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Retrospective analysis of eligibility for denosumab in patients presenting with osteoporotic fractures and renal impairment treated by orthogeriatric service at Middlemore Hospital

Michael Yoon Kang, Jessica Besley, Tina Sun, Sunita Paul

Osteoporosis is a medical condition common in older adults which is characterised by the weakening of bones resulting in increased risk of having bony fractures. Bisphosphonate is a type of medication used as a first-line therapy in New Zealand to treat osteoporosis, however it cannot be used in severe kidney failure, which is another condition common in older adults. A new medication called denosumab has been shown to be as effective as bisphosphonates in osteoporosis and safer to use in kidney failure. However, the use of this medication is currently restricted by the PHARMAC special authority criteria. This research firstly confirms that osteoporosis and kidney failure co-occur together in considerable number of New Zealand patients aged 65 years and above, which prevents the use of bisphosphonates. Secondly, our study demonstrates that current PHARMAC criteria is too restrictive, as majority of the patients with osteoporosis and kidney failure were not eligible to access denosumab. Our research sheds light on the urgent need for the PHARMAC criteria to be reviewed to improve access to denosumab in these patients.

Increasing burden of advanced hepatocellular carcinoma in New Zealand—the need for better surveillance

Cameron Schauer, Thomas Mules, Marius van Rijnsoever, Ed Gane

People with chronic viral hepatitis B or C virus infection have a high risk of developing liver cancer. Unfortunately, in most cases, the cancer is only detected when the person complains of pain or swelling when the cancer is very advanced when survival is only a few months. The main cause of this late presentation is because the individual did not know that he or she was at risk of liver cancer because he or she had never been tested for hepatitis B or hepatitis C virus infection. Earlier diagnosis of hepatitis B or C allows effective antiviral treatment which prevents cirrhosis, which is the biggest risk for liver cancer. And even in those who are already cirrhotic at the time of diagnosis of hepatitis B or C, regular screening with ultrasounds will detect small cancers which can be cured.

Cannabis-based medicinal products in arthritis, a painful conundrum

Marthe Van den Berg, Mary John, Melissa Black, Alex Semprini, Karen Oldfield, Michelle Glass, Irene Braithwaite

We reviewed the medical literature to gain an understanding of whether cannabis-based products might be helpful in the management of arthritis. We asked three main questions. 1) Is there molecular evidence that the human endocannabinoid system is associated with the disease process of arthritis? 2) Is there scientific evidence from animal trials showing that cannabis-based products or products designed to mediate the human endocannabinoid system influence the disease process of arthritis? 3) Is there evidence of cannabis-based products working in humans with arthritis? We found that there is some molecular evidence of an association between the human endocannabinoid system and arthritis, that mouse models of arthritis may be influenced by the direct administration of trial products into the joint or the spine, and that there were only two trials of similar products in humans with arthritis, one of which was terminated early, and the other that lasted only five weeks that showed some reduction in pain in rheumatoid arthritis patients. The evidence with respect to long-term efficacy and safety in this patient group does not support a prescription for cannabis-based products.

Change in smoking intentions of university students in New Zealand following simulated cigarette price increases: results of the first of two cross-sectional surveys

Ben Wamamili

This study examined the changes in smoking intentions of university students in response to simulated increases in cigarette prices. Data came from 187 students from all eight universities who currently smoked (53% aged ≥21 years, 60% male, 90% non-Māori, 18% current e-cigarette users). Results show that more students would reduce smoking, switch to e-cigarettes or quit altogether, as prices increase. Stronger intentions to quit were reported in younger students and females, while males were more likely to switch to e-cigarettes. Overall, more students indicated that they would quit than switch to e-cigarettes as prices increase.

Exploring medicinal use of cannabis in a time of policy change in New Zealand

Marta Rychert, Chris Wilkins, Karl Parker, Thomas Graydon-Guy

The new Medicinal Cannabis Scheme became operational last month (1 April 2020), but patients' access remains limited until cannabis-based products are assessed and approved by the Medicinal Cannabis Agency. Products brought within the regime must meet minimum quality standards (efficacy data does not need to be provided) and they must not be in a form intended for smoking (although dried cannabis flower intended for vaping can be approved and prescribed). Approved products can include oils, pills, sprays and lozenges, but not herbal cannabis for smoking. There is currently limited knowledge about how New Zealanders use and access cannabis for medicinal reasons.

The New Zealand nuclear veteran and families study, exploring the options to assess heritable health outcomes

David McBride, John Dockerty, Robin Turner, Guy Austin, Toby Calvert, Natasha Fasi, Ryder Fuimaono, Timothy Galt, Sam Jackson, Leanda Lepaio, Bill Liu, Darren Ritchie, Nicolas Theis

Ionising radiation can cause changes in the chromosomes carrying the genetic code; such changes having been shown in nuclear veterans, but we know neither if these changes result in disease, nor whether they can be passed on by fathers to offspring. In this survey, Mururoa veterans' fathers reported cancers much more often than offspring, but both reported high levels of anxiety and depression. Common conditions may be inherited through the way the genes express themselves through decoding; however, this 'epigenetic' mechanism is extremely complex and we need to know exactly where to look for the signals that are present. The best chance of detecting heritable change is to look at cancers, where we can look at specific changes in the code, so establishing a registry of veterans and their offspring and storing tissue samples for later analysis is the best way of doing this.

Attitudes towards cannabis and cannabis law change in a New Zealand birth cohort

Joseph M Boden, Lana Cleland, Bhubaneswor Dhakal, L John Horwood

These findings provide insight into cannabis-related views within the New Zealand context, and may help to predict voting behaviour during the 2020 Cannabis Referendum. We identified a wide range of attitudes across the cohort, however the majority tended to hold a neutral view. More than 80% of the cohort expressed support for medicinal cannabis, while 47.8% supported decriminalisation, and 26.8% expressed support for legalisation for recreational use. The strongest predictors of support for legalisation were prior use of cannabis and other drugs, while additional positive predictors included a history of depression, Māori ancestry, parental drug use, novelty seeking and higher educational attainment. Predictors of more negative attitudes were also identified, and included female gender and having dependent children.

The practice of the alcohol industry as health educator: a critique

Nicki Jackson, Rachael Dixon

Alcohol companies are entering New Zealand high schools to deliver one-off sessions to promote 'responsible drinking' to students. This paper provides an evidence-based critique of the corporate-led school-based education programme from an alcohol harm reduction and educational perspective. It finds the programme reinforces industry rhetoric, omits key information, is strategically ambiguous and can undermine educational best practice. It is likely to serve to whitewash the image of the alcohol industry, delaying the adoption of effective alcohol policies that would reduce alcohol harm to young people.

A balanced opinion? Considering the role of the external clinical advisor in ACC processes

Andrew Dickson, Joanna Manning

This paper looks critically at the role of the 'external clinical advisor' (ECA) in the processes of the Accident Compensation Corporation (ACC), particularly as they relate to birth injuries. Using the case of Dr Dickson's son's birth injury, the paper presents extracts from an external clinical advisor report to show how a power imbalance can be enacted in ACC decision-making processes. It also demonstrates that the normal checks and balances in the system, particularly those provided by the Health & Disability Commissioner, are bypassed in most cases. Finally, a recommendation is made to potential external clinical advisors to precisely following the standards set by the Medical Council in all cases when writing reports for ACC.

Challenges of virtual talking therapies for substance misuse in New Zealand during the COVID-19 pandemic: an opinion piece

Susanna Galea-Singer, David Newcombe, Virginia Farnsworth-Grodd, Janie Sheridan, Peter Adams, Natalie Walker

The article is a viewpoint on the virtual approaches to the provision of talking therapies during the COVID-19 pandemic. It refers to exciting and transformative approaches that were adopted as the spread of COVID-19 was observed in New Zealand. These approaches are likely to remain available regardless of availability of face-to-face treatment post COVID, in particular for clients for whom physical access to treatment is limited such as those in rural areas. The aim of the article is to describe some practical issues, concerns and potential solutions to the provision of virtual effective treatment.

Inhaled modified angiotensin converting enzyme 2 (ACE2) as a decoy to mitigate SARS-CoV-2 infection

Rohan Ameratunga, Klaus Lehnert, Euphemia Leung, Davide Comoletti, Russell Snell, See-Tarn Woon, William Abbott, Emily Mears, Richard Steele, Jeff McKee, Andrew Muscroft-Taylor, Shanthi Ameratunga, Natalie Medlicott, Shyamal Das, William Rolleston, Miguel E Quiñones-Mateu, Helen Petousis-Harris, Anthony Jordan

COVID-19 is a new infection for which there is currently no effective treatment and a safe and effective vaccine is at least a year away. We believe the Achilles heel of the virus is a specific protein in the lungs, ACE2, which is needed for infection. We are manufacturing ACE2 molecules to be inhaled to act as a decoy to reduce viral damage to the lungs. If successful these molecules will reduce the severity of infection and prevent deaths in many vulnerable patients. We are a group of clinicians and scientists from all over New Zealand who are using our expertise in this altruistic project and if successful, we will make our technology freely available.

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The Government's proposal to legalise cannabis in New Zealand: 10 key questions

Chris Wilkins, Marta Rychert

A national referendum on the legal status of recreational cannabis use and supply in New Zealand will be held at the next general election in September 2020.[1] The referendum will involve voting to support or oppose the Coalition Government's recently released final draft of the Cannabis Legalisation and Control Bill (CLCB).[2,3] The Government has indicated that they will conduct a public education campaign in the months leading up to the referendum to inform voters about the details of the proposal.[2,3] The aim of this editorial is to highlight a number of key questions arising from the final CLCB release, and to raise wider issues relating to the regulation and enforcement of the proposed legal cannabis market that go beyond the Bill. Our purpose is to stimulate public discussion and inform the upcoming public education campaign. We believe the questions raised will be of interest to readers regardless of whether they currently support or oppose cannabis legalisation.

Overview of the Cannabis Legalisation and Control Bill

As proposed by the CLCB, the purchase and use of cannabis will be restricted to those 20 years or older (two years older than the alcohol purchase age). There will be a daily purchase and possession limit of 14 grams of cannabis per user. Sales of cannabis will be restricted to licensed physical stores only (ie, no mail order or internet sales), and there will also be separate licensed public consumption premises for those who cannot consume at home (eg, people in shared living arrangements or renters). Advertising will be banned except for the provision of objective information (eg, price, product range) and "advice and recommendations" about products from within retail outlets. There will be a home cultivation limit of two cannabis plants per person or four plants per household. Social sharing of up to 14 grams of cannabis will be permitted. The CLCB will prohibit the public consumption of cannabis; the sale of cannabis products with alcohol and tobacco; and any importation of cannabis.

1. What will be the price of legal cannabis?

Alcohol and tobacco research has shown that price is a particularly strong influence on level of consumption and related harm, and, contrary to popular belief, heavy and younger users are particularly sensitive to price.[4–6] Cannabis is essentially a basic agricultural crop, and drug policy analysts have suggested that under legal production conditions its price could conceivably fall to a fraction of the current black market price.[7] The price of legal cannabis in US states has declined by as much as 50% since legalisation, reflecting economies of scale of legal production and growing market competition.[7–9] The CLCB includes a provision to set an excise tax on different cannabis products based on weight and THC content, but no indication of the level of the respective product excise rate (cl269(2)). The key question is will the cannabis excise be similar to beer (approx. 10% retail price) and wine (15%), or more like the excise rate on spirits (38%) or tobacco (76%)? A high legal price for cannabis will reduce legal consumption and harm, and may make non-commercial legal home growing more attractive. Conversely, high legal prices

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may encourage purchasing from the black market. Yet, the legal cannabis market will provide a range of advantages beyond strictly price, including convenience, safety and the absence of legal risk. Legal cannabis regimes that place too high a priority on reducing the black market will encourage weak regulatory regimes that generate high health costs.[10]

One way to address declining prices in legal cannabis markets is to mandate a set minimum price per unit, as has been implemented in some countries for alcohol. The CLCB includes a provision to raise the excise for cannabis for a maximum period of 12 months if the price falls too much (cl263(2)). However, the power is discretionary, time limited, and has no set minimum price for when it would be activated.

2. What will be the maximum potency of products?

Historically, the THC level of cannabis plant material from the black market has been around 5–10%, but enhanced hydroponic cultivation techniques have produced potencies as high as 15–20%.[11,12] In US legal cannabis markets, new cannabis concentrate products with THC levels of over 50–60% have become increasingly popular.[9,14] Studies of higher potency cannabis, including concentrates, have found higher risk of psychosis, psychosis relapse and dependency.[13,14] The CLCB includes a maximum THC potency of cannabis plant of 15% THC (Schedule 8). This cap appears to be at the higher end of the levels currently found in the black market. The CLCB also includes provision for the sale of cannabis edibles and extracts (concentrates), but indicates these products will initially not be approved (Schedule 7). The CLCB includes potency levels for these products (Schedule 8), but they are expressed as milligrams "per unit" and "per package", and these terms are not defined. Furthermore, the potency caps outlined in the CLCB do not appear to apply to home grown cannabis, creating the potential for social sharing of higher potency products and leakage to the black market. The possibility of future concentrate and edible sales raises the question of what will be the cap on potency on these product types. Furthermore, given the evidence of cannabis concentrates overseas, are these products consistent with the harm reduction objectives of the CLCB?

3. How strictly will retail outlets be regulated?

Alcohol and tobacco research has shown that higher outlet density and longer opening hours are associated with higher levels of consumption and harm.[5,15,16] Similar results have been found for proximity to medicinal cannabis dispensaries.[15,17,18] New Zealand's recent attempt to establish a regulated commercial market for so-called "legal highs" under the *Psychoactive Substances Act* 2013 (PSA) highlighted a number of issues with retail outlets.[19] The PSA required the development of Local Approved Products Policies (LAPP) that set minimum physical distances between stores and sensitive sites such as schools (often 500 metres), but the PSA did not include any limits on the number of outlets or opening hours.[19] As a consequence, some central Auckland legal high stores operated on a near 24-hour basis.[20]

Under the CLCB, the central government Cannabis Regulatory Authority is tasked with developing local license premise policies for *every* district and city council in the country (ie, 67 territorial authorities in total). These policies will provide guidance with respect to the location and opening hours of retail outlets (cl16(2)) and must take into account the characteristics of the territory, location of sensitive sites (eg, schools, churches, sports facilities) and whether a retail outlet will reduce the "amenity and good order" of the territory (cl16(3)). The Authority is required to "consult" with "local persons and groups who may be affected" and local government authorities (cl16(6)(7)), but it is not clear what role local government will play and the influence these local groups will have. During the PSA, there were a number of instances where there was a clear disconnect between central government licensing of legal high outlets and local government and community concerns about these outlets, indicating the need for early engagement and communication of policy aims between central and local government.[19,21,22]

4. Which government agency will administer the new sector?

The CLCB establishes the Cannabis Regulatory Authority to regulate the new regime but does not state which government agency will administer the new legal recreational cannabis sector. This will be key to how the sector is perceived and regulated.[23] Government agencies with any kind of economic development mission (ie, business, innovation or tourism agencies) will place greater emphasis on facilitating cannabis business growth and jobs. For example, the gaming machine regime is regulated by the Ministry of Internal Affairs and they have shown a willingness to respond to the needs of the gaming industry.[24] Alternatively, a health agency is more likely to focus on the adverse health outcomes from cannabis use.

5. How will the cannabis infringement scheme be operated?

The CLCB includes provisions for civil infringement fees of $200–$500 (NZD) for exceeding the 14-gram personal possession or purchase limit, exceeding the personal plant cultivation limit, and for public use and public cultivation (Part 3). Higher court fines of up to $1,000 are also included for these offences. Criminal penalties remain for supplying cannabis to underage people (ie, 19 years or younger in this case) (maximum four years imprisonment), selling without a license (up to two years imprisonment), cultivating 10 or more plants (up to three months imprisonment), importing more than 14 grams (up to two years imprisonment), and "dangerous" production of cannabis concentrates without a license (up to two years imprisonment).

The CLCB could thus potentially contribute to the Government's wider aspirations to reduce conviction and imprisonment rates, particularly among Māori.[2] Progress towards this objective will crucially depend on how the infringement scheme is applied, and the willingness of offenders to pay infringements and thereby avoid further punishment through the courts.

In Australia, the introduction of infringement schemes for minor cannabis offences initially resulted in a counterintuitive "net widening effect" where police actually penalised *more* rather than less cannabis users as it was easier for police to issue an infringement notice than proceed with an arrest under the previous approach.[25] Cannabis users were also continued to be convicted and imprisoned for non-payment of infringement notices.[26,27] One way the CLCB could improve the likelihood of payment of infringement fees is to lower the fees set for infringements and/or provide non-financial resolution options, such as attending a cannabis education session or completing community work.

6. How will purchase and possession limits be enforced?

The CLCB proposes a daily cannabis purchase limit of 14 grams per day (considered by officials to be sufficient for a week of regular use) (cl29). It is not clear how such a daily purchasing limit will be enforced in practice without a real-time retail system that includes all retail outlets and collects personal identifying information from buyers to prevent them purchasing the maximum daily quantity from multiple retail outlets. In Uruguay, a biometric system requires registered buyers to submit a thumbprint before making a purchase.[28,29] In New Zealand, police already give cannabis use and possession offences a very low priority,[30] and following cannabis legalisation it is likely that the monitoring of purchase limits will likewise receive low police priority.

7. How will home cultivation be monitored?

The limits outlined in the CLCB on number of plants permitted for home cultivation have been established to prevent exploitation of home-grown production for resale on the black market. In South Australia, organised crime groups sponsored individuals to grow the maximum home grow limit and then combined the crop for sale on the black market.[26,27] The CLCB home plant restrictions will only be credible with some plan of enforcement, but it is not clear what is planned or what agency will carry out this enforcement. Enforcement does not have to be as intrusive as routine home inspections and could involve responding to evidence of syndication and selling of combined crops on the black market. Enforcement of home plant limits also needs to be flexible enough to take account of the requirement for seedlings to maintain two adult plants over the longer term.[31]

8. What health warnings will be required?

The CLCB requires all cannabis products to include mandated health warnings (cl172(1)a). Tobacco research has shown these health warnings can reduce initiation and encourage smoking cessation.[6] The size, text and graphics of the health warnings have been found to be key to their effectiveness for tobacco products.[6]The question is will the same effective standards be applied for legal cannabis products.

9. How will production be monitored?

A key objective of cannabis legalisation is to shrink or even eliminate the black market. One component of this effort is to ensure legal cannabis production is not leaking into the black market and vice-versa.[29] Significant black markets for cannabis have persisted in jurisdictions that have legalised cannabis. For example, in Canada, 40% of cannabis users report purchasing from the illegal market.[32] The most effective way to monitor legal cannabis production is a seed-to-sale system, as established in many US states, which tracks each cannabis plant from seedling to retail sale. This system also provides excellent data to measure total production, illicit diversion, project tax revenue, and track prices and product types.[29] Uruguay has taken this further by requiring users to register and then monitoring their purchases.[29,33] Given the limited data available on cannabis use and markets in New Zealand,[34] these options could be considered, with the appropriate privacy protections, to provide important data to refine regulatory responses. The CLCB includes provisions for a "tracking and recall" system (cl265(h)), but it is not clear whether this will be as comprehensive as a "seed to sale" system that involves tracking individual plants or will be routinely used to monitor production and illicit diversion.

10. What will be the role for non-commercial suppliers?

Experience from the alcohol, tobacco, gambling and most recently, "legal high" sectors indicates commercial operators will focus on expanding sales and targeting key demographics, including youth and heavy users.[5,6,15,35] Commercial cannabis companies in the US have already recognised that daily users are the "backbone" of the industry.[36] There are examples of alternatives to commercial supply of legal cannabis around the world including government monopoly at some level of the market,[33,37] not-for-profit trusts operating retail outlets[24,38] and even cannabis social clubs providing both production and consumption places.[39,40] The advantages of non-commercial suppliers is that they are not focused on expanding the market and have wider social aspirations.

The CLCB largely outlines a "commercial", albeit highly regulated, cannabis sector, but does include options for non-commercial and not-for-profit supply options. These including home cultivation for personal use (cl. 23–28); separate licensing for "micro-cultivation" producers (referred to as "small scale cultivation") (cl58 and cl64); prioritising licensing for cultivators who partner with communities disproportionately harmed by cannabis to generate social benefit and employment (cl85(2)(a-c)); and prioritising, "where practicable", licensing retail distributors who are "not-for-profit applicants that can demonstrate a commitment to delivering social benefit to the community" (cl88(a)). However, it is not clear at this stage what priority and support these social benefit operators will actually receive, and consequently, what the proportion of the larger market they will supply.

It appears the CLCB would not permit cannabis social clubs similar to those that operate in Uruguay, Spain and Belgium.[33,39,40] The CLCB allows home cultivation for personal use and social sharing of up to 14 grams of cannabis with others, but restricts home cultivation to a maximum of four plants per household, seemingly preventing the larger communal crops required for a cannabis social club. New Zealand has a longstanding sub-culture of hobbyist cannabis growers[31] who, as has been seen in Uruguay and Spain,[33] will likely embrace cannabis social clubs, and in doing so, will assist in the transition from black market to legal regime.

Conclusions

This editorial has identified a range of issues related to the CLCB on which the Government could provide further information, including the level of the cannabis excise tax, maximum potency of edibles and concentrates, the government agency to be tasked with administration of the new sector, the proposed production monitoring system, product labeling requirements, and the priority and support that will be given to non-commercial and social benefit suppliers. We recommend the inclusion of a formal minimum price for cannabis, the lowering of the cap on the THC potency of cannabis plant products, a set proportion of licenses for social benefit operators, and a framework to allow the emergence of cannabis social clubs.

Competing interests:
Nil.

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Retrospective analysis of eligibility for denosumab in patients presenting with osteoporotic fractures and renal impairment treated by orthogeriatric service at Middlemore Hospital

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ABSTRACT

BACKGROUND: Little is known about the prevalence of renal impairment in patients presenting with osteoporotic fractures contraindicating bisphosphonate use in New Zealand, and their eligibility to denosumab.

AIM: To assess the prevalence of renal impairment contraindicating bisphosphonate use in older adults presenting with osteoporotic fractures, differences in demographic variables between those with renal impairment and those who do not, and finally to assess eligibility for denosumab based on the current PHARMAC special authority criteria.

METHOD: All patients 65 years and older with osteoporotic fractures treated by inpatient orthogeriatric service (IOS) and the outpatient fracture liaison service (FLS) at Middlemore Hospital between 1 February to 31 April 2019 were assessed. Following data was retrospectively collected—age, sex, ethnicity, preadmission residential status, type of acute osteoporotic fractures, history of previous osteoporotic fractures, cognitive impairment and its severity, history of falls, previous dual-energy x-ray absorptiometry (DEXA) scan and the worst documented T-scores over total hip, neck of femur or L1-4 spine and previous funded anti-resorptive therapy use. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault formula based on the ideal body weight according to the recorded height and serum creatinine level at the time of patient's presentation. Patients with CrCl below 35ml/min were assigned to the renal group, and those with CrCl above 35ml/min to the non-renal group. Current PHARMAC criteria for denosumab was used to assess the eligibility in the renal group.

RESULTS: Total of 190 patients (102 IOS and 88 FLS) were assessed. Thirty-four patients (17.9%) had renal impairment with CrCl less than 35ml/min and were assigned to the renal group. There were no statistically significant differences in demographic variables between the renal and the non-renal group other than for age, where the renal group was significantly older (85.4 vs 77.5 years, P-value <0.0001). Two out of 34 patients were eligible for denosumab. Reasons for ineligibility to denosumab were as follows; not meeting the definition of severe established osteoporosis due to presenting with their first ever osteoporotic fracture (64.7%), no previous DEXA scans to quantify their bone mineral density (11.8%), measured bone mineral density T-score above -2.5 (5.9%); and no preceding treatment with a funded anti-resorptive therapy for at least 12 months prior to their osteoporotic fracture (11.8%).

CONCLUSION: Considerable number of patients aged 65 years and older with osteoporotic fractures also had renal impairment contraindicating the use of bisphosphonates. There were no significant differences in demographic variables between the renal and non-renal group other than for age. Majority of patients in the renal group were ineligible for denosumab based on the current special authority criteria. These results highlight the need for further review and revision of the current PHARMAC criteria to improve access to denosumab in older adults with renal impairment and osteoporotic fractures.

Osteoporosis is a disease characterised by low bone mass, micro-architectural disruption and skeletal fragility resulting in decreased bone strength and increased risk of fracture.[1] Presence of concurrent risk factors such as ageing and hormonal changes associated with menopause means that older adults are particularly affected. The patient-related and healthcare burden of the disease is significant, and in 2007 the combined cost of treating hip and vertebral fractures in New Zealand was estimated to be at least $118 million dollars per annum.[2] Hence, there is a compelling need to prevent fractures associated with osteoporosis. Along with measures to reduce falls risk, pharmacological therapies such as bisphosphonates have been shown improve bone mineral density (BMD)[3] and reduce the risk of osteoporotic fracture,[4] and bisphosphonates are currently used as a first-line therapy for osteoporosis in New Zealand.

However, bisphosphonates are primarily excreted by the kidneys and are contra-indicated in moderate to severe renal impairment with creatinine clearance (CrCl) below 30–35ml/min due to concerns about nephrotoxicity.[5] The limitation of its use in reduced renal function is particularly important in older adults where there is also a considerable co-prevalence of osteoporosis and chronic kidney disease (CKD). A longitudinal study[6] demonstrated that average estimated glomerular filtration rate (GFR) declined by 7.5 ml/min per decade of life. This age-related decline in GFR is further accelerated by commonly encountered comorbidities such as hypertension and diabetes; and high prevalence of CKD seen in older adults is therefore unsurprising.[7] CKD itself is also an independent risk factor for fragility fractures,[8] due to CKD-associated mineral bone disorder (CKD-MBD) arising from various mechanisms, including secondary hyperparathyroidism, vitamin D deficiency and increased oxidative stress.[9] While osteoporosis and CKD-MBD are distinctly separate disease entities which are difficult to distinguish clinically without a trans-iliac bone biopsy, it is nevertheless imperative to address metabolic abnormalities arising from CKD-MBD, which includes correction of calcium and phosphate balance, repletion of vitamin D levels and addressing hyperparathyroidism.[10]

In July 2018, Denosumab was made available as a fully subsidised treatment for osteoporosis in New Zealand. Denosumab is a fully humanised monoclonal anti-receptor activator of nuclear factor kappa-B ligand antibody which induces decreased osteoclast proliferation and bone resorption.[11] In contrast to bisphosphonate therapy, pharmacokinetic and pharmacodynamic properties of denosumab are not affected by renal impairment. Currently, the use of denosumab in New Zealand is regulated by the PHARMAC criteria. Notably, the existing criteria require that a patient has to have 'severe established osteoporosis', which is defined as having measured BMD below 2.5 standard deviation below the young adult mean (ie, T-score of less than -2.5) in the presence of one or more fragility fractures,[12] with severe renal impairment defined as creatinine clearance less than 35ml/min contraindicating the use of zoledronic acid, and "at least one symptomatic new fracture after at least 12 months' continuous therapy with a funded antiresorptive agent at adequate doses", which includes bisphosphonates such as oral risedronate and alendronate, intravenous zoledronate; and raloxifene, a selective oestrogen receptor modulator.[13] There are no studies to date which have evaluated the access to denosumab based on the current PHARMAC criteria in New Zealand.

Therefore in this study we first assessed the prevalence of renal impairment in patients 65 years and older presenting to Middlemore Hospital with osteoporotic fractures contraindicating bisphosphonates use; secondly assessed for any differences in demographic variables between those with renal impairment and those without, and thirdly assessed the eligibility of denosumab among the patients with renal impairment, based on the PHARMAC criteria.

Method

All patients 65 years and older presenting acutely with osteoporotic fractures treated by inpatient orthogeriatric service (IOS) and the outpatient fracture liaison service (FLS) at Middlemore Hospital between 1 February to 31 April 2019 were included. Patients with fractures due to high impact mechanism of injury or due to underlying pathology such as cancers were excluded. For the purpose of this study, World Health Organization definition of osteoporotic fracture was used, which defines it as *"a fracture caused by injury that would be insufficient to fracture a normal bone; the result of reduced compressive and/or torsional strength of bone."*[12] Severity of cognitive impairment was classified into nil, mild cognitive impairment (MCI) and dementia, with dementia being defined as having documented severe cognitive impairment affecting the instrumented activities of daily living (iADL) according to the Lawton iADL scale,[14] and MCI being defined as having milder cognitive impairment without evidence of direct impact on the iADLs. 'Renal impairment' and hence those in the 'renal group' were defined as patients with CrCl below 35ml/min, which is the generally accepted upper threshold for the safe use of bisphosphonates.[15]

Following data was retrospectively collected by reviewing the electronic hospital records, which included discharge summaries and clinic letters: age, sex, ethnicity, preadmission residential status (independent, rest home or private hospital), type of acute osteoporotic fractures defined by site [femur, humerus, wrist, neck of femur (NOF), rib, vertebral, multiple fractures or other]; previous history of osteoporotic fractures; documented history of cognitive impairment and its severity; history of falls within the preceding 12 months; previous dual energy x-ray absorptiometry (DEXA) scan and the worst documented T-scores over total hip, neck of femur or L1-4 spine; and the preceding use of funded anti-resorptive therapy (oral risedronate and alendronate, intravenous zoledronate and raloxifene) of at least 12 months' duration prior to the fracture. CrCl was calculated using the Cockcroft-Gault formula based on the ideal body weight according to their recorded height and serum creatinine at the time of the patient presentation. Patients were then assigned to the renal group (defined as having CrCl below 35ml/min) and non-renal group (defined as CrCl above 35ml/min). Descriptive statistical analysis and statistical tests including paired t-test, Fisher's exact test and chi-square test were used to assess for statistical difference in patient characteristics between the IOS and FLS group, and between the renal and non-renal group. PHARMAC special authority criteria for denosumab was used to assess eligibility in the renal group, and any reasons for their ineligibility were recorded.

Result

Total of 190 patients were included (102 in the IOS group and 88 in the FLS group). Statistically significant differences were seen between the IOS and the FLS groups, with the former being older, having higher proportion of patients admitted from residential care, previous osteoporotic fractures, and higher rates of preceding cognitive impairment. Statistical inference was unable to be obtained for differences in specific type of acute osteoporotic fractures due to low frequency of certain fracture events; however, it is notable that NOF fractures occurred exclusively in the IOS group, and vertebral fractures in the FLS group. Mean CrCl and proportion of patients with CrCl below 35ml/min were similar between the two groups.

Thirty-four patients (17.9% of the study cohort) had CrCl of less than 35ml/min, and therefore were assigned to the renal group. Table 2 describes the comparison of demographic details between the renal and non-renal group. There were no statistically significant differences in demographic variables other than for mean age, where the renal group was significantly older (85.4 vs 77.52 years, p-value <0.0001).

Only two out of 34 patients were eligible for denosumab. As per Figure 1, majority of the patients (82.4%) were ineligible for denosumab as they did not meet the criteria for severe established osteoporosis.

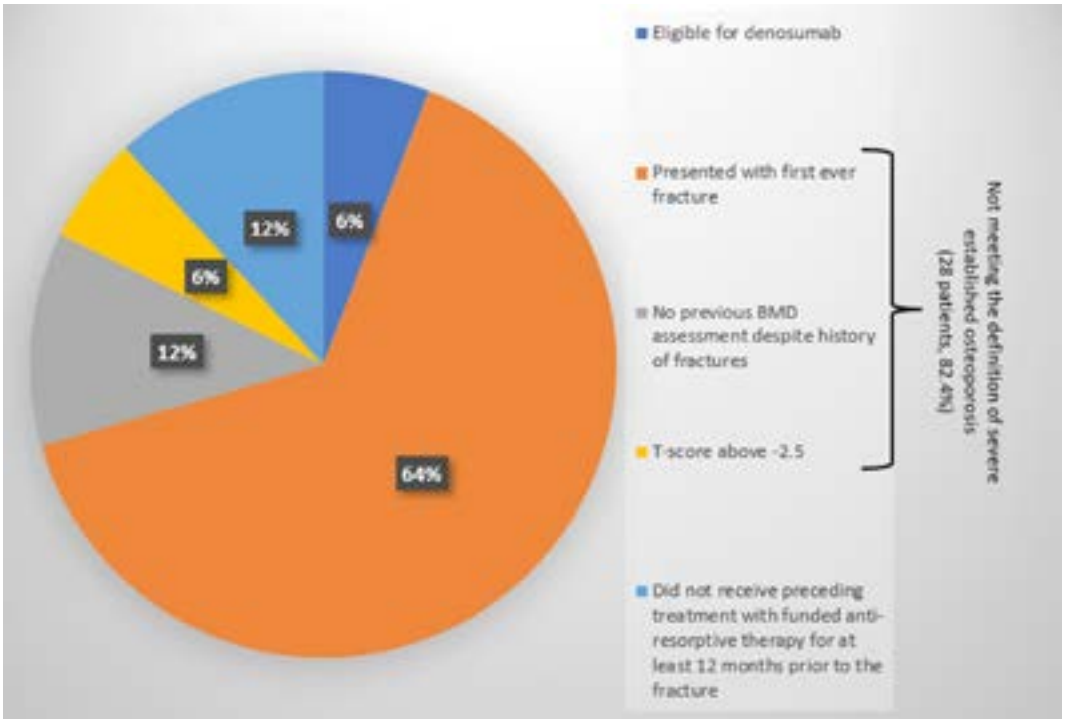
Table 1: Comparison of demographic variables between the IOS and the FLS group.

