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In this issue:

- Making industry payments to New Zealand doctors transparent
- Availability and quantity of antidotes in New Zealand
- Paediatric EEG provision in New Zealand
- Electronic cigarettes: nicotine levels

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CONTENTS

This Issue in the Journal

- 4 A summary of the articles featured in this issue

Editorials

- 6 Let the sunshine in: making industry payments to New Zealand doctors transparent
Cindy Farquhar, Tim Stokes, Andrew Grey, Mark Jeffery, Peter Griffen
- 13 Predictors of outcome for cutaneous squamous cell cancer
James H F Shaw
- 20 Availability and quantity of antidotes in New Zealand
Leo J Schep, Robin J Slaughter

Articles

- 23 Availability of antidotes, antivenoms, and antitoxins in New Zealand hospital pharmacies
John S Fountain, Brendon Sly, Alec Holt, Stephen MacDonell
- 34 Removal of Special Authority requirements for clopidogrel improved optimal care following percutaneous coronary intervention across sociodemographic groups
Suneela Mehta, Sue Wells, Rod Jackson, Jeff Harrison, Andrew Kerr
- 43 Paediatric EEG provision in New Zealand: a survey of practice
Ngaire Keenan, Lynette G Sadlier
- 51 Computer Assisted Learning for the Mind (CALM): the mental health of medical students and their use of a self-help website
Fiona Moir, Antonio T Fernando III, Shailesh Kumar, Marcus Henning, Simon A Moyes, C Raina Elley
- 59 Predicting lymph node metastases in cutaneous squamous cell carcinoma: use of a morphological scoring system
Nicholas J M Agar, Christopher Kirton, Rajan S Patel, Richard C W Martin, Neville Angelo, Patrick O Emanuel
- 68 Association of point prevalence diagnosis of delirium on length of stay, 6-month mortality, and level of care on discharge at Waitemata District Health Board, Auckland
Aik Haw Tan, John Scott
- 77 Nicotine and toxicant yield ratings of electronic cigarette brands in New Zealand
Murray Laugesen

Viewpoint

- 83 What should be the management policy for asymptomatic inguinal hernias?
Philip F Bagshaw

Clinical Correspondence

- 89 A rare case of anti-N-methyl-D-aspartate receptor encephalitis during pregnancy
Lai Wan Chan, Christer Nilsson, Jan Schepel, Christopher Lynch
- 92 Medical image. Metal pigmentation of gingiva
Makoto Adachi, Yasunori Muramatsu

Letter

- 94 The Auckland Surgical Theatre Educational Environment Measure: does attending surgery benefit house officers?

Tary Yin, Stephen Child

100 Years Ago in the NZMJ

- 99 WW1: Prices of Drugs

Methuselah

- 100 Biodegradable stents and coronary artery disease?

SUMMARIES

Availability of antidotes, antivenoms, and antitoxins in New Zealand hospital pharmacies

John S Fountain, Brendon Sly, Alec Holt, Stephen MacDonell

A survey was conducted of 24 New Zealand hospital pharmacies to identify the levels of antidotes, antivenoms and antitoxins held. Short-comings were identified in the types and quantities of certain of these pharmaceuticals when compared to an international guideline. It was considered that this situation may be improved through national rationalisation of the storage and supply of these drugs and the implementation of a national antidote database.

Removal of Special Authority requirements for clopidogrel improved optimal care following percutaneous coronary intervention across sociodemographic groups

Suneela Mehta, Sue Wells, Rod Jackson, Jeff Harrison, Andrew Kerr

Clopidogrel is a medication that was routinely used until mid-2012 to reduce the risk of clots forming within blood vessels in the heart after percutaneous coronary intervention (a common procedure used to unblock narrowed arteries in the heart). We examined if optimal clopidogrel therapy following percutaneous coronary intervention (PCI) changed by age, sex, deprivation status or ethnic group during and after special authority funding restrictions, which required hospital-specialist approval for full funding. After funding restrictions were lifted, optimal clopidogrel therapy following PCI improved by 7% across all sociodemographic groups. Irrespective of funding restrictions, almost all eligible patients received some clopidogrel therapy and there were few differences in optimal clopidogrel use between men and women, younger and older people and more and less deprived groups. However, Maori and Pacific peoples were less likely to have optimal clopidogrel therapy compared to non-Maori/non-Pacific/non-Indian patients before and after funding restrictions were removed.

Paediatric EEG provision in New Zealand: a survey of practice

Ngaire Keenan, Lynette G Sadlier

Epilepsy is a common disorder affecting ~7300 children in New Zealand. Epilepsy is diagnosed with the help of electroencephalography (EEG), an investigation that looks at electrical activity in the brain. This study investigated the procedures that hospital departments in New Zealand used to record EEGs and interpret EEG results. We found that there is variability between departments in these procedures and increased resources are required to ensure New Zealand children have equal access to EEGs.

Computer Assisted Learning for the Mind (CALM): the mental health of medical students and their use of a self-help website

Fiona Moir, Antonio T Fernando III, Shailesh Kumar, Marcus Henning, Simon A Moyes, C Raina Elley

The CALM website (Computer Assisted Learning for the Mind) was developed to provide skills-training to improve mental health and happiness. The site contains evidence-based resources with much of the content being in the form of audiofiles, so that techniques can be practiced. The CALM website was piloted on a group of New Zealand medical students over a 5-week period. This study showed that students who chose to access the site had higher initial levels of anxiety than students who did not choose to access the site.

Predicting lymph node metastases in cutaneous squamous cell carcinoma: use of a morphological scoring system

Nicholas J M Agar, Christopher Kirton, Rajan S Patel, Richard C W Martin, Neville Angelo, Patrick O Emanuel

Cutaneous squamous cell carcinoma is common in New Zealand. Usually, the outcome is very favourable for patients with this disease. Rarely, these tumours behave aggressively. We applied a new method of stratifying risk to try and better predict which tumours will behave aggressively and result in a poor outcome.

Association of point prevalence diagnosis of delirium on length of stay, 6-month mortality, and level of care on discharge at Waitemata District Health Board, Auckland

Aik Haw Tan, John Scott

Delirium is common amongst older adults who are hospitalised. This study detects delirium in hospitalised older adults using a test called the Confusion Assessment Method. This study shows that the presence of delirium in hospitalised older adults was associated with an increased likelihood of death within 6 months. It was also associated with a higher chance of being discharged from the hospital to a rest home or private hospital.

Nicotine and toxicant yield ratings of electronic cigarette brands in New Zealand

Murray Laugesen

Electronic cigarettes (e-cigs) contain nicotine but not toxins, and so they do not kill smokers. We checked out 14 brands sold in New Zealand. We found toxic aldehydes had an average concentration of under 0.5% of that found in Marlboro cigarette smoke. Nicotine concentration was one-half to two-thirds that in a Marlboro. E-cigs are comparatively safe to switch to.

EDITORIAL

Let the sunshine in—making industry payments to New Zealand doctors transparent

Cindy Farquhar, Tim Stokes, Andrew Grey, Mark Jeffery, Peter Griffin

Whilst several countries are enacting legislation to tighten requirements for disclosure of the financial ties between pharmaceutical companies and health practitioners, the situation in New Zealand remains as murky as ever. Due to a lack of transparency in New Zealand it is impossible to know to what extent monetary benefits are flowing from industry to health practitioners in the form of sponsored research, conference sponsorship, consulting fees and other financial incentives.

Although the presence of the government drug-buying agency PHARMAC makes New Zealand's situation unique, the pharmaceutical industry remains active in promoting its commercial interests to health sector personnel. The time is right for a healthy dose of sunlight to shine on these relationships, with the preferred method being legislation similar to the US Sunshine Act which would provide greater transparency for New Zealand health care consumers.

What is the Sunshine Act?

The Sunshine Act was first introduced in the United States in 1976 with the aim of improving transparency in the public sector. Initially the act was focused on the federal government, Congress, federal commissions, and other legally constituted federal bodies and was one of a number of Freedom of Information Acts (<http://www.gsa.gov/portal/content/102416>).

In 2007 a proposed amendment to the bill that would have included the health care sector was unsuccessful. Subsequently, in 2010 the Physician Payment Sunshine Act (PPSA) was passed as part of the Patient Protection and Affordable Care Act. It covers all manufacturers of drugs, devices, and biological and medical supplies covered by federal health care programs and will require the tracking of all financial relationships with physicians and teaching hospitals. It was signed into law in March 2010 and in September 2014 the information was reported publicly for the first time.¹

The extent of the payments was staggering with 4.4 million payments totalling \$US3.5 billion. More than half a million doctors and about 1,360 teaching hospitals received at least one payment (and not including continuing medical education payments).²

Why is this legislation considered necessary?

For the past half-century there has been an increasingly close relationship between health care professionals and industries such as pharmaceutical companies and device manufacturers.^{3,4} Some of these relationships are inevitable as many doctors and researchers are involved in the development of new drugs and other innovations. However, it has also become clear that the relationship has broadened from a strictly advisory one to include promotion and marketing. This is not limited to pharmaceutical products but also includes non-prescription medications such as supplements and sports drinks.⁵

Whilst doctors and scientists may have advanced the research agenda by identifying gaps in knowledge and assisting in the design of clinical studies for industry, some activities clearly do not fit into that category. Reimbursing doctors for assisting research activities may be reasonable given the widely held view that universities and hospitals should not use education or health money for research. However, it is not uncommon for doctors and researchers to receive payment for membership of

advisory boards, speaking at industry sponsored symposia, or sponsorship of travel and accommodation to conferences which often incorporate generous hospitality events and may not involve any speaking commitment. Such interactions between doctors and industry could be interpreted as receiving payment or ‘getting something for nothing’.

Increasingly, doctors are being required to disclose associations with industry when presenting at meetings or submitting manuscripts for publication. Although making a declaration of interest has become common at conferences of the major medical societies, many presenters will choose to either mention it briefly, make light of it in a humorous or dismissive way or wear it as a “badge of honour” if they have declarations from a range of companies. However, many of these interactions occur without the requirement for any official disclosure, which means that the extent and value of the interactions are unknown.

A particular area of concern is clinical guidelines, given their key role in supporting clinical decision making and promoting quality improvement in health care and the imperative that they be trustworthy.⁶ Conflicts of interest (COI) are an important potential source of bias in guideline development and there is increasing concern that COI, in particular those related to the pharmaceutical industry, may adversely affect the quality of clinical guidelines.⁷⁻¹⁰ Recent cross-sectional studies of guideline group members in North America⁸ and Europe (Denmark)¹⁰ have found that financial COIs are common but that there is under-reporting of these by guideline group members. There is evidence that such COI can directly influence the development of clinical guideline recommendations.¹¹ For these reasons it is now usual for guideline development organisations to request declarations of potential COIs.⁹

Until recently the problem of COI has been addressed by internal regulation at the level of health care practitioners, through ethical obligations, and by codes of conduct for organisations responsible for reviewing new drugs and developing clinical guidelines. Most of these organisations now have detailed policies requiring disclosure and providing guidance about how COI should be handled.¹² Given that such policies are based on trust and rely on self-disclosure there has been no way of auditing the accuracy of the declarations. In addition, these ethical standards and policies while important are, in themselves, insufficient. There is a need for industry to be accountable through external mechanisms such as the Sunshine Act.

Compliance a major issue

A national survey in the US reported that 18% of doctors had received reimbursement from industry for costs associated with attending professional meetings and 14% had received payment for consulting, lectures and enrolling patients in clinical trials.¹³ Considerable evidence suggests that the relationship between industry and practitioners influences clinical practice and especially drug prescribing. Pharmaceutical company sponsored research is more likely to favour the sponsor’s product than independently funded research.^{14,15-17} Payments to doctors have been shown to influence their prescribing behaviour.¹⁸ In many instances the recipients of industry benefits are academics or opinion leaders, presumably because of their ability to influence large number of colleagues, students and trainees, and their drive for career advancement.

There have also been concerns that medical students and postgraduate trainees, for whom there may be less scrutiny on interactions with industry, are unduly influenced to prescribe drugs that are promoted by industry. A “PharmFree Scorecard” that grades US medical schools on the presence of a policy regulating interactions between their students and faculty and the pharmaceutical and medical device industries has recently reported that students are more likely to prescribe higher cost and lower value medications if exposed to industry marketing representatives.^{19,20}

Disclosure in the United States

Until the PPSA reported on industry payments to doctors in September 2014, the majority of these payments were under the radar. ProPublica, a group of journalists in the United States mined unstructured data from dozens of websites where payments had been disclosed as a result of lawsuits involving pharmaceutical companies over the years www.propublica.org. ProPublica gathered all of these data, which in 2011 covered payments made by pharmaceutical companies responsible for half of all prescription drug sales in the US.

Developed in 2010 as a news application, ProPublica made the database searchable and freely available. The Dollars for Docs news app is updated as new information comes to hand and has been recently expanded, as the Affordable Care Act requires pharmaceutical and medical device companies to publicly report payments they make to doctors and health institutions. As a result of this project, it was possible to report that US\$2 billion in payments had been made to doctors and health care institutions since 2009 and 22 doctors were identified who earned at least US\$500,000 through such payments, with one doctor being paid over US\$1 million. However, as predicted these payments were a significant undercount as the PPSA data have now shown. Without the mandated data being released, we would still be in the dark about the extent of the payments to the doctors.

Even before the PPSA started reporting, the threat of greater transparency had an impact on the level of payments being made to doctors. In December 2013, the pharmaceutical and supplement company GlaxoSmithKline, which according to ProPublica was responsible for US\$238.6 million in payments to doctors between 2009 and 2012, said it would stop physician payments.²¹ ProPublica reports that the largest US pharmaceutical companies have begun reducing payments to doctors for promotional presentations.

Payments by Eli Lilly declined by 55% between 2011 and 2012, from US\$47.9 million to US\$21.6 million. Moreover, some of the largest pharmaceutical companies have slashed payments to health professionals for promotional lectures amid heightened public scrutiny of such spending, a new ProPublica analysis shows. Over the same period, payments of speakers' fees by Pfizer fell 62% from US\$22 million to US\$8.3 million, while payments by Novartis fell 40% between 2010 and September 2011, from US\$24.8 million to US\$14.8 million.²²

International response to the Physician Payment Sunshine Act

After the PPSA was passed into legislation in the United States, Australia and European countries have all either enacted or begun to enact similar legislation.

In 2011 New Zealand and Australian pharmaceutical companies voluntarily adopted a Trans Tasman code of conduct that was part of a global movement initiated by a series of court settlements between government agencies and a group of pharmaceutical agencies. The principles of the code are legitimacy, transparency, independence and appropriateness of the relationship between health care practitioners and companies. However, the code does not include requirement for disclosure of payment to doctors and institutions; for all intents and purposes, there has been no visible change in the practices.

At local conferences, it is still common for companies to host social occasions with generous benefits with little or no educational component. Sponsorship (via payment of airfares, accommodation and registration) to attend international meetings is the norm in some medical specialties.

Medicines Australia, a trade organisation for pharmaceutical companies, has developed a Transparency Model with the purpose of improving transparency about payments between companies and health care professionals. In May 2013 the Transparency Working Group agreed on a set of principles which included collecting and reporting details on all monetary transactions between a

<http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2015/vol-128-no-1411/6474>

company and individual health care professionals using a single, publicly accessible website. Although the code has recently been revised as outlined above the changes were agreed solely by members of Medicines Australia. However, an “opt out” option for individual health professionals is possible and it fails to implement the concept of a single website for the information.²³

In July 2013 the European Federation of Pharmaceutical Industries and Associations, the body that represents the industry across Europe, announced that its members must disclose details of payments to individual healthcare professionals from 2016.²⁴ Individual countries are yet to finalise how they intend to comply.

In the UK, there is widespread professional support for industry payments to doctors to be made public²⁵ and the Association of the British Pharmaceutical Industry (ABPI) announced in November 2013 that its member companies have agreed, as part of amendments to its Code of Practice, to disclose payments to individually named healthcare professionals, including consultancy services such as speaking and sponsorship to attend medical education meetings. This will come into effect in 2016.²⁶ It is unclear, however, if there will be any requirement to force doctors to disclose their payments if they are not willing to consent to this. The onus appears to remain on self-disclosure by professionals in line with UK General Medical Council (GMC) advice.²⁷

What is the current situation in NZ?

Currently, New Zealand does not have a mechanism for disclosure of payments to doctors from pharmaceutical and device industries. All pharmaceutical companies are required to limit the hospitality provided to doctors by including an educational component but the rate of adherence is unknown and there is no formal oversight or auditing.

An enquiry to Dr Stewart Jessamine of Medsafe, Ministry of Health elicited this reply “The situation in NZ may be different from USA and or Australia as so much of what is available in the public system is purchased via PHARMAC. This double regulatory hurdle of Medsafe's safety, quality and efficacy, and PHARMAC's cost-effectiveness may limit the scope for industry to influence prescribing decisions in terms of one brand over another” (personal communication, Dr Stewart Jessamine, July 2014).

However, not all medicines are funded, and not all health care is publicly funded and there are many drugs which continue to be prescribed by clinicians outside of PHARMAC funding. Certainly the industry is still actively promoting new medicines in New Zealand, and so there are concerns about payments to doctors influencing their prescribing. The plans to have a joint Australian and New Zealand Therapeutic Products Agency which would have harmonised the approaches of the TGA and Medsafe have now been abandoned. This transition to a new agency may have provided an opportunity to implement some changes with regard to improved transparency <http://anztpa.org/projects/harmonisation.htm>.

What could district health boards, medical societies and universities do to assist?

District health boards, medical associations and societies and universities all have a role to play in improving transparency about the interactions between doctors and industry. For example, DHBs provide funding (as part of the national multi-employer contract agreement (MECA) for senior medical officers) via a CME fund entitlement to reimburse senior doctors for expenses incurred by attending conferences and courses.

Greater scrutiny of the appropriateness of conference leave and the relevance, quality and independence of specific meetings could be introduced. This is largely left to clinical leaders to

“police” with a natural disincentive to deny leave to colleagues they work with. DHBs could request that all DHB SMOs disclose their COIs in order to receive their CME funds.

Academics in the United States have called for specialist medical societies to disengage from industry, not allow conflicted members on guidelines groups, and avoid COIs within senior positions in the organization.²⁸ Some New Zealand colleges have followed this example; notably both the Royal New Zealand College of General Practitioners and the Royal Australian and New Zealand College of Psychiatrists no longer have industry sponsors and limit the impact of industry at their conferences. Academic institutions could also assist by making available COI statements and details of payments for their staff.

Industry research is often considered a good way to advance an academic career, as it may lead to international presentations and publications and prominence in the field. In the United States, most medical faculties require disclosure and have policies for monitoring these.¹⁹

Conclusions

In the final analysis it is a matter of trust. How do we know if the information and treatments we are receiving from doctors and other health professionals have not been influenced by payments or sponsorship from certain related companies? Certainly the results of research from pharmaceutical sponsored studies have found such studies to be biased and favouring the companies’ products.

To date the focus has been on professional self-regulation but evidence from clinical guidelines suggests that it is insufficient to wholly rely on clinician self-disclosure with an expectation that clinicians will always act in accordance with their regulatory body’s code of practice. There is a need for tighter external regulation of industry as achieved through the US Sunshine Act. Whilst there is some concern that disclosure *per se* is insufficient to substantially improve matters, the impressive reduction in payments that is already happening in the United States provides evidence that change by industry is possible and will make a difference.

New Zealanders should be rightfully proud of our public health system and our access to a range of drugs and procedures at competitive prices. However, we can’t afford to ignore the fact that many commercial groups seek and establish relationships with health professionals that may undermine health policy development. There is an urgent need to have this information made transparent so that our clinicians and policy-makers are seen as making independent trustworthy decisions on health care.

We consider that New Zealand should adopt international best practice with respect to transparency over industry payments to individuals. Shining some light on the relationships is likely to be good for our health.

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EDITORIAL**Predictors of outcome for cutaneous squamous cell cancer**

James H F Shaw

Agar and colleagues,¹ in this issue of the *Journal*, present a nicely-done study applying histological predictive data from mucosal squamous cell cancer (SCC) to assess prediction of outcome for cutaneous SCC (cut-SCC). They conclude that histological predictors of outcome for cut-SCC include:

- Aggressive histology.
- Thick lesions.
- The presence of a poor immune response histologically.
- Probably peri-neural invasion (PNI).

This study is especially pertinent in view of the high and steadily increasing rates of non-melanoma skin cancer (NMSC) worldwide and especially in New Zealand where this increase involves both basal cell (BCC) and squamous cell cancer (SCC).

See Table 1 adapted from data from Swee Tan and colleagues^{2,3} demonstrating the high and steadily increasing (especially in older patients) rate of non-melanoma skin cancer (NMSC) in New Zealand.

Table 1. Changing incidence non-melanoma skin cancer (NMSC) in New Zealand

- Review of 54,000 NMSC resected over 10-year period
 - BCC incidence : 300:100,000
 - SCC incidence: 180:100,000
- Current incidence increase per year:
 - BCC: 4% per year
 - SCC: 1% per year
- Greatest increase in patients >50 years

	Age group with largest % increase per year	% increase per year
• BCC Male	>80 years	6.4%
• BCC Female	70–79 years	7.4%
• SCC Male	> 80 years	3.6%
• SCC Female	> 70 years	2.2%

Source: Table adapted from Brougham NDL, Dennett ER, Tan ST. Changing incidence of non-melanoma skin cancer in New Zealand. *A N Z J Surg.* 2011;81(9):633–636.

BCC=basal cell carcinoma/cancer; SCC=squamous cell carcinoma/cancer.

A number of other issues pertaining to cut-SCC are also mentioned by Agar et al¹ in their introduction and discussion. In particular:

- The low rate of regional disease in New Zealand: <3% of cut-SCC.³
- Individual anatomical sites can be predictive as to outcome—e.g. lip and parotid area are unfavourable according to North American data.⁴
- 5-year survival for regional cut-SCC is reported in the introduction at 13–49%.¹
- Immunosuppression has a negative impact on outcome.⁵
- Other general factors influencing outcome in cut-SCC as reported in the bibliography of Agar et al.¹ For example the reference from Veness and colleagues^{6,7} who have reported that outcome for patients with regional disease from cut-SCC is more influenced by the size of the regional disease rather than the number of nodes involved.

We have collected data recently that sheds light on, or complements a number of the findings of Agar et al¹ and the other recent New Zealand study assessing cut-SCC from Peat and colleagues.⁸ In particular our findings of relevance include the following.

Agar et al¹ experienced difficulty in detecting large numbers of matched pairs for their study. One reason for this is that only a small percentage (<5%) of cut-SCC patients develop regional disease. In our experience with 303 cut-SCC patients managed over a 30-year period, 24% had or developed regional disease. This high rate was because the majority of patients were tertiary referred having already developed regional disease.

The vast majority of cut-SCC patients are elderly (mean age in our series 78 years with male to female ratio 3:1) and most do not either develop regional disease and/or die of their cut-SCC. Rather the majority die of the common causes of death seen in patients over the age of 78 year age namely: cardiovascular disease, common cancers such as bowel, breast, and prostate, or from coexisting melanoma.

In contrast, for the node-positive patients (N+): 73 out of a total number of 303 (24% of the total) a small number of these patients died of diseases other than cut-SCC (7/73 or 10%) compared with 40% (29/73) of those with regional disease who died of disease (DOD).

The presence of regional disease has been reported as a death sentence by some investigators—e.g. O'Brien et al¹⁰ who found no patients with cut-SCC alive at 5 years, however in our series 11/73 node-positive (N+) patients or 15% were alive at 5 years, and 10/73 (14%) N+ were alive at 10 years. See Table 2.

