life is as important as a cure".[4] Although the optimal dose of vitamin C required for an improvement in quality of life has not yet been ascertained, it appears that it may be lower[4] than the pharmacologic doses normally used for cancer treatment protocols.[12] Thus, based on accumulating evidence, parenteral vitamin C should be considered for the palliative care of terminal cancer patients.

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Time to review New Zealand's antiviral stockpile for pandemic preparedness?

New Zealand (NZ) seems to have done a reasonably good job of influenza pandemic planning, as we concluded in a previous review published just before the 2009 pandemic.[1] This planning may even have contributed to some of the favourable features of the NZ health sector response to that pandemic (albeit a relatively mild pandemic compared to previous ones).[2]

Part of the NZ Ministry of Health's current planning includes stockpiling of antivirals, reported to comprise more than one million doses of oseltamivir (*Tamiflu*) and 300,000 of zanamivir (*Relenza*), costing $32 million.

However a recent Cochrane systematic review has raised questions around the effectiveness of these antivirals.[3] This review benefited from the inclusion of many previously unpublished reports from the pharmaceutical industry and also the European Medicines Agency. It found fairly modest benefits from the treatment of adults e.g., "oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours". But in terms of hospitalisations, the treatment of adults with oseltamivir had no significant effect on hospitalisations and zanamivir hospitalisation data were unreported. Furthermore, the Cochrane reviewers also noted that there were many limitations with the trials they reviewed (e.g., selection bias, attrition bias, "non-identical presentation of the placebo" and even that some of the placebo interventions "may have contained active substances").

Debate about the findings of this Cochrane review and other evidence for and against antivirals being worthwhile have featured in recent issues of the *British Medical Journal* (especially the 12 April and 3 May issues of 2014).

So given such debate, the large cost of the antiviral stockpile to the NZ taxpayer, and the need for the public and health workers to have confidence in any antiviral stockpile, it is probably desirable that NZ health authorities conduct a thorough and transparent review of this topic. This review could address the following issues:

- What information besides the new Cochrane review needs to be considered (e.g., one systematic review of observational studies suggested a benefit from antivirals;[4] and another indicated a mortality reduction benefit for hospitalised patients[5]).
- What is the evidence around the practicalities of using antivirals during a pandemic for prophylaxis and also for treatment? For example, one article on the UK experience in 2009 has suggested that antivirals were of no practical benefit for prophylaxis in the community.[6]
- What is the evidence around likely cost-effectiveness such as the cost-per-illness prevented (e.g., in an emergency worker during a pandemic) and cost-per-hospitalised patient prevented from dying? New economic modelling work might be required to answer such questions since former modelling that

included consideration of the cost-effectiveness of NZ doing stockpiling might now be outdated.[7]

- How do any of the above cost-effectiveness estimates compare with other ways to reduce spread of an influenza pandemic (e.g., mass media campaigns around improving hygiene and promoting staying at home when sick)? Or how might it compare with enhancing hospital surge capacity? Our own work based on the 2009 pandemic does suggest that hospital care was likely to be a relatively cost-effective means of preventing death from pandemic influenza.[8]
- If antivirals are ultimately thought to have a worthwhile role in pandemic control and reducing burden on the health system – then what is the best approach to obtaining them? Is it to continue to have a national stockpile (with the associated waste when expired product gets discarded), or is it more cost-effective to have a contract and annual fee payment to manufacturers for guaranteed immediate supply as per "manufacturer reserve programmes"? The issues are quite complex, as described in the economic modelling literature.[9]

Finally, such a review process might also be an opportunity to consider further upgrades to pandemic planning. In particular, it would be good to see modelling work that assessed the scope for imposing temporary restrictions at national borders and internal borders (e.g., between the North and South Islands and offshore islands).

NZ's border screening used in the 2009 influenza pandemic appeared to have been relatively ineffective,[10] so improving these processes should be a key priority. Such control could buy time to prepare better or reduce peak effects during a pandemic (with reduced risks of health services being overwhelmed). Such planning could also inform responses to other potential pandemic agents—including future genetically-engineered bioweapons.

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Patient aggression overstated

I read the conclusion of the article 'Patient aggression experienced by staff in a public hospital' published in the *New Zealand Medical Journal* 23 May 2014 with utter dismay. The authors' conclusion *'These results demonstrate many hospital staff, of all roles and workplaces experience aggression on a frequent basis'* seems somewhat overreaching.

The study design specifically sought to include accident and emergency and psychiatric settings where the authors acknowledge patient violence is known to be particularly high. At the same time, the study excluded surgical services and general medical services making the study unable to be generalised across a whole hospital setting.

