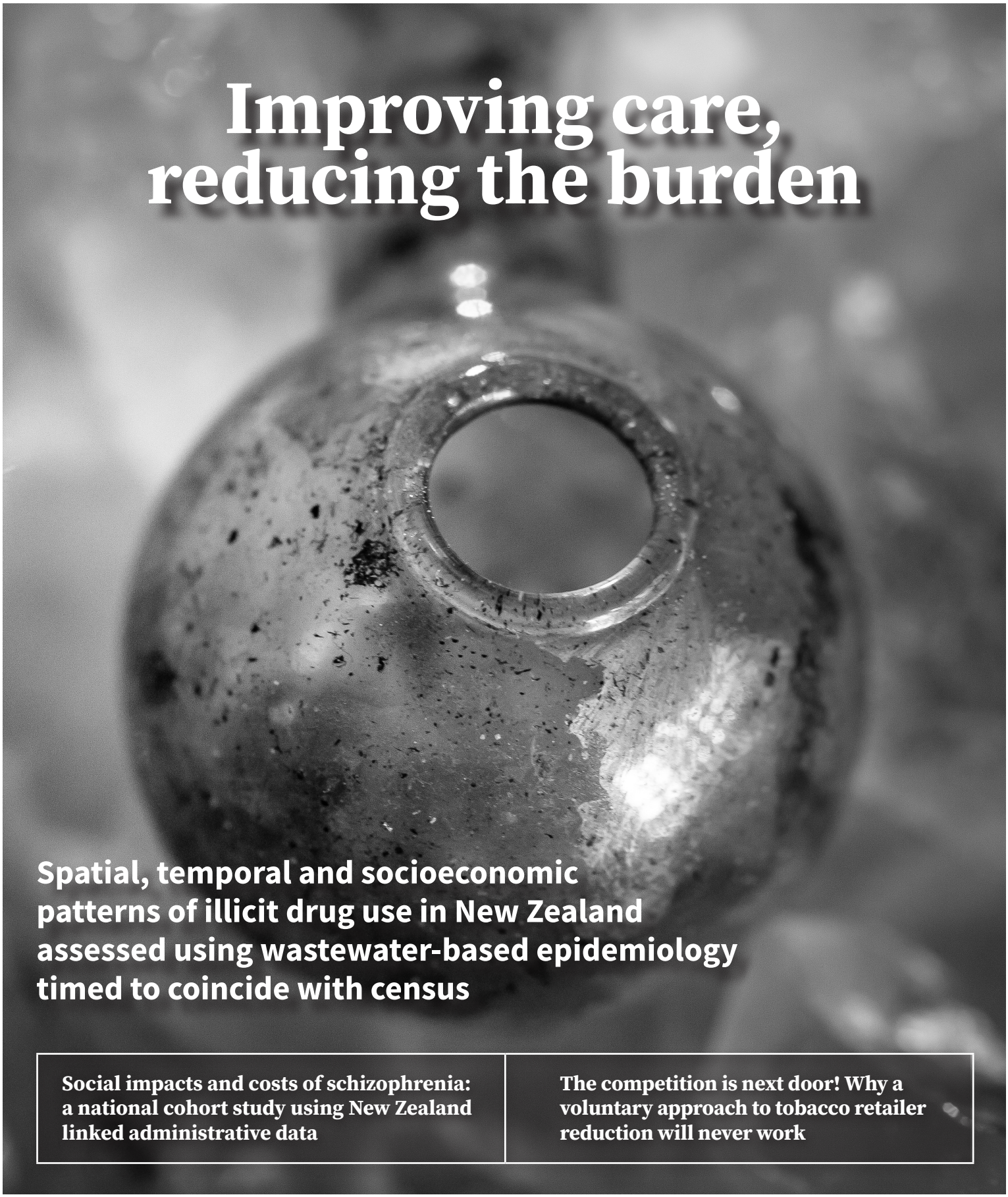
The
New Zealand
Medical Journal
Te ara tika o te hauora hapori

Journal of the New Zealand Medical Association

Vol 134 | No 1537 | 25 June 2021



Improving care, reducing the burden

Spatial, temporal and socioeconomic patterns of illicit drug use in New Zealand assessed using wastewater-based epidemiology timed to coincide with census

Social impacts and costs of schizophrenia: a national cohort study using New Zealand linked administrative data

The competition is next door! Why a voluntary approach to tobacco retailer reduction will never work

The New Zealand **Medical Journal**
Te ara tika o te hauora hapori

Publication Information

published by the New Zealand Medical Association

To contribute to the *NZMJ*, first read:
www.nzma.org.nz/journal/contribute

To subscribe to the *NZMJ*, email

julie@nzma.org.nz

Subscription to the *New Zealand Medical Journal* is free and automatic to NZMA members.

Private subscription is available to institutions, to people who are not medical practitioners, and to medical practitioners who live outside New Zealand. Subscription rates are below.

All access to the *NZMJ* is by login and password, but IP access is available to some subscribers.

Read our Conditions of access for subscribers for further information
www.nzma.org.nz/journal/subscribe/conditions-of-access

If you are a member or a subscriber and have not yet received your login and password, or wish to receive email alerts, please email: julie@nzma.org.nz

The NZMA also publishes the *NZMJ Digest*. This online magazine is sent out to members and subscribers six times a year and contains selected material from the *NZMJ*, along with all obituaries, summaries of all articles, and other NZMA and health sector news and information.

Subscription rates for 2021

New Zealand subscription rates		Overseas subscription rates	
Individuals*	$349	Individual	$486
Institutions	$604	Institutions	$650
Individual article	$33	Individual article	$33

*NZ individual subscribers must not be doctors (access is via NZMA Membership)
New Zealand rates include GST. No GST is included in international rates.
Note, subscription for part of a year is available at pro rata rates.
Please email julie@nzma.org.nz for more information.
Individual articles are available for purchase by emailing nzmj@nzma.org.nz

ISSN 1175-8716

Spatial, temporal and socioeconomic patterns of illicit drug use in New Zealand assessed using wastewater-based epidemiology timed to coincide with census

Mackay Price, Chris Wilkins, Benjamin J Tscharke, Tom Baker, Jochen F Mueller, Sam Trowsdale

Wastewater samples were collected across seven sites in three regions of New Zealand to coincide with the 2018 census. This provided a way to quantify drug use and sociodemographics and assess the accuracy of drug survey techniques. The data show the expected regional, sub-regional and temporal patterns of illicit drug use, such as more MDMA consumed on the weekends than during the week. The key take home messages is that, in combination with complementary data like censuses, surveys and seizure information, wastewater analysis can help guide harm reduction policy for the wellbeing of New Zealand.

Reducing the MRI outpatient waiting list through a capacity and demand time series improvement programme

Heera Bhullar, Bernadette County, Stuart Barnard, Anne Anderson, Mary E Seddon

A partnership between Ko Awatea and the radiology department at Counties Manukau District Health Board aimed to match the demand for magnetic resonance imaging (MRI) with the available capacity. Using quality improvement techniques, the team successfully and sustainably reduced the MRI waiting list over a two-year period, reducing the number of patients waiting from nearly 2,000 to just over 400. The innovative solutions to segment the waiting list and match capacity to demand may be instructive for other radiology departments, and other waiting list scenarios.

Does research help to inform a district health board's purpose? A qualitative thematic analysis of clinician researcher views

Lorraine Neave, Duncan Reid, Brian McKenna

This study explored, from a district health board (DHB) staff perspective, what the enablers and barriers to doing research were and whether the outcomes of research activity helped it deliver best care. It has provided insight into how organisational factors can negatively influence engagement in and with research and thereby impact the potential for research to inform the DHB's overarching purpose. These factors are all modifiable influences. The themes offer a direction for the DHB's future research strategy, where research activity is integrated into practice, where research evidence is discussed and where research achievements are celebrated. The findings from this study will likely resonate across New Zealand's DHB landscape.

How common are non-acute coronary syndrome (ACS) diagnoses in patients with suspected ACS investigated with coronary angiography in New Zealand? (ANZACS-QI 58)

Charles Yao-Cheng Ho, Mildred Lee, Seif El-Jack, Peter Barr, Mark Simmonds, Gerry Devlin, Philip D Adamson, Michael Williams, Andrew J Kerr

Falsely activated coronary catheter laboratories for acute ST elevation heart attacks are low in New Zealand. Non-ACS conditions receiving invasive coronary angiography varies between DHBs requires more investigation.

Antipsychotic and sedative medication use in long-term care facilities providing dementia care

Etuini Ma'u, Janine Burton, Elizabeth Fussell

This study aimed to quantify the use of antipsychotic and sedative medications in residents with dementia in long-term care facilities in the Waikato and identify factors associated with the prescription of these medications. Despite the increasing evidence around the relatively poor efficacy and increased risks associated with antipsychotic and sedative prescription in individuals with dementia, this study shows the use of these medications in dementia care and psychogeriatric facilities remains high, with 48.2% of residents in this study currently prescribed an antipsychotic and 22.1% prescribed a sedative. Furthermore, less than 20% of those prescribed an antipsychotic or a sedative had the most recent dose change occur within the 12 weeks recommended by guidelines, with over 30% of those prescribed an antipsychotic and 48% of those prescribed a sedative not having their dose adjusted for over a year. With clear evidence of the risks of antipsychotics in dementia, the proportion of residents prescribed an antipsychotic or sedative in this study, in conjunction with the prolonged duration of prescription, is cause for concern and needs addressing.

Social impacts and costs of schizophrenia: a national cohort study using New Zealand linked administrative data

Sheree Gibb, Naomi Brewer, Nicholas Bowden

We used data for the whole New Zealand population to compare people diagnosed with schizophrenia to similar people without schizophrenia. Compared to people without schizophrenia, people with schizophrenia experienced more adverse outcomes, including: unemployment; lower income; contact with the criminal justice system; and hospitalisation (for both mental and physical health reasons). The government costs (money spent by the New Zealand government on people's social, health and other services) were six times higher for people living with schizophrenia than for people without schizophrenia. The biggest cost differences were in healthcare, benefits and social housing.

Cannabis Legalisation and Control Bill: should doctors be concerned?

Guna Kanniah, Shailesh Kumar

The regulatory and policy changes about legalising cannabis correlate with heightened acceptance, reduced perception of risks and an increase in cannabis use in both adults and adolescents, and controlled access to cannabis can be associated with better outcomes. The evidence for use in treating psychiatric illnesses is still lacking, and people who at a greater risk of experiencing adverse mental health outcomes will still be vulnerable under the proposed legislation. Regular cannabis use predicts an increased risk of schizophrenia. Cannabis is known to disproportionately harm people who have either a risk of mental illnesses or have existing mental illness. This significant at-risk population will not be protected by the proposed legislation in its current form. Data from other countries showing the beneficial effects of cannabis use in psychiatric populations are limited and conflicting, and potential harms in patients with psychotic and mood disorders have been increasingly documented. Further high-quality studies examining the effect of cannabis/cannabinoids on mental disorders are needed before any such policy changes.

Zoledronate-induced anterior uveitis, scleritis and optic neuritis: a case report

Laura E Wolpert, Andrew R Watts

Zoledronate, a bisphosphonate medication used to treat osteoporosis, can cause inflammation of different parts of the eye. Inflammation of the iris, known as anterior uveitis, happens in about 1% of people treated with bisphosphonates. This paper describes a case of a female patient who developed inflammation of the iris, the sclera (the white of the eye) and the optic nerve following treatment with zoledronate.

The competition is next door! Why a voluntary approach to tobacco retailer reduction will never work

Richard Portch

This paper describes the distribution of tobacco retailers across Tamaki Mākaurau and compares them with community pharmacies. We used a new methodology for attributing the deprivation and demographics of neighbourhood surrounding each retailer. Our research identified significant differences in how tobacco retailers and community pharmacies are distributed across the region, including that tobacco retailers are more likely to be in residential areas than community pharmacies and are more likely to have another tobacco retailer in close proximity to their location.

ISSN 1175-8716

Improving care, reducing the burden

Wayne Miles

The conclusion from a meta-analysis of studies of the economic burden of schizophrenia was that the enormous burden is suggestive of the inadequate provision of healthcare services to patients with schizophrenia.[1] Better resource allocation and policy-orientated research is seen as a solution to this problem. The article in this *New Zealand Medical Journal*[2] provides an excellent summary of current state of play in New Zealand. It highlights the health, social and economic outcomes for those with the disorder.

Recent exploration of what matters for people with schizophrenia highlighted the need to feel safe, the opportunity for employment, access to good healthcare support and having meaningful social relationships.[3] These factors were very similar to findings of a local (unpublished) review of the long-term outcomes for people who have been through our anti-psychotic treatment trials.

The age of the institution may have passed but the messages emerging from work such as that of Sheree Gibb et al[2] might be that we still have a long way to go to deliver healthcare, social and occupational supports to people with schizophrenia that does not disadvantage them or stigmatise them.

There are good guidelines for the treatment of schizophrenia.[4] I suspect the problem is that we do not deliver according to these best evidence-guided recommendations.

The time between onset of symptoms and beginning treatment remains disappointingly high. We are used to strong pushes for the early identification of cancer because there is strong evidence that early detection and appropriate evidence-based interventions significantly alter the disease course. We do not see such initiatives for psychosis. An elegant Scandinavian study which was set up to examine differences with true early detection of psychosis showed that early treatment for first psychosis had positive effects on clinical and functional outcomes.[5]

Reasons for delay include the stigma attached to any diagnosis of a mental illness, and especially to that of schizophrenia. It is also well recognised[6] that the disorder itself causes a lack of awareness of the symptoms (anosognosia), such that an individual experiencing psychotic symptom will not have awareness of these. We have a long way to go the shift public attitude towards mental illness and to create safe environments where the young people experiencing their first episode of a psychotic disorder (illness onset is typically late adolescence to early adulthood) can present. They will often be reliant on family or close friends to assist them recognise a problem and seek help for it; thus the point of care needs to be user friendly for these support people also.

Though I do not have the data to support my clinical impression, it is likely that many presentations with schizophrenia are in crisis situations where there are concerns about the risk of the person with the disorder. They do not get seen in primary health settings, where one would ideally want an illness like this to be assessed and treated. By the time they present there is usually considerable disruption in their lives; relationships are challenged or disrupted; usual occupation or education and recreational pursuits have ceased. This loss of the usual social supports will coincide with a time of immense personal angst; the traumatic experience of identity dissolution, boundary loss and the like should not be underestimated. One only has to consider what it must be like to have some sinister voice that continues to berate you or threaten you; then, if you are brave enough to mention it to others, you then get told they cannot hear the voice—how do you assimilate that?

For my goal of dedicated public health campaigns that target early identification of and rapid interventions for those at risk of schizophrenia, it will be necessary to address the pervasive public prejudice and discrimination. This is no simple task and the available worldwide evidence of success for anti-stigma campaigns for mental illness is not reassuring.[7,8] Strategies are generally described as contact with consumers, education campaigns and social activism and protest. Both contact approaches and education campaigns do have small to medium effect sizes. There is no study of social activism approaches.

I am hopeful that dissemination of the costs of schizophrenia, both to the people who experience it and to the population as a whole, might stimulate people in influence to take the challenge to address the public health importance of reducing stigma, thereby enhancing the possibility of early access to best evidenced treatments.

Why we want to treat early and maintain good treatment is because it not only produces better outcomes regarding illness experience and function, but because it is also linked to arresting (and perhaps improving) loss of cortical matter[9] and decreasing the effect of schizophrenia on reducing life expectancy.[10] A German study[11] carefully reviewed the achievement of remission (using well defined criteria[12]) and suggests there is good reason for expectation of positive outcome from good treatment.

Competing interests:
Nil.

Author information:
Wayne Miles: Clinical Director Research and Knowledge, Waitemata DHB; Clinical Associate Professor Department of Psychological Medicine, University of Auckland.

Corresponding author:
Assoc Prof Wayne Miles, Clinical Director Research and Knowledge, Waitemata DHB; Clinical Associate Professor Department of Psychological Medicine, University of Auckland
Wayne.miles@waitematadhb.govt.nz

URL:
www.nzma.org.nz/journal-articles/improving-care-reducing-the-burden

REFERENCES

1. Chong HY, Teoh SL, Wu DB-C, Kotirum S,Chiou C-F, Chaiyakunapruk N. Global economic burden of schizophrenia: a systematic review. Neuropsychiatric Diseases and Treatment. 2016; 12: 357-73.
2. Gibb S, Brewer N, Bowden N. Social impacts and costs of schizophrenia: a national cohort study using New Zealand linked administrative data. N Z Med J. 2021; 1537(134):66-83
3. Lloyd H, Lloyd J, Fitzpatrick R, Peters M. The role of life context and self-defined well-being in the outcomes that matter to people with a disagnosis of schizophrenia. Health Expectations. 2017; 20: 1061-72.
4. Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, Killackey E, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Australian and New Zealand Journal of Psychiatry. 2016; 50 (5); 410-72.
5. Larsen TK, Melle I, Auestad B, Haahr U, Joa I, Johannessen O, et al. Early detection of psychosis: positive effects on 5-year outcome. Psychological Medicine. 2011; 41: 1461-69.
6. Pia L, Tamietto M. Unawareness in schizophrenia: Neuropsychological and neuroanatomical findings. Psychiatry and Clinical Neurosciences. 2006; 60: 531-7.
7. Corrigan PW, Morris SB, Michaels PJ, Rafacz JD, Rusch N. Challenging the public stigma of mental illness: a meta-analysis of outcome studies. Psychiatric Services. 2012; 63: 963-73.
8. Morgan AJ, Reavley NJ, Ross A, Too LS, Jorm AF. Intervetions to reduce stigma towards people with severe mental illness: Systematic review and meta-analysis. Journal of Psychiatric Research. 2018; 103:120-33.
9. van Haren NEM, Hulshoff Pol HE, Schnack HG, Cahn W, Mandl RCW, Collins DL, et al.Focal grey matter changes in

schizophrenia across the course of the illness: a 5-year follow up study. Neuropsychopharmacology. 2007; 32: 2057-66.

10. Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A et al. 11 Year follow up of mortality in patients with schizophrenia: a population-based study (FIN11 study). The Lancet. 2009; 374:620-7.
11. Schennach R, Riedal M, Obermeir M, Jager, M, Schmauss M, Laux G et al.Remission and recovery and their predictors in schizophrenia spectrum disorders: Results from a 1 year follow-up naturalistic trial. Psychiatric Q. 2012; 83: 187-207.
12. Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR, et al. Remission in schizophrenia: propsed criteria and rationale for consensus. American Journal of Psychiatry. 2005: 162: 441-9.

Spatial, temporal and socioeconomic patterns of illicit drug use in New Zealand assessed using wastewater-based epidemiology timed to coincide with the census

Mackay Price, Chris Wilkins, Benjamin J Tscharke, Tom Baker, Jochen F Mueller, Sam Trowsdale

ABSTRACT

AIMS: A discrete experiment in wastewater-based epidemiology (WBE) timed to coincide with the census was used to investigate the spatial, temporal and socioeconomic patterns of illicit drug consumption in Auckland, Bay of Plenty and Canterbury.

METHODS: For seven consecutive days over census week (6 March 2018), wastewater was sampled from seven wastewater treatment plants and analysed for methamphetamine, cocaine (as benzoylecgonine) and 3,4-methylenedioxymethamphetamine (MDMA). Detailed sewer catchment maps were developed and, together with the data, were used to analyse drug consumption.

RESULTS: Methamphetamine (mean 22.9 ± 9.9 doses/day/1000 people) was the most consumed drug, followed by MDMA (mean 1.7 ± 1.5 doses/day/1000 people) and cocaine (mean 0.5 ± 0.3 doses/day/1000 people). Methamphetamine consumption (and to a lesser extent MDMA) was high compared to that reported for Western nations, while cocaine consumption was extremely low. Cocaine and MDMA consumption were higher in cities compared to towns. In contrast, methamphetamine was typically higher in towns. Cocaine and MDMA were consumed more at weekends. Methamphetamine use was more consistent throughout the week. MDMA and cocaine were correlated with socioeconomic advantage, whereas methamphetamine was correlated with disadvantage.

CONCLUSIONS: This paper contextualises illicit drug use in three New Zealand regions containing 18.3% of the national population and confirms the pervasiveness of methamphetamine consumption in New Zealand towns. This work demonstrates how WBE can be used to explore the socioeconomic dimensions of drug use when duly combined with other data sources like censuses.

Accurate and timely information about drug consumption is important for informing health and enforcement policy. Such information is often obtained from population surveys, drug seizures and hospital and drug treatment admissions, which have important limitations.[1] Surveys can suffer from self-report biases (due to social stigma and concerns about legal repercussions) and can underrepresent certain demographics (eg, homeless, young, rural).[2,3] Drug seizures are often linked to police priorities and may reflect increased enforcement, resources or chance encounters rather than drug availability.[4] Hospital and treatment centre admissions can fail to capture recreational drug use and can under-represent those

users that do not seek help or experience medical problems.

Wastewater-based epidemiology (WBE) is an established complementary approach to assess drug use that can support these other sources of information. Through the chemical analysis of drugs excreted into reticulated sewage systems, WBE provides quantitative measures of community-scale drug consumption that are not subject to self-report biases and aggregates from all dwellings connected to the sewer network. This mitigates some of the issues of under-reporting common to population surveys.[1] WBE can be conducted frequently, which enables assessments of short-term fluctuations in drug use.

WBE has been used to assess spatio-temporal patterns in drug consumption at international, national and regional scales.[5–8] In Europe, cocaine and MDMA consumption is reportedly higher in cities compared to smaller towns, whereas methamphetamine consumption tends to be similar in both.[5,8] In Australia, drug use is generally higher in regional communities than cities, except for cocaine.[9] However, these urban–rural patterns vary across regions,[9] a reminder of the need to sample across a range of communities.

To better explain and understand these spatial patterns of drug use, attention has recently turned to examine correlations between WBE and socioeconomic information. For example, significantly higher methamphetamine use was observed in areas characterised by socioeconomic disadvantage.[10] A few studies have timed WBE to coincide with the census to better estimate drug consumption and relate such patterns to demographics.[10–13]

New Zealand has several drug monitoring systems in place, including the New Zealand Health Survey.[14] Previous drug-monitoring studies, like the Arrestee Drug Use Monitoring study (NZ-ADUM) and the Illicit Drug Monitoring System (IDMS), conducted physical interviews of frequent drug users in New Zealand's main cities, unintentionally creating the impression that drug use is an urban phenomenon.[15,16] This is perhaps unsurprising given the relative difficulty of recruiting drug-using populations for physical interviewing in more isolated, rural communities.[2] Anecdotal evidence, however, suggests that methamphetamine use is proliferating in towns and rural communities,[17–19] and this is corroborated by data on the location of clandestine laboratories[20] and drug availability.[21] WBE is gaining traction in New Zealand,[22–24] and the recently commissioned National Wastewater Testing Programme (NWTP) has expanded national understandings of illicit drug use by reporting findings at the regional level.[25] To complement this work, we present data from WBE that was specifically timed to coincide with the census and report on the spatial, temporal (within-week) and socioeconomic patterns of illicit drug use in three regions of New Zealand.

Methods

Sites and catchment mapping

Wastewater samples were collected at seven wastewater treatment plants (WWTP) across three regions of New Zealand (Table 1; Figure 1). The WWTPs were selected to cover a range of population sizes and land uses (ie, cities and towns) and enable both inter- and intra-regional comparisons to be drawn. Site selection was also pragmatic, based on our contacts in the wastewater industry. Collectively, these sites service 18.3% of the New Zealand population. Catchment maps were developed by superimposing geo-referenced sewer pipe information onto census statistical area 1 geographies[26] and trimmed to remove properties not connected to the wastewater assets. Populations for each site were calculated as the sum of the 2018 census night (*de facto*) population for these trimmed areas. The census-night dataset accounts for all individuals physically present and therefore includes domestic and international tourists.

There are well-documented issues with the 2018 census, including a lower than anticipated response rate.[27] This was not ideal, but through sampling across census we were able to capture the most accurate and representative picture of the people present in our study sites at the time of sewer monitoring. This is an improvement on much of the published WBE literature that typically relies on population estimates derived from the design capacity of the WWTP and/or a previous census, both of which may be years out of date.

Wastewater sampling and chemical analysis

Wastewater was sampled daily at each WWTP for seven consecutive days coinciding with the New Zealand census on 6 March 2018. Samples were 24-hour composites collected using time-proportional sampling of 100 mL of raw, screened influent every 15 minutes starting 6 am daily. At the end of each 24-hour period, samples were mixed and reduced to a 1-litre volume. Mechanical failure of the autosampler at site C1 was compensated for by collecting three 1-litre grab samples every eight hours (at 8 am, 4 pm and 12 am). At the end of each 24-hour period, samples were frozen, and at the end of the week they were transported on ice to the University of Auckland laboratory. During transit, two samples leaked (A3 Saturday and B1 Wednesday) and were not analysed. Within two days of arriving at the lab, samples were defrosted, filtered through a 0.2 micrometre cellulose filter and acidified to pH 2 with 2 M hydrochloric acid. The processed samples were refrozen at -80 °C and transported on ice to the University of Queensland where they were stored frozen and analysed within two months.

Sample analysis followed a validated direct injection analytical method.[28,29] Samples were defrosted and spiked with deuterium-labelled chemical standards to correct for instrument variability and matrix effects during analysis. Drug concentrations were measured by direct injection using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Concentrations of each drug/metabolite were quantified using a calibration curve of the ratio between the signal response for the unlabelled authentic drug standard and deuterated analogue. Samples were analysed for methamphetamine, cocaine (as benzoylecgonine) and 3,4-methylenedioxymethamphetamine (MDMA). Benzoylecgonine was selected as the target residue rather than cocaine because benzoylecgonine is solely an excretory by-product of cocaine consumption (unlike the parent drug), and concentrations therefore will be unaffected by the flushing of cocaine.[1] The limit of detection (LOD) for all metabolites was 33 ng/L.

Calculation of per capita consumption

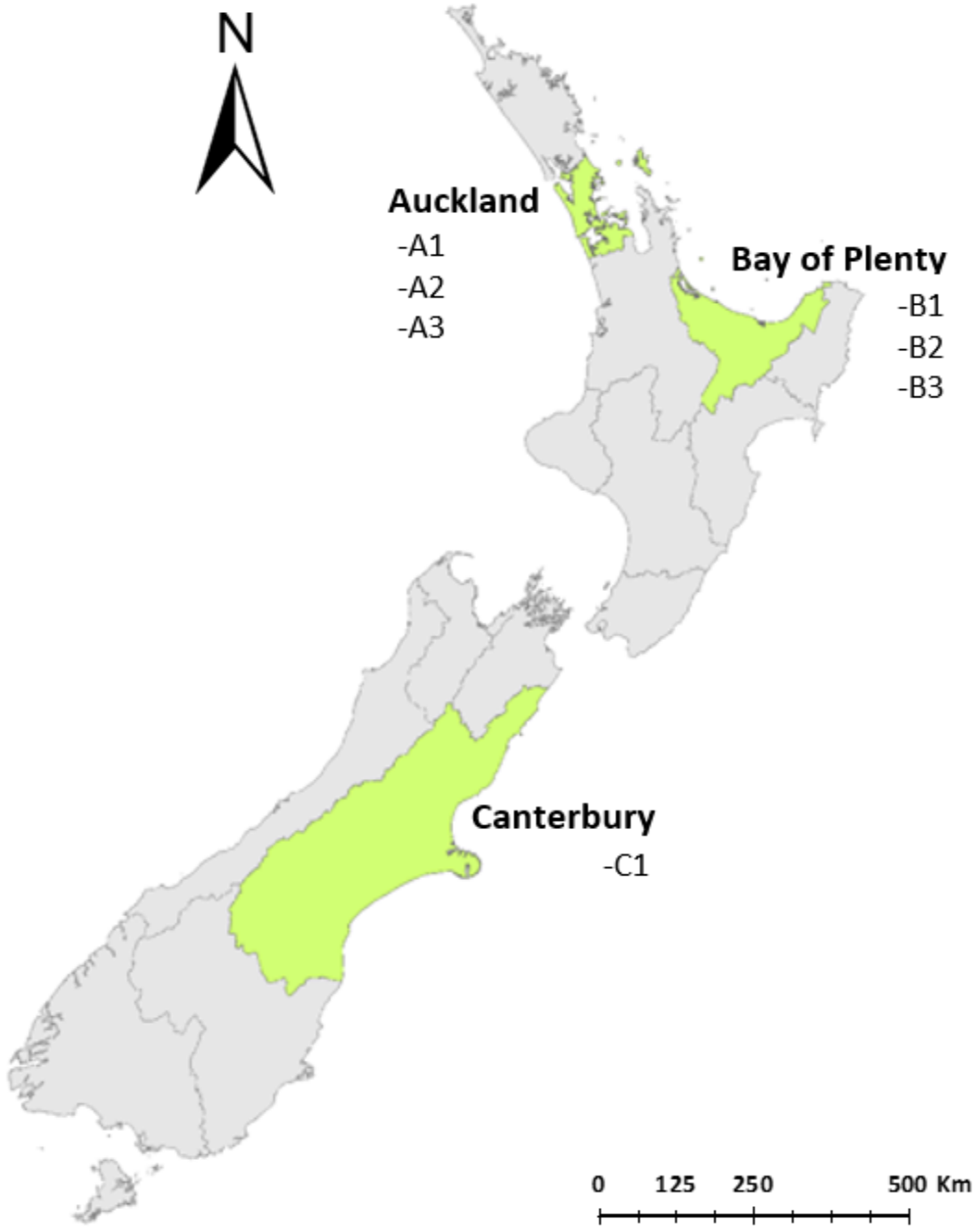
Consumption was estimated using an established back-calculation formula.[30] Briefly, mass loads (mg/day) were estimated by multiplying concentrations (mg/mL) by daily wastewater volumes (mL). Mass loads were multiplied by a correction factor that accounts for the metabolite's average excretion rate and molecular weight ratio between the metabolite and parent drug: 2.56, 3.00 and 4.44 for methamphetamine, cocaine and MDMA, respectively.[28,30,31] These back-calculation factors are based on an average excretion rate. Although people metabolise drugs at different rates, these differences will likely average-out at the population level. It is not our intention to discuss the uncertainties of excretion rates, as this has been done elsewhere.[1,32,33] However, very briefly, the back-calculation formula does

Table 1: Study site information.

Site	Region	Population Size	Community Type
A1	Auckland	4,841	Town
A2	Auckland	54,547	City with rural areas
A3	Auckland	239,522	City
B1	Bay of Plenty	48,513	City
B2	Bay of Plenty	87,298	Town
B3	Bay of Plenty	66,856	City with rural areas
C1	Canterbury	374,364	City with rural areas

Although B2 has a large population, this site has a large wastewater catchment comprising of primarily suburban and rural landcovers and hence was classified as a town.

Figure 1: Regional study site locations: Auckland, Bay of Plenty and Canterbury.



not account for sewage leakage from pipes or stormwater infiltration. We therefore checked and confirmed that there were no wastewater overflow events. Additionally, stormwater infiltration and subsequent dilution was likely negligible given the low rainfall recorded in the three regions for the duration of the study. Consumption was normalised by population and converted to doses/day/1000 people by dividing by a mean standard dose: 30, 100 and 100 mg for methamphetamine, cocaine and MDMA, respectively.[30] Please keep in mind that the exact quantity of drugs consumed (in mg) in a single dose will vary based upon variations in local drug purity and individual consumer preferences.[1] Dosages simply facilitate comparisons across countries and between individual drugs. Weekends were grouped as Saturday and Sunday, except for MDMA, which included Monday as it has a relatively long excretion time.[34]

Socioeconomic dataset

The 2018 New Zealand Index of Multiple Deprivation (IMD) provided a descriptor of relative socioeconomic status.[35] The IMD aggregates 29 indicators of socioeconomic deprivation under seven broad domains (employment, income, crime, housing, health, education and access to services) for the 2018 period across 6181 data zones that together cover all of New Zealand. Each data zone has a single rank score (from one to 6181), with higher scores representing higher levels of disadvantage. Where data zones intersected mapped catchments, data-zone rank scores were population-weighted and averaged.

Statistics

The Shapiro–Wilk test was used to assess the normality of data groups. Kruskal–Wallis followed by Dunn–Bonferroni post-hoc testing was used to compare drug consumption between sites. To assess relationships between drug use and socioeconomic disadvantage, daily drug consumption values were correlated with IMD rank scores using Spearman's correlation.

Results

Methamphetamine

Methamphetamine was detected in 100% of samples, with a mean consumption of 22.9 ± 9.9 doses/day/1000 people. Methamphetamine consumption was significantly higher in B1 and B3 than both A3 and C1 (Table 2; Appendix Table 1). Methamphetamine consumption was also significantly higher in A1 than C1. Temporal patterns of methamphetamine use were different between sites. For C1 and all Auckland sites, methamphetamine consumption was relatively consistent throughout the week, with mean weekday (Monday–Friday) and weekend (Saturday–Sunday) differences ranging from 15 to 21% (Figure 2). In contrast, methamphetamine consumption was higher on weekends for the Bay of Plenty sites, particularly B1 (32% higher) and B2 (69% higher). Methamphetamine use was significantly positively correlated with socioeconomic disadvantage: r = .402, 95% CI [.118, .616], p = .005 (Figure 3).

Cocaine

Cocaine was only detected in 21% of samples, with a mean consumption of 0.5 ± 0.3 doses/day/1000 people. The highest average cocaine consumption was observed for A3, followed by A2, B1 and B2 (Table 2). Cocaine was not detected at the other sites. Cocaine was detected infrequently throughout the week, with use restricted to weekends and discrete weekdays. Cocaine exhibited a moderate, albeit insignificant negative correlation with socioeconomic disadvantage: r = -.562, 95% CI [-.966, .192], p = .091 (Figure 3).

MDMA

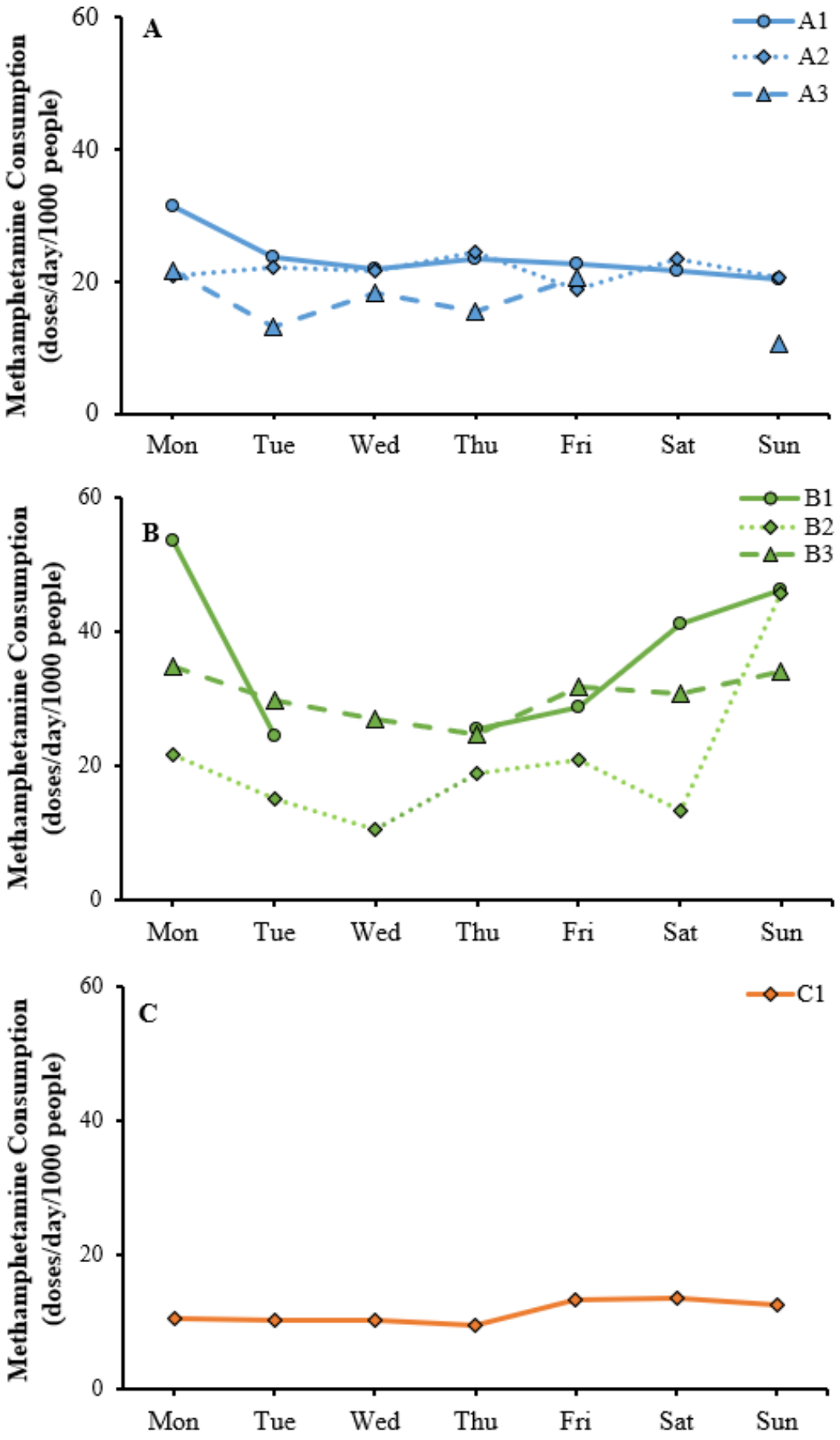
MDMA was observed in 74% of samples, with a mean consumption of 1.7 ± 1.5 doses/day/1000 people. MDMA consumption was significantly higher in A3 and C3 than B3 (Table 2; Appendix Table 1). For all sites, MDMA consumption was higher on weekends compared to weekdays. Notably, for A2, B1, B2 and B3, mean MDMA consumption was between 71 and 247% higher on weekends (Saturday–Monday) than weekdays (Tuesday–Friday). MDMA was significantly negatively correlated with socioeconomic disadvantage: r = -.614, 95% CI [-.796, -.327], p < .001 (Figure 3).

Discussion

Overview of consumption

Methamphetamine was the most widely consumed illicit drug for which we tested, followed by MDMA and cocaine, which corroborates other work in New

Figure 2: Observed weekly methamphetamine consumption (doses/day/1000 people) for all sites in Auckland (A), Bay of Plenty (B) and Canterbury (C). Saturday and Wednesday are missing for A3 and B1, respectively.



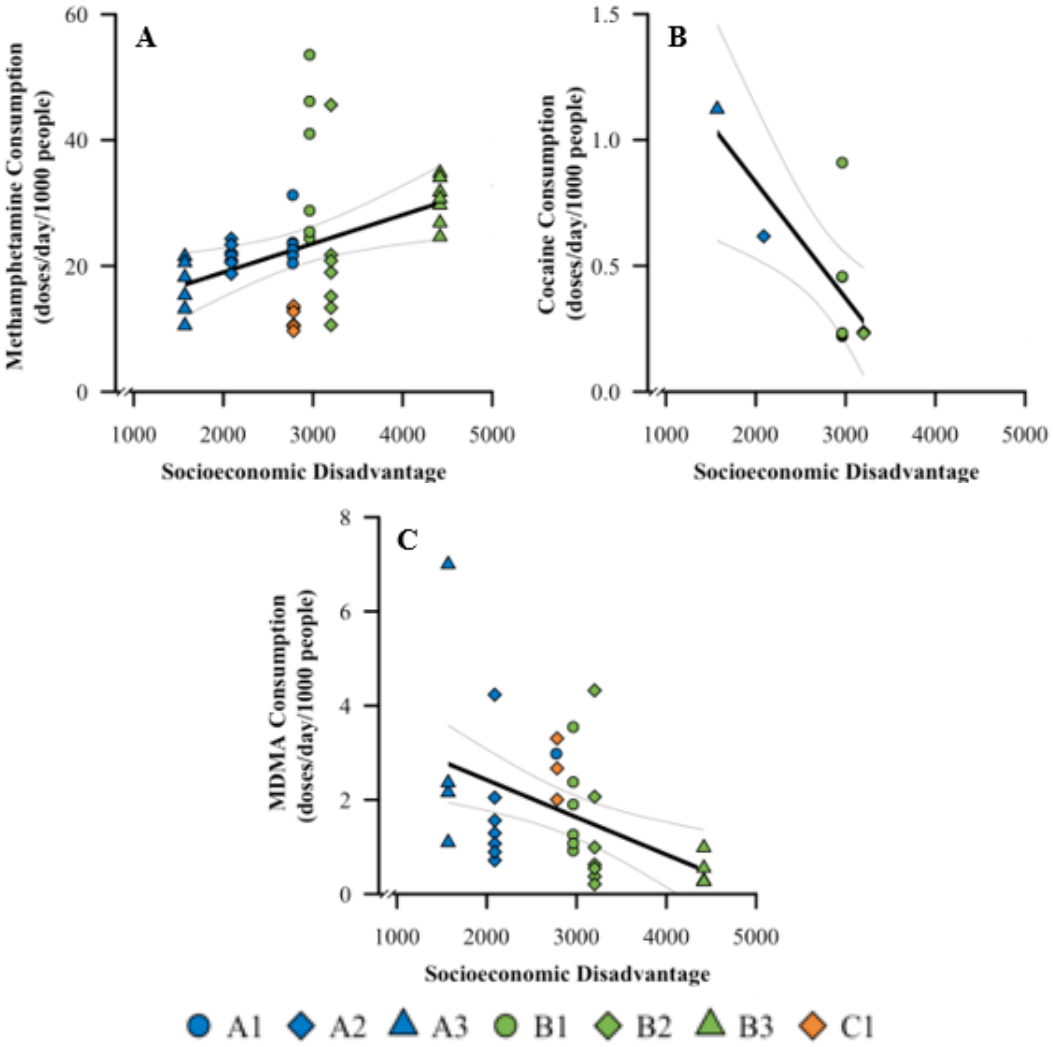
NZMJ 25 June 2021, Vol 134 No 1537
ISSN 1175-8716
www.nzma.org.nz/journal

Table 2: Observed drug consumption rates (doses/day/1000 people) for methamphetamine, cocaine and MDMA for each site.

Site	Methamphetamine		Cocaine		MDMA	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
A1	23.6 (3.6)	20.4–31.3	<LOD	<LOD	3.0 (–)	<LOD–3.0
A2	21.7 (1.9)	18.8–24.3	0.6	<LOD–6.2	1.7 (1.2)	0.7–4.2
A3	16.6 (4.3)	10.6–21.5	1.1	<LOD–1.2	3.2 (2.6)	<LOD–7.0
B1	36.6 (12.1)	24.4–53.6	0.4 (0.3)	0.2–0.9	1.8 (1.0)	0.9–3.5
B2	20.9 (11.6)	10.6–45.6	0.2 (0.0)	<LOD–0.2	1.3 (1.5)	0.2–4.3
B3	30.4 (3.7)	24.6–34.8	<LOD	<LOD	0.4 (.3)	0.3–1.0
C1	11.5(1.6)	9.7–13.6	<LOD	<LOD	2.7 (0.7)	<LOD–3.3

Standard deviation could not be estimated for A1 given that MDMA was only detected once at this site. <LOD = below limit of detection.

Figure 3: Relationship between deprivation rank scores and observed methamphetamine (A) (n = 47), cocaine (B) (n = 10) and MDMA (C) (n = 35) consumption (doses/day/1000 people) across all sites. Grey lines represent 95% confidence intervals.



NZMJ 25 June 2021, Vol 134 No 1537
ISSN 1175-8716
www.nzma.org.nz/journal

Zealand.[15,23,24] The data highlight the pervasiveness of methamphetamine in New Zealand and supports its prioritisation in public health and enforcement policy. Unlike methamphetamine (which is both imported and domestically manufactured in New Zealand), MDMA and cocaine are almost entirely imported.[16] They have low availability and low observed use, especially cocaine, likely due to New Zealand's geographic isolation, tight border controls and relatively small market. New Zealand Police and Customs are reportedly concerned about moves from international gangs to establish a larger cocaine market in New Zealand.[36,37] This makes sense given cocaine's high street price; however, it appears that this has yet to come into fruition in these regions, as evidenced in the WBE data.