		IOS (102 patients) N (%)	FLS (88 patients) N (%)	P-value
Mean age (years)		80.7	77.0	0.002
Ethnicity	NZ European	76 (74.5)	58 (65.9)	0.086
	Asian	11 (10.8)	17 (19.3)	
	Pasifika	9 (8.8)	7 (8)	
	Māori	2 (2.0)	4 (4.5)	
	Other	4 (3.9)	2 (2.3)	
Sex	Male	30 (29.4)	24 (27.3)	0.744
	Female	72 (70.6)	64 (72.7)	
Residential care status	Independent	83 (81.4)	84 (95.5)	0.011
	Rest home	8 (7.8)	1 (1.1)	
	Private hospital	11 (10.8)	3 (3.4)	
Type of acute osteoporotic fracture	NOF	54 (52.9)	0	N/A
	Femur	5 (4.9)	2 (2.3)	
	Humerus	6 (5.9)	5 (5.7)	
	Wrist	7 (6.9)	18 (20.5)	
	Vertebral	0	49 (55.7)	
	Ribs	0	5 (5.7)	
	Multiple	10 (9.8)	2 (2.3)	
	Other	20 (19.6)	7 (8.0)	
Preceding history of osteoporotic fractures	Yes	34 (33.3)	15 (17)	0.017
	No	68 (66.6)	73 (83)	
Previous DEXA scan	Yes	20 (19.6)	22 (25)	0.372
	No	82 (80.4)	66 (75)	
Cognitive impairment	Nil	77 (75.5)	80 (90.9)	0.017
	MCI	8 (7.84)	3 (3.4)	
	Dementia	17 (16.7)	5 (5.7)	
History of falls over the preceding 12 months	Yes	15 (14.7)	13 (14.8)	0.990
	No	87 (85.3)	75 (85.2)	
Preceding anti-resorptive therapy use of at least 12 months duration	Yes	26 (25.5)	16 (18.2)	0.226
	No	76 (74.5)	72 (81.8)	
Estimated creatinine clearance (ml/min)	>35	83 (81.3)	73 (83)	0.93
	<35	19 (18.6)	15 (17)	
Mean CrCl (ml/min)		50.6	49	0.6

Table 2: Comparison of demographic variables between the renal and non-renal group.

		Renal (34 patients) N (%)	Non-renal (156 patients) N (%)	P-value
Mean age (years)		85.4	77.5	<0.0001
Ethnicity	NZ European	22 (64.7)	112 (71.8)	0.659
	Asian	6 (17.6)	22 (14.1)	
	Pasifika	4 (11.8)	12 (7.7)	
	Māori	0 (0)	6 (3.9)	
	Other	2 (5.9)	4 (2.6)	
Sex	Male	8 (23.5)	46 (29.5)	0.537
	Female	26 (76.5)	110 (70.5)	
Residential care status	Independent	28 (82.4)	139 (89.1)	0.51
	Rest home	2 (5.9)	7 (4.5)	
	Private hospital	4 (11.8)	10 (6.4)	
Type of acute osteoporotic fracture	NOF	11 (32.4)	43 (27.6)	N/A
	Femur	3 (8.8)	4 (2.6)	
	Humerus	0 (0)	11 (7.1)	
	Wrist	3 (8.8)	22 (14.1)	
	Vertebral	10 (29.4)	39 (25)	
	Ribs	1 (2.9)	4 (2.6)	
	Multiple	3 (8.8)	9 (5.8)	
	Other	3 (8.8)	24 (15.3)	
Preceding history of osteoporotic fractures	Yes	12 (35.3)	37 (23.7)	0.16
	No	22 (64.7)	119 (76.3)	
Previous DEXA scan	Yes	9 (26.5)	33 (21.2)	0.50
	No	25 (73.5)	123 (78.8)	
Cognitive impairment	Nil	25 (73.5)	132 (84.6)	0.26
	MCI	3 (8.8)	8 (5.1)	
	Dementia	6 (17.4)	16 (10.3)	
Preceding history of falls over 12 months	Yes	7 (20.6)	21 (13.5)	0.292
	No	27 (79.4)	135 (86.5)	
Preceding anti-resorptive therapy use of at least 12 months duration	Yes	12 (35.3)	30 (19.2)	0.065
	No	22 (64.7)	126 (80.8)	

Figure 1: Eligibility for denosumab under the current special authority criteria in the renal group.



Discussion

This retrospective study was conducted on patients aged 65 years and older presenting with osteoporotic fracture treated at Middlemore Hospital in South Auckland, New Zealand. The orthogeriatric service at Middlemore Hospital serves a large catchment population of over 500,000 patients within the Counties Manukau region and has two major arms. IOS consists of two full-time consultant orthogeriatricians and an orthogeriatric registrar based on the orthopedic ward who provide medical support and facilitate expedited transfer to the rehabilitation service for all inpatient orthopedic patients aged 65 years and above; and FLS liaises with the Middlemore Hospital radiology service and identifies all patients with osteoporotic fractures and coordinates investigations and treatment for osteoporosis as an outpatient basis. Distinctive roles of these two services explain the significant differences in the patient characteristics seen, as the older and frailer patients with hip fractures necessitates inpatient surgical management, while as those with fractures involving non-major sites such as the vertebra and upper limb can often be managed as outpatient basis. Both IOS and FLS group consisted predominantly of New Zealand Europeans and female sex, which is consistent with the observed demographic trend associated with osteoporosis in New Zealand.[2] A point of interest is that there were no significant differences in demographic variables between the renal and non-renal group other than for age, which would otherwise alter conventional approach in management of osteoporosis.

Thirty-four patients (17.9%) had severe renal impairment contraindicating the use of bisphosphonates. A previous study[16] assessing the prevalence of CKD in women with osteoporosis aged 50 years and older using the MDRD (Modification of Diet in Renal Disease) equation showed that around 3.59% had GFR of less than 35ml/min. Although not directly comparable, considerably higher prevalence of renal impairment in our study is most likely explained by older age of the screened population and the different methods of estimating the renal function.

Out of 34 patients, only two (6%) were eligible for denosumab. The most common reason for ineligibility to denosumab was not meeting the definition of severe established osteoporosis (having an osteoporotic fracture as well as having a documented T-score of -2.5 and lower). When the reasons for not meeting this definition was further

assessed, the most common reason (64%) was due to patients presenting with their first ever osteoporotic fracture (which meant that they did not have a preceding BMD assessment with a DEXA scan) followed by four patients (12%) who did not have a preceding BMD assessment despite having a preceding history of osteoporotic fractures, and two patients (6%) whose BMD severity was above the T-score of -2.5 threshold, therefore not meeting the definition of severe established osteoporosis. Four patients (12%) were ineligible for denosumab despite meeting the criteria for severe established osteoporosis as they did not receive at least 12 months of treatment with a funded anti-resorptive therapy prior to their new fracture.

In light of above findings, two important barriers in accessing denosumab on the current PHARMAC criteria will be discussed. Firstly, many of these patients would require a BMD assessment with a DEXA scan as a part of their assessment of eligibility for denosumab. Currently, Counties Manukau District Health Board has a single DEXA scan reported by two orthogeriatricians for its older adult catchment. DEXA scan is therefore a limited resource, being prioritised for those with documented osteoporotic fractures and risk factors for secondary osteoporosis, and routine DEXA scanning to assess the risk of osteoporosis in otherwise well subjects is currently not feasible. It is also important to mention that access to publicly funded DEXA scan is widely variable across New Zealand, and therefore mandatory BMD assessment is likely to be a greater barrier for some more than the others. Of note, over half of the patients in the renal group (27 patients, 58.9%) were 75 years and older and therefore would have qualified for funded treatment with bisphosphonates without the need for a DEXA scan if it were not for their renal impairment.[17] Secondly, the current denosumab criteria stipulates that their current fracture should have occurred after at least a 12-month course of a funded antiresorptive agent. However, various reasons including pre-existing reduced renal function and adverse drug reaction could have precluded the completion of treatment duration.

Out of the currently funded anti-resorptive therapy options in New Zealand, raloxifene is an option for treatment of osteoporosis complicated by renal impairment. Clinical trials have shown that the blood levels of raloxifene and its metabolites were not affected by renal function in women with CrCl as low as 21 ml/min.[18] However, raloxifene has been shown to have only modest efficacy by reducing vertebral fracture risk without affecting the non-vertebral fracture risk[19] and was less effective than oral alendronate in improving BMD.[20] In comparison, FREEDOM trial demonstrated that denosumab improved BMD as well as reduce vertebral and non-vertebral fracture risk including hip fracture risk,[21] and denosumab was also shown to improve BMD over oral alendronate in a modest but statistically significant manner.[22] Post-hoc analysis of the FREEDOM trial also demonstrated that reduction in fracture risk and improvement in BMD did not differ significantly by the level of the kidney function.[23] It is worth keeping in mind however that FREEDOM trial only had 73 women with stage four CKD (estimated GFR of 15–29ml/min) with low rates of fracture events, and included no women with estimated GFR below 15ml/min. Severe hypocalcaemia is also a known adverse event more commonly associated with use of denosumab in reduced renal function,[24] which also needs to be taken into account.

This study is a first locally based study assessing the prevalence of renal impairment in patients presenting with osteoporotic fractures aged 65 years and above, and their eligibility for denosumab based on the current PHARMAC special authority criteria. It is appreciated that further research is needed to determine the long-term efficacy and safety of denosumab in CKD. However, these results raise the importance of ongoing discussion around the need to improve treatment options for older adults with osteoporosis complicated by renal impairment. While this study was not designed to look at the appropriateness of use of denosumab in the patients with renal impairment, baseline screening for concurrent CKD-MBD and wider consideration of patients' comorbid status and life expectancy still stands.

The main strength of this study lies in its clearly defined pre-study questions and inclusion/exclusion criteria for the study population, and inclusion of important variables such as residential care status and cognitive impairment, which are relevant in

a geriatric research setting. Main limitations include its retrospective study design, which lends itself to bias resulting from coding of diagnoses such as cognitive impairment and falls history. This study used Cockcroft-Gault formula to estimate the renal function, given that many of the drug dosing recommendations are still based on the Cockcroft-Gault formula on a historical basis,[25] and due to the perceived issue with acute kidney injuries in acutely admitted IOS patients preventing eGFR calculation using other methods such as the CKD-EPI equation. Limitations of estimating renal function using the Cockcroft-Gault equation is well appreciated,[26] and the prevalence of renal impairment in the study population may differ if the renal function was measured using gold standard markers such as inulin.

Conclusion

Prevalence of renal impairment contraindicating bisphosphonate use among patients 65 years and above presenting with an osteoporotic fracture was considerable. No statistically significant differences in demographic variables were seen between the renal and non-renal group apart from age. Majority of these patients were not eligible for funded treatment with denosumab based on the current special authority criteria. We identify a clear gap in access to treatment for older adults with renal impairment and osteoporotic fractures, and our study indicates that further review and revision of the current PHARMAC criteria is necessary in order to improve access to denosumab in this vulnerable cohort.

Competing interests:
Nil.

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Increasing burden of advanced hepatocellular carcinoma in New Zealand—the need for better surveillance

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ABSTRACT

BACKGROUND: Regular surveillance for hepatocellular carcinoma (HCC) in patients with chronic hepatitis B viral (HBV) infection and hepatitis C (HCV) cirrhosis improves survival by earlier detection of the cancer at an earlier stage when curative intervention may still be possible. We compared patient characteristics, surveillance history and outcomes in patients presenting with advanced HCC secondary to HBV and HCV.

METHOD: In this retrospective study, clinical databases and notes were reviewed in all cases of advanced HCC related to HBV or HCV referred to the tertiary HCC service in Auckland, New Zealand between 1 January 2003 and 31 December 2017.

RESULTS: Over the 15-year period, 368 patients were referred with advanced HCC secondary to HBV (HBV-HCC) and 278 secondary to HCV (HCV-HCC), representing over 50% of all cases of HCC cases secondary to viral hepatitis. Of these 646 patients with advanced HCC, 75% of patients were not receiving guideline-recommended surveillance. More patients with advanced HBV-HCC were diagnosed with HCC prior to the diagnosis of HBV, compared to patients with advanced HCV-HCC (40% vs 28%, $p<0.01$). Fewer patients with previously diagnosed HBV infection were undergoing HCC surveillance than patients with previously diagnosed HCV infection (26% vs 42%, $p<0.01$). Late diagnosed patients had the worst outcomes, with 88% receiving palliative care and surviving on average only seven months (HBV five months vs HCV eight months, $p=0.05$).

CONCLUSION: Survival in New Zealanders with hepatocellular carcinoma remains poor because the cancer is incurable in most patients at the time of detection. Because most cases are secondary to chronic hepatitis B and C infections, improved screening and linkage to antiviral therapy and HCC surveillance should improve outcomes.

Viral hepatitis accounts for the vast majority of newly diagnosed hepatocellular carcinoma (HCC) worldwide.[1] In 2012, there were 770,000 cases of HCC, of which 56% were attributable to hepatitis B virus (HBV) and 20% to hepatitis C virus (HCV).[2] In New Zealand, of the 2,601 HCC cases recorded at the tertiary HCC database in Auckland City Hospital between 1998 and 2019, 51% and 34% were due to HBV and HCV respectively.[3] The bulk of the remainder of aetiologies are split between alcoholic liver disease and non-alcoholic steatohepatitis. In Australia, 22% of HCC is attributed to HBV and 41% to HCV.[4] The American, Asian and European liver societies[5–7] recommend surveillance with six-monthly liver imaging and alfa fetoprotein (AFP) in patients with viral hepatitis at high risk for development of HCC, as it is known to improve survival through earlier detection of tumours potentially amenable to curable treatments.[3,8]

Unfortunately, many cases of viral hepatitis either remain undiagnosed or without appropriate HCC surveillance, contributing

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to advanced presentations. In New Zealand, it is estimated in 2019 that 50% of the estimated 100,000 patients living with chronic HBV infection and 40% of the estimated 45,000 patients living with chronic HCV infection remain either undiagnosed or lost to follow-up (Gane, personal communication). In Australia, 43% of the estimated 218,567 patients with chronic HBV infection and an estimated 25% of the over 230,000 patients with chronic HCV infection are undiagnosed.[9,10] Despite the introduction of universal neonatal vaccination in New Zealand in 1988, the prevalence of HBV is still increasing due to high rates of adults migrating from countries with endemic HBV, in particular Asia and the Pacific. Over the next two decades, the proportion of Asian ethnicities in New Zealand is projected to increase from 12% to 22% and Pacific Island ethnicity from 8% to 10%.[11]

Antiviral treatment in HBV and HCV viral eradication confers up to a 75% decrease in risk of HCC.[12,13] Although recent unrestricted funding of safe and effective direct acting antiviral therapy will rapidly reduce the prevalence of HCV, the number of HCV-HCCs will continue to increase until 2030 due to the large number of at-risk patients who had established cirrhosis prior to treatment.[14]

Compared to patients with HCV-HCC, those with HBV-HCC are younger, have less advanced fibrosis and often have a family history of HBV-HCC.[15] There are many other clinical and molecular differences between the two groups. However, few studies have compared the outcomes of patients with HBV-HCC and those with HCV-HCC.[16]

Regular six-monthly surveillance of high-risk patients should help enable detection of HCC at an early stage when curative treatment is possible. Therefore, higher rates of diagnosis, assessment and recruitment into HCC surveillance programmes of patients living with HBV or HCV is needed to improve outcomes. However, population data on uptake of appropriate surveillance is not readily available due to scale and logistical issues.[9] Understanding which steps in the process are failing is fundamental to inform public health, medical professionals and patients alike as to where improvement efforts can be focused. For example, a previous study noted 38% of patients with HCC missed surveillance due to a lack of surveillance orders from the provider, with only 3% due to patient non-compliance.[17] The aim of this study was therefore to review cases of advanced HCC secondary to HBV and HCV to examine differences in demographics, focusing on surveillance method of detection, but also subsequent treatments and survival.

Methods

We completed a retrospective cohort study of all cases of advanced HCC referred to the tertiary New Zealand HCC service over a 15-year period between 1 January 2003 to 31 December 2017. During this period, the total number of HCC reported was 1,818, of which 540 (30%) were HCV-related and 705 (39%) HBV-related. This service was introduced in 1998, where new HCC cases are requested to be referred by the responsible secondary care service through videoconferencing to a weekly multidisciplinary meeting at the New Zealand Liver Transplant Unit based in Auckland. Confirmation of diagnosis, treatment and management plans are then decided.

Advanced was defined as patients who were not eligible for curative therapy and who were treated with trans-arterial chemoembolisation (TACE), sorafenib (non-funded in New Zealand), or novel antitumour therapies through a clinical trial, or who received best supportive palliative care.

The HBV cohort included patients with positive hepatitis B surface antigen (HBsAg) at the time of advanced HCC diagnosis. The HCV cohort included those with current or previous Hepatitis C infection.

Patients were excluded if they had had a prior diagnosis of HCC, were not New Zealand residents, or if they were diagnosed with HCC prior to migrating to New Zealand.

A complete list of all patients with HCC from the prospectively maintained clinical database was obtained and only those meeting inclusion criteria retained. Patient demographics, dates of definitive HCC diagnosis, treatment modality and date of death, if applicable, was collected and abstracted in a standardised fashion. For detailed assessment of method of HCC surveillance, patients were grouped into four categories:

1. No known diagnosis of HBV/HCV infection prior to the diagnosis of HCC. This definition includes 'late hepatitis notification', defined as diagnosis as at the time or within two years before HCC diagnosis.[18]
2. Known HBV/HCV and met criteria for HCC surveillance but did not receive this (defined as not having had liver imaging for >2 years). For HBV, we included patients who were either cirrhotic or had a positive family history of HCC. For HCV, we only included patients who were cirrhotic (as stated on clinical correspondence, not inferred from investigation).
3. Known HBV/HCV diagnosis and receiving suboptimal HCC surveillance (defined as; for HBV: AFP without liver USS in patients who are cirrhotic or have a positive family history of HCC; or received their surveillance outside the recommended time-period). For HCV: receiving intermittent imaging only outside the recommended 6 monthly interval.
4. Known HBV/HCV diagnosis and receiving optimised HCC surveillance.

If the above information was not explicit from the referring physician, patient records were retrieved from the hospital and reviewed. These records included general practitioner referral letters and secondary care clinic letters. For patients with HBV, this also included review via the New Zealand national hepatitis foundation.

Patient and disease characteristics were summarised using descriptive statistics, including means or 95% Confidence Intervals (CI) for continuous measurements and frequencies or percentages for categorical measurements. Comparative analysis between groups was performed using the chi-square test for categorical variables. When values were smaller than 5 the Fisher's exact test was used. For normally distributed continuous variables the Student t-test was used to determine significance. Stepwise multivariable logistic regression was used to estimate Odds Ratios (ORs) and 95% CIs for surveillance. Survival from the time of HCC diagnosis was estimated by the Kaplan-Meier method and difference between groups assessed by the log-rank test. The Cox proportional hazards model was for multi-variate survival analysis. Statistical significance was defined as a two-tailed p value <0.05. Data analysis was performed using IBM SPSS Version 23.0. Armonk, NY: IBM Corp.

This study received institutional ethics approval by the Auckland District Health Board research review committee.

Results

Over 15 years from 2003 to 2018, 368 patients were diagnosed with advanced HBV-HCC due to HBV and 278 with HCV-HCC. This represents over 50% of cases of HBV-HCC and 54% of cases of HCV-HCC who were diagnosed during the study period.

Table 1: Baseline characteristics for HBV and HCV patients.

	Diagnosis		**P value**
	HBV (n=368)	**HCV (n=278)**	
Age at death (mean), years	59.1	59.9	0.41
Sex, male	305 (82.9)	231 (83.1)	0.94
Ethnicity n, (%)			
Māori	164 (44.6)	65 (23.4)	<0.01
Pacific	119 (32.0)	7 (2.58)	
Asian	56 (15.2)	19 (6.8)	
NZ European	20 (5.4)	177 (63.7)	
Other	9 (2.4)	10 (3.6)	

HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; NZ: New Zealand.

Table 1 demonstrates the characteristics of the two groups. Gender and age at death were similar for both groups. The majority of patients with HBV were Māori, Pasifika or Asian (45%, 32% and 15% respectively), while the majority of HCV patients were NZ European (64%) or Māori (23%) (P<0.01).

Differences between patients with HBV and HCV in terms of surveillance, treatments and survival from time of HCC diagnosis is shown in Table 2. Overall only 74 out of 646 (11.5%) patients were alive at their last follow-up. In patients who had been diagnosed with chronic viral hepatitis before the development of HCC, those with HBV-HCC were less likely to have either never received surveillance (26% vs 42%), but more likely to have received suboptimal surveillance (12% vs 2.5%) when compared to those with HCV-HCC (p<0.01). Also, undiagnosed viral hepatitis was more common in patients with HBV-HCC than those with HCV-HCC (40% vs 28%).

More patients with HCV were eligible for TACE and survived a mean of 2.3 months longer, p=0.03.

Table 3 demonstrates the breakdown of surveillance factors. Overall, only 25% of patients received optimised, guideline-recommended surveillance. There were significant differences between groups in terms of non-curative treatments offered and overall survival (p<0.001) (Figure 1). Patients without a known diagnosis of viral hepatitis had the worst outcomes, with 88% receiving palliative care and surviving on average only seven months.

There were no significant predictors of patients receiving optimised surveillance on univariate or multivariate analysis (Table 4).

Discussion

This study highlights the disparate outcomes of patients with late diagnosis of HBV and HCV. The high rate of undiagnosed viral hepatitis in this cohort of advanced HCC for HBV (40%) and HCV (28%) is similar to that reported in an Australian study (38% and 22%) and a recent Canadian study (46% and 31%).[18,19] The importance of this data is magnified by the associated outcome analysis, which illuminates the extremely poor outcomes for this patient subgroup, with patients surviving a mean of only seven months after HCC detection. This study, which focused on patients with advanced HCC was warranted given viral hepatitis is the most common overall cause of HCC, and most cases of HBV-HCC and HCV-HCC are detected at a late stage when treatment options are few and survival is poor.

These findings highlight the need for earlier identification of New Zealanders living with HBV and HCV to enable effective antiviral therapy to prevent progression to cirrhosis and to institute appropriate HCC surveillance in patients with risk factors.

Table 2: Surveillance Factors for HBV and HCV patients with treatment and survival.

	Diagnosis		
	HBV (n=368), %	**HCV (n=278), %**	**P**
Surveillance group			
1	146 (39.7)	79 (28.4)	<0.01
2	95 (25.8)	116 (41.7)	
3	44 (12.0)	7 (2.5)	
4	83 (22.6)	76 (27.3)	
Treatment			
TACE	75 (20.4)	81 (29.1)	<0.001
Palliative	293 (79.6)	197 (70.9)	
Survival, median (months) (95% CI)	5.2 (4.0–6.4)	8.3 (6.3–10.2)	0.05

TACE: Transarterial chemoembolisation.

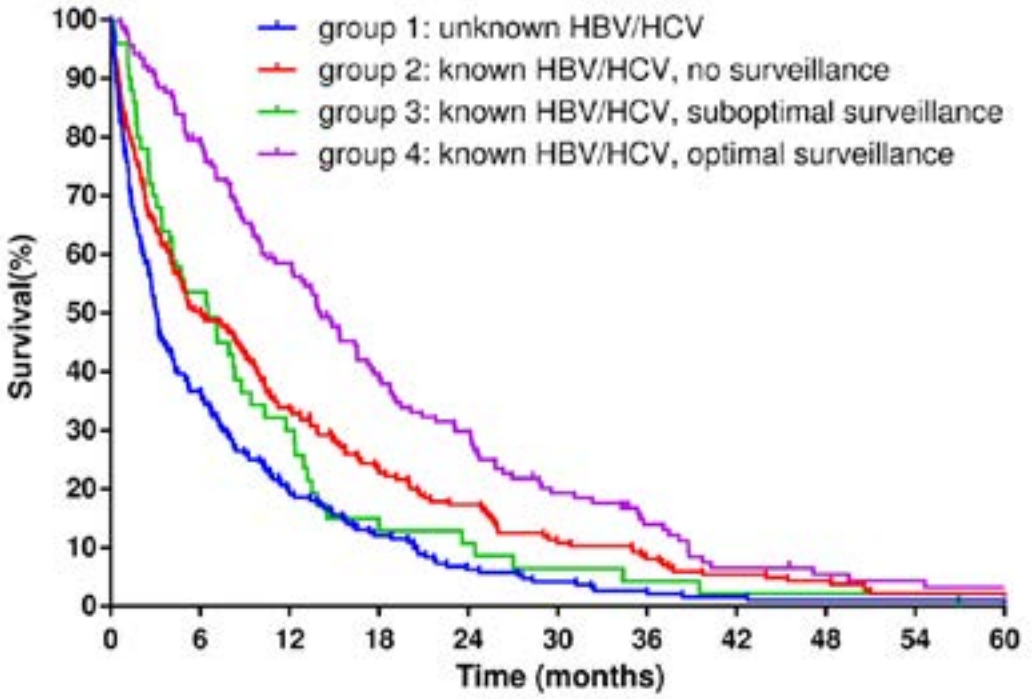
Table 3: Demographic and clinical characteristics of surveillance factors.

Surveillance factor, %	**1 (n=225) 34.8**	**2 (n=211) 32.7**	**3 (n=51) 7.89**	**4 (n=159) 24.6**	**P value**
Age at death (mean)	58.6	59.9	58	60.6	0.11
Gender					
Male, n (%)	185 (82.2)	177 (83.9)	42 (82.4)	132 (83.0)	0.77
Ethnicity, n (%)					
NZ European	51 (22.7)	85 (40.3)	8 (15.7)	53 (33.3)	0.003
Māori	81 (36.0)	67 (31.8)	22 (43.1)	59 (37.1)	
Asian	26 (11.6)	26 (12.3)	6 (11.8)	17 (10.7)	
Pacific	59 (26.2)	28 (13.3)	14 (27.5)	25 (15.7)	
Other	8 (3.6)	5 (2.4)	1 (2.0)	5 (3.1)	
Treatment, n (%)					
TACE	29 (12.9)	48 (22.7)	10 (19.6)	69 (43.4)	<0.001
Palliative	196 (87.9)	163 (77.3)	41 (80.4)	90 (56.6)	
Survival median, months (95% CI)	3.1 (2.5–3.6)	6.0 (3.6–8.5)	6.5 (3.0–10.0)	14.1 (11.3–16.8)	<0.001
Survival 25 percentile (SD)	9.3 (1.3)	16.6 (2.0)	13.0 (1.0)	25.8 (2.2)	
Survival 75 percentile (SD)	1.1 (0.2)	1.9 (0.3)	2.6 (0.6)	7.0 (1.1)	

Table 4: Analysis of predictors of surveillance (Groups 4 compared to 1,2,3).

	Univariate analysis		**Multivariate analysis**	
Variable of interest	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age at death	1.01 (0.99–1.03)	0.18	1.01 (0.99–1.03)	0.22
Gender (Male)	1.00 (0.62–1.62)	0.99	1.04 (0.61–1.80)	0.88
HCV	1.29 (0.90–1.85)	0.16	1.09 (0.64–1.86)	0.75
NZ European	1.19 (0.81–1.75)	0.37	0.84 (0.27–2.61)	0.77
Māori	1.10 (0.76–1.60)	0.62	0.88 (0.29–2.66)	0.82
Asian	0.89 (0.50–1.57)	0.68	0.54 (0.16–1.87)	0.33
Pacific	0.71 (0.44–1.15)	0.17	0.76 (0.23–2.45)	0.64

Figure 1: Kaplan Meir survival curve of survival based on surveillance group.



High-quality population-level data on HCC is scarce. In particular, there is limited information on Pasifika population outcomes as no data is available from Oceania other than Australia.[20] This paper is designed to complement and combine data from our work to illuminate these issues with viral hepatitis in our country.[21,22] We have previously shown that for our total New Zealand HCV-HCC cohort, HCC is detected through routine surveillance in 44%.[21] This routine surveillance improved overall survival, OR 0.41 (95% CI [0.32, 0.53], p<0.0001), with an overall mean survival of 91.5 months (95% CI 76.4,106.6) compared to 43.0 (95% CI 34.2,51.9) for those patients not receiving regular surveillance. Patients who received regular surveillance had a significantly greater chance of receiving curative modality treatments than those who didn't, OR 5.68 (95% CI [3.80, 8.50], p<0.001). With such compelling figures, reinstituting the prematurely halted HBV national testing programme[23,24] and commencing a national HCV testing programme must be seriously considered.

In New Zealand, most patients presenting with advanced HBV-HCC and HCV-HCC are male and die in their late 50s, within one year of diagnosis. The majority of patients (92%) with HBV-related HCC were Māori, Pacific or Asian, with only 5% New Zealand European. Māori are overrepresented in advanced HCC due to both HBV and HCV at 45% and 23% respectively. Māori only represent 15% of the population and have an HBV prevalence of 5.8%, much lower than Chinese (9.1%) or Pasifika populations (8.5%).[24] Māori have a higher prevalence of HCV given increased frequency of risk factors for infection than non-Māori (Gane, personal communication). This over-representation must represent a huge gap in access to surveillance and treatment. Patients with HBV-HCC and HCV-HCC are often primary income earners for large families in low deciles[25] with far reaching impacts on not only family (whānau) but also communities.

As could be expected within this cohort of patients, the vast majority did not receive guideline recommended surveillance, including those with prior diagnosis of chronic viral hepatitis. Certainly, high deprivation index may be a barrier to appropriate medical care. In addition, poor awareness of the risks of HCC both in patients and healthcare workers may contribute to low

surveillance uptake. Previous studies both internationally and locally have noted that HCC surveillance is difficult to apply in practice.[9,26,27] Implementation in New Zealand of a national surveillance standard with clear criteria is needed. In the 1980s, the Japanese Ministry of Health implemented the world's first nationwide surveillance program because of increasing incidence of HBV-HCC and HCV-HCC cases. This initiative has resulted in significant improvements in outcomes in patients with HCC.[28]

Compared to patients with HBV-associated HCC, more patients with HCV-associated HCC were not receiving any surveillance at the time of HCC diagnosis (42% vs 26%) $p<0.01$. This difference may reflect the work of the New Zealand Hepatitis B Foundation, which aims to track, monitor and refer patients with HBV as necessary.

One quarter of cases of advanced HCC were in patients who were receiving recommended surveillance with a similar proportion from both HBV (23%) and HCV (27%) groups. This outcome reflects the limitations of our current techniques with insensitivity of AFP and imaging modalities, which is predominately ultrasound. Aggressive tumour biology may also be contributory. It is still important to note that within this group, 44% were still able to be offered TACE, and there was an additional average 12-months' survival compared to those patients who were newly diagnosed. Patients with HCV survived on average 2.3 months longer, likely secondary to the larger number who received TACE (29% vs 20%). In one series, patients with HBV-related HCC were less likely to be eligible for curative treatment (14% vs 34%, $p<0.05$)[15] compared to HCV patients, however our cohort was more even at 50% HBV, 46% HCV.

There has been controversy as to whether HCC surveillance confers any survival benefit in the overall population at risk for HCC.[29] Only one randomised controlled study has demonstrated survival benefit of HCC surveillance in the screened population, even when transplantation was not available and the resection rate in both groups was extremely low.[8] This was because most HCCs detected in the screening group were small and much more likely to be cured, while most HCCs in the control arm were advanced and only detected after the patient presented with symptoms such as pain, weight loss or complications of portal vein invasion. The only other randomised trial was stopped because of lack of recruitment.[30] However, a recent analysis of 38 observational studies of 10,904 patients with cirrhosis reported significant benefit of HCC surveillance on patient survival (51% vs 28%).[5] Although the incidence of HCC was similar, the proportion of HCCs that were detected at an early stage and offered curative therapy was higher in patients receiving HCC surveillance (62% vs 38%). The practice of HCC surveillance is also supported by multiple retrospective studies in patients with HCC, demonstrating superior survival in those patients receiving HCC surveillance that is maintained even after correction for a lead-time bias of up to four years.[31–33]

Limitations of this study include absence of important data regarding tumour stage or staging classifications, severity of underlying liver disease or co-morbidity. As this study focused on surveillance modality, possible additional important co-factors previously noted to be significant in HBV and HCV associated HCC such as mental illness, frequency of physician visits or rural or metropolitan residence was not recorded.[18,19] Additional possible missed cases of patients that were not referred to the tertiary HCC service and palliated locally are thought to be low, and will not be captured by this data.

Strengths of this study lie in the long-term follow-up and accuracy and completeness of the data because all cases were reviewed by a central HCC multidisciplinary meeting, which provided consistency of diagnosis, investigation and subsequent management and treatment plans with core staff, Individual case review, including inclusion of information from primary and secondary care allowed insight into surveillance practice that population-based studies do not allow. One designated tertiary referral service for the country afforded us consistency of diagnosis, investigation and subsequent management and treatment plans.

Better outcomes for patients with HCC can only be achieved through early detection when curative intervention is possible. Earlier diagnosis of HBV and HCV infection through public awareness and universal screening programmes would allow both

earlier detection of those at risk for HCC and also could prevent cirrhosis through improved linkage to antiviral therapy. All HBV patients should be offered enrolment in the community-based Hepatitis Foundation national surveillance programme. HCC surveillance in patients with HBV should be expanded from the current recommendations for those with cirrhosis or family history of HCC to include all HBsAg+ with severe fibrosis or cirrhosis (liver stiffness measurement >8 kPa); all HBsAg+ males over 40 years and all HBsAg+ females over 50 years as recommended by the American Association for the Study of Liver Diseases (AASLD) guidelines.[34] A pilot study should be conducted to determine the utility of the two HCC risk scores which have been validated in Asian populations—the REACH B predictive HCC risk score in patients not on nucleos(t)ide analogue (NUC) therapy and the REAL-B predictive HCC risk score in patients maintained on NUC therapy.[35,36] In addition, the New Zealand Society of Gastroenterology is currently preparing national HCC surveillance guidelines for all primary and secondary care.

New Zealand is one of the 194 member states to adopt the 2016 World Health Organization (WHO) strategy to eliminate viral hepatitis as a major public health threat by 2030. The current national HCV action plan and proposed HBV action plan will aim to find the remaining undiagnosed cases. If the current AASLD HCC surveillance recommendations are adopted (six-monthly AFP and ultrasound in all HBV cases over 40 years and all HCV cirrhotics), this would total almost 140,000 ultrasounds per annum. Surveillance has been shown to be cost effective compared to no surveillance, with a cost effectiveness ratio comparable to currently implemented screening strategies including colonoscopy and mammography.[37,38] Appropriate funding will need to be provided for this increased demand on secondary care radiology services.

Conclusion

More than half of new diagnoses of viral hepatitis related HCC in New Zealand are diagnosed at an advanced stage. Despite the many differences between HBV and HCV, patients with advanced HCC share similar challenges with regard to poor surveillance and rapid demise. The largest challenge lies in those patients who remain undiagnosed, highlighting the need for educating and reinforcing to practitioners the importance of surveillance in those with risk factors to help reduce the incidence of patients presenting with advanced HCC.