Any attempt to use the data collected in this study to calculate rates across the whole hospital setting, or indeed the entire health workforce as the article does in the discussion of the article is unbelievable.

A non-randomised study of 227 respondents, working in selected departments in one hospital, cannot be generalised across the whole hospital. It gives an inaccurate picture of the level of aggression occurring in our hospital settings.

Shona M McLeod
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Authors' reply—We thank McLeod for taking an interest in our paper, and we share her concern about the rate of such events. She is quite correct to note that the place one surveys is an important component of the reported rate of aggression, and we consider that we did discuss that this was reporting the rate among participants from a subset of district health board health workers, not all employees of the hospital.

She suggests that if we looked at surgical and medical staff we would have found a lower rate. The one survey that deliberately targeted medical surgical staff was Coverdale et al (2001) which showed that psychiatric registrars had a significantly higher rate of the same events than medical, surgical and obstetric registrars. Even if we had included medical and surgical wards and they did have lower rates of aggression our conclusion would remain the same: some hospital staff experience high rates of aggression.

We also note that this research was part of a student summer project and as such was conducted with little time and funding. Thus, the hospital areas reached and response rate were considered to be very good under the circumstances. The student was also charged with getting reliability data for our main measure, the POPAS-NZ, and this is published elsewhere (Swain & Gale, 2014). This is the third local survey with the POPAS-NZ (Swain, Gale and Greenwood, 2014, Gale et al 2009, and McKay et al 2009). Selected results from these surveys are in Table 1.

Table 1. Percent of participants reporting that such events had happened during the last year, extracted from POPAS-NZ tables

Population	Swain et al 2014 Hospital Workers	McKay et al 2009 Medical Students	Gale et al 2009 NGO Support Workers
Verbal Anger	93	67	66
Assault	39	4	30
Injury	29	4	21
Harassment	40	45	22
Litigation	26	6	24

The rates of harassment reported in this paper are very similar to the previous medical student survey, and higher than that in a survey of community based support workers: one can take some hope that the students seem to be protected by hospital staff from assault, injury and complaint, but the rate of verbal aggression remains quite high.

We unreservedly stand by our conclusion many hospital staff experience frequent aggression. We did not attempt to calculate rates across the whole hospital or across the entire workforce as this letter suggests, and we have alluded to the reasons in our response.

We suggest the writer reserve her "utter dismay" to the lack of an evidence base around interventions to prevent violence for health care workers, trained and untrained, working in hospitals and in the community. Although early work on educational interventions is promising, more work is needed (Swain and Gale, 2014). Because, looking at the broader data—and there are another three surveys of health care workers that these authors have been involved in with other methodologies – patient aggression remains a work hazard for all caregivers.

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Presidential Address: Insanity

Excerpt from a Presidential Address by H. V. Drew, F.R.C.S. read the Annual Meeting of the New Zealand Branch [of the BMA], Timaru, 1912—and published in NZMJ 1912 March;11(41):1–8.

The next subject I have to refer to is insanity, which is becoming very prevalent—I think I read the other day an article by Dr. Forbes Winslow in which he says that insanity has doubled in the last fifty years. i.e., that 50 years ago there was roughly one case in 600, to-day there is one in 300; and that is not all, for it seems to me that there must be a large number of unregistered lunatics outside the asylums. We watch a disease increasing, and instead of trying to stop it we tinker up the affected ones in order to return them to their families to propogate the mischief anew!

The same applies to the weak-minded and criminal. The average number of children in poor families is 7—whilst the average in those who alone should be allowed to reproduce their own species is 4!

I will now read the report of a case by a committee of the London County Council: "A female aged 67—had been admitted to Colney Hatch Asylum 16 times, other asylums 11 times, had had 12 children, 5 of whom were dead, mental history of many relations bad."

The committee added:—It seems to us a striking illustration of need for legislation to prevent the increase of the unfit.—*London Times*, 8th, December, 1911.

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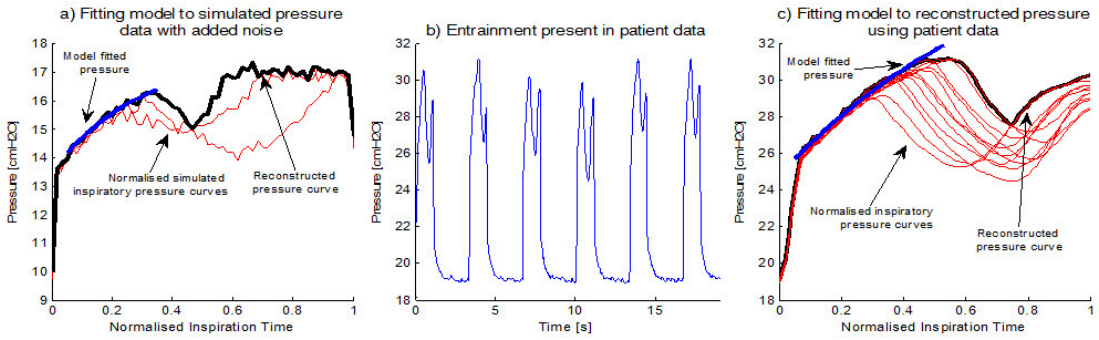
Proceedings of the Scientific Meetings of the Health Research Society of Canterbury, 16 & 30 May 2014