Table 2. Outcome for 73 node-positive cut-SCC head and neck patients

Variable	Number	Percentage
Total number of cutaneous SCC patients in series	303	
Number of node-positive patients	73	24%
Number of node-positive patients dead of disease	29/73	40%
Number of node-positive patients dead from causes other than disease	7/73	10%
Number of node-positive patients alive at the time of the study	37/73	50%
Number of node-positive patients alive at 5 years	11/73	15%
Number of node-positive patients alive at 10 years	10/73	14%
Number of node-positive patients alive at 14 years	9/73	12%

Of the patients who developed regional disease involving either parotid nodes or cervical nodes (or a combination of both), as the stage of the cancer got worse, the risk of the patient dying of disease

(DOD) approached 90–100% and the risk of death from other causes (D other) obviously decreased accordingly. See Table 3 comparing our results with O’ Brien et al.¹⁰

Table 3. Survival versus stage of disease: Sydney versus Auckland

Stage of disease	Percentage alive and well after 5 years in Sydney	Percentage alive and well at time of study in Auckland	10-year survival in Auckland*
P1	14% (6/44)	83% (15/18) FU up to 16 years	>23% (3/13)
P2	9% (3/35)	39% (7/18) FU up to 19 years	>8% (1/12)
P3	13% (1/8)	14% (1/7) FU up to 14 years	14% (1/7)
N1 1 node-positive	0% 0/14	74% (14/19) FU up to 19 years	>27% (4/15)
N2 >1 node-positive	0% (0/20)	22% (5/22) FU up to 18 years	>7% (2/30)

Source: Sydney data adapted from O’Brien et al, Head & Neck 2002.¹⁰

*All percentages are > as all numerators are absolute no of patients surviving 10 years. More patients will survive 10 years but not there yet.

FU=Follow-Up.

Certain anatomical sites were associated with increased risk of regional disease with cut-SCC and also the number of involved nodes was predictive of outcome. Unfavourable sites for developing regional disease were: Pre-auricular, ear, lip, with the single worst site being post-auricular (>80% risk of regional disease). Relatively favourable sites with lower rates of regional disease were face and neck where approximately 25% of regional disease came from primary lesions in these sites.

Our patients were staged for both parotid disease: P1: <3 cm diameter, P2: 3–6cm diameter, P3: >6 cm or facial nerve invasion or base of scull involvement, and for cervical nodal disease: N1: 1 node involved, N2a 1 node but >3 cm, N3 1 node >6 cm, N2b multiple nodes involved, N2c bilateral neck disease.

Commonest sites of regional disease were: parotid in 49% and level 2 in 36%. This is similar to what we and others have described in head and neck melanoma.^{9,12}

Some authors have indicated that the number of nodes involved in cut-SCC is not as predictive as the size of the nodes involved: for example Veness et al 2003.⁷ We found the opposite in both a previous study of head and neck melanoma patients⁹ and in the current study of head and neck cut-SCC.

In particular, for cut-SCC, the number of nodes involved had a major impact on survival. See Table 4. A single involved node even if it was large (N2a: 3–6 cm), or very large (N3: >6 cm) had a good outcome. For example one of the two patients with N3 disease was alive 14 years post-surgery at the age of 99 years.

Table 4. Outcome versus number of pathologically involved nodes

Number of involved nodes	% A & W	Median FU
1 node positive	79 % (22/28)	10 years (8 months–18 years)
2 nodes positive	50% (5/10)	5 years (10–65 months)
3 nodes positive	25% (1/4)	2 years (10–48 months); survivor is 4 years
4 or > 4 nodes positive	10% (1/10)	2 years (7–48 months)

A & W=Alive and Well; FU=Follow-Up.

Table 5 summarises the factors associated with 29 recurrences in the 73 patients with regional disease. The major factors of note were: N2b neck disease, P2 or P3 parotid disease, and the presence of a positive margin at the time of resection.

A number of investigators have highlighted the ominous significance of P3 disease for example O'Brien et al¹⁰ who only had 1 out of 8 P3 patients alive at 5 years. Our finding was similar with 1 of 7 patients (14%) with P3 disease alive and well at the time of study: 14 years after surgery and having presented with a complete facial nerve palsy.

Table 5. Factors associated with recurrence in patients with regional cutaneous SCC

Factor	Percentage of total n=29	Importance
P2 or P3	55% 16/29	No 1 =
N2b or N2c	41% 16/29	No 1 =
Positive resection margin	37% 11/29	No 3
Immune impairment	28% 8/29	No 4

1= : First equal in importance.

O'Brien et al¹⁰ concluded that the main factor governing outcome in cut-SCC head and neck was the presence of cervical nodal disease rather than parotid nodal involvement with no patients alive at 5 years who had involved regional nodes. In contrast, we found that both parotid involvement and cervical disease had a similar impact on outcome. See Table 6.

Table 6. Node-positive patients: long-term survivors

Node-positive patients: long-term survivors					
% of patients surviving 5 yrs: 15% 11/73					
% of patients surviving 10 yrs: 14% (10/73)					
P1No	31%	4/13 A&W	Mean	13 yr	(5 yr, 14 yr, 14 yr, 20 yr)
PoN1	40%	4/10 A&W	Mean	13 yr	(3 yr, 10 yr, 19 yr, 20 yr)
PoN2a	20%	1/5 A&W	@	18 yr	
P2N1	40%	2/5 A&W	@	3 yr & 19yr	
PoN3	50%	1/2 A&W	@	14 yr	
P2No	14%	1/7 A&W	@	2 yr	
P3N0	33%	1/3 A&W	@	16 yr	
PoN2b	9%	1/11 A&W	@	2.5 yr	

We also found that immunological impairment was a factor associated with recurrence in the regional disease group: 8 of the 29 patients who recurred (28%) were immunosuppressed either from corticosteroid administration or as a result of a blood malignancy. In addition, in the total group of 303 patients a total of 19 had been immune-deficient and 10 of these 19 (53%) died of their cut-SCC compared with only 10% of the group overall being DOD. This is in general accord with Peat &

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Colleagues⁸ who found that 15% of patients in the regional disease group had an immune-deficiency versus only 3% in patients without regional disease.

Peat & Colleagues⁸ found both peri-neural invasion (PNI) and lympho-vascular invasion (LVI) to be significant predictors. PNI was present in 32% of the patients with regional disease versus only 1% of controls (sig p<0.01). LVI was present in 13% of the regional disease group and in 0% of control patients. We also found PNI to be unfavourable.

Several unfavourable factors were associated with a 95% risk of becoming DOD. See Table 7.

Table 7. Final pathway: 100% DOD <3 months

Dermal metastases	7/7 patients
Permanent tracheostomy	2/2 patients
Recurrence on carotid artery	2/2 patients
Axillary dissection after neck dissection	2/2 patients
P3 recurrence	6/7 patients

However, despite the above “doom & gloom” 10 of the 73 node-positive patients (14%) survived disease free for more than 10 years. See Table 6 again.

Single modality treatment is not a good option for managing regional disease associated with cut-SCC. Probably the most favoured option is a combination of appropriate surgery and adjuvant radiation.^{7,13} To underline the importance of PORT, O’Brien et al¹⁰ observed that refusal by patients to undergo postoperative radiation (PORT) was associated with a bad outcome. We noted the same: 5 patients refused PORT and 4/5 (80%) were DOD within 6 months.

Probably the most extensive report of cut-SCC in New Zealand is from Swee Tan and his group.¹⁴ Incidentally they also found ear lesions, post-auricular lesions, and lip lesions to be unfavourable as we did—see above.

The most difficult question is what to do once a cut-SCC patient has been defined as having a high risk of developing regional disease. Peat & colleagues⁸ suggest either a sentinel node biopsy (SNB) or adjuvant radiation. The place of SNB for high risk cut-SCC has been studied very little and such a study is required. SNB has an established role in the management of patients with non-thin melanoma but the role of SNB is unclear with respect to Merkel cell skin cancer (MCC). In a recent review of the subject, John Thompson (from the Sydney Melanoma Unit)¹¹ concluded that the role of SNB in patients with Merkel cell carcinoma (MCC) is unclear and that uncertainty prevails.

As a prelude to collecting cut-SCC data for SNB we have endeavoured to begin to predict the results of such a study by comparing two sets of data. We have compared the data addressing which anatomical sites in the head and neck area drain to the individual regional beds namely parotid, and neck levels I–V.⁹ We have presented these data previously for head and neck melanoma and more recently we have collected equivalent data for cut-SCC of the head and neck area (presented but not published). 111 patients underwent therapeutic neck dissection for head and neck melanoma, and 72 patients underwent therapeutic neck dissection for cut-SCC in the head and neck region.

The distribution from individual anatomical sites to various levels of the head and neck regional beds for melanoma and cut-SCC were similar; in particular the two commonest sites for both pathologies are nodes in the parotid gland and level 2 cervical nodes with less common involvement of levels 3–5 depending on primary site location. See Table 8.

Table 8. Anatomical site of primary cancer versus level of regional bed involvement for melanoma & cutaneous squamous cell cancer in Auckland

	Ear Mel N=14	Ear SCC N=35	Face Mel N=41	Face SCC N=20	Scalp Mel N=30	Scalp SCC N=15	Neck Mel N=26	Neck SCC N=2	Total Mel N=111	Total SCC N=72
Parotid	64% (9)	37% (13)	46% (19)	70% (14)	51% (15)	53% (8)	8% (2)	—	43% (49)	49% (32)
Lev 1	—	—	10% (4)	15% (3)	7% (2)	—	4% (1)	—	11% (12)	4% (3)
Lev 2	50% (7)	30% (11)	29% (12)	45% (9)	30% (9)	33% (5)	33% (9)	50% (1)	47% (54)	36% (26)
Lev 3/4	7% (1)	6% (2)	5% (2)	15% (3)	20% (6)	7% (1)	18% (5)	—	25% (28)	8% (6)
Lev 5	—	3% (1)	5% (2)	10% (2)	28% (8)	27% (9)	46% (12)	100% (2)	9% (10)	19% (14)

Table 9 summarises predictive factors of outcome for cut-SCC utilising data from a number of investigators.

Table 9. Summary: prognostic factors predicting regional disease in cutaneous SCC

Peat et al			
Absolute predictors	High risk	1 or 2 absolute predictors	37% risk for N+
Poorly differentiated histology		Or all 3 relative predictors	37% risk for N+
PNI or LVI			
Relative predictors	Intermediate risk	2 relative predictors	5% risk for N+
Moderate differentiation			
Diameter >2 cm			
Clark level 5	Low risk	none or 1 relative predictors	0/3% risk for N+
Agar et al			
Aggressive histology			
Thick lesions (Breslow)			
Poor immune response			
PNI especially involving nerves >1 mm diameter			
AJCC			
Anatomical site: ear and upper lip			
Author of this editorial			
Anatomical site: auricular, pre-auricular, post-auricular, lip			
Impaired immunity			
Number of nodes involved			

Overall there is an ‘epidemic’ of skin cancer in New Zealand (and even more so in Australia). It is now possible to more accurately predict the relatively small percentage of patients with cut-SCC who will develop regional disease, and also predict outcome of patients who develop regional disease. The next step is probably to determine the role of SNB in cut-SCC and determine whether it will be as a useful tool as in melanoma.

Competing interests: Nil.

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EDITORIAL

Availability and quantity of antidotes in New Zealand

Leo J Schep, Robin J Slaughter

Most instances of poisoning and drug overdoses requiring medical attention can be successfully managed with appropriate supportive care; nevertheless, some patients require timely intervention with a suitable antidote to minimise the risks of morbidity and mortality. Success may depend on the availability and quantity of the desired antidote.

Overseas investigations have shown that many healthcare institutions are understocked of antidotes to treat these patients.¹⁻⁴ Despite a recent study to the contrary,⁵ the paper by Fountain and colleagues, published in this issue of the *New Zealand Medical Journal*, suggests similar problems in New Zealand hospitals with shortcomings in hospital pharmacy stocks and resupply.⁶ The paper raises concerns that many antidotes would not be stocked in sufficient quantity to manage a single 100 kg poisoned patient for 8 hours at most New Zealand hospitals.

Antidotes can be critical for the successful outcome of poisoning.⁷ For example; before the antidote for cardiac glycosides became available, all patients who suffered a sustained cardiac arrest died.⁸

Poisoning from digoxin or cardiac glycosides can occur in New Zealand, such as following the ingestion of oleander or foxglove.⁹ Nevertheless, the paper by Fountain and colleagues suggests digoxin fab antibodies to treat poisoned patients are not readily accessible in most New Zealand hospitals. Lack of availability of this antibody has also been reported in other overseas audits.^{1,2,10} This is possibly because vials are expensive, such poisonings are not a common event, it has a relatively short shelf-life and up to 20 vials may be necessary to treat one adult patient.

One initial problem is defining which antidotes are essential and how much to stock. For example, prompt antidotal treatment is critical for successful management of poisoning from digoxin and cardiac glycosides, opioids and cyanide.¹¹ Researchers in the United States have investigated this and determined a list of essential antidotes.¹¹

Debate needs to be conducted to determine which antidotes are applicable and necessary for New Zealand. While some antidotes like flumazenil, physostigmine and glucagon are described as essential in the United States guidelines, many clinicians would not regard them as such, and some antidotes (for example physostigmine, fomepizole, Prussian blue and cyproheptadine among others) are not available in New Zealand as there is no registered product on the local market.

Having input from a range of health professionals specialising in medical toxicology, emergency medicine, critical care medicine, paediatrics, hospital pharmacy along with the National Poison Centre may help to refine this list to make it more appropriate for New Zealand. As the study discusses, there are also new antidotes which may be beneficial and others which should no longer be stocked.

While having a list of essential antidotes for New Zealand would be advantageous, some antidotes, antivenoms and antitoxins which would be classed as essential, as they may be life-saving, are rarely used or are expensive and it would be prohibitive to stock them at every hospital. For example, major poisonings requiring antidotal care from some classically toxic agents like mercury or arsenic are rare nowadays, while antivenom use following envenomings from venomous creatures in New Zealand is also uncommon.¹²

As Fountain and associates suggest, centralisation of these antidotes is likely the best way to ensure stocks are available throughout New Zealand. In such cases, knowing where the antidote is held and having protocols in place for timely transport, particularly to smaller outlying hospitals, are required.

<http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2015/vol-128-no-1411/6475>

A database of stocked antidotes, readily accessible to all New Zealand hospital pharmacies, could therefore be an appropriate way of monitoring the accessibility of antidotes. In order for it to be of use and accurately display antidote holdings, it would require participating hospitals to ensure their stocks were monitored and this information was kept up-to-date in real-time.

There is presently an antidote list available, published by the New Zealand Hospital Pharmacists' Association, but unfortunately it does not appear to have been updated since November 2013.¹³ An investigation into the feasibility of a real-time database therefore seems warranted.

Antidotes are critical in treating some poisoned patients. Fountain and co-workers have highlighted inadequacies in the availability and quantity of stocks of antidotes in New Zealand. These short falls can be addressed by establishing which antidotes are necessary for New Zealand, having stocks readily available, and an up-to-date database to assist clinicians sourcing such stocks that are not available in their respective hospital pharmacies.

Competing interests: Nil.

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ORIGINAL ARTICLE

Availability of antidotes, antivenoms, and antitoxins in New Zealand hospital pharmacies

John S Fountain, Brendon Sly, Alec Holt, Stephen MacDonell

Abstract

Aim To assess the adequacy of the types and quantities of antidotes, antivenoms and antitoxins held by New Zealand hospital pharmacies.

Methods A list of 61 antidotes, antivenoms, antitoxins and their various forms was developed following literature review and consideration of national pharmaceutical listings. An Internet-accessible survey was then developed, validated and, during the period 28 February to 7 April 2014, sent to 24 hospital pharmacies nationally for completion. Results were assessed and compared with published guidelines for adequate stocking of antidotes in hospitals that provide emergency care.

Results The response rate for the survey was 100%. Wide variation in stock levels were reported with only N-acetylcysteine and octreotide held in adequate quantities by all hospitals to manage a single patient for 24 hours. While archaic compounds were still stocked, newer and more effective pharmaceuticals were not. The national replacement cost for expiring drugs was estimated at \$171,024, with smaller, more isolated facilities facing the greatest expense and difficulty in achieving timely resupply.

Conclusion Shortcomings in the types and quantities of antidotes, antivenoms and antitoxins held by New Zealand hospital pharmacies were recognised. This situation may be improved through national rationalisation of pharmaceutical storage and supply, and implementation of a national antidote database.

Poisoning is an internationally recognised burden on healthcare systems,¹ and New Zealand is not immune. Annual rates of poisoning deaths in this country reaching 6.3 per 100,000 in both 2001 and 2002; two-thirds (64.3%) related to carbon monoxide exposures,² the remainder due to a range of substances—volatile compounds,³ antidepressants,⁴ sedative/hypnotics,⁵ and the opioids in particular.⁶ Examination of adult hospital admissions due to poisoning over a 10-year period revealed a mean annual rate of 115.4 per 100,000, or 29,881 admissions.⁷

Antidotes are an important aspect of the management of many of these poisonings, and for certain intoxications their timely administration can be lifesaving. However, international studies have consistently identified the types and stocks of antidotes held by hospitals as being inadequate.^{8–11} This is a likely result of their cost: antidotes are, in general, uncommonly administered, expensive and often expire prior to use. It is therefore tempting to under-stock. Interestingly, New Zealand appears to be an exception according to a 2012 national survey that concluded that “New Zealand hospital pharmacies stock adequate supplies of essential antidotes”.¹²

However, in 2013 there were national and international warnings from the New Zealand Government concerning the sale of whey protein concentrate considered potentially contaminated by the bacterium *Clostridium botulinum*.¹³ This anaerobic, Gram-positive, spore-forming bacterium produces the toxin botulinum—the causative agent of the neurological disease botulism and described as the most toxic substance known.¹⁴ The location and assessment of the national stock holding of botulism antitoxin

became a priority. As a result the New Zealand Ministry of Health requested that the location and current stock levels of a range of antidotes, antivenoms and antitoxins held in New Zealand hospital pharmacies be surveyed, and recommendations made to remedy any shortcomings identified. This paper outlines findings of this review.

Methods

To identify relevant antidotes, antivenoms and antitoxins for a national survey, a MEDLINE search was conducted using the terms “antidote”, “antivenom” and “antitoxin” combined with the keywords “survey”, “review” and “guideline”. Bibliographies of retrieved publications were then reviewed for further pertinent articles. Twenty-two articles and seven abstracts / conference proceedings were identified as relevant.

Also reviewed was the “Antidote List”, a resource published and maintained by the New Zealand Hospital Pharmacists’ Association (NZHPA) to facilitate national location of antidotes.¹⁵ And finally, those drugs listed under the heading “Agents used in the Treatment of Poisonings ” in Section H of the PHARMAC (the government agency managing the national pharmaceutical budget) Pharmaceutical Schedule were considered; drugs in this section are those that can be used in public hospitals.¹⁶

From these resources 45 antidotes, antivenoms, antitoxins, and their (61) formulations were compiled for inclusion in the survey (Appendix 1: <http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2015/vol-128-no-1411/6477/appendix.pdf>). Not all possible pharmaceuticals were added as it was considered some would be stocked in significant quantities due to their use for other medical indications (e.g. sodium bicarbonate) or were known not to be available in New Zealand (e.g. silibinin).

The survey itself was developed as an Internet accessible questionnaire with both quantitative and qualitative sections. The quantitative section requested entry of the number of stock units and earliest expiry of the pharmaceuticals selected for inclusion, while the qualitative area collected text or check-box responses to a range of questions. This latter section was designed to anonymise responses. The survey was developed and run on Microsoft IIS (Internet Information Server), using ASP (Active Server Pages) and SQL Server (Database) technologies on a secure server located within the University of Otago.

Pharmacies for survey were selected from hospitals considered likely to manage poisoned patients, i.e. possessing level 4, 5 or 6 emergency departments (EDs). Level 4 indicating a secondary hospital ED; level 5 a tertiary hospital department; and level 6, a higher-level tertiary hospital.¹⁷ Twenty-five hospitals were identified, representing all 20 district health boards within New Zealand, experiencing annual ED patient presentations ranging from 9,500 to 92,000. Of these it was known that two level 6 facilities shared the same pharmacy, leaving 24 individual hospital pharmacy departments for survey (Table 1).

The questionnaire and web platform underwent testing and validation during February 2014, including trial by three hospital pharmacies. Support for the study was sought from the NZHPA who emailed members to encourage their participation. The chief pharmacists of the 24 selected hospitals were then contacted by telephone and invited to participate, all agreeing. Usernames and passwords allowing individual hospital access to the survey were distributed and the survey conducted from 28 February to 7 April 2014. Email and telephone follow-up was conducted during this period to encourage completion of the survey.

Table 1. The hospitals surveyed, their district health board (DHB), and emergency department (ED) level

Hospital	DHB	ED level
Auckland City/Starship	Auckland	6
Christchurch	Canterbury	6
Dunedin	Southern	6
Gisborne	Tairawhiti	4
Grey Base	West Coast	4
Hastings Memorial	Hawke's Bay	5
Hutt	Hutt Valley	4
Masterton	Wairarapa	4
Middlemore	Counties Manukau	6
Nelson	Nelson Marlborough	4
North Shore	Waitemata	5
Palmerston North	MidCentral	5
Rotorua	Lakes	4
Southland	Southern	4
Taranaki Base	Taranaki	4
Taupo	Lakes	5
Tauranga	Bay of Plenty	4
Timaru	South Canterbury	4
Waikato	Waikato	6
Wairau	Nelson Marlborough	4
Waitakere	Waitemata	4
Whanganui	Whanganui	4
Wellington	Capital and Coast	6
Whangarei	Northland	4

Results were collated and analysed using Microsoft Excel® software and the level of antidote stocks held assessed for adequacy by applying the expert consensus guidelines for stocking of antidotes developed by Dart et al.¹⁸ Ethical approval for this study was obtained from the Ngai Tahu Research Consultation Committee and the University of Otago Human Ethics Committee (Reference Number D14/064).

Results

The response rate for the survey was 100%.

Of the 61 products examined, 14 were not held by any hospital (Table 2), and a further 7 only stocked in single pharmacies (Table 3). However, drugs no longer considered as indicated for management of poisoning were identified, including the gastrointestinal decontaminant Fuller's earth, stocked by 1 hospital, and edetate disodium in 5.

Table 2. Pharmaceuticals not held in any hospital

Product
4-methylpyrazole 1,500 mg/1.5 mL inj
N-acetylcysteine 6,000 mg/30 mL inj
Atropine sulfate 1,200 ug/mL inj
Botulism antitoxin heptavalent inj
Botulism immune globulin inj
Calcium DTPA 1,000 mg/5 mL inj
Dimercaptopropane sulfonic acid
Diphtheria toxoid 30 IU inj
Ethanol 100% 20 mL/20 mL inj
Naloxone 800 mcg/mL inj
Physostigmine 2 mg/2 mL inj
Prussian blue 500 mg tab
Zinc DTPA 200 mg/5 mL

Table 3. Pharmaceuticals only held in one hospital

Product	Hospital
Botulism antitoxin trivalent	Auckland
Dimercaptosuccinic acid	Middlemore
Diphtheria antitoxin	Auckland
Fuller's earth powder	Palmerston North
Penicillamine	Nelson
Polyvalent snake antivenom CSL	Auckland
Potassium iodide	Middlemore

The adequacy of antidote stocks held by hospitals for fully treating a patient for 8 or 24 hours was assessed by applying the expert consensus guidelines for stocking of antidotes¹⁸ with shortfalls identified in a number of areas (Table 4).

Twenty-three (95.8%) of the 24 hospitals surveyed responded when asked to identify antidotes, antivenoms and antitoxins that were difficult to procure. A number listed generic groups (e.g. drugs used in the management of cyanide or organophosphate poisonings), preventing identification of specific products. However, 34 compounds were individually identified, representing 55.7% of the 61 products listed.