Global comparison of methamphetamine, cocaine and MDMA consumption

Mean methamphetamine consumption was considerably higher in New Zealand than reported in Europe (Figure 4), which likely reflects the European preference for amphetamine sulphate over methamphetamine and the wider availability of other illicit drugs.[38] Methamphetamine consumption was lower than reported in the United States, Canada and Australia. These countries provide much larger markets than New Zealand. It has been estimated that over 90% of methamphetamine trafficked to Oceania is destined for Australia.[39] In contrast, mean cocaine consumption in New Zealand ranked well below that of the United States, Australia and Europe (Figure 4). This reflects the low volume and high price of cocaine in New Zealand (€221 per gram) compared to, say, the United States (56 € per gram) and European countries like Belgium (€50 per gram) and Italy (€80 per gram).[40] Mean MDMA consumption was relatively high in New Zealand compared to many parts of Europe and North America (Figure 4). Given the paucity of cocaine, it is likely that MDMA is the substitute New Zealand party drug.[3]

Spatial patterns

The regional pattern of relatively high methamphetamine consumption in the Bay of Plenty, and MDMA (and cocaine) in Auckland and Canterbury, is consistent with observations from recent wastewater studies.[22,25] The high methamphetamine consumption observed in the Bay of Plenty also supports the high availability reported for this region.[21] The relatively high use of MDMA in Canterbury, and both MDMA and cocaine in Auckland, may simply reflect the presence of nightclubs in cities.[41] Cities have larger populations too, which can sustain larger and more diverse drug markets.[42] Cocaine and MDMA is almost entirely imported to New Zealand,[15,21] so it makes sense that their consumption was higher in the sites with ports (A3 and C1) than in site B3, which is landlocked and without an international airport.

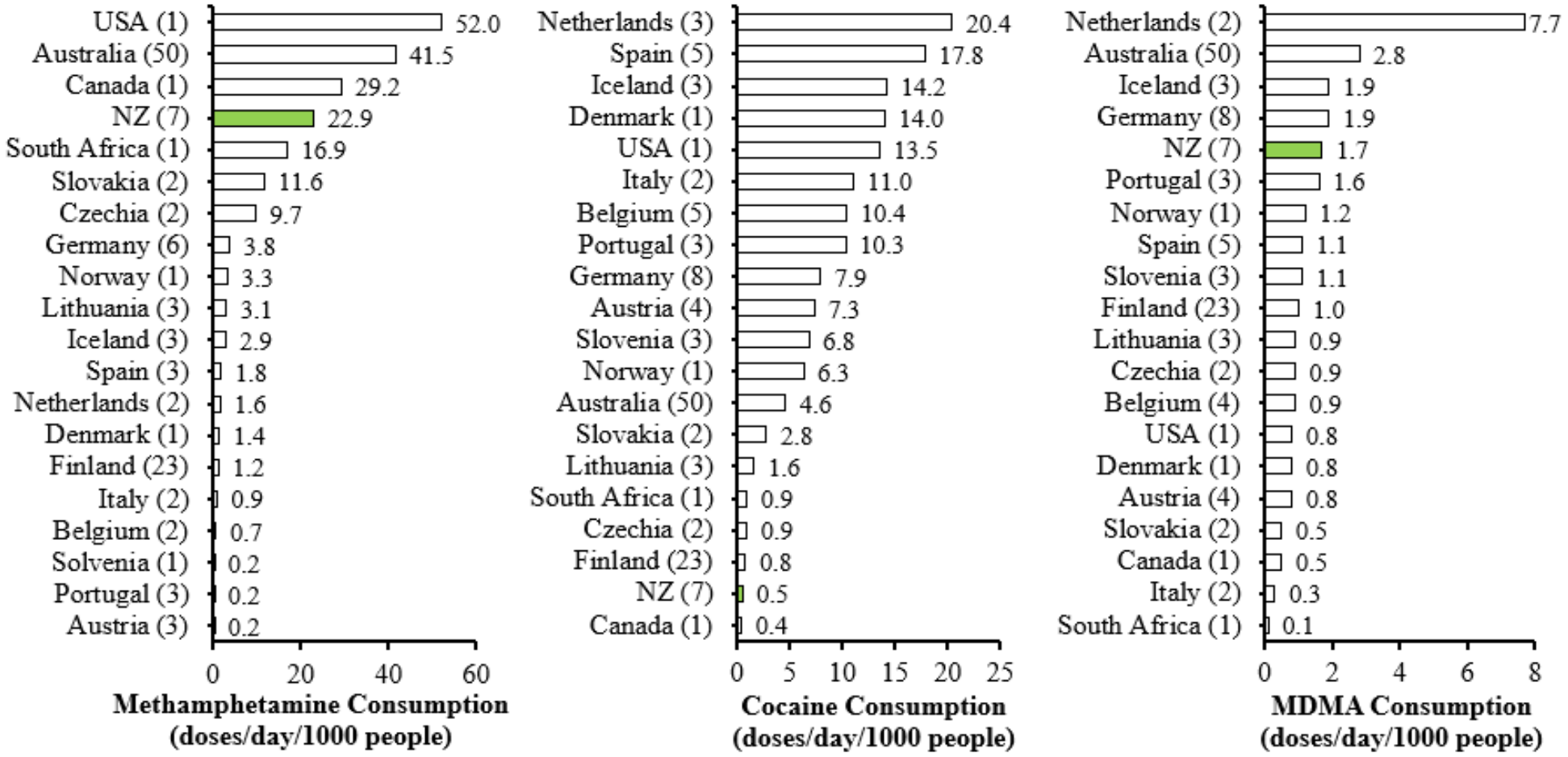
The spatial patterns of methamphetamine paint a contrasting picture. Corroborating a recent study,[21] the data show that methamphetamine consumption is greater in towns compared to cities. Methamphetamine laboratories are often located in more isolated areas to avoid detection.[20] Gangs have reportedly sought to expand methamphetamine markets in towns.[21] Local production, socioeconomic decline, fewer police personnel and a lack of market choice likely contribute to this pattern.[19,21] Wastewater studies in Australia and the United States have also observed high methamphetamine use in more rural communities.[7,9,43]

However, our data show that methamphetamine is not only used in towns. There was high consumption observed at the city site B1, which is adjacent to New Zealand's busiest port. Perhaps this area is an entry point for internationally supplied methamphetamine and/or pseudoephedrine (a chemical precursor for methamphetamine) and, therefore, a subsequent hotspot for domestic methamphetamine manufacture. This is consistent with the large number of clandestine laboratories seized in the region.[20] It is important to understand site-specific supply and demand dynamics for drug policy, and clearly WBE adds knowledge to support these efforts.

Within-week patterns

MDMA consumption was higher on weekends compared to weekdays across all sites. This weekend spike in MDMA accounts for the large standard deviation across all sites. Cocaine had a similar pattern, with consumption largely restricted to weekends

Figure 4: Methamphetamine, cocaine and MDMA consumption rates (doses/day/1000 people) estimated for New Zealand (this study) and other countries. Number in brackets is the number of WWTPs. European and North American data are from SCORE, which is presented in the National Wastewater Drug Monitoring Program Report 7 alongside Australian data.[9] All consumption rates were converted using the same excretion factors and dosages used in this study. European and North American data were collected in March 2018. Australian data were collected in December 2018.



and the odd discrete weekday. MDMA has a low dependence liability.[44] Coupled to the relatively high street prices of MDMA and cocaine, the data suggest that habitual use (ie, daily) of these drugs is uncommon.

Within-week patterns of methamphetamine use were variable. For C1 and all Auckland sites, methamphetamine was consumed relatively consistently throughout the week, supporting previous data for these regions.[22–24] Methamphetamine is highly addictive, so frequent and consistent user consumption is common.[15] Interestingly, methamphetamine consumption was higher on weekends for the Bay of Plenty sites, particularly B1 and B2. This perhaps reflects the high number of bars and nightclubs in B1. Other studies have found city populations to have more pronounced weekend drug use compared to towns.[6] B1 is also a popular tourist destination, and the high weekend consumption may be attributable, in part, to tourists.

It was surprising that different patterns of methamphetamine use were observed at sites B1, A3 and C1, given that these are all city sites (with bars and nightclubs). MDMA consumption rates were higher in A3 and C1 compared to B1 (Table 2). It may be that MDMA is more available and thus preferred as a recreational weekend drug in these sites. This would suggest that the low availability of MDMA and/or high availability of methamphetamine may facilitate recreational methamphetamine consumption. This is concerning from a public health perspective given methamphetamine's relatively high dependence liability.[16] As only a single week of samples were collected, longer-term sampling is being undertaken to confirm these findings.

Socioeconomic patterns

To better explore these spatial patterns, drug use was compared with socioeconomic disadvantage. MDMA was significantly negatively correlated with disadvantage. Cocaine was similar but not significant, being influenced by the small number of detections. Conversely, methamphetamine was positively correlated with disadvantage, which is consistent with local survey data.[16] Due to methamphetamine's relatively low street price (compared to more expensive drugs like cocaine), methamphetamine may be more accessible to lower-income individuals.[16] Additionally, clandestine methamphetamine laboratories are often more concentrated in disadvantaged communities,[20] likely making it more widely available in such areas. However, the correlation was not strong (r = .402), so the data highlight that methamphetamine is consumed by people in advantaged communities too.

These trends are different to the 2007/2008 New Zealand Alcohol and Drug Use Survey (NZADUS), which found no relationship between neighbourhood socioeconomic status and the use of methamphetamine, cocaine or MDMA.[45] It could be that the NZADUS simply did not capture heavy user groups.[2] Perhaps people were reluctant to participate in the survey for fear of stigmatisation or legal repercussions. Another contributing factor is that drug surveys may not representatively capture rural populations.[3] Regardless of the reason, our data highlight the complementary nature of WBE to other measures of drug use. The next challenge is to best align the datasets as a step towards transdisciplinary public health policy and drug intervention.

Conclusion

Wastewater-based epidemiology was timed to coincide with the 2018 New Zealand census. The data confirm the pervasiveness of methamphetamine in New Zealand and supports its ongoing prioritisation in public health and enforcement policy. There were inter- and intra-regional differences in drug consumption. Cocaine and MDMA consumption were higher in cities, whereas methamphetamine was generally higher in towns. Notably, high methamphetamine consumption was observed at Bay of Plenty's urban site, highlighting the importance of site-specific supply dynamics and local consumer preferences. Cocaine and MDMA were consumed infrequently throughout the week, with consumption largely restricted to weekends. Methamphetamine was consumed more consistently throughout the week in Canterbury and all Auckland sites. In contrast, methamphetamine consumption was higher on

weekends in the Bay of Plenty. The data show that methamphetamine is consumed both habitually and recreationally. Such patterns, however, cannot be accounted for by differences in urbanisation or population size alone. Expectedly, MDMA (and cocaine) consumption was negatively correlated with socioeconomic disadvantage, whereas methamphetamine was positively correlated. The research shows that WBE provides valuable data on the spatial, temporal and socio-economic patterns of drug use, and with complementary information can be used to help guide the development of nested local, regional and national-scale drug policy in response.

ISSN 1175-8716

Appendix

Appendix Table 1: Dunn–Bonferroni comparisons of methamphetamine consumption rates (doses/day/1000 people) between sites. Bolded values are significant.

Site comparison	Mean rank difference	Std. error	Adjusted *p*-value
C1–A3	7.6	7.6	0.999
C1–B2	13.4	7.3	0.999
C1A2	18.3	7.3	0.265
C1–A1	**22.3**	**7.3**	**0.05**
C1–B3	**33.4**	**7.3**	**< .001**
C1–B1	**34.8**	**7.6**	**< .001**
A3–B2	-5.8	7.6	0.999
A3–A2	10.7	7.6	0.999
A3–A1	14.7	7.6	0.308
A3–B3	**-25.8**	**7.6**	**0.015**
A3–B1	**-27.2**	**7.9**	**0.013**
B2–A2	4.9	7.3	0.999
B2–A1	8.9	7.3	0.999
B2–B3	-20	7.3	0.133
B2–B1	21.3	7.6	0.108
A2–A1	4.0	7.3	0.999
A2–B3	-15.1	7.3	0.815
A2–B1	-16.5	7.6	0.646
A1–B3	-11.1	7.3	0.999
A1–B1	-12.5	7.6	0.999
B3–B1	1.3	7.6	0.999

Appendix Table 2: Dunn-Bonferroni comparisons of MDMA consumption rates (doses/day/1000 people) between sites. Bolded values are significant.

Site comparison	Mean rank difference	Std. error	Adjusted *p*-value
B3–B2	8.0	5.3	0.999
B3–A2	13.3	5.3	0.188
B3–B1	15.5	5.5	0.076
B3–A3	**20.1**	**6.2**	**0.019**
B3–C1	**-21.2**	**6.9**	**0.031**
B2–A2	5.3	5.3	0.999
B2–B1	7.5	5.5	0.999
B2–A3	12.1	6.2	0.786
B2–C1	-13.2	6.9	0.824
A2–B1	-2.2	5.5	0.999
A2–A3	-6.8	6.2	0.999
A2–C1	-7.9	6.9	0.999
B1–A3	4.6	6.4	0.999
B1–C1	-5.7	7.0	0.999
A3–C1	-1.1	7.6	0.999

Competing interests:
Nil.

Acknowledgements:
We would like to thank Watercare Services Limited, Christchurch City Council, Ngāi Te Rangi and Tauranga City Council Safe Communities for their assistance with the sample collection and the facilitation of the research. We thank Arnuad Besse-Ciller for his help visualising the data. We are also grateful to the two anonymous reviewers and the section editor for their time to read and comment on the paper.

Author information:
Mackay Price: School of Environment, University of Auckland, Auckland.
Chris Wilkins: Drug Research Team Leader, SHORE & Whariki Research Centre, College of Health, Massey University.
Benjamin J Tscharke: Postdoctoral Research Fellow, Queensland Alliance for Environmental Health Sciences (QAEHS), The University of Queensland, Australia.
Tom Baker: Senior Lecturer, School of the Environment, University of Auckland, Auckland.
Jochen F Mueller: Group Leader, Queensland Alliance for Environmental Health Sciences (QAEHS), The University of Queensland, Australia.
Sam Trowsdale: Senior Lecturer, School of the Environment, University of Auckland, Auckland.

Corresponding author:
Mackay Price, School of Environment, University of Auckland, Auckland
Wpri344@aucklanduni.ac.nz

URL:
www.nzma.org.nz/journal-articles/spatial-temporal-and-socioeconomic-patterns-of-illicit-drug-use-in-new-zealand-assessed-using-wastewater-based-epidemiology-timed-to-coincide-with-the-census-2

REFERENCES

1. van Nuijs A, Castiglioni S, Tarcomnicu I, et al. Illicit drug consumption estimations derived from wastewater analysis: A critical review. Sci Total Environ. 2011;409(19):3564-77.
2. McFadden Consultancy. The New Zealand Drug Harm Index 2016 (second edition). Wellington: Ministry of Health, 2016.
3. Prichard J, Lai FY, O'Brien J, et al. 'Ice Rushes', Data Shadows and Methylamphetamine Use in Rural Towns: Wastewater Analysis. Current Issues in Criminal Justice 2018; 29(3):195-208.
4. Willis K, Anderson J, Homel P. Measuring the effectiveness of drug law enforcement. Trends & Issues in crime and criminal justice no. 406. Canberra: Australian Institute of Criminology, 2011.
5. EMCDDA. Wastewater analysis and drugs: a European multi-city study. Lisbon: EMCDDA, 2020.
6. Krizman I, Senta I, Ahel M, Terzic S. Wastewater-based assessment of regional and temporal consumption patterns of illicit drugs and therapeutic opioids in Croatia. Sci Total Environ. 2016;566:454-62.
7. Lai FY, O'Brien J, Bruno R, et al. Spatial variations in the consumption of illicit stimulant drugs across Australia: A nationwide application of wastewater-based epidemiology. Sci Total Environ. 2016;568:810-8.
8. Ort C, van Nuijs AL, Berset JD, et al. Spatial differences and temporal changes in illicit drug use in Europe quantified by wastewater analysis. Addiction. 2014;109(8):1338-52.
9. Australian Criminal Intelligence Commission. National wastewater drug monitoring Report 7, March 2017. Canberra: Australian Criminal Intelligence Commission, 2019.
10. Choi PM, Tscharke B, Samanipour S, et al. Social, demographic, and economic correlates of food and chemical consumption measured by wastewater-based epidemiology. Proc Natl Acad Sci U S A. 2019;116(43):21864-73.
11. Hart OE, Halden RU. Simulated 2017 nationwide sampling at 13,940 major U.S. sewage treatment plants to assess seasonal population bias in wastewater-based epidemiology. Sci Total Environ. 2020;727:138406.
12. O'Brien JW, Thai PK, Eaglesham G, et al. A model to estimate the population contributing to the wastewater using

samples collected on census day. Environ Sci Technol. 2014;48(1):517-25.

13. Tscharke BJ, O'Brien JW, Ort C, et al. Harnessing the Power of the Census: Characterizing Wastewater Treatment Plant Catchment Populations for Wastewater-Based Epidemiology. Environ Sci Technol. 2019;53(17):10303-11.
14. Ministry of Health. Annual Data Explorer 2018/19: New Zealand Health Survey. Wellington: Ministry of Health, 2019.
15. Wilkins C, Prasad J, Barnes HM, et al. New Zealand Arrestee Drug Use Monitoring (NZ-ADUM) 2010–2016. Auckland: SHORE & Whariki Research Centre, Massey University, 2017.
16. Wilkins C, Prasad J, Romeo JS, Rychert M. Recent trends in illegal drug use in New Zealand, 2006–2015: Findings from Illicit Drug Monitoring System (IDMS). Auckland: SHORE & Whariki Research Centre, Massey University, 2017.
17. Bayer K. Meth plague at record levels, with P-related arrests nearly doubling in 5 years. The New Zealand Herald. 2018. Available from: https://www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=12085175
18. Houlahan M. Meth is 'everywhere'. Otago Daily Times. 2017. Available from: https://www.odt.co.nz/news/dunedin/meth-everywhere
19. New Zealand Police Association [Internet]. The war on meth. Available from: https://www.policeassn.org.nz/news/the-war-on-meth#/
20. Howell AV, Newcombe DA, Exeter DJ. The geography of methamphetamine manufacture in New Zealand between 2004 and 2009. Policing. 2018;12(2):231-42.
21. Wilkins C, Romeo JS, Rychert M, et al. Determinants of high availability of methamphetamine, cannabis, LSD and ecstasy in New Zealand: Are drug dealers promoting methamphetamine rather than cannabis? Int J Drug Policy. 2018:61, 15-22.
22. Chappell A, Ashmore, E. Wastewater Pilot Programme. Institute of Environmental Science and Research, New Zealand Police, 2019.
23. Lai FY, Wilkins C, Thai P, Mueller JF. An exploratory wastewater analysis study of drug use in Auckland, New Zealand. Drug Alcohol Rev. 2017;36(5):597-601.
24. Wilkins C, Lai FY, O'Brien J, et al. Comparing methamphetamine, MDMA, cocaine, codeine and methadone use between the Auckland region and four Australian states using wastewater-based epidemiology (WBE). N Z Med J. 2018;131(1478):12-20.
25. New Zealand Police. National wastewater testing Programme Quarter 1 2019. New Zealand Police, 2019.
26. Stats NZ [Internet]. Statistical area 1 dataset for 2018 Census – updates and corrections. 2020. Available from: https://www.stats.govt.nz/reports/statistical-area-1-dataset-for-2018-census-updates-and-corrections
27. Jack M, Graziadei C. Report of the Independent Review of New Zealand's 2018 Census. Wellington: Stats NZ, 2019.
28. Lai FY, Ort C, Gartner C, et al. Refining the estimation of illicit drug consumptions from wastewater analysis: co-analysis of prescription pharmaceuticals and uncertainty assessment. Water Res. 2011;45(15):4437-48.
29. Lai FY, Anuj S, Bruno R, et al. Systematic and day-to-day effects of chemical-derived population estimates on wastewater-based drug epidemiology. Environ Sci Technol. 2015;49(2):999-1008.
30. Zuccato E, Chiabrando C, Castiglioni S, et al. Estimating community drug abuse by wastewater analysis. Environ Health Perspect. 2008;116(8):1027-32.
31. Khan U, Nicell JA. Refined sewer epidemiology mass balances and their application to heroin, cocaine and ecstasy. Environ Int. 2011:37(7):1236-52.
32. Castiglioni S, Bijlsma L, Covaci A, et al. Evaluation of uncertainties associated with the determination of community drug use through the measurement of sewage drug biomarkers. Environ Sci Technol. 2013;47(3):1452-60
33. Gracia-Lor E, Zuccato E, Castiglioni S. Refining correction factors for back-calculation of illicit drug use. Sci Total Environ. 2016;573:1648-59.
34. Melis M, Castiglioni S, Zuczato E. Metabolism and excretion of illicit drugs in humans. In Castiglioni S, Zuccato E, Fanelli, R, eds. Illicit drugs in the environment: Occurrence, analysis and fate using mass spectrometry. New Jersey: Wiley, 2011.
35. Exeter DJ, Bronwe M, Chiang, A, et al. The 2018 New Zealand Index of Multiple Deprivation (IMD2018): Indicators for social and health research in New Zealand Brief Report. Auckland: The University of Auckland, 2020.

36. Boyle C. The rise of cocaine: Drug syndicates 'determined' to create a market in NZ. The New Zealand Herald. 2019. Available from: https://www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=12257018
37. Savage J. $20m cocaine case: Eleventh hour admissions of guilt by four men about to stand trial for smuggling 46kg of drug into port of Tauranga. The New Zealand Herald. 2019. Available from: https://www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=12244312
38. EMCDDA. European Drug Report. Lisbon: EMCDDA, 2019.
39. UNDOC. World Drug Report 2019. Vienna: UNDOC, 2019.
40. Global Drug Survey [Internet]. Global drug survey 2019. 2019. Available from: https://www.globaldrugsurvey.com/gds-2019/
41. Hutton F. Kiwis, clubs and drugs: Club cultures in Wellington, New Zealand. Aust N Z J Criminol. 2010;43(1):91-111.
42. Nefau T, Karolak S, Castillo L, et al. Presence of illicit drugs and metabolites in influents and effluents of 25 sewage water treatment plants and map of drug consumption in France. Sci Total Environ. 2013;461-462:712-22.
43. Banta-Green CJ, Field JA, Chiaia AC, et al. The spatial epidemiology of cocaine, methamphetamine and 3,4□methylenedioxymethamphetamine (MDMA) use: a demonstration using a population measure of community drug load derived from municipal wastewater. Addiction. 2009:104(11):1874-80.
44. Mack AH, Brady KT, Frances, RJ, Miller, SI, eds. Clinical textbook of addictive disorders (fourth edition). New York: Guilford Publications, 2016.
45. Ministry of Health. Drug use in New Zealand: Key results of the 2007/08 New Zealand alcohol and drug use survey. Wellington: Ministry of Health, 2010.

Reducing the MRI outpatient waiting list through a capacity and demand time series improvement programme

Heera Bhullar, Bernadette County, Stuart Barnard, Anne Anderson, Mary E Seddon

ABSTRACT

INTRODUCTION: A capacity and demand improvement initiative commenced in January 2019 with the goal of reducing the growing outpatient waiting list for magnetic resonance imaging (MRI) at Counties Manukau District Health Board (CMDHB). Initial work showed that the capacity (MRI machines and staff) actually outstripped demand, which challenged pre-existing assumptions. This became the basis for interventions to improve efficiency in the department. Interventions undertaken can be split into three distinct categories: (1) matching capacity to demand, (2) waiting list segmentation and (3) redesigning operational systems.

METHODS: A capacity and demand time series during 2019 and 2020 was used as the basis for improving waiting list and operational systems. A combination of the Model for Improvement and Lean principles were used to embed operational improvements. Multiple small tests of change were implemented to various aspects of the MRI waiting list process. Staff engagement was central to the success of the quality improvement (QI) initiatives. The radiological information system (RIS) provided the bulk of the data, and this was supplemented with manual data collection.

RESULTS: The number of people waiting for an MRI scan decreased from 1,954 at the start of the project to 413 at its conclusion—an overall reduction of 75%. Moreover, the average waiting time reduced from 96.4 days to 23.1. Achieving the Ministry of Health's (MoH) Priority 2 (P2) target increased from 23% to 87.5%.

CONCLUSION: A partnership between Ko Awatea and the radiology department at CMDHB, examining capacity and demand for MRI and using multiple QI techniques, successfully and sustainably reduced the MRI waiting list over a two-year period. The innovative solutions to match capacity to demand may be instructive for other radiology departments, and other waiting list scenarios.

In 2018 an additional magnetic resonance imaging (MRI) machine was purchased, bringing the Counties Manukau District Health Board (CMDHB) total to three. This increase in physical capacity had not reduced the waiting list as expected and, despite outsourcing 60 scans per week to private providers, the backlog and waiting times for MRI scans were increasing.

At the start of the project, 1,954 patients were on the waiting list, and only 23% had MRI scans performed within six weeks—the Ministry of Health (MoH) Priority 2 (P2) target. The perception was that a lack of medical radiology technicians (MRTs) was the significant factor preventing the department from meeting demand.

In December 2018 the radiology department requested assistance from Ko Awatea (CMDHB's centre for innovation and improvement) to improve the performance of the MRI service, particularly to reduce the waiting list.

Stakeholders agreed that a demand and capacity study would be undertaken

to identify and realise opportunities to increase activity.

Method

Staff engagement

All staff groups involved with the MRI process participated in its improvement (ie, clerical booking staff, nursing, MRTs and radiologists). Regular meetings were held with staff groups, both separately and collectively, to identify perceived roadblocks; from this a framework for improvement was developed. Meetings continued regularly: mapping progress, identifying issues and defining action plans.

This initiative used Lean tools[1] and the Model for Improvement.[2] Lean aims to reduce waste in a system; waste is defined as anything that does not add value (eg, waiting for a test). These tools were used in several ways to: value-stream map the process, observe how the system actually worked and listen and work with front-line staff. The Model for Improvement uses small tests of change: Plan-Do-Study-Act (PDSA) cycles to rapidly trial different ways of working.

The Model for Improvement asks three crucial questions that guided the overall initiative:

1. What are we trying to achieve?

The aim of this study was to optimise the available capacity to better match MRI outpatient demand, reduce the waiting list to less than 500 and meet the MoH's P2 national target of 85% of scans completed within six weeks.

2. How will we know that a change is an improvement?

Not all change produces improvement—this question requires the definition of measures to confirm improvement:

- Number of people on the waiting list (measured every Tuesday).
- Number of patients waiting in each segment (<42 days, 42–90 days, 91–120 days, 121–150 days, 151–180 days, >180 days).
- P2 compliance rate—percentage of patients scanned within 42 days from the date of referral (measured weekly).
- Average waiting time (measured monthly).
- Scanning hours utilised per week.

It was important to measure demand, capacity, backlog and activity in the same units for the same period of time, and to have clear definitions of key metrics (Figure 1).

Figure 1: Definitions of terms.[3]

1. Demand: What the service is being asked to do
2. Capacity: What the service could be doing with its resources used optimally
3. Activity: What the service actually did
4. Backlog: What the service should have done but haven't

3. What changes can we make?

All improvement requires change and being specific about the primary drivers in managing the MRI waiting list was important. Change interventions (Figure 2) can be split into three distinct categories:

1. matching capacity to demand
2. waiting list segmentation
3. redesigning the operational systems.

Interventions were trialled in small tests of change (PDSA cycles) in each of the three areas.

Matching capacity to demand

The first action was to establish the relationship between departmental capacity (equipment and staff), incoming demand (referrals) and activity (completed and reported scans).

Demand and activity data were generated through the radiology information system (RIS) reports, which displayed the number and types of scans being referred and completed in chronological order. As the reports did not record the time each scan took, this was added manually.

Although the MRI machine capacity was apparent (ie, three MRI machines available 24 hours per day), the productive output was also dependent on the availability of MRTs. Capacity data, in the form of staffing rosters by scanner, were translated into available daily staffing hours.

In reviewing this capacity and demand information, it became clear that there was sufficient capacity to meet demand (Figure 3). In fact, the daily available capacity of staff was greater than incoming demand by 2.5–3 times.

Demand was outstripping activity, even though it was not exceeding the actual capacity of the unit. Understanding this became the basis for interventions to increase activity and reduce the waiting list.

Demand fluctuated throughout the week, with Mondays and Fridays being the busiest. The MRT roster was unbalanced and not matched to demand; many part-time MRTs were not rostered on Mondays or Fridays, resulting in more MRT capacity than scanner availability midweek, and insufficient capacity to run the scanners on the busiest days (Figure 4).

The 80th percentile of the variation in the number of hours of incoming demand was chosen to be the minimum number of hours that were required. This meant that a minimum of 18.5 MRT-hours per day (over the three machines) would be required every weekday to meet demand. Staff were rostered to be more evenly spread across the working week to ensure that each scanner was fully operational within working hours.

Historical staffing patterns for each MRI machine were also reviewed. When there were two MRI machines in different locations, each machine was staffed with two MRTs. When the new machine arrived and co-located with the one in the department, this staffing model continued until the staff identified that we could test a '2+1 model'. This utilised one MRT per scanner and a 'floating MRT' shared between two rooms, with the focus of ensuring an efficient flow of patients. This minimised the non-scanning dwell time between patients, as the floating MRT could ensure upcoming patients were prepped and ready to be scanned as previous diagnostic tests concluded.

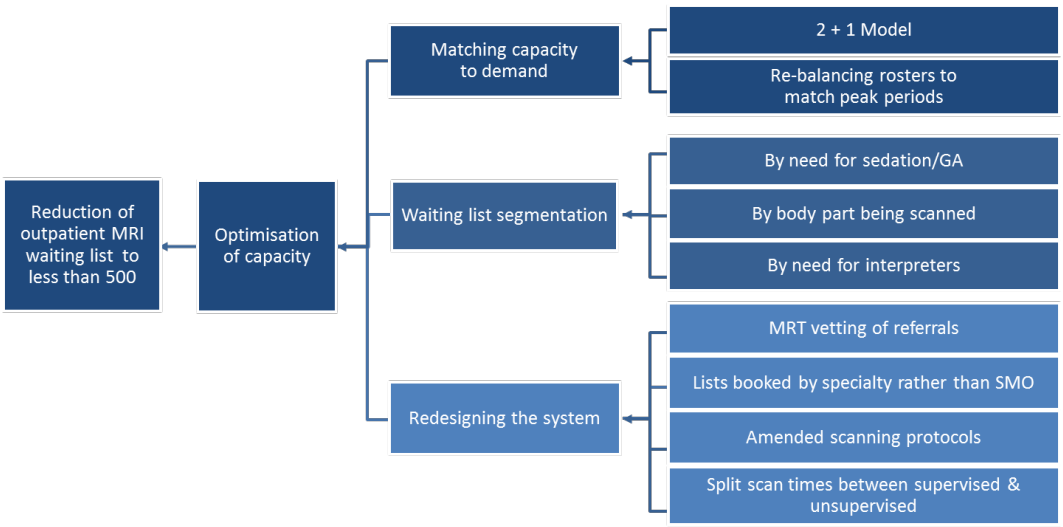
A patient care assistant (PCA) was also added to the staffing roster—this role was tasked to assist with paperwork, completing patient consenting checklists and assisting MRTs in getting patients in and out of the scanning room. The efficiency of the stand-alone scanner increased from a nadir of less than 20% to over 99% (Figure 5).

Scanning list segmentation

Initial work aimed to decrease the downtime between scans by grouping scans of the same body part (eg, head, shoulder), avoiding the need to change MRI coils between scans and allowing more scans to be completed in a list.

Patients with excessive waiting times could be grouped into five main groups (Figure 6). The average waiting time for this type of patient was close to 300 days.

Figure 2: Driver diagram for MRI optimisation.



NZMJ 25 June 2021, Vol 134 No 1537
ISSN 1175-8716

Figure 3: Demand and capacity measures over six months.

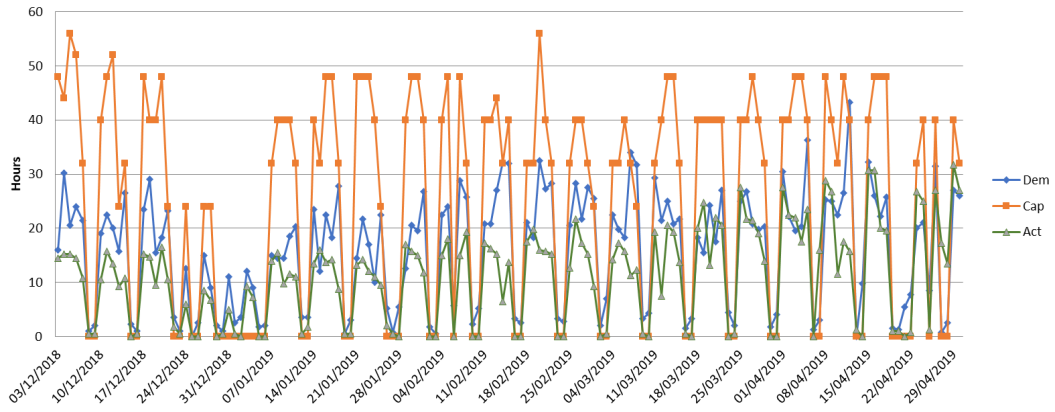


Figure 4: Capacity and demand in cumulative hours by weekday.

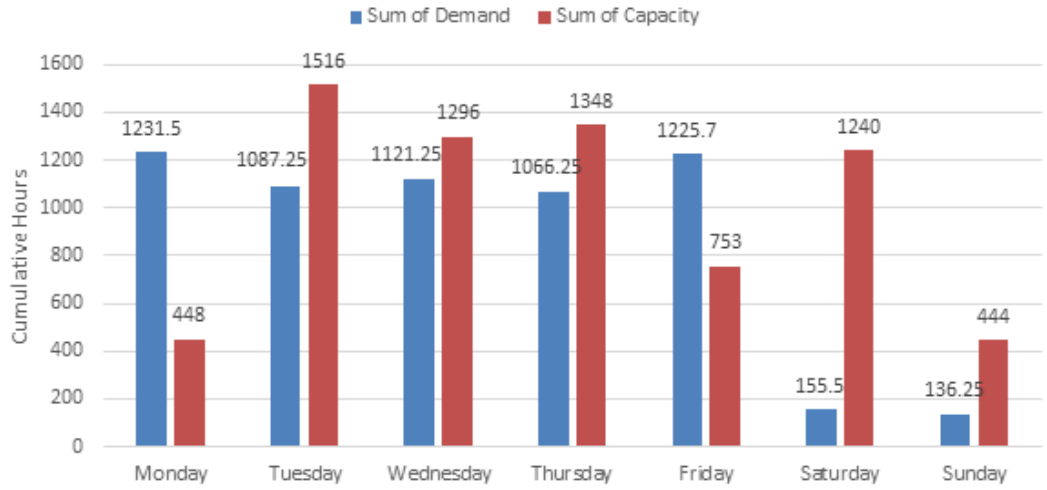
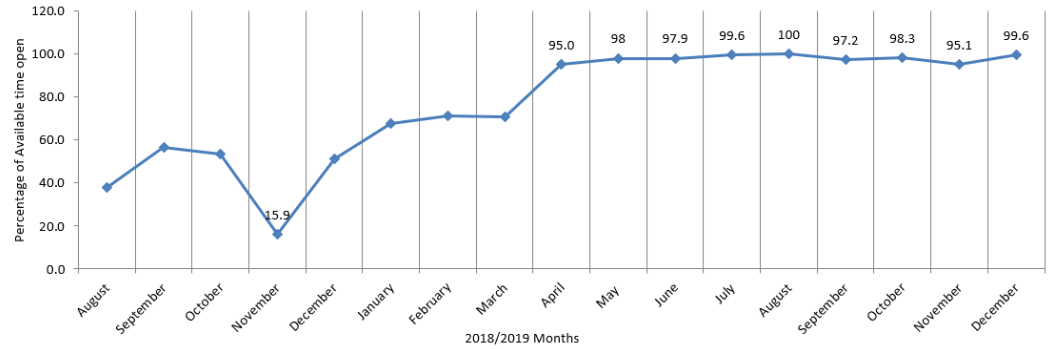


Figure 5: Standalone MRI (Building 58) utilisation.



NZMJ 25 June 2021, Vol 134 No 1537
ISSN 1175-8716

This knowledge enabled such patients to be booked onto specific segmented lists. Patients requiring sedation or general anaesthetic were scheduled together to enable the anaesthetic workforce to be used efficiently. Likewise, patients requiring the same interpreter language were grouped and scanned in the same list. The system now has alerts to notify schedulers if certain patients are being held up due to one of these characteristics.

In March 2019, the service introduced late weekday sessions, increasing scanning by two hours per day. At the same time, weekend sessions were started. Weekend sessions prioritised those patients who had been waiting the longest. Pending scans over 180 days were targeted as a priority, with cascading importance being placed on subsequent bandings. The waiting list was also segmented to utilise scanners before radiologists started work. Unsupervised scans were booked at the beginning and end of each day in one-hour blocks, enabling full utilisation of MRT capacity.

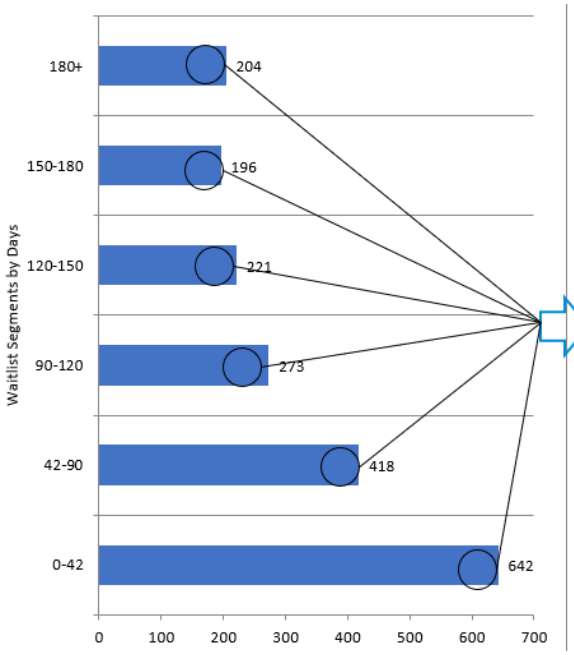
As outsourced scans were performed at a flat-rate fee by private providers, the decision matrix for outsourcing was amended to more equally distribute longer duration scans in addition to the oldest on the waiting list. This extracted better value from the contractual arrangement. The outsourcing contract was decreased from 60 scans per week to 15 in July 2019 as part of DHB cost-saving initiatives.

Redesigning MRI operational systems

A series of interventions targeted operational processes, enabling more efficient processes.

The first intervention was to modify the referral vetting process that was creating a bottleneck to workflow. This process was manual, completed by two senior medical officers (SMOs) and utilised significant administrative staff time (printing electronic referrals for SMOs and scanning referrals back into the RIS once vetting was completed). Referrals that could be vetted by the Grade MRT were identified. The SMOs' workload was reduced by redirecting lower-complexity scans while enabling the Grade MRT to perform at an expanded scope. Furthermore, the Grade MRT used the electronic system to vet referrals, speeding up the process; this encouraged the SMOs to vet electronically, which in

Figure 6: Waiting list segmentation.



Function Types	Number of cases	Average days waited
Sedations	304	298
Interpreter	209	258
Paediatric General Anaesthetic	259	247
IR Arthrogram	56	283
Prisoners	19	300

NZMJ 25 June 2021, Vol 134 No 1537
ISSN 1175-8716
www.nzma.org.nz/journal

turn reduced the workload for administrative staff.

Another operational reform refined the booking template that dictated the duration of scanning appointments. The original template was provided by the MRI vendor. However, over time, clinical protocols had been updated, as had regional and collegiate standards, and these updates were not reflected in the booking template. A revised template that accurately reflected up-to-date standard scanning times was introduced, allowing the scheduler to accurately book based on scan duration times. This resulted in efficient booking practices.

The allocation of SMOs to MRI sessions was also changed. Initially, when SMOs were allocated to work in MRI, the administrative team booked patients according to the sub-specialty interest of the SMO (eg, head and neck patients). This created issues if the SMO was unable to do the session, resulting in patients being postponed and re-booked and wasted scanning capacity. Instead, a patient-focused template was developed enabling sessions to be allocated by patient referral requirement, and SMOs were rostered to cover the sessions. This allowed the roster co-ordinator to allocate an alternate SMO should the allocated SMO be unavailable. This markedly reduced the number of cancellations and changes to patient bookings.

Results

The waiting list decreased from 1,954 in January 2019 to 413 in November 2020 (Figure7), and the target compliance for P2 scans increased from 23% to 87.5%, close to the MoH's 90% target.

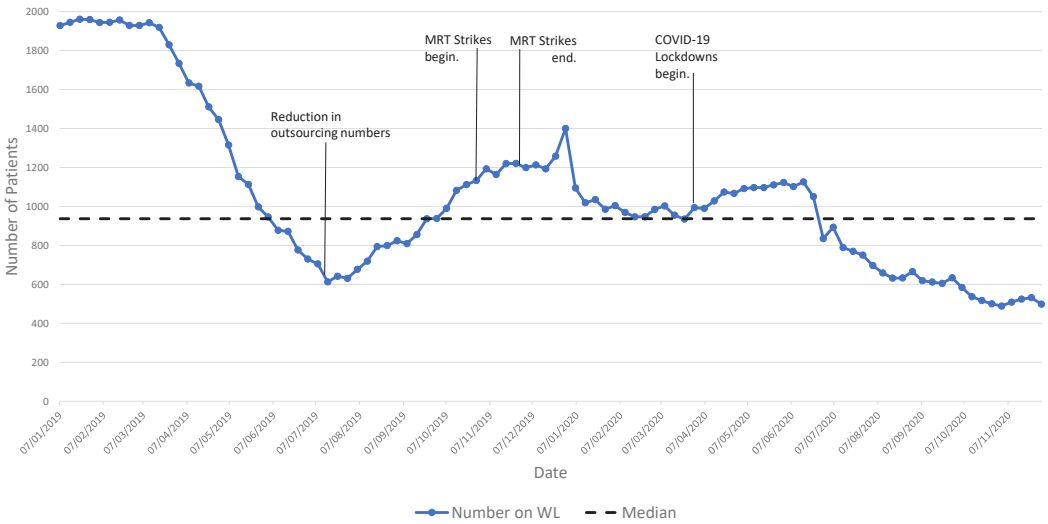
Within the overall backlog reduction, significant improvements have been made in the number of patients waiting in excess of 42 days (Figure 8). At the commencement of the project, 1,312 patients had waited over 42 days; by the end there were 48, and the whole waiting list shifted to the left. The most dramatic reduction was in the longest wait category, with 204 patients waiting more than 180 days for a scan at the start of the study, and zero by the end.

Associated with this change, patients received MRI scans in a timely manner, with 73 days being removed from the average waiting time. Simultaneously, scanning hours per week more than doubled (55.38 to 136.50)—see Table 1.

Discussion

At the start of this study, the radiology department had a limited understanding

Figure 7: Number of patients on waiting list, January 2019–November 2020.



NZMJ 25 June 2021, Vol 134 No 1537
ISSN 1175-8716
www.nzma.org.nz/journal

of their capacity and demand for MRI. In fact, the department believed more resources were required, particularly MRTs, to meet the demand. The collaborative effort between Ko Awatea and the radiology department, through this capacity and demand study, showed that in fact there was sufficient capacity to meet the demand, but that it was not organised optimally.

Through nine interventions covering three major areas—matching capacity to demand, list segmentation and redesigning operational systems—the department sustainably reduced the number of people waiting for MRI scans (from 1,954 to 413), shortened the average waiting time (from 96 days to 23 days) and decreased the number of patients with excessively long waits (from 1,312 to 48). By-products of this 'shift to the left' were an improvement in the MoH target for P2 patients (from 23% to >85%) and the exposure of the radiology department to QI methodologies and their enthusiasm to continue improvement efforts.

The use of data to drive improvement challenged several long-standing practices (eg, MRTs' expanded scope to vet referrals electronically released SMO time and encouraged SMOs to adopt electronic vetting). Likewise, understanding the characteristics of the long waits enabled specified lists for those patient groups, reducing the long waiting list tail.

This attention to detail is not common in waiting list management in New Zealand healthcare. However, understanding the principles of Lean thinking (eliminating waste and increasing value for customers) has the potential to improve many waiting lists. Adopting such manufacturing tools is not always appropriate in medicine,[4] but radiology is perhaps peculiarly suited to this production planning model, as it is a series of well-defined technical processes.