A Pressure Reconstruction Method to Estimate Respiratory Mechanics of Breathing Masked by Spontaneous Breathing Efforts, V Major[1], S Corbett[1], A Beatson[1], D Glassenbury[1], D Redmond[1], Á Szlávecz[2], B Andreu[1], S Davidson[1], NS Damanhuri[1], P Docherty[1], YS Chiew[1], C Pretty[1], G Shaw[3], JG Chase[1]; [1]Centre of Bioengineering, University of Canterbury, Christchurch, [2]Department of Control Engineering and Information Technology, Budapest University of Technology and Economics, Budapest, [3]Department of Intensive Care, Christchurch Hospital, Christchurch.

During fully controlled mechanical ventilation, patient-specific respiratory mechanics can be identified using mathematical models. However, spontaneous breathing (SB) efforts violate model assumptions and result in a loss of precision. This study investigates an iterative learning method to identify respiratory mechanics masked by SB entrainment.

A reconstruction method is proposed to enable model-based identification of underlying respiratory mechanics of breaths masked by SB entrainment. To validate this reconstruction method, it was tested on both simulated SB-entrained breaths and clinical data from a respiratory failure patient with SB entrainment during mechanical ventilation. The reconstruction method normalizes and combines several breathing cycles, resulting in a 'learned' data set with more information. This approach allows respiratory mechanics to be determined more accurately. The simulated airway pressure, patient airway pressure and pressure reconstruction method are shown in Figure 1.

Figure 1: Pressure Reconstruction Method for simulated data (a) and patient data (b &c)



To generate simulated breaths, a single compartment model is used to simulate the airway pressure and flow of a mechanically ventilated patient, with preset respiratory

elastance (25 cmH2O/l) and airway resistance (5 cmH2Os/l). A random sinusoidal waveform (f=1.6-10 Hz, amplitude 5-20% of peak pressure) is superimposed on the airway pressure data to simulate SB entrainment. These simulated breaths affect the model-based identification of respiratory elastance and resistance in the same way as real SB-entrained breaths, but the 'actual' underlying parameters are known.

The respiratory elastance and resistance calculated using the reconstruction method on simulated data were 24.6cmH2O/l, and 5.4cmH2Os/l (< 10% error). Application to patient data showed this method can provide more consistent identified elastance values and thus a better understanding of patient-specific respiratory mechanics without requiring muscle relaxants to paralyze the patient when identifying these values, thus reducing risk and invasiveness.

Association between telomere length and life stress in two New Zealand cohorts, S Jodczyk[1], JF Pearson[2], DM. Fergusson[3], LJ Horwood[3], JK Spittlehouse[3], PR Joyce[2], MB Hampton[1], MA Kennedy[1]; [1]Department of Pathology, [2]Department of the Dean, [3]Department of Psychological Medicine, University of Otago, Christchurch, New Zealand.

Telomeres are specialised structures that cap the ends of chromosomes and maintain the integrity of the genome. They shorten with each cell division, eventually reducing the telomere to a critical length and triggering cell senescence and apoptosis. Telomere length variability in the general population is thought to reflect lifetime exposure to environmental and biological stressors that impact on telomere maintenance. Previous research suggests that different stressors increase the rate of telomere shortening with potential impact on disease states and mortality later in life. Therefore, there is great interest in the application of telomere length measures as a biomarker of health or "biological age".

Average telomere length was measured in genomic DNA from human peripheral blood leukocytes using a quantitative polymerase chain reaction assay. The assay was applied to subjects from two longitudinal health studies, the Christchurch Health and Development Study (CHDS) (n=677), which has followed a birth cohort to age 35 years and the Christchurch Health, Aging and Lifestyle Cohort (CHALICE) (n=351), based on a population sample of 50 year olds.

We established and validated a modified method for accurately measuring telomere length. No associations were found between any biological or environmental stressor and telomere length for either cohort. The stressors examined in the CHDS cohort spanned each developmental domain and included birth weight, childhood maltreatment, substance use and misuse and life events. The correlations were very small ranging from -0.06 to 0.06, and none were statistically significant. The CHALICE cohort assessed biological stressors such as BMI and cholesterol levels and to measure general health status; the short form (SF36) health survey was used. All analyses led to the common conclusion that there was no evidence from these two cohorts that a wide range of life course stressors impacted on telomere length.