Competing interests:
Nil.

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Cannabis-based medicinal products in arthritis, a painful conundrum

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ABSTRACT

AIMS: The changing medicolegal climate regarding the medicinal use of cannabinoids in New Zealand will increase the likelihood of patients consulting general practitioners (GPs) about these products. Arthritis is a common medical condition for which cannabis-based products are promoted and used; however, doctors' knowledge about the efficacy and safety of these products in the setting of arthritis may be limited.

METHODS: We undertook a rapid review of the medical literature on cannabis-based medicinal products in arthritis.

RESULTS: Animal studies have identified endocannabinoid pathways in arthritis that are potentially amenable to interventions. One randomised placebo-controlled trial of Sativex® in adults with rheumatoid arthritis has shown some improvements in pain but not in comparison with a standardised pharmacological treatment regimen. Systematic reviews of cannabis-based products in arthritis have determined that there is currently insufficient evidence to recommend cannabis-based medicines for routine clinical use. There were five ongoing registered clinical trials of cannabis-based products in arthritis, the results of which are yet to be reported.

CONCLUSIONS: While animal models have identified possible endocannabinoid pathways in arthritis, there is no clear evidence of benefit in humans or comparative efficacy with current treatments. At this stage, there is little evidence to support GPs prescribing cannabis-based medicinal products for arthritis.

The legal climate regarding the medicinal use of cannabinoids and the public advocacy for access to cannabis-based medicinal products has been changing over the years. With the advent of the Misuse of Drugs (Medicinal Cannabis) Amendment Act,[1] it is increasingly likely that general practitioners (GPs) will encounter patient requests for advice and prescription of cannabis-based medicinal products in daily practice.

Patients often consult the internet ('Dr Google') prior to their GP visit[2,3] and are able to find a wealth of information about medical conditions and treatments.[3] A Google search on the therapeutic potential of cannabis for arthritis using the terms 'cannabis for arthritis' and 'cannabidiol (CBD) for arthritis' generates more than nine million and 24 million results respectively. This may generate high expectations in patients about the clinical utility of cannabis-based products for management of chronic pain arising from their arthritis and possible cure. However, websites vary enormously in purpose and design, many are commercial companies advertising their wares, and may pay little attention to published and peer-reviewed evidence of efficacy and possible adverse effects of the products they list.

Osteoarthritis (OA) is a common disorder seen in GP practice.[4,5] Chronic pain and the imperfect treatment options such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids and antidepressants with their respective side effect profiles may encourage patients to look for other options to reduce their pain.[6] Musculoskeletal pain is one of the most common reasons cited by users of cannabis in a number of jurisdictions including Canada, where 65% of Health Canada authorised users of medicinal herbal cannabis diagnosed with 'severe arthritis',[7]

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and Colorado where 93% of users are registered for 'severe pain'.[8] Arthritis pain has been cited as a reason for cannabis use in over one-third of users in Australia.[9]

In this article we will focus on an imaginary consultation with a 65-year-old patient with a history of moderate to severe OA of the knee. She has been awaiting a knee replacement for two years, and is unhappy with her current pain treatment, which includes paracetamol, NSAIDs and codeine as required. She suffers from frequent breakthrough pain. She now walks with the aid of a walking stick, and feels the pain significantly impacts her quality of life. She visits her GP to seek advice about cannabis-based products for her arthritis, as she read good stories about this 'natural product' for pain on the internet, and believes it has less side effects than the painkillers she is currently taking. She wonders whether it may be of assistance while she is waiting on her knee operation.

While GPs can access helpful resources such as those developed by the Australian Centre for Cannabinoid Clinical and Research Excellence about HOW to prescribe,[10] the rationale as to why cannabis-based products should be effective in this clinical setting is not clear. We assess the current evidence base for cannabis-based products in the management of arthritis pain and joint inflammation that may assist GPs in such a patient consultation, including the molecular rationale for or against the use of cannabis-based medicines in arthritis, the evidence in animal studies and evidence to date of safety and efficacy in established human disease.

Methods

We undertook a rapid review of the medical literature that focused particularly on the use of cannabis-based products for arthritis (both osteoarthritis and rheumatoid arthritis (RA)) in animal models as well as observational and interventional trials in humans, and currently registered, not yet reported clinical trials of cannabis-based products for arthritis in humans.

We included all joint arthritis models in animal trials, and used a deliberately wide search that included arthritis, inflammation and pain in humans to ensure we cast as wide a net as possible over the medical literature.

For pre-clinical trials, all compounds associated with the endocannabinoid system or phytocannabinoids that were used to assess effects on arthritis or any inflammatory condition were considered. For the human studies, trials on OA and RA, the two most common arthritis presentations, were included. Neuropathic pain secondary to spinal OA, the less well-differentiated chronic pains associated with other neuropathies, fibromyalgia and cancers, and neuropathic pain in isolation were not included. Systematic reviews that included identified and synthesised papers on OA and RA, and that drew conclusions based on these trials were included.

The following search strategy was applied in PubMed: ('Cannabinoids' OR 'Delta-9-Tetrahydrocannabinol' OR 'Cannabidiol' OR 'Cannabis') AND ('Arthritis'; 'Inflammation' or 'Pain'); 'Cannabidiol' AND 'Inflammation'. A search of trials was undertaken on the European Clinical Trials Database (EudraCT) and the US National Library of Medicine clinical trial registry (clinicaltrials.gov) using the search terms 'Cannab*' AND 'arth*', and then 'Cannab*' AND 'pain'.

A title and then abstract screening was undertaken by two authors. Where dispute arose with respect to inclusion or otherwise, the remaining authors were asked to review. Where identified trials were included in systematic reviews, these systematic reviews were assessed for their summary findings and relevant meta-analyses. References of included articles were further searched to identify primary literature.

Results

Is there a molecular rationale for the use of cannabis-based products in arthritis?

Cannabinoid receptors are expressed throughout the nociceptive pathways in animals and in humans, raising the possibility that modulation of this system may result in new forms of analgesia.[11] The most well-known cannabinoid receptors are CB_1 and CB_2.[12] Phytocannabinoids are naturally occurring cannabinoids found in the cannabis plant, the most well studied

of which are delta[9]-tetrahydrocannabinol (THC) and CBD. THC is known for its psychoactivity and activates both CB_1 and CB_2 receptors.[13] In contrast, CBD is an antioxidant[14] and thought to work synergistically with THC increasing the THC concentrations in serum and the brain,[15,16] but of itself does not act at the endocannabinoid CB receptors at physiologically relevant concentrations.[17]

In humans, endocannabinoid receptors have been found in the synovium of patients with OA and RA.[18] Endocannabinoids have been found in the synovial fluid of arthritic joints, but not in healthy joints,[18] suggesting some 'upregulation' of the endocannabinoid system within the arthritic joint. It is not known whether this upregulation was mirrored systemically or within the central nervous system of these patients. Nor is it clear whether this had a causative role in the arthritis, or whether this was as a result of the pain caused by the arthritis.[18]

Preclinical studies

There were 19 pre-clinical trials evaluating the endocannabinoid system and arthritis[19–37] of which seven assessed cannabis plant extracts.[19,20,30–34] The studies often appeared underpowered (insufficient animal numbers for the small effect size and large inter-animal variability). Animal models of OA can be divided into spontaneous (naturally occurring or genetic models) and induced (by surgical manipulation or intra-articular chemical injection). Spontaneous models more closely mimic the progression of human disease but tend to be more costly due to the slow progression and high inter-animal variability.[38] All cannabinoid studies identified utilised chemical injection to induce injury. These use primarily monosodium iodoacetate,[19,29,35,36] di or tri nitrobenzenesulfonic acid,[33,34] collagen[22,23,28,30] and/or Freund adjuvant.[20,22–25,27,28,30–32] These models are primarily used for studying OA pain-related behaviours, but their validity as clinical models for OA has been questioned.[38–40] When utilising these animal models, increased endocannabinoid concentrations have been observed in the spinal cords of arthritic rats, which may modulate the activity of spinal neurons via cannabinoid receptors.[29] Administration of CB1 and CB2 receptor blockers directly into the affected joints of rats with experimentally induced arthritis can change nociceptive activity, although the results are inconsistent.[35,36] CBD may mitigate the progression of induced arthritis in mice, but the exact mechanism for this remains unclear and is unlikely to be associated with CB1 and CB2 receptors.[19,30] In many of the preclinical studies, drugs were delivered daily by injection directly into the joint, spinal cord or brain,[19,29,30,32–36] and thus the applicability of these studies to the delivery of cannabis-based products in humans are unclear. Many of the studies utilised synthetic, targeted modulators of endocannabinoid receptors, rather than phytocannabinoids, thus the results may not be generalisable to a medicinal cannabis preparation.

Clinical studies (Table 1)

In our search of reported human studies, a total of 823 papers were found. There was one randomised controlled trial (RCT) of a fatty acid amid hydrolase (FAAH) inhibitor (designed to increase the concentration of circulating endocannabinoids) in OA,[41] and one RCT of Sativex® (a sublingual spray containing almost equal concentrations of THC and CBD) in RA.[42] There were two systematic reviews of RCTs of cannabis-based medicinal products in a range of arthritides.[6,43] There was one 'overview of systematic reviews in pain management and palliative medicine', which included the two systematic reviews of arthritides along with nine other reviews not specifically related to arthritis.[44] In the clinical studies identified, cannabis-based products included oral, sub-lingual and smoked preparations. Despite a wide range of topical applications available in other jurisdictions, no clinical data relating to these products was identified.

The first RCT was of a fatty acid amide hydrolase (FAAH) inhibitor in 74 patients with late-stage OA of the knee. This RCT was terminated due to futility, as an interim analysis showed that naproxen was efficacious compared to the placebo arm while the FAAH inhibitor was not.[41]

The second RCT was a placebo-controlled trial of Sativex® for pain in 58 patients with rheumatoid arthritis treated over a five-week period.[42] Sativex® treatment resulted in statistically significant improvements in pain on movement, pain at rest, and quality of sleep compared to placebo. There was no effect on morning stiffness.

Table 1: Published randomised controlled clinical trials of cannabis-based products in arthritis.

Author: Journal: Title	Blake DR et al, Rheumatology, 2006.	Huggins et al, Pain, 2012.
Study type	Randomised, double-blind, parallel group study	Randomised, double-blind, double dummy, placebo- and active-controlled crossover design
Disease	Rheumatoid Arthritis (meeting American College of Rheumatology criteria, not adequately controlled by standard medications)	Osteoarthritis
Patients	N=58 (31 Sativex®, 27 placebo)	74 (37/36)
Other medications	Continued concurrent medications NSAIDs and prednisolone had to be stabilised for 1 month and DMARDs for 3 months prior to enrolment	Discontinued all current analgesic therapy
Intervention	Sativex: oromucosal spray 1 spray: 2.7mg THC: 2.5mg Sativex®	Oral dose: 37: PF-04457845 (FAAH inhibitor) followed by placebo (or vice versa), 36: naproxen followed by placebo (or vice versa)
Dose	Started on 1 spray nocte, which was increased by 1 spray every 2/7 to a max of 6 Mean daily dose in final week(sprays) 5.4 CBM 5.3 placebo	Naproxen 500mg BD PF-04457845 (FAAH Inhibitor) 4mg QID
Duration	5 weeks	2 weeks double-blind treatment followed by 2 weeks washout period. Crossover
Outcome measurements	Primary: morning pain on movement Numerical Rating Score (NRS) Secondary: NRS measures of pain at rest, sleep quality and morning stiffness. SF-MPQ, 28-joint disease activity score (DAS28)	Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscore (0–20), WOMAC stiffness domain score, WOMAC Physical Function domain score, WOMAC Total score. 11-point NRS, use of rescue medication. Hospital and Anxiety Depression Scale (HADS [58])
Results	Statistically significant improvement in pain on movement, pain at rest (3.1 THC/CBD, 4.1 placebo), quality of sleep (3.4 THC/CBD, 4.6 placebo), DAS28 (5.0 THC/CBD, 5.9 placebo) and the SF-MPQ. No significant change in intensity of pain.	Mean differences (80% confidence intervals) from placebo in WOMAC pain score were 0.04 (0.63 to 0.71) for PF-04457845 and 1.13 (1.79 to 0.47) for naproxen, indicating that whilst naproxen seemed efficacious, PF04457845 was not differentiated from placebo. The study was stopped at the interim analysis due to futility in the FAAH arm.
Adverse events	Withdrawals 0 in the Sativex® group, 3 (11%) for placebo. SAE: 0 serious AE in Sativex® group, 2(7%) in placebo group. AE: in Sativex® group mild or moderate intensity except for 2 (6%) rated severe) vs 6 (22%) in the placebo group. THC/CBD:placebo AEs (%): Dizziness (26:4), lightheadedness (10:4), dry mouth (13:0), nausea (6:4), falls (6:0), vomiting (0:7), Palpitation (0:7), Drowsiness (3:4), Constipation (3:4)	No evidence of cannabinoid-type adverse events

The large majority of adverse events were mild or moderate, and there were no adverse event-related withdrawals or serious adverse events in the active treatment group.[42]

Both of these RCTs were included in a systematic review of RCTs of cannabinoids in rheumatic diseases,[45] which also included two RCTs of cannabinoids in fibromyalgia.[46,47] When the data for all four RCTs were combined the authors concluded that "Extremely small sample sizes, short study duration, heterogeneity of rheumatic conditions and products, and absence of studies of herbal cannabis allow for only limited conclusions for the effects of cannabinoids in rheumatic conditions. Pain relief and effect on sleep may have some potential therapeutic benefit, but with considerable mild to moderate adverse events. There is currently insufficient evidence to recommend cannabinoid treatments for management of rheumatic diseases pending further study."[45]

The second systematic review of cannabinoids in chronic pain associated with rheumatic diseases[43] contained the Sativex® rheumatoid arthritis trial,[42] the two fibromyalgia trials[46,47] and a cross-over study of nabilone versus placebo in 30 patients with chronic pain associated with a 'pathologic status of the skeletal and locomotor system'.[48] The nabilone study reported significant benefits with respect to pain reduction and quality of life, and patient preference for nabilone as a treatment in the follow-up period. The treatment periods were of four weeks' duration, the risk of bias could not be assessed and the reported statistics did not lend themselves to meta-analysis.[48] When the results of all four RCTs were combined, the authors concluded that "The low quantity and quality of data available on the efficacy, tolerability and safety of cannabinoids in chronic pain refractory to conventional treatment associated with rheumatic diseases do not allow for any current recommendation for routine clinical use."[43]

The overview of systematic reviews in pain management and palliative medicine included both the systematic reviews previously reported.[44] The authors reported that there was inadequate evidence for benefit of any cannabis-based products for any of the conditions they assessed and noted the psychiatric and central nervous system side effects. They also commented that "The public perception of the efficacy, tolerability, and safety of cannabis-based medicines in pain management and palliative medicine conflicts with the findings of systematic reviews and prospective observational studies conducted according to the standards of evidence-based medicine."[44]

The use of cannabis-based medicines that include THC was accompanied by mild to moderate adverse effects, most of which were related to dizziness, somnolence and the perception of feeling 'high'.[42–45] Both clinical trials reported were of short duration. No prospective studies investigating the long-term adverse effects of cannabis-based medicinal products were found. There were no cohort studies or cross-sectional studies specific to cannabis-based medicinal products in arthritis found. There was one observational study that found an association between high levels of smoked cannabis and high levels of bone turnover and osteoporosis.[49]

Registered clinical trials in progress

There were five clinical trials of cannabis-based medicinal products in the treatment of arthritis found in US and European trial registries.[50–54] All studies are listed as incomplete and have no results available yet.

Due to the paucity of clinical trials and the heterogeneity of products used and outcomes assessed, a meta-analysis of available data could not be undertaken.

Discussion

This rapid review shows that the endocannabinoid system might play a role in acute nociception and inflammation in both animals and humans, however the full extent of its role in arthritis is unclear. The methodology used in most animal trials apply mainly to experimentally induced arthritis and the modes of administration of the cannabis-based medicinal products are not widely generalisable to humans. In human trials, Sativex® claims some efficacy in reducing pain and improving sleep in 58 patients with RA over a five-week period, while FAAH inhibitors that increase circulating endocannabinoids had no efficacy

in OA. Beyond this, evidence is limited.[42] There are a number of trials in humans in progress, and we look forward to publication of the results.

The limited amount of evidence-based peer-reviewed medical literature concerning cannabis-based medicinal products contrasts starkly with the wealth of information that can be found on the internet, highlighting the need for the GP to be prepared, well-informed and able to provide accurate information to their patients. While we were able to generate 823 papers from our search, there were only two published RCTs specific to arthritis; one in RA,[42] and one of a FAAH inhibitor that showed promise in animal models[55] but was abandoned due to futility in human trials as it was not better than placebo,[41] highlighting the difficulty of translating the results of pre-clinical studies directly to humans.[56] The mechanism for pain and inflammation may differ between the two species, many pre-clinical trials have been undertaken on animal models of artificially initiated acute arthritis and the modes of drug administration used in animal studies (intrathecal, intra-articular or intraperitoneal for example) is often not desirable or practical in humans. Further, the comparison with a placebo arm does not reflect the current gold-standard for treatment for arthritis or chronic pain. One might expect that the magnitude of any benefits seen in cannabis-based products versus placebo would be reduced in RCTs where the comparator arm included gold standard analgesic agents and the intervention arm may have a cannabis-based product as an adjunctive therapy.

The Sativex® trial in patients with RA claims some efficacy.[42] Whether the reduction in pain is due to the psychoactive effects of the THC or some other disease-modifying mechanism is unclear. As well as reduced subjective pain with movement and at rest, the authors report a statistically significant difference in the Disease Activity Score 28 (DAS28) between the two groups and describe this as a significant depression of disease activity. The DAS28 is a composite score that includes a count of painful joints, a count of swollen joints, a measure of serum inflammatory markers, and a visual analogue score of a 'global assessment of health'.[57] Changes in the DAS28 subgroups were not reported, so it is unclear how much of the change has been driven by patient-reported global assessment of health or pain reduction compared to the more objective measures of swollen joints and inflammatory markers. The mean DAS28 in the Sativex® group was 5.9 at baseline, consistent with a high level of disease activity, and the mean score at the end of the trial was 5.0, consistent with a moderate level of activity.[57] However, a clinically meaningful reduction in the DAS28 is considered to be >1.2 when disease activity is high, greater than that reported in the RCT.[57] The proportions of patients in each group achieving a clinically meaningful reduction in disease activity according to the DAS28 is not reported, nor is the proportion of participants in each group achieving remission.

Of potential concern, an association between high levels of cannabis smoking and osteoporosis has been described,[49] suggesting that future clinical trials should consider incorporating the assessment of circulating biomarkers of bone health and disease into their clinical trial programmes, particularly when investigating chronic conditions that may require long-term treatments, and in trials associated with bone and joint health.

There were no human studies found that assessed CBD only preparations in OA or RA. CBD is considered an antioxidant,[14] with some anti-inflammatory properties.[14,58] These properties are commonly referred to on websites,[59,60] as well as reference to its 'non-psychoactive' (and by inference safe) properties.[59,60] While CBD may not make patients 'high' as THC does, CBD is an agonist at serotonin receptors,[61] and may have some psychoactive properties such as anxiolysis, possible improved mood and sedation. This is an important consideration if prescribing with other medications. Notably, in New Zealand, while CBD is no longer a controlled drug, products still require a prescription, must have less than 2% THC, and none are approved by Medsafe or funded by Pharmac, therefore any costs associated with obtaining these products are borne by the patient.

There are some limitations that should be considered in the context of this rapid review. The topic was difficult to limit to OA and/or RA, due to the heterogeneous nature of the medical literature. The two discrete trials that we identified were included in three systematic reviews, two of which covered rheumatic arthritides, and one of which covered chronic pain management and palliative care, perhaps highlighting the difficulty of clearly differentiating disease states and pain management. Neuropathic pain was excluded from this review; however, there is some evidence that there is a subgroup of patients with chronic osteoarthritis that develop central sensitisation over time.[62] There are a number of systematic reviews of cannabis-based products in chronic neuropathic pain with mixed findings, including potential short-term benefits of inhaled cannabis,[63] marginal efficacy of short- to intermediate-term adjunctive cannabis-based products but with reduced tolerability compared to placebo,[64] and that potential benefits may be outweighed by the risk of harm.[65] We did not include studies of chronic pain, as arthritis patients were not separately reported in these studies.

Conclusion

How might a GP respond to Mary's questions about cannabis-based medicinal products for her osteoarthritis? At the molecular level, endocannabinoid receptors are expressed throughout nociceptive pathways in humans and have been found in the synovium of joints affected by OA and RA. Animal models have provided some evidence of a relationship between the endocannabinoid system, pain and arthritis, the mechanism of which is unclear. There is no current published medical evidence for cannabis-based products in the treatment of OA in humans, although there may be some efficacy of Sativex® for some symptoms of RA. In all trials the duration of treatment has been short and the long-term effects, beneficial or otherwise, of cannabis-based products are not established. While acknowledging the limitations of the treatment regimen currently in place, and the negative impact of OA on Mary's quality of life, the potential adverse effects of cannabis-based products, the lack of definitive evidence of benefit in OA and the lack of information about the long-term effects of cannabis-based medicinal products do not support a prescription at this time.

Competing interests:
Prof Michelle Glass and Drs Karen Oldfield, Alex Semprini and Irene Braithwaite are members of the Medical Cannabis Research Collaborative, an impartial collaboration of academics and regulatory experts in the field of cannabis-based medicine development. The Medical Research Institute of New Zealand has undertaken research activity Helius Therapuetics, Hikurangi Enterprises and Whakaora Pharma, all of which are New Zealand-based medicinal cannabis companies. There are no other conflicts of interest to declare. The Medical Research Institute receives Independent Research Organisation funding from the Health Research Council of New Zealand.

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Change in smoking intentions of university students in New Zealand following simulated cigarette price increases: results of the first of two cross-sectional surveys

Ben Wamamili

ABSTRACT

AIM: Increasing cigarette prices is one of the most effective strategies to reduce smoking. This study examined changes in smoking intentions of university students following simulated price increases.

METHOD: Data came from a 2018 cross-sectional survey of university students. The sample comprised 187 current smokers (47% aged <21 years, 53% ≥21 years; 60% male, 40% female; 10% Māori, 90% non-Māori and 18% current vapers). Students were asked how their smoking behaviour would change if the price of a packet of their regular cigarettes or RYO tobacco was increased by $5.00, $10.00, $15.00 or >$15.00.

RESULTS: The proportion of students who would smoke the same amount declined substantially, while students who would switch to e-cigarettes increased by large margins at price increases of $5.00, $10.00 and $15.00. Quit intentions increased at all price levels, but were stronger among younger students and females. Males were almost twice as likely to switch to e-cigarettes as females. Overall, more students would quit than switch to e-cigarettes.

CONCLUSION: Results show that increasing cigarette prices by ≥$15.00 per packet could lead to significant reductions in smoking among university students. Follow-up data is required to assess the differential effects of price increases on vaping.

Smoking remains one of the leading causes of preventable death and illness in New Zealand[1] and elsewhere. Each year about 5,000 people in New Zealand die because of smoking or second-hand smoke exposure.[1] Further, smoking is also a major contributor to mortality differences between Māori and non-Māori non-Pacific people (New Zealand European), with Māori having disproportionately high mortality rates compared with non-Māori.[2]

Data from the New Zealand Health Survey show that in 2018/2019, 14.2% of adults aged 15 years or older were current smokers (ie, smoked at least once a month) and the smoking prevalence was highest among Māori compared with non-Māori (Māori 34%, Pasifika 24.4%, New Zealand European/Other 12.4%, Asian 8.4%).[3] The smoking prevalence of young adults aged 18–24 years was 19.2% in the general population[3] and 11.1% among university students.[4]

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The New Zealand Government has a goal of becoming a smokefree nation by the year 2025 (ie, the Smokefree 2025 goal).[5] The definition of 'smokefree' here is generally considered to be five percent or less of the adult population (ages 15 years or older) smoking. The goal was informed by the need to reduce the health and economic burden of smoking for the population, particularly Māori.[5] Since its inception in 2011, the Government has introduced a number of measures to reduce smoking, including annual tobacco tax increases,[6] restrictions on tobacco display in retail outlets and smokefree prisons, among others.

Increasing the price of cigarettes is an integral part of New Zealand's comprehensive tobacco control programme[7] and is considered one of the most effective tobacco control measures.[8–10] Evidence suggests that higher prices prevent smoking initiation among youth; promote cessation; reduce the number of ex-smokers who return to smoking, and lower consumption among youth and adults who continue to smoke.[8,10–13] Young adults (aged 18–24) are a crucial demographic for both the tobacco industry[14] and tobacco control; it is therefore important to consider the potential impact of high prices on smoking among this demographic.

This paper examines changes in smoking intentions of university students following a simulated four-level cigarette price increase. The author tests a number of hypotheses, including that increasing proportions of students would: 1) cut down on smoking, 2) switch to e-cigarette use (vaping) and 3) quit smoking, as cigarette prices increase.

Method

Data came from the first of two cross-sectional surveys of university students from eight New Zealand universities. The survey was conducted between 1 March and 1 May 2018 as part of the author's PhD thesis project and collected data on the prevalence and patterns of cigarette smoking and electronic cigarette use, and perceptions on the Smokefree 2025 goal. Students enrolled at any university in New Zealand were eligible to participate. The project was advertised online (student association Facebook pages and magazines) and in-person by research assistants (RAs) from participating universities. Online adverts included a link to the questionnaire, while RAs distributed and collected paper questionnaires. Random sampling was not possible because of lack of access to complete enrolment lists of students from the universities. Participation was voluntary and participants were required to consent before proceeding to complete the questionnaire, which took about five minutes. Additional information on the survey, sample and procedures used has been described elsewhere.[4]

Participants

A total of 2,180 participants took part in the survey: 46 were excluded because they were not eligible to participate and 280 were excluded because they did not have complete data for weighting. Of the remaining 1,854 participants, 187 were current smokers (ie, smoked at least once a month) and their data (demographic characteristics and smoking intentions) were included in the current paper (Figure 1 summarises the selection process).

Survey measures

Participants were asked: "How would your smoking change (if at all) if the price of a packet of your regular cigarettes or roll your own (RYO) tobacco was increased by $5.00, $10.00, $15.00 or >$15.00?" The response options were as follows: "I would smoke the same amount that I smoke today"; "I would smoke less than I smoke today"; "I would switch to other tobacco products"; "I would switch to electronic cigarette (e-cigarette)"; "I would stop smoking cigarettes altogether", and "Don't know".

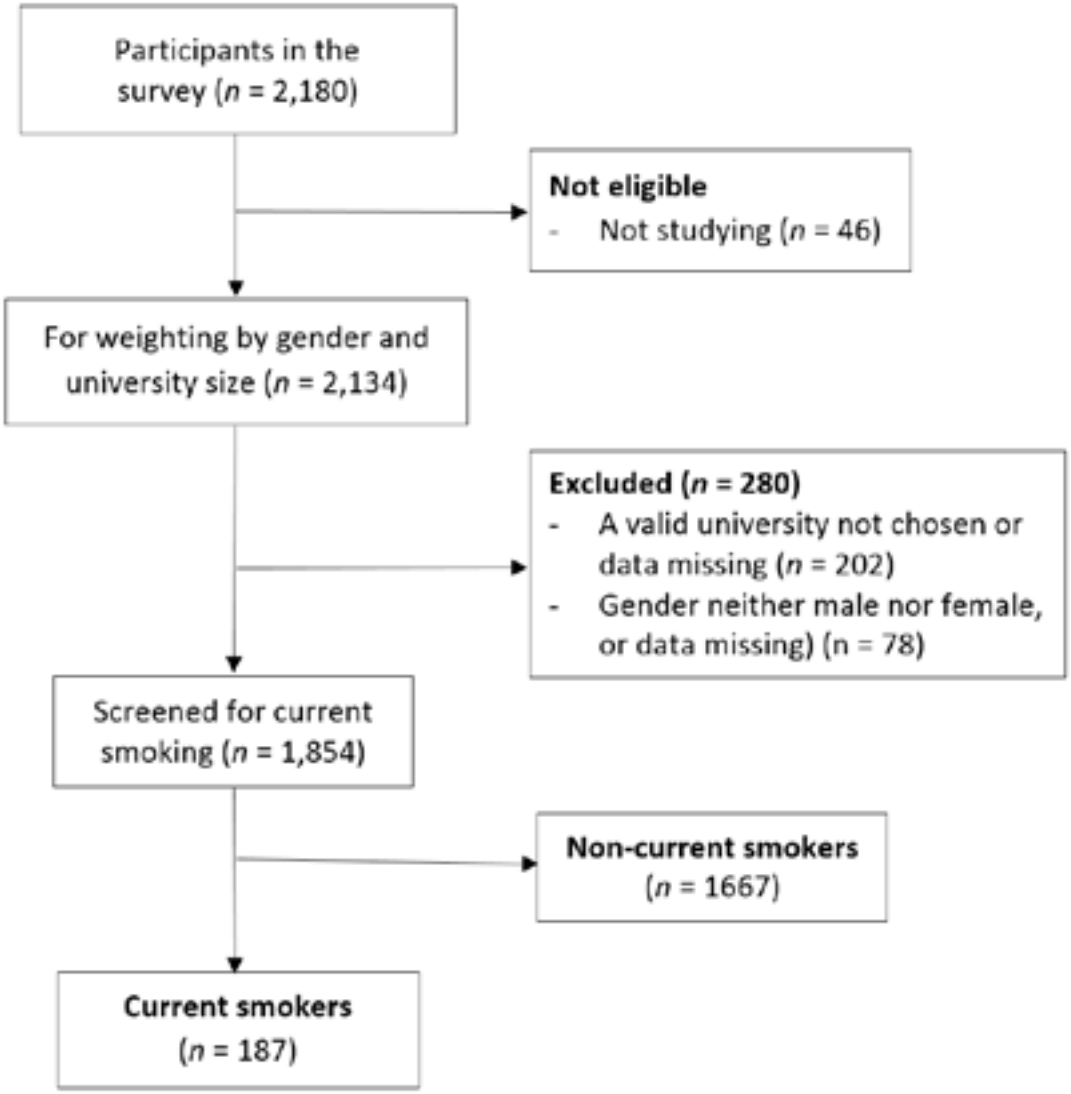
Data analysis

Data analysis was done descriptively using IBM SPSS Statistics 25 and the results reported as overall proportions, and by age and gender with associated 95% confidence intervals (CI). Responses were weighted to account for undersampling and oversampling based on gender (male and female) and university size.

Ethics approval

The University of Canterbury Human Ethics Committee approved the study (research ethics ID: HEC 2017/42/LR-PS).

Figure 1: Flow chart of the selection process of participants included in current analysis.



Results

One hundred and eighty-seven students were included: 47% aged <21 years, 53% aged 21 or older (≥21 years); 60% male, 40% female; 10% Māori, 90% non-Māori, and 18% currently vaped (ie, used an e-cigarette at least once a month).

The smoking intentions of participants according to simulated price increases are displayed in Table 1 and Figure 2. The proportion of students who indicated that they would continue to smoke the same amount declined, while the proportion of students who indicated that they would switch to e-cigarettes increased at all price levels. The proportion of students who indicated that they would quit increased by large margins at all price levels.

Table 2 presents the results of changes in smoking intentions by age and gender, focusing on switching to e-cigarettes and quitting. The proportion of students who indicated that they would quit increased with increasing prices, in both age groups and gender. These increases were stronger in younger students (<21 years) than in older students (≥21 years), and in females than in males. The proportions of students who indicated that they would switch to e-cigarettes increased by large margins across age groups and among males for the first three price levels ($5.00, $10.00 and $15.00), but overall, more students indicated that they would quit rather than switch to e-cigarettes.

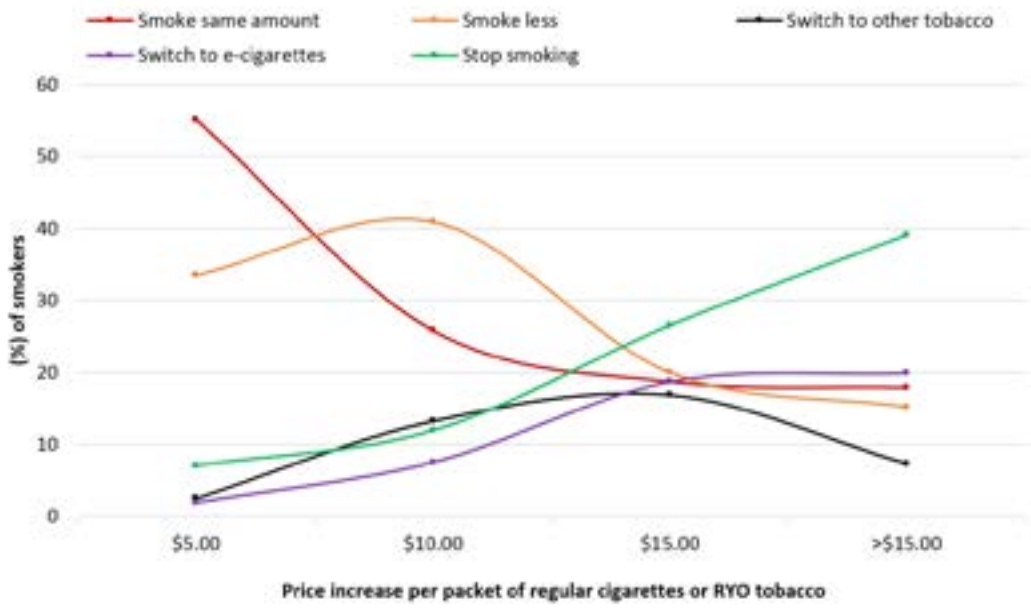
Table 1: Change in smoking intentions following simulated cigarette price increases of $5.00, 10.00, 15.00 or >15.00 per packet.