New Zealand as a whole has relatively few public MRI machines per head of population. In Counties Manukau Health, there are three for a population of 600,000 (~5 machines per million). It is not clear how many is optimal; internationally numbers range from 55 per million in Japan to 2.65 in Mexico.[5] Given the constrained resources, it is important for New Zealand to be innovative and apply the appropriate

Figure 8: Changes in waiting list numbers by waiting time segments, December 2018 to November 2020.

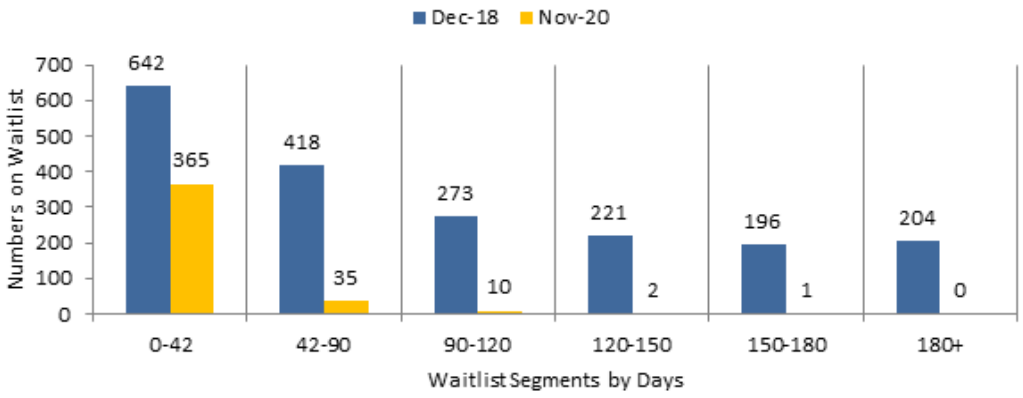


Table 1: Waiting list descriptive characteristics.

Descriptive stats	December 2018	November 2020
Total number of patients on waiting list	1954	413
Average number of days waiting	96.4	23.1
Range of days waiting	0-308	0–170
Scanning hours per week	55.38	136.50

improvement methodologies to optimise resources.

A similar approach was used by Canterbury District Health Board (CDHB)[6] when they faced increased waiting times for imaging. Using the principles of Lean, production planning and constraint theories, they worked with in-house production planning engineers to improve waiting times. In this case, the main constraint was limited radiologist hours, which was improved by rationalising and delegating some tasks traditionally undertaken by radiologists. As in Counties Manukau Health, having visibility of the gap between capacity and demand allowed several improvements in the process.

A systematic review of the application of Lean and Six Sigma (which aims to decrease defects to one in a million) approaches in radiology was published in 2016 and concluded that these methodologies had the potential to reduce errors and cost, and improve quality.[7] The five studies that looked at reducing waiting times were not representative of Counties Manukau Health's situation; starting from a much shorter baseline: decreasing the waiting time from 25 days to one. A review of MRI waiting lists in Canada[8] in 2009 noted that most centres routinely used scanners at the weekend, but only 3% were utilised on a 24/7 basis, and median scanning hours per week was 93.5, whereas our work increased this to 136.50.

There are some limitations to this study. It was neither feasible nor sensible to conduct a randomised controlled study as the team were examining the whole department and MRI process pathway. Learning and adjusting hypotheses based on small tests of change, a central tenet of most QI methods, meant that this was an iterative process with multiple tests—some sequential, some in parallel—so it is unclear which initiative had the biggest impact. Therefore, generalising results to other jurisdictions is not possible. However, the process of understanding a given department's data on capacity and demand is generalisable. Most radiology departments in New Zealand will be facing similar constraints, especially in the face of the COVID-19 lockdowns.

A further constraint is that ethnicity of each patient on the waiting list is not captured in the RIS, and it is therefore not possible to comment on any inequity in waiting times. In future it would be beneficial to conduct this work through an equity lens and, if inequity were to be identified, to use patient experience and co-design methodologies to uncover the reasons for this disparity.

The team faced several constraints that threatened the sustainability of improvements. The first challenge was the impact of national industrial action that occurred through the third and fourth quarters of 2019, severely affecting the availability of MRT staff and directly increasing the waiting list. At the same time, the outsourcing contract for 60 scans per week was reduced to 15 in July 2019, increasing demand. A further compounding factor in 2020 was COVID-19, which significantly reduced the availability of outpatient scans, particularly during the first lockdown in April 2020—consequently the backlog during this period increased.

Conclusion

Although the original premise for the long waiting times for MRI was a lack of capacity, this study showed that existing capacity was sufficient, but inefficiently matched to demand. Acting on detailed data of the causes of this inefficiency and employing Lean thinking principles and the Model for Improvement methodology, a number of innovative changes were made in the process of care, leading to a dramatic reduction in waiting times. There are lessons for other waiting lists in the healthcare system, particularly in building capability in capacity and demand analysis and other QI tools, which will be important for the New Zealand health system as it faces a future of fiscal constriction.

Competing interests:
Nil.
Acknowledgements:
The authoring team would like to acknowledge the co-operation, assistance and involvement from the MRI team at Middlemore Hospital. The staff had a direct positive impact on the uptake and retention of the improvement initiative resulting in improved patient and organisational outcomes.
Author information:
Heera Bhullar: Improvement Advisor, Ko Awatea,
Counties Manukau District Health Board, Auckland.
Bernadette County: Portfolio Manager, Ko Awatea,
Counties Manukau District Health Board, Auckland.
Stuart Barnard: Clinical Director of Central Clinical Services,
Counties Manukau District Health Board, Auckland.
Anne Anderson: Service Manager, Radiology,
Counties Manukau District Health Board, Auckland.
Mary E Seddon: Director Ko Awatea,
Counties Manukau District Health Board, Auckland.
Corresponding author:
Dr Mary Seddon, Director Ko Awatea, Middlemore Hospital, Counties Manukau District Health Board, 100 Hospital Road, Auckland 2025, +64275769669
mary.seddon@middlemore.co.nz
URL:
www.nzma.org.nz/journal-articles/reducing-the-mri-outpatient-waiting-list-through-a-capacity-and-demand-time-series-improvement-programme

REFERENCES

1. Kruskal JB, Reedy A, Pascal L et al. Quality Initiatives. Lean Approach to Improving Performance and Efficiency in a Radiology Department. Radiographics 2012; 32 (2): 573-587.
2. The Institute for Healthcare Improvement [Internet]. Available from: http://www.ihi.org/resources/Pages/HowtoImprove/ScienceofImprovementHowtoImprove.aspx Accessed 09/02/21
3. NHS Institute for Innovation and Improvement [Internet]. Improvement Leaders' Guide – Matching Capacity and Demand Process and Systems Thinking. 2005 https://www.england.nhs.uk/improvement-hub/publication/improvement-leaders-guide-matching-capacity-and-demand-process-and-systems-thinking/ Accessed 09/02/21
4. Bahensky JA. Lean sigma – will it work for healthcare? Journal of Healthcare Information Management 2005; 19 (1): 39 - 44
5. Statista [Internet]. 2019. Viewed 9th February 2021. Available from: https://www.statista.com/statistics/282401/density-of-magnetic-resonance-imaging-units-by-country/
6. MacDonald SLS, Cowan IA, Floyd R, et al. Measuring and Managing Radiologist Workload: Application of Lean and Constraint Theories and Production Planning Principles to Planning Radiology Services in a Major Tertiary Hospital. Journal of Medical Imaging and Radiation Oncology. 2013; 57: 544-550
7. Amaratunga A, Dobranowski J. Systematic Review of the Application of Lean and Six Sigma Quality Improvement Methodologies in Radiology. Journal of the American College of Radiology. 2016; 13(9): 1088-1095
8. Emery DJ, Forster AJ, Shojania KG, Magnan S. Management of MRI Wait Lists in Canada. Healthcare Policy. 2009; 4 (3):76-86

Does research help to inform a district health board's purpose? A qualitative thematic analysis of clinician researcher views

Lorraine Neave, Duncan Reid, Brian McKenna

ABSTRACT

AIM: The outcomes from research should guide the decisions of healthcare providers, policymakers and funders. This study sought the perspectives of senior hospital clinicians and researchers from a New Zealand district health board (DHB).

METHOD: A series of interviews asked participants about the purpose and benefits of research to the DHB, and to reflect upon the enablers and barriers they had experienced in conducting and translating research in a DHB context.

RESULTS: Three key themes were identified. The first theme suggested research should inform the DHB's purpose. The second theme identified how the general busyness, lack of research funding and the differing motivations of clinicians and business leaders doesn't make it easy to do research in a DHB. The third theme suggested that research barriers could be seen as opportunities. Participants placed importance on an environment that inspires enquiry; that permits staff to stop and question what they do; that overtly informs its community that research is done to improve the delivery of care; that communicates a purposeful research agenda; and that regularly discusses the intersection of research and the purpose of the DHB.

CONCLUSION: This study found the absence of an organisation-wide research ethos affected staff engagement in and with research. As a consequence, the effective transfer and translation of knowledge from research was disrupted. Key recommendations were for the DHB to integrate research activity into practice, regularly discuss research evidence and celebrate research achievements.

Research is fundamental to informing and improving healthcare outcomes[1]. A research-enabled environment can engender intellectual curiosity, positive questioning of routine practice and robust research practices that can lift process and practice in general.[2,3] The outcomes from research can also guide healthcare providers', policymakers' and funders' decisions about resource and purchasing at a national, regional and local level.[4,5] Organisationally, a positive research culture can facilitate recruitment and retention of excellent clinicians and generally improve staff attitudes, commitment and values.[6] Importantly, it can nurture a sense of inter-professional collaboration that is essential to meeting the changing and complex needs of the population.[7–9]

In New Zealand, the Government is the major health funder and supports the health of its people through the provision of a publicly funded, universal healthcare system, with district health boards (DHBs) being the prime recipients of healthcare funding. DHBs are also the prime locality for the conduct of the clinical research activity in New Zealand.[7] Yet, DHBs receive no direct capital provision for research in their annual government funding, and until 2020 DHBs' annual plans to the Minister of Health did not

require consideration of research. Little is known about how DHBs support their staff to manage their research, what things enhance or create barriers to conduct research in a DHB and whether the outcomes of that research are translated to inform practice and support the DHB purpose.

Aim

The overarching aim of this study was two pronged. Firstly, to explore from a DHB-staff perspective what the enablers and barriers to doing research were. Secondly, to investigate whether the outcomes of a DHB's research activity helped to inform that DHB's purpose of providing best care.

Method

This descriptive, qualitative research was a part of an explanatory sequential mixed method study that included documentary analysis, survey and a series of exploratory interviews, reported here. A purposeful sample of clinical leaders who are actively researching at a large metropolitan DHB were invited to participate in individual interviews, so we could ascertain their experience of conducting research and translating the outcomes of the research in the DHB context. Participants consented to the process after having read the relevant information sheets outlining the purpose of the study. The study was approved by Auckland University of Technology Ethics Committee (AUTEC), reference 17/204 AUTEC, and the DHB's locality approval was sought and given.

The semi-structured interview format explored the perceived enablers and barriers. Participants were asked: Do they consider that locally conducted research helped to inform the DHB's purpose? How had the DHB supported them in their research? Had they encountered any barriers? And what was their experience of translating the findings of research to practice? The interviews were conducted face to face at a pre-arranged time and place suited to the interviewee and were voice recorded. The recordings were transcribed verbatim, and participants were offered their transcripts to review. Only a couple of minor clarifications, which did not change the overall context of the interviews, were required.

The interviews were thematically analysed utilising a six-stage reflexive thematic analysis process described by Braun and Clarke.[10] This comprised listening to the recorded interviews multiple times to appreciate the nuanced tones, and reading the verbatim transcripts for documentary accuracy, before embarking on a recursive process of coding to capture the core semantics. In this process a series of experiential themes were inductively developed and reported in relation to the overarching research question.

Results

Eight senior clinicians recognised as research leaders were invited to reflect on their experience. Six responded to the invitation, three men and three women, each with decades of experience conducting research in a hospital context. The interviewees represented the broad disciplines of general medicine, surgery, public health and psychiatry. Two of the interviewees were also recognised for their research into indigenous health and inequity. All but one had been recipients of, or were key members of, research collaborations that had received New Zealand Health Research Council (HRC) funding. Two had significant experience conducting industry-sponsored clinical trials in the DHB context. Additionally, all had either active or honorary co-appointments with universities in the region.

Three key themes were developed from the data. The first described the participants' universal opinion that research should help to inform the DHB's purpose. The second theme was struck from a comment that, while research should inform the purpose of the DHB, the DHB doesn't make this easy. The final theme came from the interviewees' largely optimistic reference to their being "opportunities" rather than barriers for the DHB to support robust research and knowledge creation to inform its purpose. Each theme comprised a series of sub-themes.

Theme 1: research should inform the DHB's purpose

The interview participants generally concurred that research should inform the DHB's purpose (Theme 1), but that the DHB could only do this where ethically and meth-

odologically sound research was conducted and was translated to practice. A series of sub-themes emanated from the interviewee dialogue.

In the first sub-theme, interview participants defined the importance of enabling a culture of questioning within the organisation, which "makes a big difference to morale" and means "that we don't just do things because we've always done it, that we're interested in advancing knowledge to deliver better care". They indicated that while pockets of a research ethos exist in the DHB, that ethos tended to be "enthusiast driven". Participants felt the DHB could use its available resources to research more effectively and more prescriptively. In particular, they said the DHB should use the relatively untapped resource of routinely collected data focussed on specific health issues, and more generally that research should inform the DHB's purpose of improving the broader social determinants that affect health equity.

In the discussion that led to the second sub-theme, interviewees emphasised the importance for research to always be inclusive and real world, where researchers "work together with consumers… having consumers raising the [research] questions" because this "leaves people in the organisation confident that the results really are results we should listen to". They considered the outcomes of contextually relevant research to be more likely to provide decision-makers with the confidence that the associated costs of translation to practice would meet the organisation's purpose.

The third sub-theme reflected on the participants' views that DHB research should be conducted collaboratively and/or in partnership with external agencies or bodies. The interview participants universally considered that the breaking down of departmental silos to embrace interdisciplinary and cross-sectoral research collaborations was needed to support the DHB's research capacity and capability. One interviewee noted her own research relationships with universities "bring[s] in people with particular expertise around design, around models of inquiry, around analysis", who are not routinely available in a DHB.

Another commented that more clinicians are thinking that "it's quite cool to work with other [non-health] people" who bring their diverse and complementary perspectives, skills and training. Moreover, research alliances with universities means that "we also bring in some young talent through people who are in training" and thereby foster the DHB's future workforce. Participants did concede that such collaborations aren't straightforward and can be complicated by the need for additional time and effort to nurture and maintain the relationships.

In the final sub-theme, the interview participants had a collective view that knowledge creation from research must be disseminated to be translated, and that the intent to disseminate and translate must be planned for from the beginning. Moreover, translation should be easier where "the research [was conducted] in the environment it's going to be translated into" because the end users will have had the opportunity to "gauge [whether] this [is] going to be something that's going to be useful". One participant described "researching so other people will know": "I try and involve the caregivers and the community [clinicians] so that they… [are] involved and know about what was going on. That makes a big difference". Participants agreed that, for research to inform the DHB's purpose, the DHB needed to encourage greater communication about research plans, create opportunities to share the outcomes and overtly celebrate the translation of research into practices that inform the DHB's purpose when it occurs.

Theme 2: the DHB environment doesn't make it easy

In Theme 2 participants provided forthright opinions as to why research in a DHB is not easy. Four sub-themes explored the barriers encountered. The first reflected on hospital busyness, which sees research relegated rather than integrated in the organisational ethos. This issue is aggravated by a tendency for staff to resist changes in their routine, and by business processes that don't easily accommodate timely translation to practice. The overall theme was encapsulated in one participant's lament that "the DHB doesn't make it easy".

The first sub-theme also described the daily grind of hospital busyness being

a barrier to research. A participant commented, "it's very difficult for people to prioritise doing something other than their job", especially where colleagues perceive research as a distraction that doesn't directly help to address the immediate issue of "queues of patients at the door". The day-to-day busyness on the frontline of hospital operations impedes clinicians' ability to accommodate time for research. One participant typified the comments by saying, "you have to do [research] for the love of it more than anything else, and you have to sort of find the time for it and make it an important issue for yourself". Another noted, "There's plenty of interest from clinicians [in research]… if they had a bit of brain space and a bit of kind of protected time".

Translation of new evidence-based knowledge to practice should be the cornerstone of healthcare policy and process. However, the second sub-theme described a massive gap between research and clinical practice (a 'know–do gap').[11,12] One participant commented that "in terms of every day clinical practice I don't think there's an awful lot going on to really try and encourage clinicians to be thinking about putting research into practice". Others referred to the cause being a general resistance to change, which one participant described as "partly the conservative nature of our training… and partly it's just simpler to keep doing the way we've always done because everyone understands their role". Change is seen as "just more work for people… and you have to spend quite a bit of time initially to figure them out before they become easier".

To overcome the know–do gap in research, participants considered the potential for research translation must be nurtured right from the start, when the research question is being developed. This ensures the managers and clinical leaders approving the conduct of the research locally can "gauge [that] this is something that's going to be useful… [because] the question itself is framed by the service". The purpose of the research should be well communicated and involve the staff who may be affected, so that any practice change in the future will not be unfamiliar.

The third sub-theme addressed a barrier created by DHB business processes that don't easily accommodate research. Even where contextually relevant and well communicated research has provided the highest-quality evidence for change, translation can still be stalled by the business process. Participants recognised the restrictions imposed by the government-funding model, which frequently constrains the agility of business decision-making. However, they were universally critical of the inflexibility they had experienced when attempting to translate the outcomes of research. One account illustrated the frustration:

> *"We developed a [research] programme here with our people, and we trialled it here with our people, and the decision-makers were involved in that all the way through, [but] now trying to get it implemented we've just been going around and around the traps! … we've got to go through the usual big business case process, which is quite time intensive, resource intensive, nobody's really sure who should be writing it, who's championing it…"*

In the final sub-theme, participants acknowledged that "not everything is bad though". Although conducting research in the DHB was not easy for the various reasons outlined, participants noted there are some purposeful pockets of positive action to support research. Participants noted that the DHB has a research office "that you can kind of bounce ideas off or [access] some specific skills". Another commented on the research office's coordination of external grant applications "… getting all the right bits together". One participant remarked, "the most important things have been management's kind of acceptance or sometimes even active encouragement of research as something I do".

Theme 3: opportunities, not barriers

In Theme 3 participants focussed on the opportunities moving forward, where research can be an integral function of the DHB. Two sub-themes detailed how the DHB should direct its efforts to enable research to better inform its purpose. Firstly, through overt communication that research is "what

we do to improve the care we deliver. And secondly, by providing competitive seed funding for research.

The first sub-theme centred on what was perceived as a missed opportunity for the DHB to overtly inform its community that "research is what we do" to deliver the best care for everyone. One participant articulated the point best: "I think if we made [research] more of a deliberate part of what we do… it's not [seen as] our core business and so we don't tell patients necessarily this is what we do… We don't put up anything about results anywhere either, even to our own staff. We're not very good at saying… there's research going on all the time and its purpose is to improve services for our population".

The second sub-theme discussed the importance of a purposeful research budget. Interviewees appreciated that the funding the DHB receives from the Government is limited, and that the Government looks to the HRC to manage its investment in health research. However, they vociferously considered that the government-funding model is wrong, observing in other organisations, both public and private, that a "percentage of their revenue stream is applied to research and development… But in health… it's not there". Interviewees saw the opportunity for the DHB to target research partnerships for bigger projects, and to provide a deliberate competitive research fund for small research projects, where seeking external funding would not be cost or resource effective. Interviewees felt if the DHB "can get the ball rolling and provide the seed structure and the facilities to allow [research] to grow then it will grow and be self-supporting". Moreover, such a fund would allow its staff researchers to get the track records needed to apply successfully for the hotly contested HRC and similar types of awards.

Discussion

This interview series has provided insight into how a variety of organisational factors influenced staff capacity and capability engagement with research.

The executive summary of this DHB's research strategy clearly intended for the DHB to build on its research achievements and become a centre of research excellence to support the organisation's purpose. The New Zealand Health Research Strategy 2017–2027[7] likewise supports such a goal, stating that a culture of excellence in research is needed to improve the health and wellbeing of patients and communities. Similarly, the World Health Organization (WHO) has stated that "universal health coverage cannot be achieved without evidence from research", and that to ensure the relevance of research findings to local context, all nations should both be involved as producers and consumers of research.[13]

Consistent with the literature, participants in this study considered that research was made difficult by the reality of busyness[9,14–16] and business process. Differing agendas and timelines exist between the hospital business decision makers, who must prioritise their decisions to the challenges of their business reality,[17–19] and the hospital clinicians, who focus on what they know can make a difference for their patients right now.[3] Participants in this study noted that research is frequently left to the enthusiasts to conduct on top of their business-as-usual activities. This can lead to clinicians being apathetic towards engagement in and with research, which won't be simply overcome by the implementation of systems to support research.[20] Participants considered the inherent mismatch of intents between the organisation's administrators and clinicians remains a key barrier to the conduct of research. It was also seen to impact upon whether the business accepts the cost–benefit of change, and also the effective translation of research outcomes into practice or policy,[14,21] where effective dissemination of the findings is dependent upon the time other health professionals have to be aware of, agree to, adopt and adhere to a practice or policy change.[22]

Interview participants in this study concurred that the key to overcome these barriers is an overt organisational research agenda supported by proactive and early engagement of the users of the ensuing knowledge. To this end, they considered that the DHB's executive must deliberately engage with its staff (clinical and business) and potential research collaborators, to align their research questions to the DHB's priority healthcare issues. A whole-of-organ-

isation approach would integrate research deeper within the DHB's core activities and thereby enable the effective transfer and translation of research knowledge that is integral to the DHB's purpose.

A potential limitation of this study was that interviewees were from the medical profession, and this may preclude generalisation across other health professions. However, the literature suggests nurses similarly describe a lack in the time, training, exposure to and support for research as inhibitors to their engagement in the research activities.[23–27] Likewise, allied health professionals, and public health and policy evaluation professionals, report comparable barriers, with the latter noting the additional difficulties of navigating the conceptual and motivational divide between clinical researchers and public health and policy researchers.[28,29]

Conclusion

This study has provided insight into how organisational factors can influence engagement in and with research and thereby negatively impact the potential for research to inform a DHB's purpose. These factors are all modifiable influences. The themes offer a direction for the DHB's future research strategy, where research activity is integrated into practice, where research evidence is discussed and where research achievements are celebrated. The findings from this study will likely resonate across New Zealand's DHB landscape.

Competing interests

Dr McKenna reports grants from Pacific Health Research Davis Award: HRC, grants from New Zealand Law Foundation, grants from Department of Corrections, grants from Ministry of Health, grants from Marsden Foundation Fund and grants from Borrin Foundation, all outside the submitted work, and that they have a joint professorial position with the Waitemata District Health Board as a Professor in Forensic Mental Health.

Author information:

Lorraine Neave: RGON; MHSc; DHSc, Operations Manager, Research and Knowledge Centre, Waitematā District Health Board, Auckland, New Zealand.

Duncan Reid: DHSc, MHSc, PgDip HSc, BSc, DipPT, Professor of Physiotherapy, Auckland University of Technology, Auckland, New Zealand

Brian McKenna: RN, BA, MHSc, PhD, Professor of Forensic Mental Health, Auckland University of Technology, and the Auckland Regional Forensic Psychiatry Services, Waitematā District Health Board, Auckland, New Zealand; Adjunct Professor, Centre for Forensic Behavioural Science, Swinburne University of Technology, Melbourne, Australia

Corresponding author:

Dr Lorraine Neave, Research and Knowledge Centre, Waitematā District Health Board, Auckland, New Zealand, Private Bag 93503, +64 9 4868920 ext 42112

Lorraine.neave@waitematadhb.govt.nz

URL:

www.nzma.org.nz/journal-articles/does-research-help-to-inform-a-district-health-boards-purpose-a-qualitative-thematic-analysis-of-clinician-researcher-views

REFERENCES

1. Boaz A, Hanney S, Jones T, Soper B. Does the engagement of clinicians and organisations in research improve healthcare performance: a three-stage review? BMJ Open 2015;5:e009415.
2. Hanney, S, Boaz, A, Jones, T, Soper, B. Engagement in research: an innovative three-stage review of the benefits for health-care performance. Health Serv Deliv Res, 2013;1:8.
3. Saini V, Garcia-Armesto S, Klemperer D, et al. Drivers of poor medical care. The Lancet. 2017;390(10090):178-90.
4. Ministry of Health [Internet]. Statement of Intent 2015 to 2019. 2015. Available from: https://www.health.govt.nz/publication/statement-intent-2015-2019
5. Sarkies MN, Bowles KA, Skinner EH, et al. The effectiveness of research implementation strategies for promoting evidence-informed policy and management decisions in healthcare: a systematic review. Implement Sci, 2017;12:132.

6. Makkar SR, Turner T, Williamson A, et al. The development of ORACLe: a measure of an organisation's capacity to engage in evidence-informed health policy. Health Res Policy Syst. 2016;14:4.
7. Ministry of Business Innovation & Employment and Ministry of Health [Internet]. NZ Health Research Strategy 2017-2027. 2017. Available from: https://www.health.govt.nz/publication/new-zealand-health-research-strategy-2017-2027
8. Health Research Council [Internet]. New Zealand Health Research Council - About us. 2020. Available from: https://www.hrc.govt.nz/what-we-do/about-us
9. Royal College of Physicians [Internet]. Research for all. Building a research-active medical workforce. 2016. Available from: https://www.rcplondon.ac.uk/projects/outputs/research-all
10. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006; 3:77-101.
11. Andermann A, Pang T, Newton J, et al. Evidence for Health II: Overcoming barriers to using evidence in policy and practice. Health Res Policy Syst. 2016;14:17.
12. Lander B, Hanley G, Atkinson-Grosjean J. Clinician-scientists in Canada: barriers to career entry and progress. PLoS One. 2010;5:e13168.
13. Dye, C., Boerma, T., Evans, D., et al. Research for universal health coverage. World Health Organization. 2013. Available from: http://www.who.int/whr/2013/report/en/
14. Mickan S, Wenke R, Weir K, Bialocerkowski A, Noble C. Strategies for research engagement of clinicians in allied health (STRETCH): a mixed methods research protocol. BMJ Open. 2017;7:e014876.
15. Pager S, Holden L, Golenko X. Motivators, enablers, and barriers to building allied health research capacity. J Multidiscip Health. 2012;5:53-9.
16. Rahman S, Majumder M, Shaban S, et al. Physician participation in clinical research and trials: issues and approaches. Adv Med Educ Pract. 2011;7:85-93.
17. Gagliardi A, Berta W, Kothari A, et al. Integrated knowledge translation (IKT) in health care: a scoping review. Implement Sci. 2016;11:38.
18. Kothari A, MacLean L, Edwards N, Hobbs A. Indicators at the interface managing policymaker researcher collaboration. Knowledge Management Research Practice. 2011;9:203-214.
19. Williamson A, Tait H, El Jardali F, et al. How are evidence generation partnerships between researchers and policy-makers enacted in practice? A qualitative interview study. Health Res Policy Syst. 2019;17:41.
20. Rahman S, Majumder MA, Shaban SF, et al. Physician participation in clinical research and trials: issues and approaches. Adv Med Educ Pract. 2011;2:85-93.
21. Kothari A, Edwards N, Hamel N, Judd M. Is research working for you? Validating a tool to examine the capacity of health organizations to use research. Implement Sci. 2009;4:46.
22. Glasziou P, Haynes B. The paths from research to improved health outcomes. Evid Based Nurs. 2005 Apr;8(2):36-8.
23. Black A, Balneaves L, Garossino C, et al. Promoting evidence-based practice through a research training program for point-of-care clinicians. J Nurs Adm. 2015;4514-20.
24. Evans G, Duggan R, Boldy D. An exploration of nursing research perceptions of registered nurses engaging in research activities at a metropolitan hospital in Western Australia. Collegian. 2014;21:225-32.
25. Loke J, Laurenson M, Lee K. Embracing a culture in conducting research requires more than nurses' enthusiasm. Nurse Educ Today. 2014;34:132-7.
26. New K, Bogossian F. Nurse led clinical research: neonatal nurses' perceptions and experiences. Neonatal, Paediatric & Child Health Nursing. 2012;11:13-18.
27. O'Byrne L, Smith S. Models to enhance research capacity and capability in clinical nurses: a narrative review. J Clin Nurs. 2011;20:1365-71.
28. Huckel Schneider C, Milat A, Moore G. Barriers and facilitators to evaluation of health policies and programs: Policymaker and researcher perspectives. Eval Program Plann. 2016;58:208-215.
29. Makkar S, Haynes A, Williamson A, Redman S. Organisational capacity and its relationship to research use in six Australian health policy agencies. PLoS One. 2018;13:e0192528.

How common are non-acute coronary syndrome (ACS) diagnoses in patients with suspected ACS investigated with coronary angiography in New Zealand? (ANZACS-QI 58)

Charles Yao-Cheng Ho, Mildred Lee, Seif El-Jack, Peter Barr, Mark Simmonds, Gerry Devlin, Philip D Adamson, Michael Williams, Andrew J Kerr

ABSTRACT

BACKGROUND AND AIMS: The last two decades in New Zealand have seen increased availability of primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) and early invasive coronary angiography (ICA) for other high-risk acute coronary syndrome (ACS) patients. One metric to assess the clinical appropriateness of these invasive strategies is to examine the false-positive rate for the investigation (ie, the rate of non-ACS diagnoses).

METHODS: All patients presenting to New Zealand public hospitals with suspected ACS who underwent ICA between 2015 and 2019 were recorded prospectively in the All New Zealand Acute Coronary Syndrome Quality Improvement registry. The cohort was divided according to clinical impression at presentation: (1) suspected STEMI <24h and (2) other suspected ACS. The final discharge diagnosis for each patient were obtained from the registry.

RESULTS: There were 6,059 (20%) patients with suspected STEMI <24h and 24,258 (80%) with other suspected ACS. Of the suspected STEMIs <24h, 90.6% had a final diagnosis of STEMI, 3.5% non-ST segment elevation ACS (NSTEACS) and only 5.9% had a non-ACS diagnosis. Of those with other suspected ACS, 80.7% had a final ACS diagnosis. Across all New Zealand district health boards (DHBs), the proportion of non-ACS diagnoses was similar for suspected STEMI presentations. However, for other suspected ACS, the proportions were higher in DHBs with rapid access to coronary interventional facilities than in those without (17.6% vs 7.0%, p<0.001).

CONCLUSIONS: False-positive catheter laboratory activations for suspected STEMI patients are low across New Zealand. The differences in the proportion of non-ACS diagnoses according to DHB interventional capability for other suspected ACS requires further investigation.

Over the past two decades, there has been a decline in the incidence of acute coronary syndrome (ACS) and associated mortality worldwide, including in New Zealand.[1,2] This is in part due to the increased acute reperfusion therapy for ST-elevation myocardial infarction (STEMI) patients presenting within 24 hours of symptom onset, using either primary percutaneous coronary intervention (PCI) or fibrinolysis with early angiography, and a routine invasive approach for those with high risk non-ST elevation ACS (NSTEACS) and other STEMI patients, both of which have been shown to improve patient outcomes.[2–6] However, only 15–30% of patients who present with chest pain have ACS, and with the increase in primary PCI for STEMI and early coronary angiography for NSTEACS, there is potential for inappropriate invasive coronary angiography (ICA) with its associated patient and financial risks.[7,8] In particular, the out-of-hours activation of catheter laboratories for suspected STEMIs has a human cost for the staff involved in the roster, along with financial costs for the institution in maintaining the rosters.

Some studies have reported the rate of false-positive STEMI diagnosis,[9–12] but no studies have reported specifically on false-positive NSTEACS diagnosis and the appropriateness of ICA in this group of patients, despite NSTEACS comprising 60–70% of ACS presentations.[3, 13]

In this study we aim to identify the incidence and characteristics of false-positive ACS diagnosis and the respective rates of non-ACS conditions in patients presenting with suspected acute STEMI and other suspected ACS.

Method

Data source

Patients were identified from the All New Zealand Acute Coronary Syndrome Quality Improvement registry (ANZACS-QI). This is a nationwide web-based electronic database that captures all patients who present to a New Zealand public hospital with suspected ACS and who are investigated with coronary angiography. It records a mandatory dataset including admission and discharge dates, patient demographics, admission ACS risk stratification, cardiovascular risk factors, investigations, management, in-hospital outcomes, discharge diagnosis and medications. Details of this registry and data collection have previously been reported. It is audited monthly to ensure more than 99% of patients have complete data entry throughout all New Zealand hospitals, and annual independent audits check the accuracy of data entry.[14,15]

Study cohort

From the ANZACS-QI registry, consecutive patients 18 years or older presenting with suspected ACS who underwent coronary angiography between January 2015 to January 2019 were included. When patients had more than one suspected ACS admissions during the study period, only the first one was included. Patients who were not New Zealand residents were excluded. The study cohort comprised 30,317 patients. The cohort was divided into two groups according to the clinical impression at the time they entered the catheterisation laboratory:

1. 'Suspected STEMI <24h' includes all patients presenting to the catheter laboratory who were suspected of having a STEMI within 24 hours of symptom onset. In New Zealand, as elsewhere, these patients are considered for acute reperfusion therapy—either a primary PCI or fibrinolysis, which is usually followed by early angiography. The choice depends on how quickly patients can access an interventional cardiac catheter laboratory. In larger metropolitan centres most patients are managed with a primary PCI strategy, but for patients living within district health board (DHB) catchments without interventional capability, fibrinolysis is more common.[16] For this analysis the sub-group of those with suspected STEMI <24h who underwent a primary PCI strategy was also identified.
2. 'Other suspected ACS' includes all patients with suspected unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and those with suspected STEMI studied more than 24 hours after symptom onset.

Definitions

'Final ACS' or 'final non-ACS' are defined by the eventual discharge diagnosis, which is based on a combination of angiographic findings, cardiac biomarkers and clinical presentation, at the discretion of the primary medical practitioner. The diagnosis for each patient and their baseline characteristics were obtained from the ANZACS-QI registry. A 'false-positive' diagnosis refers to those who were suspected of having ACS initially but were discharged with a non-ACS diagnosis.

'Myocardial infarction' (MI) was defined according to the contemporary universal definition.[17] UA is diagnosed if one of the following occurred in the absence of biochemical evidence of myocardial necrosis: (1) >20 minutes angina pain at rest, (2) de novo Canadian Cardiovascular Society class II or III angina or (3) recent destabilisation of stable angina with at least CCS class III angina.[18] The final discharge diagnosis for each patient were reported as STEMI, NSTEACS (UA and NSTEMI) or non-ACS condition.

For the purposes of this analysis, DHBs were dichotomised into those with rapid access to a coronary interventional laboratory (Waitematā, Auckland, Counties Manukau, Bay of Plenty, Waikato, Capital and Coast, Hutt Valley, Nelson Marlborough, Canterbury and Southern DHBs) versus those without.

Non-invasive testing recorded prior to ICA included stress testing (exercise treadmill test, exercise stress echocardiogram, dobutamine stress echocardiogram or nuclear stress study) and CT coronary angiogram (CTCA).

'Obstructive coronary disease on ICA' refers to the presence of coronary stenosis 50% or more in any of the major epicardial coronary arteries.

Ethnicity was prioritised using a modified version of New Zealand Standard Ethnicity Data Protocols in the following order: Māori, Pacific, Indian, Other Asian and European/Other.[19]

Statistical analysis

Descriptive statistics for categorical data are presented as frequencies and column percentages, and continuous variables as median with interquartile ranges and/or mean ± standard deviation. Chi-squared test or Fisher exact test was used for comparison between two groups, and Wilcoxon Mann–Whitney U test or Student's T-test was used for continuous variables where appropriate. All P-values reported were two-tailed and a P-value <0.05 was considered significant. Data were analysed using SAS statistical package, version 9.4 (SAS Institute, Cary, NC).

Results

Between 2015 and 2019, a total of 30,317 patients 18 years of age or older who presented with suspected ACS were identified. This comprised 6,059 patients (20%) with suspected STEMI <24h and 24,258 patients (80%) with other suspected ACS.

Of the 6,059 patients with suspected STEMI <24h, 5,491 (90.6%) had a final diagnosis of STEMI, 212 (3.5%) had NSTEACS (191 NSTEMI and 21 UA) and 356 (5.9%) had non-ACS final diagnoses; 4,072 (67.2%) were managed with a primary PCI strategy, of whom 3,743 (91.9%) had a final diagnosis of STEMI, 61 (1.5%) had a final diagnosis of NSTEACS and 268 (6.6%) had a non-ACS final diagnosis.

Of those with other suspected ACS, 19,597 (80.8%) had a final ACS diagnosis, of which 17,993 (74.2%) were NSTEACS (14,590 NSTEMI and 3,403 UA) and 1,604 (6.6%) were STEMI. There were 4,661 (19.2%) with a non-ACS final diagnosis.

Regional variation in ACS diagnosis

Among patients suspected of having a STEMI, the rate of false-positive diagnoses across New Zealand DHBs was less than 12%. It appears to be independent of the total number of patients, as demonstrated in Figure 1. For the DHBs frequently using a primary PCI strategy, the false-positive rate was low albeit with some variation (Waitematā 9.9%, Auckland 9.1%, Counties Manukau 8.3%, Bay of Plenty 3.6%, Waikato 6.7%, Capital and Coast 2.6%, Hutt Valley 2.9%, Nelson Marlborough 3.9%, Canterbury 9.7% and Southern 7.8%, see Appendix Table 1).

In comparison, there is a wider range in non-ACS final diagnoses for other suspected ACS patients, up to 27.3%. Figure 2 demonstrates a general trend for more non-ACS final diagnoses in DHBs with ready access to

interventional catheter laboratories (17.6% (intervention capable DHBs) vs 7.0% (non-intervention capable DHBs), p<0.001).

Characteristics and investigations in patients presenting with suspected ACS

There were 1,200 patients with non-ACS final diagnoses (78 suspected STEMI <24h and 1,122 other suspected ACS) who only had demographic data available in the registry. They were excluded from the subsequent cohort characteristics comparison, which left 29,117 patients. The demographic characteristics of this reduced cohort were virtually identical to the original cohort.

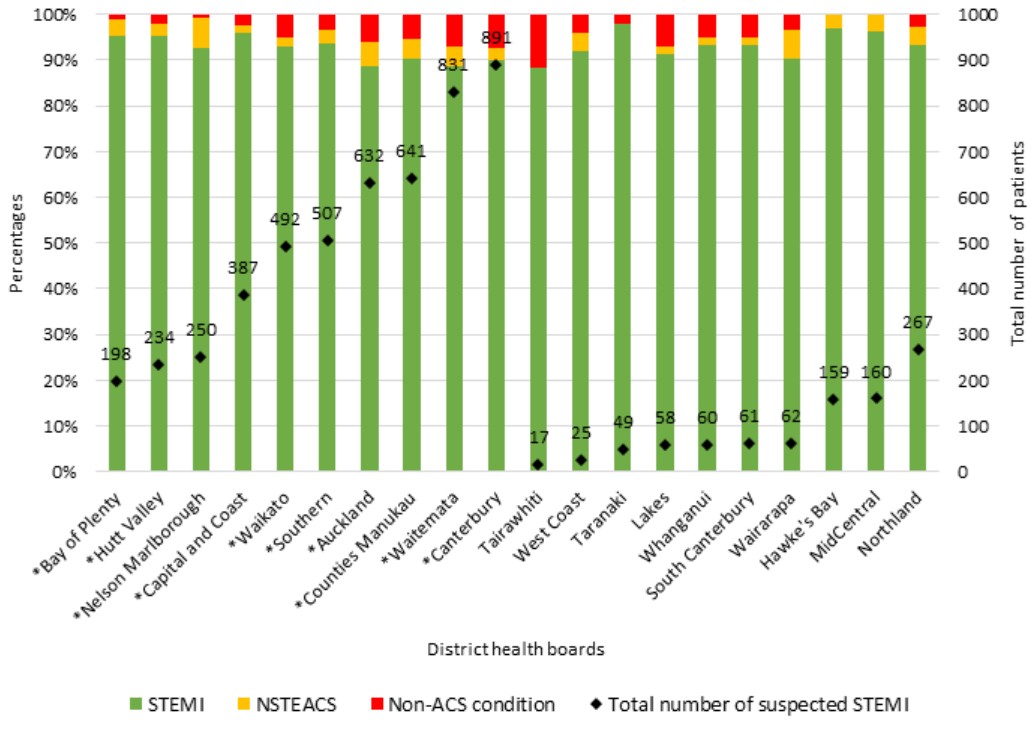
Suspected STEMI <24h: In patients presenting with suspected STEMI, those with non-ACS final diagnoses were likely to be younger (median age of STEMI 63 vs NSTEACS 63 vs non-ACS patients 59, p<0.007) and female (26% vs 29% vs 41%, p<0.03).

Patients with NSTEACS tend to have more cardiovascular comorbidities, including prior history of MI (12.9% vs 24.1% vs 11.5%, p<0.001), congestive heart failure (CHF) (1.5% vs 4.7% vs 1.1%, p<0.013) and diabetes mellitus (DM) (17.4% vs 26.4% vs 11.9%, p<0.02). Conversely, those with non-ACS conditions had the lowest burden of cardiovascular comorbidities and risk factors. Patients with a final diagnosis of STEMI were intermediate among the other two groups. Pacific patients had the highest rate of non-ACS diagnoses compared to other ethnicities (Māori 4.6%, Pacific 8.3%, Indian 5.0%, Other Asian 4.0%, European 4.4%).

The frequency of a stress testing or CT coronary angiography (CTCA) performed prior to undergoing ICA in patients presenting with suspected STEMI was appropriately low (<5%).

Other suspected ACS: Patients who presented with other suspected ACS and

Figure 1: Stacked bar graph demonstrates proportion of final diagnoses in patients presenting to the catheter laboratory with suspected STEMI <24h by DHB (percentages, left-hand y-axis). Scatter plot demonstrates total number of suspected STEMI <24h patients in each DHB (absolute number, right-hand y-axis).



* Rapid intervention capable catheter laboratory available.
STEMI, ST-segment elevation myocardial infarction; NSTEACS, non-ST segment elevation acute coronary syndrome; ACS, acute coronary syndrome.

with non-ACS final diagnoses were also younger (median age of ACS 67 vs non-ACS 62, p<0.001) and more likely to be female (31.6% vs 49.3%, p<0.001). Patients with a final ACS diagnosis had a higher burden of established cardiovascular comorbidities and risk factors (ACS CVD 22.6% vs non-ACS 12.6%, p<0.001). In contrast, those with non-ACS conditions were more likely to have underlying chronic obstructive pulmonary disease (COPD) (9.7% vs 11.5%, p=0.001). The proportion with non-ACS diagnoses was similar across all ethnic groups.

The rate of stress testing was 8% (ACS 6.5% vs non-ACS 15.9%, p<0.001). CTCA was performed in 5.5% (ACS 5.4% vs non-ACS 6.0%, p=0.206).

Angiographic findings

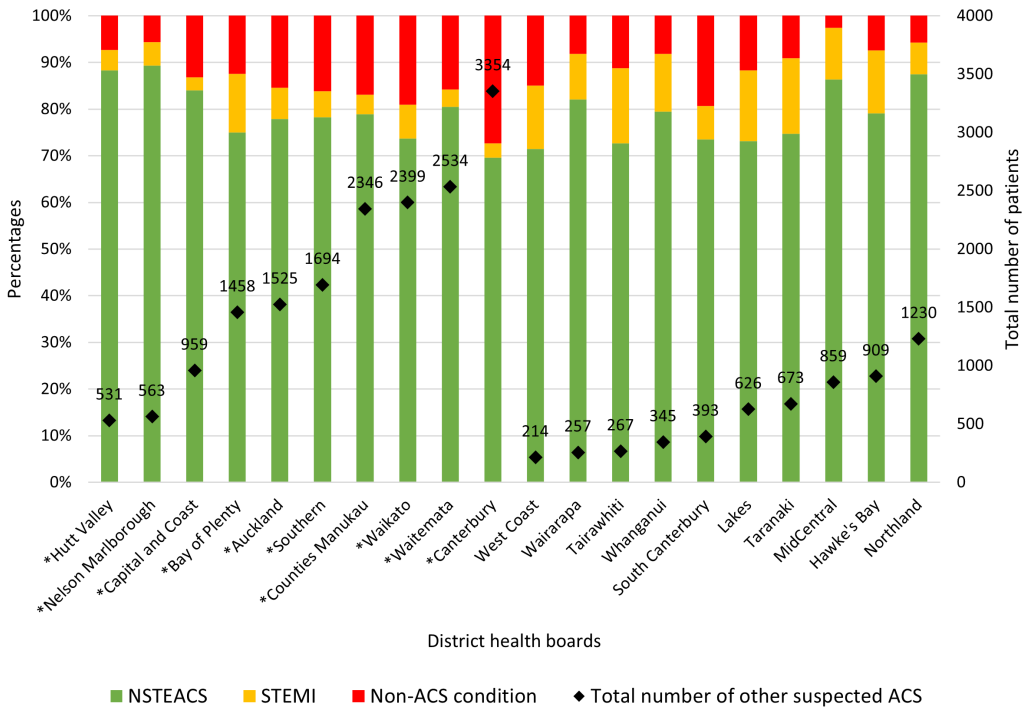
Of the patients with suspected STEMI <24h, the majority of those with non-ACS final diagnoses had no significant obstructive coronary disease (non-ACS 81.7% vs STEMI 3.5% vs NSTEACS 13.7%, p<0.001). Findings of significant single- or double-vessel obstructive coronary disease were more common in those with a final diagnosis of STEMI (75.1% vs 57.6% vs 13.3%, p<0.001). Patients with a final diagnosis of NSTEACS had higher proportion of three-vessel coronary disease or left-main stenosis than other groups (21.4% vs 28.8% vs 5.0%, p<0.001).