Deep brain stimulation of the nucleus accumbens attenuates relapse to cocaine seeking, Jennifer Hamilton[1], Jungah Lee J[1], Juan J. Canales[1]; Department of Psychology, University of Canterbury, Christchurch, New Zealand

Deep brain stimulation (DBS), a form of neurosurgical intervention that is used to modulate the electrophysiological activity of specific brain areas, has emerged as a form of therapy for severe cases of treatment-refractory addiction. Recent research suggests that the nucleus accumbens is a promising target area for DBS in addiction but optimal parameters of stimulation and long-term efficacy are yet to be established. Here, rats were implanted with a stimulating electrode in the right nucleus accumbens and exposed to chronic cocaine self-administration (0.5 mg/kg/infusion). Rats underwent drug seeking tests by exposing them to the self-administration context paired with cocaine challenge (5 mg/kg i.p.) on days 1, 15 and 30 after withdrawal from cocaine self-administration. Low-frequency (LF, 20 Hz) or high-frequency (HF, 160 Hz) DBS was applied for 30 min daily for 14 consecutive days starting one day after drug withdrawal. Rats exhibited robust drug-seeking 1, 15 and 30 days after withdrawal from cocaine self-administration, with responding being highest on day 15. Both LF and HF attenuated cocaine seeking on day 15 post-withdrawal by 36 and 48%, respectively. Both forms of stimulation were ineffective on the tests conducted on days 1 and 30. Neither LF nor HF DBS altered responding for infusions of cocaine or delivery of saccharin solution (0.1%). These data show that repeated unilateral DBS of the nucleus accumbens effectively attenuated cocaine relapse after 15 days of drug withdrawal, with therapeutic-like effects seemingly diminishing after DBS discontinuation. This evidence provides support for DBS as a promising intervention in intractable cases of stimulant addiction.

Magnetic Resonance Spectroscopy: a potential marker for cognitive impairment in Parkinson's disease, M Almuqbel[1,2], TR Melzer[1,2], D Myall[1,2], M MacAskill[1,2], L Livingston[1,2], T Pitcher[1,2], J Dalrymple-Alford[1,2,3] and T Anderson[1,2,4]; [1]Department of Medicine, University of Otago, Christchurch, New Zealand, [2]New Zealand Brain Research Institute, Christchurch, New Zealand, [3]Department of Psychology, University of Canterbury, New Zealand, [4]Department of Neurology, Christchurch Hospital, Christchurch, New Zealand

Parkinson's Disease (PD) affects 2% of those over 60. Beyond various motor symptoms, most patients develop cognitive impairment, and often dementia (PDD). Predictive biomarkers may be useful in future studies to prevent PDD. Our group has identified brain atrophy, loss of microstructure integrity and reduced perfusion in PDD with Magnetic Resonance Imaging (MRI). Magnetic Resonance Spectroscopy (MRS) was used here to identify brain metabolic changes associated with cognitive impairment and dementia in PD.

109 PD and 42 healthy participants completed neuropsychological testing. The patients were classified as either normal cognitive status (PDN, n=63), with mild cognitive impairment (PD-MCI, n=29), or with dementia (PDD, n=17). A $2\times2\times3cm^3$ MRS voxel was placed on the brain's posterior cingulate cortex (PCC) and four metabolites quantified: N-Acetylaspartate (NAA), Choline (Cho), Creatine (Cr), and myo-Inositol (mI). For each ratio (NAA/Cr, Cho/Cr, and mI/Cr), a separate

ANCOVA model assessed group differences with age, sex, years of education, and medication use as covariates. Pairwise comparisons were used to evaluate ratio differences across controls and individual PD groups.

Reduced NAA/Cr, relative to both PDN and controls, was found in PDD and likely reflects neuronal loss in advanced disease. Elevated Cho/Cr and mI/Cr was also evident in PDD and likely indicate gliosis. The intermediate and non-significant metabolic alterations in PD-MCI may suggest relatively preserved neuronal integrity; and therefore potential disease reversibility. MRS of the PCC may be a quantitative marker for cognitive impairment in PD and future anti-dementia therapy.