Intentions to smoke	$5.00	$10.00	$15.00	>$15.00
I would smoke the same amount that I smoke today	55.1 (47.0–63.0)	25.8 (19.2–33.3)	18.7 (12.9–25.8)	17.9 (12.1–24.9)
I would smoke less than I smoke today	33.5 (26.2–41.5)	40.9 (33.2–48.9)	20.0 (14.0–27.2)	15.2 (9.9–22.0)
I would switch to other tobacco products	2.5 (0.7–6.4)	13.2 (8.4–19.5)	16.8 (11.3–23.6)	7.3 (3.7–12.7)
I would switch to e-cigarettes	1.9 (0.4–5.4)	7.5 (4.0–12.8)	18.7 (12.9–25.8)	19.9 (13.8–27.1)
I would stop smoking cigarettes altogether	7.0 (3.5–12.1)	11.9 (7.4–18.0)	26.5 (19.7–34.1)	39.1 (31.2–47.3)
Total	**158 (100.0)**	**159 (100.0)**	**155 (100.0)**	**151 (100.0)**

Discussion

The findings indicate that increasing cigarette prices by $15.00 or more per packet would lead to substantial reductions in cigarette consumption, increase switching to e-cigarettes, and promote quitting. These findings are consistent with previous research that regards high prices as the most effective single intervention to reduce smoking.[8,11–13] Consistent with previous studies, the findings also suggest that the impact of higher prices is likely to be felt more strongly by younger smokers than older smokers,[15–18] and by female smokers than male smokers.[15]

Figure 2: Change in smoking intentions following simulated cigarette price increases of $5.00, 10.00, 15.00 or >15.00 per packet.



Note: To plot a linear scale, cigarette price indicated as >$15.00 was assumed to be $20.00.

Table 2: Change in smoking intentions following simulated cigarette price increases of $5.00, 10.00, 15.00 or >15.00 per packet; by age and gender.

Price increase per packet of cigarettes or RYO tobacco	Smoking intentions	Age (years)		Gender	
		<21 (%)	≥21 (%)	Male (%)	Female (%)
$5.00	I would switch to e-cigarettes	1.5 (0.0–7.9)	2.2 (0.3–7.9)	2.0 (0.3–7.2)	1.7 (0.0–8.9)
	I would stop smoking	8.8 (3.3–18.2)	5.6 (1.9–12.6)	8.2 (3.6–15.5)	5.0 (1.0–13.9)
$10.00	I would switch to e-cigarettes	8.2 (3.1–17.0)	7.1 (2.6–14.7)	10.9 (5.6–18.7)	1.8 (0.0–9.4)
	I would stop smoking	19.2 (10.9–30.1)	5.9 (1.9–13.2)	9.9 (4.9–17.5)	15.5 (7.4–27.4)
$15.00	I would switch to e-cigarettes	21.4 (12.5–32.9)	16.7 (9.4–26.4)	22.7 (14.8–32.3)	11.9 (4.9–22.9)
	I would stop smoking	38.6 (27.2–51.0)	15.5 (8.5–25.0)	21.6 (13.9–31.2)	33.9 (22.1–47.4)
>$15.00	I would switch to e-cigarettes	21.1 (12.3–32.4)	20.0 (11.9–30.4)	25.0 (16.7–34.9)	12.5 (5.2–24.1)
	I would stop smoking	50.7 (38.6–62.8)	30.0 (20.3–41.3)	37.5 (27.8–48.0)	42.9 (29.7–56.8)

A 2014 study of New Zealand smokers that looked at simulated demand for tobacco cigarettes in the presence and absence of e-cigarette availability found that demand for regular cigarettes at 'current' market prices decreased by 42.8% when e-cigarettes were available.[19] This supports one of the current paper's findings that increasing proportions of smokers intended to switch to e-cigarettes as prices increased. Two studies concluded that e-cigarettes were potentially substitutable for regular cigarettes[7,19] and another found that a 10% increase in cigarette prices was associated with a 40% increase in e-cigarette sales.[20]

An interesting finding in this paper is that more students would quit than switch to e-cigarettes when cigarette prices go up. This significant finding warrants follow-up data to establish a clear picture of the differential effects of increasing cigarette prices on vaping. If confirmed, it may imply that smokers in this population group (university students) have low nicotine addiction or are less interested in vaping, or both. It could also mean that e-cigarettes might not after all, discourage quitting as previously feared by some health experts.[21–24]

This study provides useful evidence for the likely impacts higher cigarette price increases on smoking might have on university students and possibly other tertiary students (institutes of technology, polytechnics, wānanga, etc). Compared with individuals who do not have a tertiary education, tertiary students are more likely to be lighter smokers;[4,25,26] to be aware of e-cigarettes,[27–30] and to have tried vaping.[28] Combined, these factors might make tertiary students (in general) more responsive to cigarette price increases. Thus, while the findings support research hypotheses (reductions in smoking; increased switching to vaping, and increased quitting, when prices increase), actual behaviour changes may be influenced by nicotine dependence and knowledge and use of tobacco alternatives such as e-cigarettes.

Limitations

This study is subject to a number of limitations. The survey (source of data) did not employ random sampling,[4] which may increase the risk for volunteer bias. This bias could lead to underestimation or overestimation of prevalence estimates. However, data were weighted by gender and university size to make it more representative of the university student population. Secondly, the small sample size (and smaller sub-groups) did not allow for significance tests to be performed. Confidence intervals for estimates were provided to supplement reported estimates. Lastly, the question used in this study had not previously been validated.

Conclusion

These results suggest that raising the price of cigarettes or RYO tobacco by $15.00 or more per packet above regular retail prices could result in significant numbers of students cutting down on smoking, switching to e-cigarettes or quitting altogether thus advancing public health. However, repeat data are necessary to establish a clear picture of the differential effects of cigarette price increases on switching to vaping.

Competing interests:
Nil.

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Exploring medicinal use of cannabis in a time of policy change in New Zealand

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ABSTRACT

AIMS: To explore patterns of medicinal cannabis use prior to implementation of the new Medicinal Cannabis Scheme (MCS) in New Zealand.

METHODS: An anonymous online convenience survey of 3,634 last-year medicinal users of cannabis promoted via Facebook™ from May to August 2019.

RESULTS: Fifty percent of the sample were female, 18% were Māori and the median age was 38 years. The medical conditions for which cannabis was most often used were pain (81%), sleep (66%) and mental health conditions (64%). Respondents perceived cannabis to be an effective therapy and reported reducing use of other pharmaceutical medicines. Fifty-two percent reported side effects from cannabis use, including increased appetite (29%), drowsiness (12%), eye irritation (11%), dependency (10%), memory impairment (10%) and lack of energy (9%). Smoking was the dominant route of administration. Nearly half (47%) had discussed their use of cannabis with a medical professional in the previous year, while 14% had requested a prescription and 5% accessed a prescribed cannabis-based product (mostly oral CBD).

CONCLUSION: Respondents self-medicated with cannabis to treat a wide range of health complaints. Only half discussed medicinal cannabis use with their medical professional, and a minority requested a prescription and used a prescribed cannabis-based product.

Despite limited scientific evidence for the medicinal benefits of cannabis (ie, double blind placebo-controlled trials[1,2]), a growing number of countries have facilitated greater legal access to cannabis and/or cannabis-based preparations for medicinal use, including Australia, UK, Canada, Germany, Israel, Netherlands and over half of US states.[3–6] Australia has recently made cannabis-based products legally available for medical patients, but only limited numbers of people have utilised the scheme to date, prompting a Senate inquiry into barriers to patient access.[7]

In December 2019, the New Zealand Ministry of Health (MOH) released regulations for the new Medicinal Cannabis Scheme (MSC), which will establish a domestic medical cannabis industry with cannabidiol (CBD) and tetrahydrocannabinol (THC) products available on prescription from general practitioners.[8] The new MCS regime became operational on 1 April 2020, with opening of the product applications assessment process by MOH.[9] Products brought within the regime must meet minimum quality standards as specified by MOH[10] (efficacy data does not need to be provided) and they must not be in a form intended for smoking (although dried cannabis flower intended for vaping is allowed). Therefore, products under the new MCS scheme can include tablets, capsules, oral liquids, lozenges, but not herbal cannabis for smoking.[10]

Since September 2017, medical practitioners have been allowed to prescribe products containing CBD without sign-off from the MOH. CBD products must contain no more than 2% of tetrahydrocannabinol and other psychoactive-related substances. In the first half of 2019, there were 2,504 prescriptions for CBD products (up from 2,130 for the entire year in 2018),[11] but the cost of imported products remains prohibitive. At the time of publication,

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prescriptions for products that contain more than 2% THC still require a sign-off from the MOH (with the exception of Sativex which is a consented "approved" medicine, including for off-label use from 1 April 2020).[9] This is likely to change soon as new cannabis-based products will be brought within the scheme (following their assessment against new MCS quality standards). Since December 2018, patients in palliative care have been permitted to possess and use illicit cannabis for their own medical needs without the risk of being prosecuted.[12]

Largely due to the illegality of cannabis, understanding of how New Zealanders use and access cannabis for medicinal reasons remains highly fragmented. A recent survey of medicinal cannabis users in Australia found that patients self-medicate with illegal cannabis to treat a wide range of conditions, including anxiety (51%), back pain (50%), depression (49%) and sleep problems (44%).[13] In New Zealand, an estimated 5% of the population (aged 15 years+) used cannabis medicinally at the time of the New Zealand Health Survey 2013 (NZHS).[14] Medicinal cannabis users were more likely to be male, younger, Māori, less well-educated and poor. However, the NZHS only included a handful questions on medicinal cannabis use and consequently many aspects of medicinal cannabis use in New Zealand remain unexplored, including reasons for use, modes of administration, means of procurement, interaction with legal medicines, and experience of side-effects. In addition, it is important to explore the extent to which users are aware of recent policy changes and their intention to engage with the new regime.

The aim of this study was therefore to provide exploratory research on patterns of medicinal cannabis use in New Zealand during a period of changing policy.

Methods

An online convenience survey was undertaken of adults (16 years+) who self-report using cannabis or cannabis-based products for medicinal purpose in the last 12 months in New Zealand. The survey was conducted using Qualtrics™ software and could be completed on either a desktop computer or mobile device. The survey was promoted on Facebook™ from May to August 2019 via a paid promotional campaign targeting medicinal cannabis users in New Zealand aged 16 years and older. The URL link to the survey was also shared on Facebook forums dedicated to medicinal cannabis use. The survey preamble included a phone contact for the primary researcher providing an option to complete the survey over the phone (four participants chose to do so). The survey preamble defined “medicinal cannabis” as the “use of cannabis or cannabis-based products to treat a medical condition or alleviate a symptom”. The questionnaire was developed building on a number of other overseas surveys, including a recent Australian study.[13,15,16] Ethical approval for the study was obtained from the Massey University Human Ethics Committee (SOA 19/19).

A total of 3,847 respondents commenced the survey. Completed surveys were audited for consistency and extent of completion. Surveys where respondents did not progress beyond demographic questions (ie, a total of 185 surveys) were removed. Respondents who reported they had suffered from more than 15 health conditions (n=28) or were suffering from cancer but did not have a medical diagnosis for cancer (n=42) were reviewed in detail. Six surveys were subsequently removed during this process due to lack of consistency. A custom survey software solution was developed to convert computer IP addresses into a unique number that facilitated the identification of instances where multiple surveys were completed from the same device, or from outside the country, while ensuring respondent anonymity and avoiding storage of IP addresses. Twenty-two duplicate responses were identified and removed through this process. The final sample consisted of 3,634 respondents.

Measures and analysis

The survey consisted of nine modules: (1) demographics; (2) patterns of use (types of cannabis products, main and preferred route of administration; frequency and history of use); (3) medical conditions and symptoms for which cannabis is used (including conditions diagnosed by a health professional); (4) perceived effectiveness (rated on a seven-point Patient Global Impression of Change scale) and side effects; (6) sources of cannabis supply; (7) discussions with health providers; (8) use of other pharmaceuticals; and (9) knowledge and engagement with the MCS.

Table 1: Sample characteristics.

Age (n=3,634)	Mean: 39.3 (s.d. 15.2), Median: 38, range: 16–90	
Gender (n=3,613)	Male	48.4%
	Female	50%
	Gender diverse	1.6%
Ethnicity (n=3,557)	NZ European	75.9%
	Māori	17.8%
	Pacific	1.0%
	Asian	1.8%
	Middle Eastern/Latin American/African	1.5%
	Other	2.1%
Highest level of education (n=3,508)	None	1.4%
	Primary/intermediate	1.1%
	High school	31.1%
	Polytech/technical/trade school	38.3%
	University	27.9%
	Other	0.2%
Main occupation (n=3,514)	Work full-time (includes self-employed)	41.4%
	Work part-time (includes self-employed)	14.8%
	A student	9.3%
	Retired	6.8%
	On sickness benefit	17.3%
	Unemployed	4.3%
	Parenting/unpaid work	6.1%
Household's combined annual income (before tax) (n=2,519)	$20,000NZD or less	21.4%
	$20,001–30,000	13.3%
	$30,001–50,000	17.5%
	$50,001–70,000	15.8%
	$70,001–100,000	14.8%
	Over 100,0000	17.1%
Financial benefit related to medical condition (n=2,445)	None	72.4%
	Work and Income NZ, including:	19.5%
	Supported Living Payment	16.9%
	ACC payments	7.6%
	Private medical insurance payments	1.2%

Results

Demographics

Fifty percent of the sample were female, 48.4% male and 1.6% gender diverse (Table 1). The median age of respondents was 38 years. Seventy-six percent identified as New Zealanders of European descent and 17.8% as Māori. The majority were in full-time (41.4%) or part-time employment (14.8%), and a further 17.3% reported they were on a sickness benefit. Overall, 27.6% were receiving some financial benefit related to their medical condition. Over half the sample (52.2%) reported a combined annual household gross income of $50,000 NZD or less (Table 1).

Patterns of cannabis use for medicinal reasons

Participants had used cannabis for medicinal reasons for a median of five years (mean 10 years, s.d. 11 years, n=3,128). Approximately two-thirds of respondents

Table 2: Conditions treated with medicinal cannabis in the past 12 months and medical diagnoses.

Conditions for which cannabis is used	**%**	**N**	**% diagnosed by a health professional**	**% seeing a doctor for this health condition**
Pain conditions	**80.9**	**2,338**	**78.9**	**60.4**
Back pain	45.6	1,371	80.1	56.6
Headaches (including migraines)	29.5	885	65.5	50.0
Neck pain	28.8	864	70.9	53.7
Arthritis (including rheumatoid or osteoarthritis)	24.0	720	83.1	63.0
Neuropathic pain (nerve pain)	20.3	609	85.4	68.1
Fibromyalgia	9.8	295	86.9	76.2
Gynaecological pain	8.6	257	80.7	61.3
Spinal cord injury	6.7	200	93.3	76.9
Cancer-related pain	2.8	84	82.9	72.0
Complex regional pain syndrome	0.7	21	95.0	100.0
Other chronic non-cancer pain	11.3	339	89.8	71.1
Sleep conditions	**65.9**	**1,906**	**49.3**	**37.4**
Insomnia (any type)	54.8	1,647	49.1	37.3
Sleep-related movement disorder (eg, restless leg syndrome)	11.5	344	45.5	33.3
Parasomnias (eg, sleep walking, nightmares)	4.8	143	41.4	32.4
Sleep apnoea or other sleep-related breathing disorder	4.4	133	65.6	45.7
Narcolepsy or other hypersomnia	0.5	16	46.7	60.0
Other sleep disorder	3.2	97	55.3	45.7
Mental health and substance use disorders	**64.0**	**1,851**	**78.3**	**55.8**
Anxiety disorder (eg, generalised anxiety, panic disorder, OCD)	45.5	1,367	79.1	60.4

Table 2: Conditions treated with medicinal cannabis in the past 12 months and medical diagnoses (continued).

Depression	41.9	1,259	86.0	61.2
Post-traumatic stress disorder	22.2	668	82.8	59.5
Addiction (including alcohol, opioids, amphetamine)	8.5	255	49.6	28.7
Attention deficit disorder (ADHD)	8.3	248	76.8	37.8
Eating disorders (eg, anorexia/bulimia/obesity)	7.9	237	54.1	32.9
Bipolar disorder	4.6	137	73.7	56.7
Schizophrenia or other psychosis	1.6	49	85.4	62.5
Borderline personality disorder	0.9	27	96.3	74.1
Other mental health condition	1.6	47	62.2	55.6
Gastrointestinal conditions	**17.1**	**494**	**85.4**	**65.5**
Irritable bowel syndrome	12.3	368	83.7	58.4
Crohn's disease	1.7	51	82.0	82.0
Ulcerative colitis	1.2	36	91.7	80.6
Diverticulitis	0.5	14	100.0	78.6
Other gastro-intestinal conditions	2.9	88	89.7	77.4
Neurological conditions	**12.2**	**352**	**82.4**	**68.4**
Epilepsy/seizure disorder	3.3	99	94.8	84.7
Autism	2.8	85	70.2	38.1
Multiple sclerosis	1.2	35	97.1	97.1
Glaucoma	0.8	23	65.2	52.2
Brain injury	0.6	19	88.9	77.8
Parkinson's disease	0.6	18	66.7	66.7
Tourette's syndrome	0.4	11	72.7	27.3
Dementia (including Alzheimer's)	0.3	8	62.5	50.0
Huntington's disease	0.1	2	0.0	0.0
Other neurological condition	2.7	80	86.1	79.7
Cancers	**6.7**	**195**	**78.8**	**74.2**
Skin cancers (melanoma)	1.4	43	76.7	62.8
Gastrointestinal cancer (bowel, colon, stomach, pancreatic)	1.2	36	51.5	48.5
Breast cancer	1.0	30	90.0	79.3
Blood cancers (leukaemia, lymphoma, myeloma)	0.5	16	75.0	81.2
Brain cancers (glioblastoma, neuroblastoma, mesothelioma)	0.6	17	76.5	81.2
Lung cancer	0.5	14	92.9	92.9
Other forms of cancer	2.0	59	88.1	86.2

Table 2: Conditions treated with medicinal cannabis in the past 12 months and medical diagnoses (continued).

Other conditions	**29.8**	**861**	**86.9**	**72.9**
Skin condition (eg, eczema, psoriasis, dermatitis)	10.8	323	79.4	55.1
Auto-immune condition (eg, SLE, chronic fatigue disorder)	9.4	282	87.2	80.8
Gynaecological condition (eg, endometriosis, PMS)	5.5	166	89.0	76.4
Respiratory disease (eg, asthma, cystic fibrosis)	4.5	135	93.8	80.8
Cardiovascular condition (eg, poor circulation, ischaemic heart disease)	2.7	81	86.8	80.3
Diabetes mellitus	2.0	59	96.6	91.2
Infectious disease (eg, viral hepatitis)	0.8	24	100.0	79.2
AIDS/HIV	0.3	9	88.9	66.7
Other condition	3.1	94	89.2	73.9

(68.5%) reported daily or near daily use of cannabis for medicinal purposes, a further 17.5% used it "once or twice per week", and 9.6% "once or twice a month" (n=3,240). A median twice-daily frequency of administration was reported.

Medical conditions and symptoms

Participants were asked to select all the medical conditions and symptoms for which they had used cannabis from structured lists. The condition groups for which cannabis was used most often were: pain (80.9% of respondents used cannabis for at least one pain condition), sleep (65.9%) and mental health conditions (64.0%), followed by gastrointestinal (17.1%) and neurological (12.2%) conditions and cancers (6.7%) (Table 2).

Participants reported the highest rates of medical diagnoses for gastrointestinal conditions (85.4%) and neurological conditions (82.4%), and the lowest for sleep disorders (49.3%).

History of medicinal cannabis use

Nearly half the participants (47.2%) were using cannabis recreationally at the time they started using it for medicinal reasons. A further 38.4% had tried cannabis before using it medically but never used it regularly, and 14.5% had never used cannabis recreationally (n=3,228). Nearly 60% (58.5%) reported that, in addition to their medicinal use, they had also used cannabis for recreational reasons in the past year.

Reasons for changing levels of medicinal cannabis use

Most respondents (54.5%) reported their use of cannabis for medicinal reasons had not changed in the last year. One in four (25.6%) reported a decrease in medicinal use of cannabis, including 5.7% who completely stopped (n=3,224). The main reasons for stopping or reducing cannabis use for medicinal reasons were participants' concerns over related "legal risks", "improvement of the health complaint", financial cost or inability to find a supplier (Table 3). The leading reasons for using more medicinal cannabis were: "like effect on my wellbeing", "in order to reduce use of other medicines" and "need more to get relief from symptoms" (Table 3).

Modes of administration

Smoking was the most common way of administering cannabis for medicinal reasons: in the last year 66.3% of participants smoked cannabis in a joint; 53.2% smoked cannabis through a water pipe or bong; 48.4% smoked cannabis through a dry pipe. This was followed by eating cannabis in baked edibles (48.4%), taking cannabis by mouth as a tincture or oil (32.9%), vaping (31.5%) and topical application (29.5%) (n=3,588). Respondents were asked to identify the main way they used cannabis in the past 12 months and the most preferred way they would like to use it (if they could

Table 3: Reasons for stopping, reducing or using more cannabis for medicinal reasons during past 12 months (multiple responses permitted).

Reasons for stopping medicinal use of cannabis (n=183)	
Worried about legal risks	34.3%
Unable to find the supply	27.4%
Can't afford it	24.6%
No longer suffer from health complaint/health complaint improved	17.1%
Don't like the side effects	13.7%
Don't like the psychoactive aspect	8.6%
I use other medicines now	5.7%
It never worked	8.6%
Reasons for reducing use (n=643)	
Worried about legal risks	34.5%
Health complaint improved	33.6%
Can't afford it	33.1%
Unable to find supply	32%
Don't like the side effects	5.2%
Don't like the psychoactive aspect	5.0%
I use other medicines now	3.9%
It doesn't work well	2.4%
Reasons for using more (n=641)	
Like the effect on my wellbeing	46.2%
To reduce use of other medicines	44.6%
Need more to get relief from symptoms	42.8%
Found reliable supply	32.2%
Condition is worse and I need more	31.4%
Can afford more now	15.1%
Found a health professional who prescribes	3.2%

access any form). Both response categories were topped by smoking cannabis through a water pipe (Figure 1).

Perceived effectiveness of medicinal cannabis

Participants overwhelmingly believed their symptoms had improved since starting to use cannabis for medicinal reasons. Seizures received the highest scores for perceived improvement (ie, 97.2% who suffered from seizures reported their symptoms had improved) (Figure 2).

Interaction with legal medicines

Eighty-nine percent of participants reported using pharmaceutical medications to treat their health condition(s) in addition to using cannabis. The pharmaceutical drugs used most often included: NSAIDs (eg, ibuprofen) and paracetamol (70.5%); opioids (55.5%), antidepressants (46.5%) and benzodiazepines (34.6%) (n=2,841). High rates of substituting pharmaceutical medicines with cannabis were reported, particularly for opioids: 95% of those who

Figure 1: Main route of cannabis administration during the past 12 months and preferred way.

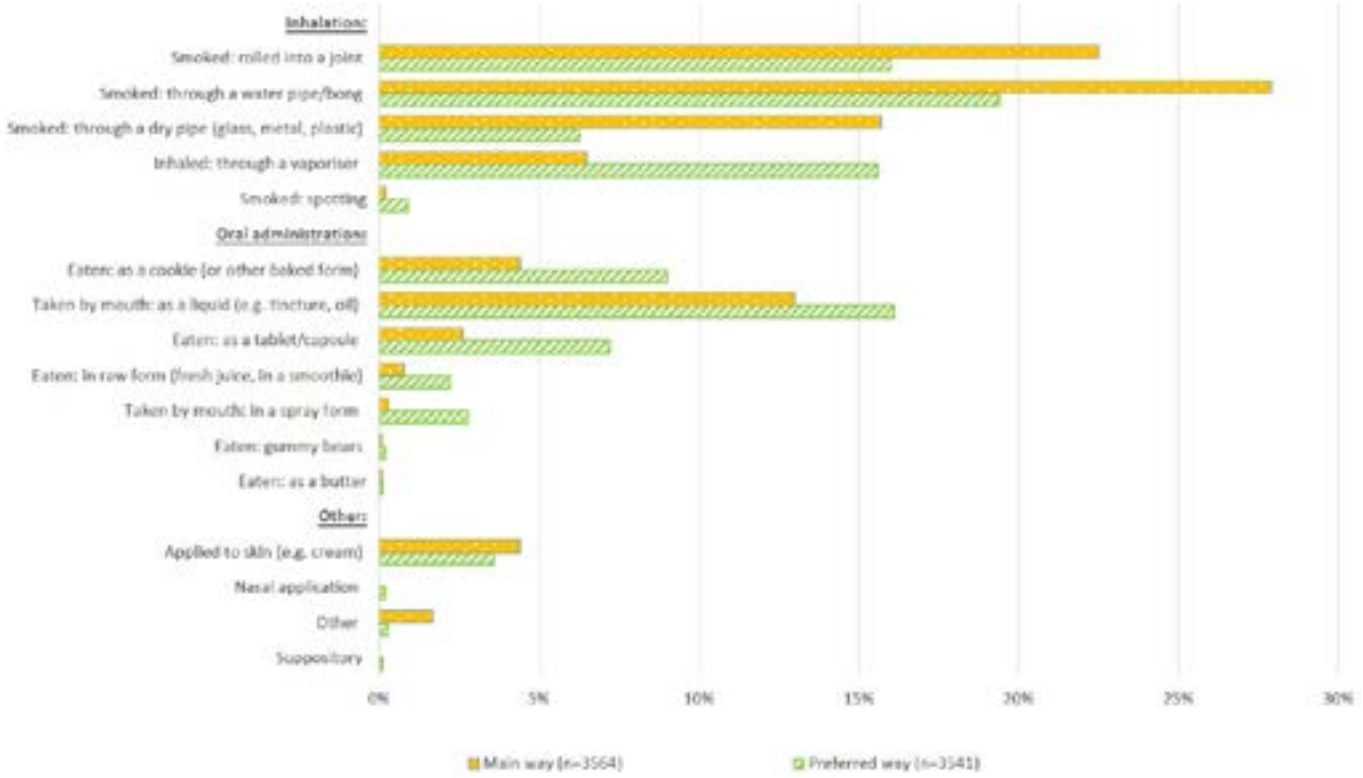


Figure 2: Perceived impact of medicinal cannabis use on the severity of symptoms assessed using Patient Global Impression of Change scale.

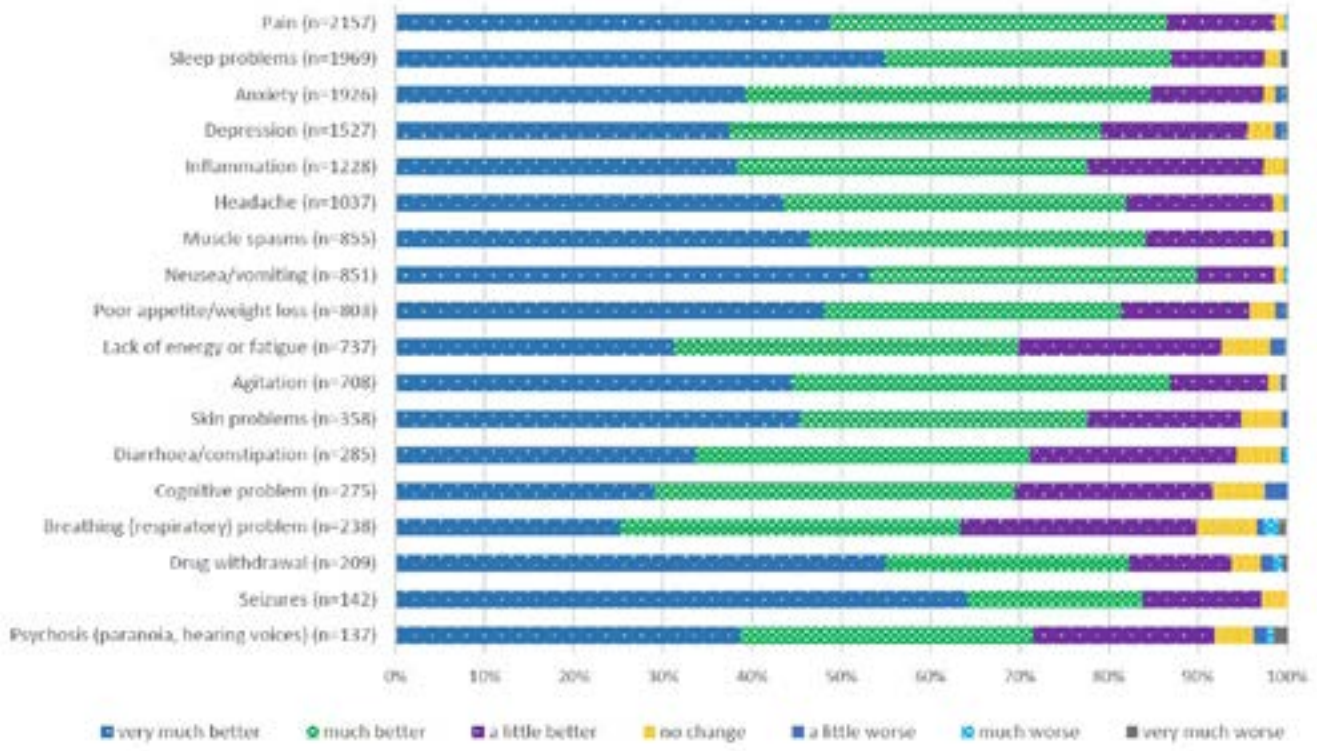
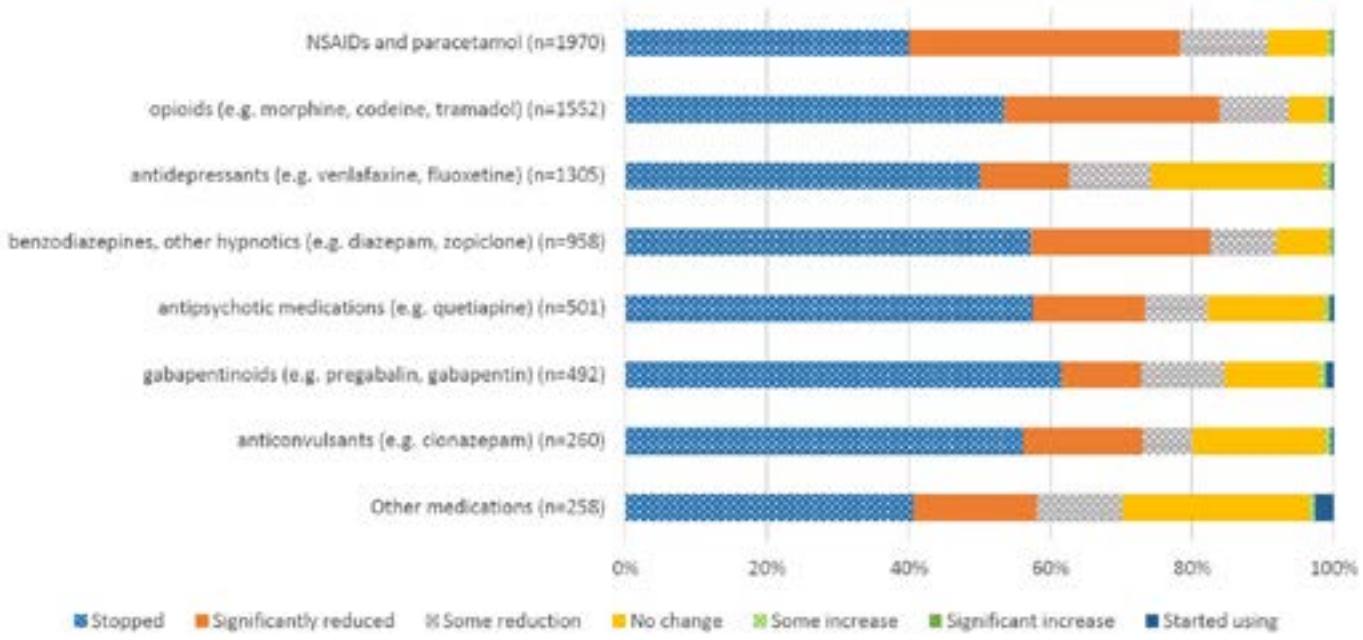


Figure 3: Self-reported change in use of non-cannabinoid pharmaceutical medicines due to use of cannabis for medicinal reasons.



used opioid medications reported reducing their opioid dose since using medicinal cannabis, including 53% who stopped opioid treatment completely (Figure 3).

Side effects

Approximately half the respondents (51.8%) experienced side effects from their use of cannabis in the past 12 months. The most common side effects were increased appetite (29.2%), drowsiness (11.6%), eye irritation (11.1%), craving for cannabis (dependency) (10.4%) and memory impairment (10.3%). A minority reported psychological problems including anxiety (6.4%), paranoia (4.1%), confusion (3.8%) and "depressed mood" (3.1%) (Table 4). Those who experienced side effects reported a median of two side effects in the past year.

Access and the cost of cannabis therapy

The majority of respondents (51.4%) reported accessing medicinal cannabis from multiple sources. The main method of access was by purchase from a drug dealer (27.7%), followed by home-growing (12.6%), buying from friends and family (12.2%,) and gifts from friends or family (10.0%). Only 4.7% of respondents reported accessing cannabis via prescription (Figure 4).

Participants spent an average $305NZD (median $217) on medicinal cannabis supply per month. Over a quarter (27.7%) received all their medicinal cannabis supply for free (ie, by growing their own or as gifts from friends or family) (n=3,074). Those who accessed legal cannabis via prescription reported an average monthly spend on prescribed products of $656 NZD (median $350).

Discussions with health providers

Nearly two-thirds of respondents (63.5%) had discussed their use of cannabis for medicinal reasons with a health provider, and nearly half of the sample (46.6%) had done so in the past year (n=2,810). GPs were most commonly consulted (89.8%), followed by specialist doctors (45.5%), counsellors or psychologists (39.2%), nurses (21.8%), alternative health providers (21%) and pharmacists (11.1%) (n=1,770).

Fourteen percent (14.1%) of participants requested a prescription for a medical cannabis product in the past year and 4.9% had been prescribed a medical cannabis product. The top three prescribed cannabis products were: Tilray CBD100™ (43%), Tilray CBD25™ (31%) and Sativex (18%). Participants who did not ask for a prescription (85.9%) were asked about reasons for not

Table 4: Side effects from use of medicinal cannabis experienced in the past 12 months (n=2,639, multiple responses were allowed unless the "no side effects" response was chosen).