Table 4. Percent of hospitals holding adequate antidote stocks to manage a single (100kg) patient

Antidote	Meets stock level recommendation for:		
	8 hours(%)	24 hours(%)	No answer(%)
N-acetylcysteine	100.0	100.0	0.0
Atropine sulfate	83.3	50.0	0.0
Calcium chloride	87.5	87.5	8.3
Calcium gluconate	70.8	70.8	8.3
Calcium disodium EDTA	12.5	4.2	33.3
Cyanide antidotes	75.0	70.8	8.3
Deferoxamine	29.2	0.0	0.0
DigFAB	0.0	0.0	45.8
Dimercaprol	62.5	12.5	12.5
Ethanol	41.7	12.5	16.7
Fomepizole	0.0	0.0	0.0
Flumazenil	75.0	54.2	4.2
Glucagon	8.3	0.0	0.0
Methylene blue	58.3	58.3	16.7
Naloxone	70.8	12.5	0.0
Octreotide	100.0	100.0	0.0
Physostigmine	0.0	0.0	0.0
Pralidoxime	25.0	4.2	4.2
Pyridoxine	4.2	0.0	20.8

Note: This assessment follows the recommendations of Dart et al.¹⁸

Responders also assessed difficulty in locating drugs in an emergency (Table 5). Results indicate that lower-level (i.e. more isolated) facilities found this more challenging, level 4, 5 and 6 facilities possessing satisfactory arrangements in 36%, 75% and 80% of responses respectively (one level 6 facility did not answer this question).

Table 5. Difficulty in locating drugs in emergency

Degree of difficulty	Number	Percent
Very difficult	2	8.3
Difficult	9	37.5
Satisfactory	12	50.0
Easy	0	0.0
Very easy	0	0.0
Did not answer	1	4.2

Note: One level 6 facility did not respond to this question.

A range of methods was declared for transporting antidotes between hospitals (Table 6), the most common being courier, taxi and private vehicle; used by 92%, 71% and 58% of hospitals respectively. Clearly movement of antidotes was required over large distances with both fixed-wing aircraft and

helicopters being deployed by 50% and 33% of hospitals respectively, level 4 facilities being the main users.

Table 6. Methods utilised for transporting antidotes, antivenoms and antitoxins

Hospital ED level	Number	Courier	Taxi	Private vehicle	Fixed-wing	Helicopter	Police	Other
4	14	12	10	10	7	6	3	1
5	4	4	4	4	2	2	2	0
6	6	6	3	0	3	0	0	1
Total	24	22	17	14	12	8	5	2

Note: One level 4 facility did not respond to this question: more than one method was used by individual hospitals.

All hospitals responded when asked whether they had protocols for obtaining antidotes, antivenoms and antitoxins. However, only five (21%) confirmed they possessed such protocols; one hospital considered its protocol as inadequate if drugs were required for more than one patient, leaving four (17%) pharmacies with formal procedures considered adequate for obtaining emergency resupply.

Fifteen (63%) of the 24 pharmacies responded when asked to estimate the annual cost of replacing expired listed drugs. The mean expense was reported as \$7,127 (range \$1,000 to \$20,000). The smaller the facility, the greater the loss: level 4, 5 and 6 facilities estimating mean costs at \$8,055, \$7,133 and \$4,500 respectively. If the calculated mean was applied to all 24 hospitals in the survey, the estimated total annual cost of expired antidotes, antivenoms and antitoxins reached \$171,024.

When questioned if an Internet-accessible national antidote database would be useful, 100% (24) of respondents agreed, 21% replying that it would be useful, 79% that it would be very useful. There were also a number of text comments highlighting the desirability of such a resource. However, some associated issues were raised, particularly in regard to the procedures for and frequency of updating such a database and related resource implications.

Discussion

This study has identified national shortcomings in hospital pharmacy antidote, antivenom and antitoxin stock and resupply. These findings are in agreement with similar surveys conducted in a number of other countries including the United States, the United Kingdom, Canada, South Africa and Australia,^{9–11,19,20} but do not repeat the conclusions of a previous survey reported in New Zealand.¹²

While 14 listed drugs were identified as not held by any hospital pharmacy, many were in fact alternative formulations of drugs otherwise stocked (e.g. acetylcysteine 6 g/30 mL inj, diphtheria toxoid 30 IU inj, ethanol 100% 20 mL/20 mL inj and naloxone hydrochloride 800 ug/2 mL inj). Other drugs not held, while considered important in overseas reviews, may not be of significance in New Zealand. These include pharmaceuticals for the treatment of those exposed to radiological agents (i.e. calcium DTPA, Zinc DTPA and Prussian blue): New Zealand does not possess a nuclear industry.

However, some antidotes not currently stocked may merit consideration for introduction to the New Zealand pharmacopeia including: 4-methylpyrazole (fomepizole), a cost-effective alternative to ethanol for the treatment of toxic alcohol and glycol ingestion;²¹ dimercaptopropane sulfonic acid, a

heavy metal chelating agent considered superior to many currently held;²² and, physostigmine salicylate, indicated for the reversal of severe anticholinergic toxicity.²³

Further agents, while not included in this survey, may also merit consideration: glucarpidase, indicated for the management of elevated methotrexate levels in the presence of renal failure;²⁴ silibinin, considered to be of benefit following (amatoxin) mushroom poisoning;²⁵ and, uridine triacetate, an antidote for 5-fluorouracil overdose.²⁶

Interestingly, compounds no longer considered as antidotes continue to be stocked. Fuller's earth, a diatomaceous earth once administered for the gastrointestinal decontamination of paraquat, has been superseded by activated charcoal;²⁷ and edetate disodium, previously indicated for hypercalcaemia and digitalis toxicity, has been replaced by safer alternatives.²⁸ Their continued stocking is likely supported by inclusion of these compounds in Section H of the PHARMAC Pharmaceutical Schedule.

Of those antidotes held, few were found in sufficient quantity to fully treat a single patient for 24 hours.¹⁸ The two exceptions were N-acetylcysteine and octreotide. N-acetylcysteine, indicated following paracetamol overdose, is commonly administered due to the frequency of this presentation,²⁹ likely accounting for high stock levels. Octreotide, used in the management of less commonly encountered sulfonylurea overdoses,³⁰ is primarily indicated for the treatment of neuroendocrine tumours, which may account for its holdings.

That the other antidotes were poorly stocked is cause for consideration.

It is reasonable for smaller hospitals to hold lesser quantities of antidote, as they may transport severely poisoned patients to higher-level facilities to receive both advanced care and, presumably, increased access to pharmaceuticals.

However, the smaller hospitals, to provide a reasonable standard of care, still need appropriate drugs available to initiate treatment and maintain the patient during their hospital transfer. Indeed, in some cases (e.g. cyanide exposure) the rapidity of the poisoning and lack of effective supportive care is such that immediate treatment with an appropriate antidote(s) may be lifesaving.

Even if a patient is safely transferred, hospitals at all levels, including level 6 facilities, rarely stocked adequate levels of reserve antidote in their pharmacies for the complete treatment of one patient. Should there be presentation of multiple poisoning victims, say from an industrial accident, then antidote stocks could be insufficient.

Given this situation, the rapid location of pharmaceuticals for resupply is important. Usefully, half the responders felt that their ability to locate drugs, whilst not easy, was satisfactory. However, these hospitals tended to be level 6 facilities located close to other large hospitals or pharmaceutical distributors. Only 36% of level 4 facilities responded similarly. Furthermore, only four (17%) hospitals declared possession of written protocols they considered adequate for rapidly obtaining significant quantities of antidotes, antivenoms and antitoxins.

Once emergency resupply is sourced, drugs still require transfer to the requesting pharmacy. A wide range of transportation means was identified, with courier the most common. That both fixed-wing aircraft and helicopters featured heavily, particularly for level 4 hospitals, is indicative of the urgency, distance and cost of resupply.

Improving the efficiency of the location, level and resupply of antidotes, antivenoms and antitoxins could be addressed. However, this is not straight forward; many countries have recognised similar difficulties without successfully introducing effective measures to rectify their situation.

Neither publication of research findings nor medical toxicology teaching has been shown to positively impact stocking levels.^{31,32} Similarly the development and promulgation of guidelines describing appropriate antidotes, antivenoms and antitoxins, and what quantity to hold, have proven ineffective. Researchers have noted that while improvements were recognised, fully satisfactory stocking of antidotes did not result.^{11,19,20,33}

A tempting answer is simply to increase stockholdings of these types of pharmaceuticals in all hospitals. However, unless carefully considered, this approach could be unreasonably costly for these expensive and uncommonly used drugs. Even at current (inadequate) levels, the estimated national annual cost to pharmacies from expiry of antidotes, antivenoms and antitoxins was \$171,024, with smaller hospitals again disadvantaged, paying almost twice that of level 6 facilities. Without a nationally rationalised approach this cost could be considerable.

One solution that holds promise is the institution of a national antidote database. While one did exist in New Zealand—the New Zealand Online Antidote Database (NZOAD)—it is now defunct. Such an initiative, the Banca Dati Nazionale degli Antidot (BaNdA) established in Italy, is an Internet-accessible (www.cavpavia.it) password-protected database established in 2005 to allow optimal management of national hospital antidote holdings.³⁴ A retrospective review of the utility of this resource over the period 1 January 2007 to 15 November 2012 concluded that the database successfully allowed the “optimization of all the national hospital stockpiles of antidotes.”³⁵ Unfortunately, the evidence presented in this publication did not allow an adequate assessment of this approach. However, this remains the only intervention for which there is a claim of significant improvement in cost-effective antidote stocking and supply.

When questioned about the utility of a national antidote database, all pharmacists agreed this approach would be useful, 79% thinking it very useful. If populated with appropriate data (e.g. type of drug held, quantity and expiry) such a database has potential to allow rationalisation of antidote, antivenom and antitoxin distribution and procurement. Following clinical need, a pharmacist could rapidly identify the location of available pharmaceuticals and arrange urgent resupply. Careful consideration of the levels and locations of these stocks would further allow the co-ordinated distribution and replacement of drugs, with benefits both for patient management and the national pharmaceutical budget.

Such a database would support more centralised holdings of uncommonly utilised antidotes, antivenoms and antitoxins. This centralisation is already occurring to some extent with the Auckland Hospital pharmacy the main holder of drugs not stocked elsewhere (e.g. polyvalent snake antivenom and botulism antitoxin). While this approach cannot be used for all antidotes, if applied appropriately in conjunction with a national database, it may help rationalise the national holdings of these types of drugs.

There were limitations to this study. The survey relied on self-reported data without independent confirmation of the accuracy of the responses. Furthermore it represents a snapshot of hospital pharmacy antidote, antivenom and antitoxin stock holding when such levels likely fluctuate over time. However this approach seems reasonable, and has been applied in a number of similar studies.

Not all stock held by a particular hospital was assessed, only drugs located in the pharmacy. While quantities of certain drugs are likely held on wards, it was considered that these would not generally be made available for redistribution to other facilities, quantification of pharmaceuticals that could be mobilised in time of need was a major interest of this study. The holdings of drug distributors and any national stockpiles established by Government were similarly not assessed.

When assessing the adequacy of stocks, a published North American expert consensus guideline was applied which quantified the total dose of antidote required to manage a single patient for either eight or 24 hours.¹⁸ However, these recommendations may not universally be accepted as appropriate.

While there was a pleasing 100% return of surveys, not all questions were answered by all respondents. The level of completions was, however, adequate to provide a good understanding of the study questions.

Conclusion

This national survey of the types and quantities of antidotes, antivenoms and antitoxins held by hospital pharmacies identified a range of apparent shortcomings. This finding is consistent with those of international studies. Smaller, generally more isolated facilities bore the greatest cost burden and faced greater difficulties with timely resupply of these pharmaceuticals. And while certain effective antidotes were not stocked, some archaic or potentially dangerous compounds were.

Potential remedies include consideration of the introduction of safer and more effective antidotes, and the rationalisation of distribution and supply of these pharmaceuticals. This may include centralised location of certain drugs and the development and implementation of a national antidote database.

Competing interests: Nil.

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ORIGINAL ARTICLE

Removal of Special Authority requirements for clopidogrel improved optimal care following percutaneous coronary intervention across sociodemographic groups

Suneela Mehta, Sue Wells, Rod Jackson, Jeff Harrison, Andrew Kerr

Abstract

Aim To examine if optimal clopidogrel therapy following percutaneous coronary intervention (PCI) differed systematically by sociodemographic characteristics during and after special authority (SA) restrictions, which required hospital-specialist approval for full funding.

Method National health databases were anonymously linked for New Zealanders discharged following publicly-funded PCI between 1/07/2009–31/12/2009 when SA criteria applied and from 1/09/2010–28/02/2011 after funding restrictions ceased. The proportion of days that patients were dispensed clopidogrel in the two 6-month periods post-discharge was calculated (medicine possession ratio; MPR). Optimal clopidogrel-dispensing (defined as a MPR \geq 0.8) was analysed by sociodemographic characteristics.

Results During the first discharge period, 74% (95% CI 72–75%) of patients (n=2416) had optimal dispensing compared with 81% (95% CI 79–82%) of discharges from 1/09/2010–28/02/2011 (n=2347). In both discharge periods, 2–3% of patients received no therapy. Minimal relative differences in optimal dispensing were noted by age, sex, or deprivation status in either discharge period. However, optimal clopidogrel-dispensing was 13–14% less likely among Māori and Pacific peoples relative to ‘Other’ patients during funding restrictions. Relative ethnic differences changed little once funding restrictions ended despite absolute increases in dispensing.

Conclusions Optimal clopidogrel coverage following PCI improved by 7% across sociodemographic groups after funding restrictions ceased, but ethnic disparities were unaltered.

Clopidogrel is an antiplatelet agent that, when combined with aspirin, has greater efficacy in reducing the risk of coronary thrombosis following percutaneous coronary intervention (PCI) than aspirin alone.^{1,2} Delays in clopidogrel therapy post-PCI are associated with worse clinical outcomes.^{1–4} The use of clopidogrel in the 6 months following PCI was standard practice in New Zealand from 2006 until a newer agent, ticagrelor, became available in mid-2012.

Clopidogrel required special authority (SA) approval from the Pharmaceutical Management Agency of New Zealand (PHARMAC) for fully-funded therapy until 1 September 2010, when this restriction was lifted. These criteria specified that patients who had undergone a stent insertion in the preceding four weeks were eligible for 6 months of funded clopidogrel therapy. (See Appendix 1 for the complete SA criteria for clopidogrel. See all Appendices at <http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2015/vol-128-no-1411/6478/appendices.pdf>.)

SA applications were completed by hospital clinicians at or prior to hospital discharge. However, the application and prescribing process used to access fully-funded clopidogrel was inconsistent across the country. The application could either be made electronically or on a hard copy form which was faxed or mailed to the Ministry of Health. If the application was completed electronically, the SA number was potentially available before discharge.

These patients were issued with a fully-funded 3-month prescription for clopidogrel prior to leaving hospital, and a General Practitioner (GP) would need to prescribe the last 3 months of therapy using this same SA number. For other patients where the SA application number was not accessible at discharge, a free 1 to 2-week supply of clopidogrel was often issued. These patients were either given

a clopidogrel prescription to fill once the special authority number was available or may have been advised to see their GP to have it prescribed.

Demographic groups whose health is most vulnerable and who are in greatest need of adequate healthcare are often least likely to receive it.⁵ The existence of barriers to equitable healthcare access, such as financial factors, health literacy and institutionalised racism are well documented.⁶ The multiple and variable steps required for each patient to receive a fully-funded clopidogrel prescription with the appropriate approval number are another potential impediment to optimal maintenance post-PCI. Our aim was to explore whether the SA requirements implemented in New Zealand represented a barrier that resulted in differential access to clopidogrel by sociodemographic status.

Methods

Study population—All New Zealanders with publicly-funded admissions for PCI who were discharged between 1 July 2009 and 31 December 2009 (while SA criteria for clopidogrel were applicable) and from 1 September 2010 to 28 February 2011 (after removal of SA requirements) were included.

The 1 July 2009 to December 2009 time period was chosen to allow at least 6 months of follow-up prior to the 1 September 2010 removal of the funding restriction. In the instance that an individual had multiple admissions during the periods of interest, the first admission was used. The following hospital discharge procedural codes were used to identify patients discharged from hospital following PCI:

- ICD10-AM version 3: 3530400, 3530500, 3531000, 3531001, 3531002.
- ICD10-AM version 6: 3830000, 3830300, 3830600, 3830601, 3830602.

All patients who died as inpatients were excluded.

Data sources—Over 98% of New Zealand residents have a National Health Index (NHI) number that uniquely identifies them within the New Zealand health system.⁷ Encrypted NHI numbers were used to anonymously link hospitalisation, mortality, pharmaceutical claims and NHI databases. The pharmaceutical claims database (PHARMS) is administered by the New Zealand Ministry of Health, and collects data on government-subsidised medications dispensed by community pharmacies nationwide.⁸ From 2009 onwards, more than 96% of PHARMS data were reliably identifiable by NHI numbers. The NHI database contains patient demographic information and, together with the mortality and hospitalisation datasets, is also administered by the New Zealand Ministry of Health.

Main outcome of interest—Clopidogrel use in the 6 months following hospital discharge for PCI was assessed by calculating a medicine possession ratio (MPR) for each patient. The MPR was derived from the number of days that the patient was dispensed clopidogrel post-discharge divided by the number of days from the start until the end of the follow-up period or until date of death, whichever came first. Days spent in hospital were not included as medications dispensed for inpatients do not require special authority approval.

For patients dispensed clopidogrel in the 90 days prior to hospitalisation, the number of supply days remaining at the time of admission was added to the numerator of the MPR. Optimal clopidogrel dispensing was defined as a MPR ≥ 0.8 (i.e. the patient had clopidogrel in their possession for at least 80% of the 6-month period following discharge).⁹

Other variables—Age, sex and ethnicity data were obtained from the NHI database. Age was stratified according to 10-year intervals. Ethnic groups were defined according to the New Zealand Ministry of Health's Ethnicity Data Protocols for the Health and Disability Sector.¹⁰ Ethnic groups of interest were: Māori (Level 2 code 21), Pacific (Level 2 codes 30–37), Indian (Level 2 code 43), and Other (Level 2 codes 10–12, 40–42, 44 and 51–99). The 'Other' group are mainly European New Zealanders. Quintiles of deprivation, according to the New Zealand Index of Deprivation 2006 (NZDep06) scores, were used to approximate socioeconomic status. NZDep06 is a census-based index of deprivation for small areas that uses population census data relating to eight dimensions of deprivation.¹¹

Statistical analysis—For the periods during and after SA restrictions, binomial regression modelling was used to estimate relative risks (RR), with 95% confidence intervals (CI), of having a MPR ≥ 0.8 following PCI for each of the sociodemographic characteristics considered. Two-sample t-tests using a 95% level of significance were used to evaluate whether the proportions of patients dispensed clopidogrel and after funding restrictions changed significantly. Data was analysed using STATA 10.0 statistical software.

Ethical approval—The study process was approved by the Multi-region Ethics Committee in 2010 (MEC/10/090/EXP).

Results

Between 1 July 2009 and 31 December 2009, 2451 people were discharged from hospital following publicly-funded PCIs. From 1 September 2010 to 28 February 2011, 2388 discharges were recorded. For the two periods, 35 and 41 people were excluded respectively because death had occurred in hospital or within one day of discharge.

The baseline characteristics for the remaining patients discharged following PCI during the last 6 months of 2009 ($n=2416$) and in the 6 months immediately following removal of SA restrictions ($n=2347$) are detailed in Table 1.

As expected, the characteristics of patients discharged during the two periods were similar. In each discharge group, around three-quarters of patients were aged between 45 and 75 years, men comprised more than 70% of the study population and Māori, Pacific and Indian groups accounted for around 15% of discharges. Patients within each 6-month period were relatively evenly spread across quintiles of deprivation.

Table 1. Baseline characteristics of New Zealanders with publicly-funded admissions for percutaneous coronary intervention who were discharged between 1 July 2009–31 December 2009 and 1 September 2010–28 February 2011

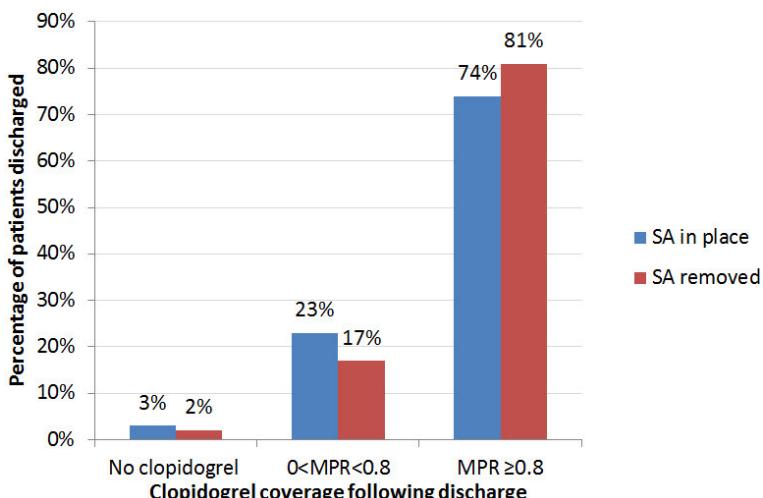
Baseline characteristic		Number (%) discharged between 01/07/09–31/12/09	Number (%) discharged between 01/09–28/02/11
Age (years)	<45	144 (6%)	139 (6%)
	45–54	465 (19%)	407 (17%)
	55–64	655 (27%)	658 (28%)
	65–74	710 (29%)	691 (29%)
	≥75	442 (18%)	452 (19%)
Sex	Male	1793 (74%)	1698 (72%)
	Female	623 (26%)	649 (28%)
Deprivation Quintile (assessed using NZDep06)*	Quintile 1: NZDep 1–2	421 (17%)	394 (17%)
	Quintile 2: NZDep 3–4	449 (19%)	415 (18%)
	Quintile 3: NZDep 5–6	492 (20%)	500 (21%)
	Quintile 4: NZDep 7–8	580 (24%)	568 (24%)
	Quintile 5: NZDep 9–10	474 (20%)	464 (20%)
Ethnicity	Māori	163 (7%)	179 (8%)
	Pacific	84 (4%)	93 (4%)
	Indian	77 (3%)	73 (3%)
	Others:	2092 (87%)	2002 (85%)
Total number discharged following PCI		2416	2347

*quintile data was missing for 6 people for the period 01/09/10–28/02/11.

Figure 1 shows the proportions of patients discharged during and after SA restrictions who had an optimal MPR (i.e. $MPR \geq 0.8$), a suboptimal MPR (i.e. $0 < MPR < 0.8$) or who received no clopidogrel following discharge. The change in proportions between the two discharge periods was significant ($p < 0.05$) for patients in each of the three categories of dispensing considered. Overall, 74% (95% CI 72%–75%) of patients had a $MPR \geq 0.8$ while clopidogrel SA criteria were in place compared with

81% (95% CI 79%–82%) of hospital discharges once funding restrictions were lifted. In both discharge periods, 2–3% of patients received no clopidogrel following discharge.

Figure 1. Clopidogrel coverage among patients discharged while Special Authority criteria were in place (1/07/2009–31/12/2009) and after Special Authority criteria were lifted (1/09/2010–28/02/2011)



SA: Special authority.

Table 2 shows the breakdown of patients who received no clopidogrel in the first and second 3-month periods after discharge. Patients required successful completion of the SA process in order to receive clopidogrel in the first 3-month period. Irrespective of funding restrictions, the proportion of patients who received no clopidogrel was similar in the first 3 months and the entire 6-month period but increased during the second 3 months after discharge.