Rapid osseointegration of titanium scaffolds in a sheep model, S.J. Tredinnick[1,2,4], M.A. Woodruff[3], T.B.F. Woodfield[3,4], J.G. Chase[2]; [1]New Zealand ICT Innovation Institute (NZi3), University of Canterbury, New Zealand, [2]Department of Mechanical Engineering, University of Canterbury, New Zealand, [3]Biomaterials and Tissue Morphology Group, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia, [4]Christchurch Regenerative Medicine & Tissue Engineering Group, Department of Orthopaedic Surgery & Musculoskeletal Medicine, University of Otago, Christchurch, New Zealand

The osseointegration of three novel titanium scaffold materials, Cranial Mesh (CM) and Labrynth (L1 & L2), and a monolithic material, As Grown (AG), was evaluated for efficacy as orthopaedic biomaterials using a drill hole model in 12 sheep. All samples were manufactured by electron beam melting Ti6Al4V powder and shared a microsphere surface topography. A total of 120 cylindrical implants (Ø5mm x 6mm) were press fit in tibial defects in a distribution that mitigated location dependent healing. Scaffold materials had porosities and pore sizes that enabled rapid infiltration and long-term fixation in bone: L1 (73%, 660 μm), L2 (71%, 580 μm) and CM (65%, 480 μm).

Animals were sacrificed at 3, 6, and 12 weeks to investigate early fixation. Cortical bone samples were subjected to mechanical push-out testing and the peak stress and energy to failure (EtoF) measured (n=6). Cortico-cancellous bone samples were embedded in Technovit 9100 methacrylate resin and ground sections prepared (n=4). Midline sections (50 μm thickness) were stained with Goldner's trichrome, then imaged with an x5 objective. Regions of interest were standardized across all samples and blinded semi-automated histomorphometry was performed using OsteoMeasure (OsteoMetrics, Atlanta, USA). Tissue mineralization was compared with von Kossa and methylene blue – basic fuchsin stains.

Push-out stress increased with time for all samples up to maximum of 78% of that of the bone (L1, 12 weeks). Push out stress and EtoF was generally higher for L1 than L2 and CM, and for L1, L2, and CM vs. AG. Extensive direct bone to implant contact (BIC) was observed for the AG surface. Bone in-growth and BIC increased with time for all porous samples and newly formed bone completely infiltrated L1, L2 and CM at 12 weeks. These results show that all samples were able to strongly osseointegrate with the host tissue within 12 weeks.

Sequencing of pharyngeal pressure during wake and sleep swallowing, K Lamvik[1, 2], K Erfmann[2], R Jones[1,2], M-L Huckabee[1, 2]; [1]Communication Disorders, University of Canterbury, Christchurch, [2]Swallowing Rehabilitation Research Laboratory, New Zealand Brain Research Institute, Christchurch.

Recent clinical experience identified a patient cohort with an atypical swallowing impairment (dysphagia) characterized by mis-sequenced pharyngeal constriction, whereby patients are unable to coordinate streamlined bolus transfer from the pharynx to the oesophagus. This disruption in temporal sequencing has been suggested to be a maladaptive compensation to chronic dysphagia rather than a primary pathophysiologic feature. If true, we hypothesized that during sleep, with a reduction of supratentorial modulation, pharyngeal mis-sequencing seen in awake swallowing would return to a normal pattern.

Two male patients (33 and 46 years old, respectively) presented with severe pharyngeal mis-sequencing, with a separation of peak pressures in the upper and lower pharynx > 2 SD below the mean of 239 ms (95% CI, 215-263 ms). The latency of pharyngeal pressure generation was measured with discrete sensor pharyngeal manometry during sleep.

Immediately prior to the sleep study, the mean peak-to-peak latency of Patient 1 was 31 ms (95% CI, -71-133 ms), but this reverted to -58 ms (95% CI, -120-4 ms) when asleep. These outcomes were replicated in Patient 2, whose peak-to-peak latency regressed to -7 ms (95% CI, -83-97 ms) during sleep, from his pre-sleep latency of 93 ms (95% CI, 19-166 ms). Both patients reverted to a pattern of peak pressure in the lower pharynx occurring prior to peak pressure in the upper pharynx during sleep, consistent with their pre-treatment physiology. These case reports negate the role of maladaptive behaviour as a primary aetiology for pharyngeal mis-sequencing, and document the utility of comparing sleep to wake conditions to inform regarding parameters of cortical modulation of swallowing.

Skin Electroporation: Test Cell Re-Configuration, S Becker[1], D Collinson[1], E Mansell[1], J Robertson[1], A Hannon[1], B Zorec[2], N Pavselj[2]; [1]Department of Mechanical Engineering, University of Canterbury; [2]University of Ljubljana, Ljubljana, Slovenia

Skin electroporation involves the application of intense electric fields to in order to radically increase transdermal drug delivery across the skin's barrier layer, the stratum corneum (SC). A generally held view in the field of skin electroporation is that the skin's drop in resistance (to transport) is proportional to the number of pulses administered. Contrary to this belief, previous experiments by this group show that the application of high voltage pulses prior to the application of low voltage pulses act to decrease the total transport compared to the application of low voltage pulses alone. In order to further reconcile these unexpected experimental results with the underlying physics, the current group is redesigning the experimental Franz diffusion test cell specifically for the purposes studying such aspects of enhanced transport.