	%
No side effects	48.2%
Increased appetite	29.2%
Drowsiness	11.6%
Eye irritation	11.1%
Craving for cannabis (dependency)	10.4%
Memory impairment	10.3%
Lack of energy or fatigue	8.9%
Respiratory complaints (eg, cough)	8.7%
Anxiety	6.4%
Racing heart	4.7%
Paranoia	4.1%
Confusion	3.8%
Decreased appetite	3.7%
Dizziness	3.6%
Depressed mood	3.1%
Sweating	3.4%
Sleep disturbance	3.1%
Headaches	2.6%
Panic attack	1.5%
Nausea and/or vomiting	1.4%
Shaking	1.4%
Constipation	1.2%
Diarrhoea	1.2%
Hallucinations	1.2%
Other	1.2%

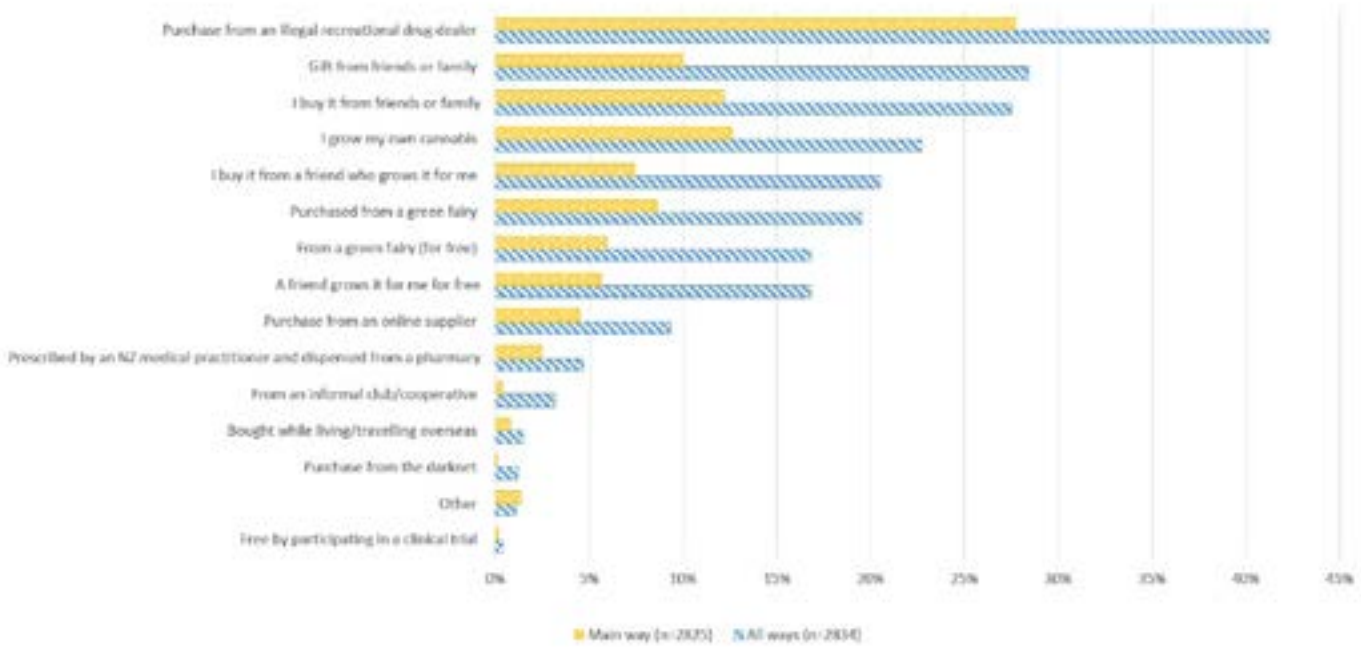
doing so. The main reasons given were lack of faith that the health provider would prescribe a cannabis product (40.8%), the bureaucracy involved in access (39.8%) and unaffordable prices (36.2%) (Table 5).

Anticipated engagement with future regime and preferred legal access

Participants were asked if they were aware of the new Medicinal Cannabis Scheme being developed at the time of data collection. Three quarters (78.2%) were aware of the regime and around two-thirds of those (66%) said they were "likely" or "very likely" to use it. Those who did not intend to engage with the new scheme most often explained their position in terms of the anticipated high financial cost of accessing products (Table 5).

Asked to choose their preferred way of accessing medicinal cannabis in a legal regime, most participants indicated home-growing (77.7%) and purchase from a licensed dispensary (73.9%) (n=2,573,

Figure 4: Ways of accessing medicinal cannabis in the past 12 months.



multiple responses permitted). Less popular were social supply arrangements (ie, "buying from a green fairy or a friend", 40.9%) and access from a pharmacy on prescription (as proposed under the Medicinal Cannabis Scheme) (39.1%).

Discussion

Consistent with similar research overseas[13,15,17] we found that cannabis is used to treat a wide range of health complaints, with most users taking it to manage pain, anxiety, depression and sleeping problems. Cannabis use has been associated with mental health problems, including depression,[18] and consequently the level of using cannabis to medicate these disorders reported in our survey indicates the need for further research to determine efficacy and best practice.

Smoking was the most common way of administering cannabis in our sample, reflecting the fact that cannabis flower is currently the most common form available on the black market. Smoking cannabis exposes users to respiratory health risks, which could be addressed if the new MCS succeeds in encouraging users' transition to other forms, including oral administration. Cannabis users in our survey were cognisant of alternative delivery methods that minimise respiratory damage, including oral administration and vaping cannabis. Vaping can potentially reduce respiratory harms from smoking,[19,20] but safety may vary depending on the vaping method[21] and the long-term effects of cannabis vaping have not been studied.

Despite some relaxation in access to cannabis-based products in New Zealand in the last two years, only 14% of this survey sample had asked their health professional for a prescription for a cannabis-based product, and only 5% received a prescription. Medicinal cannabis users noted the barriers of price and the limited range of cannabis-based products available on prescription, something the new MCS aims to address. However, many respondents also explained they were reluctant to ask for a prescription due to the fear of being judged. As reported by our respondents, only one in three patient requests for a cannabis prescription were successful.

Table 5: Reasons for not asking for a prescription and intention not to engage in the Medicinal Cannabis Scheme (multiple responses permitted).

Why not asked for a prescription for cannabis-based product? (n=2,402)	**%**
I think my provider wouldn't prescribe	40.8%
Process too bureaucratic	39.8%
The current products are not affordable	36.2%
Because I was scared of being judged	34.0%
I wasn't aware that cannabis-based products are available on prescription	33.3%
I am happy with my current supply arrangements	26.8%
The range of products is too limited	24.4%
I don't believe that private industry should profit from my use of cannabis for medicinal reasons	18.2%
I prefer to grow my own	16.7%
I am worried about the use of pesticides and other chemicals in factory produced cannabis	16.4%
Other reasons	4.4%
Why not intending to engage with the new Medicinal Cannabis Scheme? (n=351)	
I don't believe that the products will be affordable enough	56.4%
I don't believe prescriptions will be easy to obtain	48.8%
I am happy with my current supply arrangements	43.9%
I prefer to grow my own	39.4%
I don't believe that private industry should profit from my use of cannabis for medicinal reasons	32.7%
I am worried about the use of pesticides and other chemicals in factory-produced cannabis	32.1%
Other	7.0%

This is in line with other recent New Zealand research where approximately two out of three surveyed GPs did not prescribe a cannabis-based product at the time of patient request.[22] Under the planned reforms there is currently no list of eligible conditions and the decision about prescribing is left to treating clinicians.

The MCS will not require efficacy data (unlike for standard medicines). The scarcity of high-quality evidence for cannabis therapy in specific conditions has been a major challenge in implementing medical cannabis schemes overseas.[23] Our survey shows a clear discord between user-reported experiences with a range of conditions and symptoms and the existing medical evidence. Based on the currently available studies, there is a reasonable level of evidence that medical-quality cannabis preparations and cannabinoids help reduce symptoms of epilepsy, nausea and vomiting.[24,25] Cannabinoids are superior to placebo for chronic pain, but only marginally so, and the recent systematic review of controlled trials and observational studies concluded that the evidence for effectiveness of cannabinoids in chronic non-cancer pain remains "limited".[26] The evidence for effectiveness of cannabinoids for the treatment of mental disorders also remains scarce.[27,28] CBD has been found to reduce anxiety symptoms at the time of a stressful events[29] but larger studies are needed to verify its usefulness in the treatment of social anxiety disorder. Overall, medical research on cannabis is in its early stages and more evidence will be available in the coming years.

The high efficacy scores reported in our survey may reflect sampling bias (those having positive experiences being more likely to participate in the survey) and a placebo effect. Many participants also reported reducing or stopping their use of other pharmaceutical drugs, and the improvement in symptoms may be due to the reduction of side effects from pharmaceutical drugs or negative interactions between different pharmaceuticals. On the other hand, the positive therapeutic benefits of the pharmaceutical medicines would also be lost, complicating this explanation. The interaction of medicinal cannabis with traditional pharmaceutical medicines deserves further study. Some American studies have found reduced opioid overdose deaths in US states with medical cannabis programmes.[30]

Despite the limited engagement of medicinal cannabis users with the current legal access route, most respondents indicated their willingness to engage with the new MSC. The legality and consistency of legal products may encourage the transition from unofficial sources of supply to legal supply, but the availability of potentially cheaper cannabis from the black market will also provide an alternative if administrative barriers are high.[31] Finally, the legalisation of cannabis for recreational use, pending results of the September 2020 referendum, may also provide an alternative way of supply, with the convenience of price and access but at the expense of medical oversight.

A challenge in studying medicinal cannabis use lies in the blurred boundary between medical, therapeutic and recreational uses of cannabis. Like other studies,[32,33] including previous analysis of New Zealand Health Survey data,[14] we found a significant proportion of medicinal cannabis users also use cannabis recreationally.

Limitations

The study has a number of important limitations. As outlined, the survey was a convenience sample, and consequently is not representative of the medicinal cannabis user population in New Zealand. At the very least, our recruitment strategy is likely to be biased towards Facebook™ users. New Zealand has a high level of digital engagement by international standards.[34] For example, 2.3 million New Zealanders log on to Facebook™ every day (from a total population of 4.8 million).[35] Further, the challenges and costs of recruiting a representative sample of a small hidden population of medicinal cannabis users are likely to be high.[36] Representative household surveys also have their own issues, including low response rates, particularly with regard to hard-to-reach, stigmatised populations.

Our online sample broadly resembles the demographic profile of the New Zealand population. For example, 50% of our online sample were female, 18% Māori and 76% European (as compared to the wider New Zealand population at the 2018 Census, of whom 17% were Māori and 70% European[37]). Our online sample included lower proportions of Asian people (<2%) compared to the Census (where 15% identify with at least one Asian ethnicity).[37,38] The online survey sample were more likely to have university qualifications compared to the national 2018 Census (28% had a university degree compared to 23% in the Census[38]). Furthermore, employment was lower in the online survey than in the general population (ie, 56% of the online sample was in full-time or part-time employment vs 65% employment according to the 2018 Census data). Support from a government benefit was also more common in our online sample, eg, 17% of the sample were receiving Supported Living Payments (compared to 2–3% estimates for the New Zealand population[38,39]). It is unclear the extent to which these differences represent specific characteristics of medicinal cannabis users or the consequences of the online convenience sample recruitment.

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The New Zealand nuclear veteran and families study, exploring the options to assess heritable health outcomes

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ABSTRACT

AIMS: To describe health conditions in New Zealand nuclear veterans and their offspring, and examine the utility of tests to assess their heritability.

METHOD: An online survey, open to all veterans and offspring, with questions on health conditions, the GHQ12 to measure psychological distress, the Euroquol-5D visual analogue scale (EQ5D VAS) to measure health state, and free text items on veteran support.

RESULTS: Eighty-three responses (56%) were from veterans, 65 (44%) from offspring. Anxiety and depression were prevalent in both groups, with cancers (n=31, 37%) and joint conditions common in veterans (n=26, 31%). Few offspring reported cancer, rather problems with fertility (n=18, 40%). The free text themes fell into four domains, official commitment, health, emotional and information support; however, little support had been sought.

CONCLUSION: Cancers have utility in assessing heritability, but a low prevalence and lack of diagnostic data rules this out. Psychological conditions may be heritable, but the techniques to assess this are still developing. Chromosomal damage in veterans and offspring can be detected, but with present knowledge cannot explain health outcomes. Future work should assemble a veteran and family register with linkage to routine data-sets. Veterans and offspring should be encouraged to seek support.

Over the past century, knowledge regarding the harmful effects of exposure to radiation has increased. It is now known that exposure to radiation can damage living cells by altering DNA. Normally such damage is repaired, however this process is not infallible. As a result, alterations in DNA can persist and may lead to cancer. Furthermore, if cells containing hereditary information are affected, disorders may transcend generations.[1]

In New Zealand there are two principal cohorts of nuclear test veterans. Firstly, those who witnessed the operation Grapple atmospheric tests carried out by the UK at Christmas and Malden Islands in 1957-58, and secondly, the Mururoa veterans who witnessed the French nuclear explosions in 1973, both groups being concerned about radiation exposure, chromosome damage, and heritability.

In response to the growing concern among veterans in New Zealand regarding the effects of exposure to ionising radiation, the New Zealand Ministry of Defence commissioned a study analysing patterns of mortality and cancer incidence among New Zealand Operation Grapple veterans. The results of the cohort studies of the 528 servicemen were presented by Pearce et al in 1990[2] and 1997,[3] the latter follow-up finding a relative risk (RR) of mortality from haematological cancers of 3.8, 90% confidence interval (95% CI) 1.4 to 10.8 and from leukaemia RR 5.6, 95% CI 1.0 to 41.7.

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In response to the findings of this study, the New Zealand government announced that test veterans who developed haematological cancers would be eligible for war pensions.

As knowledge regarding the hereditary nature of genetic mutations grew, an inquiry into the health status of the children of both Vietnam and Operation Grapple veterans was commissioned in 1998. This was informed by a report from the then Director of the National Radiological Laboratory, concluding that there was no evidence that Grapple veterans had been exposed to radiation that could give rise to health effects in themselves or their offspring, and that "no radiation-induced hereditary effects have been reported in human populations, even those exposed to doses giving rise to deterministic effects".[4] The inquiry subsequently found, for the children of Grapple veterans, evidence "limited/suggestive of no association" between their fathers' exposure to radiation and health effects.[5] However, the inquiry did note that scientific analysis at the time could not definitively disprove that children had been harmed as a result of their parents' service, recommending that children whose condition had sufficient or suggestive evidence of an association to their parents' exposure be provided with non-means-tested medical treatment and social care. In addition, they recommended the establishment of a special programme offering case management, family counselling and genetic counselling for natural-born children of Operation Grapple veterans, conceived after their parent's service.

The research effort then shifted to detecting genetic changes possibly attributable to radiation, and in 2005, the sister chromatid exchange study was commissioned by the Board of the War Pensions Medical Trust Fund. The study compared operation Grapple veterans to a referent group of military and police referents, finding elevated sister chromatid exchanges in peripheral blood lymphocytes in veterans.[6]

A subsequent cytogenetic analysis using three different tests to assess genetic damage found that one test method, Multicolour-FISH (mFISH) consistently showed an increase in the rate of rearrangement of chromosomal translocations and dicentrics at a statistically significant level.[7]

The study team indicated the presence of sufficient evidence that Operation Grapple veterans suffered long-term genetic damage, most likely from radiation exposure.

The Ministerial Advisory Group on Veterans' Health subsequently reviewed the cytogenetic studies, finding that "one of the three tests in the cytogenetic study showed statistically significant elevated frequencies of some chromosomal abnormalities in exposed veterans, which may indicate long-term damage from radiation exposure. However, causality cannot be definitively attributed to radiation alone. The actual health consequences or seriousness of these chromosomal changes are not certain."

Paternal transmission of environmental exposures in general has been suspected for decades, has been shown in animal studies, and is now starting to emerge in human studies.[8] A radiation-exposed father developing a condition, especially a cancer, and offspring developing the same condition would be good candidates to inform such research efforts.

We were asked by the Mururoa Veterans Group (MVG) to revisit the problem by investigating the health of New Zealand nuclear veterans and their offspring to establish the number of veterans and their offspring that could be contacted, assess their health for conditions held in common and evaluate the utility of genetic testing in this group.

Aims

The main health aims of this study were to obtain a 'health profile' of self- and doctor-diagnosed health conditions among veterans and family; undertake comparisons between the health of veterans and their offspring and evaluate what help, care and support has (or has not) been made available to veterans and their families.

The main feasibility aims of this study were to determine the study base; through identifying the health conditions reported, identify options for genetic testing and determine the level of interest among nuclear veterans in undergoing such testing.

Methods

Study population

The study base was members of the crews of HMNZS Otago and HMNZS Canterbury deployed to Mururoa on 21 and 28 July 1973 respectively, along with their offspring. The complement for each crew was 242 and 256 respectively, a total of 498 personnel. Veterans from Operation Grapple, 528 servicemen who served at Christmas (now Kirimite) and Malden Islands in 1957 and 58 during the British atmospheric tests were also encouraged to participate, as were veterans of J Force occupying Japan immediately after the Hiroshima and Nagasaki bombings. Apart from Grapple and Mururoa veterans, the number of the other nuclear veterans and their descendants is unknown. Participants were excluded from the study if they were younger than 18 years of age, were not a nuclear veteran or descended from a veteran.

Recruitment to this study was voluntary, primarily through MVG, who travelled to the major centres in New Zealand during 2018, also commissioning a media campaign. Potential participants registered their interest by enrolling with the MVG by email. These participants were then sent a link to an electronic survey, through which we collected our data. Paper or phone surveys were made available if participants felt unable to complete the electronic survey.

Survey design

The survey collected demographic information, and participants were asked about self-diagnosed and physician-diagnosed medical conditions.

Symptoms of distress were assessed using the General Health Questionnaire 12 (GHQ-12). This measure includes 12 items with a four-point response scale. Items are summed to yield an overall total score, with higher scores indicating greater distress.[9]

The EuroQol visual analog scale (EQ VAS)[10] is a vertical scale graduated from 0 to 100, which participants mark with a cross and write the indicated number into a box, with 100 indicating 'the best possible health you can imagine', and 0 'the worst possible health you can imagine'.

Support was assessed by asking whether or not they received any support as a nuclear veteran or a family member, (yes/no) what the support was (open text) and if so were they satisfied with it (very satisfied/satisfied/neutral/unsatisfied/neutral), also "what support or additional support do you think is needed".

Participants were finally asked whether they might be willing to give consent to genetic testing in a subsequent study, although it was made clear that there was no obligation to participate in such a study, nor would the refusal to do so have a negative impact.

The project was carried out by a group of Trainee Interns, final year medical students, carrying out a 'health care evaluation project' as part of their studies. Ethics approval was given by the University of Otago Human Research Ethics Committee, reference no. HE19/008, and the Ngāi Tahu Research Consultation Committee advised us on the implications of the project for Māori.

Analysis

The analysis of distress, health status and health conditions was descriptive, the STATA statistical package being used to calculate mean GHQ and EQ VAS scores and construct 95% confidence intervals (95% CIs) around these estimates where appropriate. An inductive analysis was carried out on the free text data, with grouping into themes by two team members and independent confirmation by a third.

Results

We received 148 completed responses to the questionnaire. Of these responses, 83 (56%) were from veterans of Mururoa or Operation Grapple and 65 (44%) were from family members of a veteran. Of the veterans who responded, nearly all served at Mururoa, a 77% response rate from the 111 members, and 95% of respondents were either a Mururoa veteran or a descendant of a Mururoa veteran. The majority of the veterans were of New Zealand European ethnicity, and aged between 65–74 years of age (Table 1). Of the family members, 95.3% were of New Zealand European ethnicity, and the majority of respondents were between 35–44 years of age. Approximately 3–4% of both groups identified 'other' for ethnicity, and these included Irish and Australian nationals.

Table 1: Demographics of participants.

Ethnicity	Veterans (%)	Descendants (%)
NZ European	64 (77)	52 (80)
Māori	13 (16)	9 (14)
Pacific Islander	0 (0)	1 (2)
Other	6 (7)	3 (4)
Age	**Veterans (%)**	**Descendants (%)**
18–24	0 (0)	9 (14)
25–34	0 (0)	9 (14)
35–44	0 (0)	35 (54)
45–54	0 (0)	6 (9)
55–64	14 (17)	4 (6)
65–74	67 (81)	2 (3)
>75	2 (2)	0 (0)
Total	**83**	**65**

Health conditions reported by respondents and diagnosed by health professionals were skin disease and cancer, predominantly in the veterans' group (Figure 1). These cancers included a number of skin cancers, both melanoma and non-melanotic skin cancers, prostate cancer, non-Hodgkin lymphoma and leukemia. Although thought to be associated with radiation exposure, very few identified thyroid conditions, and were more likely to be in offspring.

Anxiety and depression were reported by both, the former with greater prevalence in offspring, the latter in veterans.

Of note, 40% of offspring reported issues with fertility, citing endometriosis, miscarriages and polycystic ovarian syndrome (PCOS) as contributors. By contrast, only 16% of veterans identified fertility as an issue.

The mean values, along with 95% confidence intervals (95% CIs) for the GHQ-12

Figure 1: Selected self-reported and health professional-diagnosed* health condition.

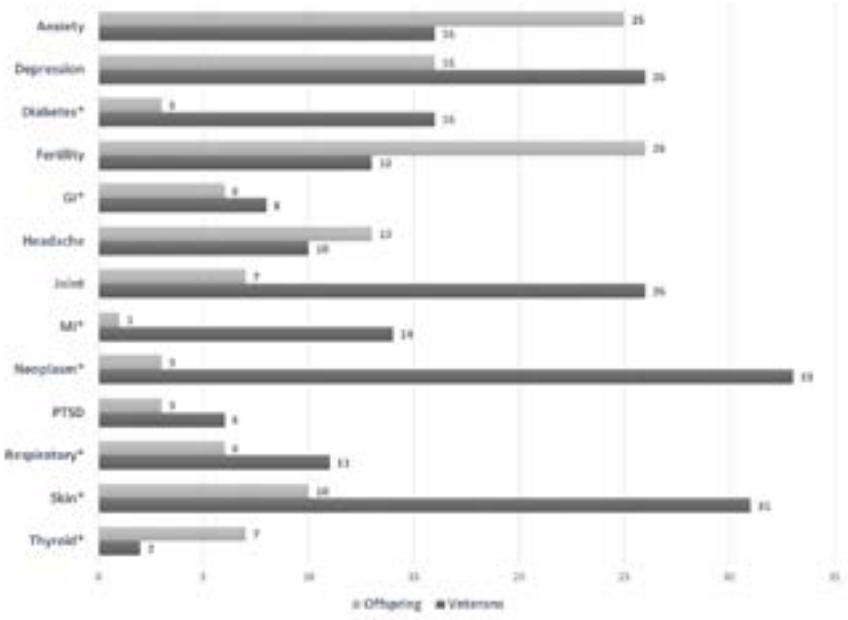

Table 2: Mean GHQ-12 and EQ VAS scores between groups.

	n (%)	GHQ-12 Mean Score (95%CI)	EQ-5-VAS Mean Score (95% CI)
Total	148 (100)	14.1 (13.1–15.1)	64.2 (60.2–68.2)
NZ European	119 (80)	13.9 (12.7–15.1)	65.7 (61.1–70.3)
Māori	22 (15)	13.5 (10.6–16.4)	63.1 (51.6–74.6)
Veteran	83 (56)	13.9 (12.4–15.4)	61.3 (55.8–66.8)
Family	65 (43)	14.3 (12.8–15.8)	66.9 (61.2–72.6)
Mururoa	141 (95)	14.2 (13.1–15.3)	63.9 (59.8–68.0)
Grapple	7 (5)	16.4 (10.6–22.2)	66.4 (50.8–82.0)
Support	27 (18)	15.0 (12.8–17.2)	60.9 (51.3–70.5)
No support	117 (79)	14.0 (12.8–15.2)	65.0 (60.4–69.6)

and EQ5D-VAS scores are shown stratified for demographic factors in Table 2, with no significant between-group differences. The mean of 14.1, 95% CI 13.1–15.1, can be compared with the mean GHQ-12 score in the Australian and New Zealand population of 8.98,[11] this latter value not falling within the confidence limits, meaning there is more distress in respondents than the general population.

The GHQ scores are also reflected in the self reported prevalence of anxiety and depression.

The mean EQ VAS scores lay the range 60.9 to 66.9. In New Zealand, the mean EQ-VAS scores are stable across the age range from 18–65, with lower and upper bound values of 82.4 (age group 18–24) to 81.6 (age group 55–64), falling to 79.6 in the 65–74 year old group.[12]

The free text themes fell into four domains, commitment, health support, emotional and 'other' supports, and information support. Commitment was mentioned by several veterans and family members, also in terms of government culpability: "some recognition of what they did was wrong would be a start." The need for health support was frequently reported, physical issues and mobility being specifically mentioned, along with the need for health and medical screening and 'checks', with the inclusion of families in these mechanisms.

The requirement for other supports included emotional support, one family member mentioning this as "emotional support, ie, recognition of how living with our father affected my mental, and possibly our physical health." The need for financial support was often expressed. The requirement for information also emerged, including the need to collate information, to gather information about long-term effects in this group, so that veterans could grow knowledge "just to understand what has happened to my body" and on the part of family members "just to understand what they went through". Only two respondents suggested genetic testing as a form of support, however 132 registered their interest in future research participation.

Only 21 veterans and three descendants received support, 77% not receiving any support. Some reported that although they felt support was available, they weren't aware of what, in specific terms, was available or how to access it. Thirty-five respondents felt that the Government, or the Government through New Zealand Veterans Affairs (NZVA), were responsible for providing support, five that NZVA alone were responsible and three the New Zealand Defence Force (NZDF).

Discussion

Although this is essentially a descriptive analysis, compared with population normative values, distress is higher and health status lower in Mururoa veterans and their offspring.

Cancers seem to be prevalent among the surveyed veterans, those reported including skin and haematological disorders. The prevalence of the former may however be explained by the average age of this population and the high incidence of skin cancers in New Zealand. The age-adjusted incidence rate for non-melanotic skin cancer in New Zealand is 786.1 per 100,000 people in the non-Māori population, and 51.0 per 100,000 people in the Māori population.[13] Based on the responses in our study, the cumulative incidence among the veterans may equate to 10,280 per 100,000 people, which may represent a greater proportion of the veteran population affected compared to the general New Zealand population.

By contrast, the rates of the remaining diseases associated with exposure to ionising radiation, including thyroid conditions diagnosed by a health professional, was equally low among both veterans and descendants.

Interestingly, a significant proportion of descendants (40%) reported having issues with fertility. When asked to specify, many reported endometriosis or polycystic ovarian syndrome. However, some reported taking a year to conceive children, but this does not meet the criteria for infertility. Some also said they had chosen not to have children because of their fathers' exposures to the nuclear tests.

The strengths of the study lay in the support of the veterans and their family members, however the main limitation was the response rate from both groups. A total of 498 men are on the crew lists of HMNZS's Canterbury and Otago. At least 80% will have survived to age 65, and as 16% of our Vietnam veteran cohort, of similar age, was living overseas it means that just in excess of 300 veterans would be alive and living in New Zealand. That being so, the 83 replies represent approximately 27% of the ships' complements and 75% of the 111 MVG members. The situation will be worse with families, as we do not know the study base. Bias is also possible, for instance, those involved in the MVG may already be more concerned about possible medical conditions relating to their exposure, be more distressed and more willing to participate in our study. The participation of Grapple veterans was extremely low, however they have their own association, the New Zealand Nuclear Test Veterans Association, whose view is that no further testing of veterans is desirable, the focus should be shifted to children.[14]

Furthermore, by conducting an electronic survey, we restricted our responses to people who not only had access to a computer but to those who were able to navigate the survey. We considered using a paper questionnaire distributed by post, but this six-week project presented a time constraint. Our results may not therefore represent the underlying distribution of distress and health status in this population.

Previous cross-sectional surveys have been carried out in Grapple veterans. Roff et al[15] reported in 1999 on a survey sent to 388 of the Grapple servicemen or their families with responses from 235 (62% of questionnaires, 45% of servicemen) and 97 from families (41%). The major conditions reported were skin (49), cardiovascular (47), respiratory (22), arthritic (20), infertility (18) and bilateral cataracts (10). In children, skin (33), respiratory (29), other skeletal (24), cardiovascular (20), arthritic and 'other' blood (14) conditions were reported.

In 2005, Podd et al[16] carried out a case-referent study on 50 Grapple veterans and 50 referents with military or police service. Cancers (n=24 v 2) and chronic skin conditions (40 v 12) were prevalent in veterans. Psychological problems were evident in veterans having higher scores, and variability, in the Geriatric Depression Scale, with a mean of 3.92, standard deviation (SD) 3.5, than referents mean 0.9, SD 0.97. They also had uniformly lower scores on the Short Form 36 Health Survey, including the general, physical and mental health items, which the authors ascribe to long-term stress.

The reason for the high levels of distress in the sample may be partly ascribed to worry about ionising radiation exposure, however a recent review has emphasised that distress is common in veteran populations, and the type of service undertaken, along with a unsuccessful transition from a military to a

civilian life, can also have a negative effect on wellbeing.[17] Contemporaneous external monitoring was carried out by the National Radiological Protection Laboratory, the results being more recently reviewed by the Institute of Environmental Science and Research Centre for Radiation Science.[18] Based on external gamma radiation monitoring, pocket dosimeters and pump systems on board the ships, they found that exposure was less than 0.001 mSv/h, with no airborne radioactivity detected on HMNZS Otago, and only 0.005mSv on HMNZS Canterbury. Personal monitoring was below the detectable limit of 0.12 mSv, similar to background radiation. Calculations also suggested that there was no fallout on either ship, that there would not have been any fallout into the sea and therefore no water contamination. Veterans however trust neither the equipment nor the calculations, and are concerned about internal, rather than external, radiation dose.

This idea is reflected in the results of our survey, where many veterans expressed their dissatisfaction at having been sent to observe nuclear detonations without being informed of the possible health consequences. There was significant ill-feeling among the veterans toward the Labour government in power at the time. The previous nuclear veteran health investigations all suggested support to deal with uncertainty, this need being reinforced by our respondents. When asked to elaborate on the support required, a large proportion emphasised the need to support the physical health of veterans, and help to access the benefits. There was strength of feeling that the New Zealand Government and New Zealand Veterans Affairs should provide this support. This support is however available, so it is essential that veterans actually seek it.

The support that is currently available for New Zealand nuclear veterans includes access to a war disablement pension provided their illness is on any one of the 'presumptive lists'. These lists include a list of illnesses linked to potential exposure to ionising radiation modelled on a US Department of Veterans Affairs list. Unfortunately, conditions that are on a 'regulatory list' of radiogenic diseases in the US are not automatically awarded in New Zealand; this because of additional requirements including the amount and duration of radiation exposure, and a minimum latent period between exposure and onset of the disease. New Zealand nuclear veterans can however make claims for conditions on this latter list under the provisions of the Veteran Support Act 2015.

Furthermore, in June 2002 the war pension status of Mururora Veterans was changed from 'routine' to 'emergency' service. As a result, any war pension claims from that time forward are now considered using more relaxed evidence requirements. In addition, claims that were declined prior to June 2002 can now be reconsidered if a veteran believes the condition is related to exposure to ionising radiation. By contrast, Australia does not give disability pensions to nuclear test veterans. Instead, all British Atmospheric nuclear test programme personnel in Australia can access treatment for all malignant cancers, even cancers not linked to exposure to radiation.

As regards future directions, this is a problem with no easy solution: paternal transmission of the effects of environmental exposure to radiation, just as with other public and environmental health problems, demands both epidemiological and technical approaches.

In terms of future work, assembly of a Mururoa veteran register is possible. Although the crew lists contain only surname and initials, forenames and dates of birth can be found in the NZDF archives. That being achieved, the National Health Index (NHI) number, unique to each individual, can be traced with an inception date in 1988, the date of first NHI assignment. The NHI can then be linked to the Mortality Collection and Cancer Registry data. Offspring would however have to register for the two sets of data to be linked for genetic testing.

An alternative for offspring would include tests for chromosomal abnormality testing, similar to those carried out in Grapple veterans. If offspring of both Grapple and Mururoa veterans were tested in comparison with a control group and a similar difference were found, it would add weight to the argument.

Another approach has been taken by a team from Brunel University London, who

are recruiting 50 nuclear test trios: veteran, child, child's mother.[19] The referent group will be veterans who served in the tropics at the same time. Cytogenetic evidence for radiation will be sought in veterans and, in the first-generation children of test veterans, differences in the frequency and spectra of DNA mutations and chromosomal aberrations will be compared with those in the control family group.

New Zealand nuclear test veterans might be offered a similar opportunity.

This however does not answer the question about disease outcome, which can only be answered epidemiologically. If offspring had the same disorder, for example cancer, a genomic investigation using stored tissue might have utility. Collating and updating the register should therefore be a priority.

Competing interests:
Nil.

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Attitudes towards cannabis and cannabis law change in a New Zealand birth cohort

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ABSTRACT

AIMS: Personal cannabis use is common across New Zealand, and an upcoming referendum will enable the public to vote on whether this should be legalised. The present research aimed to examine the attitudes of midlife New Zealand adults on cannabis use and legalisation, and to identify potential predictors of those attitudes.

METHODS: At age 40, 899 participants drawn from the Christchurch Health and Development Study were interviewed about the perceived harmfulness of cannabis use, opinions on legalisation for recreational use and supply, and the use of cannabis for medicinal purposes. In addition, a range of potential predictors of legislative attitudes were examined.

RESULTS: We identified a wide range of attitudes across the cohort, however the majority tended to hold a neutral view. More than 80% of the cohort expressed support for medicinal cannabis, while 47.8% supported decriminalisation, and 26.8% expressed support for legalisation for recreational use. The strongest predictors of support for legalisation were prior use of cannabis and other drugs, while additional positive predictors included a history of depression, Māori ancestry, parental drug use, novelty seeking and higher educational attainment. Predictors of more negative attitudes were also identified, and included female gender and having dependent children.