A similar trend was demonstrated in patients with other suspected ACS. Among the non-ACS group, 79.6% had no significant obstructive coronary disease.

Non-ACS diagnoses

The non-ACS conditions most likely to raise suspicion for ACS on presentation and undergo ICA included stress cardiomyopathy (11.9%), arrhythmia (10.4%), stable angina (9.3%) and myocarditis (7.9%). In

Figure 2: Stacked bar graph demonstrates proportion of final diagnoses in patients presenting to the catheter laboratory with other suspected ACS by DHB (percentages, left-hand y axis). Scatter plot demonstrates total number of other suspected ACS patients in each DHB (absolute number, right-hand y-axis).



* Rapid intervention capable catheter laboratory available
STEMI, ST-segment elevation myocardial infarction; NSTEACS, non-ST segment elevation acute coronary syndrome; ACS, acute coronary syndrome.

Table 1: Demographics, cohort characteristics and investigations (excludes 1,200 patients without clinical details other than basic demographic information).

	Suspected STEMI <24h (n=5981)						**Other suspected ACS (n=23136)**		
Final diagnosis	STEMI n=5491 (91.8%)	NSTEACS n=212 (3.5%)	Non-ACS n=278 (4.6%)	p-value, STEMI vs NSTEACS	p-value, STEMI vs non-ACS	p-value, NSTEACS vs non-ACS	ACS n=19597 (84.7%)	Non-ACS n=3539 (15.2%)	p-value
Age (years)									
<65 n (%) ≥65 n (%) Median (IQR)	3,125 (56.9) 2,366 (43.1) 63 (54 to 72)	123 (58.0) 89 (42.0) 63 (54 to 71.5)	181 (65.1) 97 (34.9) 58.5 (47 to 70)	0.749	0.007	0.109	9,145 (46.7) 10,452 (53.3) 67 (58 to 74)	2,117 (59.8) 1,422 (40.2) 62 (53 to 71)	<.001
Sex, n (%)									
Male Female	4,064 (74.0) 1427 (26.0)	151 (71.2) 61 (28.8)	164 (59.0) 114 (41.0)	0.365	<.001	0.005	13,401 (68.4) 6,196 (31.6)	1,796 (50.7) 1,743 (49.3)	<.001
Ethnicity, n (%)									
Māori Pacific Indian Other Asian European/Other	542 (9.9) 255 (4.6) 312 (5.7) 247 (4.5) 4,135 (75.3)	20 (9.4) 21 (9.9) 14 (6.6) 11 (5.2) 146 (68.9)	27 (9.7) 25 (9.0) 17 (6.1) 11 (4.0) 198 (71.2)	0.010	0.025	0.956	2,174 (11.1) 1,012 (5.2) 884 (4.5) 592 (3.0) 14,935 (76.2)	452 (12.8) 210 (5.9) 136 (3.8) 127 (3.6) 2,614 (73.9)	0.001
Past medical history and risk factors									
History of CVD, n (%)	1,042 (19.0)	67 (31.6)	38 (13.7)	<.001	0.027	<.001	6,874 (35.1)	866 (24.5)	<.001
History of MI, n (%)	711 (12.9)	51 (24.1)	32 (11.5)	<.001	0.485	<.001	4,432 (22.6)	445 (12.6)	<.001
History CHF, n (%)	80 (1.5)	10 (4.7)	3 (1.1)	0.002	0.798	0.013	782 (4.0)	150 (4.2)	0.490
Diabetes, n (%)	955 (17.4)	56 (26.4)	33 (11.9)	0.001	0.017	<.001	4,828 (24.6)	602 (17.0)	<.001
COPD, n (%)	395 (7.2)	16 (7.5)	20 (7.2)	0.845	1.000	0.882	1,906 (9.7)	406 (11.5)	0.001
BMI									
Mean ± SD	28.5 ± 5.6	29.2 ± 5.8	27.7 ± 6.9	0.111	0.012	0.04	29.4 ± 6.0	29.6 ± 6.8	0.418
Total cholesterol (mmol/l)									
Median (IQR)	4.8 (4.0 to 5.7)	4.9 (3.8 to 5.9)	3.9 (3.5 to 4.8)	0.934	0.003	0.004	4.7 (3.8 to 5.7)	4.6 (3.6 to 5.4)	0.079

	Suspected STEMI <24h (n=5981)						Other suspected ACS (n=23136)		
LDL (mmol/l)									
Median (IQR)	2.9 (2.2 to 3.6)	2.8 (2.0 to 3.6)	2.4 (1.8 to 3.1)	0.335	<.001	<.001	2.7 (2.0 to 3.6)	2.7 (2.0 to 3.5)	0.211
Smoking status n (%)									
Non-smoker Ex-smoker Current smoker	2,364 (43.1) 1,426 (26.0) 1,701 (31.0)	98 (46.2) 60 (28.3) 54 (25.5)	145 (52.2) 59 (21.2) 74 (26.6)	0.233	0.011	0.183	8,475 (43.2) 6,914 (35.3) 4,208 (21.5)	1,891 (53.4) 1,042 (29.4) 6,06 (17.1)	<.001
Clinical presentation									
Killip Class									
I II–IV	4,943 (90.0) 548 (10.0)	192 (90.6) 20 (9.4)	260 (93.5) 18 (6.5)	<.001	0.055	0.225	17,838 (91.0) 1,759 (9.0)	3,213 (90.8) 326 (9.2)	0.652
Admission systolic BP (mmHg)									
Median (IQR)	133 (116 to 151)	135 (129 to 150)	130 (114 to 150)	0.565	0.352	0.274	141 (126 to 160)	138 (122 to 155)	<.001
Investigations									
Stress test done, n (%)	46 (0.9)	2 (0.9)	5 (1.8)	0.699	0.097	0.704	1,276 (6.5)	561 (15.9)	<.001
CTCA done, n (%)	224 (4.1)	11 (5.2)	8 (2.9)	0.425	0.320	0.189	1,065 (5.4)	211 (6.0)	0.206
LVEF*									
Normal (≥50%) Mild (40 to 49%) Moderate or severe (<40%) No EF documented	2,087 (38.0) 1,409 (25.7) 1,139 (20.7) 856 (15.6)	92 (43.4) 35 (16.5) 32 (15.1) 53 (25)	-	<.001	-	-	9,543 (48.7) 2,496 (12.7) 2,182 (11.1) 5,376 (27.4)	-	-
Revascularisation*	5,045 (91.9)	146 (67.9)	-	<.001	-	-	12,935 (66.0)	-	-
CABG	239 (4.4)	30 (14.2)	-	<.001	-	-	2,788 (14.2)	-	-
PCI	4,806 (87.5)	116 (54.7)	-	<.001	-	-	10,147 (51.8)	-	-

	Suspected STEMI <24h (n=5981)						Other suspected ACS (n=23136)		
Acute reperfusion strategy*									
Primary PCI Thrombolysis None	3,880 (70.7) 1,174 (21.4) 437 (8.0)	-	-	-	-	-	-	-	-
Angiographic findings									
CAD >50% stenosis on angiogram, n (%)									
No obstructive disease Single/double vessel disease Three vessel disease and/or LMS >50%	192 (3.5) 4,123 (75.1) 1,172 (21.4)	29 (13.7) 122 (57.6) 61 (28.8)	227 (81.7) 37 (13.3) 14 (5.0)	<.001	<.001	<.001	3,025 (15.5) 10,438 (53.4) 6,087 (31.1)	2,811 (79.6) 519 (14.7) 203 (5.8)	<.001
Time from admission to angiogram (days)									
n Mean ± SD	5487 0.24 ± 0.86	212 0.75 ± 1.35	278 0.19 ± 0.78	<.001	0.058	<.001	19,550 2.66 ± 2.36	3,533 2.66 ± 3.05	0.090

STEMI, ST-segment elevation myocardial infarct; NSTEACS, non ST elevation acute coronary syndrome; CVD, cardiovascular disease; MI, myocardial infarction; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; BMI, body mass index; LDL, low density lipoprotein cholesterol; BP, blood pressure ;CTCA, CT coronary angiogram; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; CAD, coronary artery disease; LMS, left main stem.
*Data regarding LVEF and revascularization are not collected for non-ACS patients in the ANZACS-QI registry.

patients suspected of STEMI <24h, stress cardiomyopathy (23%), myocarditis (13.3%) and pericarditis (14.4%) were most common, whereas stress cardiomyopathy (11.1%), arrhythmia (10.7%) and stable angina (10%) were more common in those suspected of having other ACS (see Appendix Table 2 for a detailed breakdown).

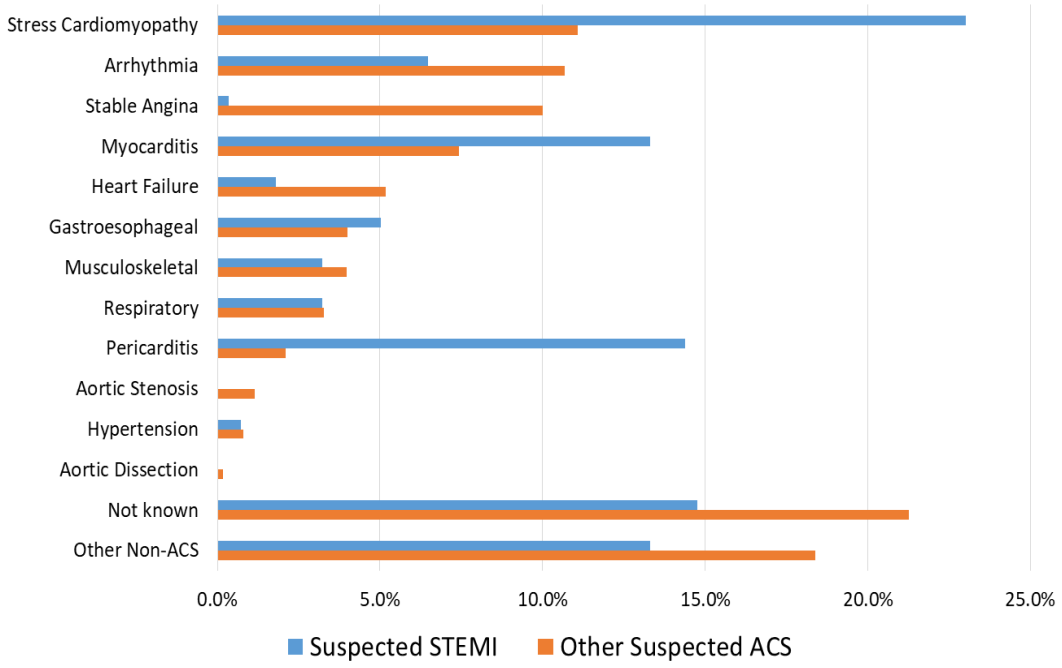
Discussion

This nationwide ANZACS-QI study demonstrates one in twenty patients undergoing ICA for a suspected acute STEMI <24h had a non-ACS diagnosis. Of the sub-group managed with a primary PCI strategy, the proportion was similar. Of patients with other suspected ACS, one in five had a non-ACS final diagnosis. Half of non-ACS final presentations were for other cardiac-related conditions. For patients investigated with other suspected ACS, the rate of non-ACS diagnosis was greater in DHBs with interventional capability, but for those with suspected STEMI the rate was similarly low across all DHBs.

Suspected STEMI <24h

It is reassuring that the rate of non-ACS diagnosis across the DHBs was low, suggesting that current guidelines are generally working well for selecting the appropriate patients for acute coronary angiography. However, even in the high-volume centers, there was some variability, with false-positive rates approaching 10% in the metropolitan Auckland and Waikato DHBs compared to 3% in the Wellington region. We are unable to determine from this study whether this DHB variation is because the criteria and processes to activate the catheter laboratories are too restrictive, resulting in some patients who should be studied early being missed, or too liberal, resulting in unnecessary activations with the associated patient risks and staff impacts. Our false-positive rate is relatively low, however, compared to those reported in other series, which can range from 5% to 40%.[9-12,20,21] The wide variability in reported rates can be partially explained by the different criteria used to define a false-positive diagnosis of STEMI. In some studies, it is based on the absence of angiographically identifiable lesions and/or absence of myocardial necrosis biomarkers. In others, combinations of angiographic and clinical data or a discharge diagnosis other than STEMI have been used.[9,10,12] We defined

Figure 3: Proportion of non-ACS diagnoses according to suspected ACS sub-types.



'false-positive' as a discharge diagnosis of non-ACS condition. Of the 'true positives', the majority were STEMI, with a very small proportion (less than 5%) of other NSTEACS diagnoses. Although these NSTEACS cases also have a high rate of revascularisation, they would not necessarily require this performed on as urgently.

The National Cardiac Network and New Zealand ambulance services have recently developed the National Out-of-Hospital STEMI Pathway to improve STEMI care.[22] This pathway stipulates time frames for reperfusion and recommends criteria for entering the primary PCI pathway. Ongoing audit of false-positive cases will be important to ensure that patients are not harmed by inappropriate referrals for urgent angiography.

The non-ACS conditions most likely to mimic a STEMI on presentation, and therefore to be considered during the acute clinical assessment, included stress cardiomyopathy (23%), myocarditis (13.3%) and pericarditis (14.4%). ICA is appropriately performed as a diagnostic tool for these conditions that are associated with marked ECG changes and symptoms that can mimic potentially life-threatening STEMI.

Other suspected ACS

In contrast, there is a paucity of prior data on false-positive rates in other suspected ACS presentations. We have previously reported the overall rate of coronary angiography for ACS in New Zealand to be lower in comparison to similar European countries.[1–3] This is even more pronounced in non-interventional DHBs.[23] Although at 19.2% the non-ACS rate for suspected other ACS in our study is higher than for suspected STEMI, it is still much lower than the proportion of patients presenting with chest pain who have a final diagnosis of ACS. This is consistent with the use of diagnostic pathways to select those more likely to have ACS for invasive angiography. These patients have less well defined ECG changes and more cardiovascular comorbidities, in particular pre-existing history of MI and diabetes mellitus, which may lower the threshold for ICA in equivocal presentations. Because of its role as a non-urgent diagnostic test, a higher false-positive rate is appropriate for this group of patients. The reasons for the observed lower proportion of non-ACS diagnoses in DHBs without rapid access to coronary intervention requires further investigation, but possible reasons include variation in referral practice and greater use of non-invasive investigations for case selection. Although the use of non-invasive investigation was low in this study, the registry does not capture patients who had a non-invasive test and were not referred for angiography.

As for suspected STEMI patients, around half of the non-ACS diagnoses were cardiac related—stress cardiomyopathy (11.1%), arrhythmia (10.7%) and stable angina (10%) were the common non-ACS diagnoses.

A third of patients with a final NSTEACS diagnosis who had angiography did not require revascularisation. There are recent studies assessing the utility of non-invasive imaging in reducing unnecessary invasive tests. The use of CTCA demonstrated a high diagnostic accuracy to rule out significant coronary artery disease in patients with NSTEACS in the VERDICT trial.[24] Likewise, initial cardiac MRI or CTCA appears to reduce unnecessary invasive coronary angiography in CARMENTA.[25] However, the RAPID-CTCA trial was unable to show any benefit in early CTCA utilisation when hard end-points such as death and myocardial infarction were assessed.[26] Non-invasive imaging as a routine diagnostic tool in suspected ACS is likely to evolve in the near future.

Demographic considerations

We found that women suspected of having a STEMI or other ACS were more likely to have a non-ACS diagnosis,[9,10,12] which is similar to the findings reported in other studies. This may reflect the known greater difficulty in making ACS diagnoses due to atypical and equivocal symptoms more often observed in women.[5,18] Moreover, stress cardiomyopathy, the most common non-ACS diagnosis in our study (suspected STEMI 23%, other suspected ACS 11.1%), occurs predominantly in women, which may contribute to the gender differences.[5,17,18] Non-ACS diagnoses were also more common in younger patients. This may represent their lower prevalence of atherosclerotic disease relative to other conditions. It is also possible that clinicians are more likely to refer these patients when the presentation is equivocal.

Ethnic differences in false-positive STEMI diagnoses in non-Europeans have been reported on internationally, such as higher rates of false-positive STEMI in African Americans in the Activate-SF Registry.[10] In our study, Pacific patients appear to have a higher rate of false-positive diagnosis in comparison to other ethnicities when presenting with a suspected STEMI, but not in suspected other ACS. A recent study by Grey et al demonstrated that ischaemic heart disease (IHD) mortality for Māori and Pacific people remains twice that for Europeans in New Zealand, despite an overall declining trend in IHD deaths and hospitalisations across all ethnic groups—albeit this decline was smaller among Pacific people.[27] It is therefore conceivable that the diagnostic threshold for interpreting an equivocal presentation or ECG as a STEMI in Pacific patients may be lower. However, it is unclear why this was not observed in Māori patients and suspected other ACS patients in our study. This highlights a perspective for future studies to assess diagnostic differences between ethnic groups in ACS.

Limitations

The study cohort was patients with suspected ACS who were referred and underwent ICA. We have no information regarding how many patients with ACS might have been missed due to the condition not being suspected and/or not being referred for ICA. All MIs have been included as final ACS diagnoses for this study. There is a small proportion of NSTEMI cases (6%) recorded as Type II MI in the cohort. Whilst reallocation of Type II MIs to the non-ACS group would increase the false-positive rate, this may be misleading because the cases clinically selected for invasive coronary angiography often requires it to make the diagnosis and a third of these patients received revascularisation for stable coronary artery disease. Although the final ACS and broad non-ACS diagnoses were available and reported for all patients, the more detailed non-ACS diagnoses and other data were not captured. This occurred in a small number of DHBs, making systematic bias unlikely.

Conclusions

Patients who present with suspected ACS and have a final non-ACS diagnosis were more likely to be younger, female and have fewer cardiovascular comorbidities. False-positive catheter laboratory activations for suspected STEMI <24h patients are generally low across New Zealand. The difference in the proportion of non-ACS diagnosis in other suspected ACS presentations between DHBs with and without rapid access to coronary interventional facilities requires further investigation.

Competing interests:
Nil.

Author information:
Charles Yao-Cheng Ho: Department of Cardiology,
Counties Manukau District Health Board, New Zealand.
Mildred Lee: Department of Cardiology,
Counties Manukau District Health Board, New Zealand.
Seif El-Jack: Department of Cardiology, Waitematā District Health Board, New Zealand.
Peter Barr: Department of Cardiology, Auckland District Health Board, New Zealand.
Mark Simmonds: Department of Cardiology,
Capital and Coast District Health Board, New Zealand.
Gerry Devlin: Department of Cardiology, Gisborne Hospital, New Zealand.
Philip D Adamson: Department of Cardiology, Canterbury District Health Board,
New Zealand; Department of Medicine, University of Otago, New Zealand.
Michael Williams: Department of Cardiology, Southern District Health Board,
New Zealand; Department of Medicine, University of Otago, New Zealand.
Andrew J Kerr: Department of Cardiology, Counties Manukau District Health Board,
New Zealand; Department of Medicine, University of Auckland, Auckland, New Zealand.
Corresponding author:
Dr Charles Yao-Cheng Ho, c/o Department of Cardiology, Middlemore Hospital,
Otahuhu, Auckland 93311, New Zealand
charles.ho4168@gmail.com

URL:
www.nzma.org.nz/journal-articles/how-common-are-non-acute-coronary-syndrome-acs-diagnoses-in-patients-with-suspected-acs-investigated-with-coronary-angiography-in-new-zealand-anzacs-qi-58

REFERENCES

1. Wang TKM, Grey C, Jiang Y, et al. Trends in cardiovascular outcomes after acute coronary syndrome in New Zealand 2006–2016. *Heart*. 2020.
2. Timmis A, Townsend N, Gale CP, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2019. *European Heart Journal*. 2019; 41:12-85.
3. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation*. 2019; 139:e56-e528.
4. Wang TKM, Grey C, Jiang Y, Jackson R, Kerr A. Epidemiology of acute coronary syndrome by subtype in New Zealand 2006–2016: an ANZACS-QI nationwide linkage study of hospitalisation, procedures and case fatality. *European Heart Journal*. 2019; 40.
5. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2017; 39:119-77.
6. ST-elevation myocardial infarction: New Zealand Management Guidelines, 2013. *New Zealand Medical Journal*. 2013; 126:127-64.
7. Launbjerg J, Fruergaard P, Hesse B, Jorgensen F, Elsborg L, Petri A. Long-term risk of death, cardiac events and recurrent chest pain in patients with acute chest pain of different origin. *Cardiology*. 1996; 87:60-6.
8. Lindsell CJ, Anantharaman V Fau - Diercks D, Diercks D Fau - Han JH, et al. The Internet Tracking Registry of Acute Coronary Syndromes (i*trACS): a multicenter registry of patients with suspicion of acute coronary syndromes reported using the standardized reporting guidelines for emergency department chest pain studies. *Annals of Emergency Medicine*.
9. Regueiro A, Fernandez-Rodriguez D, Freixa X, et al. False Positive STEMI Activations in a Regional Network: Comprehensive Analysis and Clinical Impact. Results From the Catalonian Codi Infart Network. *Rev Esp Cardiol (Engl Ed)*. 2018; 71:243-9.
10. McCabe JM, Armstrong EJ, Kulkarni A, et al. Prevalence and factors associated with false-positive ST-segment elevation myocardial

infarction diagnoses at primary percutaneous coronary intervention-capable centers: a report from the Activate-SF registry. *Arch Intern Med*. 2012; 172:864-71.

11. Lu J, Bagai A, Buller C, et al. Incidence and characteristics of inappropriate and false-positive cardiac catheterization laboratory activations in a regional primary percutaneous coronary intervention program. *Am Heart J*. 2016; 173:126-33.
12. Larson DM, Menssen KM, Sharkey SW, et al. "False-Positive" Cardiac Catheterization Laboratory Activation Among Patients With Suspected ST-Segment Elevation Myocardial Infarction. *JAMA*. 2007; 298:2754-60.
13. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J*. 2016; 37:3232-45.
14. Kerr A, Williams MJ, White H, et al. The All New Zealand Acute Coronary Syndrome Quality Improvement Programme: Implementation, Methodology and Cohorts (ANZACS-QI 9). *New Zealand Medical Journal*.
15. Kerr AJ, Lee M, Jiang Y, et al. High level of capture of coronary intervention and associated acute coronary syndromes in the all New Zealand acute coronary syndrome quality improvement cardiac registry and excellent agreement with national administrative datasets (ANZACS-QI 25). *New Zealand Medical Journal*. 2019; 132:19-29.
16. Kerr A, Lee M, Grey C, et al. Acute reperfusion for ST-elevation myocardial infarction in New Zealand (2015-2017): patient and system delay (ANZACS-QI 29). *The New Zealand medical journal*. 2019; 132:41-59.
17. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *European Heart Journal*. 2018; 40:237-69.
18. Roffi M, Patrono C, Collet J-P, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2016; 37:267-315.
19. Health Mo. HISO 10001:2017 Ethnicity Data Protocols. Wellington: Ministry of Health., 2017.
20. Lange DC, Rokos IC, Garvey JL, Larson DM, Henry TD. False Activations for ST-Segment Elevation Myocardial Infarction. *Interv Cardiol Clin*. 2016; 5:451-69.
21. Lange DC, Conte S, Pappas-Block E, et al. Cancellation of the Cardiac Catheterization Lab After Activation for ST-Segment-Elevation Myocardial Infarction. *Circ Cardiovasc Qual Outcomes*. 2018; 11:e004464.
22. New Zealand National Out-of-Hospital STEMI Pathway. New Zealand National Cardiac Network, 2018.
23. Williams MJA, Harding SA, Devlin G, et al. National variation in coronary angiography rates and timing after an acute coronary syndrome in New Zealand (ANZACS-QI 6). *New Zealand Medical Journal*. 2016; 129:66-78,6.
24. Linde JJ, Kelbæk H, Hansen TF, et al. Coronary CT Angiography in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. *J Am Coll Cardiol*. 2020; 75:453-63.
25. Smulders MW, Kietselaer B, Wildberger JE, et al. Initial Imaging-Guided Strategy Versus Routine Care in Patients With Non-ST-Segment Elevation Myocardial Infarction. *J Am Coll Cardiol*. 2019; 74:2466-77.
26. Gray AJ, Roobottom C, Smith JE, et al. The RAPID-CTCA trial (Rapid Assessment of Potential Ischaemic Heart Disease with CTCA) - a multicentre parallel-group randomised trial to compare early computerised tomography coronary angiography versus standard care in patients presenting with suspected or confirmed acute coronary syndrome: study protocol for a randomised controlled trial. *Trials*. 2016; 17:579.
27. Grey C, Jackson R, Wells S, et al. Trends in ischaemic heart disease: patterns of hospitalisation and mortality rates differ by ethnicity (ANZACS-QI 21). *New Zealand Medical Journal*. 2018; 131:21-31.

Antipsychotic and sedative medication use in long-term care facilities providing dementia care

Etuini Ma'u, Janine Burton, Elizabeth Fussell

ABSTRACT

AIM: This study aimed to quantify use of antipsychotic and sedative medications in residents with dementia in long-term care facilities in the Waikato District Health Board (DHB) catchment and to identify factors associated with the prescription of these medications.

METHODS: Resident records and the medication charts of 271 residents with a diagnosis of dementia from 13 dementia units in the Waikato DHB catchment, as well as the psychogeriatric (PG) unit, were reviewed for current prescriptions for any antipsychotic or sedative medication and the date those medications were most recently prescribed.

RESULTS: Antipsychotics were prescribed for 133 (49.1%) residents, with a mean (95% CI) of 401 (354–448) days since the most recent prescription was made. Only 16.8% of antipsychotic prescriptions were prescribed in the preceding 12 weeks, with 31.3% of prescriptions prescribed more than a year prior. Residents were more likely to be prescribed an antipsychotic if they were male (56.9% vs 42.6%, p=.019) or had an incident form completed (30.8% vs 19.6% p=.03). Regression analysis showed only gender (OR 1.79, 95%CI 1.07–2.98, p=.026) was associated with antipsychotic medication prescription. Sedatives were prescribed for 60 (22.1%) residents, with a mean (95%CI) of 487 (431–544) days since the most recent prescription was made, and 44.8% of prescriptions were dated more than a year prior. Residents were more likely to be prescribed a sedative if they entered the facility at a younger age (76.9 vs 79.5, p=.042) or had been in the current facility longer (980 vs 734 days, p=.048). Following regression analysis, no individual factors were significantly associated with sedative prescription.

CONCLUSION: With clear evidence of the risks of antipsychotics to patients with dementia, the proportion of residents prescribed an antipsychotic or sedative in this study, in conjunction with the prolonged duration of prescription, is cause for concern and needs addressing.

Dementia, a syndrome characterised by progressive decline in cognition and daily functioning, increases in prevalence with advancing age. As the proportion of the New Zealand population aged 65 years and older increases, there will be a concomitant increase in dementia cases. Cases of dementia are projected to triple to 170,000 by the year 2050.[1] This in turn will increase the prevalence of those presenting with the unique challenges associated with the behavioural and psychological symptoms of dementia (BPSD). BPSD is defined by the International Psychogeriatric Association (IPA) as symptoms of disturbed thoughts, mood, perception or behaviour frequently occurring in people with dementia. BPSD is common, with an estimated point prevalence of 60–80% and a cumulative risk of 95%.[2] The resultant distress of BPSD causes both individual suffering and increased caregiver burden.[3] It is also associated with worsening cognition and a hastened progression to a more severe dementia.[4]

The causes of BPSD are usually multifactorial in nature, with a complex interplay of both biological and psychosocial factors contributing to both aetiology and pathogenesis. As such, BPSD treatment guidelines[5] emphasise a holistic understanding of the patient, their symptoms and the circum-

stances within which the symptoms occur. The mainstay of management centres around psychosocial interventions, with the use of psychotropic medications only considered when trials of behavioural or psychological interventions have not been of adequate benefit and the risks associated with medication use have been weighed up.[5] Evidence for the efficacy of antipsychotic medication in BPSD is poor, with 5–11 patients needing to be treated to achieve clinically significant improvement in one additional patient.[6] Furthermore, recent studies have demonstrated that implementing an antipsychotic deprescribing protocol after 12 weeks on an antipsychotic is not associated with any increase in BPSD symptoms in 67–80% of patients.[7,8]

The risks associated with the use of antipsychotics are significant and include cerebrovascular events, gait disturbance, orthostatic hypotension, sedation, QT prolongation and increased mortality.[9] There is also evidence of an association between duration of antipsychotic use and mortality,[10] with an additional death in 100 patients with BPSD treated for 12 weeks increasing to 17 additional deaths in 100 patients with BPSD treated for two years.[11] These risks resulted in an FDA black box warning in 2005 against the use of antipsychotics in patients with dementia.[12] Despite these known risks and the black box warning, use of antipsychotics and benzodiazepines in residential care remains common. Indeed, a recent systematic review and meta-analysis[13] reviewing 89 international studies of central nervous system medication use in aged residential care calculated an overall pooled estimate of 26.1% for antipsychotic and 36.2% for benzodiazepine use.

When no longer able to be safely cared for at home, long-term care for those aged 65 years and older in New Zealand is provided by one of four types of aged residential care (ARC) facilities. Rest homes and hospital level care provide care for those requiring physical assistance with activities of daily living. Dementia care is utilised by those who need a secure facility but have limited physical care needs. Psychogeriatric (PG) care, the highest level of care, is reserved for those with complex mental, cognitive or physical needs.[14] Although those in dementia level care require a diagnosis of dementia to be eligible, it has been estimated that 55% to 77% of those in the other types of care also have a diagnosis of dementia.[15]

Most ARC facilities are privately owned enterprises contracted by district health boards (DHBs) to provide an agreed number and type of residential care beds.[16] Facilities operate to a national standard of services, but variability remains, including in the use of psychotropic medication, as a result of a combination of individual facility characteristics and organisational culture.[17] Studies investigating the prescription of psychotropic medications in a New Zealand setting are heterogenous, with some focussed on prescribing rates in the general population and others on psychotropic prescribing in aged residential care.

Three studies investigate psychotropic medication prescribing in the general population aged 65 years and older. Ndukwe et al[18] conducted a population-level study using pharamaceutical dispensing data to describe and characterise the prescription of psychotropic medication in the 65+ population between 2005 and 2013. They demonstrated a 27.5% increase in the dispensing of a defined daily dose per 1,000 older people per day (DDD/TOPD) for antipsychotics, a 10.3% increase in the DDD/TOPD for sedatives/hypnotics, and a 5.9% decrease in the DDD/TOPD for anxiolytics. In the same period there was a 22.5% increase in the prescription of any psychotropic medication, with the proportion of psychotropic prescriptions accounted for by antipsychotics increasing from 4.3% to 4.5% and decreasing for both hypnotics/sedatives (37.2% to 33.5%) and anxiolytics (7.1% to 5.5%). Jackson et al[10] used the New Zealand Atlas of Healthcare variation to examine the dispensing of antipsychotics and benzodiazepines in the New Zealand 65+ population between 2008 and 2012. Across the four-year period of the study, antipsychotic prescription increased from 22.4 to 23.8 per 1,000 people, and benzodiazepine prescription increased from 106 to 109 per 1,000 people. The study also commented on a relationship between antipsychotic dispensing and dementia/psychogeriatric-occupied bed days but did not present data to support this statement. Using Ministry of Health prescribing data, Wilkinson and

Mulder[19] also showed a 49% increase in antipsychotic prescribing across all ages between 2008 and 2015. They demonstrated that rates of prescribing by ethnicity were the highest across both genders in the 65+ age group for Europeans (male 3.97% and female 5.04%), Pacific peoples (male 3.51% and female 3.61%) and Asian (male 1.68% and female 2.53%) and for Māori females (4.09%). Rates of antipsychotic prescribing in Māori males aged 65+ (3.50%) were second only to Māori males in the 25–44-year-old age group (4.77%).

Five New Zealand studies investigate psychotropic medication prescribing in aged residential care. Kerse[20] carried out a medication chart and medical record audit of 606 residents in 14 randomly selected aged residential care facilities in 1999–2000, 50% of whom had a diagnosis of dementia. Benzodiazepines were prescribed in 33.5% of all residents and 'major tranquilisers' in 17% of residents. Compared to those without dementia, residents with a diagnosis of dementia were more likely to be prescribed a major tranquiliser (25% vs 10%, p<.001). Tucker and Hosford[21] surveyed the prescription of psychotropic medications in 1,053 residents from 26 rest homes (including five dementia units and 11 private hospitals) in 2005 and compared the findings to a similar survey carried out in 1990. They showed an increase in antipsychotic prescribing from 21.9% to 23.7%, with a higher level of antipsychotic use in dementia units (59.5%) compared with 17% for rest homes and 29.5% for hospital level care. Benzodiazepine prescribing over the same period reduced from 29.6% to 12.4%. Heppenstall et al [22] reviewed the electronic records of a stratified random sample of 222 residents from the 2008 Older Persons' Ability Level (OPAL) study of all aged residential care facilities within the Auckland region's three district health boards. They reported antipsychotics prescription in 19.1% of residents, benzodiazepines in 21.0% and a non-benzodiazepine hypnotic (zopiclone) in 12.5%. Tordoff et al [23] undertook an audit of 228 residents across 13 dementia and psychogeriatric units in 2011 and found antipsychotic prescription in 50.4% and benzodiazepine prescription in 39%. Prescribing had reduced to 38.2% and 25.8% respectively when remeasured in 2013 following a range of interventions to improve prescribing practices. Peri et al[17] investigated 537 residents across 14 residential care facilities (including four dementia units) and found antipsychotics prescribed in 20%, hypnotics in 31% and sedatives in 19% of all residents.

These studies indicate the prescription of antipsychotics in New Zealand has at best remained unchanged, if not increased, since 1990. The prevalence of antipsychotic use is further magnified in dementia and psychogeriatric care facilities where the majority of residents have a diagnosis of dementia. The aim of this study was to quantify use of antipsychotic and sedatives in dementia units and the PG unit in the Waikato District Health Board (WDHB) catchment area and potentially identify factors associated with the prescription of psychotropic medication.

Methods

This study was approved by the New Zealand Ministry of Health's Health & Disability Ethics Committee, approval number 16/STH/135.

Setting and participants

Dementia units and the PG unit in the WDHB catchment area were invited to participate in the study in December 2016. These facilities are all privately owned enterprises, contracted to WDHB to provide aged residential care beds at dementia or PG level care. PG is the highest level of residential care and is required for dementia residents with more complex physical and/or behavioural care needs that cannot be adequately provided in a dementia unit. Spanning both rural and urban areas, the WDHB is one of 20 district health boards in New Zealand, with a 65+ population of 65,000. At the time of the study there were 18 dementia units and a psychogeriatric hospital in the region. All 14 dementia units within Hamilton City and the Waikato, South Waikato, Matamata-Piako, and Waipa districts were approached. Due to geographical practicalities, the four dementia units situated further afield in the Thames/Coromandel, Hauraki and Ruapehu districts were not approached. Thirteen of the 14 dementia units approached, as well as the PG unit, agreed to participate. Resident records and the medication charts

of all 280 residents in participating units were reviewed. Following exclusion of nine residents with primary diagnoses of schizophrenia, bipolar disorder or an intellectual disability, 271 residents with a primary diagnosis of dementia were included in the analysis.

Data collection

Baseline demographic data were collected for all residents and included age, gender, ethnicity, diagnosis, age at entry and duration of stay in their current facility. Each resident's current medication chart was reviewed for current prescription of any antipsychotic and/or sedative medications. Antipsychotic medication included both first- and second-generation antipsychotics. Sedative medications included all benzodiazepines and zopiclone, a non-benzodiazepine hypnotic. The date the medication was most recently prescribed was used as a proxy for the duration (in days) since the medication was last reviewed. All resident files were also reviewed for formal incident forms completed by staff in the preceding six months, as a proxy for BPSD in excess of what would reasonably be expected in a secure dementia facility.

Data analysis

Continuous data are summarised by means and standard deviations (SD) and ranges and counts by numerators and denominators and proportions expressed as percentages. For the continuous variables, normality assumptions were reasonably well met, and t-tests and ANOVA were used as appropriate for comparisons of groups. For categorical variables, Chi-square tests of independence were used to compare groups. Binomial logistic regression was used to assess confounding between independent variables. Statistical analysis was carried out using the Statistical Package for Social Sciences version 20.0 (SPSS Inc., Chicago, Il, USA).

Results

Demographic details are presented in Table 1. Residents had a mean (95% CI) age of 81 (80.0–81.9) years, 54.6% were female and 90.8% were New Zealand European/Pākehā. Mean age of entry into their current home was 78.9 (77.9–79.9) years, for an average duration of 791 (706–877) days. Sixty-eight residents (25.1%) had at least one incident form completed in the preceding six months.

Antipsychotics were prescribed for 133 residents for a mean (95% CI) of 401 (354–448) days, giving a point prevalence of 49.1% (43.0%–55.2%). Sedatives were prescribed for 60 residents for a mean of 487 (431–544) days, giving a point prevalence of 22.1% (17.3%–27.6%). Among those prescribed an antipsychotic, 16.8% of the current prescriptions were issued in the preceding 12 weeks, with 31.3% of prescriptions unadjusted for >52 weeks. Among those prescribed a sedative, 19% were issued their prescriptions in the preceding 12 weeks, with 44.8% of prescriptions unadjusted for >52 weeks.

Resident characteristics of those prescribed antipsychotics to those who were not are compared in Table 2. There was no difference in resident age (80.1 vs 81.9 years, p=.072), age at entry into their current dementia unit (78.2 vs 79.6 years, p=.187), or duration of residence in their current unit (727 vs 849 days, p=.169). Residents were more likely to be prescribed an antipsychotic if they were male (56.9% vs 42.6%, p=.019) or had an incident form completed (30.8% vs 19.6% p=.034). A binomial logistic regression was performed to ascertain the effects of age, age at entry into care, duration in current care home, gender and having an incident form on the likelihood of being prescribed an antipsychotic (Table 3), with only male gender shown to be a predictor of antipsychotic prescription (OR 1.79, 95%CI 1.07–2.95, p=.026).

Resident characteristics comparing those prescribed sedatives to those who were not are presented in Table 4. There was no difference in resident age (79.6 vs 81.4 years, p=.140), gender (24.4% vs 20.3%, p=.416) or having had an incident form completed (31.7% vs 23.2% p=.183). Residents were more likely to be prescribed a sedative if they entered the facility at a younger age (76.9 vs 79.5 years, p=.042), had been in the current facility longer (980 vs 734 days, p=.048) or were resident in psychogeriatric hospital (36.6% vs 15.9%, p<.001). A binomial logistic regression (Table 5) showed no factor significantly predicted sedative prescription.

Table 1: Demographic characteristics of residents.

		Total (N=271)
Age (years)	Mean 95% CI	81.0 80.0–81.9
Age at entry into facility (years)	Mean 95% CI	78.9 77.9–79.9
Gender (%)	Male Female	123 (45.4) 148 (54.6)
Ethnicity (%)	New Zealand European/Pākehā Māori Other	246 (90.8) 10 (3.7) 15 (5.5)
Duration at current facility (days)	Mean (SD) 95% CI	791 706–877
Residents with incident forms (%)	Number of residents (%)	68 (25.1)
Antipsychotic (%)	N (%)	133 (49.1)
Antipsychotic duration (days)	Mean 95% CI	401 354–448
Antipsychotic duration (%)	<12 weeks 12–52 weeks >52 weeks	22 (16.8) 68 (51.9) 41 (31.3)
Sedative (%)	n(%)	60 (22.1)
Sedative duration (days)	Mean 95% CI	487 431–544
Sedative duration (%)	<12 weeks 12–52 weeks >52 weeks	11 (19) 21 (36.2) 26 (44.8)
Level of care (%)	Dementia care Psychogeriatric	189 (69.7) 82 (31.3)

Table 2: Characteristics of residents prescribed an antipsychotic compared to those who were not.

		Prescribed anti-psychotic N=133	Not prescribed antipsychotic N=138	Sig.
Age (years)	Mean 95% CI	80.1 78.6–81.6	81.9 80.6–83.3	.072
Age at entry into care (years)	Mean 95% CI	78.2 76.7–79.3	79.6 78.2–81.0	.187
Duration in current home (days)	Mean 95% CI	727 703–878	849 722–977	.169
Gender	Female Male	63 (47.4) 70 (52.6)	85 (61.6) 53 (38.4)	.019
Ethnicity	New Zealand European/Pākehā Māori Other	121 (94.5)) 5 (3.9) 3 (1.6)	125 (93.3) 5 (3.7) 4 (3.0)	.945
Incident forms	Yes (%)	41 (30.8)	27 (19.6)	.034
Prescribed a sedative	Yes (%)	40 (30.1)	20 (14.5)	.002

Table 3: Univariate (unadjusted OR) and logistic regression (adjusted OR) comparing residents prescribed an antipsychotic to those who were not.

	Unadjusted OR (95%CI)	Sig.	Adjusted OR (95%CI)	Sig.
Age	0.97 (0.95–1.00)	.073	0.96 (0.53–1.73	.892
Age at entry	0.98 (0.95–1.01)	.187	1.02 (0.57–1.84)	.942
Gender	1.78 (1.10–2.89)	.019	1.79 (1.07–2.98)	.026
Incident form	1.82 (1.05–3.20)	.034	1.72 (0.97–3.22)	.062
Duration in current facility	0.99 (0.99–1.00)	.172	0.99 (0.99–1.00)	.908

Table 4: Characteristics of residents prescribed a sedative compared to those who were not.

		Prescribed sedative N=60	Not prescribed sedative N=211	Sig.
Age (years)	Mean 95% CI	79.6 77.3–82.0	81.4 80.3–82.5	.140
Age at entry into care (years)	Mean 95% CI	76.9 74.5–79.5	79.5 78.4–80.6	.042
Duration in current home (days)	Mean 95% CI	980 753–1,208	734 643–825	.020
Gender	Female Male	30 (50) 30 (50)	118 (55.9) 93 (44.1)	.416
Ethnicity	New Zealand European/Pākehā Māori Other	53 (89.8) 3 (5.1) 3 (5.1)	193 (94.6) 7 (3.4) 4 (2.0)	0.347
Incident forms	Yes (%)	19 (31.7)	49 (23.2)	0.183
Prescribed an antipsychotic	Yes (%)	40 (66.7)	93 (44.1)	.002

Table 5: Univariate (unadjusted OR) and logistic regression (adjusted OR) of comparing residents prescribed a sedative to those who were not.

	Unadjusted OR (95%CI)	Sig.	Adjusted OR (95%CI)	Sig.
Age	0.97 (0.94–1.01)	.140	.98 (0.49–1.99)	.972
Age at entry	0.97 (0.93–1.00)	.044	.99 (0.49–2.00)	.980
Gender	1.27 (0.71–2.25)	.417	1.29 (0.70–2.38)	.411
Incident form	1.54 (0.82–2.88)	.185	1.61 (0.85–3.11)	.148
Duration in current facility	1.00 (1.00–1.00)	.023	1.00 (0.99–1.00)	.649

Discussion

Despite the increasing evidence around the relatively poor efficacy and increased risks associated with antipsychotic and sedative prescription in individuals with dementia, this study shows the use of these medications in dementia care and PG facilities remains high. Although there was a trend towards reduced prescribing of antipsychotics in dementia units, from 59.5% in 2005[21] to 50.4% in Auckland in 2011,[23] the 48.2% of residents in this study currently prescribed an antipsychotic suggests this trend has plateaued.