The transport of calcein (molecular charge: 4-) across dermatomed porcine skin was previously studied [2] in standard vertical glass Franz diffusion cells that are thermo

regulated at 37 °C by water circulation. A unipolar square wave pulse generator Cliniporator (Igea, Italy) was used for pulse delivery. The concentration of calcein was measured with spectrofluorometer (Jasco, FP-6300). The ability to perform experiment in the previous study, however was constrained by the configuration of the existing diffusion cells. The current project is instead using the experimental protocol as the criteria in order to design the geometry of the diffusion cells.

Theoretical investigations show that the increase in permeability to transport resulting from the large LTR evolution is hindered when the pre-existing SC has a high density of very small defects. Such defect size and distribution are attributed to the high intensity HV pulse. In order to better capture electroporation data, we use a diffusion cell that maximizes the ratio of aperture size to receiver volume that incorporates active enhancement technology into the test cell.

Trace amine-associated receptor 1 activation modulates methamphetamine's neurochemical and behavioural effects, Yue Pei[1], Rachel Cotter[1], Anja Harmeier[1], Damiana Leo[1], Raul R. Gainetdivov[1], Marius Hoener[1], Juan J. Canales[1]; Department of Psychology, University of Canterbury, New Zealand

Methamphetamine (METH) is currently a major source of public concern in New Zealand, but treatments for METH addiction are not yet available. The newly discovered trace amine-associated receptor 1 (TAAR1) has emerged as a promising target for treatment in stimulant addiction due to its ability to strongly regulate dopamine function. Here, we tested in rats the ability of RO5203648, a selective TAAR1 partial agonist, to modulate METH's physiological and behavioural effects. In experiment 1, RO5203468 dose- and time-dependently altered METH-induced locomotor activity, producing an early attenuation followed by a late potentiation of METH's stimulating effects. In experiment 2, rats received a 14-day treatment regimen during which RO5203648 was co-administered with METH. RO5203648 dose-dependently attenuated METH-stimulated hyperactivity with the effect becoming more pronounced as treatment progressed. After chronic exposure and 3-day withdrawal, rats were tested for locomotor sensitization. RO5203648 administration during the sensitizing phase prevented the development of METH sensitization. However, RO5203648, at the high dose, cross-sensitized with METH. In experiment 3, RO5203648 dose-dependently blocked METH self-administration without affecting operant responding maintained by sucrose, and exhibited lack of reinforcing efficacy on its own when tested as a substitute for METH. Neurochemical assays revealed that RO5203648 did not affect METH-mediated DA efflux and uptake inhibition in striatal synaptosomes. However, the results of in vivo microdialysis experiments showed that RO5203648 was able to acutely inhibit METH-induced accumulation of DA overflow in the nucleus accumbens. Taken together, these data highlight the significant potential of TAAR1 to modulate METH's neurochemical and behavioural effects, thus supporting the candidacy of TAAR1 as a therapeutic target for stimulant addiction.

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Preeclampsia and the risk of later life cardiovascular disease

It has been widely thought that the effects of hypertension in pregnancy reversed after delivery and hypertension values returned to their pre-pregnancy level as it was seen as a disease of short duration in otherwise healthy young women. However, recent studies have demonstrated the principal underlying abnormality, endothelial dysfunction, remains in women who had preeclampsia and that it is this damage that increases the risk of developing cardiovascular disease in later life.

This comprehensive review examines this problem in depth and considers the abnormalities in lipid and lipoprotein metabolism that occur in pregnancy. The authors note that it remains uncertain whether the statins themselves are safe in pregnancy and as always, caution needs to be apparent in any investigation in pregnancy.

The authors conclude that although measures to control blood pressure in pregnancy have been in place for several decades, there is little consensus around the treatment of mild to moderate rises and whether treatment in pregnancy contributes to an improvement in overall cardiovascular risk. Targeting early blood pressure and lipid evaluations (annual or bi-annual checks) and appropriate intervention could be recommended to women whose pregnancies are complicated by preeclampsia and gestational hypertension.

Heart, Lung and Circulation 2014;23:203–12.

Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care

Does symptom management in patients with acute respiratory tract infections improve when advice is given to use ibuprofen alone or ibuprofen and paracetamol compared with paracetamol alone; to take regular doses rather than as required; and to use steam inhalation compared with no inhalation?