Table 2. Patients with no clopidogrel dispensed during 3-month periods of follow-up while Special Authority criteria were in place (1/07/2009–31/12/2009) and after Special Authority criteria were lifted (1/09/2010–28/02/2011)

Period following discharge	Number (%) of patients in each discharge period	
	01/07/09–31/12/09	01/09/10–28/02/11
0–3 months	82 (3.4%)	59 (2.5%)
4–6 months	194 (8.0%)*	149 (6.4%)*
0–6 months	72 (3.0%)*	51 (2.1%)*

*Change in proportions between the two discharge periods was significant ($p<0.05$).

Table 3 presents the numbers and proportions of people with MPRs ≥ 0.8 , and adjusted RRs with 95% CI according to age, sex, deprivation and ethnic group. Crude RRs are not presented as they were not appreciably different to the adjusted RRs.

The proportion of patients with optimal clopidogrel dispensing improved across all sociodemographic strata once SA requirements were lifted. These increases were statistically significant ($p<0.05$) for all groups except those aged 55–64 years, patients over 75 years of age and for Pacific patients.

Across the sociodemographic characteristics examined, Māori and Pacific patients had the lowest proportion with a MPR ≥ 0.8 irrespective of whether SA criteria were in effect. However, optimal therapy increased by 12% for Māori patients and 8% for Pacific patients after funding restrictions ended, with increases also noted for the Indian group (16%) and Other patients (6%).

The relative comparison between age groups and by sex showed no clinically relevant differences in the likelihood of optimal clopidogrel dispensing during either discharge period.

Minimal differences in dispensing by deprivation status were noted while funding restrictions were in place. Compared with quintile 1, optimal clopidogrel dispensing was 8% less likely among patients in quintile 3 (RR 0.92, 95%CI 0.86–0.99) and 10% less likely among quintile 4 patients (RR 0.90, 95%CI 0.84–0.97). No significant dispensing differences were found after SA criteria were lifted.

Compared with the ‘Other’ group, Māori patients had a 14% lower likelihood of optimal clopidogrel dispensing (RR 0.86, 95% CI 0.76–0.97) and Pacific peoples were 13% less likely (RR 0.87, 95%CI 0.73–1.02) while funding restrictions were in place. These findings did not change appreciably following removal of SA requirements.

Table 3. Likelihood of a clopidogrel medicine dispensing ratio ≥ 0.8 according to sociodemographic characteristics

Sociodemographic characteristics	Discharge period			
	01/07/09–31/12/09		01/09/10–28/02/11	
	Number (%) with MPR ≥ 0.8	Adjusted RR (95% CI) [†]	Number (%) with MPR ≥ 0.8	Adjusted RR (95% CI) [†]
Age^a	<45	96 (67%)*	0.91 (0.80–1.02)	117 (84%)*
	45–54	318 (68%)*	0.93 (0.87–1.01)	314 (77%)*
	55–64	491 (75%)	1.01 (0.95–1.07)	520 (79%)
	65–74	536 (75%)*	1	578 (84%)*
	≥ 75	342 (77%)	1.02 (0.96–1.09)	361 (80%)
Sex^b	Male	1,309 (73%)*	1	1,353 (80%)*
	Female	474 (76%)*	1.04 (0.99–1.10)	537 (83%)*
Deprivation^c	1	331 (79%)*	1	327 (83%)*
	2	346 (77%)*	0.99 (0.92–1.06)	344 (83%)*
	3	356 (72%)*	0.92 (0.86–0.99)	399 (80%)*
	4	405 (70%)*	0.90 (0.84–0.97)	442 (78%)*
	5	345 (73%)*	0.97 (0.90–1.05)	373 (80%)*
Ethnicity^d	Māori	103 (63%)*	0.86 (0.76–0.97)	134 (75%)*
	Pacific	53 (63%)	0.87 (0.73–1.02)	66 (71%)
	Indian	57 (74%)*	0.99 (0.87–1.15)	66 (90%)*
	Other	1570 (75%)*	1	1624 (81%)*

[†] Crude relative risks were not presented as they were not appreciably different to the adjusted relative risks.

*Change in proportions between the two discharge periods was significant ($p<0.05$).

^a Relative risks by age were adjusted for sex, ethnicity and deprivation.

^b Relative risks by sex were adjusted for age, ethnicity and deprivation.

^c Relative risks by deprivation were adjusted for age, sex and ethnicity.

^d Relative risks by ethnicity were adjusted for age, sex and deprivation.

Discussion

Among patients who had undergone publicly-funded PCI across New Zealand, optimal clopidogrel coverage in the 6 months following hospital discharge increased from 74% to 81% once SA criteria were lifted, with improvement noted across all sociodemographic strata.

Only 2-3% of patients in both discharge periods received no clopidogrel therapy during follow-up. However, Māori and Pacific peoples were the most undertreated post-PCI. Removal of SA requirements did not change relative ethnic differences to any extent, despite absolute increases in optimal dispensing for all ethnic groups. Smaller relative differences in clopidogrel dispensing were noted by age, sex and deprivation status, irrespective of whether SA criteria were in place.

Our study included all publicly-funded acute and elective hospital admissions for PCI recorded across New Zealand during the last half of 2009 and between September 2010 and February 2011. The proportion of all PCIs that are performed in the private health sector is currently unknown, but is likely to be in the order of 10-20% for both the discharge periods considered in this study.

All data were obtained through routinely collected and relatively comprehensive national health databases, which aids the generalisability of the findings. Data regarding dispensed medications were abstracted from a nationwide database recording medications dispensed by community pharmacists. This minimised the potential for misclassification error based on patient self-report or incomplete health provider records.

Our analyses are based on observational data, and a systematic change in clinical practice over time could have contributed to the improvement in dispensing after SA criteria were lifted. This is unlikely, however, since there was no change to national or international guidelines regarding clopidogrel use post-PCI over the study period, or introduction of quality or performance incentives associated with guideline adherence. Furthermore, the increase in dispensing after SA removal could not be accounted for by changes in clopidogrel dispensing patterns over time. (See Appendix 2 for the monthly proportions of the study population who received no clopidogrel and optimal therapy between July and December 2009 and between September 2010 and February 2011).

We could not identify whether patients actually took medications that were dispensed to them, though this is a minor limitation since our focus was to determine if SA criteria differentially restricted *access* to medications by sociodemographic status. We also did not consider re-admission during follow-up, or exclude the very small number of non-New Zealand residents who received publicly-funded PCIs and who may have left the country post-procedure. The latter may comprise part of the patient group who were not dispensed any clopidogrel following discharge.

Few other studies have been published regarding the effect of funding restrictions on the sociodemography of patients accessing medications. Ostini et al explored clopidogrel use in Australia using anonymised routinely collected data for Queensland and New South Wales. Clopidogrel use following stenting was associated with being older and male sex, in contrast with our findings of minimal differences in clopidogrel coverage post-PCI by age and sex.¹² However, stenting was not a government-subsidised indication for clopidogrel prescription in Australia at the time of publication so financial barriers would have been greater than in our study and utilisation by ethnicity or socioeconomic status were not examined.

We noted an absolute improvement in optimal dispensing by 7% across all sociodemographic groups once SA criteria were removed, which is supported by evidence that restricted funding policies for clopidogrel have detrimental effects on therapy following discharge.

A Canadian study of 13663 patients who underwent stenting between January 2000 and September 2004 found that restricted access to clopidogrel resulted in a lack of filling at least one prescription following hospitalisation or delays in this process in around 20% of patients.¹³ However, this proportion is not directly comparable to our results as we used optimal coverage post-discharge rather than a binary measure of prescription-filling, and we did not examine therapeutic delays directly.

Another Canadian study also noted negative effects on clopidogrel prescription-filling among 112 patients post-stenting in Alberta as a result of a prior authorisation process.¹⁴ The association between restrictive reimbursement policies and lower rates of medication utilisation has also been noted for a range of other medications¹⁵⁻¹⁹, although dispensing by demographic characteristics was not examined.

While funding restrictions applied, only 3% of patients received no clopidogrel therapy in the 3 months after discharge (Table 2) indicating that the SA process was successfully completed for almost all patients in our study population within this time-frame. Nevertheless, administrative errors or delays, and general confusion about the process among patients and health professionals are likely to have contributed to the reduced clopidogrel coverage associated with the prior approval policy. However, the use of clopidogrel as part of a routine clinical pathway following PCI was probably a protective factor, without which the SA process may have even further restricted access.

Our analyses showed sub-optimal clopidogrel coverage for Māori and Pacific patients post-PCI relative to other ethnic groups which remained after funding restrictions were lifted. Inadequate maintenance of other CVD medications has also been observed across New Zealand among Māori and Pacific peoples. Among a national cohort of 11 348 patients aged 35 to 84 years of age who were discharged from hospital with Acute Coronary Syndrome in 2007, Māori and Pacific patients were 13–25% less likely to have a statin MPR \geq 0.8 as compared with the European/Other group.²⁰ A number of factors could be relevant in the undertreatment of Māori and Pacific patients including language or other cultural barriers, and variation in prescribing practices by ethnicity which may result in differential utilisation of medications.^{6, 21-23}

It would be useful to explore the factors influencing clopidogrel use following PCI among different ethnic groups, and particularly whether sub-optimal coverage is related to health professional behaviour, other factors such as hospital readmission or patient-related barriers to filling clopidogrel prescriptions. The influence of SA requirements on clinical outcomes is also relevant, given evidence suggesting that restrictive pharmaceutical access policies for clopidogrel following coronary stenting can be associated with increased rates of hospitalisation and death.^{13, 24} In future, we also intend to compare clopidogrel and aspirin use post-PCI.

We examined dispensing separately for the 3 months immediately following hospitalisation and the four-to-six month period post-discharge (see Tables b-e in Appendix 3). Within each 3 month period, the absolute and relative differences across sociodemographic strata were similar to the 6-month data presented in Table 3.

Irrespective of funding restrictions, however, the proportion of patients with a MPR \geq 0.8 decreased by about 5% from the first 3 months to the 4-to 6 months after discharge across all sociodemographic groups. One factor that may account for the slight reduction in optimal coverage during the second 3-month period post-hospitalisation is the mix of stent types inserted during PCI, although we were unable to determine which stents were used among our study population. Two different types of stent are available: drug eluting stents for which 6 months of clopidogrel therapy was typically indicated, and bare metal stents (used if there is increased risk of bleeding) where 3 months of clopidogrel coverage was more common.

We were concerned that the short supply of clopidogrel issued to some patients whose SA application had not yet been approved at the time of hospital discharge may have contributed to sub-optimal MPRs for these patients, since dispensing directly from hospitals to patients is not captured by the national dispensing database. We could not examine time to first dispensing episode, as our study population was not large enough to allow meaningful stratification by DHB. However, the slightly higher proportion of patients with optimal dispensing in the 3 months immediately post-discharge implies that this short period of unrecorded medication supply is unlikely to have been a significant issue.

The 3-month dispensing data also indicate that health sector publicity accompanying removal of SA criteria on 1 September 2010 is unlikely to have affected clopidogrel dispensing rates. Hospital

doctors (who likely provided the majority of prescriptions for 3 months of clopidogrel immediately following hospital discharge) would have already been aware of the need for clopidogrel therapy post-PCI. Publicity could, however, have affected prescribing by GPs during the second 3 months after discharge, but the similar (5%) reduction in optimal dispensing between the first and second 3-month periods post-PCI that was observed both during and after funding restrictions implies that health sector notification had little influence on dispensing rates.

Funding restrictions are a necessary cost-containment strategy intended to appropriately manage limited national health resources, and maximise pharmaceutical access for patients that most need it. However, the SA criteria for clopidogrel following PCI restricted access to optimal therapy across all sociodemographic groups of eligible patients. The access barrier resulting from funding restrictions could be minimised in two ways. Firstly, standardisation of the application process is necessary so that authority numbers are routinely available for prescriptions and discharge paperwork prior to hospital discharge. In order to achieve this, PHARMAC needs to engage the Ministry of Health, which provides information technology services to the health sector, regarding provision of a more reliable and user-friendly electronic process.

Development by individual hospital services of a local protocol for SA application that is initiated at a uniform point in the care pathway is also important. For clopidogrel and other anti-platelet therapies, the logical place to commence the application process is the cardiac catheter laboratory. Secondly, PHARMAC should consider more extensive monitoring of medication access than is currently undertaken for those pharmaceuticals where restrictive criteria have been applied. Though logistically labour-intensive, greater monitoring would enable timely identification of possible access issues associated with the SA process so that appropriate remedial action can be initiated.

In conclusion, SA requirements for clopidogrel appeared to have been an access barrier to optimal therapy across all demographic groups of patients who had undergone PCI. However, almost all patients received some clopidogrel therapy in both discharge periods. Removing the requirements did not appear to reduce the small relative disparity in anti-platelet coverage following PCI among Māori and Pacific patients, and the factors contributing to undertreatment in these two ethnic groups require further exploration.

Competing interests: None

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ORIGINAL ARTICLE

Paediatric EEG provision in New Zealand: a survey of practice

Ngaire Keenan, Lynette G Sadlier

Abstract

Aim Epilepsy is a common neurological disorder in children. Electroencephalography (EEG) is integral to the diagnosis of an electroclinical epilepsy syndrome. Here we aim to describe provision of paediatric EEGs in New Zealand.

Method All neurophysiology departments in New Zealand performing paediatric EEGs were invited to participate. Personal interviews were conducted to ascertain the number and type of EEGs performed in children and the paediatric protocols used in each department.

Results 12 of the 13 eligible neurophysiology departments participated. These departments performed between 2–950 paediatric EEGs each year. Waiting times were variable: urgent (8 hours–14 days); semi urgent (1 day–8 weeks); routine (1 week–4 months); with two centres unable to perform urgent or semi urgent EEGs. Seven departments routinely sleep deprived children. The percentage of all outpatient paediatric EEGs that were sleep deprived ranged from 1–100%. Children's EEGs were reported by either paediatric (five departments) or adult neurologists (seven departments).

Conclusions There is marked variability between neurophysiology departments in the provision of EEGs for New Zealand children. As EEGs are important for epilepsy diagnosis, increased resources are required to ensure New Zealand children have equitable access to timely quality paediatric EEGs.

Epilepsy is a group of disorders classified into electro-clinical syndromes defined by age of onset, type of seizures, electroencephalographic (EEG) features and comorbidities.¹ It is the most common serious neurological disorder of children affecting ~7300 New Zealand children under 14 years of age.² Although individuals may live normal lives, 30% have seizures resistant to current therapy with major social, psychological, physical and cognitive sequelae.^{3,4}

Mortality in children with severe epilepsy is 25% by 20 years of age.⁴ Epilepsy syndrome diagnosis is essential as it directs investigations for aetiology, guides therapy and allows accurate prognostic information to be given.^{2,3,5–8} Misdiagnosis leads to inappropriate unnecessary investigations and poor outcomes with significant impact on individuals, families and the New Zealand health system.³

An electroencephalography (EEG) is an integral part of the diagnosis of an epilepsy syndrome and is also often important for monitoring the effectiveness of ongoing therapy.^{2,3,5–8} The ideal Paediatric EEG (PEEG) would show epileptiform discharges in all children with epilepsy. Unfortunately this is not the case as only 29–50% of children with seizures have epileptiform discharges in their first routine EEG.^{6,8} To increase this diagnostic yield, guidelines recommend activating procedures such as hyperventilation, photic stimulation, sleep deprivation and sleep be performed.^{5–12}

Although guidelines for recording EEGs have been developed, gaps are evident and departmental protocols vary significantly.¹³ Departmental audits are an effective way of assessing common practice⁶ and provide a basis for future research questions and recommendations. In this audit, we surveyed the delivery of paediatric EEGs (PEEGs) in New Zealand.

Methods

All neurophysiology departments in New Zealand were contacted and invited to participate if they performed any paediatric EEGs (PEEGs) in 2009. PEEGs were defined as EEGs performed on children 16 years and under. Due to reported poor response rates from postal questionnaires,¹³ interviews in person or via teleconference were conducted between December 2009 and February 2010 with senior clinical physiologists from each participating department. Following the pilot of an initial questionnaire with one department, a revised questionnaire was emailed to all departments for their perusal prior to the interview. Departments that were unable to undertake a personal interview were posted the questionnaire and contacted if further information was required.

The questionnaire collected information on: protocols for PEEGS (standard PEEGs, sleep-deprived PEEGs, early PEEGs defined as performed within 48 hours of a seizure, and sedated PEEGs); number of PEEGs; referral patterns; waiting times; protocols for intermittent photic stimulation (IPS), hyperventilation (HV) and response testing; number, training and experience of clinical physiologists; and who reported the PEEGs. Attempts were made to gather actual numbers of EEGs performed in 2009. In departments where these statistics were not available estimates from the senior physiologists were used.

Results

Twelve of the 13 neurophysiology departments in New Zealand who performed PEEGs elected to participate (92%, 11 public departments/ 1 private department). One small private neurophysiology department declined participation.

EEG departments—Both adult and paediatric EEGs were performed in all departments. The number of EEGs performed by each department varied from ~50 – ~1900 per year. The number of PEEGs varied from 2 – ~950. Four of the 12 departments performed >300 PEEGS per year with five departments performing <100 PEEGs per year.

Nine departments had child-friendly rooms with three having a dedicated PEEG room or a room which was predominantly used for PEEGs. PEEG referrals were accepted from paediatricians, neurologists (adult and paediatric), psychiatrists, and junior medical staff in all departments. Six departments accept referrals from general practitioners with two departments screening these referrals by the reporting neurologist prior to them being accepted. Information sheets explaining EEGs were sent to families by all departments.

Departments were asked how they prioritised PEEG referrals, specifically what their definition and indications were for urgent, semi-urgent and routine. Two hospital departments did not do urgent or semi-urgent PEEGs as the technician was not based in the area. One department did not prioritise EEGs. Indications and desired and actual waiting times for urgent, semi urgent and routine EEGs are seen in Table 1.

Table 1. Indications and timing of Paediatric EEGs

Variable	Urgent	Semi urgent	Routine
Number of departments	10	10	12
Indications	Status, repeated frequent seizures, encephalopathy, brain death, and sub-clinical seizures	Recurrent seizures prior to initiation of AEDs, radical change in seizure frequency, epileptic encephalopathy	Single afebrile seizures, on AEDs, if likelihood of the epilepsy is not high
Desired wait time	8 hrs–7 d	<24 hrs to 3 w	<3 w–3 m
Actual wait time	8 hrs–14 d (<48 hrs in 8 dept)	1 d–8 w	1 w–to 4 m (<4 w in 5 dept)
Reporting time	<24 hrs in 7 dept (24–48 hrs in 2 dept)	<24 h–2 w (<1 w in 8 dept)	1 d–3 w (<2 w in 10 dept)

Hrs=hours, w=weeks, m=months, dept=department, AED=antiepileptic drug

PEEG protocol—Prior to recording PEEGs, equipment was calibrated either before (three departments) or before and after (nine departments) the recording. An impedance of <5 kΩ (10 departments) or <10 kΩ (two departments) was desired. Measuring the 10–20 system for electrode placement in older children was standard in each department. One department used an electrode cap in children under 4 years.

The recording time for routine PEEGs was usually between 20 to 30 minutes (10 departments). Two departments recorded routine PEEGs for greater than 30 minutes (up to 40 min or up to 45 minutes). Nine departments routinely recorded PEEGs with video monitoring. Eleven departments had the technology to copy EEGs onto disk which could be read off site. Four departments had remote access to EEGs. After hours and weekend services were available in three departments.

Intermittent photic stimulation (IPS) and hyperventilation (HV) were attempted in all capable children in each department. The photic frequency range of IPS varied. One department started at 0.5 Hz, eight from 1 Hz, two from 2 Hz and one from 3 Hz. One department used photic frequencies up to 20 Hz, 1 to 22 Hz, 8 to 30 Hz, 1 to 50 Hz and 1 to 60 Hz. The duration of each frequency was 6 seconds for one department, 10 seconds for 10 departments and 15 seconds for one department.

Three departments tested IPS for 20 seconds if a history of light sensitivity was present. IPS was commonly tested at the end of the recording (ten departments). The lamp was placed 30cm from the face in eight departments (range 15–40 cm). All departments tested IPS with eyes both open and closed. In the event of a photoparoxysmal response, the photic stimulus was stopped by all centres. Ten of the 12 departments then tested the sensitivity range and five tested IPS occluding one eye.

Hyperventilation (HV) was induced in young children by instructing the child to blow on a tissue or windmill in all hospital departments. HV was performed for 3 minutes in 9 of the 12 departments. The three remaining departments performed HV for 2–3 minutes, 3–4 minutes or 4 minutes. If an absence seizure was suspected but not precipitated, HV was lengthened (three departments), repeated (four departments) or both (five departments).

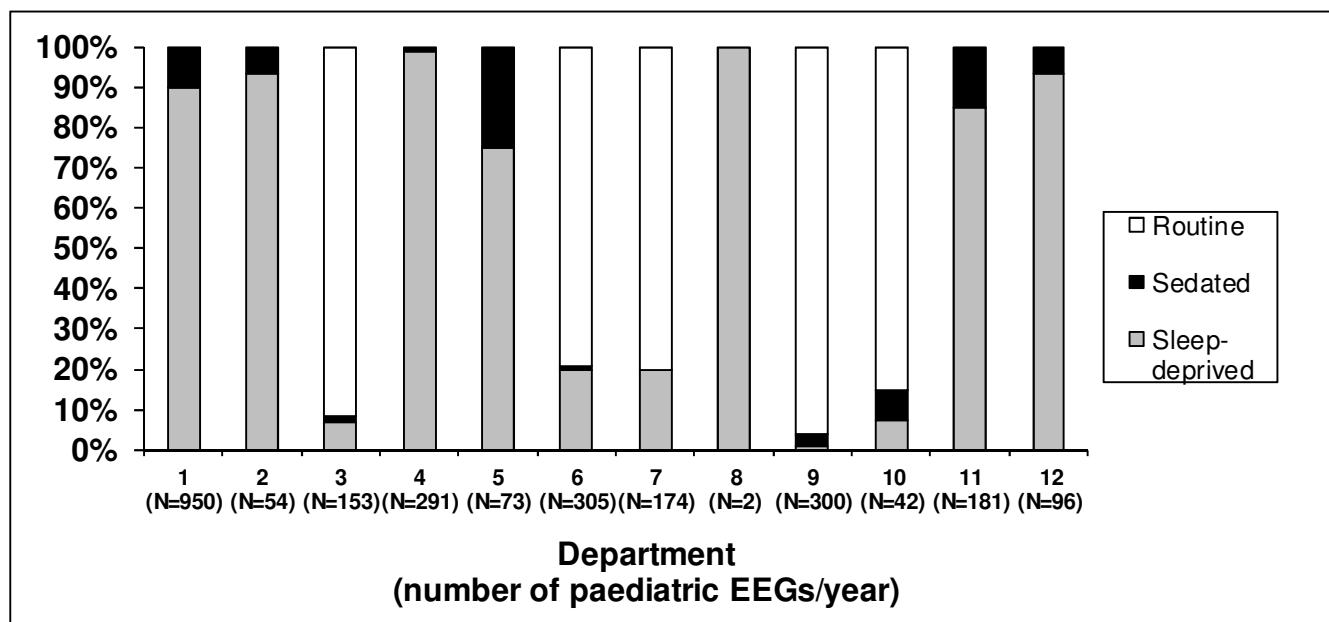
Response testing during an epileptic event was routinely performed in 11 of the 12 departments. Testing techniques included: repeating a word (4 departments); performing a task such as counting (10 departments); calling out questions or the child's name (8 departments); and applying a tactile stimulus (1 department). In 5 departments, testing was practiced interictally.

Sleep-deprived PEEG and sedated PEEGs were performed in all hospital departments. Figure 1 shows the proportion of these in each department (Figure 1). In seven departments, sleep-deprived PEEGs were routinely performed for all outpatients apart from those in whom a physician had specifically requested a sedated EEG.