CONCLUSIONS: These findings provide insight into cannabis-related views within the New Zealand context, and may help to predict voting behaviour during the 2020 Cannabis Referendum.

Cannabis use is widespread within New Zealand, with an estimated 70–80% of the population having tried cannabis by age 25.[1–3] International approaches to the regulation of cannabis have changed in recent years, which has led the New Zealand Government to release a draft Cannabis Legalisation and Control Bill, which proposes legalisation and regulation of cannabis for recreational use and supply. A referendum in September 2020 will provide the New Zealand public with an opportunity to vote on whether cannabis should be legalised. Although the referendum itself will be a useful indication of views on cannabis use, the ongoing public debate highlights uncertainty as to the outcome of the referendum.

In order to predict voting behavior in the referendum, a first step is to explore attitudes towards cannabis and changes to the legal status of cannabis. Although attitudes towards cannabis tend to vary considerably between individuals, they appear to be less negative than for other illicit drugs.[4] Views on cannabis legalisation are influenced by a variety of environmental and personal characteristics. In particular, international research suggests that characteristics such as gender and age are important, with women and older individuals having more conservative views.[5,6] Perceptions of cannabis as being dangerous have been found to be associated with more negative attitudes, while individuals with a history

of cannabis use generally express greater support for legalisation.[6] The media is also understood to have a widespread influence on attitudes towards cannabis use and legalisation, with reports of a relationship between positive media coverage and support for legalisation.[7] Such a relationship may not be limited to recreational cannabis use, as testimonials about the benefits of medicinal cannabis have been observed to increase positivity towards medicinal cannabis use.[8]

Given the key role of public perceptions and attitudes in the 2020 cannabis referendum, it is important to develop a more in-depth understanding of attitudes towards cannabis use and potential cannabis law change in New Zealand. One way to do this is to use data from an established New Zealand cohort that has well-defined data on cannabis use and problems with cannabis over the life course, as well as a range of measures of individual, family and demographic factors that may influence these attitudes. The present study aimed to explore these issues within a cohort of midlife New Zealanders studied since birth, and examined attitudes towards cannabis use, perceived harmfulness, decriminalisation and legalisation of cannabis, and predictors of these attitudes.

Method

Participants

Participants were drawn from the Christchurch Health and Development Study (CHDS), a birth cohort of 1,265 individuals recruited in Christchurch, New Zealand in 1977. The cohort was assessed at birth, four months, annually to age 16, and then at ages 18, 21, 25, 30, 35 and 40. A total of 904 participants (74% of the surviving cohort) were assessed at age 40, of whom 899 responded to questioning on cannabis. The age 40 data collection took place between June 2017 and June 2019, meaning that most cohort member's interviews were conducted before the announcement of the referendum on the Cannabis Legalisation and Control Bill in New Zealand in 2020, and also prior to changes to the Misuse of Drugs Act (1975)[9] in August 2019 that served to decriminalise most forms of drug possession in New Zealand. All aspects of study design and conduct have been approved by the New Zealand Health and Disabilities Ethics Committee.

Measures

Attitudes towards cannabis law reform and self-report use of cannabis for medicinal purposes

At the age 40 assessment, cohort members were asked a series of nine custom-written questions intended to explore various aspects of cannabis law reform, including questions about medicinal cannabis, decriminalisation of cannabis use, legalisation of cannabis use and views as to the extent to which cannabis is harmful. Questions were answered on a five-point Likert scale ranging from 1 ('strongly disagree') to 5 ('strongly agree'), with 3 representing a neutral option. Five of the items were scored such that higher scores represented more positive attitudes towards cannabis, while four were scored in the reverse manner.

The items were analysed for reliability and suitability for use as a single-factor scale using confirmatory factor analysis (CFA) and an internal consistency analysis (Chronbach's alpha), using all nine items of the scale. The results of these analyses are described below in the Results section. Then, items were summed (after reversing the four negatively-worded items) to create a total scale score reflecting positive attitudes towards cannabis liberalisation. It should be noted that items pertaining to the legal age for using cannabis were set at age 18.

In addition, cohort members were also asked whether they had ever used cannabis to "relieve chronic pain or nausea, or for some other medicinal purpose". This question was answered "yes" or "no", and if answered "yes", cohort members were then asked to report the context (reasons for using, how often, effectiveness) under which they had used cannabis medicinally.

Predictors

A range of measures drawn from the CHDS database were selected for inclusion in the analysis on the basis that they were of interest from a policy perspective and/or were identified in preliminary analysis as predictive of cannabis attitudes.

Lifetime cannabis exposure (ages 14–15 to 39–40)

At the assessments from age 15 to age 40, cohort members were asked about the frequency with which they used cannabis for each 12-month period since the previous assessment, resulting in 26 years of cannabis frequency data being collected for each year from age 14–15 to age 39–40. Cohort members who reported using cannabis at least weekly (or more frequently) during any year were classified as having had used cannabis "regularly" during that year. These classifications were summed over the period 14–15 years to 39–40 years in order to create a measure of the number of years in which the cohort member used cannabis regularly.

Other illicit drug use (ages 14–15 to 39–40)

Parallel to the assessment of cannabis use, participants were also questioned about their use of other illicit drugs in each 12-month period. This questioning spanned use of solvents; stimulants; barbiturates; other prescription medications that were illicitly obtained; opiates, including both heroin and morphine; cocaine; hallucinogens including ecstasy, LSD and PCP; and any other substances (primarily plant extracts) including mushrooms and datura. The data thereby provided an account of the individual's reported frequency of use of a range of other illicit drugs for each year from ages 14–15 to age 39–40. A measure of the extent of use of other illicit drugs was constructed based on a count of the number of years the participant reported using other illicit substances at least monthly.

Major depression (ages 16–40)

At each assessment from age 18 to age 40, cohort members were asked about their experience of symptoms of major depression since the previous interview, based on the Composite International Diagnostic Interview (CIDI)[10] pertaining to DSM-IV[11] symptoms of major depression. Those cohort members who met criteria for major depression during any interview period (ages 16–18; 18–21; 21–25; 25–30; 30–35; 35–40) were classified as having major depression during that assessment period. A measure of the chronicity/severity of depression was constructed based on a count of the number of occasions across the six interview periods that the individual met criteria for major depression.

History of violent/property offending (ages 16–40)

At each assessment from age 18–40, participants were questioned about their engagement in offending since the previous assessment. Items from the Self Report Delinquency Inventory (SRDI)[12] were used to assess the extent to which the participant reported engaging in violent or property offending. A measure of severity/chronicity of offending was constructed based on the number of interview periods from age 16–18 to age 35–40 during which the cohort member reported engaging in violent or property offending.

Gender

Gender was measured at birth.

Māori ancestry

At birth, and ages 14, 21 and 25, cohort members/parents were asked a series of questions pertaining to Māori ethnicity, and whether the cohort member had any Māori ancestry. Those cohort members who reported having Māori ancestry at any assessment were classified as Māori (16.7 % of the sample).

Dependent children (age 40)

Cohort members were asked about their current family situation at age 40. Those who reported that they had a dependent child under the age of 18 living in the family home were classified as having dependent children (73.6% of the sample).

Educational attainment (to age 40)

At each assessment from age 21 to age 40, cohort members were asked about attainment of educational/vocational qualifications. Educational attainment was coded on a five-point scale reflecting the highest level qualification attained by age 40. This scale was: no qualifications; high school-level qualifications; tertiary qualifications below degree level; bachelor's level degree; higher-level degree qualification.

Novelty seeking (age 16)

When sample members were aged 16 years they were administered the novelty seeking items of the Tridimensional Personality Questionnaire.[13] These items were summed to produce an overall novelty

seeking measure. The reliability of this scale was α=.76.

Parental history of illicit substance use

When sample members were aged 11 their parents were questioned about parental use of illicit drugs including cannabis. On the basis of this questioning, 27.5% of the sample were classified as having parents who used illicit drugs.

Results

Response distribution for cannabis attitude items.

Table 1 shows the response distribution for the items on the cannabis attitude survey. The table shows a diversity of opinions regarding cannabis among the CHDS cohort. For example, over 80% of the cohort either 'agree' or 'strongly agree' that doctors should be able to prescribe medicinal cannabis products, and a similar percentage believed that cannabis products are an effective form of relief from chronic pain or physical health problems. On the other hand, there was only a somewhat positive view of cannabis decriminalisation (47.8% agreed v 27.2% against), and a slightly greater proportion of the cohort opposed legalisation (49.8% against v 26.8% in favour). Most cohort members agreed that cannabis use is harmful (54.4%), and most (70.3%) agreed that it should remain illegal for private individuals to sell cannabis, and a large majority (90.3%) felt that it should remain illegal for those under 18 to use cannabis. However, more people disagreed than agreed (41.9% v 32.3%) that cannabis decriminalisation would increase drug problems in the community.

Table 1: Response distribution on cannabis attitude items (N=899).

Item	Strongly disagree %	Disagree %	Neutral %	Agree %	Strongly agree %
Doctors should be able to prescribe cannabis based products for medicinal purposes (eg, to relieve chronic pain) without restriction	2.0	4.2	10.1	42.8	40.8
Personal use of cannabis should be decriminalised	7.0	20.2	25.1	28.4	19.4
Cannabis should be legalised and available for sale to people aged 18 or over, like alcohol and tobacco	14.1	35.7	23.4	18.1	8.7
Cannabis use is harmful	3.8	13.0	28.8	44.3	10.1
Decriminalising cannabis will increase the number of people in the community with drug problems	7.3	34.6	25.8	24.7	7.6
People should be allowed to grow cannabis for their own personal use	7.5	26.6	21.0	34.0	11.0
It should remain illegal for private individuals to sell cannabis	2.7	11.7	15.4	52.6	17.7
It should remain illegal for people under the age of 18 to use cannabis	0.7	2.6	6.5	51.7	38.6
Cannabis or cannabis-based products can be an effective form of relief for people experiencing chronic pain or physical health problems	0.8	1.0	10.3	53.2	34.7

Table 2: Item response profile across levels of attitudes to cannabis liberalisation scale (percentage of sample who agree or strongly agree with each item).

Item		Attitudes to cannabis liberalisation					
	Group	1 (very negative)	2	3	4	5 (very positive)	r[1]
	Percentile	1–10	11–30	31–70	71–90	91–100	
Doctors should be able to prescribe cannabis based products for medicinal purposes (eg, to relieve chronic pain) without restriction		48.2	73.6	87.1	97.5	100	0.57
Personal use of cannabis should be decriminalised		3.6	5.2	49.0	91.4	99.0	0.84
Cannabis should be legalised and available for sale to people aged 18 or over, like alcohol and tobacco		0.0	0.5	17.9	57.4	85.2	0.78
Cannabis use is harmful		95.2	79.7	52.8	27.8	15.8	0.62
Decriminalising cannabis will increase the number of people in the community with drug problems		94.0	55.7	23.2	8.0	2.0	0.70
People should be allowed to grow cannabis for their own personal use		2.4	7.1	44.0	85.8	98.0	0.80
It should remain illegal for private individuals to sell cannabis		100.0	93.9	69.8	52.5	26.7	0.56
It should remain illegal for people under the age of 18 to use cannabis		100.0	96.7	88.9	90.1	74.3	0.31
Cannabis or cannabis-based products can be an effective form of relief for people experiencing chronic pain or physical health problems		60.2	82.6	90.0	96.9	100.0	0.53

[1]Pearson correlation between scale item and total scale score.

Properties of the cannabis attitude scale

Confirmatory factor analysis of the item level data in Table 1 showed that the attitude items were consistent with a unidimensional scale reflecting the degree of positive attitudes towards cannabis liberalisation. Goodness of fit indices for a single factor model were: model X^2 (df)=35.6 (23), p=0.05; RMSEA=0.025; CFI=0.98. A scale score was constructed by summing the item level data for each participant, with all items scored such that higher scores reflected more positive attitudes to cannabis and cannabis law reform. The scale was of good reliability (α=0.83), and closely approximated a normal distribution (M=27.3, SD=5.9).

The item response profile is shown in Table 2, with scores on the overall scale grouped into five groups ranging from those in the lowest decile (most negative) to those in the highest decile (most positive). The table shows that for all but one item (whether it should remain illegal for people under 18 to use cannabis), there were moderate to strong item-scale correlations, ranging from .53 to .84. The low correlation for the item concerning cannabis use by those under 18

Table 3: Multiple regression model predicting attitudes to cannabis liberalisation scale.

Measure	B (SE)	P	Standardised beta
Cannabis use (no. yrs ≥ weekly use)	0.31 (0.04)	<0.001	0.29
Other illicit drug use (no. yrs ≥ monthly use)	0.18 (0.05)	0.001	0.12
Depression severity (no. of episodes)	0.40 (0.15)	0.006	0.09
Educational attainment	0.34 (0.17)	0.047	0.06
Female gender	-0.66 (0.38)	0.08	-0.06
Māori ethnicity	1.46 (0.4)	0.003	0.09
Dependent children	-1.02 (0.40)	0.011	-0.08
Novelty seeking	0.09 (0.04)	0.015	0.08
Parental history of Illicit drug use	0.72 (0.42)	0.09	0.05
History of violent/property offending	0.21 (0.22)	0.34	0.03

Adjusted R squared 0.23.

reflected the fact that the great majority of the cohort agreed with the statement.

Examination of the individual item profiles suggests a very wide spectrum of opinions across the cohort. While those with the most negative scores (Group 1) showed moderate levels of agreement with statements about medicinal use, nearly all held strongly negative opinions concerning cannabis decriminalisation or legalisation. At the other extreme among those with the most positive scores (Group 5) the great majority agreed with statements supporting medicinal use, decriminalisation and legalisation for recreational use and supply, but few agreed with statements concerning cannabis-related harms. In the middle of the distribution (Group 3) the response profile was intermediate between the extremes with strong support for medicinal use, moderate support for decriminalisation and recreational use and supply, but only minority support for full legalisation.

Predictors of cannabis attitudes at age 40

As noted above, a series of predictors were drawn from the CHDS database in order to examine what factors were associated with positive attitudes towards cannabis. These predictors are shown in Table 3, which displays the results of a multiple regression model (adjusted R^2=.23) in which cannabis attitude scale scores were regressed on a set of predictors. The table shows that:

1. The two strongest predictors of positive attitudes towards cannabis were experience in using cannabis (number of years of weekly use of cannabis; β=.29), and use of other illicit drugs (number of years of at least monthly use; β=.12).
2. Participants who scored higher on a measure of novelty-seeking, and those with a history of depression (number of depressive episodes, age 16–40) were also more likely to have positive attitudes towards cannabis, although the strength of association was lower for both (β=.08 and .09, respectively).
3. Māori cohort members were also more likely to endorse positive attitudes towards cannabis (β=.09).
4. Women (β=-.06) had marginally more negative attitudes towards cannabis, and those with dependent children (β=-.08) had significantly more negative attitudes towards cannabis. However, cohort members whose parents had reported using illicit drugs (when the cohort member was aged 11) had marginally more positive views of cannabis (β=.05).
5. Higher educational attainment was associated with more positive attitudes to cannabis (β=.06), while having a history of violent or property offending appeared to be unrelated to cannabis attitudes when other factors were taken into account.

Table 4: Self-reported medicinal uses of cannabis.

Reason	n	%
Headache, migraine	13	9.7
Period pain	6	4.5
Medical condition (eg, endometriosis, fibromyalgia, gout, cancer)	12	9.0
Injury/joint pain	43	32.0
Other pain	14	10.4
Any pain (any of the above)	84	62.7
Nausea	30	22.4
Sleep, relaxant	31	23.1
Mental health	13	9.7
Other	4	3.0

134 (14.9%) reported medicinal use in the past.

The use of cannabis for medicinal purposes

Cohort members were also asked about the use of cannabis for medicinal purposes. Of the cohort, 134 respondents (14.9% of the sample observed at age 40) reported medicinal use of cannabis at some prior point. The reasons for use are shown in Table 4, along with the number and percentage of respondents reporting that reason (multiple reasons could be chosen). The table shows that the primary reason for medicinal use of cannabis was pain control (62.7%), with "injury/joint pain" (32%) being the most common form of pain treated with cannabis. Other common reasons included "sleep, relaxant" (23.1%) and "nausea" (22.4%). In addition, of those reporting medicinal use, 110 (82%) reported that cannabis was effective for at least one condition, as opposed to eight (5.9%) who reported that it had not been effective. Eighteen participants (13.4%) did not report on efficacy.

Finally, we examined the associations between reports of using cannabis for medicinal purposes and the cannabis attitudes scale, finding that those who had reported using cannabis to relieve pain or other medical issues had significantly ($p<.0001$) more positive attitudes towards cannabis use.

Discussion

The present study used data from a New Zealand longitudinal birth cohort studied for 40 years to examine attitudes towards cannabis and cannabis law reform at age 40, and the life course factors that predict positive or negative attitudes towards cannabis and changes in legislation concerning cannabis. Overall, attitudes towards cannabis use and associated legislation change varied widely across the cohort, ranging from strongly positive to strongly negative. The majority responded favourably to items regarding the efficacy and legalisation of cannabis for medicinal purposes, which reflects an increasing level of international support for medicinal cannabis.[14] In contrast, the cohort was considerably less positive towards decriminalisation of cannabis, and even less so for legalisation of cannabis for recreational use. The relatively low proportion of participants in support of cannabis legalisation contrasts with findings reported by Ellis and colleagues[6] who found almost half of their web-based adult sample to be in favour of legalisation. One reason for this discrepancy is that in the study by Ellis et al, data were drawn from the US state of Michigan, which had legalised medical cannabis 10 years prior to the conduct of

the web survey, which had not happened in New Zealand prior to the present study. A large majority of our cohort felt that use by those under 18 should remain illegal, which is consistent with findings that 93% of an adult sample expressed concern about adolescent cannabis use.[15]

Although our sample held a somewhat more cautious view concerning the effects of cannabis use, international data suggest that perceptions of risk are decreasing.[16] One reason for the more cautious attitudes among our cohort may involve the timing of the interviews, with most having occurred between 2017 and mid 2018. At this point, the Misuse of Drugs Act (1975)[9] remained unchanged, while the Misuse of Drugs (Medicinal Cannabis) Amendment Act (2018)[17] was not passed until December of that year. Furthermore, as noted in Methods, the questions concerning the legal age for cannabis use were set at 18, as the research was conducted prior to the announcement of the proposed age 20 limit in May 2019, which may have had some effect on attitude strength.

Within our cohort, the strongest predictors of cannabis-related attitudes were previous experience with cannabis and other drugs. Those with longer durations of drug use, and particularly cannabis use, tended to hold the most positive views towards cannabis use and decriminalisation/legalisation. These findings are generally consistent with the literature that suggests that research participants who have used cannabis tend to both support its legalisation,[6] and are less likely to stigmatise users.[4]

Other factors that predicted more positive attitudes towards cannabis included novelty seeking and educational level, in that higher levels of each were associated with more positive attitudes. Again, these findings are consistent with the literature, and the novelty-seeking findings are consistent with earlier research with this cohort that showed that higher scores on novelty seeking measures tend to be associated with the use of cannabis and other drugs.[2,18]

Demographic features of the cohort also served as predictors, with female gender being associated with more negative views on cannabis-related issues, as has been observed in previous research.[5] Being a parent of dependent children was also associated with more negative attitudes towards cannabis and cannabis law change. One reason for this may be that that the onset of parenthood is associated with lower rates of cannabis use, which may in turn lead to more negative attitudes towards cannabis.[19] Another important demographic variable was Māori ethnicity, where Māori cohort members had more positive views of cannabis/cannabis law reform than non-Maori. It could be argued that for Māori cohort members, both higher rates of cannabis use[20] and greater risk of being arrested or convicted for a cannabis-related offence[21] may have contributed to more positive attitudes towards cannabis law change in this group.

Approximately one in seven cohort members reported using cannabis for issues such as pain and nausea, with a large majority reporting that it helped to alleviate one or more of these complaints. Use of cannabis for pain relief and other medical purposes was also strongly associated with more positive attitudes regarding cannabis use. While it is unclear whether experience with the use of cannabis for medicinal purposes caused more positive attitudes towards use in general, there is evidence to suggest that developing more positive views on the medicinal benefits of cannabis also has a spillover effect on views of recreational use.[8]

The present study has a number of limitations. Firstly, all of the measures are self-reported and subject to the limitations of such assessments. Second, the age of the sample is particularly limited (all cohort members having been born over a four-month period in mid-1977), which limits the extent to which these data generalise to the wider population. In addition, the cohort is not representative of the Christchurch population as it is currently constituted, as well as New Zealand more generally. Fourth, the assessment of cannabis attitudes took place before the announcement of the 2020 Referendum. Further research should endeavour to compare the views of different generations, and to identify how younger generations may vote when permitted.

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The practice of the alcohol industry as health educator: a critique

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ABSTRACT

Adolescence marks a developmental period with heightened vulnerability to alcohol use and its consequences. In this viewpoint paper, we examine the involvement of the alcohol industry in alcohol and other drug (AoD) education from both an alcohol harm reduction and a school-based health education perspective, using the example of the Smashed programme to illustrate our critique. We issue caution to schools that are invited to participate.

Due to typically heavy patterns of drinking as well as differences in alcohol sensitivities and risk-taking behaviours, adolescents experience disproportionately more harm from their drinking than older drinkers.[1] New Zealand secondary school students report experiencing a range of acute alcohol-related harms, with significant inequities suffered by students of Māori and Pacific ethnicity and/or living in socio-economic disadvantage.[2] In 2017/2018, one in every eight presentations among those aged 15 to 19 years to Auckland Hospital's Emergency Department was found to be alcohol-related.[3] Heavy drinking is also associated with poor mental health and suicidal ideation.[4]

Long-term harms of drinking can include irreversible impairment of brain structure and cognitive functioning, as the maturing brain is sensitive to the neurotoxic effects of alcohol.[5] Other significant chronic harms include seven types of cancer,[6] with research indicating that exposure to alcohol between menarche and first pregnancy may be important in the development of breast cancer, as breast tissue is likely to be at its most vulnerable stage.[7] Finally, adolescence is a period of increased risk of alcohol abuse and dependence.[8] In New Zealand, almost 50% of cases of alcohol abuse and dependence were found to have developed by the age of 20 years and 70% by the age of 25.[9]

Although the discourse surrounding adolescent drinking commonly focuses on binge drinking, there is no safe level of consumption for children and young people.[1] This underpins the Health Promotion Agency's low-risk drinking advice that recommends "not drinking alcohol is the safest option for children and young people under 18 years".[10]

Encouragingly, New Zealand adolescents are mirroring global trends and showing significant reductions in alcohol use that have been maintained over time.[11] For example, between 2006/07 and 2011/12, significant declines in the prevalence of past-year drinking (from 74.5% to 59.6%) and hazardous drinking (from 19.5% to 11.7%) were found among 15 to 17 year-olds.[12] However, profound inequities remain persistent and preventable, with rangatahi Māori males and females reporting a substantially higher (two to three times) prevalence of hazardous drinking than non-Maori.[13]

Given the known risks of alcohol harm to this group, there are substantial benefits from prevention and early intervention. To reduce harms (and inequities), evidence-based and cost-effective policies are required. These include increasing alcohol prices, reducing availability, restricting alcohol advertising and sponsorship and increasing the legal purchase age.[14]

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Evidence pertaining to the effectiveness of school-based education is less consistent and often contains methodological limitations.[15] Despite the large number of studies in this area, few show long-term behavioural change. Evidence-based recommendations[16] for school-based alcohol education draw from a limited number of high-quality studies, describing the need to: 1) use a spiral curriculum (whereby students study the same topics in ever-increasing complexity throughout their time at school to reinforce previous lessons), 2) integrate alcohol education into a whole-school approach to wellbeing, 3) link classroom health education curriculum activities with pastoral support of students, 4) create a supportive environment through development of school alcohol and wider policies (eg, school climate), and 5) incorporate activities that involve parents/guardians, families and communities. It is further recommended that teachers and others require sufficient planning time and training, that the use of scare tactics be avoided, and external providers only be used if they offer content that is consistent with the whole-school approach and are quality-assured.

Alcohol industry involvement in school-based health education

Alcohol companies have a long history of delivering alcohol education in schools. Powell[17,18] offers extensive critique of 'corporate philanthropy'—the practice of commercial agents entering into pedagogical spaces. In New Zealand, the Health and Physical Education learning area (curriculum) space is an attractive site for a wide range of food and beverage corporations (among others) who develop resources for teachers and learners, provide teachers with professional learning and development opportunities, and enter the classroom to teach students directly.[18]

Powell describes the use of corporate philanthropy as a strategy to divert public attention from less altruistic practices (marketing, lobbying, avoidance of stricter regulations, requirement to make a profit, etc.) and rather shape their corporate image to being trusted, caring, socially responsible and even healthy.[17] A similar approach is currently occurring in New Zealand via the increasing number of alcohol industry partnerships with cancer, mental health, wellbeing and environmental charities. For decades, tobacco control advocates have warned of the tobacco industry embracing teenage prevention campaigns, knowing perfectly well that any education programme won't hurt their profits but will show them to be 'doing something'.[19]

One example of corporate philanthropy in the school-based AoD education space is Smashed, entitled "A responsible drinking education programme". Sponsored by Diageo (a multi-national alcohol company), it commenced in the UK in 2005 and has so far engaged more than half a million students internationally.[20] A common approach to get political buy-in has been to hold a parliamentary reception to launch the programme.[20]

Smashed has now made its way to New Zealand, almost 15 years since its inception. Smashed utilises a 'theatre in education' approach, with three paid actors providing a 30-minute live theatre performance followed by a 30-minute interactive workshop to consolidate the information provided. As described on its website and teacher resources, the programme seeks to raise awareness of personal responsibility in making informed decisions around alcohol.[21] The objectives of the programme are to explore key themes of alcohol awareness, potential risks of underage drinking (such as physical and mental health issues, anti-social behaviour, accidents and injury), as well as impacts on relationships and school. Causes of underage drinking are explored, such as peer pressure, and local resources and support services available are signposted. A set of teacher resources are also available, should they choose to carry out any sessions before or after the main session. There is no evidence that the use of the lesson plans is compulsory.

In 2019, Smashed was delivered to 20,463 Year 9 students across 94 New Zealand high schools in 135 performances, and information suggests is to be further rolled out nationally in 2020 and beyond. In New Zealand, it is funded by the Tomorrow Project, a group comprising the multinational beer, wine and spirits makers. It is delivered in high schools via partnership with Life Education Trust, a group that has been reported to have had previous partnerships with Lion and British American Tobacco.[22]

Critique of Smashed: alcohol harm reduction perspective

At first glance, many would read the teacher resources and consider them to be suitable for school-based AoD education. They contain common educational components such as the health risks from alcohol misuse, the negative impact of peer pressure, available support services and so forth. However, an examination of the (often subtle) messaging throughout Smashed is recognisable as common strategies used by alcohol industry programmes internationally. The teacher resources also highlight an obvious language discrepancy, as 'underage drinking' is irrelevant in New Zealand given there is no legal drinking age (in contrast to other countries, eg, US). In New Zealand, the focus of interest is consumption and associated harm, not the health or safety risks in terms of disobedience.

One common thread throughout the teacher resources is the strong focus on "personal responsibility". Other terms used in Smashed include "make responsible choices" and "drinking responsibly". Literature describes the long history of this industry approach, showing that it is used to individualise alcohol problems, while neglecting the role of the wider alcogenic environment that plays a much stronger role in enabling risk behaviours.[23] The personal responsibility approach is strategically ambiguous,[24] encourages the drinker to shift responsibility to others[23] and has the potential to sustain stigma for those with alcohol problems.[25] From a brain development perspective, there is an obvious conflict between an adolescent's ability to make 'responsible choices' and consider long-term risks, when the required part of the brain to undertake those tasks is under-developed. It is also obvious that the ability to make 'responsible choices' is severely compromised once under the influence of an intoxicating drug.

The use of the term 'personal responsibility' is not isolated to school-based programmes; it is echoed in policy debates. For example, in its submission to the Law Commission, New Zealand's largest alcohol producer, Lion, stated that "individual responsibility is key to behaviour change" (p.4),[26] and rejected evidence-based population-based policies to reduce the harms from adolescent drinking, such as increasing the price of alcohol or restricting alcohol advertising.

A second feature of the resources is the omission of information. For example, in the Smashed resources, only cancers of the mouth and throat are included as cancer-related health risks from alcohol. More prevalent breast and bowel cancers are omitted, despite breast cancer being the leading cause of alcohol-related death in New Zealand women.[27] Omission of alcohol-cancer links, especially for breast and bowel cancer, has also been found among alcohol industry websites.[28] This important omission contradicts the notion that adolescents can make informed and 'responsible choices' as a result of participation in the Smashed programme.

A third feature, and common to the alcohol industry internationally, is the incorrect construction of a dichotomy of alcohol drinking patterns or subpopulations into 'misuse' versus 'responsible drinking'. As the name (ie, Smashed) perhaps suggests, a focus on alcohol misuse, abuse and binge drinking is found within the programme, although there is a conspicuous absence of definitions of these terms, especially in terms of actual amounts of alcohol. Of particular concern is the lack of discussion in the teacher resources pertaining to the importance of not starting drinking, as recommended in New Zealand's low-risk drinking advice.[10]

It is suggested that the strategy of dichotomisation is used by the industry to convey a straightforward but over-simplified separation of drinking patterns, into those who use and misuse.[29] The former is to represent a non-problematic population, while the latter a minority who drink in an uncontrolled manner and experience the range of health and social problems.[29] This approach is also reinforced within policy debates, with Lion's submission to the Law Commission[26] stating "the problem at issue is alcohol abuse and related harm… measures are required to fix the behaviour of a minority, by making excessive drinking socially unacceptable" (p.3).

In reality, there is consistent evidence that no simple dichotomy exists. Risk curves describing the relationship between alcohol use and harms (eg, cancers[30]) show a

continuum of harm across different patterns of drinking. There is no magic point where alcohol harms suddenly appear.[31] For this reason, public health professionals dismiss the validity of an alcohol consumption dichotomy that boxes off alcohol harms from the majority of consumers, while the alcohol industry rejects the continuous model of harm in favour of interventions targeted at the relatively small group of heaviest drinking individuals at the extreme end of the continuum.[29]

A fourth feature is the lack of independent evaluation of Smashed, also reported to be common to alcohol industry programmes.[32] In New Zealand, the evaluation is authored by the UK company that originally created the Smashed project.[33] As detailed in the evaluation, the pre-programme response rate to the questionnaire was 27%, dropping to 15% post-programme. Any details about non-responders and/or limitations of poor response are not discussed in the evaluation report but should highlight the caution required when interpreting the claims relating to improvements in knowledge and understanding. Further concerns regarding the evaluation are discussed later.

From an alcohol harm reduction perspective, New Zealanders should be seriously concerned about programmes such as Smashed. Not only are they likely to be ineffective in reducing harm to our vulnerable populations, they are designed to whitewash the alcohol industry image. When approached for participation, principals and teachers should be critical of why multinational alcohol companies would choose to invest in school-based education in New Zealand. New Zealand can look to the strong statements made by Ireland's Health Minister[34] and Education Minister[35] on the need to separate out the alcohol industry from being part of the conversation, with the former stating that "it's completely and utterly bizarre that you'd have a body funded by the drinks industry educating our kids about the dangers of alcohol… I mean it's ridiculous" (para. 3).[34]

Critique of Smashed: health education perspective

From a school-based health education perspective, programmes that offer pre-packaged resources and teaching activities (eg, Smashed) have the potential to contradict aspects of educational policy and guidelines for effective practice in AoD education, as well as undermine the professional practice and autonomy of trained health education teachers.

Health education is one of three subjects in the Health and Physical Education learning area (HPE) of *The New Zealand Curriculum*.[36] As is the case in other learning areas, learning experiences in HPE are mandated until the end of year 10 (around 15 years of age). AoD education is located within the 'mental health' key area of learning within HPE, which indicates more than a sole biomedical focus for AoD. Stepping back from HPE, aspects of *The New Zealand Curriculum* are common to all learning areas. Included here are seven aspects of effective pedagogy—actions that a teacher takes to bring about student learning. While external providers do not make claims to fulfil all aspects of the curriculum, the extensive use in health education of programmes such as Smashed counteracts aspects of effective pedagogy. For example, teachers are expected to *create a supportive learning environment, make connections to prior learning and experience* and *inquire into impact of their teaching*.[36] When an external provider makes their entry into the pedagogical space, these teacher actions are unable to take place, and—worst case scenario—previous work on the part of the teacher in enacting these aspects of effective pedagogy can unravel.

A second aspect of educational policy is 'Our Code, Our Standards', which contains the professional standards against which teachers are assessed for registration.[37] For example, *learning-focused culture* prioritises aspects as safety, respect and students as active participants in learning. *Design for learning* requires planning for, carrying out and assessing the impact of pedagogical actions to meet learners' needs and to show progression of learning. *Teaching* requires adaptations to meet diverse needs, feedback on progress for learners and a repertoire of teaching strategies.[37] External providers may or may not be registered teachers and as such do not make claims to meet the professional standards for teachers. However, when pre-packaged programmes (especially those delivered by external providers) enter

schools, the potential of a teacher to demonstrate evidence of meeting the expected standards might be diminished, because a lot of the teacher's work is effectively done for them. This is particularly an issue when teachers of subjects such as health education over-rely on external providers and/or pre-packaged programmes.

Perhaps a more compelling argument central to a health education critique arises when we examine the messages contained within the array of guidance documents that have been written to support teaching in AoD education contexts. Here, the guidelines for teachers and schools published by the Ministry of Education,[38] New Zealand Health Education Association[39] and Tūturu/NZ Drug Foundation[40] further cement this critique. A message common to each group's assertions is that one-off sessions are educationally ineffective. Furthermore, the groups press the point that any external providers entering the teaching space need to connect and add value to the health education programme already in place, as well as revise content to meet the needs of individual schools based on the learners' needs therein. Student learning needs should drive the planning and teaching and "a positive classroom environment for AoD education, with social interaction promoting respect, concern for others and shared responsibility for learning, is important (p.10)".[38] Smashed is typically delivered to large groups of students at one time (for example, all year 9 students in a school), and has set dates for their tour across the country. This is problematic for two reasons. First, it undermines the need for an established safe and supportive learning environment. Second, teachers may either change the timing of health education teaching units to align with when the tour is in town, or potentially teach unrelated content in health education at the time of the visit, with Smashed a disconnected add-on. The latter is particularly an issue when people other than health education teachers in a school agree to book the session, and give the health education staff little or no notice about its occurrence. It is therefore not difficult to conclude that pre-packaged programmes such as Smashed are—from an educational perspective if nothing else–problematic and troubling.