This question is examined in this randomised trial carried out in Southampton, England. 889 patients aged 3 years or more (median 30 years) with acute respiratory tract infections were randomised to 5 options—take paracetamol; ibuprofen; or both; dosing of analgesia (take as required *v* regularly); and steam inhalation (no inhalation *v* steam inhalation). Outcomes sought were symptom severity on days two or four (primary outcome), temperature, antibiotic use, and reconsultations.

The researchers report that “none of these strategies significantly improved symptom control. Advice to use ibuprofen might help more among those with chest infections and in children but is also associated with more reconsultations with new or unresolved symptoms.”

BMJ 2013;347:f6041.

Expanding role of ultrasonography

Diagnostic ultrasonography has replaced auscultation as the primary method of evaluating the mechanics of the heart and peering into the abdomen, vasculature, and uterus without exposing patients or fetuses to ionizing radiation.

This perspective paper reviews the future for ultrasonography bearing in mind that ultrasound technology has advanced so much—viz ultrasound devices are available that can be carried in the pocket. Some American medical schools now offer ultrasound training early in the undergraduate curriculum.

Apart from the fact that these devices are very expensive (about US$10,000) there are other problems. The risk of misdiagnosis is high when diagnostic ultrasound is used by inexperienced practitioners. Another concern is that these devices may distract students from the core principles of physical diagnosis and interpose another layer of technology between doctor and patient.

N Engl J Med 2014;370:1083–5.

Multitarget stool DNA testing for colorectal-cancer screening?

The use of fecal immunochemical test (FIT) for haemoglobin in the stool is well established as a colorectal cancer screening test. This study evaluates whether a multitarget stool DNA test might be superior. They have compared these two tests in 9989 subjects with an average risk for colorectal cancer.

The researchers report significantly better results with the DNA test with respect to both colorectal cancer and precancerous lesions. However, specificity was lower with the DNA test resulting in a false positive result in approximately 10% of cases.

An editorial commentator applauds the study but notes that the greater expense and lower specificity of the DNA test are an impediment.

N Engl J Med 2014:370:1287–97.

THE NEW ZEALAND MEDICAL JOURNAL
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Possession of objectionable material (Med 12/228P)

Charge

A Professional Conduct Committee (PCC) charged that Dr Vikram Abraham Joseph (the Doctor) had been convicted of offences that reflected adversely on his fitness to practise as a medical practitioner. The particulars of the charge were:

On 2 July 2012 in the District Court, the Doctor pleaded guilty to and was convicted of 6 charges of possession of objectionable material (including videos depicting children aged between 5 and 14 years engaged in sexual intercourse and other penetrative sexual acts with adults and one another) which are offences each punishable by a term of imprisonment not exceeding 5 years.

Finding

The Doctor admitted the charge and that the convictions reflected adversely on his fitness to practise. The Tribunal found that the Doctor's conviction on each of the six charges in question, individually and cumulatively reflected adversely on his fitness to practise medicine.

Background

The Doctor's flatmate entered his bedroom in their flat and accessed the Doctor's computer. The flatmate saw several files with titles that led her to believe that they contained child pornography. The flatmate subsequently advised the Police that she suspected the Doctor of downloading child pornography. As a result Police seized the Doctor's computer and located 6 videos involving exploitation of children for sexual purposes. The Doctor was charged, convicted and sentenced for possession of objectionable material.

Penalty

The Doctor was censured and suspended from practice for 12 months. On resumption of practice the Doctor was ordered to meet the costs of and practise under conditions which are summarised below:

- He is to provide a written undertaking to the Tribunal and the Medical Council that he will not access objectionable material.
- He is to undertake clinical psychological treatment and assistance as required by the SAFE Network programme or an alternative clinical psychological treatment programme if the Medical Council is satisfied that the alternative programme will meet the Doctor's psychological needs.
- He is to comply with any conditions imposed by the Health Committee of the Medical Council.
- On completion of his treatment he is to provide a psychological assessment that satisfies the Medical Council that he is fit to practise.

- He is required to have professional supervision to monitor and report on his health as required by the Medical Council.
- If he is involved in training, a support person, approved by the Medical Council, must be present in each clinical attachment if he is in the presence of any child under 16 years. The support person will be responsible for supervision. However, when he is treating a patient over 16 years where there are children present, the presence of the patient will suffice as supervision for those children. He is to meet any costs associated with this condition.
- If he examines or physically treats a patient under the age of 16 years, a chaperone must remain present at all times during the examination or treatment. He is to meet the cost of the chaperone.
- He is to advise any future employer of the Court convictions, the Tribunal decision and the above conditions.

The Tribunal ordered the Doctor to pay costs of $12,173.