Recommendations for the amount of sleep in young children (definition varied from <1 year to <5 years) for sleep-deprived PEEGs included staying up 1–2 hours later and woken 1–2 hours earlier than their regular routine (three departments), half their regular sleep (one department), 5–6 hours (one department), 2–3 hours less than their normal sleep (one department) or to remain awake for the morning of the test (five departments).

Older children were recommended to have 5–6 hours of sleep (six departments), to stay up 2 hours later and wake 2 hours earlier (four departments), half the child's normal sleep (one department) or 2–3 hours less than their normal sleep (one department). All departments encouraged sleep and if the child slept they were left to sleep for 10–20 minutes (11 departments).

Figure 1. Histogram showing the percentage of PEEG types in each department



Sedated PEEGs were conducted after a failed first attempt at a sleep-deprived PEEG in nine departments, in children who were expected by their parents or doctor to not cooperate in five departments or in one department routinely in children 1–3 years old.

Ten departments used chloral hydrate as their first-line sedation medication. One department had no sedation protocol and one did not do sedated EEGs. Prior to sedation, the child was firstly seen by a consultant then chloral hydrate was administered by a doctor (three departments), nurse (five departments) or technician (one department). One department was unsure who administered the medication. No departments had a protocol for recording early PEEGs.

Staff—The number of full-time equivalent clinical physiologists in each department varied from 0.1–4.8 with 23 clinical physiologists in total. Six departments had a single part-time clinical physiologist,

although this was the same clinical physiologist in three departments. The remaining departments had two (two departments), three (three departments) or six (one department) clinical physiologists.

Of the 23 clinical physiologists, 18 had formal neurophysiology qualifications and 3 had previously worked in a dedicated paediatric department overseas. PEEG reporting was predominantly performed by either paediatric neurologists (five departments) or adult neurologists (seven departments). Two departments posted PEEGs to a larger centre to be read by paediatric neurologists.

Discussion

There is international recognition based on class I and II evidence that an EEG helps determine seizure type, epilepsy syndrome, risk of recurrence and management in children with epilepsy.^{2,7-9,11} It is therefore international standard that all children with new onset seizures have an EEG.

Recording of both awake and sleep states as well as hyperventilation (HV) and intermittent photic stimulation (IPS) are recommended to increase diagnostic yield.⁵⁻¹² There is very little data available on aspects of epilepsy diagnosis or management in New Zealand.

A survey of New Zealand paediatricians in 2006 found that only 89% of paediatricians requested an EEG after a child presents with new onset seizures. The authors suggested that paediatricians with poor EEG services were less likely to order EEGs.¹⁴

Although it is well recognised that EEGs should be performed in children with epilepsy, there is variability in how PEEG services are provided. A 2006 survey of EEG departments in Great Britain performed with similar methodology to our study identified a range of practice and operational procedures that were felt to have implications on investigation and management of people with epilepsy. The UK study sent written questionnaires to all EEG departments in Great Britain and had responses from only 52 departments (42% response rate).¹³

Our audit is the first survey of PEEG provision in New Zealand. With a high response rate of 92% of all departments and 100% of all hospital-based departments, we are able to provide comprehensive data on how PEEGs are performed in New Zealand. Our New Zealand EEG audit found that HV and IPS protocols were similar between departments. The number and type of PEEG performed, the waiting times for PEEGs and the specialist reporting the PEEGS however varied considerably.

We found considerable variation between the type of EEG that was performed on children in New Zealand. Sleep-deprivation or an early EEG within 24 hours of a seizure are generally recommended to increase the yield of an EEG.^{6,8,9,11,12} No departments had specific early EEG protocols although PEEGs were likely to have been performed early in some centres due to their short waiting times.

The percentage of sleep-deprived EEGs in each department varied from 1–100%. Certain types of epileptic activity are provoked by drowsiness, sleep, or on awakening.^{7,8} It is therefore recommended that a period of relaxation, and if possible, sleep is captured in an EEG.^{7,9,15} This is supported by reports of increased yield in sleep-deprived EEGs compared to routine^{15,16} and sedated EEGs.¹⁵

Many departments in New Zealand do not routinely perform sleep-deprived EEGs instead opting for an initial routine EEG and a subsequent sleep-deprived EEG if that is not informative. This may be partly due to concern over the burden of sleep-deprivation for a family.^{16,17} Given children and families would prefer to be sleep-deprived than have venepuncture it seems that the burden/distress of sleep deprivation for the family is no greater than other routine hospital investigations¹⁸ and so may not be sufficient reason to defer sleep deprivation.

Waiting times differed by up to 4 months between departments in New Zealand. Only 8 of the 12 departments were able to perform and report PEEGS on new onset seizures within the internationally recommended 4 weeks.^{2,11} This finding is consistent with what was reported in the UK EEG audit

where over two-thirds of departments were unable to meet this waiting-time recommendation.¹³ As expected, departments with more staff had shorter waiting times than those with one part-time technician.

PEEGs differ significantly from adult EEGs due to developmental variation in normal features and increased artefact making their interpretation more difficult than adult EEGs.^{3,13} The interpretation of PEEG abnormalities and specific correlation with clinical presentation is also unique to paediatrics as there is a wide range of paediatric epilepsy syndromes not found in adults.^{1,3} The majority of departments had clinical physiologists with formal training although only three had previous specific paediatric experience or training in a dedicated Paediatric EEG department. PEEGs were commonly read by adult neurologists. This is consistent with the UK survey that found only 50% of physiologists and 60% of EEG reporters had formal paediatric training.¹³

It is concerning that the number of PEEGs reported in some departments is so small that the reporters may struggle to remain competent in paediatric EEG reporting. This lack of specific PEEG training of clinical physiologists, predominance of reporting by adult neurologists and lack of significant ongoing experience in some centres creates a risk that PEEGs may be misinterpreted.^{3,13}

It has been suggested that in the UK all paediatric EEGs should be read by either paediatric neurologists or adult neurologists with considerable and ongoing paediatric EEG experience.³ This is perhaps even more relevant to New Zealand where there is a shortage of paediatric neurologists. Consequently in New Zealand the majority of the PEEG reports go to general paediatricians who may lack the necessary specific paediatric epilepsy syndrome knowledge to be able to effectively interpret reports from adult neurologists who also do not have this knowledge.

EEGs do not need to be reported onsite as they can be copied and posted, or read online by a paediatric neurologist remotely.¹⁹ It would therefore be possible to have all PEEGs in New Zealand reported by paediatric neurologists which would improve the standard of care for New Zealand children with epilepsy.

A weakness of this survey is that statistical data on total number and number of different types of PEEG were not recorded in all departments. We took a pragmatic approach and used estimates from the senior technicians in departments where this was the case. Although not ideal, senior EEG technicians are best placed to give accurate estimates.

Conclusion

There is marked neurophysiological department variability in the provision of EEG for New Zealand children. As an EEG is integral to the diagnosis of an electro-clinical epilepsy syndrome, all New Zealand children should have access to PEEGs performed to an international standard in an internationally recommended time frame.

The misdiagnosis of epilepsy or the specific epilepsy syndrome due to over or under interpretation of the EEG has significant impact on management and subsequent outcome for children with epilepsy. Guidelines should be developed to direct PEEG provision and resources made available to enable these to be followed. Specifically children should have access to sleep-deprived or early EEGs within 4 weeks of the onset of their seizures.

To allow for appropriate interpretation of EEG abnormalities and correlation with paediatric epilepsy syndrome diagnosis, PEEGs should be reported by paediatric neurologists. This could be achieved by increased use of offsite reporting.

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ORIGINAL ARTICLE

Computer Assisted Learning for the Mind (CALM): the mental health of medical students and their use of a self-help website

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Abstract

Aims The aim of this study was to develop an evidence-based self-help website, Computer Assisted Learning for the Mind (CALM) designed to improve mental health amongst medical students; and to assess the proportion, demographics and mental health of students who chose to use the site.

Methods All 2nd and 3rd year medical students from one New Zealand university were invited to participate. Demographics and mental health scores of those accessing CALM were compared with those not accessing it. Outcome measures included depression (PHQ-9) and anxiety (GADS-7) scores recorded at baseline. Anonymous identifiers were used to track website use.

Results Baseline questionnaires were completed by 279/321 (87%) of eligible students. CALM was accessed by 80/321 (25%) of the students over a 5 week period. Those who accessed CALM and could be linked by unique identifier (n=49) had significantly higher anxiety scores ($p=0.01$) but not higher depression scores ($p=0.067$) at baseline, than those who did not access CALM (n=230). Of those students with both PHQ-9 scores and GAD-7 scores ≥ 10 (at risk of significant depression and anxiety) at baseline, 41% went on to access CALM.

Conclusions The CALM website was used by 25% of medical students, particularly those with poorer anxiety scores. Self-selection to a web-based resource may provide assistance to those most in need, but further research would be needed to assess effectiveness.

High levels of depression and anxiety in tertiary students in New Zealand is an area of concern.¹ Support, resilience, coping strategies and treatment for mental disorders are protective factors for suicide,² and resilience can be increased with training.³ However, there is a paucity of New Zealand research looking at the identification of effective interventions, and the factors enabling their successful implementation in the tertiary student population.

Self-care and help-seeking behaviour of medical students need to be improved because such attributes impact on their credibility with patients,⁴ as well as affecting the way that they talk with patients about preventive health.⁵ There is growing evidence that the way that doctors care for themselves affects the way they care for their patients.⁵

If medical students develop psychological difficulties, this can have adverse effects on empathy⁶ and sometimes lead to attrition from the medical programme.⁷ Medical students using stress management programmes experience less depression and anxiety, and have increased empathy and more positive coping skills.⁸ However, it is clear that despite the existence of effective interventions, medical students often do not seek professional help, even when they are unwell.⁹ Reasons given for this are the lack of time, cost and concerns about confidentiality and stigma: a perception that they will be labelled 'weak' or that it may affect their future career plans.^{9,10}

It has been stated that to enhance their students' psychological health and prevent burnout, medical schools could provide a confidential resource to treat depression, and equip students with self-care strategies and skills.¹¹ One such strategy may be to provide an evidence-based, anonymous electronic

service. Web-based resources to improve health have been found to be feasible and effective in a tertiary student population.¹²

Amongst the general population, there is evidence that internet-based self-help treatments using cognitive behavioural therapy for panic disorder and mild to moderate depression can be effective.¹³ However, adherence to such interventions is low, and there is a need for shorter on-line interventions, or ways of providing brief electronic information to promote resilience as well as help-seeking.¹⁴ Furthermore, there is limited knowledge about the mental health of those who choose to access computer-assisted care, in comparison with those who do not, as most studies only collect data about user profiles.¹⁵ Such research is important as it investigates who are most at risk of experiencing psychological issues, and who are accessing available mental health resources.

The aim of this study was to develop an evidence-based on-line mental health intervention, Computer Assisted Learning for the Mind (CALM), and to assess the mental health and use of CALM in a sample of medical students.

Methods

The first part of the study involved development of the CALM website. The second part of the study piloted CALM and assessed the mental health and CALM usage across two classes of medical students. Using a prospective cohort design, the uptake of CALM over a 5-week period was measured, and the depression and anxiety scores of medical students who accessed the site were compared with those who did not. Demographic information and mental health scores were collected in-class at baseline.

All 2nd and 3rd year medical students at one New Zealand University were invited to participate in the study midway through the academic year. No students were excluded.

Outcome measures included PHQ-9 depression scores and GAD-7 anxiety scores. The PHQ-9 has been shown to have a specificity of 88% and a sensitivity of 88% for major depression in comparison to clinical interview, using a cut-off point of ≥ 10 .¹⁶ This tool has also been shown to be reliable in a tertiary student population, with an internal consistency of 0.85, and a good one month test-retest reliability ($r=0.89$, $p<0.001$).¹⁷

For the GAD-7, a cut-off point of ≥ 10 has sensitivity for diagnosing Generalised Anxiety Disorder of 89% and a specificity of 82% compared with diagnostic interview.¹⁸ The GAD-7 has been shown to have good reliability and criterion-related validity against clinical interview, as well as good agreement between self-report and interviewer administered versions of the scale.¹⁹

The intervention was a self-care website (CALM) containing written information and audiofiles to promote good mental health and wellbeing. The content was devised by the authors (FM, AF and SK), and the site was built and run by a team of web developers. Several interventions were chosen to enhance psychological health, based on their research credibility. The authors included a broad range of strategies to maximise user choice, and to create a focus on promoting wellness as well as preventing illness. Accordingly, the website was divided into three sections: ‘managing stress, anxiety and depression’; ‘mental resilience’; and ‘finding meaning in life’.

The first section contained explanations as to why stress, depression and anxiety can occur and some of the common symptoms or experiences. It included audiofiles on techniques for managing stress such as progressive muscle relaxation and self-hypnosis, as well as multiple tracks of mindfulness meditation of varying lengths. A 2011 Cochrane review concluded that the evidence supports that ‘Mindfulness Based Stress Reduction’ improves mental health, and that ‘Mindfulness Based Cognitive Therapy’ prevents relapse of depression.²⁰ A 2012 Cochrane review concluded that mindfulness-based therapies were effective in reducing depressive symptoms.²¹ Furthermore, there is evidence demonstrating that mindfulness interventions are effective at improving mental health and wellbeing in tertiary students,²² and specifically in a medical student population.²³

The second section of the CALM website included information and exercises to aid the development of positive mind-states and attitudes, such as exercises in gratitude and compassion, which have been shown to enhance wellbeing.²⁴ A review of ‘Loving Kindness Meditation’ stated that it can cause a decrease in stress and an increase in empathy and other positive emotions, and that it could be a useful adjunct to other psychological therapies.²⁵

The third section of the CALM website focussed on the importance of connection to other people, beliefs and values. Having ‘a meaning in life’ and paying attention to one’s non-professional life has been reported to have protective effects against burnout.²⁶ In CALM, this concept was described as having ‘something beyond the daily grind’ that led to the inclusion of a section on finding meaning in life, whether that be religion, a cause or a philosophy.

The format of the CALM site was designed to be as user-friendly as possible, with words being kept to a minimum. Audiofiles could either be listened to directly from the computer, or downloaded onto an I-pod or MP3 player for multiple use. Many of the topic web pages also had links to other relevant evidence-based websites, in line with one of the key principles of youth development: enabling young people to have access to accurate information.²⁷

Demographic information for the whole student group (years 2 and 3) was collected using administrative databases. Demographic and mental health characteristics of participants were assessed in class at the baseline measures meeting, and participating students created an anonymous ‘unique identifier’, a reproducible personal code, on their paper baseline questionnaire. They re-entered this code if they chose to access CALM on-line. These codes were used to track each participant whilst maintaining their anonymity.

Seven weeks after baseline assessment, the CALM website was made available to participants for a 5-week period. During this 5-week trial, CALM could only be accessed by the participants and not by the public. Students were informed about CALM at baseline, and were reminded in a lecture and by one email when the website was launched.

Demographic and mental health characteristics of all study participants are described at baseline and the proportion of those at risk of depression or anxiety calculated. The proportion and characteristics of the medical students who accessed CALM are also described, and are compared with those who did not access CALM. Accuracy of data entry was checked by using double data entry and an electronic comparison of the two datasets. Means and standard deviations were calculated to describe characteristics of the total and sub-samples of participants. Chi-squared and t-tests were used to assess differences between those accessing CALM and others. Only data that were present were included in the analyses, with no imputation.

The CALM study was approved by the University Ethics committee (no. 2008/216 Appendix 1) in 2008.

Results

Table 1 shows the characteristics of the 321 medical students. Of these, 279 (87%) completed PHQ-9 and GAD-7 assessment at baseline with mean scores of 5.14 (SD 4.1) and 3.91 (SD 3.7), respectively. The proportion of students at risk of any degree of depression was 48% (n=133), with 2.5% (n=7) moderately severely depressed (PHQ ≥ 15), 12% (n=33) moderately depressed (PHQ=10–14), and 33% (n=93) mildly depressed (PHQ=5–9).

The proportion of students at risk of any degree of anxiety was 37% (n=103), with 2% (n=6) moderately severely anxious (GAD-7 ≥ 15), 7% (n=20) moderately anxious (GAD-7=10), and 28% (n=77) mildly anxious (GAD-7=5–9).

Over the 5 weeks of the website availability, 80/321(25%) students visited CALM at least once. There was no significant difference in the proportion accessing CALM from different ethnic groups ($p=0.4$).

Table 1. Baseline characteristics of Year 2 and Year 3 medical students

Characteristics	Total class of 2nd and 3rd year medical students (n=321)	Those accessing CALM website (n=80)
Female n (%)	167 (52)	38 (47.5)
Male n(%)	154(48)	42(52.5)
Age in years, mean (SD)	22.2 (2.9)	21.1 (3.2)
European n (%)	147 (45.7)	36/147 (24.5)
Māori n (%)	11 (3.42)	3/11 (27.2)
Pacific Islander n (%)	27 (8.4)	4/27 (14.8)
East Asian n (%)	36 (11.2)	12/36 (33.3)
South Asian/Other Asian n (%)	76 (23.7)	13/76 (17.1)
Other n (%)	20 (6.2)¶	6/20 (30.0)‡

Note: No significant differences were noted between the distribution of ethnicity in the class and in those that accessed the CALM website ($p=0.4$). 4 missing values; ‡6 missing values.

Only 49/80 (61%) students used the same unique identifier on the website as they had used at baseline. The mean baseline scores from this group of 49 web-users were compared with the mean baseline scores from the 230 participants who could not be shown to have accessed CALM.

Those who accessed CALM and could be linked by unique identifier to baseline class scores (n=49), had significantly higher anxiety scores ($p=0.01$) but not higher depression scores ($p=0.067$) at baseline than those who did not access CALM (or who accessed CALM and could not be linked) (Table 2).

Table 2. Comparison of baseline depression and anxiety scores of those who did and did not access CALM according to linked data

Clinical characteristics	Did not access by linked data Baseline in-class score (n=230)	Accessed by linked data Baseline in-class score (n=49)	P-value
PHQ9, mean (SD)	4.93 (4.00)	6.10 (4.26)	0.067
GAD7, mean (SD)	3.65 (3.59)	5.14 (4.10)	0.01

Out of the participants who entered mental health scores at baseline (n=279), 40 students had a PHQ-9 ≥ 10 and 26 students had a GAD-7 score of ≥ 10 at baseline. Of the 17 students who had both a baseline PHQ-9 and GAD-7 of ≥ 10 , 7 (41%) went on to access CALM (Table 3).

Table 3: Percentage of students with PHQ-9 and GAD-7 scores ≥ 10 , who did and did not access CALM according to linked data

	Proportion of whole class (n=279) with baseline mental health score ≥ 10	Accessed CALM (according to linked data)
Both PHQ-9 ≥ 10 and GAD-7 ≥ 10	17/279 (6%)	7/17 (41%)
PHQ-9 ≥ 10 (but GAD-7 <10)	23/279 (8%)	4/23 (17%)
GAD-7 ≥ 10 (but PHQ-9 <10)	9/279 (3%)	3/9 (33%)

Discussion

The CALM study complements previous research demonstrating that electronic interventions can be effective^{13,14,28} by analysing which groups of people actually use the electronic resource in terms of their demographics and mental health characteristics. In other words it provides some answers to the question, “who chooses to access this resource?” This study has not demonstrated the effectiveness of the website, but it was not designed to do so.

The CALM study showed that one quarter of year 2 and 3 medical students chose to access a self-care mental health website over a five week period. The site was accessed by those students with significantly higher anxiety scores but not higher depression scores, in comparison to those who did not access the website. The reasons for this are not clear, but one possible explanation is that the loss of interest and energy associated with depression may result in less motivation to experiment with a new website than for those with anxiety. Alternatively, it could be that depressed students were in fact more likely to access the website, but that the study was not powered enough to show this as being statistically significant.

The rates of moderate or moderately severe depression and anxiety in the medical students participating in the CALM study were shown to be 14.5% and 9% respectively, using the cut-off score of ≥ 10 . These results are similar to another New Zealand study that found a prevalence of 16.9% for depression and 13.7% for anxiety in medical students.²⁹ However, the cut-off for anxiety in this previous study was a GAD-7 score of ≥ 8 , which could be one reason for the higher anxiety rate in comparison to the CALM study.

The CALM study finding that the percentage of students with risk of any degree of depression was 48% is also similar to a large multicentre US study which stated that 49% of medical students had depressive symptoms.³⁰ In the CALM study 2.5% of students had a score of ≥ 15 . Although this is a small percentage, it is important, as one US study showed that 28.5% of tertiary students with a PHQ-9 score of ≥ 15 also identified themselves as having suicidal ideation.³¹ The average PHQ-9 score for the class in the CALM study was not very high at 5.14, but there was quite wide variation (sd. 4.06), indicating that there were reasonable numbers of students with symptoms of depression present in the class.

There was a high participation rate with 87% of the medical students in the two classes completing the baseline questionnaires in class, which supports the internal and external validity of findings. However, there were some limitations. The data were collected by self-report questionnaires, and although the measures used were well-validated, it does introduce a subjective element to the responses or potential response bias. A gap of 7 weeks between the date of the baseline assessments and the CALM launch occurred because of delay in website development. The students only had a 5 week interval in which to visit the site, which could have affected the number of visitors. However, the fact that CALM was not immediately available after being told about it in class but was available some time later may have been a more realistic assessment of the proportion likely to use such a site (25%) in an every-day setting.

Although the use of unique identifiers did provide an anonymous method of linking in-class students to those who accessed CALM, it was a study limitation, as 31 identifiers entered on the website could not be linked to those used at baseline. It is possible that those 31 students were not in class on the days of the baseline questionnaire, or that individual students used one or more unique identifiers, possibly due to concerns about being identified. The study design allowed for this, as the authors did not want to withhold a therapeutic intervention from students concerned about privacy. This may affect the generalizability of the findings but reflects the reality of conducting studies of a sensitive

topic in a vulnerable population. The low level of linkage may have also limited the sample size and the ability to draw conclusions about differences between those who accessed CALM and those who did not.

Even so, the CALM study demonstrates that electronic interventions can be accepted and used by medical students. Other online mental health resources have been developed for tertiary students such as Ulifeline³² in the USA. However, a point of difference with the CALM website was the experiential nature of much of the content, as the audiofiles enabled students to practice techniques.

The results from the CALM study also contribute to the existing literature by demonstrating that students with higher anxiety scores are more likely to access a self-care website than students with lower scores, as well as adding to the New Zealand data about the prevalence of depression and anxiety in medical students. This research has important implications for medical schools and beyond, as it suggests that medical students in need may use a confidential web-based resource designed to improve mental health. The use of audiofiles to provide experiential training in stress-management and positive thinking provides an affordable and anonymous way of targeting this high risk group to enhance self-care and enable early intervention. The health of our future doctors is important given the effect on practitioner quality of life, patient safety and the challenge of retention.^{33,34}

The modules and information on the CALM website could also be of benefit to other student groups and patient populations. Therefore, after the conclusion of the study, minor structural changes were undertaken, and the CALM website was made available to the public (www.calm.auckland.ac.nz), later being linked to the New Zealand National Depression Initiative³⁵ and many Universities internationally.

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ORIGINAL ARTICLE

Predicting lymph node metastases in cutaneous squamous cell carcinoma: use of a morphological scoring system

Nicholas J M Agar, Christopher Kirton, Rajan S Patel, Richard C W Martin, Neville Angelo, Patrick O Emanuel

Abstract

Background Predicting which patients will develop nodal metastasis from cutaneous squamous cell carcinoma (cSCC) remains difficult. This study evaluates a recently described histological risk model validated for mucosal head and neck SCC (HNSCC) when applied to cutaneous tumours. In this model, morphologic variables including worst pattern of invasion, lymphocytic host response and perineural invasion were shown to predict disease recurrence, loco regional recurrence and overall survival in mucosal HNSCC.