The mean duration since the prescription of either an antipsychotic or sedative was last adjusted was also high, at 401 and 487 days for antipsychotics and sedatives respectively. Only 16.8% of those prescribed an antipsychotic and 19% of those prescribed a sedative had the most recent dose change occur within the recommended 12-week period.[5] The use of the date of prescription as a proxy for duration since the medication dose was last reviewed is acknowledged as a limitation of this study, as it is possible there was a review of the rationale for the medication in the preceding weeks and an active decision made not to make any adjustment. It is also a possibility that the last medication change reflected a dose decrease and that the resident was being actively monitored before consideration of a further dose reduction. However, 31.3% of those on antipsychotics and 48.4% of those on sedatives had not had their prescriptions adjusted for over a year, far exceeding the 12-week recommendation and suggesting that reviews are not actively occurring.

Residents prescribed antipsychotics were more likely to be to male and have had an incident form completed in the last six months. Those prescribed sedatives were more likely to be younger and to have been in their current home for longer. The finding that antipsychotic prescriptions were more likely to be for male residents (1.79x) and those who had an incident form completed (1.82x) likely reflects the fact that the behaviour of these residents was interpreted as more threatening, and that the assessed risk of harm from that behaviour is higher. However, gender was also associated with having an incident form completed, and regression analysis showed only male gender (OR 1.78x, p=.026), not a completed incident form (OR 1.72, p=.062), was associated with antipsychotic prescription. Dual prescribing of antipsychotics and sedatives was common, with 40 (14.8%) residents prescribed both. Residents prescribed an antipsychotic more than twice as likely to be prescribed a sedative compared to those not prescribed an antipsychotic (30% vs 14.5%, p=.002).

While it is reassuring other demographic factors have not been shown to be influencing antipsychotic prescribing, it is concerning that medication prescription was not associated with the completion of incident forms, which are usually completed when residents manifest BPSD in excess of what would usually be expected for their level of care. Only 30.8% of those prescribed an antipsychotic and 31.7% of those prescribed a sedative had at least one incident form for behavioural concerns completed in the preceding six months. It is possible that the behaviour of some residents may have been noted to be escalating and was therefore dealt with before the threshold for an incident form was reached. It is also possible the presence of symptoms severe enough to warrant an incident form being completed may have resulted in an active decision not to make any psychotropic medication changes for some residents. However, over two-thirds of residents prescribed an antipsychotic or sedative had not manifested behaviours meeting the threshold for completing an incident form in the preceding six months and could potentially have trialled a medication decrease.

A strength of this study is that 13 of the 14 dementia units approached, and the PG unit, agreed to participate in the research, reducing the risk of selection bias and providing an accurate cross-sectional snapshot of antipsychotic and sedative medication use as of December 2017 in the Waikato DHB catchment area. As described above, there are limitations to both using the date of medication prescription as a proxy for duration since the medication dose was last reviewed and using incident forms as a proxy for BPSD severity. However, the proportion of residents who had not had incident forms completed or had their medications altered for over 12 months is

significant and suggests that active medication reviews are not occurring.

With clear evidence of the risks of antipsychotics to patients with dementia,[6] the proportion of residents prescribed an antipsychotic or sedative in this study, in conjunction with the prolonged duration of prescription, is cause for concern and needs addressing. Recent evidence that antipsychotic deprescribing regimens[7,8] are not associated with an escalation in BPSD indicate that active and regular reviews of prescribing, in conjunction with the upskilling of care staff,[23] can significantly reduce unnecessary antipsychotic and sedative prescription in this population.

Competing interests:
Nil.
Acknowledgements:
This research was funded by a summer studentship research grant from the Waikato Clinical School, University of Auckland. The authors would like to thank the participating aged residential care facilities for their involvement.
Author information:
Etuini Ma'u: Senior Lecturer, University of Auckland.
Janine Burton: Clinical Nurse Specialist, Waikato District Health Board.
Elizabeth Fussell: Consultant Psychiatrist, Waikato District Health Board.
Corresponding author:
Etuini Ma'u, Department of Psychological Medicine, Peter Rothwell Academic Centre, Waikato Clinical Campus, University of Auckland, Private Bag 3200, Hamilton 3240
Etuini.ma'u@auckland.ac.nz
URL:
www.nzma.org.nz/journal-articles/antipsychotic-and-sedative-medication-use-in-long-term-care-facilities-providing-dementia-care

REFERENCES

1. Deloitte Access Economics. Dementia Economic Impact Report 2016. Wellington: Alzheimers New Zealand; 2017.
2. Steinberg M, Shao H, Zandi P, Lyketsos C, Welsh-Bohmer K, Norton M, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatry. 2008;23(2):170-7.
3. Feast A, Moniz-Cook E, Stoner C, Charlesworth G, Orrell M. A systematic review of the relationship between behavioral and psychological symptoms (BPSD) and caregiver well-being. Int Psychogeriatr. 2016;28(11):1761-74.
4. Canevelli M, Adali N, Cantet C, Andrieu S, Bruno G, Cesari M, et al. Impact of behavioral subsyndromes on cognitive decline in Alzheimer's disease: data from the ICTUS study. J Neurol. 2013;260(7):1859-65.
5. RANZCP [Internet]. Antipsychotic medications as a treatment of behavioural and psychological symptoms of dementia 2016. Available from: https://www.ranzcp.org/files/resources/college_statements/practice_guidelines/pg10-pdf.aspx
6. Banerjee S. The use of antipsychotic medication for people with dementia: Time for action. 2009.
7. Van Leeuwen E, Petrovic M, van Driel M, De Sutter A, Stichele R, Declercq T, et al. Discontinuation of Long-Term Antipsychotic Drug Use for Behavioral and Psychological Symptoms in Older Adults Aged 65 Years and Older With Dementia. J Am Med Dir Assoc. 2018;19(11):1009-14.
8. Brodaty H, Aerts L, Harrison F, Jessop T, Cations M, Chenoweth L, et al. Antipsychotic Deprescription for Older Adults in Long-term Care: The HALT Study. J Am Med Dir Assoc. 2018;19(7):592-600 e7.
9. Steinberg M, Lyketsos CG. Atypical antipsychotic use in patients with dementia: managing safety concerns. Am J Psychiatry. 2012;169(9):900-6.
10. Jackson G, Gerard C, Minko N, Parsotam N. Variation in benzodiazepine and antipsychotic use in people aged 65 years and over in New Zealand. N Z Med J. 2014;127(1396):67-78.
11. Ballard C, Hanney ML, Theodoulou M, Douglas S, McShane R, Kossakowski K, et al. The dementia antipsychotic withdrawal trial (DART-

AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol. 2009;8(2):151-7.

12. Food and Drug Administration [Internet]. Atypical antipsychotic drugs. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150688.htm
13. Hasan SS, Zaidi STR, Nirwan JS, Ghori MU, Javid F, Ahmadi K, et al. Use of Central Nervous System (CNS) Medicines in Aged Care Homes: A Systematic Review and Meta-Analysis. J Clin Med. 2019;8(9).
14. Ministry of Health [Internet]. Residential care questions and answers. Available from: https://www.health.govt.nz/our-work/life-stages/health-older-people/long-term-residential-care/residential-care-questions-and-answers
15. Stewart R, Hotopf M, Dewey M, Ballard C, Bisla J, Calem M, et al. Current prevalence of dementia, depression and behavioural problems in the older adult care home sector: the South East London Care Home Survey. Age Ageing. 2014;43(4):562-7.
16. Technical Advisory Services (TAS) [Internet]. Aged residential care (ARC). Available from: https://tas.health.nz/dhb-programmes-and-contracts/health-of-older-people-programme/aged-residential-care/
17. Peri K, Kerse N, Moyes S, Scahill S, Chen C, Hong J, et al. Is psychotropic medication use related to organisational and treatment culture in residential care. J Health Organ Manag. 2015;29(7):1065-79.
18. Ndukwe H, Tordoff J, Wang T, Nishtala P. Psychotropic medicine utilization in older people in New Zealand from 2005 to 2013. Drugs Aging. 2014;31(10):755-68.
19. Wilkinson S, Mulder R. Antipsychotic prescribing in New Zealand between 2008 and 2015. N Z Med J. 2018;131(1480):61-7.
20. Kerse N. Medication use in residential care. New Zealand Family Physician. 2005;32(4):251.
21. Tucker M, Hosford I. Use of psychotropic medicines in residential care facilities for older people in Hawke's Bay, New Zealand. N Z Med J. 2008;121(1274):18-25.
22. Heppenstall CP, Broad JB, Boyd M, Hikaka J, Zhang X, Kennedy J, et al. Medication use and potentially inappropriate medications in those with limited prognosis living in residential aged care. Australas J Ageing. 2016;35(2):E18-24.
23. Tordoff J, Ailabouni N, Browne D, Al-Sallami H, Gray A. Improvements in the prescribing of antipsychotics in dementia and psychogeriatric units in New Zealand. Int J Clin Pharm. 2016;38(4):941-9.

Social impacts and costs of schizophrenia: a national cohort study using New Zealand linked administrative data

Sheree Gibb, Naomi Brewer, Nicholas Bowden

ABSTRACT

AIM: To identify a national population of individuals living with schizophrenia in New Zealand, and to examine health, social support, justice, economic outcomes and estimated government costs compared to a matched comparison group.

METHODS: Data were sourced from the Integrated Data Infrastructure. Individuals with a schizophrenia diagnosis in public hospital discharge or specialist secondary mental health service data, aged 18 to 64 and living in New Zealand were included in the schizophrenia population. Propensity score matching was used to select a comparison group of individuals without schizophrenia from the New Zealand resident population and compare outcomes and costs.

RESULTS: In 2015 there were 18,096 people living with schizophrenia in New Zealand, a prevalence of 6.7 per 1,000 people. Compared to the matched comparison population, individuals with schizophrenia had higher hospitalisation rates for mental (OR=52.80) and physical (OR=1.18) health conditions. They were more likely to receive social welfare benefits (OR=17.64), less likely to be employed (OR=0.11) and had lower income ($26,226 lower). Per-person government costs were higher for the schizophrenia group across all domains, particularly health ($14,847 higher) and social support ($11,823 higher).

CONCLUSION: Schizophrenia is associated with a range of adverse health, social and economic outcomes and considerably higher government costs compared to the general population.

Schizophrenia is a chronic and disruptive illness and has been ranked one of the top 25 causes of disability globally.[1] The illness typically presents in the early adult years and has a chronic course, usually requiring lifelong treatment and monitoring.[2–6]

Estimates of schizophrenia prevalence vary worldwide, with a recent meta-analysis finding a median lifetime prevalence of 0.48% (interquartile range 0.34–0.85%)[7] and another finding a median lifetime prevalence of 0.40% (interquartile range 0.30–0.66%).[8] Despite the relatively low prevalence, the health, social, economic and personal costs associated with schizophrenia are substantial. Individuals with schizophrenia are at increased risk for premature death, both from suicide and from physical health conditions.[9–11] The early adult onset and chronic course of schizophrenia has a considerable impact on economic and social outcomes including employment, income, housing and contact with the justice system.[12,13] For example, in an international review, employment rates among adults with schizophrenia ranged from 11.9% to 39.0%,[14] and a recent study found that the cumulative earnings among working age individuals with schizophrenia was equivalent to only 14% of those without schizophrenia.[15]

These adverse outcomes for individuals living with schizophrenia are associated with a range of direct and indirect financial costs. A recent systematic review of international studies found annual costs for the schizophrenia population ranged

from US$94 million to US$102 billion (2013 dollars), and the economic burden of schizophrenia was estimated to range from 0.02% to 1.65% of gross domestic product.[16] In the United States, estimated excess direct healthcare costs attributed to schizophrenia in 2013 were US$37.7 billion while indirect costs totaled US$117 billion.[17] Similarly, in England, societal costs of schizophrenia were estimated at £6.7 billion in 2004/05, including direct government costs of £2 billion.[13] In Australia, costs of psychosis to society have been estimated at AU$4.91 billion annually (as of 2010), of which AU$3.52 billion were borne by the Australian government.[18]

There is limited New Zealand epidemiological research on schizophrenia. Studies using administrative data on health service use have suggested a 12-month incidence of 0.5 per 1,000 for Māori and 0.3 per 1,000 for non-Māori,[19] and a 12-month prevalence of 1.0 per 1,000 for Māori and 0.3 per 1,000 for non-Māori.[20] Other studies have examined various clinical aspects of schizophrenia illness and treatment.[21–23] However, there has been little research on the social and economic outcomes and associated government costs for people living with schizophrenia in New Zealand.

Previously, the investigation of the life outcomes of schizophrenia at a national level has been limited by the lack of available social and economic measures in administrative health service data. The recent development of New Zealand's Integrated Data Infrastructure (IDI) now provides an opportunity to quantify the health, social support, justice sector and economic outcomes for individuals with schizophrenia in New Zealand.[24] The IDI also contains a range of cost information that can potentially be used to estimate government costs, although methods for using these costs are underdeveloped.

The aims of this paper are to use linked data from the IDI to:

1. identify a national population of individuals living with schizophrenia in New Zealand in 2015
2. examine the health, social support, justice sector and economic outcomes for individuals with schizophrenia, and to contrast those with a comparison group who do not have schizophrenia
3. construct broad estimates of government costs for individuals with and without schizophrenia across a range of sectors.

Methods

Data source: the Integrated Data Infrastructure

Data were sourced from Stats NZ's IDI. The IDI is a large database containing linked individual-level microdata about people and households in New Zealand.[24] Data come from a range of government and non-government administrative and survey data sources including health, tax, welfare and justice. All data are probabilistically linked and de-identified; only approved researchers can access data in a secure environment; and all outputs must be aggregated, confidentialised and checked by Stats NZ before release.

For more information about IDI, see https://www.stats.govt.nz/integrated-data/integrated-data-infrastructure.

Participant population

The base population used for this study was the IDI estimated resident population of New Zealand (IDI-ERP) for 31 December 2015, created using established methods for identifying a resident population within the IDI.[25,26] This population aims to capture all individuals who were alive and living in New Zealand as at 31 December 2015. All individuals in the schizophrenia and comparison populations were drawn from this population.

Individuals were included in the schizophrenia population if they had a diagnosis of schizophrenia, defined as:

1. having a public hospital discharge in the National Minimum Dataset (NMDS) between the dates of 1 January 1988 (date the dataset begins) and 31 December 2015 with a primary or secondary diagnosis code for schizophrenia using International Classification of Disease (ICD)-9 or ICD-10 (see Appendix Figure 1 for list of codes), or
2. having a record in the Programme for the Integration of Mental Health

Data (PRIMHD) diagnosis dataset for secondary mental healthcare between the dates 1 July 2008 (date the dataset begins) and 31 December 2015 with a diagnosis code for schizophrenia using Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, ICD-9 or ICD-10 (see Appendix Figure 1 for list of codes).

For comparison, a cohort of individuals without schizophrenia was identified. The absence of a diagnosis code for schizophrenia in either NMDS or PRIMHD over the same time periods defined this group. This cohort was matched to the schizophrenia population on age, sex and ethnicity (see the subsection *Analytical sample* for further details).

The schizophrenia and comparison populations were further restricted to individuals aged 18 to 64 as at 31 December 2015 to capture the typical working age population, because many of the outcome measures are only relevant for working age individuals, and because mental health care for ages 65 and over is not well recorded in PRIMHD.[27]

Outcome measures

Unless otherwise stated all outcomes were estimated for the 2015 calendar year.

Health

Public hospital admissions

NMDS data were used to identify admissions to a public hospital.

Inpatient psychiatric admission

PRIMHD data were used to identify admissions to an inpatient psychiatric facility.

Emergency department visits

National Non-Admitted Patient Collection (NNPAC) data were used to identify attendance at an emergency department.

Accident Compensation Corporation support

Accident Compensation Corporation (ACC) data were used to identify individuals who had received ACC support through either income compensation or having their medical expenses paid for by ACC.

Social support

Social welfare benefit received

The Ministry of Social Development (MSD) Benefit Dynamics Dataset was used to identify individuals who received one of the Tier 1 working age benefits (Jobseeker Support, Supported Living Payment and Sole Parent Support).

Social housing

Kāinga Ora data were used to identify individuals who were an applicant on a social housing tenancy agreement.

Socioeconomic deprivation: the New Zealand Index of Deprivation 2013

Address notification data were used to identify each individual's meshblock of residence and the corresponding New Zealand Index of Deprivation 2013 (NZDep2013) score. NZDep2013 measures socioeconomic deprivation based on the meshblock (small area geography comprising approximately 100 households) in which individuals live.[28] It is available for everyone who has an address recorded in the IDI (over 99% of the sample). Deprivation scores were collapsed into deciles, with 1 representing the least deprived and 10 the most deprived.

Justice sector

Police proceedings

New Zealand Police data were used to identify individuals who had police proceedings initiated against them (including warrants, arrests and charges, but excluding infringement notices).

Conviction

Ministry of Justice data were used to identify individuals who were convicted of a crime.

Imprisonment

Department of Corrections data were used to identify individuals who were incarcerated.

Economic

Income

Inland Revenue (IR) data were used to calculate the total taxable income from: wages and salaries; withholding payments; government benefits (including Jobseeker Support, Supported Living Payment, Sole Parent Support and New Zealand Superannuation); student allowance; paid parental leave; pensions (superannuation); claimants compensation; and declared self-employment income.

Income estimates do not include investment income, cash income or income earned overseas, as these sources of income are not reliably recorded in IR records.

Employment

IR data were used to identify employed individuals, defined as all those who received income from wages, salaries or self-employment.

Costs

All costs were calculated for the 2015 calendar year in New Zealand dollars. Unless otherwise stated, costs were drawn from the Social Investment Analytical Layer (SIAL) (https://swa.govt.nz/what-we-do/analytics/social-investment-analytical-tool/) produced by the Social Investment Agency, which calculates individual-level government service costs within the IDI.

Health

Health costs included government costs for: hospital admissions; emergency department (ED) attendances; outpatient visits; community pharmaceuticals; laboratory tests; general medical subsidies; specialty mental health services; and ACC. They did not include primary healthcare, private healthcare or patient co-payments. Hospital admission costs were calculated by multiplying the case mix cost weight by the purchase unit cost for the relevant year, with no further adjustment. Outpatient and ED costs were calculated from purchase unit costs in the NNPAC dataset. The general medical subsidy and the government subsidies for laboratory tests and community pharmaceuticals were obtained directly from the community laboratory or pharmaceutical table.

Mental health costs were calculated using purchase unit costs obtained from the Social Investment Agency, which were applied to events in the PRIMHD dataset. These included all publicly funded secondary mental health consultations and treatments, including both inpatient and outpatient general, forensic and addiction services. It included pharmaceuticals given in inpatient settings but excluded private treatment, community dispensed pharmaceuticals (which are included under the pharmaceuticals cost category above) and mental health treatment given in primary care.

ACC costs were calculated by summing payments made for medical expenses (from ACC records) and compensation for income loss (from IR records). All medical expenses costs were allocated to the year in which the accident occurred. Compensation was allocated to the year in which the compensation was paid.

Social support

Benefit costs were calculated by summing the Tier 1 (as previously defined) benefit payments from the IR tables (which record actual amount paid) and Tier 2 (payments and allowances such as housing supplements and child disability allowances) entitlements from MSD Benefit Dynamics Dataset tables (which record entitlement: actual amount paid is not available for Tier 2 benefits).

Social housing costs included total government rent subsidies for social housing, calculated from the Kāinga Ora tables in the IDI. The total social housing cost was allocated to the person who was the main applicant on the social housing application. Therefore, individuals living in social housing where they were not the main applicant on the application (eg, if they were the partner of the main applicant) will not have social housing costs recorded.

Justice sector

Justice costs were taken directly from the Ministry of Justice and Department of Corrections data collections in the IDI. Costs included government costs for charges, court proceedings, imprisonment and other sentences. Where a sentence lasted more than a year, only the current year of costs was included.

Total government costs

This was calculated as the sum of all health, social support and justice sector costs.

Demographics

Age (18–24, 25–34, 35–44, 45–54, 55–64 years), sex (male/female) and ethnicity were sourced from the personal detail table in the IDI. Ethnicity was recorded in total response format (so an individual can identify with more than one ethnic group) and, for this study, restricted to Level 1 groupings (European, Māori, Pacific, Asian). The Middle Eastern, Latin American and African

(MELAA) and Other ethnic categorisations had small counts and were therefore not used in this study.

Procedure

Data were accessed from the September 2017 refresh of the IDI. Data were extracted using SAS version 7.1[29] and analysed using R version 3.6.1[30] and Stata/MP version 15.[31] Random rounding to base 3 was applied to all counts, in adherence to Stats NZ confidentiality requirements.

Statistical analysis

Calculation of prevalence

Schizophrenia prevalence was calculated as the proportion of the New Zealand IDI-ERP of 18 to 64 year olds for 2015 who had a schizophrenia diagnosis identified any time until 31 December 2015. Prevalence was calculated overall and by sex, age and ethnicity. Odds ratios (ORs) were generated using logistic regressions for each sociodemographic sub-group. ORs for ethnicity were adjusted for age and sex to take account of differences in population structure between ethnic groups.

Analytical sample

The analytical sample for the outcomes analysis contained a schizophrenia group defined as all those in the New Zealand IDI-ERP of 18 to 64 year olds for 2015 with a schizophrenia diagnosis for at least two years on or prior to 31 December 2013, and who had complete data on the matching variables of age, sex and ethnicity. We restricted the sample to individuals with at least a two-year history of schizophrenia in order to exclude impacts that are related to the period of initial diagnosis. To examine whether a longer delay from diagnosis to outcomes might be required, a sensitivity analysis was run on an alternative schizophrenia population whose diagnosis was recorded on or prior to 31 December 2010 (indicating they had been living with schizophrenia for at least five years). Results were not substantively different to those from the main analysis (see Appendix Tables 1–6), so we opted to use the two-year restriction as it retains a larger sample size.

For comparison, a matched sample without schizophrenia was also generated from the IDI-ERP of 18 to 64 year olds for 2015. Propensity score matching methods were used to select the comparison group of individuals without schizophrenia. Nearest neighbour one-to-one matching was undertaken using the MatchIt package version 3.0.2 in R. Matches were drawn without replacement from the IDI-ERP for 2015. Matching variables were age at the end of 2015, sex and ethnicity. These variables were selected because they were available for almost all individuals and rarely change over time. Individuals who had ever been diagnosised with schizophrenia or who had missing data on any of the matching variables were not eligible to be selected as matches.

We also conducted two sensitivity analyses with variations to this matching method in which each individual with schizophrenia was matched to five and ten controls respectively. Results were not substantively different to the single matching, so we elected to stay with single matching for the analysis (see Appendix Tables 1–6).

Comparisons of outcomes and costs

To compare outcomes between the schizophrenia and comparison groups we fitted linear (for continuous outcomes) or logistic (for dichotomous outcomes) regression models in which the outcome was modelled as a function of schizophrenia population membership. Estimated odds ratios (for dichotomous outcomes) and beta coefficients (for continuous outcomes) were drawn from these models.

Ethics approval

This study was approved by the University of Otago Human Research Ethics Committee (Reference: H17/062). The study was reviewed as a 'Minimal Risk Health Research – Audit and Audit related studies' proposal. Access to IDI data was approved by Stats NZ.

Results

Schizophrenia population size and prevalence

A total of 18,096 individuals aged 18 to 64 had a schizophrenia diagnosis recorded on or prior to 31 December 2015. This is equivalent to a prevalence of 6.7 per 1,000 people, or 0.67%.

Table 1 shows the number and corresponding prevalence of individuals with schizophrenia in New Zealand by age, sex and ethnicity. Schizophrenia prevalence

was significantly lower among females compared to males (OR 0.52) and higher in Māori and Pacific ethnic groups compared to non-Māori and non-Pacific (ORs 3.36 and 1.70 respectively). Prevalence was highest in the middle adult years (35 to 54) and lowest in the youngest (18 to 24).

Description of the population for outcomes analysis

After excluding from the schizophrenia population all individuals whose diagnoses were only recorded in the last two years or who had missing data on any of the matching variables (see section *Methods*), 15,639 individuals with schizophrenia remained. A pool of 2,691,342 individuals without a schizophrenia diagnosis existed from which to select the matched cohort.

Table 2 displays the demographic characteristics of the analytical sample (N=31,278) after one-to-one matching. Note that the one-to-one matching resulted in the schizophrenia and non-schizophrenia sub-groups being identical on the demographic measures, so for the purposes of presenting the analytical sample, the groups have been combined. The majority (63.8%) of the analytical sample were male. Approximately two thirds (65.4%) identified as European, one third (35.4%) as Māori, 11.2% as Pacific and 5.6% as Asian. The majority were in the middle age groups (35–54 years); only 3.9% were aged 18-24; 18.9% were aged 25–34, and 19.7% were in the oldest age group (55–64 years).

Health and social outcomes

Table 3 shows a range of outcomes for the schizophrenia population and the matched comparison group for 2015. Individuals in the schizophrenia group were significantly more likely than the comparison group to have a general hospital admission (OR 1.18), a psychiatric inpatient admission (OR 52.80) or an emergency department attendance (OR 2.35). Individuals with schizophrenia

Table 1: Prevalence of schizophrenia in New Zealand as at 31 December 2015 by age, sex and ethnicity.[a]

	Number with schizophrenia	Prevalence (per 1,000)	OR[b] (95% CI)
Overall	18,096	6.7	
Sex			
Male (reference group)	11,577	8.9	-
Female	6,519	4.7	0.52 (0.51, 0.54)
Ethnicity[c]			
European	11,730	6.3	0.77 (0.74, 0.79)
Māori	6,624	16.7	3.36 (3.26, 3.47)
Pacific	2,106	10.9	1.70 (1.62, 1.78)
Asian	1,065	3.0	0.39 (0.36, 0.41)
Age group			
18–24	1,068	2.5	0.38 (0.35, 0.41)
25–34 (reference group)	3,582	6.5	-
35–44	4,854	8.9	1.37 (1.31, 1.43)
45–54	5,169	8.2	1.26 (1.21, 1.32)
55–64	3,423	6.3	0.96 (0.92, 1.01)

[a] Sub-group values may not sum to totals due to Stats NZ rounding requirements.
[b] Ethnic comparisons are adjusted for age and sex.
[c] Reference groups for ethnic comparisons are non-European, non-Māori, non-Pacific and non-Asian respectively.

were significantly more likely to be receiving a social welfare benefit (OR 17.64) and living in social housing (OR 3.39). Justice system interactions were also significantly more common among the group with schizophrenia; they were around twice as likely to have police proceedings initiated against them (OR 2.15), receive a conviction (OR 1.78) and receive a prison sentence (OR 2.49) than individuals in the comparison group. Finally, individuals with schizophrenia were significantly less likely to be employed than the matched comparison group (OR 0.11), and while their odds of receiving any income were higher than the control group (OR 2.40), their average annual income was less than half that of those without schizophrenia. People with schizophrenia were also significantly more likely to live in areas of higher socioeconomic deprivation (mean NZDep2013 score 7.4 compared to 5.9).

Government costs

Table 4 displays the estimated government costs for health, social support and the justice sector for those with and without schizophrenia. Costs were significantly higher for the schizophrenia group than in the matched comparison group across each of these domains. The largest difference was in health costs, where the average per-person cost for the schizophrenia group was nearly seven times higher than for the control group. Social support costs were five times higher among the schizophrenia group and justice sector costs nearly two times higher.

Discussion

This paper identified a national cohort of working age individuals living with schizophrenia in New Zealand, examined a range of health and social outcomes for those individuals and estimated associated government costs using information available from linked administrative data in the IDI.

The schizophrenia population included 18,096 individuals corresponding to a preva-

Table 2: Demographic characteristics of the analytical sample as at 31 December 2015 by age, sex and ethnicity.*

	N	%
Overall	31,278	
Sex		
Male	19,959	63.8
Female	11,322	36.2
Ethnicity		
European	20,445	65.4
Māori	11,403	36.5
Pacific	3,504	11.2
Asian	1,743	5.6
Age group		
18–24	1,209	3.9
25–34	5,901	18.9
35–44	8,646	27.6
45–54	9,363	29.9
55–64	6,162	19.7

* Sub-group values may not sum to totals due to Stats NZ rounding requirements.

Table 3: Health, social support, justice sector and economic outcomes for schizophrenia and matched comparison populations.[a]

	Schizophrenia population (N=15,639)	Matched non-schizophrenia population (N=15,639)	OR / difference in means (95% CI)
Health			
Non-mental health inpatient stay (%)	13.0	11.2	1.18 (1.10, 1.26)
Mental health inpatient stay (%)	12.2	0.3	52.80 (38.72, 72.01)
Emergency department visit (%)	6.7	3.0	2.35 (2.10, 2.62)
ACC compensation (%)	16.3	29.8	0.46 (0.43, 0.48)
Social support			
Any social welfare benefit (%)	78.8	17.4	17.64 (16.68, 18.67)
Social housing (%)	13.2	4.3	3.39 (3.09, 3.71)
Justice sector			
Police proceedings against (%)	9.4	4.6	2.15 (1.96, 2.36)
Conviction (%)	4.7	2.7	1.78 (1.58, 2.01)
Prison sentence (%)	2.3	0.9	2.49 (2.05, 3.03)
Economic			
Employed (%)	27.6	78.2	0.11 (0.10, 0.11)
Any income (%)	91.0	80.7	2.40 (2.24, 2.57)
Mean income ($)	17,865	44,092	-26,226 (-27,067, -25,384)
Mean NZDep13 (decile)	7.4	5.9	1.53 (1.47, 1.59)

[a] Sub-group values may not sum to totals due to Stats NZ rounding requirements.

Table 4: Government health, social support and justice sector costs (in New Zealand dollars) for schizophrenia and matched comparison populations.[a]

	Schizophrenia population (N=15,639)	Matched non-schizophrenia population (N=15,639)	Cost difference (95% CI)
Health ($)	17,333	2,486	14,847 (14,340, 15,354)
Social support ($)	14,667	2,845	11,823 (11,649, 11,997)
Justice sector ($)	795	431	363 (267, 459)
Total government ($)	32,795	5,762	27,033 (26,467, 27,599)

[a] Costs may not sum to totals due to Stats NZ rounding requirements.

lence of 6.7 per 1,000 people in the working age (18 to 64) population. This estimate is in line with previous international estimates of the prevalence of schizophrenia,[7,8] but it is slightly higher than previous New Zealand estimates, a difference that may be accounted for by the previous estimates having used smaller time windows[32] or more limited data sources.[19] The higher prevalence for Māori reported in this study is consistent with previous New Zealand studies that used administrative data and found schizophrenia incidence and prevalence rates around two to three times higher for Māori than for non-Māori.[19,32] Higher rates among Māori could reflect higher rates of schizophrenia. But these rates could also reflect that Māori are more likely than non-Māori to be given a schizophrenia diagnosis when they have psychosis symptoms.[33] Our finding that the prevalence of schizophrenia is higher among males than females adds to the existing literature where conclusions about sex difference in prevalence are inconclusive.[8,34] Prevalence rates are highest among the 35–54 age group. The lower rate for the 55–64-year-old cohort is likely because our available data do not enable us to look back far enough to the peak (early adult) diagnosis ages for that group. In contrast, for the younger cohorts, in particular those aged 18 to 24, it is probable that a schizophrenia diagnosis has yet to be formalised for many.

Compared with matched controls, people living with schizophrenia had more ED visits and more inpatient hospital admissions for both mental and physical health reasons. The high rates of mental health service use are unsurprising given the substantial mental health burden of living with schizophrenia, and increased ED and hospital use has been reported previously.[35,36] There is evidence that people living with schizophrenia have poorer physical health and higher rates of co-occurring medical conditions,[11,37,38] and this, along with ED visits directly related to schizophrenia, may account for the high levels of ED and hospital use. Our finding of lower ACC use among the schizophrenia population is likely due to lower employment rates in the schizophrenia group and therefore reduced eligibility for income compensation.

Our finding that people with schizophrenia have higher rates of interactions with the criminal justice system than the general population aligns with existing literature.[39–42] However, our finding that approximately one in ten working-age individuals with schizophrenia have criminal justice system involvement is at the lower end of existing estimates.[41,42] Methodological differences likely explain some of this variation. However, it is also possible that some of this difference is due to the time period covered: the risk of offending may be highest in the pre-diagnosis period,[43] which our study did not include.

Our estimated employment rate among the schizophrenia group of 27.6% is consistent with findings from a recent international review where employment rates ranged from 11.9% to 39.0%.[14] Our finding of low incomes among the schizophrenia population, in particular relative to the non-schizophrenia group, is also consistent with existing literature.[15,44] This is likely explained by low employment rates and the high proportion of individuals receiving social welfare benefits that provide a low income. International evidence has demonstrated that employment among individuals with schizophrenia can decrease the reliance on mental health services.[45,46] Given the substantial use of healthcare associated with schizophrenia, this suggests that targeting resources towards providing stable and meaningful employment for those with schizophrenia may be cost saving. This is an area of research that could be explored further.

This is the first study to provide information about the government costs for a New Zealand schizophrenia cohort, which totalled $32,795 per person and were more than five times higher than for individuals without schizophrenia, consistent with overseas studies.[13,17,47,48] The largest areas of costs, both in absolute terms and relative to the non-schizophrenia population, were health ($17,333 per person, seven times higher) and social support ($14,667 per person, five time higher).

Our reported costs for the schizophrenia population are lower than those in a 2010 Australian study that reported total government costs of AUD$55,403 per person. That study employed a prevalence-based, bottom-up approach utilising

survey data and unit costs from government and non-government ogranisation (NGO) sources.[18] Furthermore, the Australian study included some large costs that were not available for inclusion in our study, such as primary healthcare and tax foregone. The low employment rates and high use of healthcare among our schizophrenia population suggest that costs related to primary care and tax foregone would be high and, if included, would bring our estimates closer to those of the Australian study.

The cost estimates in this paper were drawn directly from recorded costs in the IDI without additional refinements, and therefore may contain some level of error. In addition there are government costs that were not able to be captured from the IDI, such as the costs of primary and private healthcare, which may have led to an underestimation of the true government cost of schizophrenia. However, as the same costing methods were applied to the schizophrenia and comparison groups, the relative differences in costs between the two groups are likely to be more reliable.

Social sector cost data have not been widely used for research and there is little information available about the best way to use these costs. One exception is the health sector, where complex methods do exist for refining health costs.[49] It may be useful to develop similar protocols for using costs from other sectors, such as justice or social support. Incorporating these refinements would improve the accuracy of the cost estimates in future work that uses cost data from the IDI.

Schizophrenia has many costs that cannot be captured from existing administrative data. Examples include caregiver costs, time and productivity loss and intangible costs related to pain and suffering. Detailed survey data, such as those used in the Australian psychosis costing study,[18] may be required to quantify those costs that are not collected in administrative data.

The use of linked administrative data from the IDI confers a number of advantages. Whole-of-population data meant we were able to identify a national cohort living with schizophrenia in New Zealand. In addition, individuals were removed from the analysis if they died or moved overseas after their schizophrenia diagnosis, leaving a more relevant population for measuring outcomes and costs. Linked health and non-health data enabled us to consider outcomes and government costs across a range of areas including health, social support, justice and the labour market. Finally, we were able to select a comparison group of individuals without schizophrenia, who were also living in New Zealand, and match these to the schizophrenia population on age, sex and ethnicity. From this we are able to understand how outcomes and costs for those with schizophrenia compare to an equivalent subset of the general population without schizophrenia.

The use of administrative data also has some limitations. The identification of schizophrenia diagnoses relied on records of hospital admissions and specialist secondary mental health service use. Although we expect that most individuals with diagnosed schizophrenia will have been treated by specialist mental health services at some point, we will have missed a number of individuals who were being managed solely in primary care, by NGOs or by family and whānau. A New Zealand study indicated as many as 30% of those with psychosis do not seek medical help at all.[50] In addition, our method of identification relies on the accuracy of diagnosis attribution as well as the quality of clinical coding. The extent to which these result in incorrect identifications or missed identifications remains unknown.

Although the comparison group in this study was matched to the schizophrenia population on age, sex and ethnicity, it is possible that the comparison population differs from the schizophrenia population in other ways that may be related to the measured outcomes, such as deprivation or family background. Due to the restricted time series of many datasets in the IDI, for most people these potential matching variables were not available prior to the onset of schizophrenia. Future studies may be able to match more comprehensively as the time series of data in the IDI continues to lengthen.

Schizophrenia is one of the most prospectively consistent psychosis diagnoses over time.[51,52] However, we acknowledge that for a small proportion of our schizophrenia cohort there may be a recovery or a change

in diagnosis over time. Further research could explore the extent to which different diagnostic trajectories are associated with different health, social and economic outcomes.

The use of administrative data in New Zealand for research purposes is legal, and the use of IDI data is highly regulated. Nonetheless, there are ethical concerns, including concerns around social licence and especially in relation to the IDI, which now links data at the individual level across a range of domains. As discussed by Bowden et al, further consultation around these concerns is necessary, in particular given that comparisons across ethnic groups may disadvantage Māori and Pasifika.[53,54]

Administrative data are a useful tool for providing a whole-population perspective on the impact of mental health conditions. This is especially true when multiple data sources are combined in resources such as the IDI, which allow us to consider impacts across different domains. Further methodological development, especially around costing, would improve the usefulness of this resource for researchers.

Disclaimer

These results are not official statistics. They have been created for research purposes from the Integrated Data Infrastructure (IDI) which is carefully managed by Stats NZ. For more information about the IDI please visit https://www.stats.govt.nz/integrated-data/.

Appendix

Appendix Figure 1: diagnosis codes used to define schizophrenia

- Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) codes of 295.1 to 295.9, excluding 295.7, or
- International Classification of Diseases, Tenth Edition, Australian Modification (ICD-10-AM) codes of F20.0 to F20.9, or
- International Classification of Diseases, Ninth Edition, (ICD-9) diagnosis codes of 295.0 to 295.9, excluding 295.7.

Appendix Table 1: Health, social support, justice sector and economic outcomes for schizophrenia and matched comparison populations for (five-year schizophrenia diagnosis).[a]

	Schizophrenia population (N=12,045)	Matched non-schizo-phrenia population (N=12,045)	OR / difference in means (95% CI)
Health			
Non-mental health inpatient stay (%)	13.0	10.6	1.25 (1.16, 1.36)
Mental health inpatient stay (%)	11.5	0.2	67.69 (44.79, 102.29)
Emergency department visit (%)	6.7	2.7	2.56 (2.25, 2.92)
ACC compensation (%)	16.8	29.5	0.48 (0.45, 0.51)
Social support			
Any social welfare benefit (%)	78.0	17.4	16.83 (15.79, 17.94)
Social housing (%)	13.2	4.3	3.35 (3.02, 3.71)
Justice sector			
Police proceedings against (%)	8.6	4.2	2.15 (1.92, 2.39)
Conviction (%)	4.1	2.8	1.45 (1.26, 1.67)
Prison sentence (%)	1.9	0.9	2.04 (1.62, 2.56)
Economic			
Employed (%)	27.5	78.0	0.11 (0.10, 0.11)
Any income (%)	91.0	80.4	2.45 (2.27, 2.65)
Mean income ($)	18,175	43,754	-25,575 (-26,477 -24,673)
Mean NZDep13 (decile)	7.4	5.8	1.58 (1.51, 1.65)

[a] Sub-group values may not sum to totals due to Stats NZ rounding requirements.

Appendix Table 2: Government health, social support and justice sector costs (in New Zealand dollars) for schizophrenia and matched comparison populations (five-year schizophrenia diagnosis).[a]

	Schizophrenia population (N=12,045)	Matched non-schizophrenia population (N=12,045)	Cost difference (95% CI)
Health ($)	16,695	2,619	14,070(13,491, 14,649)
Social support ($)	14,760	2,907	11,850 (11,649, 12,054)
Justice sector ($)	642	414	228 (129, 324)
Total government ($)	32,096	5,942	26,150 (25,505, 26,795)

[a] Costs may not sum to totals due to Stats NZ rounding requirements.

Appendix Table 3: Health, social support, justice sector and economic outcomes for schizophrenia and matched comparison populations (five matched controls for every schizophrenia case).[a]

	Schizophrenia population (N=15,639)	Matched non-schizophrenia population (N=78,195)	OR / difference in means (95% CI)
Health			
Non-mental health inpatient stay (%)	13.0	10.7	1.24 (1.18, 1.31)
Mental health inpatient stay (%)	12.2	0.2	56.12 (48.35, 65.15)
Emergency department visit (%)	6.7	2.9	2.45 (2.27, 2.64)
ACC compensation (%)	16.3	29.7	0.46 (0.44, 0.48)
Social support			
Any social welfare benefit (%)	78.8	17.5	17.58 (16.85, 18.34)
Social housing (%)	13.2	4.3	3.37 (3.18, 3.57)
Justice sector			
Police proceedings against (%)	9.4	4.5	2.19 (2.05, 2.33)
Conviction (%)	4.7	2.6	1.82 (1.67, 1.99)
Prison sentence (%)	2.3	0.9	2.56 (2.26, 2.91)
Economic			
Employed (%)	27.6	78.2	0.11 (0.10, 0.11)
Any income (%)	90.9	80.5	2.43 (2.3, 2.57)
Mean income ($)	17,865	44,092	-26,226 (-27,067, -25,384)
Mean NZDep13 (decile)	7.4	5.8	1.57 (1.52, 1.62)

[a] Sub-group values may not sum to totals due to Stats NZ rounding requirements.

Appendix Table 4: Government health, social support and justice sector costs (in New Zealand dollars) for schizophrenia and matched comparison populations (five matched controls for every schizophrenia case).[a]

	Schizophrenia population (N=15,639)	Matched non-schizophrenia population (N=78,195)	Cost difference (95% CI)
Health ($)	17,331	2,535	14,802 (14,535, 15,072)
Social support ($)	14,667	2,868	11,796 (11673, 11,916)
Justice sector ($)	795	411	387 (321, 453)
Total government ($)	32,798	5,815	26,983 (26,668, 27,300)

[a] Costs may not sum to totals due to Stats NZ rounding requirements

Appendix Table 5: Health, social support, justice sector and economic outcomes for schizophrenia and matched comparison populations (10 matched controls for every schizophrenia case).[a]

	Schizophrenia population (N=15,639)	Matched non-schizophrenia population (N=156,390)	OR / difference in means (95% CI)
Health			
Non-mental health inpatient stay (%)	13.0	11.2	1.18 (1.10, 1.26)
Mental health inpatient stay (%)	12.2	0.3	52.80 (38.72, 72.01)
Emergency department visit (%)	6.7	3.0	2.35 (2.10, 2.62)
ACC compensation (%)	16.3	29.7	0.46 (0.44, 0.48)
Social support			
Any social welfare benefit (%)	78.8	17.4	17.64 (16.68, 18.67)
Social housing (%)	13.2	4.3	3.39 (3.09, 3.71)
Justice sector			
Police proceedings against (%)	9.4	4.6	2.15 (1.96, 2.36)
Conviction (%)	4.7	2.7	1.78 (1.58, 2.01)
Prison sentence (%)	2.3	0.9	2.49 (2.05, 3.03)
Economic			
Employed (%)	27.6	78.2	0.11 (0.10, 0.11)
Any income (%)	91.0	80.7	2.4 (2.24, 2.57)
Mean income ($)	17,865	44,092	-26,226 (-27,067, -25,384)
Mean NZDep13 (decile)	7.4	5.9	1.53 (1.47, 1.59)

[a] Sub-group values may not sum to totals due to Stats NZ rounding requirements.

Appendix Table 6: Government health, social support and justice sector costs (in New Zealand Dollars) for schizophrenia and matched comparison populations (10 matched controls for every schizophrenia case)[a]

	Schizophrenia population (N=15,639)	Matched non-schizophrenia population (N=15,639)	Cost difference (95% CI)
Health ($)	17,333	2,486	14,862 (14,649, 15,075)
Social support ($)	14,667	2,845	11,769 (11,655, 11,889)
Justice sector ($)	798	435	363 (300, 423)
Total government ($)	32,795	5,762	26,983 (26,668, 27,300)

[a] Costs may not sum to totals due to Stats NZ rounding requirements.