Over the past year, many health education teachers have become more critical consumers of the organisations that knock on their classroom doors, are increasingly inquiring into the place, purpose and added value of programmes they are offered, and are seeking student or others' feedback before making decisions about who enters their health education learning environment. While external providers at times offer valuable support to health education and its teachers,[39] programmes such as Smashed need to be critiqued by teachers and schools to ensure that they complement and connect to the overall health education teaching programme and meet learners' needs.

Finally, an educational critique of the evaluation of Smashed's 2019 performances in New Zealand finds it to be based on UK measures[33] and learning outcomes for students that do not align with a New Zealand curriculum understanding of HPE, health education or AoD education. Coupled with its issues relating to lack of independence and poor response rate, any application of evaluation findings to the current context is problematic.

Conclusion

Evidence-based alcohol education resources exist for use in high school settings in New Zealand. This critique of the alcohol industry Smashed programme should signal strong caution to schools seeking to engage the services of these external providers. Though a school's interest in preventing alcohol harm to young people is absolutely commendable, engagement in this programme has the ability to undermine effective education principles and can inadvertently contribute to further delays in the adoption of evidence-based policies to effectively protect current and future generations of New Zealand children from alcohol harm. Students deserve more than edutainment on New Zealand's most harmful drug; they deserve best practice. The diversity among students, classes and schools also presents an issue as to how a one-size-fits-all programme can ever truly meet the needs of rangatahi in Aotearoa, or, indeed, anywhere else in the world.

Competing interests:
Rachael Dixon reports that in 2018 Cheers funded her travel to Sydney to preview and give advice on Smashed.

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A balanced opinion? Considering the role of the external clinical advisor in ACC processes

Andrew Dickson, Joanna Manning

ABSTRACT

The role of the external clinical advisor is critical to the adjudication of complex claims in the processes of the Accident Compensation Corporation (ACC). This is particularly true of claims for treatment injury that occur during birth, which are often very complicated. In most cases external clinical advisors are non-treating doctors, whose opinion strongly guides the hand of ACC. This viewpoint considers the impact of the role of the external clinical advisor by using extracts from an external clinical advisor's report to show how a power imbalance can be enacted in ACC decision making processes. Also considered are the way that the normal checks and balances in the system, particularly those provided by the Health & Disability Commissioner, are bypassed in most cases. Finally, a recommendation is made to potential external clinical advisors to precisely following the standards set by the Medical Council in all cases when writing reports for ACC.

The role of the external clinical advisor (ECA) is critical to the adjudication of complex claims in the processes of the Accident Compensation Corporation (ACC).[1] This is particularly true of claims for 'treatment injury' that occur during birth. In broad terms, to establish a claim for 'treatment injury,' the claimant must establish that s/he has suffered personal injury caused by the seeking or receiving of treatment (defined broadly), where that injury is not a necessary part, or ordinary consequence of the treatment, taking into account all of the circumstances, including the claimant's underlying clinical condition and the state of clinical knowledge at the time of the treatment.[2] 'Personal injury' includes physical injuries, but excludes 'personal injury caused wholly or substantially by a gradual process, disease or infection'.[3] This reflects the fundamental distinction at the base of the scheme since its inception between accidental injury, which is generally covered, and disease/illness, which, apart from some exceptions, is not; a distinction which reflects pragmatic cost realities, but which most would agree is responsible for a fundamental inequity.

Because ACC is a cause-based system,[4] the Corporation is charged with establishing the cause of an injury in order to determine whether a claim falls within its legislative mandate. Birth, of course, is a very complicated process. Although it is ostensibly 'natural', medicine has been successfully 'intervening' in this process for hundreds of documented years,[5] and doubtless many more before that. We have used the single quotation marks above on purpose, to draw attention to a dichotomy between nature and medicine that is often used in birth injury cases for a precise reason—to decide that a personal injury is 'covered' by the scheme, ACC must conclude that first, the injury was caused by the treatment or caused by the failure to provide treatment in a timely manner, or importantly for the example we use here, the failure to obtain informed consent regarding the treatment and second, that it was "not a necessary part or ordinary consequence of [the] treatment".[6]

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The motivation for this viewpoint article comes from personal experience; the son of the first author (Author 1) suffered a brain injury during his birth in 2010. His name is Ben, and he is a splendid boy. Fortunately, Ben was spared the often-tragic worst consequences of birth injury. He was born in a tertiary-level hospital in Aotearoa, with a top class NICU facility just down the hall and has grown from those beginnings into a genuine treasure. He has a voracious appetite for Minecraft literature and a cheeky sense of humour. But he also has needs that are special. For instance, he has mild ataxic cerebral palsy, which means he cannot easily join a sports team or walk up and down stairs, and although he can read above his years, he cannot yet spell without the assistance of voice recognition technology. He also has a tic disorder which is worse or better depending on stress, and a selection of other learning and emotional disabilities not seen in most children his age.

It is difficult to pin down how many children, like Ben, suffer brain injuries during their birth, although we do know that up to 360 babies per year are diagnosed with neonatal encephalopathy.[7] It is more difficult to work out how many of these babies end up with ACC cover, because ACC does not keep specific data on birth injury cases. Our best guess following several Official Information Act requests is around 45 per year, approximately 12.5% of diagnosed cases. The rest receive no cover from ACC and generally face challenges in gaining access to services, because the systems they have to access (health; disability; welfare; education) are not well 'joined-up' and funding has not kept pace with costs.[8]

Both Ben and his mother have a rare form of skeletal dysplasia (Léri-Weill dyschondrosteosis), an inherited genetic disorder. Relatively little is known regarding the possible impact of Léri-Weill dyschondrosteosis (LWD) on a pregnancy, and as such it has become a significant part of Ben's claim for ACC cover. Typically, LWD is described as a mesomelic dwarfism, meaning that it usually affects the limbs, particularly the lower ones, though it can also have a range of other effects across the musculoskeletal structure.[9–13] It is typically diagnosed by the obvious physical signs; many (but not all) people with LWD have short stature, and bilateral Madelung deformities. However, LWD is a syndrome in the sense that it describes a group of people who have a variety of deletions in or near the SHOX region of the X chromosome. It has a wide phenotypic variation because it also has a wide genotypic variation.[14–16] The state of the literature on LWD is arguably still at a preliminary stage; it is only recently that advanced genetic testing was able to show the precise genetic changes that are passed on in certain familial lines, and as such the parers for diagnosis are not clear.[17]

The pregnancy included genetic counselling prior to conception, and multiple consultations with specialists during pregnancy (including an obstetrician and a maternal-fetal medicine specialist), though this was primarily concerned with the likelihood of Ben inheriting LWD. However, during an obstetrics referral (at 28 weeks) a doctor made a point of noting that Ben's mother was very short, and that this was linked to a higher chance of requiring a caesarean section delivery. However, no recommendation was made, and a record of the discussion was not included in the clinical notes. No further discussion of LWD and its implications for delivery occurred during the pregnancy. In the maternal-fetal consultation Ben was observed on ultrasound. His limbs were measured and the risks and merits of amniocentesis to test genetically for LWD were discussed and declined based of the risks. Importantly there was no discussion of maternal LWD and possible complications of birth.

In New Zealand, maternity care is provided by an LMC, typically a registered midwife. There are a range of circumstances where care is recommended to be transferred to an obstetrician. These are detailed in a Ministry of Health document: *Guidelines for Consultation with Obstetric and Related Medical Services (Referral Guidelines)*.[18] The only mention in this document of genetic conditions is a section in Table 2 that identifies conditions and their associated referral category. All genetic conditions, aside from Marfan's, are covered in the entry 1032 "Any known genetic condition significant in pregnancy" p. 22, which carries the referral category 'transfer', meaning that the agreed protocol is for the care to be transferred to a specialist, in consultation with the mother.

In Ben's case, care was not transferred to a specialist, nor was it recommended. This has become one of the issues that has been subject to scrutiny by the ECAs who have provided opinions on Ben's case with regard to informed consent regarding delivery options, specifically failure to recommend and/or offer delivery by caesarean section.[19]

ACC almost always seek external clinical advice from a doctor or other registered health professional when determining cover and causation in birth injury cases. They have a system for doing this, including publishing a guide for providing 'objective clinical advice' for health practitioners (most recently updated in May 2018)[20] and a schedule of fees. It is also well documented that they end up using a relatively small pool of advisors and sometimes get into a relationship that is unhelpful, where one advisor is heavily relied on, sometimes writing hundreds of clinical opinions per year.[21–22] In 2016, Miriam Dean QC published a comprehensive report which examined a range of ACC issues, including access to medical experts. We do not have the scope to cover the entirety of these here but for those interested, part six of Dean's report[22] is essential reading. Although ACC undertook to address the matters regarding expert opinion raised in the Dean report, those closely following the changes suggested by Dean remain unconvinced,[23] with the core power imbalance remaining essentially intact. This creates a profound problem: doctors providing expert advice to ACC are in an extremely powerful position. In relation to birth injuries, this position can fundamentally change the life course of a brain-injured baby and their family. It is an unenviable position, and not well compensated given the opportunity costs; hence the reluctance of many doctors to participate.

It is precisely because of this power imbalance that we sought to write this viewpoint. In general, doctors hold significant power over their patients, and this is particularly true in colonised countries like Aotearoa New Zealand.[24] But there are significant checks and balances on this power; health practitioners are subject to a range of legislation, most notable in terms of performance are the Health and Disability Commissioner Act 1994 and the Health Practitioners Competence Assurance Act (HPCAA) 2003, the first of which provides for legislated rights of consumers and correlative provider duties and a complaints process, though significant issues with the HDC complaints process have been raised recently,[25] and the second established a process by which a registered health practitioner can be held to account in terms of competence. Also relevant is the role of the Medical Council of New Zealand, which stipulates standards according to which doctors should practise. This includes the standards of practice expected of doctors employed as non-treating external clinical advisors writing third party reports, including for ACC.[26]

However, there is a serious difficulty with proper enforcement of the very appropriate standards in the Council's *Statement*. The checks and balances normally at play within the profession are bypassed. The Health and Disability Commissioner does not have jurisdiction over complaints relating to the conduct of a non-treating doctor, where s/he performs no medical assessment of a patient, but the assessment is based solely on information in the patient's file. Despite the Medical Council being the statutory regulator of such non-treating doctors, it advises patients to direct their complaints directly to the third party. And it refers complaints to the HDC, who itself refers the complaint to the third party (in our case ACC), who has no incentive whatsoever to question the professional standard of reports and recommendations in its favour, being at best compromised.

In Ben's case, ACC contracted an external clinical advisor who had already written two opinions for ACC on the case, regarding other areas of concern, to provide an opinion. This doctor is registered in New Zealand with a vocational scope of practice in obstetrics and gynaecology and is regularly called on by ACC—in 2018 providing opinion on almost 100 cases. ACC asked:

"Is there any evidence to support that during the antenatal and perinatal period the Obstetric Service did not obtain informed consent for the vaginal birth they assisted with?"

In the claim decision letter, under the heading 'Antenatal', ACC made the following comments, and relied on these to decline Ben's claim:

"[The ECA] noted that there is an expectation that pregnant women would labour and attempt vaginal delivery. Obstetric intervention can be indicated in some situations, which [The ECA] outlined.

[The ECA] noted [Ben's mother] had a reasonably rare condition (Dwarfism), which caused her to be referred to a Materno-Feto-Medical subspecialist for consultation during the pregnancy. [The ECA] concluded that this condition, in [Ben's mother's] case, did not affect her pelvis or make vaginal delivery a risk to her or the baby. [Ben's mother's] short stature would not be expected to cause fetal growth restriction, preterm birth (the child was born postdates), or fetal intolerance of labour…"

This is the relevant section from the ECA opinion quoted by ACC:

"[Ben's mother] has a reasonably rare condition called [sic] *which has a number of reproductive implications. This is why she was appropriately referred to a Materno-Feto Medicine sub-specialist for a consultation during her pregnancy. Leri Weill dwarfism is an inherited condition and [Ben] has the same form of dwarfism as his mother. It is possible that [Ben's mother] has other affected family members. It is also possible that [Ben's mother] knows more knows more* [sic] *people with this condition and knows more about her condition than any of the health care professionals she met during her pregnancy.*

In terms of considering actual risk in the pregnancy and at the time of delivery the following observations are relevant;

A. The effect of her dwarfism on her pelvic dimensions.

[Ben's mother] has a type of dwarfism which usually causes abnormal shortening of the lower arms and legs. As far as I can tell from my reading the bony pelvis is not affected in this type of Dwarfism. I do not believe this condition per se carries a contra-indication to an attempt at vaginal delivery. There was no recommendation from the MFM specialist that [Ben's mother] should have an elective caesarean section."

No references were included with the ECA report; though there is research available looking at skeletal dysplasia and birth outcomes.[27]

To conclude, we want to reflect on the duty of care that our current system requires of doctors writing third-party reports. There is minimal oversight and almost no legitimate vehicle for contest regarding these opinions. There are at least two concerns regarding the ECA opinion above, notably the speculative suggestion that Ben's mother 'knows more' than the obstetrics professionals about LWD and the lack of any references provided for the conclusion that LWD is not relevant in pregnancy. However, as we have explained, no adequate complaints process exists for a claimant to contest an ECA opinion. Thus, we argue that doctors writing third-party reports must apply a level of professional rigour commensurate with the vulnerability of the patient and the importance of the ECA's opinion to the outcome of their claim, and the likely heavy reliance that the third party will place on their opinion, with no incentive to contest a recommendation which accords with its financial interests. ACC's own *Guide* instructs experts to give opinions *only* on matters within their own expertise and to decline appointment if not suitably qualified. Experts have a duty to be independent and not to act as hired guns: The Medical Council's *Statement* warns doctors that they must not allow the financial interests of either the patient or the third party to influence their assessment, opinion or recommendations. It requires a doctor's professional opinion and recommendations to be "accurate, objective, and based on all the available evidence"; the doctor to be suitably qualified; that the non-treating doctor adhere to the professional standard of care set in the Code of Rights; that the doctor's report be restricted to medical issues, and be accurate, objective and not based on speculative, insufficient or flawed evidence.

Doctors also have a professional responsibility to ensure that they are properly informed in their instructions of the relevant, applicable legal principles, so that they can address their opinions and recommendations to the proper legal tests. For example, the Court of Appeal has authoritatively interpreted the words "a failure to provide treatment or to provide treatment in a timely manner" for the purposes of "treatment" in cover for treatment injury. It decided that, while these words necessarily incorporate a departure from a normative standard of care, that standard is not the

civil standard of reasonable care and skill; no finding of negligence is required. Rather, the Court accepted the 'experienced specialist' standard advocated in research by the second author, which requires proof that the injury would likely have been avoided if an experienced specialist in the field would have acted differently at the time, thereby avoiding the injury.[28] And, even though negligence sets a higher standard of proof than that under ACC, in a recent landmark decision, the UK Supreme Court stated that the negligence standard requires a practitioner to take reasonable care to ensure that a patient is aware of the 'material' risks of injury that are inherent in proposed treatment and of the reasonable alternative or variant treatments. It defined a 'material' risk as: "whether, in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk or alternative option, or the doctor is or should be aware that the particular patient would be likely to attach significance to it".[29] Additionally, given the cardinal importance of causation in determining treatment injury claims, ECAs need to be aware that the legal, not scientific, test for causation applies, what that test is, and notably that New Zealand's leading decision on causation in ACC treatment injury recognises that, because causation can be an insuperable barrier for claimants, it is sometimes appropriate for ACC (guided by responsible, independent and professional ECAs) to draw an inference of causation between treatment and injury, ie, ACC or a judge may decide that causation is probable, even though "positive or scientific proof of causation has not been adduced" and "medical science is only prepared to say that there is a possible connection".[30]

The purpose of this viewpoint is to remind the profession of the importance of the work of an ACC external clinical advisor. The advisor's report is often *determinative* of the outcome of an ACC case, but, short of the claimant obtaining additional advice contesting it, is *largely unassailable* within the process. This disjunction can too easily result in advice falling below proper professional standards and perverse outcomes. Our recommendation is that any ECA writing a report for a third party such as ACC, consider that their words and reasoning may one day find themselves under the close scrutiny of a court as part of the appeal process, and ask themselves whether they will then feel comfortable defending it. Only by precisely following the standards set by the Medical Council in all cases will they be justified in doing so.

Competing interests:
Dr Dickson reports that his son suffered a brain injury in 2010 during his birth. There is an ongoing ACC claim related to this injury that has generated a number of external clinical advisor reports. This experience is what inspired the idea for the viewpoint and is explained in the article.

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Challenges of virtual talking therapies for substance misuse in New Zealand during the COVID-19 pandemic: an opinion piece

Susanna Galea-Singer, David Newcombe, Virginia Farnsworth-Grodd, Janie Sheridan, Peter Adams, Natalie Walker

ABSTRACT

The COVID-19 pandemic requires us to rethink how virtual approaches might work for people who use alcohol and other drugs. Are virtual clinics only suitable for clients with whom clinicians have already formed a therapeutic relationship? How well would virtual clinics work for new clients presenting to services, for clients in acute distress, and for those with complex problems? Addressing the sustained change required to maintain substance-free lives or a safe substance-use life requires robust psychotherapeutic approaches, which have traditionally been delivered through physical contact, whether they are one-to-one or group-based interventions. The challenge during this time of the COVID-19 pandemic is to deliver effective talking therapies while avoiding physical contact. How then should services continue to offer counselling and support in such an environment? How can we learn from the COVID-19 situation to deliver treatment to individuals who may have difficulties attending traditional clinic-based care, such as those in more rural areas with transport difficulties? This article focuses on identifying practical issues and providing some solutions.

In November 2019, the world was hit by a novel coronavirus, SARS-CoV-2 (referred to as COVID-19). The first cases emerged from Wuhan in China, but rapidly spread across the world.[1] On 11 March 2020, The World Health Organization classed the COVID-19 global situation as a pandemic—affecting all people including individuals and whānau/families struggling with addictions.

In New Zealand, confirmed COVID-19 cases initially steadily increased, with a reduction in the rate of increase as New Zealand moved through different alert levels, flattening the peak of COVID-related demand on the New Zealand health system. District health boards and other health service providers across New Zealand, although 'essential services', are still required to operate within the boundaries of the various alert levels. The requirement to maintain physical distancing has had a significant impact on the standard in-person forms of treatment delivery. In response, many primary-care and secondary-care consultations are now being conducted virtually where appropriate and possible. How does this change in health service delivery affect clinicians working with people who use alcohol and other drugs?

Treatment providers for substance misuse

Treatment providers for substance misuse, including non-governmental organisations (NGOs) and other community providers, also fall under the class of 'essential services' and have continued to provide treatment. A number of national bodies such as National Association of Opioid Treatment Providers (NAOTP), National Committee for Addiction Treatment (NCAT), Health Promotion Agency

(HPA) and many other district health board and NGO agencies continue to provide a coordinated approach, providing guidance to people who use alcohol and other drugs, their whānau, clinicians and leaders, on how to continue receiving and providing effective treatment.

For some people using alcohol and other drugs, the immediate treatment need is pharmacological. Practical concerns such as access to pharmacotherapies, safer injecting equipment and guidance on safer drug use practices, dealing with lack of access to street drugs, etc, emerge during times of national crisis. The New Zealand Drug Foundation has acted quickly, providing online advice and support for people who use alcohol and other drugs, their whānau and treatment providers (http://www.drugfoundation.org.nz/covid-19).

However, pharmacological treatment is often only one component of the treatment package for people who use alcohol and other drugs. Most treatment interventions are 'talking therapies', generally provided in person.[2] Addressing the sustained change required to maintain substance-free lives or a safe substance-use life requires robust psychotherapeutic approaches which have traditionally been delivered through in-person contact, whether they are one-to-one or group-based interventions. The challenge during this time of the COVID-19 pandemic is to deliver effective talking therapies while avoiding physical contact. How then should services continue to offer counselling and support in such an environment? How will the current use of technology impact on ongoing service provision in the long term? This article focuses on identifying practical issues and providing some solutions.

Virtual clinics: our 'new' model of care

Telehealth, video consultations and online treatment have emerged over the past few years as novel ways of working, reaching both the population engaged, as well as those not engaged, in treatment services. Such virtual approaches are also useful for providing clinician-to-clinician support, consultation and advice (www.digital.health.nz).[3–5]

Several studies on virtual approaches (both video and non-video) to delivering treatment for substance misuse indicate that virtual clinics are an acceptable way of providing treatment, with high levels of satisfaction reported by both clients and staff.[6–10] In addition, the resources needed to deliver such services are considerably less and therefore less costly than more traditional ways.[11] However, a limitation of these studies is that they include cohorts of clients who are relatively stable (or not in an acute stage/experiencing a disorganised lifestyle).[12] In addition, the reported success of these virtual clinics is in the context of having such clinics running alongside traditional in-person clinics. Would they be as successful if virtual clinics were the only source of care provided? Would they be as successful if they did not have a parallel traditional system to deal with the more acute or complex cases?

Over the years, virtual novel approaches for people who use alcohol and other drugs have been gradually increasing in both number, popularity and utility.[10–13] The COVID-19 pandemic has required us to rapidly adopt such approaches, which begs the question of how virtual approaches might work.[14,15] For example, are virtual clinics only suitable for clients with whom clinicians have already formed a therapeutic relationship? How well would virtual clinics work for new clients presenting to services, for clients in acute distress, and for those with complex problems?

Virtual talking therapies for substance misuse problems: the challenges

Talking therapies for substance misuse problems range from educational and supportive to more structured therapeutic approaches (such as motivational interviewing, brief interventions, 12-step programmes). The majority of talking therapies were designed to be provided in person, either one-to-one or in group sessions, following well-tested practice guidelines.[2] Shifting talking therapies into the virtual space is a major change that is transformative and exciting, but also raises some concerns. Many of these concerns are the same regardless of whether virtual sessions are delivered one-to-one or in group sessions or whether the virtual therapies are video, non-video or other online approaches.

Safety

Virtual talking therapies are safer in terms of transmission of COVID-19, but how safe are they in the detection of high-risk situations such as suicidal ideation? The virtual nature of the therapeutic intervention could present difficulties in picking up visual or other sensory cues. An assessment of an individual's mental state is essential in understanding the psychological space they might be in, and in capturing the individual's readiness to change and support they might require. During traditional face-to-face sessions, the assessment is based on observation of an individual's general behaviour and interaction, as well as the responses to assessment questions. However, assessing an individual's behaviour and interaction virtually could be a challenge—and could result in inappropriate interpretation—particularly if the session is not video-enabled.

Transparency

Talking therapies assume transparency. Therapies facilitate a safe space for experiences, thoughts, feelings, fears and intentions to be shared with the counsellor or other healthcare professional, or with other clients if within a group session. The therapeutic relationship and peer relationships (in group sessions) foster a sense of trust, optimism and mutual respect. Facilitating such a safe space virtually could be challenging.

In addition, individuals under the influence of substances while attending a talking therapy session would generally be asked to leave the session and to re-engage with the next session. Within in-person sessions, the healthcare professional would be able to observe behaviours and be exposed to sensory stimuli (eg, smell), indicative of intoxication. Within a virtual session, assessment of intoxication may be possible if both video and sound was enabled. Without video, the clinician would be only reliant on verbal expression by the client.

Inclusion

People routinely hold meetings using video-conferencing tools, such as Zoom™ or Skype™. Delivering group-based talking therapies to people who use alcohol and other drugs would therefore be possible using such video-conferencing tools. Efforts would need to be made to ensure all parties in the meeting feel included and have equal opportunity to share their views.

Virtual approaches also enable more distant access, potentially improving specialist help for rural populations, those whose transport options are limited, and others who have difficulties attending, such as those with childcare commitments. Ensuring privacy and data protection could make it possible for such populations to be reached.[16]

Equity

Although the majority of individuals in New Zealand possess smartphones, the minority who do not might need talking therapies the most. People without smartphones could have access to library computers, and with headphones, could potentially engage in therapy. However, such options could be limited during pandemic times. In addition, using smartphone technology requires a strong internet connection, which also generally utilises large amounts of data—this might not be an option for those from lower socioeconomic backgrounds. In this light, virtual provision may not be equally accessible giving rise to health inequities.

Cultural issues

Culturally appropriate talking therapies are respectful of various cultural beliefs. In New Zealand, it is important to ensure that the mode of delivery of talking therapies do not inadvertently disadvantage Māori and Pasifika peoples and other cultural groups. Ensuring that virtual delivery is culturally appropriate is new territory to most counsellors and clinicians,[17] and good cultural guidance from Māori and Pasifika elders and other leaders from other cultural groups is required.

Effectiveness

Virtual clinics have been linked with high satisfaction rates[8,9,18] and high demand rates,[19] but their efficacy in achieving sustained changes in use of substances remains questionable.[12,20–22] It is unclear whether they are as effective as traditional clinic-based care and whether the outcomes of traditional clinic-based care are equivalent or comparable to virtual clinics in the treatment of substance misuse. In addition, the impact of the potential 'reach' of virtual clinics as

compared to traditional clinics, on the overall burden of alcohol and other drug use on population health, remains unclear.[10,23]

Literature on virtual approaches for people with more acute or severe alcohol and other drug problems is sparse and often limited (eg, only reporting on brief interventions, small cohorts, significant drop out rates, etc), making it difficult to confidently state that virtual approaches are effective.[23,24] More research in this area is needed.

Motivational interviewing (MI) is a collaborative conversation style that is indicated for individuals with more severe problems, to help them strengthen their own motivation and commitment to change.[25] Studies report that MI for tobacco cessation can be delivered by phone[26,27] and that visual contact may increase visual cues and may add to client satisfaction;[18,28] however, it is unclear whether visual cues increase the impact of MI in this context. Ultimately, clinicians working from an MI framework ensure the spirit of MI is maintained while attending to the central processes that form the flow of MI—engaging, focusing, evoking and planning.[25] These processes may flow into each other, overlap and recur whether in traditional in-person or virtual clinic delivery. It could be argued that the effectiveness of the MI conversation would hinge on the ability of the clinician to navigate the MI processes virtually:

1. Engaging: This is the process by which both parties establish rapport and a collaborative working relationship—ensuring both parties feel comfortable, respected and involved. The quality of engagement is central to therapeutic outcomes. A virtual clinic has the added benefit of limiting external visual distractions and shifting the focus more pertinently onto the change language. This helps cultivate an environment of reflective listening where reflective statements are used to ensure less defensiveness and encourage greater exploration. Non-verbal facial expressions (such as nodding, eye contact) provide reciprocal clues about attention and understanding; however, poor virtual technical issues may limit some of this valuable interchange—an area that begs further research.
2. Focusing: Engaging leads to a focus on an agenda topic. It helps to develop and maintain a specific direction in the conversation about change. It is an ongoing process of seeking and maintaining direction while finding more specific achievable goals. Sometimes there is a clear single focus, sometimes there are multiple topics and sometimes there is uncertainty and further exploration is needed. No matter what the clinical environment (whether in person or virtual), the clinician needs to be alert to finding and maintaining the direction of the conversation.
3. Evoking: With a clear change goal as a focus, the process of evoking involves eliciting the client's own motivations for change. A virtual clinic may enhance physical distance that promotes a client to voice their own arguments for change by limiting the clinician's righting reflex to voice those arguments themselves. A clinician comes with an attitude of acceptance of what the client brings. This involves honouring the inherent worth of their client, taking an active interest in understanding their internal perspective, respecting the capacity of self-direction and affirming their strengths and efforts to move towards change. It can be argued that despite the clinical environment this will need a skilful clinician.
4. Planning: This marks a readiness to change; it encompasses both developing commitment to change and formulating a specific plan of action. It is a conversation about action that elicits a client's solutions. It promotes their self-efficacy by reflecting on their strengths and skills. It is an ongoing process that can be revisited, which is so often the case following relapse to substance use.

A virtual clinic could be just as well positioned to work collaboratively to revisit evoking in order to consolidate motivation and confidence to implement new plans. These areas are rich for further research to explore.

Privacy and confidentiality

The privacy of the medium used for virtual consultation is of utmost importance. A number of platforms—eg, Zoom™—can be encrypted to ensure privacy of issues discussed. Another issue to consider is whether the client and the clinician are alone in the rooms when engaging in the session. This issue is especially pertinent in group sessions and in non-video consultations.

Technical qualities

The quality of virtual consultations is dependent on a number of factors, such as the ability of participants to use the technology appropriately, access to a computer with a camera and a microphone, stability of internet within geographical areas, access to timely technical support, licensing of technological platforms, etc. Such factors, as well as a quiet and private space, can be a challenge and hinder the effectiveness of talking therapies.

Some tips going forward

Having an awareness of mentioned challenges permits us to put in place processes to mitigate them and facilitates the development of good practice going forward. The following are some tips that could be useful. The tips are by no means exhaustive.

Protocols/standard operating procedures

Adapting existing protocols and standard operating procedures for the new 'virtual' approach will help clarify expectation of practice for both staff and clients. The rapidity of measures adopted in New Zealand during the COVID-19 pandemic has resulted in service providers changing to virtual approaches quickly. It would be difficult in such situations to implement a co-design approach with clients and staff to develop protocols and standard operating procedures. However, transparency around the need to act without such consultation, and requesting feedback from staff through email communication and from clients during the virtual sessions, post, is acceptable.

Ensuring privacy and confidentiality

Staff should adopt virtual platforms suggested and supported by their IT departments. Personal client information will need safeguarding and security should be heightened.[4,5,29] In addition, a discussion between client and clinician around privacy and confidentiality is a fundamental part of the talking therapy session. Both parties need to understand and respect the importance of being strict around ensuring no third party is privy to the therapeutic virtual encounter. Prior to starting the session, it is advisable to disclose the clinician identity and to confirm the identity of the client (such as date of birth) to ensure that the person behind the phone or screen is who they say they are.

Furthermore, the rapid adoption of telehealth has occurred with some clinicians using personal devices to make calls. It is important to ensure that personal numbers are not displayed.

Support and supervision for clinicians

Most services have organisational structures based on clinical governance frameworks. These structures often provide clarity around accountability, support and supervision pathways. Despite the 'work from home' where possible and 'physical distancing' mandatory processes, it is important to ensure that support and supervision is available in-person or virtually.

Training for clinicians

With every new model of care, regular training is a necessity. The aim is not only to train on core principles and theory, but also to do 'on-the-job' training or coaching. This could be achieved by ensuring experienced clinicians are present during virtual sessions to observe the 'how'. Consent from the client/s will need to be sought.

Running group sessions

Running effective group sessions virtually can be challenging. Factors below could facilitate an effective session:[29]

- Have a phone conversation with each participant before inviting them to join the group. This would provide opportunity for the clinician to explain and request feedback for the group protocol or standard operating procedure; the 'rules' of the group; likely other participants in the group (not names); expectations of the group; and potential/likely outcomes.

- If a client is clearly intoxicated during the session or is finding the session difficult or challenging, suggest they exit the session immediately and re-engage in a one-to-one session later. Following the session the clinician should contact the client to ensure their safety.
- Communication:
    - Clinicians should adopt an empathetic, supportive and encouraging communication style, reflecting back—reinforcing and restructuring where appropriate.
    - Clinicians will need to manage communication. For interactions with individuals in the group the majority of communication should occur between the clinician and each client, with other clients prompted/invited to share/comment if necessary.
    - Allow each client at least three minutes to talk. This will ensure all clients are included in the session.
    - Free-form communication (ie, speaking without prompting) should be discouraged.
- Having a theme for each session facilitates the discussion.

The suggestions above could apply to family/whanau group as well as sessions with clients.

Acute/complex clients

A good assessment is an important part of all client interactions, and for those with acute or complex issues, a good assessment can identify urgent client needs. In the first instance, it is advisable to facilitate a virtual one-to-one session to clarify client needs, goals and immediate suitable treatment plan. Initially talking therapies are likely to take the form of empathic, supportive and educational communication, as opposed to more structured therapeutic options. Group-based approaches may not be indicated as a first-line approach. It may also not be feasible to continue providing treatment virtually, and in-person sessions (with appropriate physical distancing) may need to be considered.[2,30]

New clients

As with acute/complex clients, new clients will require careful assessment.[30] If their needs are acute, the process above will need to be followed. However, if needs are less acute, virtual sessions, one-to-one or group could be offered. It is important that the client is familiar with what is offered by the service, how it is offered and to ensure they are aware of how to alert the service of increased risks if such situations arise.

Some final thoughts

The novel virtual therapeutic approaches emerging during the COVID-19 pandemic are exciting and transformative. The need to adopt such approaches within a short period of time has created a unique opportunity for innovation and creativity. Being united against COVID-19 has also created a space within which we are all vulnerable (with some being more vulnerable than others) and within which we are seeking solutions together. Indeed, it is likely that such approaches will remain available regardless of availability of in-person treatment, in particular for clients for whom physical access to treatment is limited such as those in rural areas. This article highlights some practical ways of reducing the spread of COVID-19 while continuing to provide effective treatment. Research will be required to determine the effectiveness of such novel approaches, compared to traditional clinic-based approaches.

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Nil.

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Inhaled modified angiotensin converting enzyme 2 (ACE2) as a decoy to mitigate SARS-CoV-2 infection

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ABSTRACT

COVID-19 is a new zoonotic disease caused by the SARS-CoV-2 virus. Since its emergence in Wuhan City, China, the virus has rapidly spread across the globe causing calamitous health, economic and societal consequences. It causes disproportionately severe disease in the elderly and those with co-morbidities, such as hypertension and diabetes. There is currently no proven treatment for COVID-19 and a safe and effective vaccine is at least a year away. The virus gains access to the respiratory epithelium through cell surface angiotensin converting enzyme 2 (ACE2). The receptor binding domain (RBD) of the virus is unlikely to mutate without loss of pathogenicity and thus represents an attractive target for antiviral treatment. Inhaled modified recombinant human ACE2, may bind SARS-CoV-2 and mitigate lung damage. This decoy strategy is unlikely to provoke an adverse immune response and may reduce morbidity and mortality in high-risk groups.