Methods Patients with cSCC and known metastatic spread were identified from the author's database over a 5-year period between July 2007 and July 2012. Histology specimens from the original primary tumour were separately analysed by 2 histopathologists. Scores were compared against T-Stage matched control specimens without metastatic spread.

Results 27 patients with metastatic cSCC were identified. Scores for worst pattern of invasion (WPOI) were significantly higher in individuals with lymph node metastases ($p=0.02$).

Conclusions Adverse pattern of invasion, defined as presence of small tumour islands or tumour satellites may be an independent risk factor for developing nodal metastases in cSCC. These tumours are difficult to investigate histopathologically as it is difficult to be confident the correct primary is chosen for study.

Cutaneous squamous cell carcinoma (cSCC) is highly prevalent in New Zealand with an incidence of 118 per 100,000.¹ The majority of these (70–80%) occur in the head and neck region, and for the most part these tumours present early and can be cured with excision. However, a small proportion of cSCCs behave aggressively, with approximately 3–4% of patients developing lymph node metastases. Interestingly, the rates of metastasis is lower than this (1.9–2.6%) in New Zealand studies.² The presence of metastases is a powerful prognosticator, carrying a 5-year survival of between 13–49%.^{3,4}

The 7th edition of The American Joint Committee on Cancer (AJCC) TNM staging guidelines identifies high-risk features of the primary lesion which will upstage a patients' T-status.⁵ This revised staging system has generated significant debate—much of it acknowledging a marked improvement on the 6th edition. These high-risk features are: thickness >2mm, Clark level ≥ 4 , perineural invasion, anatomical site being the ear or the hair bearing lip, and poorly or undifferentiated tumours.

The presence of one or more of these risk factors carries an increased risk of nodal metastases (Table 1). All of these high risk features can be assessed somewhat objectively with the exception of the degree of differentiation, which is more subjective. In 2003 a survey of dermatopathologists revealed that only 54% reported the histological grade, and only 49% felt that this grade reflected prognosis.

In our practice we have found that AJCC T2 tumours are very common, but many of these tumours appear to have a favourable clinical course. In our view, further refinement of the AJCC staging protocol could be achieved to more accurately stratify risk of metastasis associated with these tumours.

Table 1. High risk factors for lymph node metastases^{6,7}

Risk Factor	Metastatic Likelihood
Size > 2cm	20-30%
Thickness ≥5mm	16-45%
Poorly differentiated	12-32%
High grade/desmoplasia	12%
Perineural invasion	40-47%
Lymphovascular invasion	40%
Location near parotid or lip	10-30%
Local recurrence	25-62%
SCC in existing scar	38%
Immunosuppression	13-20%

Brandwein et al⁸ have validated a novel histologic risk assessment tool for predicting disease progression, loco regional recurrence and overall survival in 305 patients with mucosal head and neck SCC. This model is based on three hallmark histological factors—being:

- Worst pattern of invasion,
- Perineural invasion, and
- Lymphocytic host response.

Tumours with a poorly defined advancing front with infiltrating nests and cords of tumour cells had a significantly higher rate of loco regional recurrence than did those with a broad pushing front. Furthermore tumours with perineural invasion carried a poor prognosis, as did tumours in which the host immune response against the tumour was not perceptible.⁹

While mucosal tumours affect different patients and have different aetiologies, they have an identical histopathology and share numerous morphologic risk factors with cSCC (e.g. perineural invasion, tumour grade, tumour thickness etc); we therefore thought this tool could have some utility in cSCC.

As no additional resources are needed, Brandwein's tool is relatively easy to apply in the community laboratory setting. The pattern of invasion is now an integral part of synoptic reporting for mucosal head and neck SCC.

The aim of this study is to evaluate this histologic risk assessment tool when applied to a retrospective cohort of patients with cutaneous SCC.

Materials and Methods

Study design—Ethics approval was obtained from the Northern Regional Ethics Committee. 27 patients with cSCC and known metastatic spread were identified from the authors (RP, RM) database over a 5-year period from July 2007 to July 2012. Only cases in which there was no doubt we had the correct primary and corresponding metastasis were included.

Much to our surprise, while metastases from cSCC is not an extraordinarily rare event in our population, being able to confidently isolate the primary for any given case is rather rare. We did not, for example, include cases in which there was a history of any invasive cSCC in the region of the draining lymph nodes. We did include cases with regional basal cell carcinoma, actinic keratoses (histologically proven) and the various forms of squamous cell carcinoma *in situ* as nearly patient had a history of these lesions in the region.

Twenty-two stage T2 (AJCC 7th edition) tumours were retrieved from our archives to serve as matched controls. The control specimens were cross-checked to ensure disease-free survival at 5 years. Data was collected from the electronic patient record and de-identified. Demographic details and tumour variables such as Breslow thickness, Clark level, and AJCC T-stage were recorded for each patient. The tumour size was difficult to discern in many cases so was not able to be statistically scrutinised.

All tumours were reported to be completely excised with wide surgical margins. The presence of immunosuppression was not recorded. We found the presence of absence of immunosuppression and the degree of immunosuppression is very difficult to ascertain with great certainty with a chart review.

Morphologic scoring—Each of the archived histologic specimens were retrieved and analysed using the morphologic scoring system described by Brandwein et al (see Table 2). Representative slides were selected, each slide de-identified then read by 2 pathologists (PE, NA). These were read independently to excellent concordance. 5 cases showed discordance. These cases were then discussed by the pathologists around a multiheaded microscope and a score was agreed upon.

Data analysis—Morphologic scores were recorded and results statistically analysed using the unpaired t-test to compare groups. P values of 0.05 or less were considered to be statistically significant. Categorical variables were analysed using the chi square test with the control group as a comparison for expected normative values.

Table 2. Morphologic Scoring System (Brandwein et al)

Variable	Definition	Point assignment
WPOI	Type 1 Pushing border	0
	Type 2 Finger-like growth	0
	Type 3 Large separate islands, more than 15 cells per island	0
	Type 4 Small tumour islands, 15 cells or fewer	+1
	Type 5† Tumor satellites $\geq 1\text{mm}$ away from the main tumour ($\times 20\ddagger$) or next closest satellite	+3
LHR	Type 1 Strong Dense complete host response rimming tumor. Lymphoid nodules at advancing edge in each $4\times$ field	0
	Type 2 Intermediate Intermediate host response. Lymphoid nodules§ in some but not all $4\times$ field.	+1
	Type 3 Weak Little or no host response. No lymphoid nodules.	+3
PNI	Type 1 None	0
	Type 2 Small nerves Tumour wrapping around nerves $<1\text{mm}$ in diameter.	+1
	Type 3 Large nerves ($\times 20$). Tumour wrapping around nerves $\geq 1\text{mm}$ in diameter	+3

Add the total points from each variable for each case. If total points score = 0 then low risk; if score = 1 or 2 then intermediate risk; if score = 3 or greater then high risk. LHR; lymphocytic host response, PNI; perineural invasion, WPOI; worst pattern of invasion.

†POI 5 includes spread in lymphatics or PNI equal to or greater than 1mm away from next closest satellite.

‡ $\times 20$ field = 1mm in diameter

§Lymphoid nodule = dense collection of inflammatory cells adjacent to carcinoma seen at $\times 4$ then confirm density of inflammation at $\times 20$. Immune response should comprise at least 50% of a $\times 20$ field adjacent to carcinoma. Assess Immune response immediately adjacent to carcinoma, include carcinoma *in situ*.

Results

The demographics of both the study group and control group show well matched cohorts (Table 3).

Table 3. Patient demographics

Patient Demographics	Metastatic Group n=27	Control Group n=22
Age – median	81	78
Age – range	55-93	40-85
Male	18	14
Female	9	8

The tumour features ascertained retrospectively from the medical record are presented in Table 4. There was no significant difference in primary tumour site between the metastatic and control groups with the majority of lesions in both groups originating in the head and neck region. Breslow thickness was significantly higher in the metastatic group. Furthermore, a significantly higher number of poorly differentiated tumours were seen in the metastatic group.

Table 4. Tumour parameters

Tumour Parameters	Metastatic Group n=27	Control Group n=22	
Tumour Site			
Head & Neck	15	14	
Limb	10	7	
Trunk	2	1	
Clark Level mm (mean)	4.7	4.5	
Breslow Thickness mm (mean) and range	9.2 (3.8-15)	5.8 (3.6-12)	p = 0.006
Differentiation			
Poor/Undifferentiated	12	4	P = 0.003
Moderate	14	15	
Well	1	3	

Morphologic scores were obtained using the scoring system detailed in Table 2 and are displayed in Table 5. Worst pattern of invasion (WPOI) scores were significantly higher in the metastasis group (1.00 vs. 0.36, p = 0.02). There was no difference in lymphocytic host response (LHR) or perineural

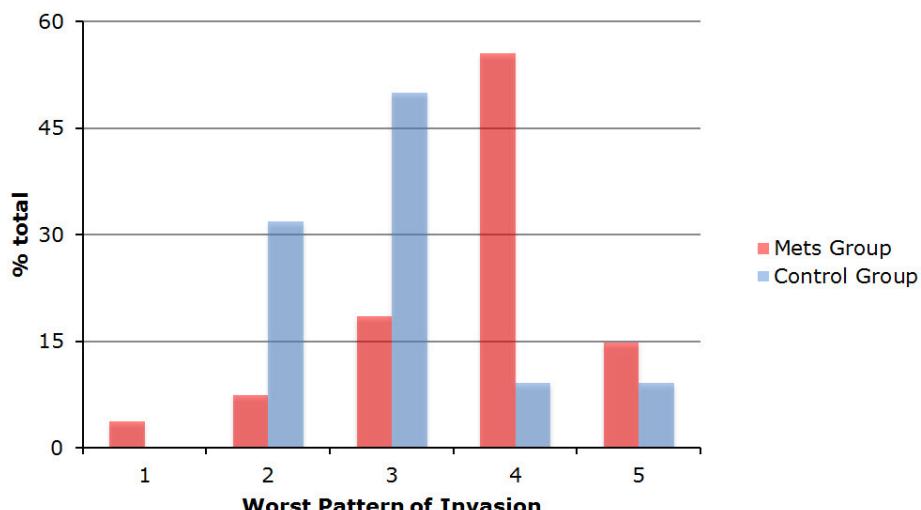
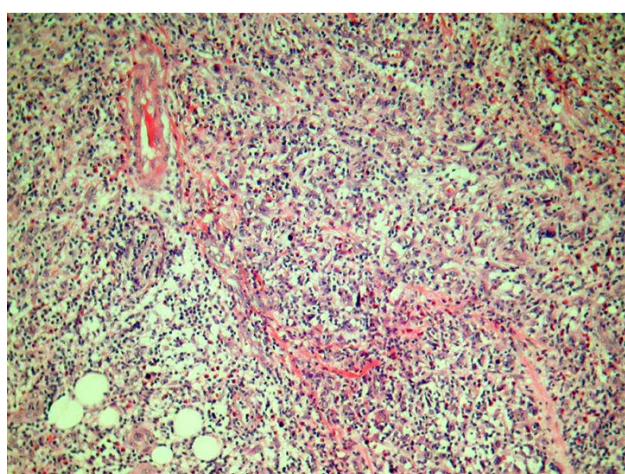
Table 5. Morphological scores (mean weighted scores)

Morphology	Metastatic Group n=27	Control Group n=22	Statistical significance
Worst Pattern of Invasion	1.00	0.36	P=0.02
Lymphocytic Host Response	1.52	1.68	P=0.77
Perineural Invasion	0.48	0.27	P=0.41
Total Score	3.00	2.32	P=0.17

Table 6 and Figure 1 show a significantly higher proportion of patients with metastases with type 4 or 5 WPOI (19 of 27, 70% vs. 4 of 22, 18%; p < 0.001). Patients with type 4 (small tumour islands) or type 5 (tumour satellites >1mm from the main tumour) had a significantly higher risk of developing regional lymph node metastases.

Table 6. Worst pattern of Invasion

Pattern of invasion	Mets Group n=27	%	Control Group n=22	%
Type 1 Pushing border	1	3.7	0	0
Type 2 Finger like growth	2	7.4	7	32
Type 3 Large separate islands >15cells	5	18.5	11	50
Type 4 Small tumorislands <15cells	15	55.5	2	9
Type 5 Satellites ≥1mm from main tumor	4	14.8	2	9
Type 4 or 5	19	70%	4	18%

Figure 1. Worst pattern of Invasion graphical representation**Figure 2. An invasive cSCC with a highly infiltrative growth pattern consisting of single malignant keratinocytes and small nests (HE stain 40×). WPOI type 4 with a dense lymphocytic response.**

Discussion

Ch'ng et al¹⁰ confirmed the major prognostic role of nodal metastases in cSCC. Their study found that nodal metastases once present are the primary determinant of prognosis and that the T-stage of the primary is of little importance in all but well differentiated primary lesions. Improved prognostication of primary tumours likely to metastasize is therefore of high importance for improving outcomes in cSCC. In 2008 Brantsch et al¹¹ completed a prospective study on 615 patients with cSCC and demonstrated in particular the importance of tumour thickness, tumour site, the presence of desmoplasia and the patients' immune status as key factors in staging.

More recently, Peat and colleagues¹² retrospectively studied 78 patients who developed metastasis and 92 control patients over a 5-year period. They quantified the value of various risk factors so that a system of risk stratification can be developed. The two 'absolute' (highest) risk factors for development of metastatic disease were poor histological differentiation and perineural/lymphovascular infiltration.

A growing body of evidence supported the fact that both local recurrence and distant metastases were dependent on more than just the horizontal size of the lesion. Many factors have been put forward as high-risk features for nodal metastasis in cSCC as laid out in Table 1. Most studies highlighting these risk factors are retrospective in nature and like this study do not include multivariate analysis to prove independent validity of any single feature.

Given that the control group was selected to match the study group in terms of being T2 with the AJCC staging protocol statistical comparison of the AJCC risk parameters may have limited value. However, our study does emphasise a relationship between increased Breslow thickness and the risk of metastases was confirmed, with a mean Breslow thickness of 9.2 mm in the metastatic group compared to 5.8mm in the control cohort. Furthermore the degree of differentiation was noted to be of relevance even in this study which compares two groups of patients with T2 tumours: 44% of the metastatic group were graded as poorly differentiated compared to 18% in the control group.

With respect to the histological model described by Brandwein, only the pattern of invasion bore a significant relationship to the risk of metastatic disease in our study. The assessment of the lymphocytic-host response bore no correlation—which may relate to the inherent differences in immune surveillance of the integument compared with mucosa, or factors related to immunosuppression (note: lymphocytic response in cSCC is not included in the AJCC staging). While perineural invasion was almost twice as common in the metastatic group compared with control group this did not reach statistical significance. It is interesting to note that while perineural invasion is known to be a risk factor for nodal metastases it has a stronger likelihood of being associated with local recurrence - this may have contributed to the lack of statistical significance in this study.¹³

The small number of cases studied is a clear limitation of this study. We found that in most cases of metastatic cSCC the patient had had innumerable previous cSCCs and the primary tumour could not be determined with confidence. These cases were excluded from our study which limited numbers.

We found the task of confidently selecting cases with primary cSCC which subsequently metastasised extraordinarily difficult, a fact not frequently mentioned in previous literature. Many previous studies have relied solely on pathology reports for analysis rather than examining the sections of each tumour to confirm the diagnosis and exclude cases for which the primary cSCC is not clear. Reviewing pathology reports rather than the tissue sections also adds the significant variable of different reporting styles and trends that exist between different pathologists.

The significant finding in this study is the higher proportion of malignant behaviour with WPOI type 4 pattern of invasion than WPOI Type 3. This hinges on the cutoff of 15 cells or fewer per island. The cut-off value of 15 cells is based on the model proposed by Anneroth and colleagues, and subsequently used by Brandwein-Gensler who have shown this is a practical and effective threshold for stratifying risk.^{9,14}

It is perhaps unsurprising that the control group had less poorly differentiated tumours when compared with the study group. Pattern of invasion may be regarded as a proxy of differentiation. The differentiation of squamous cell carcinoma is in many cases subjective and there is no doubt that there is considerable variation in thresholds amongst practicing pathologists. We believe the pattern of invasion offers an easy and reproducible method of assessing risk in cSCC.

The pattern of invasion seen in histologic sections derives from basic attributes of a tumour such as migrational ability and interaction with the adjacent mesenchyme. Future studies are planned to examine the molecular basis behind these attributes in aggressive cSCC.

Conclusion

Brandwein's mucosal HNSCC model is not a perfect fit for cutaneous SCC. It is clear from the current AJCC guidelines and from the medical literature to date, that there are multitudes of both patient and tumour factors which are of importance when trying to identify high-risk tumours. Our study, albeit with a small patient cohort, has highlighted the importance of pattern of tumour invasion as a predictor of nodal metastasis.

Competing interests: Nil.

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ORIGINAL ARTICLE

Association of point prevalence diagnosis of delirium on length of stay, 6-month mortality, and level of care on discharge at Waitemata District Health Board, Auckland

Aik Haw Tan, John Scott

Abstract

Background Delirium in hospitalised older persons is common and is correlated with adverse outcomes. Few studies of this have been done in New Zealand. The study aimed to measure the impact of delirium on 6-month mortality, length of inpatient stay and level of care.

Method We performed a retrospective analysis utilising data from the Delirium Point Prevalence Audit conducted at Waitemata District Health Board. The subjects were older inpatients (>65 years) surveyed between 15/05/2012 to 24/07/2012. Delirium was defined as screening positive on the Confusion Assessment Method (CAM). Patients were dichotomised into those with delirium or without.

Results 250 patients were identified. 28(11.2%) were CAM-positive while 222 (88.8%) were CAM-negative. Mortality at 6 months for the CAM-positive group was 39%, compared to 10% in the CAM-negative group ($p<0.005$). The mean inpatient day stay for the CAM-positive group was 25.4 days; for the CAM-negative group it was 21.6 days ($p=0.721$). The proportion requiring an increased level of care at discharge was 66.6% for the CAM-positive group, while for CAM-negative persons the rate was 13.8% ($p<0.00003$).

Conclusion In hospitalised older adults, the presence of a positive CAM test for delirium was strongly associated with both a higher mortality rate at 6 months and a requirement for an increased level of care at discharge as compared to a negative CAM. No effect was observed on inpatient length of stay.

Delirium is defined as an acute change in cognition that occurs within a few hours to days that cannot be accounted for by pre-existing dementia or cognitive impairment.^{10,11,15} It is very common in hospitalised older adults, with a reported range in studies of medical inpatients of 15–40%^{1–7} and in the post-surgical setting of 7–52%.^{1–7}

The impact of delirium in the older adults is typically measured by looking at mortality rates, change in level of care and length of inpatient stay.^{3,7–9,12,13,26,27} A common finding is that delirium is highly correlated with rates of mortality 6–12 months after diagnosis, and also with an increased rate of institutionalisation. Some studies that suggest that inpatient delirium is associated with an increased length of inpatient stay, although this is not consistent.^{3,7–9,12,13,26,27}

Mortality—Most studies show a strong association between inpatient delirium and an increased risk of death between 3 months and 1 year later (see Table 1).^{7,8,16–19} This association has been noted from medical inpatient, emergency department, and ICU-based studies.^{8,19} However McAvay et al found that resolution of delirium while an inpatient removed the increase in mortality.^{16–18}

Table 1. Delirium and mortality

Authors	Setting	Number	Age	Duration of followup	Mortality
McCusker et al. (2002)(16)	Medical inpatients	Delirium: 243 Control: 118	>65, both groups similar in age on multivariate analysis	12 months	Unadjusted HR 3.44 (95% CI 2.05-5.75) Adjusted HR 2.11(95%CI 1.18-3.77)
Han et al. (2010) (17)	Emergency Department	Delirium 108 Control 520	Delirium 78 No delirium 74	6 months	HR 1.72 (95%CI 1.04-2.86)
McAvay et al. (2006) (18)	Inpatient, medical	Delirium: Resolved 31 Did not 24 Control 378	Resolved 80.2+/-7.1 Did not 79.6+/-6.1 Control 81.8+/-8.1	1 year	Unresolved HR 2.64 (95%CI 1.60-4.35) Resolved HR 1.53 (95%CI 0.96-2.43)
Van den Boogard (2010) (19)	ICU	Delirium 332 Control 1408	Delirium 61+/-35 Delirium 66+/-14	Inhospital, up to six months	OR 3.22(95%CI 2.23-4.66)
Gonzalez (2009) (8)	Medical inpatient	Delirium 192 Control 350	Delirium 81.5 Control 75.8	3 months	25.9% delirious died as opposed 5.8% non delirious, p<0.0001

Level of care—Most studies show an association between inpatient delirium and an increased risk of institutionalisation (see Table 2).^{13,18,21,24,25} Some studies have assessed institutionalisation at discharge while others have measured the status 3 to 6 months after discharge. McAvay found that even if delirium resolved as an inpatient, the rate of institutionalisation was still higher compared to controls.¹⁸

Table 2. Delirium and level of care

Author	Setting	Number	Age	Outcome
McCusker et al. (2001) (13)	Older hospital inpatient	Delirium and dementia 164 Only Delirium 56 Only dementia 53 No dementia or delirium 42	All equal, >65	Patients with delirium and dementia likely require higher level of care (Adjusted O/R 3.18, 95% CI 1.19 to 8.49).
Inouye et al. (1998) (24)	Medical ward	Delirium 88 Non delirium 639	Not stated but overall age 78.9	OR for three month new resthome placement 3.0(95%CI 1.5-6.0)
McAvay et al. (2006) (18)	Inpatient, medical	Delirium: Resolved 31 Did not 24 Control 378	Resolved 80.2+/-7.1 Did not 79.6+/-6.1 Control 81.8+/-8.1	Delirium did not resolve, HR 2.64 (95%CI = 1.60-4.35) Delirium resolved, HR 1.6, 95%CI 1.04-3.13)
Adamis (2006) (21)	Inpatient elderly care unit	Delirium 33 None 61	Not reported but group mean age 82.8+/-6.5	Significant risk of being discharged into a new cared setting, p<0.01
George (1997) (25)	Hospital inpatient	Delirium 171 Control 95	Delirium = 81 years Control = 80 years	OR to new residential care in six months 4.3 (95%CI 1.58 -14.59)

Length of stay—This is a frequently measured outcome in many delirium studies,^{3,7,20–24} usually defined as total number of days the patient stays in an inpatient unit or hospital.^{20–24} Most studies show a trend towards longer length of stay with delirium, though this often does not reach statistical difference (see Table 3).^{7,20–24}

The literature also suggests that certain subtypes of delirium may be associated with increased length of stay; for example McCusker found that new onset delirium during an inpatient admission was associated with increased length of stay but that being delirious at admission did not change length of stay.²⁰ O’Keefe found that hypoactive delirium was associated with statistically increased length of stay.²²

Table 3. Delirium and length of stay

Author	Setting	Number	Age	Length of stay (LOS)
McCusker (2003) (20)	Medical Inpatient	Prevalent:- Delirium 204 Incident: Delirium 37 No delirium:- Control 118	Prevalent:- 83.61+/-7.4 Incident:- 82.30+/-6.28 Control:- 83.64+/-6.58	-No increase with prevalence -Incidence increases excess day of stay by 7.78 days (95%CI 3.07-12.48)
Adamis (2006) (21)	Inpatient elderly care unit	Delirium 33 None 61	Not reported but group mean age 82.8+/-6.5	Longer LOS with delirium, (Mann-Whitney U 572.5, p = 0.047)
O’Keefe (1999) (22)	Acute geriatric unit	Delirium Subtype:- Retarded 27 Agitated 20 Mixed 40	Retarded: 83 years Agitated: 82 years Mixed: 82 years	Only retarded/Hypoactive delirium stayed longer, p<0.005
Han et al. (2011) (23)	Emergency department	Delirium 108 None 520	Delirium: 78 years No delirium: 74	Median LOS delirium 2 days (0-5.5), non delirious 1 day (0-3). P<0.0001
Inouye et al. (1998) (24)	Medical ward	Delirium 88 Non delirium 639	Not stated but overall age 78.9	Delirium (8.5) versus delirium (7.3 days), P,0.07

To our knowledge there is only one other published study looking at delirium outcomes in New Zealand—a study by Holden et al that reported data from Kenepuru and the Hutt Hospitals.²⁶

That study sampled 216 adults over age 65 in a medical inpatient setting. Delirium was assessed with the Confusion Assessment Method (CAM). In this cohort of patients, 56 patients were CAM-positive, giving a prevalence of 23.4% and an incidence of 5.7%.²⁶

Holden et al reported an inpatient mortality of 7% in their population with delirium as opposed to 3.7% in those with no delirium. However this did not reach statistical significance. Length of inpatient stay for patients with delirium was eight days versus four days for those without, though no significance value was given. Delirium was strongly associated with requiring higher level of care on discharge, with a p-value of <0.001.²⁶

Research question—To determine if a diagnosis of delirium in elderly inpatients (>65 years) made during a point prevalence study was associated with mortality at 6 months post diagnosis, length of stay in the hospital (total inpatient stay), and /or a change in level of care from admission to discharge.