Competing interests:
Mr Bowden, Dr Brewer and Dr Gibb reports grants and personal fees from Janssen Cilag Pty Ltd during the conduct of the study.
Acknowledgements:
This research was funded by grants provided by Janssen Cilag Pty Ltd to the University of Otago.
Author information:
Sheree Gibb: Department of Public Health, University of Otago, Wellington, New Zealand.
Naomi Brewer: Department of Public Health, University of Otago, Wellington, New Zealand; Centre for Public Health Research, College of Health, Massey University, Wellington, New Zealand.
Nicholas Bowden: Department of Women's and Children's Health, University of Otago, Dunedin, New Zealand.
Corresponding author:
Sheree Gibb: Department of Public Health, University of Otago, Wellington, New Zealand, PO Box 7343, Wellington South, Wellington, New Zealand 6242
sheree.gibb@otago.ac.nz
URL:
www.nzma.org.nz/journal-articles/antipsychotic-and-sedative-medication-use-in-long-term-care-facilities-providing-dementia-care

REFERENCES

1. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2015;386(9995):743-800.
2. Mason P, Harrison G, Glazebrook C, Medley I, Croudace T. The course of schizophrenia over 13 years: a report from the International Study on Schizophrenia (ISoS) coordinated by the World Health Organization. The British Journal of Psychiatry. 1996;169(5):580-6.
3. Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, Killackey E, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Australian & New Zealand Journal of Psychiatry. 2016;50(5):410-72.
4. Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, et al. A Systematic Review and Meta-Analysis of Recovery in Schizophrenia. Schizophrenia Bulletin. 2012;39(6):1296-306.
5. van der Werf M, Hanssen M, Köhler S, Verkaaik M, Verhey FR, van Winkel R, et al. Systematic review and collaborative recalculation of 133 693 incident cases of schizophrenia. Psychological Medicine. 2014;44(1):9-16.
6. Morgan VA, McGrath JJ, Jablensky A, Badcock JC, Waterreus A, Bush R, et al. Psychosis prevalence and physical, metabolic and cognitive co-morbidity: data from the second Australian national survey of psychosis. Psychological Medicine. 2014;44(10):2163-76.
7. Simeone JC, Ward AJ, Rotella P, Collins J, Windisch R. An evaluation of variation in published estimates of schizophrenia prevalence from 1990□2013: a systematic literature review. BMC Psychiatry. 2015;15(1):193.
8. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS medicine. 2005;2(5):e141.
9. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. The Lancet Psychiatry. 2017;4(4):295-301.
10. Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. Journal of psychopharmacology. 2010;24(4_suppl):81-90.
11. Cunningham R, Sarfati D, Peterson D, Stanley J, Collings S. Premature mortality in adults using New Zealand psychiatric services. N Z Med J. 2014;127(1394):31-41.
12. Knapp M, Mangalore R, Simon J. The global costs of schizophrenia. Schizophrenia bulletin. 2004;30(2):279-93.
13. Mangalore R, Knapp M. Cost of schizophrenia in England. The journal of mental health

policy and economics. 2007;10(1):23-41.

14. Jonsdottir A, Waghorn G. Psychiatric disorders and labour force activity. Mental health review journal. 2015.
15. Hakulinen C, McGrath JJ, Timmerman A, Skipper N, Mortensen PB, Pedersen CB, et al. The association between early-onset schizophrenia with employment, income, education, and cohabitation status: nationwide study with 35 years of follow-up. Social Psychiatry and Psychiatric Epidemiology. 2019;54(11):1343-51.
16. Chong HY, Teoh SL, Wu DB-C, Kotirum S, Chiou C-F, Chaiyakunapruk N. Global economic burden of schizophrenia: a systematic review. Neuropsychiatric disease and treatment. 2016;12:357.
17. Cloutier M, Aigbogun MS, Guerin A, Nitulescu R, Ramanakumar AV, Kamat SA, et al. The economic burden of schizophrenia in the United States in 2013. The Journal of clinical psychiatry. 2016;77(6):764-71.
18. Neil AL, Carr VJ, Mihalopoulos C, Mackinnon A, Morgan VA. Costs of psychosis in 2010: Findings from the second Australian National Survey of Psychosis. Australian & New Zealand Journal of Psychiatry. 2014;48(2):169-82.
19. Tapsell R, Hallett C, Mellsop G. The rate of mental health service use in New Zealand as analysed by ethnicity. Australasian Psychiatry. 2018;26(3):290-3.
20. Kake TR, Arnold R, Ellis P. Estimating the prevalence of schizophrenia among new Zealand M a ori: a capture–recapture approach. Australian and New Zealand Journal of Psychiatry. 2008;42(11):941-9.
21. Wheeler AJ. Treatment pathway and patterns of clozapine prescribing for schizophrenia in New Zealand. Annals of Pharmacotherapy. 2008;42(6):852-60.
22. Joyce PR. Changing trends in first admissions and readmissions for mania and schizophrenia in New Zealand, 1974 to 1984. Australian & New Zealand Journal of Psychiatry. 1987;21(1):82-6.
23. Gureje O, Miles W, Keks N, Grainger D, Lambert T, McGrath J, et al. Olanzapine vs risperidone in the management of schizophrenia: a randomized double-blind trial in Australia and New Zealand. Schizophrenia research. 2003;61(2-3):303-14.
24. Milne BJ, Atkinson J, Blakely T, Day H, Douwes J, Gibb S, et al. Data Resource Profile: The New Zealand Integrated Data Infrastructure (IDI). International journal of epidemiology. 2019.
25. Zhao J, Gibb S, Jackson R, Mehta S, Exeter DJ. Constructing whole of population cohorts for health and social research using the New Zealand Integrated Data Infrastructure. Australian and New Zealand Journal of Public Health, in press. 2017.
26. Gibb S, Bycroft C, Matheson-Dunning N. Identifying the New Zealand resident population in the Integrated Data Infrastructure (IDI). Statistics New Zealand; 2016. Report No.: 0908350333.
27. Statistics New Zealand. IDI Data Dictionary: Programme for the integration of mental health data October 2015 edition. 2015.
28. Atkinson J, Salmond C, Crampton P. NZDep2013 index of deprivation. 2014.
29. SAS Institute Inc. SAS 7.1. Cary, NC: SAS Institute Inc; 2014.
30. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.
31. StataCorp. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.; 2017.
32. Kake T, Arnold R, Ellis P. Estimating the prevalence of schizophrenia among New Zealand Māori: a capture–recapture approach. Australian and New Zealand Journal of Psychiatry. 2008;42(11):941-9.
33. Petrović-van der Deen FS, Cunningham R, Manuel J, Gibb S, Porter RJ, Pitama S, et al. Exploring indigenous ethnic inequities in first episode psychosis in New Zealand–A national cohort study. Schizophrenia Research. 2020;223:311-8.
34. McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC medicine. 2004;2(1):13.
35. Salsberry PJ, Chipps E, Kennedy C. Use of general medical services among Medicaid patients with severe and persistent mental illness. Psychiatric Services. 2005;56(4):458-62.
36. Hackman AL, Goldberg RW, Brown CH, Fang LJ, Dickerson FB, Wohlheiter K, et al. Use of emergency department services for somatic reasons by people with serious mental illness. Psychiatric services. 2006;57(4):563-6.

37. De Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World psychiatry. 2011;10(1):52.
38. Jeste DV, Gladsjo JA, Lindamer LA, Lacro JP. Medical comorbidity in schizophrenia. Schizophrenia bulletin. 1996;22(3):413-30.
39. Blaauw E, Roesch R, Kerkhof A. Mental disorders in European prison systems: Arrangements for mentally disordered prisoners in the prison systems of 13 European countries. International Journal of Law and Psychiatry. 2000;23(5-6):649-63.
40. Corrado RR, Cohen I, Hart S, Roesch R. Comparative examination of the prevalence of mental disorders among jailed inmates in Canada and the United States. International Journal of Law and Psychiatry. 2000;23(5-6):633-47.
41. Swanson JW, Frisman LK, Robertson AG, Lin H-J, Trestman RL, Shelton DA, et al. Costs of criminal justice involvement among persons with serious mental illness in Connecticut. Psychiatric Services. 2013;64(7):630-7.
42. Moore KE, Oberleitner LM, Zonana HV, Buchanan AW, Pittman BP, Verplaetse TL, et al. Psychiatric disorders and crime in the US population: results from the National Epidemiologic Survey on Alcohol and Related Conditions Wave III. The Journal of clinical psychiatry. 2019;80(2).
43. Silverstein SM, Del Pozzo J, Roché M, Boyle D, Miskimen T. Schizophrenia and violence: realities and recommendations. Crime psychology review. 2015;1(1):21-42.
44. Kessler RC, Heeringa S, Lakoma MD, Petukhova M, Rupp AE, Schoenbaum M, et al. Individual and societal effects of mental disorders on earnings in the United States: results from the national comorbidity survey replication. American Journal of Psychiatry. 2008;165(6):703-11.
45. Knapp M, Patel A, Curran C, Latimer E, Catty J, Becker T, et al. Supported employment: cost□effectiveness across six European sites. World Psychiatry. 2013;12(1):60-8.
46. Bush PW, Drake RE, Xie H, McHugo GJ, Haslett WR. The long-term impact of employment on mental health service use and costs for persons with severe mental illness. Psychiatric Services. 2009;60(8):1024-31.
47. Wu EQ, Birnbaum HG, Shi L, Ball DE, Kessler RC, Moulis M, et al. The economic burden of schizophrenia in the United States in 2002. Journal of Clinical Psychiatry. 2005;66(9):1122-9.
48. Goeree R, Farahati F, Burke N, Blackhouse G, O'Reilly D, Pyne J, et al. The economic burden of schizophrenia in Canada in 2004. Current medical research and opinion. 2005;21(12):2017-28.
49. Blakely T, Foster R, Wilson N. Burden of Disease Epidemiology, Equity and CostEffectiveness (BODE3) Study Protocol: Version 1.02011. Available from: https://www.otago.ac.nz/wellington/otago019355.pdf.
50. Gale C, Wells J, McGee M, Oakley Browne M. A latent class analysis of psychosis□like experiences in the New Zealand Mental Health Survey. Acta Psychiatrica Scandinavica. 2011;124(3):205-13.
51. Heslin M, Lomas B, Lappin JM, Donoghue K, Reininghaus U, Onyejiaka A, et al. Diagnostic change 10 years after a first episode of psychosis. Psychological Medicine. 2015;45(13):2757-69.
52. Haahr U, Friis S, Larsen TK, Melle I, Johannessen JO, Opjordsmoen S, et al. First-episode psychosis: diagnostic stability over one and two years. Psychopathology. 2008;41(5):322-9.
53. Bowden N, Gibb S, Thabrew H, Audas R, Camp J, Taylor B, et al. IDI trends in antidepressant dispensing to New Zealand children and young people between 2007/08 and 2015/16. The New Zealand Medical Journal. 2019;132(1505):48-61.
54. Durie M. Measuring Māori wellbeing. New Zealand Treasury Guest Lecture Series. 2006;1:2007-09.

Cannabis Legalisation and Control Bill: should doctors be concerned?

Guna Kanniah, Shailesh Kumar

ABSTRACT

A referendum on the Cannabis Legalisation and Control Bill was held in New Zealand. The Bill was meant to oversee government control over the production, supply and use of cannabis and reduce cannabis-related harm. Public health control was proposed over cannabis market by imposing licenses and cultivation, the quality and strength of marketed cannabis, and sale restrictions. Under this Bill, cannabis was only meant to be available to adults aged over 20 years through licenced stores. The potency of cannabis was to be limited. Cannabis use and was going to be permitted in private homes and specifically licensed premises. The Electoral Commission announced on 6 November 2020 that 50.7% of voters opposed the Bill and 48.4% supported it. Despite the outcome of the referendum, legalisation of cannabis may remain a live issue for many people, and doctors need to have an informed view about the impact of legalisation on mental health conditions. Experience from other countries shows that access to and potency of cannabis increased with legalisation. Despite the intent to prevent harm, cannabis legislation has been associated with adverse effects on mental health, emergency hospital presentations and crime. Public health strategies, including educating public about harm associated with cannabis, surveillance of potency and labelling, increasing minimal age for legal recreational cannabis use and bolstering treatment capacity for problematic cannabis use, including those with psychiatric disorders, should be funded by revenue generated from cannabis legislation.

Cannabis is the most commonly used illegal drug in New Zealand, even though the unauthorised possession of any amount of cannabis is a crime under the Misuse of Drugs Act 1975. A non-binding referendum was held on 17 October 2020 regarding a proposed Cannabis Legalisation and Control Bill (the Bill).[1] The Bill outlined government control over the production, supply and use of cannabis, with the intent to reduce cannabis-related harm to individuals, families/whānau and communities. It did not cover medicinal cannabis, hemp, driving while impaired or workplace health and safety issues, which were already covered by existing laws.[1] The Electoral Commission of New Zealand released official results of the referendum on 6 November 2020, with 50.7% of voters opposing the legalisation and 48.4% in support. The referendum is over but the issue of cannabis policy reform remains and deserves critical appraisal. Proponents of legalising cannabis may revisit the issue in the future and doctors will need to have an informed view on whether legalising cannabis can result in increased access, usage and harm to vulnerable sections of society. This article examines data relevant to the health of New Zealanders who are potentially most at risk.

A recent paper has stated New Zealand has one of the highest rates of cannabis use in the Western world, and that rates nearly increased one-and-half times from 2011/2012 to 2016/2017.[2] We also know from two world-class New Zealand longitudinal studies that a dose-dependent relationship exists between cannabis use and a range of adverse health outcomes, including loss of cognitive capacity, increased respiratory and periodontal disease, poor educational and occupational outcomes, higher rates of criminal convictions, poor relationships and driving impairments.[3] Furthermore, Māori are not only disproportionately represented among the population using it,[2] but also among those facing legal complications associated with cannabis usage.[2,4]

While prevalence of cannabis use in the general population for 2018/2019 was 15%, the figure for the same period jumped to 32% for Māori.[4] These trends are already worrying, and any risk of their potential worsening needs to be carefully assessed while considering the appropriateness or need for legalisation of cannabis.

These statistics[3,4] are based on the availability of cannabis in the illegal market, which could potentially change if cannabis is to be legalised. We acknowledge the vast majority of people who use cannabis in New Zealand do not suffer any serious health or social consequences. But the negative effects on people who do suffer harm from cannabis is significant. Among people who use cannabis, those with mental illnesses are particularly vulnerable. This paper primarily focusses on this subgroup of the population.

Currently, the majority of cannabis users in New Zealand access cannabis from an uncontrolled, illicit market. Criminal and antisocial activities are associated with the illicit cannabis market. Measures to legalise and control cannabis, as outlined in the Bill,[1] would have put strict public-health controls over this market by imposing licenses and regulation over the cultivation, quality and strength of products made, and by restricting the sale of cannabis products. Under the Bill, cannabis would have only been available to adults aged 20 years or older through specialist stores licensed by the Government. Cannabis would not have been sold to teenagers. The potency of cannabis was to be limited. Cannabis use was to be permitted in private homes and specifically licensed premises, and it could not have been used in public. Marketing and advertising would have been banned to help prevent and reduce youth use and consumer, and health warnings would have been required. In essence, the Government was to control the cannabis market from seed to sale and proposed to use the revenue to fund mental health and addiction services, freeing up resources currently used in fighting criminal activities associated with cannabis.[1]

It is our view legalising cannabis correlates with heightened acceptance, reduced perception of risks and an increase in cannabis use in both adults and adolescents. The proposal in the Bill[1] to not allow sale of cannabis to adolescents was positive because this group is at higher risk of experiencing impairment in psychological, social and/or occupational functioning and suffering negative psychiatric consequences.[3] It is possible that taking a health-focused approach driven by legislation may encourage people with complications associated with cannabis use to seek treatment and give them access to regulated cannabis products without adulterants. The exact impact of legalisation on help-seeking behaviour may not become evident immediately.

We do, however, know that a substantial proportion of people with mental illnesses in New Zealand already use cannabis and suffer adverse mental health outcomes.[4] There was no provision in the Bill[1] to restrict people with existing mental illnesses from buying cannabis. With easier and increased access to cannabis, the subgroup of the population with existing mental illnesses, or at risk of developing mental illnesses, will use more cannabis and may suffer greater harm. The relationship between cannabis use and harm to mental health is well documented,[5] and yet activism and commercial interests have contributed to legalisation of cannabis in many parts of the world. Murray and Hall (2020) recently noted, "the legalisation of cannabis production and sale has created a rapidly growing industry with a strong financial interest in promoting cannabis use."[6] Emerging data from the USA show cannabis legalisation could indeed be linked with increased usage and increases in motor vehicle accidents, alcohol use and incidents of overdose injuries.[7] It remains unknown whether legalisation of cannabis, by affecting availability, access and restrictions on usage, can truly disempower well-established black markets.[2]

The prevailing belief behind the New Zealand referendum was that controlled access to cannabis can be associated with better outcomes. It is highly likely that legalisation would make access to cannabis easier for many New Zealanders, and that its overall use could increase along with adverse effects on mental health. In this paper we review the experience of other countries who have legalised cannabis, in terms of its effect on access, usage and mental health. We will not examine the

impact on mental health of New Zealand's medicinal cannabis scheme, which has been in effect from 1 April 2020.[8]

Increased access to cannabis under a legalised model

The Netherlands decriminalised recreational cannabis in 1976 by permitting its sale in approved outlets and possession of up to five grams for personal use. Contrary to expectations, changes in cannabis use in Netherlands developed rather independently of cannabis policy.[9] Korf (2002) examined nearly four decades of post-decriminalisation data and described two waves of changes in cannabis use, which first peaked around 1970, fell to a low during the late 1970s and early 1980s and then peaked again in the mid-1990s. Cannabis use among youth in the Netherlands occurred in parallel to four identified stages in the availability of cannabis: peaking when cannabis was distributed through an underground market (late 1960s and early 1970s), decreasing when the number of house dealers superseded the underground market in the post-decriminalisation period, but again stabilised or slightly decreased by the end of the 1990s when the number of coffee shops was reduced. The Dutch experience, therefore, shows questionable effects of changes in cannabis policy on trends in cannabis use. Indeed, it has been questioned whether legalisation and easy access to cannabis can reduce the overall usage of cannabis in a given country.[2]

In other countries that have legalised cannabis, the prevalence of cannabis use has increased over time along with associated complications. For example, in the USA legalisation was followed by increased emergency department visits for cannabis-related presentations (cannabis intoxication and cannabis-related hyperemesis).[10] In New Zealand, the Bill[1] was criticised for being vague about the cannabis production and supply chain, despite proposing that a wide range of cannabis products will be available, including raw (fresh and dried) cannabis, resin, cannabis concentrates and cannabis infused products such as edibles and drinkables.[2] A study from Northern America found the prevalence of daily, weekly and monthly use of cannabis in states that had legalised cannabis increased compared to states where it was not legalised.[11] Furthermore, cannabis was used in a greater variety of forms, including concentrate, vaped oils, edibles and drinks in states that had legalised it.[11] Similarly, another American study reported legalisation of cannabis was associated with increased prevalence of cannabis-use disorder.[7] It is highly likely that with legalisation and an availability of a wider range of products (eg, for smoking, in edible form etc) cannabis use would increase in New Zealand, as has occurred in other countries.

Most proponents of legalising cannabis identify the benefits of reducing criminal activities, minimising the harm associated with cannabis use and protecting the youth, who are especially at a higher risk, from the harmful effects of cannabis. The impact of legalisation, however, varies on these parameters and data are still emerging. For instance, legalisation of cannabis created a stronger illicit market for cannabis sales and associated criminal activity in Canada.[12] Early post-legalisation data from a subsequent nationally representative study[13] of cannabis use and related behaviours, conducted in the months immediately before and after cannabis was legalised in Canada, indicated that cannabis use among youth had not increased. Cannabis use in the older age group increased in the short and longer term post legalisation. Driving after using cannabis did not change post legalisation. The survey acknowledged post-legalisation users had continued to procure cannabis from, and share it with, family and friends. The overall risk of developing cannabis use disorder post legalisation increased in Canada.[13] The findings of this survey suggest that, while criminal activities associated with cannabis may reduce with legalisation, other associated harms may not.

Furthermore, the concentration of tetrahydrocannabinol (THC) in cannabis has steadily increased with legalisation, from approximately 3% in many traditional herbal forms to anywhere between 10% and 70% in Europe and North America.[14,15] The wider availability of cannabis in the 29 states of the USA that had 'Medical Marijuana Laws' was associated with increased

cannabis potency between 1990 and 2014, more unintentional childhood exposures between 2000 and 2013 and greater adult cannabis use and adult cannabis use disorder between 2002 and 2014.[15] These changes were reported over a period of two decades, from 1990 to 2010.[15] This trend is worrying because use of high-potency cannabis is associated with increased risk of developing psychotic disorders. A multicentre case control study spread across Europe and Brazil found that if high-potency cannabis were no longer available, 12.2% of cases of first-episode psychosis could be prevented across all the 11 sites.[16] Placing a cap on potency can be helpful given the harmful effects of potent cannabis. Experience from countries that have legalised cannabis does suggest potency increased over time.[14,15] Canada has experienced significant policy changes post legalisation, including legal sale of more potent products and edibles (both with their own associated special risks) and the opening of the market for retail cannabis by removing the cap on the number of private stores in some states, like Ontario.[13] This could also occur in New Zealand even if a cap on potency was to be placed in any future law.

Thus legalisation in some countries has resulted in increased access to cannabis, in a diverse range of preparations and in increased potency, especially in the highly commercialised markets. The impact of any attempts to legalise and/or to control cannabis in New Zealand will have to have provisions to rigorously monitor the potency of cannabis post legalisation, given the relationship between use of potent cannabis and the risk of adverse outcomes, including escalation to other drug use, especially in the younger population.[3]

Cannabis use and mental illnesses

If it is true that with legalisation access to and use of cannabis increases, then any negative effects on mental illnesses need to be considered carefully. The relationship between cannabis use and the risk of developing psychotic symptoms has been well documented.[3] In countries that have legalised or decriminalised cannabis, its price has fallen while dependence and the risk of psychosis has increased.[6] Increasing access to cannabis, especially to potent cannabis, may increase the risk of developing psychosis, particularly in the younger age group. The Dunedin Multidisciplinary Health and Development Study found age-related associations between cannabis use and mental disorder. Mental disorder at age 15 led to a small but significantly elevated risk of cannabis use at age 18. By contrast, cannabis use at age 18 elevated the risk of mental disorder at age 21. These findings suggest that the primary causal direction leads from mental disorder to cannabis use among adolescents and the reverse in early adulthood[17]—findings echoed by Meier et al.[18] Despite the proposed controls around age in the Bill, people at greater risk of experiencing adverse mental health outcomes may still be vulnerable, although how legalisation will affect mental health parameters and usage of cannabis may be difficult to predict.

The impact of cannabis use, especially use of high-potency varieties, on adverse mental health outcome is worth examining in greater detail. A cohort study (n= 1,087) found that use of high-potency cannabis was associated with a significant increase in the frequency of cannabis use, cannabis problems and anxiety disorder. The likelihood of psychotic experiences increased among users of high-potency cannabis, but the risk was attenuated after adjustment for frequency of cannabis use.[19] An Australian study, on the other hand, found cannabis use precipitated the onset of psychosis in the vulnerable and exacerbated the course in people with existing psychosis.[20] Individuals with psychosis who are regular cannabis users have more positive symptoms, more frequent relapses and require more hospitalisations.[21] Regular cannabis use predicts an increased risk of schizophrenia, even after controlling for confounding variables.[21] In a meta-analysis, the pooled estimate for the time course between regular cannabis use initiation and age at onset of psychosis was 6.3 years.[22] This meta-analysis challenged the popular notion that cannabis is initiated by many as a form of self-medication for the positive symptoms of psychosis, although cannabis may have some anxiolytic effects.[22] With such a well-established relationship between cannabis use and risk of developing

or aggravating psychosis, the potential of increased harm among people with existing, or at risk of developing, mental illnesses needs to be considered if cannabis were to become widely available with no safeguards to limit access to cannabis for people in the high-risk category.

It is not just the risk of psychosis that increases with cannabis use. A range of potential harms in patients with psychotic and mood disorders secondary to cannabis have been increasingly documented in other countries.[5] A greater level of depressive symptoms are also reported in heavy cannabis users compared to light users and nonusers.[23] Associations between cannabis use and negative outcomes in bipolar affective disorder, such as worsened affective episodes, psychotic symptoms, rapid cycling, suicide attempts, decreased long-term remission, poorer global functioning and increased disability, have been reported.[5,24] After controlling for multiple confounders, cannabis use predicted the development of anxiety disorders, depression, suicidal ideation (nearly threefold), personality disorders and interpersonal violence, especially in adolescents relative to adults, and a younger age of initiation increases the risk of developing mental health disorders.[25]

In summary, cannabis is known to disproportionately harm people who are either at risk of mental illnesses or who have an existing mental illness.[5] Current data from England, Denmark and Portugal indicate the incidence of schizophrenia and hospitalisation rates for psychotic conditions increased post cannabis legalisation.[6] Such risks may increase with greater access to cannabis, especially if potency was to increase. Doctors as a group, and psychiatrists in particular, will need to proactively monitor and make submissions on how people at risk of mental illness, or with existing mental illnesses, are affected by the legalisation of cannabis in New Zealand. We may achieve greater clarity in this regard as legalisation and liberalisation of cannabis occurs in many countries, including New Zealand, and as we accumulate empirical data that will help us understand the role of public policy on cannabis legalisation.[12] Until then, we can use the experiences of other countries that have legalised cannabis to prepare a framework for clinicians and policy-makers to approach these concerns by incorporating the following steps:[26]

i. A sound general population education strategy
ii. Limits on cannabis potency and clearer product labelling
iii. A minimum age for legal recreational cannabis use
iv. A national surveillance strategy before and after cannabis legalisation strategy
v. Developing an enhanced treatment capacity for problematic cannabis use, such as for those with psychiatric disorders

There was provision in the Bill[1] for an education strategy to be implemented. Here we emphasise that legalising drugs like cannabis needs to occur in conjunction with evidenced-based preventive and early intervention efforts to reduce harmful cannabis use, with a strong focus on education.[3] Taking a public-education approach was, therefore, a positive aspect of the Bill, along with the provisions to control potency and enforce clear product labelling and a minimum age of 20 for recreational cannabis use—by introducing this age limit, we stood the chance of reducing the harm caused by early adolescent initiation, although young adults may still have been at risk of experiencing adverse mental health conditions, particularly psychosis. The choice of 20 years as the minimum age was criticised as "being mainly founded in opinion or speculation combined with political calculations rather than concrete scientific evidence".[2] Furthermore, New Zealand policy-makers need to consider the impact of legalisation on the health and wellbeing of people who are younger than 20 years old.[2]

In Canada, the proportion of people accessing cannabis from friends and family and thus not paying for cannabis did not change with legalisation.[13] This suggests at least some young people in New Zealand may continue to access cannabis from friends and family post legalisation. Taking a gradual, educational approach, rather than holding a binary referendum, has been proposed as better alternatives to legalisation.[3] Post-legalisation creep in

activism for more potent cannabis and for wider range of cannabis products, such as raw (fresh and dried), resin, vaping concentrate and edibles, to be made available[6] has occurred in other parts of the world.[6,11] This could also occur in New Zealand. An effective system of surveillance for limiting potency and enforcing labelling across the full range of products will be essential because, compared to dried cannabis, other products have different properties, such as delayed onset of effect and higher potency.[11] Consumers will need to be informed of such differences. If possible, the legislative framework should protect people with mental illnesses from the harms associated with increased access to cannabis.

Conclusions

The data presented above are relevant for regulators, public health officials and policymakers considering the impact of legalisation of cannabis for recreational use as in New Zealand. These findings also have implications for mental health policy in terms of education on risks and harm-minimisation strategies for products containing cannabis, and for research into effects in people who might be vulnerable to mental illness. There are strong reasons to approach cannabis legalisation cautiously. We need to closely monitor the impact of different forms of legalisation of cannabis in other countries as we evaluate the effects of changes in our own.

Competing interests:
Nil.

Author information:
Guna Kanniah: M.Clin.Pharm., PG Cert.Psychopharmacotherapy, Senior Clinical Pharmacist, Mental Health and Addictions Services, Waikato Hospital, PO Box 3200 Hamilton, New Zealand
Shailesh Kumar: FRANZCP, MRCPsych, MPhil (London), DPM, Dip CBT, MD (Auck), Consultant Psychiatrist, Midland Regional Forensic Psychiatric Service, Honorary Clinical Associate Professor, University of Auckland

Corresponding author:
Guna Kanniah M.Clin.Pharm., PG Cert.Psychopharmacotherapy, Senior Clinical Pharmacist, Mental Health and Addictions Services, Pharmacy Services, Waikato Hospital, Selwyn Street, Hamilton 3204, +6421 54 99 27
Guna.Kanniah@waikatodhb.health.nz

URL:
www.nzma.org.nz/journal-articles/cannabis-legalisation-should-doctors-be-concerned

REFERENCES

1. Wilkins C, Rychert M. Assessing New Zealand's Cannabis Legalization and Control Bill: prospects and challenges. Addiction. 2021 Feb;116:222-230. doi: 10.1111/add.15144. Epub 2020 Jul 4.
2. Fischer B, Bullen C. Emerging prospects for non medical cannabis legalisation in New Zealand: An initial view and contextualization. International Journal of Drug Policy. 2020. Feb;76:102632. doi: 10.1016/j.drugpo.2019.102632. Epub 2019 Dec 24.
3. Poulton R, Robertson K, Boden J, Horwood J, Theodore R, Potiki T, Ambler A. Patterns of recreational cannabis use in Aotearoa-New Zealand and their consequences: evidence to inform voters in the 2020 referendum. Journal of the Royal Society of New Zealand. 2020. 50:2. 348-65. doi: 10.1080/03036758.2020.1750435
4. Ministry of Health [Internet]. Available from: https://minhealthnz.shinyapps.io/nz-health-survey-2018-19-annual-data-explorer/_w_c21841e3/#!/explore-topics.
5. Lowe D, Sasiadek J, Coles A, George T. Cannabis and mental illness: a review. European Archives of Psychiatry and Clinical Neuroscience. 2018 April; 269:1-14.
6. Murray RM, Hall W. Will Legalisation and Commercialization of Cannabis Use Increase the Incidence and Prevalence of Psychosis? JAMA Psychiatry. 2020; 77(8):777-8.
7. Delling FN, Vittinghoff E, Dewland TA, Pletcher MJ, Olgin JE, Nah G,

Aschbacher K, Fang CD, Lee ES, Fan SM, Kazi DS, Marcus GM. Does cannabis legalisation change healthcare utilisation? A population-based study using the healthcare cost and utilisation project in Colorado, USA. BMJ Open. 2019 May 15;9(5):e027432. doi: 10.1136/bmjopen-2018-027432. PMID: 31092662; PMCID: PMC6530411.

8. Medsafe [Internet]. Medicinal Cannabis Scheme. Prescriber Update. 2020 [cited 2020 August 10]. Available from: https://www.medsafe.govt.nz/profs/PUArticles/PDF/Prescriber_Update_Vol_41(1)_M arch_2020.pdf.
9. Korf DJ. Dutch coffee shops and trends in cannabis use. Addict Behav. 2002 Nov-Dec;27(6):851-66. doi: 10.1016/s0306-4603(02)00291-5. PMID: 12369472.
10. Leung J, Chiu J, Chan V, Chan G, Stjepanović D, Hall W. What have been the public health impacts of cannabis legalisation in the USA? A review of evidence on adverse and beneficial effects. Current Addiction Reports. 2019; 6(4): p. 4) 418-428.
11. Goodman S, Wadsworth E, Leos-Toro C, Hammond D; International Cannabis Policy Study team. Prevalence and forms of cannabis use in legal vs. illegal recreational cannabis markets. Int J Drug Policy. 2020 Feb;76:102658. doi: 10.1016/j.drugpo.2019.102658. Epub 2020 Jan 9. PMID: 31927413.
12. Bahji A, Stephenson C. International Perspectives on the Implications of Cannabis Legalisation: A Systematic Review & Thematic Analysis. Int J Environ Res Public Health. 2019;(16):3095.
13. Rotermann M. What has changed since cannabis was legalized? Health Rep. 2020 Feb 19;31(2):11-20. doi: 10.25318/82-003-x202000200002-eng. PMID: 32073644.
14. Hall W, Stjepanović D, Caulkins J, Lynskey M, Leung J, Campbell G, et al. Public health implications of legalising the production and sale of cannabis for medicinal and recreational use. Lancet. (2019); 394(10208):1580-90.
15. Hasin D. US epidemiology of cannabis use and associated problems. Neuropsychopharmacology. 2018; 43(1):195-212.
16. Di Forti M, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry. 2019; 6(427–36).
17. McGee R, Williams S, Poulton R, Moffitt T. A longitudinal study of cannabis use and mental health from adolescence to early adulthood. Addiction. 2000; 95; 95(4):491-503.
18. Meier M, Hill M, Small P, Luthar S. Associations of adolescent cannabis use with academic performance and mental health: A longitudinal study of upper middle class youth.. Drug Alcohol Dependence. 2015; 156:207-12.
19. Hines L, Freeman T, Gage S, Zammit S, Hickman M, Cannon M, et al. Association of High-Potency Cannabis Use With Mental Health and Substance Use in Adolescence. JAMA psychiatry. 2020;(e201035).
20. Degenhardt L, Hall W, Lynskey M. Testing hypotheses about the relationship between cannabis use and psychosis. Drug Alcohol Depend. 2003; 71(1):37-48.
21. Hall W, Degenhardt L. Cannabis use and the risk of developing a psychotic disorder. World Psychiatry. 2008; 7(2):68-71.
22. Myles H, Myles N, Large M. Cannabis use in first episode psychosis: Meta-analysis of prevalence, and the time course of initiation and continued use. Aust N Z J Psychiatry. 2016; 50(3):208-19.
23. Lev-Ran S, Roerecke M, Le Foll B, George T, McKenzie K, Rehm J. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Psychol Med.. 2014; 44(4):797–810.
24. van Rossum, I, et al Does Cannabis Use Affect Treatment Outcome in Bipolar Disorder? A Longitudinal Analysis J Nerv Ment Dis 2009;197:35–40
25. Copeland J, Rooke S, Swift W. Changes in cannabis use among young people: impact on mental health. Curr Opin Psychiatry. 2013; 26(4):325-29.
26. George T, Hill K, Vaccarino F. Cannabis Legalisation and Psychiatric Disorders: Caveat “Hemp-tor”. The Canadian Journal of Psychiatry. 2018; 63(7):447-50.

Zoledronate-induced anterior uveitis, scleritis and optic neuritis: a case report

Laura E Wolpert, Andrew R Watts

Bisphosphonates, such as zoledronate, are used by approximately 55,000 people per year in New Zealand[1] to prevent the loss of bone density in a range of conditions such as osteoporosis, Paget's disease of the bone and bone metastases.[2] Although ocular side effects are rare, bisphosphonates have been associated with acute anterior uveitis (AAU)[3,4] and scleritis.[4,5] There have also been case reports of optic neuritis following bisphosphonate use.[6–8] Here we report a case of a patient who progressively developed AAU, scleritis and optic neuritis following a zoledronate infusion.

Case report

A 61-year-old woman with a past medical history of previous morbid obesity with sleeve gastrectomy, severe reflux and ileostomy secondary to hemicolectomy for severe diverticular disease presented to the eye clinic with a three-day history of right eye pain, photophobia and blurred vision. These symptoms commenced one day following her first zoledronate infusion for osteoporosis. She had no significant past ophthalmic history.

Right eye visual acuity was 6/15 and left eye visual acuity was 6/9. Intraocular pressures were normal. She had right circumlimbal injection with cells and flare in the anterior chamber. Fundal examination was normal. An initial diagnosis of AAU was made and treatment with prednisolone 1% eye drops and cyclopentolate 1% eye drops was commenced.

Two days later the patient presented with worsening pain and vision and pain on eye movements. Right visual acuity had decreased to 6/24. She had red desaturation with proptosis, periorbital oedema, conjunctival chemosis and injection and cells and flare in the anterior chamber (Figure 1A). There was no evidence of vitritis, and fundal examination was normal.

A B-scan of the right eye showed scleral thickening (Figure 2). The patient underwent a CT scan of her orbits, which revealed right-sided proptosis with intraconal fat stranding and inflammation surrounding the globe and optic nerve, consistent with scleritis and retrobulbar optic neuritis (Figure 3). Investigations, including serum ACE, treponemal serology, ANA and QuantiFERON-TB Gold, were unremarkable.

A diagnosis of zoledronate-induced uveitis, scleritis and optic neuritis was made. The patient received 1g intravenous methylprednisolone, which resulted in a rapid improvement of her symptoms and signs by the following day (Figure 1B). The patient was then discharged on a weaning course of oral prednisone, topical prednisolone 1% eye drops and cyclopentolate 1% eye drops. At one week follow-up the inflammation had resolved.

Discussion

Orbital inflammation is an uncommon side effect of zoledronate infusion. The incidence of zoledronate-associated AAU has been reported at around 1.1%.[3] To our knowledge, there are only two case reports of zoledronate-associated optic neuritis,[7,8] although optic neuritis has been seen with other bisphosphonates in a few cases.[6]

There is little information on bisphosphonate rechallenge following adverse ocular events. Adverse ocular events have been reported following bisphosphonate

Figure 1: (A) The patient's right eye five days following a zoledronate infusion, showing proptosis, lid oedema and conjunctival chemosis. (B) The patient's right eye after treatment with intravenous methylprednisolone, which resulted in reduced peri-ocular swelling and chemosis. The pupil is dilated due to cyclopentolate drops.

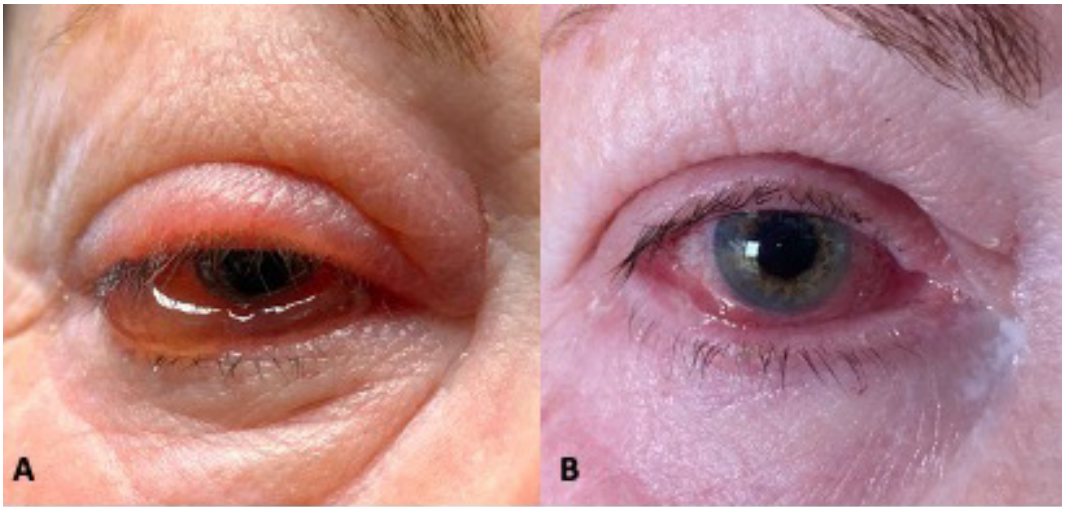
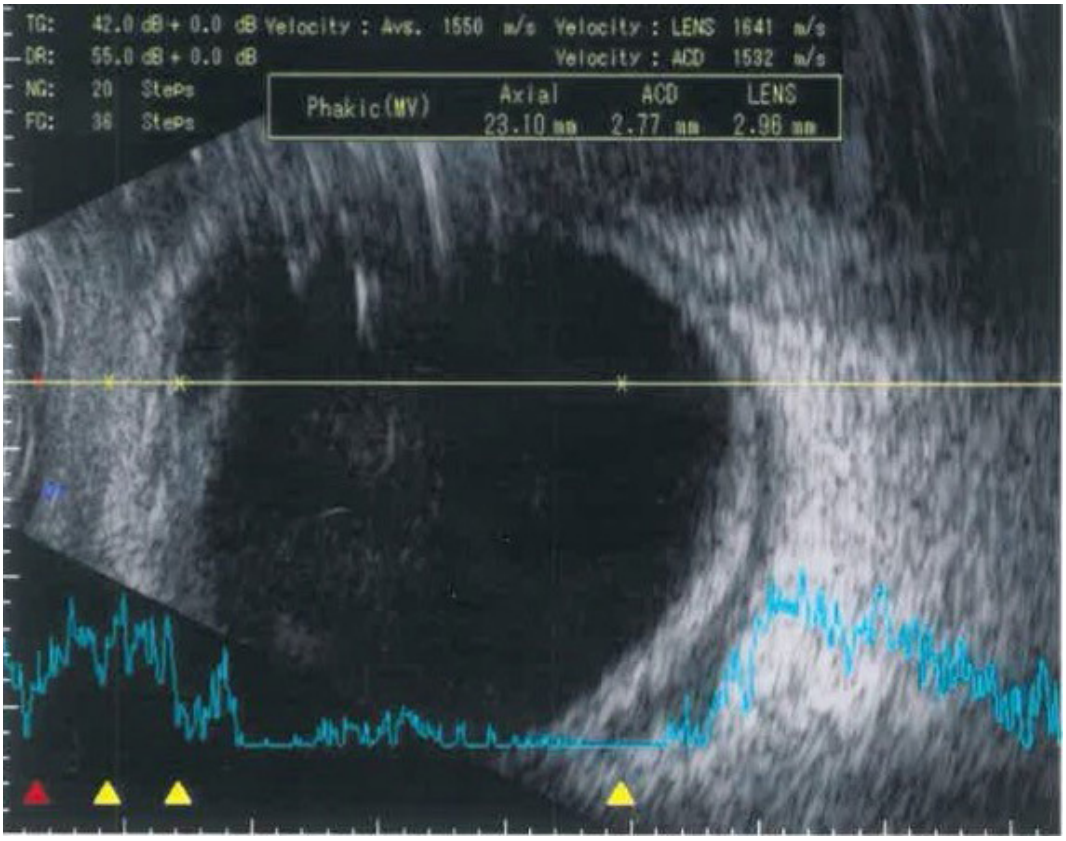


Figure 2: A B-scan of the patient's right eye showing scleral thickening (white arrow).

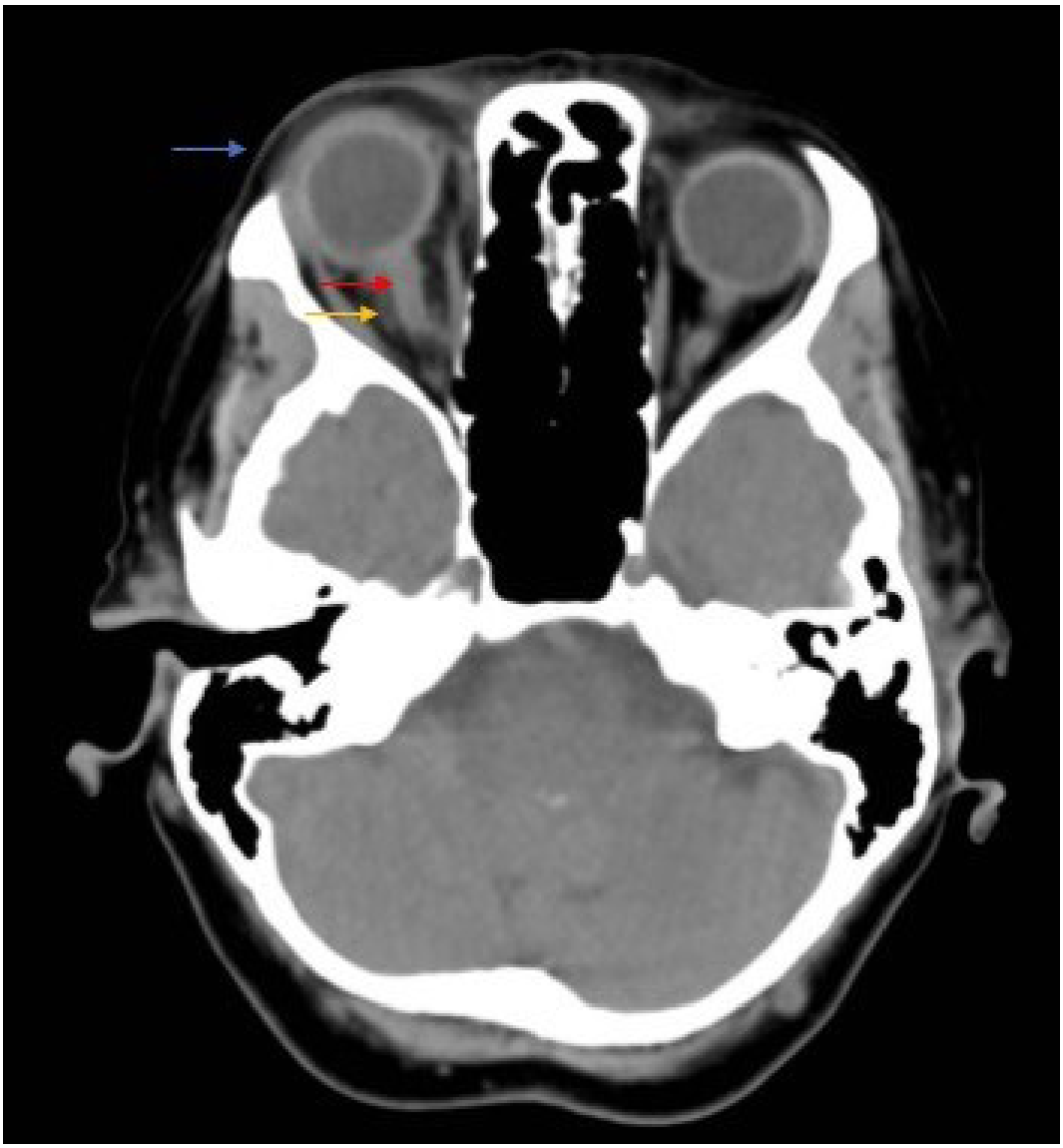


NZMJ 25 June 2021, Vol 134 No 1537
ISSN 1175-8716

rechallenge but do not occur in all cases.[9,5–7] Although inflammation associated with bisphosphonate use is usually mild and shows complete resolution after cessation of the precipitating agent and treatment of the ocular inflammation, in the context of potentially sight-threatening conditions such as scleritis and optic neuritis, rechallenge may not be advisable.