The Tribunal directed that a notice stating the effect of its decision be published in the New Zealand Medical Journal and the decision and summary be published on the Tribunal's website.

THE NEW ZEALAND MEDICAL JOURNAL
Journal of the New Zealand Medical Association

John William Macdonald Boyd

The family's favourite photo of John Boyd shows him taking the polar plunge from an upper deck of Russian cruise ship *MV Akademik Shokalskiy* in the Antarctic. The Linwood GP was an adventurer—a flying doctor who also sailed, an alpine skier who also climbed mountains, a 4WD trekker and jetboater. The risks he took were meticulously calculated, enabling him to survive in extreme conditions. Tall, slim and fit, he died suddenly at home. He was 58.

He was born to doctor parents in Blenheim but moved to Wellington with his family when he was 6.

He learned to sail on Wellington Harbour and developed a passion for setting and surpassing challenges.

Leaving Wellington College he studied medicine at Otago University and completed his clinical training at Christchurch Hospital.

He graduated and served as an intern at Auckland's Middlemore Hospital. His registrar there was Dr Robynanne Milford. They fell in love and married. Their daughter, Zanny, is one of 13 doctors in the wider family.

He and Robynanne established the Ponsonby Medical Centre in 1982. They remained a devoted couple and professional partners in Auckland, Queenstown and Christchurch until his death.

Adventure activities began in a mundane way—grubbing gorse from land they bought as investments. Boyd had a love-hate relation with gorse, Robynanne says: "He hated it and he loved to grub it out."

He learned to fly and competed in the 1991 race around New Zealand. With Robynanne as navigator, Boyd flew a Cessna 172 on 15 legs of the circumnavigation. Bad weather caused the cancellation of the 16th (final) leg and the race was never finished.

After winning a national sailing title, he competed in the Kenwood Cup off Hawaii as a member of Bevan Woolley's crew. Years later, he bought a 42-foot yacht with the intention of sailing solo to Tonga and back. Sons Oliver and Sebastian insisted he take them as crew and he relented. Two boats were lost in a storm on the way but the Boyds made it unharmed. They returned home within the 3 months they had allowed.

Boyd sailed the inland waterways of North America—a huge "circle" from Miami to Montreal, New Orleans and back to Miami.

He climbed almost to the summit of Aoraki-Mt Cook. Bad weather forced Boyd and others of his party to turn back at the summit rocks. A Canadian and an American climber continued upwards. Conditions deteriorated and they fell to their deaths.

Boyd enjoyed alpine skiing and acted as ski doctor at Queenstown. He served also as a police medical officer.

His maritime adventures included three Antarctic cruises as ship's doctor and an Arctic Circle venture from Norway to Greenland. These trips were tough going as he was sole doctor on board and was on-call 24 hours a day with no nursing support. He also drove Zodiac crafts to ferry passengers between ship and shore. In the Arctic expedition he put his shooting experience to good purpose, carrying a rifle in case of polar bear attack.

He was to have done the North- West Passage but the expedition was cancelled. He was booked on a cruise of Scotland's Outer Hebrides but his unexpected death intervened.

Boyd's sons say he was a careful and systematic planner with an eye for detail. He was a stickler for checklists.

He and Robynanne bought land in Queenstown during their four years there. Boyd designed a grand home in Queenstown. A draughtsman finished the drawings but Boyd did much of the work, including building, plastering, painting, electrics and plumbing. The finished house made the house-of-the-year finals of magazine House and Garden. It was an early example of the modern use of corrugated steel wall cladding.

Moving to Christchurch, he renovated a stately house on Mt Pleasant. He and Robynanne bought an 80-hectare section, steep, mostly unfenced and covered in gorse and weeds, near Oxford. Camping in a tractor shed Boyd got rid of the gorse and turned the land into a productive farm. Apart from hiring contractors for a few jobs, he did the work himself. It was all for the challenge, his family says.

Zanny says her father was a "brilliant" GP and obstetrician. He kept up to date with new advances, was attentive to details, was fast and efficient and made good decisions. She and many other doctors valued his professional advice.

He was involved in medical politics through the NZ Medical Association and helped design strategy for sexual abuse care.

Robynanne says this quiet man loved intellectual debate and testing people's opinions as a "devil's advocate". He had a broad general knowledge and a photographic memory.

John William Macdonald Boyd, born Blenheim, 27 March,1956; died Christchurch, 27 April 2014. Survived by wife Robynanne, daughter Alexandra (Zanny) and sons Oliver and Sebastian.

Mike Crean wrote this obituary, which originally appeared in *The Press* newspaper (Christchurch) on 10 May 2014. We thank them for the reprint permission.