Method

The study is an extension of the Delirium Point Prevalence Audit conducted at the Waitemata District Health Board which started in 2012. The study is registered under RM12152 with an ethics approval number of NTX/12/EXP/052.

The main audit aimed to assess all elderly patients once every fortnight for a period of 18 months in one medical ward, one orthopaedic ward and one assessment, treatment and rehabilitation ward.

Delirium was assessed in the audit using the Confusion Assessment Method (CAM) Diagnostic Algorithm. All audit patients were administered the Mini Mental State Examination (MMSE) which served as a standardised clinical interaction during which the subject was observed for signs of inattention, altered level of consciousness or disorganized thinking. If any of these were observed, further information was sought to determine whether or not the observed findings represented an acute departure from the subjects' normal state.

The assessment was done by a team of doctors, specialist nurses, and occupational therapists who were trained in administration of the CAM and used the CAM training manual and coding guide.⁴³ The study excluded patients who were unable to communicate in English, who were not available for assessment at the time of ward visit by the audit team, who declined consent, or who in the clinical judgment of the interviewer were too unwell to be burdened with assessment.

A positive CAM is assumed to be equivalent to a diagnosis of delirium. A negative CAM is taken to be equivalent of having no delirium at the time of the audit. However in common with all studies of delirium ascertainment will have been less than 100% as it is inevitable that some persons with resolved delirium, or who had not yet developed delirium, were included in the "negative" count.

All three outcome measures are based on information recorded in the patient management system used throughout Waitemata District Health Board. Mortality at 6 months was timed from the date of the CAM assessment. (PIMS data is updated at least 3-monthly with information from Births, Deaths and Marriages)

Inpatient stay is defined as the time from admission into hospital to the time of discharge back into the community or into long term residential care. Inter-hospital transfers, where a patient is transferred from one hospital to another for medical treatment or investigations as well as inter-ward transfers were all counted as part of the total inpatient stay.

Increase in level of care is defined as persons living in the community being discharged to residential aged care facilities, or persons in lower level (rest home) care prior to admission being discharged to private hospital care.

In addition to the entry criteria to the Point Prevalence Study, to be included in this extension study, the patient had to have a CAM score, be over 65, have attempted between 28 to 30 questions of the MMSE, and have been in audit cycles 3 to 7 (15/05/2012 to 24/07/2012).

Exclusion criteria for this study is anyone under 65 years of age, incorrect NHI, absent CAM scores, less than 28 questions of the MMSE attempted and inability to communicate in English.

Results

There were 341 assessments attempted during the above audit cycle. 75 were excluded due to incomplete forms/wrong NHI, 14 were duplicates (i.e. patients were in hospital during more than one audit cycle and thus assessed more than once), 3 were excluded as the total attempted MMSE questions were below 28.

As a result, 250 patients were included in this analysis.

Table 4. Characteristics of CAM-positive and CAM-negative patients

Variable	CAM-positive	CAM-negative	P value
Number (percentage)	28 (11.2%)	222 (88.8%)	
Age	83.44	79.86	P=0.06
MMSE total	13.92	23.0	P<0.001

In this study, 11.2% of the patients were found to be CAM-positive while 88.8% of the patients were found to be CAM-negative. While the CAM-positive group were slightly older, with an average age of 83.44 years versus the CAM-negative group of 79.86, this was not statistically significant.

The average MMSE in the CAM-positive group was 13.92 while the total MMSE in the CAM-negative group was 23.0. This difference was highly significant, with a p<0.001.

Table 5. Delirium and mortality at 6 months

Variable	Number	Rate
CAM-positive	222	10%
CAM-negative	28	39%

There was a substantially increased mortality rate in the CAM-positive group.

The rate of death at 6 months in the CAM-negative group was 10% while that in the CAM-positive group was 39%, with an absolute difference of 29.4% (95% CI 9.6% to 49.0%), with a p<0.05.

Table 6. Delirium and length of inpatient hospital stay

Variable	Number	Mean length of stay (days)	Standard Deviation (days)
CAM-positive	222	21.6	18.6
CAM-negative	28	25.4	19.7

There was a trend towards increasing mean length of inpatient stay in the CAM-positive group (25.4 days) as opposed to the CAM-negative group (21.6 days), p=0.34.

Table 7. Delirium and increase in level of care (note that the denominator here is 244 as 6 patients who died while in hospital were excluded)

Variable	Number	Rate
CAM-positive	219	13.8%
CAM-negative	25	66.6%

There was a substantially higher rate of patients requiring increased level of care on discharge from hospital in the CAM-positive group.

The rate of patients requiring increased level of care following discharge from hospital in the CAM-negative group was 13.8%. This rate was 66.6% in the CAM-positive group. This difference was very significant, at a p<0.00003.

Discussion

Our study confirmed that a positive CAM score on a point prevalence study was strongly associated with higher mortality at 6 months. It is also associated with an increased rate of discharge to a higher level of care at discharge. We did not show a significant difference in inpatient length of stay.

These findings are consistent with the results of previous trials.^{3,7-9,12,13,26,27}

This study is limited by the following factors:

- These figures are derived from a point prevalence study, meaning that for most patients only one assessment is taken during the entire admission. The assessment was done during office hours (0800hrs to 1600hrs) on weekdays. Given the fluctuating and evolving nature of delirium, this method is certain to have undercounted the incidence of delirium. This is likely one of the explanations as to why the prevalence of delirium in this study, which is 11.2% is relatively low by the standards of published studies.
- For the same reasons though it is also possible that those delirious patients we did detect were likely to be members of the subgroup who had a more prolonged delirium, which may help to explain the strong correlation with poor outcomes.
- Because we only analysed patients who were able to complete the assessment, it is likely that some of the patients were excluded due to communication difficulty secondary to active delirium. Once again, this would lead to a falsely low prevalence of delirium in this study. The exclusion of very unwell persons will also produce a bias towards a lower count.
- Our audit was not able to take into account differences in disease burden or frailty between the groups. Studies show that delirium is more common in frailer individuals and in individuals with higher comorbidity.^{35,36,37} The higher mortality rate and higher level of institutionalisation of the delirium group may be caused by increased frailty or disease burden.
- Similarly, as we did not evaluate cognition after the end of the trial we cannot say whether the lower MMSE found in the CAM-positive group represents a dementia or whether it is an effect of the delirium. As dementia alone is known to be associated with worse health outcomes in the older adults, the higher level of institutionalisation and mortality of the delirium group may be due to dementia.^{38,39}
- We did not differentiate between subtypes of delirium in this study. This differentiation may have assisted in the assessment of the outcome of inpatient length of stay as one study had shown that it is the hypoactive variant of delirium that results in longer length of stay.²²

A strength of the study is its representative patient population. The patients were all elderly individuals sampled on specific days from one medical, orthopaedics and rehabilitation ward. The results from this study are more generalisable to a busy acute hospital than studies studying single department presentation of medicine, ICU or emergency medicine.

An area of growing interest is the interaction between frailty and delirium and to determine if the deleterious outcomes often associated with delirium may be driven by frailty.^{35,37} The authors recommend future studies to utilise a validated frailty measurement indices such as the Studies of Osteoporosis Index or Cardiovascular Health Study Index to include frailty measures into the analysis.^{40,41} A multivariate analysis utilising various morbidities, including delirium as dependent variables may be able to provide guidance on whether frailty, disease burden or delirium contributes to the many deleterious outcomes that are associated with delirium.

In summary, based upon this study a single positive point prevalence CAM is associated with a markedly higher rate of mortality at 6 months and high risk of increase in level of care from admission to discharge, though not with length of inpatient stay.

The challenge of providing appropriate care for hospital inpatients who are increasingly elderly, frail, comorbid and likely to have cognitive impairment due to dementia or delirium is an international one.

We hope that this data will help emphasise the importance of delirium and its association with poor outcomes when planning for and providing hospital care in New Zealand.

Competing interests: Nil.

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ORIGINAL ARTICLE

Nicotine and toxicant yield ratings of electronic cigarette brands in New Zealand

Murray Laugesen

Abstract

Aims To analyse electronic cigarette (EC) brands available in New Zealand for nicotine and toxicant yield ratings.

Method Fourteen EC brands were analysed before and after nicotine exhaustion for nicotine and nine for major toxicants. Concentration of nicotine and aldehydes in vapour was measured and compared with the nicotine and aldehydes in the smoke of a Marlboro cigarette.

Results ECs labelled as high strength (16–18+ mg nicotine) contained 5–46 mg nicotine. Nicotine EC brands yielded 19–93 mcg nicotine per puff compared to 147 mcg per puff for Marlboro cigarettes, and emitted 200 times less toxic aldehydes (acetaldehyde, formaldehyde and acrolein) than Marlboro cigarette smoke. Compared with the first generation EC, study ECs emitted 73% less aldehydes. Diethylene and monoethylene glycol were not detected in vapour.

Conclusion ECs available in New Zealand in 2013 exposed users to higher levels of nicotine than in older brands but lower than cigarettes, and to far lower levels of toxicants than cigarettes and earlier ECs, indicating potential as safer substitutes for tobacco.

Electronic cigarettes (ECs) are battery-powered devices that generate an aerosol of propylene glycol and/or glycerol, usually with nicotine and flavours, from a cartridge or reservoir of solution ('e-liquid'), for inhalation (vaping). Unlike cigarettes, ECs do not combust tobacco—no smoke is involved.

Most ECs are cigarette lookalikes ('cigalikes'), some are disposables (lacking re-chargeability), and some are 'second-generation' models containing a larger tank that permits the user to refill with e-liquid, and a larger battery, with ability to alter power or voltage.

The original EC from which all subsequent ECs have evolved was invented in 2003 by a North Chinese pharmacist, Hon Lik, and developed into a marketable product by the Beijing-based company, Ruyan. Early research on this product conducted by the University of Auckland found that among smokers without prior EC use, the Ruyan EC produced reductions in cigarette craving and low levels of nicotine delivery into the bloodstream, comparable with the pharmaceutical nicotine inhaler.¹ Several laboratory studies of early ECs found toxic aldehydes, at levels far lower than in cigarette smoke.^{2,3}

In 2013, Bullen et al published a randomised controlled trial (RCT) comparing the cessation efficacy of Elusion brand EC popular in New Zealand (NZ) with nicotine and zero-nicotine cartridges, versus nicotine patches. This study suggested the EC at 6 months after quitting was at least as effective for sustained cessation as patches.⁴ To date, one other cessation RCT has confirmed this result.⁵ However, both trials were underpowered.

A recent Cochrane review included a meta-analysis of these studies, and concluded that the evidence for a cessation benefit compared with nicotine replacement therapy (NRT) was not sufficiently strong to change current regulations. ECs with nicotine, however, were more effective for cessation than ECs without nicotine.⁶

ECs have been available for sale in NZ since 2007 and have grown in popularity since, despite a regulatory regimen that treats nicotine as a medicine. Under the Medicines Act individuals may import ECs and e-liquid with nicotine for personal use only. If the EC or e-liquid contains nicotine or if therapeutic (i.e. cessation) claims are made then they cannot be sold. Nevertheless, ECs are widely available, although few retailers openly sell ECs. E-liquid with nicotine is thus generally purchased online from a range of overseas sources.

Remarkably, very little is known about the chemical composition of ECs available in NZ. In this paper I present findings from an analysis of 14 leading EC brands available in NZ in 2013.

Method

Selection of products—We selected 14 ECs based on probable origin—8 popular brands sold by importers direct from China, and 6 from the UK and USA based on popular brands promoted in e-cigarette forums. Nine were cigarette lookalikes with refill capacity, 3 were disposables (K, L, M in Table 1) which cannot be refilled, and two contained cartomisers (mouthpiece and nicotine reservoir) with a larger tank and battery (such as A and C in Table 1). “Mods” (modified by individual users) were not included.

We purchased products via the Internet from the distributors in 2013. Sales data for individual brands was not known due to the illegality of sales. All ECs were labelled as having high nicotine content (16–18 mg or higher) except for one with 14.5 mg, one with 11 mg and one with zero nicotine. Only tobacco flavour variants were tested. Brands were excluded if they lacked manufacturer information, if they failed to generate 150 puffs, or were expensive with no future access to refills.

Comparators—We compared the results from 2013 models of the products with those of the Ruyan classic V8 EC, tested in 2008 by Health New Zealand Ltd,³ and with those from testing in 2005 of the Marlboro king size filter cigarette, a globally known brand, by Labstat under Health Canada Intensive mode (one 55 mL puff every 30 seconds.⁷) To compare EC vapour with volume of puff from cigarettes we set mean daily cigarette consumption at 12 per day based on findings from a New Zealand study of manufactured cigarettes.⁸ We derived puffing parameters from Polish research⁹ but set puff duration longer at 3 seconds (not 1.8 seconds) to ensure ECs with heating coils slower to heat were included.

Selection of toxicants in vapour—Toxicants tested in the vapour were the volatile aldehydes: formaldehyde, acetaldehyde and acrolein; and the glycols (diethylene glycol [DEG] and monoethylene glycol [MEG]). We did not test tobacco-specific nitrosamines, as Goniewicz and other researchers who did so found nitrosamines NNN and NNK present in only trace quantities in 12 EC tested,⁹ similar to findings for nicotine gum and patches. We did not test for particulates as these have been found not to include the carcinogenic particulates found in diesel, cigarette or coal exhaust; nor for diacetyl.

Procedures—Labstat International ULC, Ontario, Canada, tested 9 of the EC brands for toxic aldehydes and glycols. The puffing parameters were derived from methods developed with Health Canada: 70 mL puff volume, inter-puff interval 10 seconds, puff duration 3 seconds, modified slightly from the Canadian Tobacco Reporting Regulations.¹⁰ Test ECs were vaped on a linear smoking machine. For nicotine and humectants, 60 puffs per brand were collected, and for testing of carbonyls, 150 puffs per brand were collected. Each EC was vaped in series of 15 puffs.

The first series of puffs, a priming series intended to ‘stabilise’ the EC deliveries, were vaped onto a pad that was subsequently discarded. After 5 minutes, the second series of 15 puffs was initiated, collecting the solids on a pre-weighed and conditioned pad, then repeated until a total of 60–150 puffs were collected on to the pad. Toxic aldehydes in vapour were analysed by passing the vapour through two impingers containing acidified 2,4-dinitrophenylhydrazine in acetonitrile. Impinger contents were filtered and diluted with trizma base in aqueous acetonitrile.

<http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2015/vol-128-no-1411/6483>

Table 1. Brands of e-cigarettes available and tested in New Zealand in 2013–2014

Brand and identifier		Nicotine concentration by label mg/mL	Nicotine container	Factory nicotine concentration mg/mL (as % fraction of label)	Nicotine concentration Unused mg/cartomisers	Nicotine concentration exhausted mg/cartomiser (CHL)	Nicotine concentration Used mg/cartomiser (CHL)	Number of 70 mL puffs (HNZ)	Nicotine per 70 mL puff Mcg
									CHL or Labstat
A	Elusion Ego	16	RC	17.85 (116)	22.1	6.5	15.6	194	80
B	Republic/ Citizen	18	C	13.95 (78)	N	N	N	252	20
C	Innokin SVD & Iclear 30	16	RC	15.2 (95)	45.6	32.1	13.5	145	93
D	Liberro Realis	18	CB	16.3 (91)	5	1.3	3.7	203	18
E	Easy Puff	18	C	14.7 (82)	12.7	8.3	4.4	225	20
F	Blu	14.5	C	13.2 (91)	7.0	3.5	3.5	194	18
G	Mirage Goldstar	18	C	20.8 (116)	26.7	12.7	14.0	307	46
H	Greensmoke	18	C	17.2 (96)	16.9	8.2	8.7	153	57
I	Elusion	16	C	11.5 (72)	8.6	2.3	6.3	194	32
J	Elusion Zero Nicotine	0	C	0	0	0a	0a	194	0
K	Vype	18.6	D	21.4 (115)	13.7	10.3	3.4	100	34
L	Republic/ Citizen	18	D	12.2 (68)	N	N	N	86	N
M	Elusion	11	D	9.0 (82)	9.0	4.5	4.5	266	17
N	KiwiCig	23	C	27.4(119)	22.5	8.8	13.7	270	51
<i>Average</i>				16.8 (94)	18.1	9.4	8.7	199	42.6

N= Not obtained. For average data we counted EC cartomisers containing 14 mg or more of nicotine. Brands B and L were removed from the NZ market in 2013. C= cig- look alike, rechargeable from a new battery. CB= cartomiser rechargeable from bottle. D= disposable, (not rechargeable). RC = Refillable clearomiser while on battery. Innokin was sold using the same high strength liquid as used in Elusion Ego.

High-performance liquid chromatography with ultraviolet detection (365 nm) was then used to achieve separation using a reverse phase C18 column (250×4 mm, 100, RP 18e) with a mobile phase gradient consisting of water, acetonitrile, tetrahydrofuran and isopropyl alcohol. To measure nicotine and its alkaloids in liquid, an entire EC cartomiser was transferred to a 15 mL glass culture tube, 10 mL of alkaloids extraction fluid added, the tube capped, then after 3 hours in a ultrasonic bath shaken by wrist action of 0.5 hours, analysis of the extract by gas chromatography with a thermionic specific detector equivalent to a nitrogen-phosphorus detector was undertaken. Separation was achieved using a fused silica coated column with base deactivated polyethylene glycol (PEG) stationary phase $30\text{ m} \times 0.25\text{ mm} \times 0.25$ micrometres.

At Health New Zealand Ltd (HNZ) total vapour volumes were estimated by suctioning standard puffs of 70 mL from the ECs, using fully re-charged batteries, syringe and leak-free three-way tap until no more visible mist was obtained.

Canterbury Health Laboratories, Christchurch, New Zealand (CHL) measured the nicotine content in each EC before and after exhaustion of the nicotine by suction. In cartomiser ECs, nicotine content was determined by dismantling the cartomisers and dissolving the nicotine in ethanol. Nicotine delivery per cartomiser was calculated as the product of nicotine per puff and the number of standard puffs.

Results

In Table 1 considering those labelled 14 mg or more, the mean nicotine value was 18.1 mg (range 5 mg–46 mg) per cartomiser, and after average 199 (range 100–307) puffs per cartomiser a mean 8.7 mg (range 3 mg–16 mg) was available to be used by the vaper before exhaustion. ECs had a nicotine mean value of 43 mcg per puff (range 18 mcg–93 mcg per puff). Puff volumes were highest for clearomisers and lowest for cigalike brands. Nicotine content per puff of Elusion Ego (80 mcg per puff) and Innokin (93 mcg per puff) was about one-half to two-thirds that of the 147 mcg of nicotine per puff from a Marlboro cigarette.

Table 2. Aldehyde yields from nicotine ECs in 2013, compared with Ruyan and Marlboro yields in previous years

Laboratory: Labstat Canada		Formaldehyde, (F) Acetaldehyde (Aa), Acrolein (Acr)						
E-cigarette brand name		As micrograms per litre (mcg/L) of vapour or smoke			As percentage of Marlboro toxicants yields			Mean
		F	Aa	Acr	F	Aa	Acr	
H	Greensmoke	2.50	1.52	1.90	2.1	0.1	0.9	1.0
E	Easy Puff	0.51	0.58	3.58	0.4	0.0	1.8	0.7
I	Elusion 16 mg	0.48	0.64	0.13	0.4	0.0	0.1	0.3
A	Elusion Ego	0.82	0.58	0.13	0.7	0.0	0.1	0.4
B	Republic	1.32	0.63	0.42	1.1	0.0	0.2	0.5
L	Republic Liberty disposable	1.46	0.58	0.42	1.2	0.0	0.2	0.8
F	Blu	0.56	0.58	2.39	0.5	0.0	1.2	0.2
G	Mirage Goldstar	0.70	0.58	0.13	0.4	0.0	0.1	0.2
D	Liberro Purity	0.48	0.64	0.13	0.6	0.0	0.1	0.2
<i>Average 2013</i>		1.07	0.81	1.06	0.93	0.04	0.43	0.48
Ruyan classic		1.47	5.52	3.77	1.3	0.2	1.6	1.05
Marlboro KSF		116	2282	231	100	100	100	100

Table 2 shows mean yields in the vapour for the toxicants formaldehyde, acetaldehyde and acrolein of around 1 mcg per litre of liquid. Mean aldehydes in the ECs were 73% lower on average than the same aldehydes tested in Ruyan EC vapour in 2008. A litre of Marlboro cigarette smoke in 2005

yielded over 100 times more formaldehyde, 2800 times more acetaldehyde and over 200 times more acrolein than the study EC brands. Propylene glycol (103 mg, range 63–149 mg per cigarette) exceeded glycerol (41 mg, range 23–103 mg per cigarette) in seven brands tested. DEG and MEG were below the level of detection (0.12% for DEG, 0.18% for MEG).

Discussion

Our analyses indicate that since 2008 the amount of nicotine in EC vapour has increased but is still lower per puff than that of a Marlboro cigarette. The ASCEND trial used a 2011 Elusion 16 mg cartomiser model,⁴ but by 2013 Table 1 shows eight brands had a higher nicotine content than the 2011 Elusion product. It is possible that if the ASCEND trial was repeated using current products the results for cessation might have been more impressive. We found differences between labelled and actual nicotine content. These highlight a lack of quality control that should be attended to through monitoring as part of a regulatory regimen.

The level of aldehydes in EC vapour has reduced over time and is 200 times lower than for the Marlboro cigarette. Formaldehyde concentrations for most brands were below the level at which mild sensory irritation in humans occurs (≥ 1 ppm) and at which respiratory tract cancer risks are considered very low.¹¹ The level of non-nicotine alkaloids is also low, making up 0.49% of the nicotine content of the liquid in the refills or bottles. This is similar to the findings of Etter et al in 2013.¹²

The levels of propylene glycol and glycerol vapour are of no great concern. Propylene glycol has been tested long-term in rats, primates and children with no marked adverse effect;³ glycerol is non-toxic. Importantly, no DEG was detected in any of the brands.

Diacetyl may be toxic but was not tested for. Metals were found to be under the limit found acceptable for use¹² but were not tested for. We did not test for particulates as these have been found not to include the carcinogenic particulates found in diesel, cigarette or coal exhaust.¹³

ECs are being used by many New Zealanders. A recent NZ Health Promotion Authority survey showed that 23% to 39% of respondents had used ECs (with the highest level among those who had quit or tried to quit recently), and 8–16% had used them in the past 2 weeks.¹⁴ These data and NZ research.^{1,4,13} suggest that ECs have potential to encourage smokers to switch from smoking cigarettes to using ECs, which the current study indicates are likely to be far safer.