Recognition of drug-induced ocular inflammation is critical to allow for prompt referral to an ophthalmologist and withdrawal of the drug in question. Patients receiving bisphosphonate treatment should be counselled to seek medical attention if they develop symptoms of visual loss, eye pain or eye redness.

Figure 3: CT scan showing right eye proptosis (blue arrow), intraconal fat stranding (yellow arrow) and optic nerve thickening (red arrow).



Competing interests:
Nil.

Author information:
Laura E Wolpert: Ophthalmology Registrar, Department of Ophthalmology, Whangarei Hospital, Northland District Health Board, Maunu Road, Whangārei 0148, New Zealand.
Andrew R Watts: Consultant Ophthalmologist, Department of Ophthalmology, Whangarei Hospital, Northland District Health Board, Maunu Road, Whangārei 0148, New Zealand.
Corresponding author:
Dr Laura Wolpert, Department of Ophthalmology, Whangarei Hospital, Northland District Health Board, Maunu Road, Whangārei 0148, New Zealand, 09 430 4100
laura@wolperts.com

URL:
www.nzma.org.nz/journal-articles/zoledronate-induced-anterior-uveitis-scleritis-and-optic-neuritis-a-case-report

REFERENCES

1. Best Practice Advocacy Centre New Zealand [Internet]. An update on bisphosphonates. Accessed Jan, 2021. Available from: www.bpac.org.nz
2. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc. Sep 2008;83(9):1032-45. doi:10.4065/83.9.1032
3. Patel DV, Bolland M, Nisa Z, et al. Incidence of ocular side effects with intravenous zoledronate: secondary analysis of a randomized controlled trial. Osteoporos Int. Feb 2015;26(2):499-503. doi:10.1007/s00198-014-2872-5
4. Keren S, Leibovitch I, Ben Cnaan R, et al. Aminobisphosphonate-associated orbital and ocular inflammatory disease. Acta Ophthalmol. Aug 2019;97(5):e792-e799. doi:10.1111/aos.14063
5. Samalia P, Sims J, Niederer R. Drug-induced ocular inflammation. N Z Med J. Dec 2020;133(1527):83-94.
6. Stack R, Tarr K. Drug-induced optic neuritis and uveitis secondary to bisphosphonates. N Z Med J. Mar 2006;119(1230):U1888.
7. Brulinski P, Nikapota AD. Zolendronic acid-induced retrobulbar optic neuritis: a case report. Clin Oncol (R Coll Radiol). May 2013;25(5):328-9. doi:10.1016/j.clon.2012.12.006
8. Lavado FM, Prieto MP, Osorio MRR, Gálvez MIL, Leal LM. Bilateral retrobulbar optic neuropathy as the only sign of zoledronic acid toxicity. J Clin Neurosci. Oct 2017;44:243-5. doi:10.1016/j.jocn.2017.06.048
9. Patel DV, Horne A, Mihov B, Stewart A, Reid IR, McGhee CN. The Effects of Re-challenge in Patients with a History of Acute Anterior Uveitis Following Intravenous Zoledronate. Calcif Tissue Int. Jul 2015;97(1):58-61. doi:10.1007/s00223-015-0015-4

Vildagliptin-induced bullous pemphigoid

Annabelle Yi Zhang, Paul Jarrett

In New Zealand, vildagliptin became fully subsidised by PHARMAC on 1 October 2018. Bullous pemphigoid is an autoimmune blistering disorder that typically affects the elderly. Dipeptidyl peptidase-four inhibitors (DPP4is, or gliptins) are a cause of drug-induced bullous pemphigoid.

Case presentation

A 69-year-old Caucasian man with type two diabetes mellitus (T2DM) and no known dermatological conditions presented with a one-month-old, widespread pruritic blistering rash. This rash developed nine months after the addition of vildagliptin to his diabetic medication regimen. The Naranjo algorithm score of causality was five, indicating a 'probable' adverse drug reaction.

There were widespread crusted erosions with scattered tense bullae over the scalp, trunk and limbs, and mucosal erosion on the lower lip (Figures 1 and 2). The diagnosis of bullous pemphigoid was confirmed by histology, which showed a subepidermal split with increased numbers of dermal eosinophils and positive anti-basement membrane antibody of 1:1280 titre. Direct immunofluorescence staining was not possible. Vildagliptin was ceased and oral doxycycline (200mg daily) initiated.[1] Re-epithelialisation on doxycycline monotherapy progressed slowly, therefore oral prednisone (40mg daily) was added, resulting in rapid re-epithelialisation. Blood glucose levels were monitored closely and managed with metformin and correctional scale insulin while the patient was taking prednisone.

Discussion

Bullous pemphigoid is an autoimmune condition. Autoantibodies target hemidesmosomes in basal keratinocytes, causing loss of adhesion between the epidermis and dermis.[2] It is characterised by localised or generalised bullae with preceding and/or accompanying pruritus. Bullous pemphigoid is most commonly observed in the seventh to ninth decade of life and is associated with neurological diseases, including cerebrovascular accidents.[3] The mainstay of treatment is steroid therapy. However, high-dose systemic corticosteroid treatment (prednisolone equivalent >40mg daily) is associated with significantly higher mortality during the first year.[4] A randomised controlled trial comparing the efficacy and safety profile of doxycycline and oral prednisolone concluded non-inferiority of high-dose doxycycline (200mg oral daily) as a first-line treatment for bullous pemphigoid.[1]

Figure 1: Bullous pemphigoid on the back, consisting of vesicles, erosions from ruptured bullae and an erythematous urticated rash.

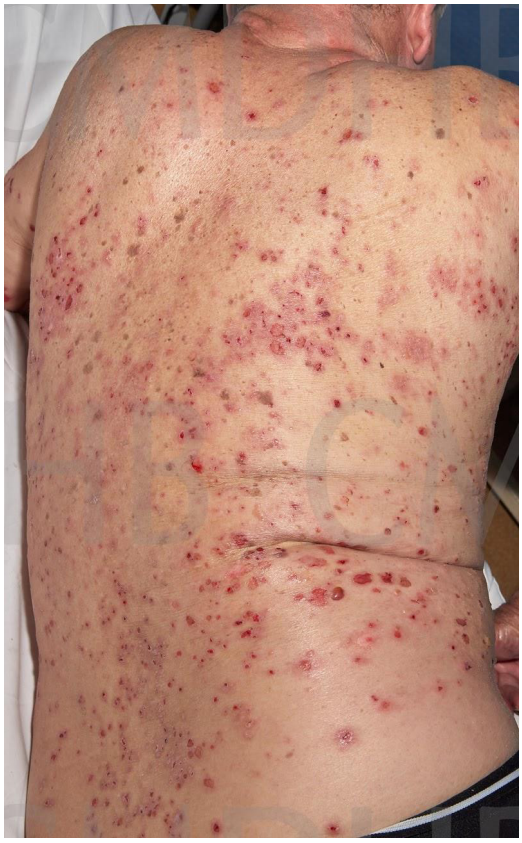
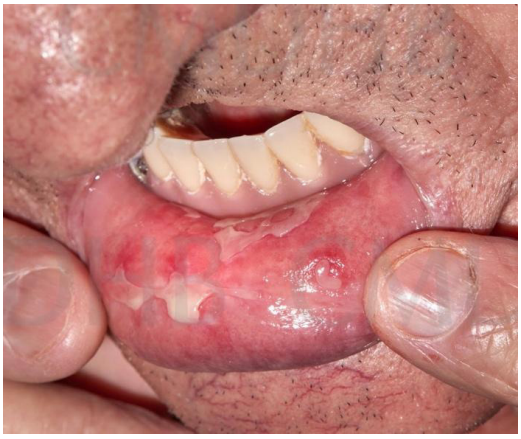


Figure 2: Mucosal involvement.



DPP4is have become a popular second-line treatment in T2DM as they do not cause weight gain and have a lower adverse effect profile than sulphonylureas. However, in the last decade an increasing number of case reports and epidemiological studies have been published suggesting there is a relationship between bullous pemphigoid and DPP4is.[5-7] The latency time between the initiation of DPP4is and onset of bullous pemphigoid ranges from 1 to 37 months in case reports.[5,6] The association between bullous pemphigoid and DPP4is was first described in 2011.[8] There are several hypotheses about the pathogenesis of DPP4i-induced bullous pemphigoid, but the exact mechanism remains unknown.[3] Five cases of bullous pemphigoid in patients who had been on dual metformin and DPP4i therapy for 2 to 13 months prior to disease onset were described, and two cases were resistant to immunosuppressive therapy but later achieved stable remission upon cessation of DPP4is.[8] A meta-analysis of case-control studies further supported this association and found that vildagliptin had a higher degree of association with bullous pemphigoid compared to sitagliptin and linagliptin.[9] The other available oral hypoglycaemic agents available in New Zealand do not cause blistering as a common adverse effect.

In New Zealand, vildagliptin became fully subsidised by PHARMAC on 1 October 2018. Before then, no cases of DPP4i-associated bullous pemphigoid had been reported to the Centre for Adverse Reactions Monitoring (CARM). Eight cases were reported between October 2018 and September 2020.[10] There were six females, and the average age was 75 years (standard deviation ± 10 years). The Australian Database of Adverse Event Notifications has recorded three cases of suspected vildagliptin-related pemphigoid. This increased incidence reflects the wider use of vildagliptin in the community since subsidisation. Bullous pemphigoid should be suspected in a patient on vildagliptin who develops an inflammatory rash with blisters.

Competing interests:
Nil.
Acknowledgements:
Dr Natalie Poppito, Consultant Histopathologist, Middlemore Hospital.
New Zealand Pharmacovigilance Centre, University of Otago
Author information:
Annabelle Yi Zhang, Medical Student: Faculty of Medical and Health Sciences, University of Auckland, New Zealand.
Paul Jarrett, Dermatologist: Department of Dermatology, Middlemore Hospital, Counties Manukau District Health Board, Auckland, New Zealand; Department of Medicine, The University of Auckland, Auckland, New Zealand.
Corresponding author:
Dr Paul Jarrett, Module 7, Manukau SuperClinic, PO Box 98743, Manukau 2241, Auckland, New Zealand, +64 9 276 0000 (phone), +64 9 276 0282 (fax)
Paul.Jarrett@middlemore.co.nz
URL:
www.nzma.org.nz/journal-articles/vildagliptin-induced-bullous-pemphigoid

REFERENCES

1. Williams H, Wojnarowska F, Kirtschig G, Mason J, Godec T, Schmidt E et al. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial. The Lancet. 2017;389(10079):1630-8.
2. Nishie W. Update on the pathogenesis of bullous pemphigoid: An autoantibody-mediated blistering disease targeting collagen XVII. Journal of Dermatological Science. 2014;73(3):179-86.
3. Tasanen K, Varpuluoma O, Nishie W. Dipeptidyl Peptidase-4 Inhibitor-Associated Bullous Pemphigoid. Frontiers in Immunology. 2019;10.
4. Rzany B, Partscht K, Jung M, Kippes W, Mecking D, Baima B et al. Risk Factors for Lethal Outcome in Patients With Bullous Pemphigoid. Archives of Dermatology. 2002;138(7).
5. Béné J, Jacobsoone A, Coupe P, Auffret M, Babai S, Hillaire-Buys D et al. Bullous pemphigoid induced by vildagliptin: a report of three cases. Fundamental & Clinical Pharmacology. 2014;29(1):112-4.
6. Yoshiji S, Murakami T, Harashima S, Ko R, Kashima R, Yabe D et al. Bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitors: A report of five cases. Journal of Diabetes Investigation. 2017;9(2):445-7.
7. Plaquevent M, Tétart F, Fardet L, Ingen-Housz-Oro S, Valeyrie-Allanore L, Bernard P et al. Higher Frequency of Dipeptidyl Peptidase-4 Inhibitor Intake in Bullous Pemphigoid Patients than in the French General Population. Journal of Investigative Dermatology. 2019;139(4):835-41.
8. Skandalis K, Spirova M, Gaitanis G, Tsartsarakis A, Bassukas I. Drug-induced bullous pemphigoid in diabetes mellitus patients receiving dipeptidyl peptidase-IV inhibitors plus metformin. Journal of the European Academy of Dermatology and Venereology. 2011;26(2):249-53.
9. Phan K, Charlton O, Smith S. Dipeptidyl peptidase-4 inhibitors and bullous pemphigoid: A systematic review and adjusted meta-analysis. Australasian Journal of Dermatology. 2019;61(1).
10. New Zealand Pharmacovigilance Centre. Vildagliptin Review. October 2020.

Endogenous endophthalmitis following computerised tomography colonography

Deepesh Mehta, Helen Long, Neil Aburn

Endogenous endophthalmitis is a rare and potentially blinding condition resulting from infection within the ocular tissues and accounts for 10% of all endophthalmitis cases.[1] In contrast to exogenous endophthalmitis, which typically results from external ocular procedures such as cataract surgery, endogenous endophthalmitis usually occurs in immunocompromised patients.[1] Gram-positive species are the predominant causative organisms in bacterial endogenous endophthalmitis, with streptococcal and staphylococcal bacteria being the most commonly isolated species.[1,2]

Case report

A 64-year-old male presented to the acute eye clinic with a one-day history of right loss of vision, chills and muscle aches, after having undergone computerised tomography colonography (CTC) two weeks prior for investigation of gastrointestinal (GI) bleeding while on anticoagulation. On examination, best corrected visual acuity (BCVA) in the right and left eye was 6/18 and 6/9 respectively. Additionally, there was evidence of bilateral anterior chamber inflammation, with keratic precipitates more severe in the right eye relative to the left. Furthermore, a 0.2mm hypopyon was evident in the right eye with mild vitritis. Right fundus examination showed solitary white-yellow fluffy lesions in the periphery and white-centred retinal haemorrhages. A diagnosis of possible endogenous endophthalmitis was made and the patient underwent inflammatory blood tests, blood cultures, right vitreous tap, chest x-ray and trans-oesophageal echocardiogram (TOE) to rule out infective endocarditis (IE). He was given intravitreal ceftazadime and vancomycin to both eyes prophylactically and started on intravenous acyclovir. The patient was found to be anaemic and to have an elevated erythrocyte sedimentation rate and C-reactive protein. The remainder of the blood tests were unremarkable. The vitreous PCR was negative for any organisms and the TOE showed no evidence of valvular vegetation. The blood culture was positive for *Streptococcus dysgalactiae*, and the patient was subsequently started on intravenous ceftriaxone, to which he responded well. He was discharged on oral amoxicillin, prednisone acetate eye drops and dexamethasone eye ointment. At one-week follow-up, examination the BCVA improved to 6/6 and 6/9 in the right and left eye respectively, with improving inflammation. At the final six-month follow-up, his visual acuity was stable with no signs of inflammation in either eye and he was discharged.

Discussion

The pathophysiological mechanism of endogenous endophthalmitis usually results from bacteraemia secondary to seeding from other infected organs.[1] Interestingly, the right eye is more commonly affected compared to the left, likely because it has a more direct arterial supply from the internal carotid artery.[1]

Streptococcus dysgalactiae is a type of pyogenic beta haemolytic streptococci that rarely causes endogenous endophthalmitis, with reported cases being more common in the elderly.[3] It forms part of the natural human microflora, occupying areas such as the skin and the gastrointestinal tract.[3]

Owing to its high virulence, infection of ocular tissues can have devastating visual consequences.[3] Infection of ocular tissue by this organism warrants investigation of underlying IE.[3] Additionally, infection of ocular tissues can cause secondary IE.[3]

Patients undergoing CTC have a small risk of acquiring transient bacteraemia secondary to colonic insufflation causing local ischaemia, thereby allowing translocation of enteric pathogens into the bloodstream and potential infection of distant tissues.[4] However, the risk of bacteraemia is very low, and routine antibiotic prophylaxis prior to CTC is not recommended.[4] Thus, colonic ischaemia secondary to CTC could have been the reason for development of endogenous endophthalmitis in the present case.[4]

In conclusion, endogenous endophthalmitis may present in patients following CTC secondary to colonic insufflation. We illustrate a novel case where *Streptococcus dysgalactiae*, which forms part of the normal GI microflora, resulted in endogenous endophthalmitis. Thus, clinicians should be aware of CTC as a rare cause of endogenous endophthalmitis.

Competing interests:
Nil.

Author information:
Deepesh Mehta: Ophthalmology Non-Training Registrar,
Ophthalmology Department, Capital and Coast District Health Board, Wellington.
Helen Long: Consultant Ophthalmologist,
Ophthalmology Department, Capital and Coast District Health Board, Wellington.
Neil Aburn: Consultant Ophthalmologist,
Ophthalmology Department, Capital and Coast District Health Board, Wellington.
Corresponding author:
Deepesh Mehta, Ophthalmology Non-Training Registrar,
Ophthalmology Department, Capital and Coast District Health Board, Wellington
mehde493@gmail.com

URL:
www.nzma.org.nz/journal-articles/endogenous-endophthalmitis-following-computerised-tomography-colonography

REFERENCES

1. Ness T, Pelz K, Hansen LL. Endogenous endophthalmitis: microorganisms, disposition and prognosis. Acta ophthalmologica Scandinavica. 2007;85(8):852-6.
2. Mak CY, Sin HP, Chan VC, Young A. Klebsiella endophthalmitis as the herald of occult colorectal cancer. BMJ case reports. 2018;2018.
3. Hagiya H, Semba T, Morimoto T, Yamamoto N, Yoshida H, Tomono K. Panophthalmitis caused by Streptococcus dysgalactiae subsp. equisimilis: A case report and literature review. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy. 2018;24(11):936-40.
4. Ridge CA, Carter MR, Browne LP, Ryan R, Hegarty C, Schaffer K, et al. CT colonography and transient bacteraemia: implications for antibiotic prophylaxis. European radiology. 2011;21(2):360-5.

The competition is next door! Why a voluntary approach to tobacco retailer reduction will never work

Richard Portch

In 2011, Te Kāwanatanga o Aotearoa (The New Zealand Government) set the goal to become smokefree by 2025 and have less than 5% of the population smoking daily.[1] A decade on, adult (15 years+) daily smoking rates have decreased from 16.3% to the current 11.6%, over double the intended goal, and with 32% of wāhine Māori still smoking daily,[2] significant disparities still exist. Aotearoa is not on track to achieve Smokefree 2025, and to do so will require a significant reduction in uptake plus a quick increase in cessation.[3–5] The reduction of tobacco supply is an important sector-supported strategy to ensure the success of the Government's Smokefree 2025 Action Plan.[6–8] Marsh et al have previously published on the abundance of tobacco retailers, identifying 5,243 tobacco retailers across Aotearoa.[9] They found that schools were more likely to have a tobacco retailer within 500m or 1,000m as well as a greater number of tobacco retailers compared to community pharmacies.

In this letter we share preliminary findings from a tobacco retailer study across the three Tāmaki Makaurau (Auckland) district health boards (DHBs) interrogating tobacco accessibility and density, using community pharmacies as a comparison. This builds on the work of Marsh et al, using Census 2018 and New Zealand Index of Deprivation (NZDep2018) data. We have used a new methodology for attributing deprivation and demographics to an address whereby the average of all Statistical Area 1 (SA1) within a 1km radius of the address is calculated. The advantage of using this methodology is that the deprivation and demographics attributed to each address represent their surrounding neighbourhood, rather than the small area unit the address resides in. We calculated how many retailers of the same type were within a 100m and 250m radius of each retailer.

A total of 1,794 tobacco retailers and 425 community pharmacies were identified in Tāmaki Makaurau. Across the three DHBs there were an estimated 1,591,797 inhabitants, with 144,144 (11.3%) of the adults who responded to the New Zealand Census 2018 stating they smoke daily. Therefore, people have greater access to tobacco than pharmacies, with one tobacco retailer for every 887 inhabitants compared to one community pharmacy for every 3,745 inhabitants. This equates to one tobacco retailer for every 80 people who smoke daily. Comparing the DHBs, there is one tobacco retailer for every 51 people who smoke in Auckland DHB, one for every 115 people who smoke in Counties Manukau DHB and one for every 86 people who smoke in Waitematā DHB. Tobacco retailers were similarly distributed across local boards and district health boards as community pharmacies, by percentage. There was a significant difference in distribution across council zones, with 25% of tobacco retailers being in residential zones versus 17.6% of community pharmacies.

Tobacco retailers were found to be more densely located in proximity to each other than pharmacies, with 55.4% of tobacco retailers having another tobacco retailer within 100m vs just 22.6% of pharmacies. At 250m the difference was 75.9% and 51.1%, respectively. An initial logistic regression model using retailer type as a predictor found tobacco retailers to have greater odds of having a retailer within 100m and 250m than pharmacies (OR: 4.26, 95%CI: 3.30–5.50,

p<0.001 and OR: 3.03, 95%CI: 2.45–3.76, p<0.001, respectively). Including NZDep2018 score and population with district health board and council zone the association remained (OR: 5.75, 95%CI: 4.37–7.57, p<0.001 and OR: 4.85, 95%CI: 3.76–6.26, p<0.001, respectively). Next we compared how many closely located retailers each type had and found 15% of tobacco retailers had three or more other retailers within 100m, whereas zero community pharmacies did. At 250m the difference was 42% and 13%, respectively.

The findings of our research demonstrate how abundant tobacco retailers are across Tāmaki Makaurau and detail what could be addressed in the Government's Smokefree 2025 Action Plan. Tobacco retailers have previously expressed voluntarily stopping to sell tobacco is not likely, particularly when other retailers close to them continue to sell.[10–12] The voluntary approach will not be enough to reduce tobacco supply and a mandated reduction in supply is required, particularly in high deprivation areas, which are most affected by smoking.[2]

Competing interests:
Richard Portch notes that they work for a health sector agency working in tobacco harm reduction and control.

Author information:
Richard Portch: Health Promoter/Data Analyst, Health Improvement Team, Auckland Regional Public Health Services, Auckland.

Corresponding author:
Richard Portch, Health Promoter/Data Analyst, Health Improvement Team, Auckland Regional Public Health Services, Cornwall Complex, Building 15 (Level 4), Greenlane Clinical Centre, Greenlane, Auckland
rportch@adhb.govt.nz

URL:
www.nzma.org.nz/journal-articles/the-competition-is-next-door-why-a-voluntary-approach-to-tobacco-retailer-reduction-will-never-work

REFERENCES

1. New Zealand Parliament [Internet]. Government Final Response to Report of the Māori Affairs Committee on Inquiry into the tobacco industry in Aotearoa and the consequences of tobacco use for Māori, presented to the House of Representatives in accordance with Standing Order 248 (J.1) - New. Available from: https://www.parliament.nz/en/pb/papers-presented/current-papers/document/49DBHOH_PAP21175_1/government-final-response-to-report-of-the-māori-affairs (2011).
2. Ministry of Health NZ [Internet]. Annual Data Explorer 2018/19: New Zealand Health Survey [Data File]. Available from: https://minhealthnz.shinyapps.io/nz-health-survey-2019-20-annual-data-explorer/ (2019).
3. NZIER [Internet]. N. Z. I. of E. R. Smoking targets A microsimulation analysis. Available from: www.nzier.org.nz (2012).
4. Ikeda, T, Cobiac, L, Wilson, N, Carter, K & Blakely, T. What will it take to get to under 5% smoking prevalence by 2025? Modelling in a country with a smokefree goal. Tob. Control 24, 139–145 (2015).
5. Tobias, M I, Cavana, R Y & Bloomfield, A. Application of a system dynamics model to inform investment in smoking cessation services in New Zealand. Am. J. Public Health 100, 1274–1281 (2010).
6. Der Deen, F S P Van et al. Restricting tobacco sales to only pharmacies combined with cessation advice: A modelling study of the future smoking prevalence, health and cost impacts. Tob. Control 28, 643–650 (2019).
7. Robertson, L & Marsh, L Estimating the effect of a potential policy to restrict tobacco retail availability in New Zealand. Tob. Control 466–468 (2018) doi:10.1136/tobacco-control-2018-054491.
8. Wilson, N., Thomson, G. W., Edwards, R. & Blakely, T. Potential advantages and disadvantages of an endgame strategy: A 'sinking lid' on tobacco supply. Tob. Control 22, i18 (2013).
9. Marsh, L., Doscher, C., Cameron, C., Robertson, L. & Petrović-van der Deen, F. S. How would the tobacco

retail landscape change if tobacco was only sold through liquor stores, petrol stations or pharmacies? Aust. N. Z. J. Public Health 1753-6405.12957 (2020) doi:10.1111/1753-6405.12957.

10. Robertson, L., Marsh, L., Hoek, J., McGee, R. & Egan, R. Regulating the sale of tobacco in New Zealand: A qualitative analysis of retailers' views and implications for advocacy. Int. J. Drug Policy 26, 1222–1230 (2015).
11. Witt, M. et al. How important to dairies is selling tobacco? Views of dairy owners and managers on tobacco retailing. NZMJ 131, 1479 (2018).
12. Badu, E. & Fowler, E. 'If government can't stop the smokes, no way we can stop selling them': why retailers want Government to act. NZMJ 131, 1482 (2018).

ISSN 1175-8716

Rupture of the Urinary Bladder

1921

J.H., aged 65, arrived at Queenstown by boat at 7.30 p.m. on 27th April, 1921. He stayed at an hotel, where he was a stranger; had a good tea with a glass of beer. Later obtained half a teaspoonful of sweet spirits of nitre from the proprietor, which he took in a little gin, saying that his water was bad. At 1.30 the proprietor heard groans coming from his room, where he found him lying on the floor, evidently in very great agony, and asking for more nitre. Medical aid was sent for, but the patient had expired just prior to arrival. There was blood coming from the penis.

At post-mortem a ruptured bladder was discovered. A ragged tear about one inch long situated posteriorly above the trigone. All other organs healthy except the mucosa of the stomach, which showed signs of a small healed ulcer. No evidence of poisoning. The pelvic peritoneum was acutely inflamed and of a brilliant scarlet colour, doubtless from the extravasated urine. The prostate was enlarged, inflamed, and contained pus. The bladder mucosa was injected and œdematous, and there was a small uric acid stone the size of a bean embedded in the bladder wall. Ureters were normal and not dilated, nor was the pelvis of the kidney. There were no signs of an injury or external violence on the abdomen. Verdict given that death was due to shock and collapse resulting from acute peritonitis caused by free urine in the abdomen.

URL:
www.nzma.org.nz/journal-articles/rupture-of-the-urinary-bladder

Proceedings for the 256th Otago Medical School Research Society Masters/ Honours Student Speak Awards, Wednesday 4 November 2020

The light activated chloride channel GtACR2 is a novel potential therapeutic to treat chronic pain.

N Lyons[1,2], L Schoderboeck[1], MF Ibrahim[2], SM Hughes[1], RM Empson[2].

[1]Department of Biochemistry, [2]Department of Physiology, School of Biomedical Sciences, Brain Health Research Centre, University of Otago, Dunedin.

Chronic pain affects 1 in 5 New Zealanders costing our society approximately $14 billion in 2016. Opioids are used to treat chronic pain but show poor long-term efficacy and high rates of addiction. Innovations for effective, personalised chronic pain treatments are desperately needed. Aberrant pain signalling, arising from disinhibition of spinal cord pain projection neurons, is proposed to underlie chronic pain. Altered chloride transporter expression in these neurons disrupts their chloride balance eroding the effectiveness of inhibitory input.

We propose that expressing and activating the light-activated chloride channel *Guillardia theta* anion channel rhodopsin 2 (GtACR2) in spinal cord pain projection neurons will restore their chloride balance, re-establish inhibition, and reduce pain. Here, we produced a lentiviral vector encoding a red fluorescence tagged GtACR2 construct and confirmed its expression and function *in vitro*.

We successfully targeted GtACR2 expression to the cell body of iPSC-derived, cultured human neurons. This subcellular localisation is required to influence chloride balance solely in the cellular compartment where it is altered in chronic pain. Whole-cell patch clamp electrophysiology of GtACR2-expressing neurons showed light-induced ionic photocurrents (N = 15 cells) and transient silencing of action potential activity. Illumination of GtACR2-expressing cultures successfully silenced neuronal network activity for the entire 30 second illumination period, as detected using a genetically encoded fluorescent calcium indicator (N = 3 wells, 21 recordings across 4 days).

Our successful generation and *in vitro* validation of this unique optogenetic tool, and its viral delivery vector, paves the way for its *in vivo* testing in an animal model of chronic pain. Our results provide strong evidence for the novel use of GtACR2 to restore inhibition of spinal cord pain projection neurons. GtACR2 is promising as a specific, light-tuneable therapeutic to re-establish normal pain signalling and alleviate chronic pain.

Supported by a Maurice and Phyllis Paykel Trust Honours Scholarship in Medical and Health Sciences.

Microparticles produced from human papillomavirus type 16 E6 and E7 expressing keratinocytes regulate antigen-presentation by Langerhans cells.

V Ticar, B Nair, M Wilson, M Hibma.

Department of Pathology, Dunedin School of Medicine, University of Otago, Dunedin.

Persistent infection by human papillomavirus (HPV), such as HPV16, initiates around 5% of all human cancers. The progression from persistent infection to cancer is associated with the over-expression of HPV16 E6 and E7 (E6/E7), and modulation of antigen-presenting cells (APCs). Microparticles (MPs) are small (100 to 1000 nm), cell membrane-derived vesicles. This study aimed to understand the role of MPs produced from HPV16 E6/E7-expressing cells on antigen-presentation by Langerhans cells (LCs), the only APCs that are co-located with HPV-infected keratinocytes.

To measure the effects of MPs on T cell proliferation in response to LC-presented ovalbumin (OVA), E6/E7 or control (Ctrl) MPs purified from E6/E7 expressing or control C57Bl/6 mouse keratinocytes were incubated with bone marrow-derived LCs, pulsed with OVA and co-cultured with CD8 T cells. CD8 T cell proliferation was increased following

incubation with Ctrl MPs (76.23 ± 15.68, mean percent ± SD) compared to no MPs (39.31 ± 16.43, $P < 0.01$, Kruskal-Wallis, Dunn's multiple comparisons). CD8 T cell proliferation was reduced following incubation with E6/E7 MPs (48.80 ± 15) compared to Ctrl MPs (N = 8 mice, Kruskal-Wallis, Dunn's multiple comparisons). When LCs derived from Transporter associated with Antigen Processing 1 (TAP1) knockout mice were used, CD8 T cell proliferation was significantly reduced in E6/E7 (22.84 ± 5.46, $P < 0.001$) and Ctrl (19.95 ± 7.47, $P < 0.0001$) MP cultures (N = 8 mice, Two-way ANOVA, Sidak's multiple comparisons).

Here we show that MPs increase proliferation of CD8 T cells upon incubation with LC-pulsed OVA, and that E6/E7 MPs suppresses this effect. Additionally, the effects of MPs were ablated in the absence of TAP1 supporting the involvement of the antigen-presentation pathway of LCs. HPV16 E7 has been previously reported to repress TAP1. The measurement of TAP1 expression in LCs could indicate a potential mechanism for the E6/E7 MP suppression of antigen-presentation.

An in vitro investigation of the effect of environmental contaminants nitrate, nitrite, and N-nitrosodiethylamine on colorectal cancer.

MT Howes, RJ Rosengren.

Pharmacology and Toxicology, School of Biomedical Sciences, University of Otago, Dunedin.

Epidemiological studies have correlated elevated concentrations drinking water nitrate with an increased risk of developing colorectal cancer (CRC). Nitrate is rapidly absorbed *in vivo*, where 0.02 – 0.04% is converted to N-nitrosodiethylamine (NDEA), a class 2A carcinogen. How such environmental contaminants affect CRC cells is not well understood. This project investigated the potential for nitrate, nitrite, and NDEA at concentrations relevant to drinking water, to affect CRC cell viability *in vitro*. The effect of NDEA on CYP2E1 expression was also assessed as a source of reactive oxygen species which may serve as a mechanism of NDEA toxicity.

The cell viability of HT-29 and Caco-2 CRC cells following 72 hours exposure to nitrate (0 – 400 mg/L), nitrite (0 – 20 mg/L), or NDEA (0 – 200 nM) was determined using the sulforhodamine B assay (N = 3). Western immunoblotting was used to assess the expression of CYP2E1 at 24 and 72 hours in both cell lines exposed to NDEA (200 nM and 200 μM, N = 1).

While no concentration of nitrate and nitrite significantly altered cell viability in either cell line, NDEA at 100 nM and 200 nM significantly increased cell viability in HT-29 cells by 13% (± 3.18) and 12% (± 3.79) respectively (mean ± SD, $p < 0.05$, ANOVA, Bonferroni adjustment), with no effect observed in Caco-2 cells. Initial Western immunoblotting indicates that NDEA at 200 nM and 200 μM increases CYP2E1 expression in both Caco-2 and HT-29 cells at 24 hours, however two further biological replicates are required to confirm this.

Toxic NDEA as a product of drinking water nitrate may increase the cell viability of CRC cells accounting for correlations between elevated drinking water nitrate and incidence of CRC. However, toxicokinetic studies would be required before extrapolating these *in vitro* results to true carcinogenic risk from these environmental contaminants.

Ca^{2+}-imaging in rat adrenal slices reveals chromaffin cell heterogeneity.

W Aye, T Georgescu, S Bunn.

Centre of Neuroendocrinology, Department of Anatomy, School of Biomedical Sciences, University of Otago, Dunedin.

The ability to undergo physiological adaptations to stress is critical to life. An important aspect of this stress response is the release of catecholamines from adrenal medullary chromaffin cells into the circulation. This secretion is caused by a rise in intracellular Ca^{2+} ($[Ca^{2+}]i$) in response to several physiological stimuli. Increasing evidence suggests that the adrenal medullary anatomical organisation and cell interconnectivity contributes greatly to this $[Ca^{2+}]i$.

The current study thus aimed to characterise this stress response by examining the stimulus-dependent $[Ca^{2+}]i$ changes in individual chromaffin cells within rat adrenal slices. Adrenal vibratome sections were prepared from adult male Sprague Dawley rats, loaded with the Ca^{2+}-indicator Fluo-4, and changes in $[Ca^{2+}]i$ recorded from individual cells using fluorescence microscopy.

Nicotinic stimulation, mimicking the acute stress response, induced a sharp $[Ca^{2+}]i$ rise which, in some cells (N = 17/66), returned to basal in the continued presence of nicotine. In contrast to studies on isolated cells, most recorded cells (N = 49/66) entered a sustained, elevated plateau phase for the duration of ncotinic exposure. Pituitary adenylate cyclase-activating peptide (PACAP), mimicking a persistent stress response, increased $[Ca^{2+}]i$ in approximately half of the recorded cells (N = 33/67), but this response was delayed by approximately 10 min after exposure. Histamine, a non-neuronal chromaffin cell stimulator, induced a rapid $[Ca^{2+}]i$ rise in most cells (N = 50/55). These responses varied greatly between cells and consisted of multiple complex peaks, differing in duration and magnitude. Despite intercellular differences, histaminergic responses were highly reproducible within an individual cell.

Each examined stimulus produced heterogeneous responses with novel $[Ca^{2+}]i$ characteristics not reported in isolated chromaffin cells. The results, therefore, provided evidence for contributions of cell-cell interactions to

Ca^{2+}-signalling and subsequent secretory output from the chromaffin cells, while highlighting avenues for future research into cellular and functional heterogeneity of the adrenal medulla.

Access to dietetic services for inflammatory bowel disease patients in New Zealand – a patient view.

NE McCarthy[1], M Schultz[2], CL Wall[1].

[1]Department of Medicine – University of Otago, Christchurch Campus, [2]Department of Medicine - University of Otago, Dunedin

International guidelines recommend that inflammatory bowel disease (IBD) patients should have access to specialised dietitian support. This patient group is at high risk of malnutrition and nutrition interventions can reduce disease activity and improve quality of life. Anecdotal reports suggest that New Zealand (NZ) IBD patient access to dietitians is variable.

This research aimed to investigate factors associated with patient access to a dietitian and whether access meets patients' expectations. In early 2020, an anonymous electronic survey was disseminated to patients (and parents) by Crohn's and Colitis NZ and IBD health professionals via email and social media, with a reach of approximately 2000 people. Quantitative responses were analysed via chi-square and Fisher's exact tests and qualitative responses were analysed using a general inductive approach.

The respondents (N = 407) were mostly female (74%) and NZ European (91%), 5% identified as Māori. While 95% of respondents had topics they would like to discuss with a dietitian, only 52% had ever seen a dietitian and 45% had never been referred. Of those who had seen a dietitian, 37% had self-funded their appointment, many because they were unable to access publicly funded appointments. Patients more likely to have seen a dietitian were: younger ($P < 0.001$); diagnosed with Crohn's disease ($P = 0.001$); had previous IBD surgery ($P < 0.001$); on biologic therapy ($P = 0.005$). Common themes identified through general inductive analysis identified that there is a lack of publicly funded dietetic services, that dietitians need specialist IBD knowledge, that patients/respondents want routine referrals to dietitians and to have ongoing dietitian access.

Results indicate that there is inequitable and inadequate access to dietetic services for IBD patients in NZ, with variable referral rates and substantial numbers of patients required to pay for dietitian appointments. Poor access increases malnutrition risk in this vulnerable patient group, potentially leading to worse health outcomes and negative impacts on quality of life.

Supported by the Rabbitt Fund, managed by the Friends of Dunstan Hospital and the Department of Medicine, University of Otago, Dunedin

RFamide-related peptide neurons modulate chronic glucocorticoid-induced reproductive suppression.

A Mamgain, GM Anderson.

Department of Anatomy, Centre of Neuroendocrinology, University of Otago, Dunedin.

Globally, one in four couples are affected by infertility. Chronic stress is often a result, but also a possible cause of reproductive dysfunction. Regulation of gonadal function by luteinizing hormone (LH) from the pituitary gland is suppressed during chronic stress. However, the mechanisms are poorly understood. We investigated whether hypothalamic RFamide-related peptide (RFRP) neurons mediate this suppressive effect of glucocorticoids.

Cre recombinase-dependent DREADDs (designer receptors exclusively activated by designer drugs), activated by the synthetic DREADD agonist clozapine-n-oxide (CNO, 2 mg/kg), were used to selectively manipulate RFRP activity in the transgenic mice. Immunohistochemical staining of the neuronal activity marker Fos-related antigen confirmed downregulated RFRP neuronal activity in the inhibitory DREADD-expressing mice ($P < 0.0001$) and upregulated activity in the excitatory DREADD-expressing mice ($P < 0.0001$) compared to non-DREADD controls in both sexes (t-tests). The effect on LH pulse frequency (mean ± SEM) was measured by tail tip blood sample collection every 6 mins for 3 hours in awake, freely-moving mice.

As expected, control mice had a marked reduction in LH pulse frequency in response to 4 days of subcutaneous ~100 mg glucocorticoid (corticosterone) implant treatment (males: 1.38 ± 0.19 before and 0.92 ± 0.06 pulses/h after corticosterone, $P = 0.030$, N = 8; females 1.54 ± 0.15 pulse/h before and 0.38 ± 0.11 pulses/h after corticosterone, $P = 0.0001$, N = 7). In contrast, LH pulse frequency was rescued from these glucocorticoid effects in RFRP-silenced females (1.23 ± 0.10 before and 1.074 ± 0.12 pulses/h after corticosterone, $P = 0.120$, N = 9), but not males (1.29 ± 0.15 before and 0.86 ± 0.12 pulses/h after corticosterone, $P = 0.030$, N = 8) (2-way ANOVA with corticosterone treatment and RFRP inhibition as factors and Holm-Sidak's multiple comparison post-hoc test). Supporting a sexually-dimorphic role for RFRP neurons in LH suppression, upregulation of RFRP neuronal activity reduced LH pulse frequency in female mice (controls: 1.7 ± 0.01, N = 5; RFRP-excited: 0.6 ± 0.19 pulse/h, N = 3; $P = 0.004$) but no effect was observed in male mice (controls: 1.1 ± 0.11, N = 5; RFRP-excited: 1.3 ± 0.15 pulses/h, N = 5; $P > 0.999$) (t-tests).

These results reveal a novel sex-specific requirement of RFRP neurons in modulating

suppressive effects of stress steroids on LH secretion and highlight complexities in neuronal signaling associated with reproductive dysfunction.

oCOm-21 has an anti-inflammatory effect via the NLRP3 inflammasome.

FM Payne, S Thwaite, JC Harrison, IA Sammut.

Department of Pharmacology and Toxicology, School of Biomedical Sciences, University of Otago, Dunedin.

During cardiac bypass procedures, the heart is subjected to repeat cycles of ischaemia reperfusion injury (IRI). Pro-inflammatory signalling involving the NLRP3 inflammasome, has been identified as a key contributor in the pathogenesis of cardiac remodelling. Recent research highlighted the capability of carbon monoxide (CO) releasing compounds to reduce injury via the NLRP3 inflammasome. This study aimed to test whether a novel organic CO releasing molecule, oCOm-21, produces an anti-inflammatory effect by reducing NLRP3 levels within hearts undergoing IRI.

Male CYP1a1-Ren2 rats were induced to develop either non-hypertrophic or moderately hypertrophic hearts before being randomly allocated to vehicle or oCOm-21 (1 – 10 μM) treatment groups prior to IRI (N = 3/group). Hearts were sectioned for histology to evaluate the damage from IRI and immunofluorescence staining for determination of NLRP3 expression. Ventricles were homogenised for Western blotting to determine protein expression levels. Results were analysed using a One-way ANOVA with a post-hoc Bonferroni analysis.

Untreated controls in both normotrophic and hypertrophic groups sustained greater histological damage than oCOm-21 treated hearts. Immunofluorescence examination showed a 2- and a 3-fold decrease in NLRP3 within non-hypertrophic hearts treated with 3 μM and 10 μM oCOm-21, respectively compared to vehicle ($P < 0.01$). Moderately hypertrophic hearts treated with 3 μM of oCOm-21 had a 1.96-fold decrease in NLRP3 staining compared to the vehicle ($P < 0.05$). No significance was observed between vehicle and 1 μM oCOm-21 for both hypertrophic groups. Western blotting indicated no significance between vehicle and oCOm-21 treated hearts ($P > 0.05$).

These preliminary results strengthen the hypothesis that IRI evokes an inflammatory response, resulting in cardiac damage, which may be attenuated with oCOm-21 via the inhibition of NLRP3. Although the immunohistochemical results demonstrates a promising link between CO and NLRP3 inhibition, the lack of reproducibility with Western blotting requires additional research. The current research performed has provided evidence that CO can reduce myocardial IRI through the NLRP3 inflammasome within a diseased heart model similar to healthy hearts.