COVID-19 is an emerging zoonotic disease, caused by SARS-CoV-2, which appears to have been transmitted to humans in late 2019 in the Hubei province of China, probably from an intermediate host in a live animal market. The viral sequence bears close similarity to bat (Chiroptera) coronaviruses,[1] although the proximate animal host source for this spillover event remains unidentified.[2] SARS-CoV-2 belongs to the family of beta coronaviruses, which have previously caused pandemics including SARS-CoV in 2003 and the Middle Eastern respiratory syndrome (MERS-CoV) in 2012.[3]

Following the initial outbreak in Wuhan City, there has been rapid spread of the virus across the globe with catastrophic health, economic and societal consequences.[4] The virus spreads from human to human via respiratory droplets, aerosols, fomites and by other body contact including the hands. Countries around the world have been attempting to block transmission of the virus by physical distancing and restricting movement of individuals including extreme measures of quarantining entire regions and countries.[5] Occult transmission of the virus by presymptomatic and asymptomatic persons may challenge healthcare systems attempting to eliminate the virus.[6]

Morbidity and mortality

Current case fatality rates (CFR) vary widely between countries from approximately 0.1% to 11% with a more recent overall estimate closer to 0.99%.[7] There appears to be a steep age-related mortality gradient with rates approaching 20% in those over 80 years of age.[8] Younger patients have also been severely affected, including medical and nursing healthcare workers

(HCW) who were exposed to high concentrations of the virus before the use of personal protective equipment (PPE).[9]

Epicentres in Europe have experienced large numbers of cases and deaths, which have overwhelmed healthcare systems. At the time of writing, the US death toll is rapidly approaching 100,000 and modelling by various authorities predict up to two million deaths depending on the effectiveness of preventative measures.

Individuals with co-morbidities such as hypertension, obesity, ischaemic heart disease, chronic pulmonary disease and diabetes are at increased risk of severe outcomes. Current advice is that patients on ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) should continue treatment for hypertension.[8] Patients at risk of severe morbidity and death may experience rapid spread of the virus through the respiratory tract leading to viral pneumonia, sepsis, acute respiratory distress syndrome (ARDS) and multi-organ failure. Many patients have died in spite of invasive ventilation and extracorporeal membrane oxygenation (ECMO).[8]

Receptor for SARS-CoV-2

Like SARS-CoV (2003), SARS-CoV-2 enters human cells through the angiotensin converting enzyme 2 (ACE2) expressed on the membranes of type 2 pneumocytes of the respiratory tract.[10] There are two subtypes of ACE in humans.[11] ACE1 catalyses angiotensin 1 to its more active form angiotensin 2. ACE2 has approximately 40% sequence similarity to ACE1. Its main function is to produce angiotensin 1–7 and 1–9, which are physiological antagonists to angiotensin 2.[12] ACE2 also hydrolyses apelin, a pleiotropic peptide ligand with multisystem effects.

Membrane-bound ACE2 is cleaved by a metalloproteinase, tumor necrosis factor alpha convertase (TACE, ADAM17)[13] to produce a soluble ectodomain that is shed into the extracellular space. This cleaved ACE2 appears to maintain its catalytic function. Its exact physiological role is uncertain but it may act as a negative regulator of blood pressure control.[14]

Strategies to combat the virus

Apart from the effective public health strategies to self-isolate and maintain social and physical distancing, a variety of antiviral methodologies have been considered to combat the virus. These include the recent trials of COVID-19 candidate vaccines in several countries.

Multiple clinical studies are evaluating the efficacy of antiviral drugs such as favipiravir, remdesivir and ritonivir as well as other drugs including hydroxychloroquine and azithromycin, which appear to be less effective.[15] The cell surface protease, TMPRSS2 plays a critical role in activating both SARS-CoV and SARS-CoV-2 viruses.[16] *In vitro* studies suggest drugs such as camostat mesilate, which inhibits TMPRSS2, are effective in preventing viral entry into respiratory epithelial cells.[17,18] Large clinical studies will determine the precise efficacy of these treatments. Currently there are limited supplies of some drugs.

Passive immunisation with convalescent neutralising sera has also been considered.[19] It is however concerning that some patients with high titres of anti-SARS-CoV-2 sera had high viral loads.[9] Although such antibodies neutralised virus *in vitro*, they seem to be less effective *in vivo*. There is also concern about antibody-dependent enhancement (ADE) of disease.[20] It is likely patients who recover from COVID-19 have qualitative differences in antibody responses analogous to hepatitis B.

Similarly, monoclonal antibodies to the receptor-binding domain (RBD) have been considered but have not yet been deployed in clinical trials.[21] Competitive inhibition with peptides has been used in animals to counter SARS-CoV, but given the differences in spike protein sequences, it remains to be determined if SARS-CoV-ACE2 interaction is identical to that of SARS-CoV-2-ACE2.[22,23] Such peptides, particularly if coupled to IgG Fc fragments, also risk provoking an adverse immune response.

Inhaled modified soluble recombinant human ACE2 to treat COVID-19

We believe the Achilles heel of SARS-CoV-2 is the RBD sequence of the spike glycoprotein, which is critical for viral entry. Viral evolution of SARS-CoV-2 RBD is unlikely to be tolerated without loss of pathogenicity. Our strategy is to produce modified recombinant soluble human ACE2 (shACE2) molecules, which are similar to those cleaved from the cell surfaces of the respiratory mucosa.[24] Two amino acid

substitutions will abolish the catalytic activity of ACE2 (R273A) and reduce N-glycosylation (N90D) to increase affinity for the RBD of unactivated SARS-CoV-2 to inhaled shACE2. If the structure of these inhaled modified shACE2 molecules is preserved, the virus will bind to these decoy receptors.[25]

Soluble human ACE2 has high affinity (14.7 nM) for the SARS-CoV spike (S) glycoprotein and has been demonstrated to block the SARS-CoV virus from infecting cells in culture.[26] This is comparable to the affinity of a single-chain variable region fragment neutralising antibody against SAR-CoV-S.[27] As the SARS-CoV-2 S spike glycoprotein shares 77% protein sequence similarity to SARS-CoV S glycoprotein, it is anticipated that modified shACE2 will bind SARS-CoV-2 with similar high affinity.

The shACE2 will be delivered to the lungs by the Respimat® inhaler to newly diagnosed infected patients, particularly those with co-morbidities and the elderly, who might not be offered ventilation.[28] The Respimat® is an ideal drug delivery device as it induces lower shear stresses, which is less likely to denature the protein. Furthermore, since it is a closed system, it does not pose an additional danger to HCWs or family members. Unlike nebulisers, the Respimat® does not generate hazardous aerosols and more of the drug will be deposited in the respiratory system. Dry powder inhalers are unsuitable as they generate high shear stresses which could denature the proteins.

Binding of SARS-CoV-2 to the modified shACE2 decoy could alter the trajectory of the infection, delaying or halting the destruction of the pulmonary epithelium and allowing appropriate protective immune responses to the virus. Soluble ACE2 has been shown to inhibit *in vitro* SARS-CoV-2 infection of human organoids, supporting our approach.[29,30] We shall check the binding affinity of modified shACE2 by ELISA and its *in vitro* efficacy by viral cytopathic inhibition studies both before and after passage through the Respimat® inhaler.

The proposed strategy includes administering several treatments over a few days until there is clinical evidence of improvement in terms of fever, cough, dyspnea, myalgia and lethargy. Early resolution of fever, improved gas exchange and reduction in inflammatory markers may be reliable signs of efficacy in randomised trials.

Another ACE2 product conjugated to an Fc domain will be created for systemic use.[25] A shACE2-Fc construct could however aggravate the cytokine storm in such patients, although it may be more effective in removing the virus rapidly and reducing damage to the respiratory epithelium.[19] It could be used in patients on ECMO to reduce the duration of pulmonary failure. Data from China shows patients who succumb to COVID-19 have persistent, unrelenting viral sepsis.[8] This product, with the appropriate ethics approvals could be considered in severely affected individuals at a future date. There are now clear prognostic markers of death in such patients including unrelenting viremia, persistent lymphopenia, raised d-dimers, etc.

Potential benefits

The use of modified decoy shACE2 is a novel and relatively low-risk approach to mitigate the effects of a lethal infection. A decoy strategy is a compromise between safety and efficacy for a new class of biopharmaceutical agents. While ACE2-Fc constructs might generate rapid antiviral responses, they may also aggravate ARDS. If the strategy is successful, it may reduce the morbidity and mortality of COVID-19. It will convert those with severe disease to milder forms. Apart from reducing mortality, it may ease pressure on intensive care units and reduce the need for ventilators.

It is also possible this treatment may enhance the efficacy of other antiviral drugs, which may have only modest efficacy against SARS-CoV-2. Similar to HCV or HIV, a combination of drugs may lead to rapid improvement of disease if administered early in the infection.

Such agents could be used prophylactically for family members of COVID-19 cases and HCWs, who are at high risk of infection and transmission to their families and other patients.[31] The molecules may also be useful as prophylaxis in care homes experiencing outbreaks of infection. In countries

with widespread community transmission, deployment of these products in new infection clusters may allow development of protective herd immunity with a lower risk of death in the elderly. In countries without herd immunity such as New Zealand, these biopharmaceuticals could play a role in reducing the reproductive number (R0) of the virus. By decreasing the viral burden in an infected person, these molecules might decrease the risk of transmission.

The best-case scenario is shortening the duration of the current pandemic with saving large numbers of lives with low risk of adverse effects. These molecules may bridge the gap until a safe and effective vaccine is identified. In the event SARS-CoV-2 becomes more virulent by increasing its affinity to ACE2, these biopharmaceuticals could become even more effective. This strategy may also mitigate future pandemics caused by novel coronaviruses utilising ACE2 for viral entry.

Efficacy

It is not known if this experimental strategy will be effective. It is uncertain if the inhaled modified shACE2 will bind the unactivated virus with the same high affinity as cell surface ACE2, following activation by the TMPRSS2 protease. It is possible larger doses of these biopharmaceuticals will be required but administration will be initially limited by the yields from *in vitro* production.

A similar product, APN401 (Apeiron Biologics AG, also known as GSK2586881) was well tolerated in high doses but ineffective when administered to ARDS patients intravenously.[32] Importantly, there was no evidence of disease enhancement. The key to efficacy in moderating the progression of COVID-19 may be early administration through the respiratory route, with a product, which blocks viral entry and replication.

Potential risks and adverse effects

Because of the sequence similarity of shACE2 to the physiologically cleaved wild-type ACE2, an immediate adverse immune response to the protein is unlikely. Even if the few amino acid differences prove immunogenic, treatment would have been discontinued before an adverse immune response develops. It is very unlikely shACE2 will provoke a long-term autoimmune disorder.[33–35]

It is uncertain if there will be an adverse immunological response to SARS-CoV-2-shACE2 complexes. These complexes are likely to be engulfed by macrophages, which are well equipped to eliminate the virus compared to pulmonary epithelial cells, which undergo cytopathic destruction. It is unlikely these soluble complexes will be internalised through the alternate endosomal pathway previously described for SARS-CoV leading to worsening damage to the respiratory mucosa.[16] Other SARS-CoV-2-shACE2 complexes will be removed by the mucociliary ladder and swallowed, likely resulting in hydrolytic destruction of the virus in the stomach.

The risks of this experimental treatment must be considered in the context of the known morbidity and mortality of this infection for which there is no effective treatment. Given the rapid reduction of new COVID-19 cases in New Zealand, large-scale randomised clinical trials of these biopharmaceuticals will be conducted internationally. Preclinical safety studies could be undertaken in New Zealand. If successful, these products will be made available to New Zealand patients and HCWs on a compassionate basis once relevant ethics and regulatory approvals have been received. The clinical availability of such biopharmaceuticals will depend on how quickly each jurisdiction assesses and approves such novel products in this global crisis.

Competing interests:
Dr Rolleston reports affiliation with South Pacific Sera Ltd outside the submitted work; and is the Chair of the Life Sciences Network. Dr Petousis-Harris reports grants from GSK outside the submitted work.

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Acute onset internuclear ophthalmoplegia responsive to treatment with intravenous alteplase

Karim M Mahawish, Adarsh Aravind

Isolated pontine infarcts account for approximately 3% of ischaemic strokes in hospital registry studies.[1] Symptoms may include sensory or motor power loss, involuntary movements (eg, palatal myoclonus, periodic limb movements), impairment of consciousness and emotional disturbances (eg, pathological laughing or crying). Internuclear ophthalmoplegia (INO) occurs due to dysfunction of the medial longitudinal fasciculus within the pons due to occlusion of paramedial branches of the basilar artery and is the main presenting feature in 0.5% of all ischaemic stroke patients.[2] An INO is characterised by paralysis of adduction of the ipsilateral eye for all conjugate gaze movements and nystagmus of the contralateral eye when this eye is in abduction. Here we present the case of a young man presenting with acute INO which responded rapidly to treatment with intravenous alteplase.

Case report

A 29-year-old man with a past medical history of excess alcohol consumption, hypertension and gout presented with a one and a half hour history of sudden onset right-sided weakness and double vision. There had been no history of head or neck injury or demyelinating illness and he denied any illicit drug use. National Institutes of Health Scale (NIHSS) was 1 and was notable for an INO (Video 1).

Video 1:

Video 2:

Computed tomography of the brain with angiography did not demonstrate any evidence of ischaemia, haemorrhage nor large vessel occlusion/wall irregularity. He received alteplase at two hours and eight minutes following onset of symptoms. After 15 minutes, the INO resolved (Video 2).

Follow-up magnetic resonance imaging including diffusion weighted imaging (MRI-DWI) demonstrated normal appearances of the brain. Investigations to date including vasculitis screen, antiphospholipid screen, syphilis screen, human immunodeficiency testing and telemetry are unremarkable. He is currently awaiting a bubble echocardiogram.

Discussion

Recent worldwide trends show that stroke in patients aged 50 years and younger are increasing due to a number of factors, including increasing burden of classic and emerging risk factors, greater stroke awareness and access to brain imaging.[3] Stroke in the young is of great importance given the major social and economic impacts at the peak of their most productive years. Urgent modern stroke treatment with intravenous alteplase and mechanical thrombectomy is very effective in improving functional recovery and survival.

Mild stroke is the most commonly cited reason for withholding alteplase in acute ischaemic stroke in those otherwise eligible for treatment. Patients with minor, non-disabling symptoms were excluded from large randomised control trials as the risk of haemorrhage was considered to be greater than the potential benefit. Prospective data suggest that 30% of such patients have functional disability when assessed at 90 days following stroke.[4] Reasons for this include early worsening of symptoms, underappreciated symptoms and deterioration of medical co-morbidities.

There is limited data available about the prognosis from ischaemic INO. One case series showed that approximately one in five patients failed to recover from an INO.[5] The decision to administer thrombolysis was a consensus between two experienced stroke physicians, both deeming the deficit functionally disabling. Further, the risk of haemorrhagic complications from treatment was considered to be very low due to the age of the patient, neurological deficit, imaging findings and time of onset to admission to hospital. Recently, the PRISMS trial,[6] enrolled patients with an NIHSS <5 and non-disabling symptoms, randomised to aspirin or alteplase in a double-blind manner. It is unclear if any patients with an INO were included in the trial or whether

such a patient would have been eligible. The trial was stopped early due to slow recruitment and so it is difficult to draw conclusions form this trial, however final analysis did not demonstrate a significant benefit in functional outcomes at 90 days with alteplase.

The normal follow-up MRI could be expected in this patient. Though MRI-DWI is sensitive for ischaemic stroke, it may be falsely negative in almost one-third of patients with mild stroke (NIHSS <5).[7] The key role of MRI in stroke is in localising pathology and clarifying pathophysiology, rather than simply diagnosis.

This case demonstrates the value of acute stroke therapy in highly selected patients with mild, yet disabling symptoms considered at low risk of complications.

Competing interests:
Nil.

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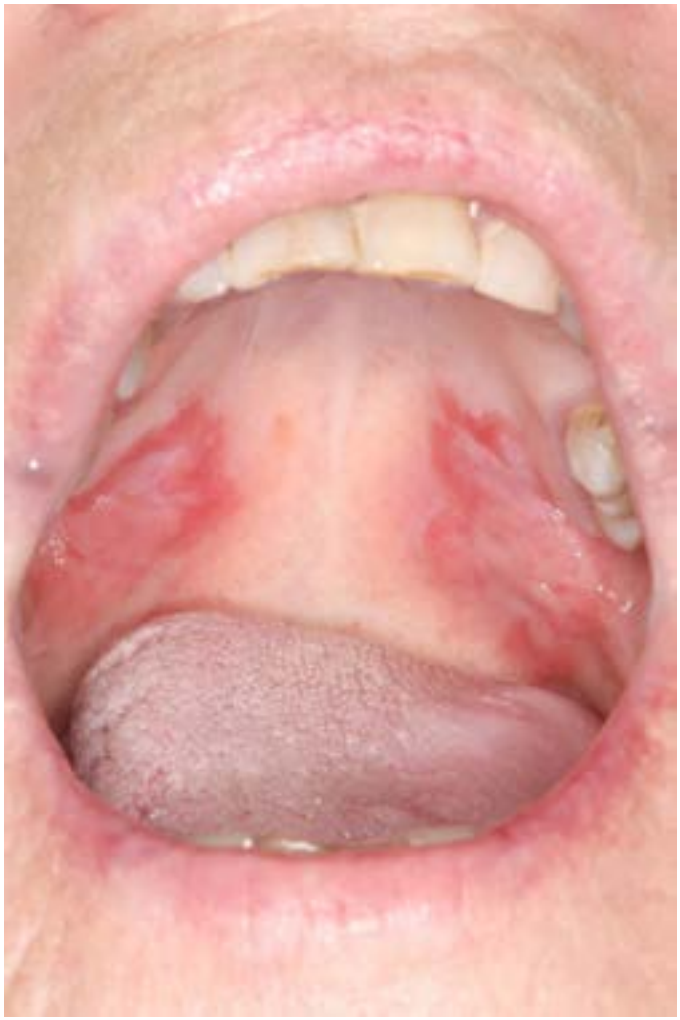
A memorable case of secondary syphilis

Gerhard Eichhoff, Stephen Hogg

A 50-year-old female with no significant medical history suffered an 18-month-long illness with recurrent painful mouth lesions that culminated in mucous patches (Figure 1), together with headaches and episodes of blurred vision, recurrent anogenital lesions, and near-continuous fatigue and arthralgias. She had no skin manifestations beyond a transient palmar rash.

Over a 12-month period she was reviewed by dentistry, general surgery, general medicine, gynaecology, ophthalmology, gastroenterology, rheumatology and dermatology services—over 18 specialist appointments were attended. Investigations for auto-immunity and HIV infection were negative. Biopsies from vulva, perineum and mouth showed nonspecific inflammatory changes. Given a provisional diagnosis of autoimmune disease, she was treated with immune suppression, including Azathioprine, Infliximab, intravenous methylprednisone and multiple courses of oral glucorticoids. No treatment was helpful.

Figure 1: Mucous patches on hard palate.



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On later review of the oral biopsy histopathology, a preponderance of plasma cells prompted consideration of syphilis.[1,2] Serology confirmed infection (RPR 1:128; TPPA reactive), and the patient was seen by Infectious Diseases. Despite reporting most-recent sexual activity as four years prior, she had clinical secondary-stage syphilis—atypical in its duration and unremitting course. The patient claimed the painful oral mucous patches had been unchanged for several months. Earlier ulcerations had been more discrete and transient. Her headaches were symmetrical, intermittent and frequent, though not disabling, and she had no confusion or focal neurological deficit at any stage; nonetheless, lumbar puncture was performed in light of the immune suppression, and confirmed neurosyphilis (CSF VDRL 1:4). Repeat ophthalmology review excluded ocular syphilis, and audiometry was normal. She was treated with two weeks of intravenous benzylpenicillin, followed by intramuscular benzathine penicillin in the third week.

After a dramatic initial improvement, she re-presented two months later with relapsed fatigue, arthralgias and blurred vision, without mucocutaneous pathology. Ophthalmology found new left eye vitritis. RPR was 1:64. She received a further two weeks of intravenous benzylpenicillin, with prednisone in the first 24hr, followed by four weeks of oral amoxicillin, and has made a slow recovery since. Subsequently, RPR titre at six months from first treatment was 1:32.

Syphilis has re-emerged in recent years, with incidence rates rising in many countries, including New Zealand. This case illustrates an unfortunate delay to diagnosis and an unusually protracted and severe secondary-stage illness in the context of significant intercurrent iatrogenic immunosuppression. It is difficult to know whether the clinical relapse after treatment represented treatment failure or a delayed immunological (hypersensitivity) reaction—though the latter is not well-described in syphilis infection. Compared with baseline titre, the RPR at relapse was not significantly different (one dilution); this does not exclude relapse of infection—particularly in a 'sanctuary site' such as the eye. Furthermore, her recent heavy immunosuppression makes interpreting serology tests fraught. Tissue histopathology would be potentially informative, but there was no reasonable site to sample at time of relapse. No other tests are contributory in differentiating between relapse of infection and immunopathology from residual treponemial antigen. In clinical practice, it is usually prudent to repeat relatively safe syphilis treatment when in doubt, and consider prescribing glucocorticoids when the inflammatory response is causing signficant tissue injury or threatens organ function.

Syphilis should be considered when investigating any mucocutaneous ulcerative disease, regardless of the presence of traditional risk factors for infection.[3,4] Given the recent epidemiologic trends, screening selected patients for syphilis infection is worth considering prior to planned immunosuppressive treatment.

Competing interests:
Nil.

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Beyond COVID-19: five actions which would improve the health of all New Zealanders

Emma Espiner, Selah Hart, Garth Poole, Tamara Glyn Mullaney, Su Mei Hoh

We congratulate the New Zealand government for the unprecedented steps taken to protect our population from the potentially catastrophic threat to public health posed by the COVID-19 pandemic.

In recent weeks, we have witnessed the capacity of government to enact sweeping changes which alter the day-to-day lives, economic fortunes and civic freedoms of all New Zealanders. As citizens, most of us have followed the new rules, buying into the premise that by doing so, we're saving lives.

The medical community has been unanimous in supporting the need for action against the novel coronavirus COVID-19. Modelling provided to the Government by Prof Wilson from The University of Otago suggests that, without intervention, up to 3.32 million New Zealanders could be infected with Covid-19, 146,000 requiring hospital admission, 36,600 requiring ICU-level care, and 27,600 potential deaths.[1] For context, in 2017 there were 33,599 deaths from all causes in New Zealand.[2]

We should not simply aim to survive the pandemic, but to filter our perception of what is possible through this lens. We need to reflect carefully on the fact that in 2020 our political leaders united in bipartisan agreement to make dramatic changes to our way of life in the interests of public health. How should we ensure that this impetus for change is captured to improve the future health of the same citizens who withstood fear, uncertainty, job losses, restriction on their freedom of movement and separation from their loved ones for the greater good?

We have entrenched problems in the health system in New Zealand which, until now, have seemed hopelessly lost causes. Advocates for Māori health equity, tobacco control, alcohol law reform, gambling harm prevention and reform of the obesogenic food environment have languished in the antechambers of MPs' offices, battling ignorance, reluctance to act, well-funded and highly connected corporate lobbyists, and the inertia of institutional legacies. Tobacco and obesity alone are two of the leading causes of morbidity and mortality, contributing 9.1% and 7.9% respectively to our overall health loss, quantified in DALYs.[3,4]

With the exception of a few significant wins in tobacco control, such as the excise tax increases, plain packaging and the introduction of Smokefree Environments legislation,[5] advocates for New Zealanders' health have heard time and again that the necessary changes are too hard and too inconvenient to implement. We have fiddled around the edges of issues like alcohol harm, which are corrosive and permeate across generations, because our political leaders have had little appetite to impinge on people's personal freedoms for the greater good. One of the most egregious missed opportunities has been in the regulation of the obesogenic environment, an oversight which has led to unprecedented increases in co-morbidities related to obesity, including many of the risk factors for complications from infection with COVID-19; diabetes, coronary artery disease and hypertension.[6]

There is a range of evidence-based public health interventions which would have

far-reaching positive consequences for the health of the entire population, if they were to be implemented with the same commitment seen in recent weeks. Importantly, they would contribute to addressing health equity as Māori are more likely than non-Māori to be affected by the morbidity and mortality associated with each of these issues. The following interventions could be rapidly implemented and would have long-lasting benefits for the population, and would contribute to reducing inequities if paired with Māori-led capacity development and leadership.

1. Full implementation of the recommendations from the 2010 report of the Law Commission on the regulatory framework for the sale and supply of liquor. This includes increased excise taxes, regulation of alcohol advertising and sponsorship, and increased investment in treatment and support services.[7]
2. Introduction of a tax on sugary drinks in line with the NZ Dental Association Consensus Statement on Sugary Drinks,[8] which aligns with advice from the WHO.[9]
3. Limitation of marketing of junk food to children and increased authority of local authorities to audit licensing of fast food premises with a view to reducing the availability of outlets as outlined in the NZ Medical Association 2014 policy briefing on tackling obesity.[10]
4. A commitment to reducing pokies in the communities most affected by gambling-related harm, stringent regulation of the emerging online gambling industry, and the introduction of sustainable funding opportunities for communities to reduce the reliance on pokies revenue.
5. Introduction of supply reduction policies for tobacco to complement existing interventions, in order to reach the New Zealand Government's Smokefree 2025 goal.[5]

There is no doubt that COVID-19 is a significant threat and that extraordinary measures are warranted. Beyond COVID-19, we should remember the potential for significant health protection with strong leadership and bipartisan commitment for novel public health interventions.

Competing interests:
Nil.

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Survey of public understanding regarding SARS-CoV-2

Roland Crantock

Coronavirus is undoubtedly one of the 21st century's most publicised diseases. Community education is important in the prevention of SARS-CoV-2 transmission and may reduce the impact of this disease on our community. A short survey of 48 persons attending a private medical practice revealed interesting observations regarding public understanding of SARS-CoV-2. COVID-19 was declared as a pandemic on 11 March 2020. This brief study aimed to gauge public understanding of COVID-19 through a series of multiple choice and extend response questions in order to provide insight into baseline knowledge of the virus and explore if there is a need for further community education regarding the disease. Forty-eight participants responded with ages ranging from 18 to 84. The findings of this research promote an ongoing community-orientated health education campaign regarding novel coronavirus.

Methods

Design

This cross-sectional survey was conducted at a specialist medical practice in Melbourne, Victoria. Ethics committee approval was obtained in consultation with the medical advisory committee at the GI Health Hospital (provider number: 0037060T). All participants provided written and signed informed consent prior to completing the survey on a participant information sheet. The surveys were handed out to the patients in the waiting room of the practice and informed that their participation was voluntary and that this would not affect their planned treatment in any way. The survey contained 18 questions including both multiple choice and short answer formats. The questions were designed to gauge the participants' pre-existing knowledge of COVID-19, as well as provide an opportunity for them to express their beliefs, queries and concerns. Moreover, the questions hoped to provide insight into whether current community awareness education aimed at COVID-19 was proving to be successful.

Participants

A total of 48 participants completed the survey with ages ranging from 18 to 84 years. This survey was conducted from the 20 March 2020 till 23 March 2020 and was prematurely ceased due to stricter social distancing legislation within Victoria. For reference, the study was conducted during "Stage 1 Restrictions" introduced by the Victorian Government.[1] As such, the sample size of the research was limited to 48 responses due to this strict social distancing legislation.

Results

While all 48 participants were aware of the terms "coronavirus" and "COVID-19", only 20/48 identified the correct name of the virus as "SARS-CoV-2". Further to this, when questioned if "this virus is the first corona virus to infect humans" 23/48 responded no, of which 10/23 were able to correctly identify at least one other type of corona virus.

All participants correctly identified "close contact with a confirmed case" as a route of transmission; 30/48 recognised transmission by "aerosol droplets" and 39/48 identified "contact with contaminated objects" as further routes of transmission. Moreover, 16/48 believed food or faecal material to be main mediums of spread.

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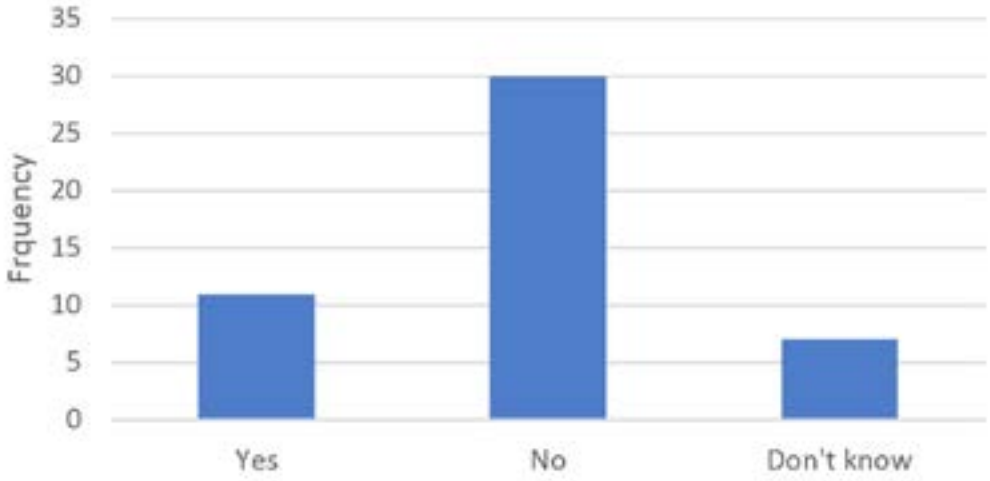
Figure 1: Has enough been done to prevent the spread of coronavirus?



The results of Figure 1 demonstrate a belief that not enough is being done to curb the spread of the virus which was reaffirmed by 37/48 participants, who claimed that "border control was inadequate". Eight participants listed "economic instability" as their greatest concern while 35/48 listed "health of family and friends" as their major worry.

Forty-five participants believed social distancing to be the most effective means of prevention while the remaining three were unsure of an answer. Forty identified fever, shortness of breath, a dry cough, fatigue and sore throat to be the main symptoms of the virus. Nine participants reported that diarrhoea is associated with infection. All participants were aware that there is no vaccine currently available and 31/48 correctly identified the virus to survive for approximately 48–72 hours on hard surfaces.[2]

Twenty-five participants believed those older than 80 years to be at greatest risk of serious complications while 7/48 suggested those aged 60 to 80 years were at greatest risk. Six believed those younger than five years were most at risk while 10 were not sure of an answer.

Gauging participants' recent purchasing history, 18/48 reported that they had bought a greater number of products than usual and cited reasons such as: "preparing in case of need to self-isolate" (7/18), "preparing in case of supply shortage" (5/18), "buying products while available" (4/18) and "buying because everyone else was" (2/18).

Conclusions

This brief study, performed during the early stages of the coronavirus pandemic, suggests that perceptions of coronavirus vary greatly within the sample group and that the majority of participants were well educated about SARS-CoV-2.

The findings of participants' purchase history illustrated a degree of fear within the studied group, given that they were anticipating the potential consequences the virus may have had. Moreover, the results of Figure 1 illustrated dissatisfaction in the sample in that the participants were not content with the early efforts made to combat the spread of COVID-19.

However, the results regarding commonly experienced symptoms and the age most at risk of serious complications illustrated that there is a good general understanding of the virus within the community. Additionally, the findings regarding participant knowledge of a vaccination and viral transmission suggest that community education campaigns have proven successful in raising awareness of pandemic prevention within the studied group. These findings suggest that the education programmes to date have proven effective and successful in improving public understanding of COVID-19 and further encourages an ongoing community-orientated health education campaign regarding coronavirus. Campaigns exploring the use of social media networks, mainstream media and primary health could further improve the success and reach of such public health initiatives.

Further research could more deeply explore awareness of coronavirus transmission and provide insight into how perceptions of the virus within the community have changed since the early stages of the pandemic to now.

Competing interests:
Nil.

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Organisation of National Health

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The last Annual Meeting of the New Zealand Branch of the British Medical Association was remarkable for the recognition of the need for social service by the profession beyond the scope of private practice. There is much work to be done for the improvement of public and private hospitals. It is well recognised that the hospital treatment of patients able to pay for medical attention and nursing is too haphazard at the present time. Undoubtedly as regards national health the State will need to enlarge its functions. If six-pence were spent by a Ministry of Health for every pound expended on the war, the public would marvel at the results achieved. There are many obstacles, however, to be encountered. The people generally look upon the Public Health Department as a collection of officials having to do with drains and infectious diseases, and with these alone: this should be a small part of public health administration. It is difficult to find a political head of the Department who can lift it out of its regular routine, a consummation devoutly longed for, we are sure, by the medical officers of the Department. It is entirely wrong that the head of the health service of New Zealand should receive appointment merely because of his political service, or because of political exigency, and worse still that this important office should be merely an appendage to others considered of more importance. The Department, hitherto, has been unable, we think, to direct the Minister in the way he should go. It is not possible at present apparently, to have a doctor appointed one of the chief difficulties, for the Minister would have both knowledge and enthusiasm. The solution at present is to obtain larger powers of initiative for the Health Board, so that the combined influence of the Board and the Department on the Minister will result in something worth while being accomplished.

The Medical Association, strong though it is, has little or no power to make such recommendations as emanted from the recent Annual Meeting accomplished facts. The weakness of our profession lies in its inability or incapacity for public propoganda, which is against the instinct of the profession, and at the same time it is true that doctors have no time to attend to anything outside their own practices. For instance, the aims and objects of the Plunket Society were at the outset communicated to the Association, and would have made no progress unless lectures, committees and other agencies of propaganda were used to influence the public and the Government. At the present day it is too often the case that politicians do not lead, but they are driven by public opinion, which means votes. The medical profession through its Association has few votes, and cannot influence to any extent public opinion, but the medical profession wants to make this a healthier and a happier country, and knows where there is room for much improvement, and it can make its voice heard on the Public Health Board if the functions and powers of the Board are extended. Such a course will be to the advantage of the public, the Health Department, and the profession. Political control, if it is essential (which we doubt), can be safe-guarded by the Cabinet or the Minister providing the money, and giving rather a free hand to the non-political and expert administrators. In America it has been found that reform and progress are so much hindered by those who unfortunately are handicapped by political experience that there is an agitation to have expert commissions appointed to get things done.

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