Epicardial adipose tissue morphology diversity in Māori, Pacific and New Zealand/European post-mortem cases.

GRR Hight[1], HM Aitken-Buck[1], IC Fomison-Nurse[1], S Coffey[2], RD Tse[3], RR Lamberts[1].

[1]Department of Physiology, School of Biomedical Sciences, University of Otago, Dunedin. [2]Department of Medicine, HeartOtago, Dunedin School of Medicine, Dunedin Hospital, Dunedin, New Zealand. [3]Department of Forensic Pathology, LabPLUS, Auckland City Hospital, Auckland, New Zealand.

Obesity is the leading cause of morbidity and heart disease in New Zealand (NZ), and Māori and Pacific people are disproportionately affected. Obesity is characterized by adipose tissue expansion. The fat surrounding the heart, Epicardial Adipose tissue (EAT), has recently been identified as a diagnostic tool for cardiovascular disease. Recent discoveries show that obesity-induced morphological changes to EAT are dissimilar to changes in subcutaneous or visceral adipose tissues. While adipocyte size in subcutaneous, appendicular and pericardial adipose tissues increased in relation to body mass index (BMI), EAT adipocyte size did not. Additionally, the well-established relationship between increased EAT thickness and BMI was not observed in Māori, nor Pacific people. Our study aimed to investigate how obesity affects EAT morphology and EAT localization in diverse ethnic New Zealand populations.

In post mortem cases of NZ/European (N = 57), Māori (N = 16) and Pacific (N = 6) people, adipocyte size was determined in histological slices of different adipose depots, whereas myocardial adipose infiltration and fibrosis were determined in histological slices of the left ventricle. In subcutaneous, appendicular and pericardial adipose tissue, the adipocyte size positively correlated with BMI in NZ/European and Māori populations, while not in Pacific cases. Additionally, there was no correlation between EAT adipocyte size and BMI in any cases ($P = 0.706$). Furthermore, EAT adipocyte size positively correlated with myocardial fibrosis in NZ/European ($P = 0.0015$, $r^2 = 0.5263$) however not in Māori/Pacific ($P = 0.2954$). Finally, a positive correlation was observed between EAT adipocyte size and myocardial adipocyte infiltration, but only in Māori/Pacific ($P = 0.023$, $r^2 = 0.5455$).

In conclusion, the differences in adipocyte morphology between Māori, Pacific people, and NZ/European, highlight possible physiological ethnic variances, which may associate with diverse risk factors and disease characteristics. This should trigger discussions on the validity of current diagnostic and potential treatment strategies for cardiovascular disease and obesity in NZ populations.

Characterisation of the inflammatory response to injury in an *ex vivo* rodent model of spinal cord injury.

CBM McCrostie[1], L Wise[2].

[1]Department of Pharmacology and Toxicology, School of Biomedical Sciences, University of Otago, Dunedin.

Spinal cord injury (SCI) is a significant injury, and a burden to the patient, their family and to the healthcare system. The inflammatory response that follows the injury exasperates tissue damage and scarring, which prevents neuronal regeneration and patient recovery. Current *in vivo* models are problematic due to the extreme suffering of animals receiving the injury. This study aimed to assess the extent and source of inflammation in the *ex vivo* model that has the potential to reduce animal usage and suffering.

Spinal cord segments were dissected from adult Sprague-Dawley rats (7 weeks post-natal), with random segments receiving a compression injury after 24 hr culture (T0). Segments were harvested immediately after dissection (T-1), or 24 hr (T1) and 7 days (T7) after injury. Quantitative PCR and immunohistochemistry were performed to assess the mRNA levels of inflammatory regulators and the distribution of resident immune cells, respectively.

Interleukin (IL)-6 expression was upregulated by 1400- and 4200-fold, respectively, for uninjured (UI) and injured (I) tissue at T1 compared to T-1, indicating that an inflammatory response to injury is occurring (N = 2). In addition, IL-1β was upregulated by 1.9- and 6.5-fold, for UI and I tissue at T1 compared to T-1, again indicating that an inflammatory response to injury is occurring (N = 2). Also, at T1, increased activation of macrophages through calprotectin staining was observed while increased expression of resident microglia through mannose staining was observed.

These results suggest that pro-inflammatory signalling by resident immune cells occurs within the *ex vivo* model of SCI at 24 hr post-injury. This model may therefore have utility for testing therapeutics aimed at reducing SCI-induced inflammation.

URL:
www.nzma.org.nz/journal-articles/proceedings-for-the-256th-otago-medical-school-research-society-masters-honours-student-speak-awards-wednesday-4-november-2020

Abstracts for the 255th Otago Medical School Research Society PhD Student Speaker Awards, Wednesday 19 August 2020

Theoretical reduction in the anticholinergic burden in older adults with dementia in New Zealand

SS Bala[1], HA Jamieson[2], PS Nishtala[3], R Braund[1].

[1]Department of Preventive and Social Medicine, Dunedin Campus and [2]Department of Medicine, Christchurch Campus, University of Otago, New Zealand, [3]Department of Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom.

A high prevalence of prescribing potentially inappropriate medications, particularly medications with anticholinergic properties (MAP), has been observed in older adults (>65 years of age) with dementia in New Zealand. MAP have been associated with several adverse outcomes in this vulnerable population, specifically the risk of accelerating cognitive decline in patients with pre-existing dementia. The purpose of this study was to compile a comprehensive list of therapeutic alternatives to MAP prescribed for comorbidities in individuals with dementia. Further, the list was used in a cohort of patients with dementia, to determine theoretically if a reduction in the anticholinergic burden (ACB) could be achieved.

An extensive literature review of ACB scales and serum anticholinergic activity of numerous medications was conducted. The list was applied to the individuals who had a standardised comprehensive clinical assessment, the International Resident Assessment Instrument Home-Care (interRAI-HC), to determine the reduction in the ACB. Using a Paired-Samples Test, we compared the results of the ACB before and after the theoretical intervention of the pharmacological alternatives to MAP.

The 2015 interRAI dataset constituted 75,410 community-dwelling older adults, of which 12,984 (17.2%) were diagnosed with dementia. Of these, 49.5% (6,430) individuals were prescribed at least one MAP. By incorporation of the recommendations, we observed a mean reduction of the ACB by 0.49 (95% CI, 0.47-0.51). We could theoretically reduce the prescription of MAP by suggesting therapeutic alternatives in 2,006 older adults with dementia (31.2%).

The list of alternatives to MAP is intended to be a useful tool for health professionals that manage individuals with dementia. The implementation of the recommendations for prescribing therapeutic alternatives to MAP in this vulnerable population along with an awareness created among prescribers has the potential to reduce untoward effects associated with the prescription of MAP.

Building a brain – from genes to phenotypes.

BJ Halliday[1,2], ZA Jenkins[1], DM Markie[2], SP Robertson[1].

[1]Department of Women's and Children's Health, Otago Medical School – Dunedin Campus, University of Otago, Dunedin, [2]Department of Pathology, Otago Medical School – Dunedin Campus, University of Otago, Dunedin.

Cortical malformations arise from *in utero* disruption of neurogenesis, the process of proliferation, differentiation, and migration of neurons in the developing brain. Finding attributable genetic causes for these malformations will sharpen diagnosis and prognostication for patients. However, the heterogeneous nature of these abnormalities creates challenges for assigning pathogenicity. The aim of this study was to apply high throughput sequencing methods to a cohort of 205 patients with periventricular nodular heterotopia (PVNH), a cortical malformation characterised by grey matter nodules abutting the lateral ventricles of the brain due to a failure in neural migration.

Aligned sequence data from patients was processed using a range of custom pipelines designed to capture short genetic variants, as well as large structural events and somatic mutations. Data for parental samples was available for 137 patients, permitting filtering based on inheritance models, along with identification of *de novo* events and causal biallelic genotypes. A filtering method based on recurrence with known and suspected disease genes was adopted for patients without complete parental data.

Pathogenic variants were identified for 17 patients with parental data, along with several candidate variants of

uncertain diagnostic significance. Of these variants, only two genes were recurrently mutated, *FLNA* (n = 4, $P < 0.001$, binomial) a known PVNH gene, and *SON* (n = 5, $P < 0.001$, binomial), associated with the multisystem developmental disorder ZTTK syndrome. Using known and candidate disease-gene patterns, another 12 pathogenic variants were found in patients without parental data, including an additional *SON* variant.

The identification of six patients with *SON* variants heavily implicates it in the pathogenesis of PVNH, increasing our understanding of the molecular pathways critical for neurogenesis. Further, the association between PVNH and ZTTK syndrome is underappreciated and may provide a distinctive radiological marker pointing to this diagnosis in the absence of genetic testing.

Supported by a University of Otago Doctoral Scholarship.

Repurposing the hypoglycemic agent, metformin, for targeted lung cancer.

AR Bland, N Shrestha, RL Bower, RJ Rosengren, JC Ashton.

Department of Pharmacology and Toxicology, School of Biomedical Sciences, University of Otago, Dunedin.

Lung cancer accounts for the highest incidence of cancer mortality worldwide. The EML4-ALK chromosomal rearrangement is involved in 2-7% of lung cancer cases. Crizotinib, the first-line treatment for ALK+ lung cancer is an effective treatment, however, resistance develops usually after one year. To prevent/overcome resistance, novel strategies are being explored. Epidemiological studies show a reduction in the risk of cancer with the use of a hypoglycemic agent, metformin. We aimed to test a combination of metformin and crizotinib for toxicity and efficacy in a xenograft model of lung cancer.

For toxicity analysis, balb/c mice (n = 6) were administered (P.O.) vehicle, metformin (100 mg/kg), crizotinib (25 mg/kg) or the combination once daily for 14 days. On the 15th day serum was extracted for ALT and creatinine analysis. For efficacy testing, Nu/J mice (n = 6) were subcutaneously injected with ALK+ H3122 cells in the flank region. Mice were administered the same dosing regimen as in the toxicity study. Tumor volumes were weighed daily and full necropsies were performed on day 15.

The serum markers of liver (ALT) and kidney (creatinine) toxicity both remained under the normal threshold for all treatment groups. When examining the efficacy of the drugs; metformin, crizotinib and the combination significantly decreased tumor volume compared to vehicle (612, 424 and 552 vs. 943 mm^3, respectively, $P < 0.001$). However, the combination produced no added benefit when compared to crizotinib alone.

The combination produced no additional toxicity and while metformin alone was able to slow tumor growth, the combination did not have any greater therapeutic benefit compared to the monotherapies. We hypothesize that crizotinib is limiting the entry of metformin into cells via an inhibition on organic cation transporters. Nevertheless, metformin alone produced a significant difference in tumor growth compared to the control. This provides justification to further examine the effect and mechanisms of metformin in cancer.

Supported by a University of Otago Doctoral Scholarship.

An investigation into dysfunctional feed-forward inhibition within the cortico-thalamocortical network on absence seizure generation.

S Panthi, B Leitch.

Department of Anatomy, School of Biomedical Sciences, Brain Health Research Centre, University of Otago, Dunedin.

Brain function depends on a balance between excitation and inhibition. Feed-forward inhibition (FFI) within the brain controls the firing of principal excitatory neurons and prevents runaway excitation. It is primarily mediated by parvalbumin-expressing (PV+) inhibitory interneurons. Abnormal functioning of these interneurons leads to neurological disorders, including epileptic seizures. In the cortico-thalamocortical (CTC) network, dysfunctional FFI has been implicated in absence seizure generation. The hallmark of absence seizures is spike-wave discharges (SWDs) measuring 3-4 Hz on an electroencephalogram (EEG) with concomitant behavioural arrests termed absences. Our laboratory has previously reported defects in the activation of PV+ interneurons in the stargazer mouse model of absence epilepsy, which could underlie hypersynchronous excitation leading to seizures. The aim of the current study was to investigate the impact of dysfunctional FFI within CTC network on absence seizure generation and behaviour.

We used Designer Receptors Exclusively Activated by Designer Drug (DREADDs) technology to silence/excite PV+ interneurons. To target these interneurons, mice expressing Cre recombinase in PV+ interneurons (PV-Cre) were bred with inhibitory Gi-DREADDs or excitatory Gq-DREADDs mice. We confirmed selective expression of DREADDs in PV+ interneurons via confocal microscopy. Simultaneous video/EEG recordings were made after silencing/exciting PV+ interneurons within CTC microcircuits.

Silencing PV+ interneurons generated absence-like SWDs and reduced ambulation in Gi-DREADD animals. The mean duration and frequency of SWDs were 2.9 ±0.3 sec and 5.5 ±0.5 Hz, respectively. SWDs were blocked by administrating the anti-absence epileptic drug ethosuximide. Conversely, activating PV+ interneurons

during pentylenetetrazole (PTZ) induced seizures in Gq-DREADD animals delayed the latency, decreased mean duration and total number of PTZ-induced absence-SWDs.

These data indicate that loss of FFI within the CTC network is one causative mechanism for pathological SWD oscillations. This could be a target for future improved treatment strategies since current anti-epileptic drugs are ineffective or cause serious side-effects in one-third of patients.

Supported by a University of Otago Doctoral Scholarship and a Roche Hanns Möhler Doctoral Scholarship.

Inhibitory receptor expressing T cells produce functional cytokines and are enriched in the tumour compared to the non-tumour bowel and peripheral blood of patients with colorectal cancer.

J Harte[1], J Leman[1], F Munro[2], J McCall[2], H McGuire[3,4,5], R Kemp[1].

[1]Department of Microbiology and Immunology, Otago School of Medical Sciences, University of Otago, Dunedin, [2]Department of Surgical Sciences, Otago Medical School – Dunedin Campus, University of Otago, Dunedin, [3]Ramaciotti Facility for Human Systems Biology, The University of Sydney and Centenary Institute, Sydney, Australia, [4]Discipline of Pathology, School of Medical Sciences, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia, [5]Charles Perkins Centre, University of Sydney, Sydney, Australia.

Expression of inhibitory receptors (iRs), such as CTLA-4 and PD-1, are associated with impaired immune cell function and can limit anti-tumour immune responses. Therapies that block inhibitory receptors (immune checkpoint blockade, ICB) can enhance the anti-tumour immune response and improve patient survival. A high infiltrate of iR+ T cells are present in the tumours of patients with colorectal cancer (CRC); however, ICB is not effective in many CRC patients. The aims of this study were to determine iR expression on T cells in CRC and associate iR expression on T cells with T cell functionality *ex vivo* and *in vitro*. We hypothesised that expression of iRs does not correlate with impaired immune cell function and iR+ T cells are important in the anti-tumour immune response.

High dimensional analysis of mass cytometry data from patient samples (n = 8) identified heterogeneous populations of iR+ T cells. Two populations of T cells were significantly enriched in the tumour compared to blood of CRC patients: CD4+FOXP3+BLIMP-1+ "effector Tregs" (P = 0.0009, Dunn's multiple comparisons); and CD4+PD-1+CTLA-4+CD39+ T cells (P = 0.035, Dunn's multiple comparisons). These iR+ T cells, enriched in the tumour, secreted anti-tumour molecules (Granzyme B, IFNg, TNF; n = 8). Therefore, iR expression does not indicate impaired function within CRC tumours. PD-L1 ligation *in vitro* did not significantly alter cytokine expression (IL-2) or proliferation (Ki67) in PD-1+CD4+ T cells. However, PD-1 ligation decreased cytokine production and proliferation in CD4+FOXP3+ T cells (n = 4, P = 0.0625, Wilcoxon sign-rank test), suggesting these two T cell populations respond differently to PD1 signalling. Ongoing *in vitro* tumour conditioned media experiments will determine the effect of the tumour microenvironment on these populations.

This study identifies populations of functional iR+ T cells in CRC tumours, which may explain a lack of clinical efficacy of ICB in these patients.

Supported by a PhD scholarship from the Cancer Society of New Zealand.

Arrhythmogenic and inotropic effects of long-chain acylcarnitines in the human heart.

HM Aitken-Buck[1], I van Hout[1], J Krause[2], PJ Davis[3], RW Bunton[3], DJ Parry[3], MJA Williams[4], S Coffey[4], T Zeller[2], PP Jones[1], RR Lamberts[1].

[1]Department of Physiology, HeartOtago, School of Biomedical Sciences, University of Otago, Dunedin, [2]University Heart and Vascular Centre, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany, [3]Department of Surgical Sciences, Otago Medical School – Dunedin Campus, Dunedin Hospital, Dunedin, [4]Department of Medicine, HeartOtago, Otago Medical School – Dunedin Campus, University of Otago, Dunedin.

Long-chain acylcarnitines (LCACs) are metabolites essential for lipid metabolism in the heart. Recent metabolomic studies have revealed that high plasma levels of LCACs, especially the 18:1 species, are associated with increased risk of cardiovascular diseases, including atrial arrhythmias. This study aimed to address whether LCAC 18:1 directly alters the susceptibility for arrhythmias and contractility of human heart muscle.

Human heart muscles (N = 32) were mounted in a tissue superfusion bath and stimulated to contract were at 1 Hz. The propensity for spontaneous muscle contractions in the absence of external stimulation was used to assess *ex vivo* arrhythmias. Relative to baseline conditions, exposure to LCAC 18:1 at a 25 µM dose for 45-minutes (n = 8) increased the proportion of spontaneously active muscles by 50% (Fishers exact test, P < 0.05). Furthermore, LCAC 18:1 concurrently increased the contraction force of the muscles in a dose-dependent manner (1, 5, 10, and 25 µM, n = 8 for each), with the 25 µM dose inducing a 1.5-fold increase (P < 0.01, repeated measures one-way ANOVA). Both the arrhythmogenic and inotropic effects of LCAC 18:1 were reversed following LCAC wash-out. To gain mechanistic insight, recombinant HEK293 cells were loaded with the cytosolic Ca^{2+} indicator, fluo-4, and were superfused with 25 µM LCAC 18:1. LCAC 18:1 induced a marked cytosolic Ca^{2+} overload in this cardiac cell model, as well as a reduction in the intracellular Ca^{2+} store size. These effects were augmented

by increasing extracellular Ca^{2+} concentrations, suggesting that LCAC 18:1 enhances Ca^{2+} flux across external and internal membranes.

This study is the first to show that LCAC 18:1 can promote arrhythmias and contractility changes in human cardiac muscle, which are linked to cytosolic Ca^{2+} overload. This first use of human heart tissue is a critical step in improving the translatability of LCAC pathophysiology and metabolomics to a clinical setting.

Supported by a University of Otago Doctoral Scholarship.

Calcium calmodulin dependent protein kinase II δ in the pathogenesis of atherosclerosis.

LPI Worthington, JR Erickson, AK Heather.

Department of Physiology, School of Biomedical Sciences, University of Otago, Dunedin.

Atherosclerosis is the leading cause of death in the developed world. The build-up of atherosclerotic lesions within the arterial wall are responsible for life threatening events including stroke. The vascular wall is exposed to a number of stresses that require cellular responses to maintain homeostasis. The calcium/calmodulin-dependent protein kinase II (CaMKII) isoform family has important roles in maintaining vascular homeostasis but more recently emerged in the context of vascular dysfunction.

Previously, we showed that systemic inhibition of CaMKII leads to a reduction of atherosclerosis in the brachiocephalic artery of a mouse model of atherosclerosis ($ApoE^{-/-}$). The next critical step in translating this work to a clinical intervention is to investigate which isoform of CaMKII contributes to atherogenesis.

The aortic tree of 13- and 20-week $ApoE^{-/-}$ mice was dissected and the aortic arch and carotid artery isolated. In addition, human umbilical vein endothelial cells and human coronary artery smooth muscle cells were cultured. PCR and Western blotting was carried out in all samples for the two primary vascular isoforms of CaMKII (δ and γ). Results showed calcium calmodulin-dependent protein kinase II (CaMKIIδ) as the predominant isoform. We next employed a genetic approach by crossing $ApoE^{-/-}$ mice with $CaMKII\delta^{-/-}$ to generate an $ApoE^{-/-}CaMKII\delta^{-/-}$ (dKO) mouse model. Analysis of the aortic sinus at 20 weeks showed extensive atherosclerosis in female groups. Female dKO mice had a 162 ± 31 μm^3 reduction in aortic sinus lesion volume compared to female $ApoE^{-/-}$ (mean ± SEM, n = 11, $P < 0.05$, t-test). Finally, adeno-associated viral vectors (AAVs) expressing either CaMKIIδ-mCherry or control-mCherry were introduced to ligated carotid arteries of dKO mice and 4-weeks later the extent of lesion development was assessed to show the contribution of CaMKIIδ in atherogenesis.

Collectively, our results show that CaMKIIδ is a major promoter of atherosclerosis lesion development. Importantly, we have identified a specific therapeutic target that could provide impetus for drug development.

URL:
www.nzma.org.nz/journal-articles/abstracts-for-the-255th-otago-medical-school-research-society-phd-student-speaker-awards-wednesday-19-august-2020

Proceedings for the 254th Otago Medical School Research Society Research Speaker Awards, Wednesday 24 June 2020

Network meta-analysis of antibiotics and bowel preparation in elective colorectal surgery

K Clifford, JC Woodfield, B Schmidt, G Turner, MA Amer, J McCall.

Department of Surgical Sciences, University of Otago, Dunedin.

There are discrepancies in guidelines on bowel preparation for colorectal surgery. While intravenous (IV) antibiotics are commonly administered, the use of mechanical bowel preparation (MBP), enema (E) and/or oral antibiotics (OA) is controversial. This controversy stems in part from the historical use of inadequate IV antibiotics. Our aim was to summarise all data from randomised controlled trials (RCT) by using network meta-analysis (NMA) to determine the ranking of different bowel preparation treatment strategies. This NMA is the first comprehensive review of this topic that accounts for the impact of antibiotic type and compares the efficacy of all bowel preparation options in reducing postoperative infections.

NMA was performed according to PRISMA guidelines. RCT of adult patients undergoing elective colorectal surgery cover were included. The search included Medline, Embase, Cochrane and SCOPUS databases. Primary outcomes were wound infection (SSI) and anastomotic leak (AL). The NMA was performed in Stata v15.1, using three models: all identified studies, studies with appropriate (aerobic and anaerobic) cover when combining IV and OA, and those with appropriate IV antibiotic cover. Sub-analyses were performed using studies examining rectal, left-sided, and right-sided regions of the colon.

We identified 75 RCTs including 16,891 patients. Treatments compared MBP+IV (5,642 patients), IV (2803 patients), IV+E (397 patients), IV+OA± E (649 patients), MBP+IV+OA (4821 patients), MBP+OA (2093 patients) and OA (486 patients). The likelihood of SSI was significantly lower for IV+OA±E (rank 1) and MBP+IV+OA (rank 2) when compared to other treatments (IV, MBP+IV, MPB+OA and OA), both $P < 0.001$. The addition of OA to IV antibiotics reduced SSI by approximately 50%. There were minimal differences in AL and in secondary endpoints.

This NMA supports the addition of OA to IV antibiotics for patients undergoing elective colorectal surgery. Additional research should assess the effectiveness of IV+OA±E and MBP+IV+OA.

Supported by a University of Otago Research Grant.

A scalable, efficient machine learning pipeline to quantify myocardial collagen in whole slide histological images.

L Ariyasinghe, M Moharram, S Coffey.

Department of Medicine, Otago Medical School, Dunedin Campus, University of Otago, Dunedin.

The collagen mesh found in the extracellular matrix (ECM) of the myocardium plays a critical role in preserving tissue architecture and mechanical properties. Dynamic remodelling of the ECM occurs in different myocardial pathologies; this can manifest as a change in chamber geometry and/or mechanical properties which ultimately impacts overall cardiac performance. Therefore, precise quantification of collagen in the myocardium is of particular importance in histological characterisation of myocardial diseases.

Using Masson's trichrome (MTC) to detect collagen is a widely accepted standard in histopathology. However, manual examination of collagen in stained slides can be time-consuming and is non-quantitative, while off-the-shelf computational approaches lack scalability and have rarely been formally validated. Accordingly, we developed a highly scalable and reproducible Machine Learning (ML) pipeline to quantify the amount of collagen in MTC-stained Whole Slide Images (WSIs).

The ML pipeline consists of three distinct phases. 1) Preprocessing—splits the WSI into smaller images (tiles) and removes any tiles with no tissue present. 2) ML inference—applies the ML algorithms, namely, K-Nearest Neighbors (K-NN), Support Vector Machines (SVM) and Random Forest (RF). The ML algorithms were trained on 4567

pixels from manually annotated tiles of right atrial appendage samples, obtained from patients undergoing cardiac surgery. 3) Segmentation—creates a fully segmented tile by classifying each pixel into one of the three classes, specifically, collagen, non-collagen and blank. The results from each tile are then aggregated to provide a value for the WSI as a whole.

We estimated the classification accuracy using a test set of 87200 pixels, obtained from samples from 10 patients. Consequently, reported accuracies are as follows: K-NN—98.3%, SVM—99.6% and RF—98%. In addition to this remarkable accuracy, our ML pipeline provides workflow efficiency and ability to scale up to handle large number of WSIs.

Supported by funding from the Department of Medicine and the New Zealand Heart Foundation.

Structural basis for active-site probes targeting Staphylococcus aureus serine hydrolase virulence factors.

M Fellner[1], CS Lentz[2,3], SA Jamieson[1], JL Brewster[1], L Chen[2,4], M Bogyo[2], PD Mace[1].

[1]Biochemistry Department, School of Biomedical Sciences, University of Otago, [2]Department of Pathology, Stanford University, USA, [3]Department of Medical Biology, The Arctic University of Norway, Norway, [4]Shanghai Institute of Materia Medica, Chinese Academy of Sciences, China

Around a third of healthy humans are carriers of *Staphylococcus aureus*, they have the bacteria on their skin without any active infection or disease. Despite being harmless in most individuals, *S. aureus* can cause pathogenic infections. It often exists in biofilms in human tissue, resulting in a biomolecular matrix that is largely impermeable to the immune system and many traditional antibiotics. The increased occurrence of community-acquired antibiotic-resistant *S. aureus* strains, often linked to biofilm formation, is a major health threat, requiring urgent development of new diagnostic and therapy options.

Serine hydrolases are a large family of enzymes that play key roles in bacterial homeostasis and survival at the host-pathogen interface during infection. They play a role in biofilms, contributing to the difficulty of achieving effective treatment. This makes serine hydrolases promising new anti-virulence and anti-infectivity targets.

Activity-based profiling identified a family of serine hydrolases, designated fluorophosphonate-binding hydrolases (Fphs), which contribute to virulence of *S. aureus* in the biofilm niche. Here we report a structure-function characterization of one of these serine hydrolases, FphF, expressed during biofilm forming conditions. We determined that FphF is a promiscuous enzyme, able to cleave hydrophobic lipid substrates with a range of acyl chain lengths. Using this newly acquired structural data and similarities among the Fph family, we show that other Fph proteins, including FphB which was linked directly to virulence, may have a more well-defined substrate specificity. Our structural and biochemical studies confirm that FphF is distinct from previously characterized enzymes, making it an important reference enzyme in the serine hydrolase superfamily. Overall, our results provide the first insight into the specificity and the mechanism of substrate and chemical probe binding to the Fph protein family. This information will aid in future efforts to targeting serine hydrolase virulence factors from *S. aureus* and other related bacteria.

This work was supported by a University of Otago Health Sciences Postdoctoral Fellowship.

URL:
www.nzma.org.nz/journal-articles/proceedings-for-the-254th-otago-medical-school-research-society-research-speaker-awards-wednesday-24-june-2020

Abstracts for the 253rd Otago Medical School Research Society Summer Student Sepeaker Awards, Wednesday 22 April 2020

The developmental effects of disrupting DONSON – a gene involved in genetic microcephaly.

MR Mulligan[1], DE Jenkins[1], E Damsteegt[2], C Beck[2], LS Bicknell[1].

[1]Department of Pathology, Dunedin School of Medicine, [2]Department of Zoology, University of Otago, Dunedin.

The clinical features of many genetic disorders are often caused by complex mechanisms that are poorly understood. Recently, mutations in DONSON, a DNA replication protein, have been found to cause microcephaly (reduced brain size) in children. The developmental processes that cause this reduction in size remain unknown. This project aimed to study the effects of disrupting Donson using the CRISPR Cas9 editing tool in the developing brain of Xenopus laevis (African clawed frog).

To study how disruption of Donson affects the developing brain, Xenopus embryos were microinjected with Donson sgRNA at 400 or 800 pg/embryo plus Cas9 protein, with control embryos uninjected or injected with only Cas9 protein. PCR of the cleavage site and T7 endonuclease was used to confirm editing status in DNA from injected tadpoles. Four tadpole heads from each condition were fixed and sectioned into 4 μm sections, which underwent haematoxylin and eosin (H&E) staining to analyse general histology. Expression profiles of Sox2 and Tubb2b, markers of neuronal proliferation, were examined by immunohistochemistry and qPCR.

There was a 55% decrease in Sox2 and a 69% decrease in Tubb2b mRNA (markers of neural proliferation) in anterior tissues in the Donson 800 pg edited tadpoles relative to the controls. H&E staining alongside markers of neuronal proliferation, suggested a reduction in the area of the fourth ventricle and decreased thickness and organisation of the developing brain, specifically in the Donson 800 pg tadpoles, relative to the controls.

The morphological changes suggested alterations to proliferation, which would fit with the role of DONSON in DNA replication. This is further supported by a reduction in transcripts for neural proliferation. Further studies will provide further insight into the exact mechanism underlying such a reduction in proliferation, to understand the link between DONSON and microcephaly.

Supported by a University of Otago Division of Health Sciences Summer Research Scholarship.

High definition transcranial infraslow pink noise stimulation for improving executive functioning in healthy older adults – A pilot safety trial

F Whittington, D De Ridder, D Adhia.

Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin.

Dementia, characterised by progressive deterioration of cognitive functions, is a significant and growing health challenge, with a huge social and economic impact. Current available treatments have limited efficacy, warranting new targeted interventions. Several studies demonstrate dysfunctional electrical activity in brain-wide functional networks, particularly involving the dorsal anterior cingulate cortex (dACC), in individuals with cognitive impairments. Non-invasive transcranial electrical stimulation, can normalize dysfunctional brain activity, thereby improve cognition. This pilot, double-blinded (participants and assessor) randomised sham-controlled parallel trial evaluated the safety and explored the immediate trend of effect of a novel, dACC targeted, high-definition transcranial infraslow pink noise stimulation technique (HD-tIPNS) on cognition in healthy older adults.

Ten cognitively healthy participants were randomised to receive either HD-tIPNS or Sham stimulation, for a single session of 30 minutes. Adverse effects were recorded throughout the intervention period. Cognitive tests [Stroop tests (ST), trail making test (TMT), and digit span recall test (DSRT)] and resting-state electroencephalography (EEG) were conducted at baseline and immediately post-intervention. Descriptive statistics were used to explore

the trend of effect of HD-tIPNS on cognitive outcomes. EEG data were analysed using sLORETA to explore changes in brain activity (BA) and functional connectivity (FC).

No adverse outcomes were reported. All ST variables improved post-treatment, irrespective of the group. TMT demonstrated a positive trend of effect in the HD-tIPNS group. No effect was observed in DSRT. A trend towards significant effects of HD-tIPNS was evident on the infraslow, alpha, and theta bands in dACC network (P = 0.06), compared to sham (P = 0.93). Increased and decreased FC of dACC with the dorsolateral prefrontal cortex and the posterior cingulate cortex respectively, was observed in HD-tIPNS group (P < 0.001).

These results implicate the safety and ability of HD-tIPNS technique to modulate the activity and FC of dACC, suggesting that it has potential for use as a treatment tool.

Supported by a scholarship from the Australia and New Zealand Society of Geriatric Medicine.

Pilot study of ketamine in phobic participants using virtual reality stimuli.

A Krijgsman, S.Gallagher, S Neehoff, P Glue.

Department of Psychological Medicine, Dunedin School of Medicine, University of Otago, Dunedin.

Treatment for specific phobia, an anxiety disorder characterized by unreasonable fears related to specific objects or situations, is limited to psychological interventions with no approved drug treatments. Recent research identified an incidental effect of low-dose injected ketamine on anxiety ratings for a specific phobia (blood/needle phobia). This study aimed to extend this finding by using oral ketamine (minimal side effects), a more common phobia (spider phobia), and a more controllable experimental paradigm (virtual reality (VR) exposure), in a cross-over active-controlled design.

Participants received one of the following medications (0.5 mg/kg or 1.5 mg/kg oral ketamine or 0.02mg/kg oral midazolam (psychoactive control)). One hour later, they experienced a 5-level VR spider simulation. At higher simulation levels, spiders numbers increased, as did their size and movement. We obtained vital signs measurements and a visual analogue scale (VAS) for anxiety (range 0–100) before and at each level of the VR spider simulation. Participants returned for all three sessions. The study is ongoing, with data presented for 11 participants.

Significantly more simulation levels were completed after 1.5 mg/kg ketamine compared with midazolam dosing (mean (SD) 1.0 (1.2), t = 2.6, P = 0.03). A two-way repeated measures analysis of variance identified significant treatment x time interactions for VAS anxiety and respiration rate (RR) during the simulation (VAS anxiety F = 2.02, df = 8, P = 0.05; RR F = 2.94, df=8, P = 0.007). Heart rate changes were not statistically significant between dose groups.

Most of the assessments reported support our hypothesis that ketamine has an anti-phobic effect in patients with spider phobia, compared with midazolam. This is consistent with our earlier research and supports a theory that ketamine may work across a broad range of internalizing disorders via effects on a central neuroticism process. This study adds support to the use of ketamine as an acute treatment for specific phobia.

Supported by the Division of Health Sciences.

Factors related to the presence of toxicological investigation following fatal injury: a retrospective quantitative review of Coronial records in New Zealand.

L Nie[1], G Davie[1], R Lilley[1].

[1]Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, Dunedin.

The National Coronial Information System (NCIS) is a repository containing investigative data of all deaths reported to a Coroner in Australasia. A Coronial investigation can include toxicological analysis at the discretion of the Coroner. Little is known both within New Zealand, and internationally, about potential biases related to toxicology report requests.

This study undertook a retrospective review of New Zealand injury deaths in 2014. Data was collected from the NCIS and the Mortality Collection. Variables of interest, such as circumstances of death and characteristics of decedents, were extracted from the Coronial files. Eligible injury-related deaths referred to the Coroner that had toxicological investigations were compared to those that did not.

Of the 744 unintentional injury Coronial cases in those under 85 years of age, 560 (75%) received toxicological analysis. Females were less likely to have a toxicology report (67%; males 78%; 95%CI for difference -5%, -18%), as were the young and the elderly (58% and 55% respectively compared to 88% for those aged 25–34). Māori were more likely to recieve toxicological analysis compared to NZ European (83% and 73% respectively; 95%CI for difference 3%, 17%). Only 44% of decedents that died as a result of a fall received a toxicology report. There was a clear relationship between receiving a toxicology report and the time between injury and death; 86% for those that died on the same day as their injury compared to 13% in those that this period was over a week. Opioids were detected in 23% of cases that received toxicological screening tests.

It is currently unknown whether the observed patterns are justifiable or whether they relate to subconscious biases. Follow-up qualitative research is required to understand this

further. Better understanding of Coronial processes helps inform policymakers, researchers, and practitioners, and contributes to injury prevention and improved health policies.

Supported by a Otago University Division of Health Sciences Summer Studentship.

ABM300, a new negative allosteric modulator of the CB_1 cannabinoid receptor, exhibits a similar mechanism of action as ORG27569.

N Khalajiassadi, D Finlay, M Patel, M Glass.

Department of Pharmacology and Toxicology, School of Biomedical Sciences, University of Otago, Dunedin.

The extensive role of the endocannabinoid system in homeostatic regulation and the fact that G protein-coupled receptors (GPCRs) are the most common drug targets makes the cannabinoid receptor 1 (CB1) a suitable subject for development of novel therapeutics. Recently, research on CB1-targeting drugs has shifted to allosteric modulators in the hope that they offer fewer adverse effects than orthosteric ligands. Allosteric binding sites are distinct from orthosteric sites and are less conserved in comparison, allowing allosteric ligands to exhibit a greater receptor selectivity. In contrast to promising in vitro studies, the existing allosteric modulators such as ORG27569 have not demonstrated substantial activity in vivo. ABM300, a novel allosteric modulator has been shown to alleviate abnormal behaviours in hyperdopaminergic mice models. We aimed to characterise ABM300 in vitro (in HEK293 cells), in comparison with ORG27569.

Pilot data (n = 3) suggested that ORG27569 and ABM300 exert similar effects on CB1 cAMP signalling, as the co-administration of either allosteric modulator with potent CB1 agonist CP55,940 leads to blockade of agonism, and subsequent inverse agonism. Radioligand binding competition assays performed demonstrated that ABM300 has an enhanced ability (pEC50 7.133 ± 0.201) compared to ORG27569 (pEC50 6.316 ± 0.101) in increasing the binding of CP55,940 to the CB1. We also found that ABM300 (10 μM) abolishes the effect of CP55,940 on phosphorylation of ERK1/2 (PerkinElmer AlphaLISA Surefire kit), resulting in pERK1/2 levels at 23% ± 6.8 of maximum CP55,940-induced ERK1/2 phosphorylation, similar to ORG27569. Furthermore, pilot data indicated that both ABM300 and ORG2769 lead to a concentration-dependent decrease in CP55,940-mediated β2-arrestin recruitment.

This study has made a start in understanding the ABM300 mechanism of action and found strong similarities to that of ORG27569; that is, that the allosteric modulator prevents the activity of the orthosteric agonists.

Supported by a Fastier Summer Student Research Fund scholarship.

Thyroid cancer recurrence prediction using regression approaches.

J Li[1], J Zeng[1], R Turner[2], C Nylén,[3] M Sywak[3].

[1]Department of Preventive and Social Medicine, Dunedin School of Medicine, [2]Centre for Biostatistics, Division of Health Sciences, University of Otago, Dunedin, [3]Endocrine Surgery Unit, University of Sydney, Sydney, Australia.

Prediction of thyroid cancer recurrence is important information for planning post-surgical follow-ups. Cancer stage is a well-known predictor of thyroid cancer and the American Thyroid Association offers a thyroid cancer staging calculator that helps predict the stage of thyroid cancer using preoperative clinical and demographical information. The current calculator, however, is missing information on serum thyroglobulin which is a critical predictor to evaluate the cancer stage of patients. The objective of this study was to develop a regression model that updates the calculator with serum thyroglobulin information.

In this study, we used both the logistic regression and the LASSO methods for model building. Records from 3962 thyroid patients were analysed for training models for recurrence prediction. A-priori twelve variables were investigated (age at operation, sex, number of carcinomas presented in the operation, size of the greatest tumour, histologic type of carcinoma, extrathyroidal extension status of tumours, pathologic staging of the primary tumour, presence of venous invasion of the primary tumour, immunohistochemistry for the primary tumour, presence of extranodal spread, number of lymph nodes and serum thyroglobulin level presented in the scans) as predictors of recurrence.

Both approaches demonstrated excellent performance. Logistic regression (with an AUC of 0.874) had a slightly better performance, whereas lasso regression (with an AUC of 0.856) utilized fewer variables to achieve a similar result. The LASSO method had identified five crucial variables for predicting structural recurrence of thyroid cancer. These include extrathyroidal extension status of tumors, the pathologic staging of the primary tumor, the presence of extranodal spread, the number of lymph nodes that are involved by carcinoma and the serum thyroglobulin level presented in the scans.

Recurrence of thyroid cancer can be predicted with reasonable accuracy with as little as five clinical variables. This information can be used to help plan post-surgical follow-up of patients. Future work will investigate whether these variables also predict survival.

Supported by a Dunedin School of Medicine Summer scholarship.

Upregulation of GAD65 in somatosensory cortex of stargazer absence epileptic mice.

N Lyons, S Panthi, B Leitch.

Department of Anatomy, School of Biomedical Sciences, University of Otago, Dunedin.

Childhood absence epilepsy is one of the most common paediatric epilepsies. It is characterised by frequent non-convulsive seizures causing brief loss of consciousness. Absence seizures arise within the cortico-thalamo-cortical (CTC) network; however, the precise molecular mechanisms are not fully understood and are likely multifactorial. This may account for the variability in patients' responses to antiepileptic drugs (AEDs). Although AEDs greatly improve quality of life for most patients, one third cannot be effectively treated and there is no cure for epilepsy. Understanding underlying molecular causes is imperative. The stargazer mouse model of absence epilepsy has a mutation reducing excitatory input to feed-forward inhibitory (FFI) interneurons; FFI prevents runaway excitation in networks. The stargazer mutation specifically affects CTC parvalbumin containing GABA (γ-Aminobutyric acid) interneurons, causing FFI deficits and altered GABA levels. This study aimed to investigate whether changes in GABA levels are due to altered expression of its production enzymes, glutamate decarboxylases (GADs 65&67), and/or transport proteins, GABA transporters (GATs 1&3).

Confocal immunohistochemistry of sections double labelled for parvalbumin and GAD/GAT showed no differences in cortical expression pattern between epileptic and non-epileptic animals. However, semi-quantitative western blotting detected significantly increased GAD65 in somatosensory cortex of epileptic mice compared to non-epileptic littermates (P = 0.0324, Mann-Whitney U test, N = 11 Epileptic/13 Non-Epileptic). No significant change in GAT3 or GAD67 levels was detected (P > 0.05, Mann-Whitney U test, N = 9 Epileptic/14 Non-Epileptic or 10 Epileptic/14 Non-Epileptic respectively); although GAD67 trended towards elevation in epileptic animals above controls.

GAD65 upregulation may be a mechanism of compensating for reduced FFI, and account for the heightened somatosensory cortex GABA levels previously observed. This discovery provides the foundation for investigating the cell-type specificity of GAD65 elevation and interrogating its role in absence seizure genesis and maintenance over the developmental timespan. GAD65 may itself constitute a therapeutic target or may allow discovery of an underlying mechanism to therapeutically target.

Supported by the Otago Medical Research Foundation - EMM Haynes Charitable Trust Summer Research Scholarship.

Investigation of exhaled nitric oxide as a measure of left atrial pressure.

S Jones[1], A Prothero[2], S Myerson[2,3], B Prendergast[4], S Coffey[1,3].

[1]Department of Medicine - HeartOtago, Dunedin School of Medicine, University of Otago, Dunedin, [2]Oxford University Hospitals NHS Trust, [3]Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, [4]Department of Cardiology, St Thomas' Hospital, England.

During left-sided heart failure, left atrial pressure (LAP) increases, producing pulmonary congestion. Previous studies examining patients with symptomatic heart failure or rheumatic heart disease suggest a relationship between increased LAP and fractional exhaled nitric oxide (FeNO), which can be measured by a reliable portable hand-held analyzer. If such a relationship existed, a portable diagnostic test could be used to supplement current assessments.

This observational study examined a subset of the OxVALVE cohort, a UK population-based cohort aged 65 years and older. Participants were eligible for inclusion if they did not have a previous diagnosis of valvular heart disease, and could provide informed consent. Each participant had echocardiography performed at their local general practice. The E/e' ratio, measured via transthoracic echocardiography, was used as a surrogate of LAP. A consecutive subset of 277 participants had FeNO measurement attempted using a NIOX VERO electrochemical analyzer.

Mean age of participants was 73.5 ± 6.3 years, with 45% female. Only 10 participants had an NYHA class of III or more (New York Heart Association classification of heart failure patients). FeNO was successfully measured in 227 participants, with a mean FeNO of 24.2 ± 15.6 ppb. Mean E/e' was 11.5 ± 3.5. There were 58 participants with high E/e' (>14), and these were older than those with normal E/e' (<8) (76.8 ± 7.4 years vs 72.0 ± 5.5 years, P < 0.001). No relationship between FeNO and E/e' was seen on regression analysis (linear regression R^2= 0.007).

These results illustrate that FeNO is not an accurate predictor of elevated E/e' in predominantly asymptomatic patients in a general practice setting.

Supported by a Heart Foundation Summer Scholarship.

URL:

www.nzma.org.nz/journal-articles/abstracts-for-the-253rd-otago-medical-school-research-society-summer-student-sepeaker-awards-wednesday-22-april-2020

NZMJDigest

published by the New Zealand Medical Association

NZMJDigest

http://www.nzma.org.nz/publications/nzmjdigest

The NZMA publishes the e-magazine NZMJDigest 10 times a year. It contains news and views from the profession and the NZMA, including the NZMA Chair's editorial, along with highlights from and links to the New Zealand Medical Journal.

Click on the image above to view the latest issue.

We welcome contributions from members and readers. To contribute to the NZMJDigest, please email digest@nzma.org.nz

---