Competing interests: Agencies which sold EasyPuff, Elusion, Greensmoke, and KiwiCig contributed to expenses of testing, as had Ruyan for 2008 samples. These contributions did not influence the design or conclusions of this study.

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VIEWPOINT

What should be the management policy for asymptomatic inguinal hernias?

Philip F Bagshaw

Abstract

Elective surgical repair was the general policy for the treatment of asymptomatic and minimally symptomatic inguinal hernias, based on reducing the risks of possible future bowel obstruction or visceral strangulation. Two randomised controlled trials in 2006 suggested that an alternative policy of "watchful waiting" was safe and appropriate. As a result, some health authorities in the UK withdrew funding for elective surgical repair for asymptomatic hernias in 2010. The long-term follow-up results of these two trials, however, showed high rates of surgery in the watchful waiting arms due to the development of symptoms. Two recent studies have called the watchful waiting policy into question on the basis of cost-effectiveness, quality of life and mortality data.

The current article shows the results of an Official Information Act request of the New Zealand Ministry of Health and the 20 District Health Boards on their current policies for the management of such hernias. The results show a range of policies, with two District Health Boards employing watchful waiting, seven with policies or health pathways that can restrict or deny access to treatment, and all District Health Boards required to comply with Ministry of Health performance indicators. It is concluded that, at least with some District Health Boards, patients with asymptomatic and minimally symptomatic inguinal hernias are given a lower priority for surgical treatment than they might merit on clinical grounds. Further research is needed to formulate appropriate policy for the management of this common disorder, and should perhaps be extended to cover other similarly common conditions.

Background

Until about 8 years ago it was generally believed by surgeons and the wider medical community in countries with Western-style healthcare systems that early Elective Surgical Repair (ESR) was indicated for inguinal hernias. The reasons were to reduce the associated pain for symptomatic hernias and the risks of the acute complications of bowel obstruction and visceral strangulation for all such hernias. These complications have high associated morbidity and mortality rates, even for asymptomatic and minimally symptomatic inguinal hernias.¹ These two groups are practically inseparable in routine clinical management. The general belief, however, was not based on a sound knowledge of the natural history of Asymptomatic and Minimally Symptomatic Inguinal Hernias (A&MSIH) or on cost, risk and benefit analyses of management options.

In 2006, two prospective Randomised Controlled Trials (RCTs) were published, which challenged this belief. One was from the USA the other was from the UK.^{2,3} They compared ESR with no surgery but a regular surveillance programme called Watchful Waiting (WW). They showed that, after follow-up periods of 2 to 4.5 years and 1 year respectively, the incidences of acute complications requiring emergency surgery were small, and concluded that WW is an acceptable option for men with A&MSIH. Furthermore, a cost-effectiveness analysis was also performed on the USA RCT participants at 2 years of follow-up.⁴ This concluded that WW is a cost-effective treatment for men with A&MSIH.

Around the same time, support for the WW policy came from another quarter. The replacement of sutured hernia repair techniques with the use of tension-free prosthetic meshes had already been shown to have produced a substantial reduction in hernia recurrence rates after both elective and acute surgery.^{5,6}

Following this important advance, attention shifted onto the issue of chronic postoperative pain after inguinal hernia surgery, which was shown to correlate with types of hernia repair materials, and with operative and patient-related factors.⁷ The claimed high incidence of such chronic pain added support for the WW policy for patients presenting with A&MSIH.

The results of the USA and UK RCTs, and concerns about chronic postoperative pain, led the European Hernia Society to publish guidelines recommending WW as the first-line management for A&MSIH in men.⁸ They did not, however, describe how this policy might be effectively implemented.

These developments were seized-on by some health administrators in the UK and elsewhere, who were aware that:

- (i) Inguinal hernias are very common;
- (ii) Up to one-third are asymptomatic or minimally symptomatic;
- (iii) Elective inguinal hernia repair is the most frequent operation performed by general surgeons; and,
- (iv) The need for such surgery will probably increase with future population aging.^{9,10} They therefore sought ways to reduce spending on this costly part of the health budget by having WW (as opposed to ESR) accepted as the policy for the management of A&MSIH. In 2010 this policy change was implemented by the clinical commissioners of the UK National Health Service, who withdrew funding for ESR for such hernias.¹¹

The new WW policy for the management of A&MSIH was also supported by an extensive literature review in 2011, which concluded that it is safe for fit men under 50 years of age, with signs for more than 3 months. This review also concluded that the WW policy is cost-effective but found no difference in chronic pain and quality of life measures between WW and ESR.¹²

The long-term follow-up results of the UK RCT were published in 2011; those of the USA RCT in 2013. The UK RCT reported on participants followed-up for a median of 7.5 years and found an estimated crossover rate of 72% from the WW arm to the ESR arm, mostly due to pain. The authors concluded that most patients with painless inguinal hernias develop symptoms over time, and therefore recommended ESR for medically fit patients with A&MSIH.¹³

After an additional 7 years of follow-up, WW randomised participants in the USA RCT had a high estimated rate of proceeding to ESR, 68%, mostly related to pain. Participants over 65 years had a higher rate again, 79%, compared to 62% for younger participants. There was also the need for a small number of emergency operations in the WW group but no associated mortality. The authors concluded that men who present with an inguinal hernia, even when minimally symptomatic, should be counselled that although WW is a reasonable and safe policy, symptoms are likely to progress and an operation will be needed eventually.¹⁴

Two recent studies have raised concerns about the WW policy. In 2013, a Swedish prospective study was published of participants having open inguinal hernia repair surgery showing that, at 12 months follow-up, 77.2% had less groin pain and 5.4% had increased groin pain. Overall, however, symptoms and quality of life measures improved in the majority of participants, and treatment was cost-effective regardless of pre-operative symptom severity. The authors criticised the USA and UK RCTs on the grounds that in the former trial only 10% of screened men were entered into the ESR arm, and that the latter trial only included men over 55 years of age.¹⁵

This year a retrospective study from the Birmingham and Solihull primary care trust in the UK was published, which defined some unintended consequences of the WW policy. It compared the outcomes for patients having inguinal hernia repair surgery during the 16-month period immediately

before a WW policy was introduced, with those having such surgery during the 16-month period immediately afterwards. The WW policy was associated with a higher incidence of adverse clinical outcomes after its implementation: overall adverse events 18.5% compared to 4.7%, emergency surgical repairs 5.5% compared to 3.6%, and higher mortality 5.4% compared to 0.1%.

Whilst conceding some weaknesses in their study design, and that their data did not establish a causal link between the WW policy and the adverse outcomes, the authors concluded that the policy may be putting patients at risk and might increase overall costs. They also criticised the USA and UK RCTs on the basis that the regular specialist surgical follow-up of participants in the WW arms, and high crossover rates to the ESR arms in both studies, indicated that they may not reflect ‘real world’ practice.¹¹

From these recent developments it appears that we have nearly come full circle. Certainly we know more about the natural history of A&MSIH than we did before. The evidence base for the WW policy is in doubt, however, and might become more so, as future advances in laparoscopic and open surgical techniques, and new repair materials are increasingly employed.¹⁶ Further research is clearly needed now to verify the results of the most recent studies and to formulate appropriate policy for the surgical management of A&MSIH.

New Zealand management policies

What are the implications for the management of A&MSIH in New Zealand? To investigate this issue the Chief Executive Officers of the Ministry of Health and the 20 District Health Boards (DHBs) were sent an Official Information Act request on 25 July 2014 asking the question: “..... whether the [Ministry of Health or DHB] has a policy for the management of asymptomatic inguinal hernias? If so, what is it, who was involved in developing it, and on what evidence was it based?”

Table 1. Responses from health authorities to Official Information Act requests on their policies for management of asymptomatic inguinal hernias (2014)*

Health authority (response dates)	Management policy for asymptomatic inguinal hernias	Those involved in policy development	Evidence base for policy
Ministry of Health (1 Aug)	No policy.	NIP	NIP
Auckland DHB (5 Aug)	No policy. Symptomatic and asymptomatic hernias seen and surgery offered if medically appropriate.	NIP	NIP
Bay of Plenty DHB (19 Aug)	From referral letters surgeons assign a clinical priority for an assessment. Not all asymptomatic hernia may have the same priority. This priority is matched to “financially sustainable threshold” criteria to be seen.	NIP	NIP
Canterbury & West Coast DHBs (20 Aug)	CDHB Health Pathways March 2014: “Christchurch Hospital does not usually take referrals for hernias unless they are large and significantly symptomatic e.g., persistently painful or causing difficulty with micturition”.	Health Pathways Document Owner: General Surgery Team	NIP
Capital & Coast DHB (27 Aug)	Patients referred are assessed against clinical assessment criteria. Where they do not reach threshold as with majority of asymptomatic hernias they are referred back to GP. GPs advised that should condition deteriorate or they have concerns, to re-refer back.	NIP	NIP
Counties Manukau (25 Aug)	All inguinal hernia referrals, including asymptomatic, seen. Treatment offered according to individual patient clinical criteria, risks and potential benefits.	Discussion with Clinical Head of General Surgery	NIP
Hawke’s Bay DHB (31 Jul)	No Policy.	NIP	NIP
Lakes DHB (12 Aug)	No policy.	NIP	NIP

MidCentral DHB (31 Aug)	Asymptomatic referrals which do not meet prioritisation score are referred back to GPs for re-referral if they become symptomatic.	NIP	NIP
Nelson & Marlborough DHB (15 Aug)	Adult Health Pathways: “these guidelines are clear that asymptomatic inguinal hernias do not require treatment and are declined unless other individual significant issues are related to this.”	Health Pathways Document Owner: General Surgery Team	NIP
Northland DHB (20 Aug)	Symptomatic referrals accepted but watchful waiting for A&MSIH.	NIP	NIP
South Canterbury DHB (25 Aug)	Aoraki Health Pathways for Adults, July 2012: “Hernias are low priority and may not be seen unless they are large and significantly symptomatic.”	Based on CDHB Pathways and reviewed by local surgeons to meet local requirements.	Ref ²⁰ cited.
Southern DHB (18 Aug)	No policy. Each case is assessed by a clinician and along with CPAC the treatment plan is made.	NIP	NIP
Tairawhiti DHB (19 Aug)	No policy. All hernia referrals seen whether symptomatic or asymptomatic. Surgery is offered to those that are medically appropriate.	NIP	NIP
Taranaki DHB (8 Aug)	No policy	NIP	NIP
Waikato DHB (4 Aug)	No policy. All referrals prioritised by clinicians. Surgery not offered for most asymptomatic inguinal hernias but referred back to GPs for re-referral if condition deteriorates.	NIP	NIP
Wairarapa & Hutt Valley DHBs (19 Aug)	No policy for either DHB. But Health Pathways for Hutt Valley DHB say “Publicly funded treatment is not currently offered for patients with: ▪ symptomatic inguinal or umbilical hernias ▪ asymptomatic hernias”.	NIP	NIP
Waitemata DHB (7 Aug)	No policy	NIP	NIP
Whanganui DHB (1 Aug)	Since 2008 a “watch and wait” approach.	“ .. in line with the policy developed by Waikato Hospital.”	Refs ^{2,3} & ⁴ cited.

Legend: *PDF copies of responses available from the author on request. NIP - No Information Provided. CPAC – Clinical Priority Assessment Criteria. CDHB – Canterbury District Health Board.

Table 1 shows a surprising range of management policies. At one end of the range there was access to assessment and possible surgery for patients with A&MSIH who were deemed medically appropriate, through an apparently middle ground of WW, to refusal to see and assess patients for treatment at the other end. What is not clear from these data, however, is whether what was claimed to be WW, included initial specialist assessment and regular appropriate clinical reviews thereafter or was, in practice, no different from refusal to see and treat.

Table 1 also points to some inconsistencies. For example, Wairarapa & Hutt Valley DHBs reported no policy but the latter had a version of Health Pathways, which made clear to general practitioners (GPs) that referrals for A&MSIH were not accepted. Hawke’s Bay DHB also reported no specific policy in their Surgical Referral Acceptance Guidelines and categorised “most abdominal hernias” as “Routine”, resulting in referral for ongoing assessment and management back to the patient’s GP. These data, however, do not show how many other DHBs had similar referral pathway constrictions and obstructions, and how much DHB policies differed from day-to-day practices. It is also noteworthy that Whanganui DHB’s “wait and watch” approach was said to be in line with Waikato Hospital policy, when the latter DHB claimed to have no policy.

Conclusions

It is easy to understand how this confused picture has arisen. DHBs find themselves in an invidious position in a perfidious environment. They are forced by central government to make short-term strategic decisions to reduce elective healthcare for non-life-threatening disorders to keep within budget whilst, at the same time, appearing publicly to still provide universal access healthcare. Until recently this was achieved by prioritisation through CPAC and financial thresholds.¹⁷ To this was added the National Waiting Times standards, as currently embodied in the Elective Services Performance Indicators, to which all DHBs must adhere.¹⁸ Recently Health Pathways have started appearing. These are supposedly helpful and educational. A real motivation, however, is to work hidden from public gaze “..... to alter the trajectory of demand”.¹⁹ The WW policy, by legitimising delay in treatment, fits well into this environment.

It is consoling to learn that we have not generally followed some UK authorities in accepting the WW policy for the management of patients with A&SMIH. Those of our DHBs who have embraced the policy, either overtly or covertly, should be aware that it is seriously in doubt. The story of the changing fortunes of the WW policy should teach us all the lesson that sudden policy changes in the management of common disorders should only be made on the basis of broad research findings, not on short-term outcome data. Also, all policies should be regularly reviewed in the light of new research findings.

Inevitably there will be speculation on whether there are similarly wide inter-DHB ranges of policies for the management of other common surgical disorders such as symptomatic cholezystolithiasis and haemorrhoids. If so, they might cause wide disparities in levels of access to treatment and clinical outcomes. Further research is needed to address these speculations.

Summary

Although only two DHBs indicated that they have adopted the WW policy, seven have declared policies or health pathways that can seriously restrict or deny access to effective surgical treatment, and all DHBs must comply with performance indicators laid down by the Ministry of Health. It is therefore likely that, at least in some DHBs, patients with A&MSIH are ascribed a lower priority, and are less likely to receive surgical treatment, than they might well deserve.

Competing interests: None.

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CASE REPORT

A rare case of anti-N-methyl-D-aspartate receptor encephalitis during pregnancy

Lai Wan Chan, Christer Nilsson, Jan Schepel, Christopher Lynch

Abstract

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis was first described as a severe form of encephalitis by Dalmau et al in 2006. This is an autoimmune disorder usually associated with paraneoplastic mechanism that manifests as neuropsychiatric disorder affecting mainly women of child-bearing age. Nevertheless anti-NMDA receptor encephalitis is a rare condition during pregnancy. To date, there have been only four reported cases during pregnancy.

We report a case of a 23-year-old primigravida in first trimester pregnancy with altered mental status and multiple neurological symptoms related to anti-NMDA receptor encephalitis. To the best of our knowledge, this is the first reported anti-NMDA receptor encephalitis during pregnancy in Australasia.

Anti-NMDA receptor encephalitis has been increasingly reported over the last decade, predominantly in young women harbouring ovarian teratomas. Removal of the tumour and immunotherapy often result in recovery. In all syndromes, deficits may be reversible despite the duration or severity of symptoms. This also holds true in patients who fall ill during pregnancy. The current literatures show that anti-NMDA receptor encephalitis can have good outcome for both the mother and new-born.

Case report

A 23-year-old primigravida in first trimester pregnancy presented with 3-day history of fever (38°C), acute confusion, disinhibited behaviour, auditory hallucinations and generalised body shaking without loss of consciousness. She had history of multiple suicide attempts but no previous history of psychosis or illicit substance use. At the time of onset, she also experienced extreme social stressors with recent demise of her grandfather.

The pregnancy unfortunately ended with miscarriage within 2 days of hospitalisation. She was treated initially as herpes simplex virus (HSV) encephalitis with poor response. A week after admission, she developed decrease level of consciousness with Glasgow coma scale of 6 requiring intubation and admission into intensive care unit (ICU). She also experienced increasingly dysautonomic symptoms and frequent limb dyskinesia. These symptoms were difficult to control despite high dose of sedatives (propofol, remifentanil, midazolam and isoflurane).

Cerebrospinal fluid (CSF) analysis showed leucocytosis $374 \times 10^6/\text{L}$, 94% lymphocytes, glucose 3.5 mmol/L (normal range: 2.8–4.4 mmol/L), protein 0.57 g/L (normal range: 0.15–0.45 g/L).

General culture, HSV DNA, varicella zoster virus (VZV) DNA and enterovirus RNA were negative. CT brain showed normal brain parenchyma. Brain MRI without contrast showed abnormal signal within the right hippocampus, cerebellar hemispheres and cerebellar vermis, which were hyperintense on T2 and FLAIR imaging. It was not associated with diffusion restriction.

Initial electroencephalogram (EEG) showed rhythmic slow delta waves of 2.5–3.5 Hz over both hemispheres. Repeat EEG showed widespread bilateral rhythmic and semi-rhythmic delta activities which were predominantly frontal.

Autoimmune encephalitis was considered after 12 days of hospitalisation. Serum NMDA antibody was positive confirming diagnosis of anti-NMDA receptor encephalitis. CSF was not tested. Initial pelvic and transvaginal ultrasound were unremarkable. A pelvic CT scan showed 2 cm right ovarian teratoma, which was subsequently removed. She was also treated with methylprednisolone,

plasmapheresis and rituximab. She received prolonged intensive care treatment for over 4 months requiring intubation and tracheostomy.

Five months post oophorectomy, she showed reduced general psychomotor status requiring walking stick to mobilise and slow language function. She continued to make good recovery and steady improvement. One and half years later, she is independent with mobility and able to converse in short sentences.

Discussion

Anti-NMDA receptor encephalitis is increasingly recognised as a multistage illness that progresses from psychosis, memory deficits, seizures, language disturbance to autonomic instability. Diagnosis of anti-NMDA receptor encephalitis is based on identification of antibodies in serum or CSF. The disorder predominantly affects young adults, particularly women (80%) of child-bearing age. The antibody subtypes (IgG1, IgG3) can cross the placenta raising concern about effects on the fetus during pregnancy.¹ Our patient's serum showed presence of NMDA receptor antibody. CSF was not tested.

Gresa-Arribas et al suggests that the sensitivity of NMDA receptor antibody testing is higher in CSF than in serum.⁶ The antibody titres in CSF and serum correlate with clinical outcome with higher levels in patients with poor outcome or teratoma than in patients with good outcome or no tumour.

There are four reported cases of anti-NMDA receptor encephalitis during pregnancy to date. All the cases had ovarian teratomas. In two cases, the pregnancies went to term with delivery of healthy babies. In one case, emergency caesarean section was performed at 32 gestation weeks with delivery of a healthy baby and the fourth case with termination of pregnancy in a patient with recurrent bilateral ovarian teratomas.¹

Previous case reports reported accelerated recovery after delivery or termination of pregnancy. Our patient miscarried in first trimester and she underwent prolonged recovery period which included 4 months of ICU stay.

The majority of cases with anti-NMDA receptor encephalitis are associated with neoplasm, especially germ cell tumour. Analysis of 400 patients confirms that the tumour is less likely to be detected in younger patients (age < 25 years).² In our patient, the initial pelvic and transvaginal ultrasound did not yield any abnormal findings.

Pelvic CT showed evidence of a right ovarian tumour. Prior to detection of the ovarian tumour, she was treated with methylprednisolone, plasmapheresis and rituximab. The current literature shows that patients who are treated with tumour resection and immunotherapy respond faster to treatment in comparison to patients without tumour who receive similar immunotherapy.

Recovery from anti-NMDA receptor encephalitis occurs slowly. Social behaviours and dysexecutive symptoms are usually the last to improve, preceded by several months of hospitalisations and rehabilitation. One and half years post-discharge, our patient is functioning well in the community and she is planning to resume her job as a caregiver.

This case highlights the importance of including anti-NMDA receptor encephalitis in differential diagnosis in young patients with acute psychosis. Early diagnosis and treatment can improve outcomes for this severe disease.

Competing interests: Nil.

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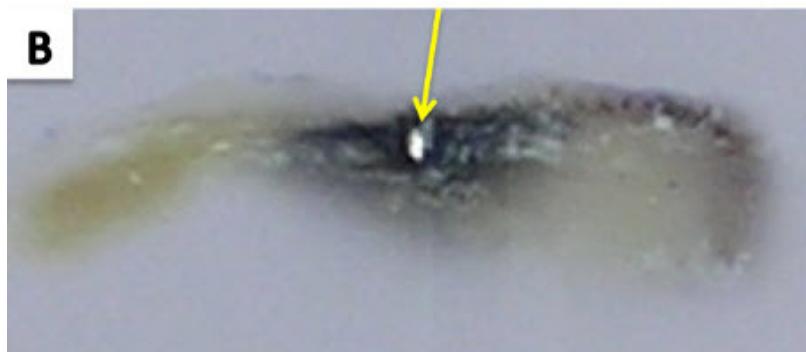
MEDICAL IMAGE

Metal pigmentation of gingiva

Makoto Adachi, Yasunori Muramatsu

A 45-year-old man was referred to an oral and maxillofacial surgery clinic with a black lesion on the gingiva at the lower left canine (Picture A). Two years earlier, his dentist pointed out the lesion when the patient received dental cleaning. This lesion was asymptomatic during the 2 years.

The intra-oral examination and assessment found that the black lesion was 4×4 mm in diameter. An excisional biopsy was performed under local anaesthesia and the small metal piece was found in the specimen (Picture B).



<http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2015/vol-128-no-1411/6485>

The final diagnosis confirmed that the mass was a metal pigmentation of gingiva. After surgery, the patient had no symptoms and there was no recurrence of the lesion. The differential diagnosis of black lesion of oral mucosa should be considered. It includes pigmented nevus and malignant melanoma.

Competing interests: Nil.

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LETTER

The Auckland Surgical Theatre Educational Environment Measure: does attending surgery benefit house officers?

Tary Yin, Stephen Child

Surgical knowledge, procedural and interventional skills form an integral part of the learning objectives for New Zealand house officers (prevocational doctors) however the role of the operating theatre in house officer learning is unclear.¹ This study aims to assess whether attending the operating theatre is perceived as beneficial by house officers utilising an easy to use and administer method.

The Surgical Theatre Educational Environment Measure (STEEM) was one of the first tools developed specifically for measuring the operating theatre learning environment.² This was validated on surgical trainees in the United Kingdom who rated their environment a mean overall score of 74.4%.² This research was subsequently reproduced with general surgical residents in Canada, medical students in the United Kingdom as well as Australian and New Zealand surgical trainees with similar scores.³⁻⁵

Subsequently, a condensed Mini-STEEM, was created after discovering that 13 out of 50 of the survey questions covered 73.2% of the total variance.⁶ Each of these studies were validated by demonstrating a high internal consistency and using exploratory factor analysis these studies were then able to divide their inventories into various subscales reflecting distinct areas of the surgical theatre educational environment.⁷

Our study utilised items from the mini-STEEM and full STEEM to construct a short 15-item, house officer-focused, Likert-type scale questionnaire called the Auckland Surgical Theatre Educational Environment Measure (ASTEEM; Appendix 1). For each Likert-type scale question, a score of 5 was given if the participant ‘strong agreed’, 4 if ‘agreed’, 3 if ‘uncertain’, 2 if ‘disagreed’ and 1 if ‘strongly disagreed’. For negative statements (questions 14, 15, 19, 20, 24, 25 and 26), the scoring was reversed. An overall total score and three subscale scores were calculated based on the mini-STEEM’s subscales.⁶

In addition, 11 questions preceding the ASTEEM were included (Appendix 1 & 2) which asked about gender, level of training, district health board, current run, run experiences, New Zealand Curriculum Framework procedural learning outcomes achieved, opportunity to admit undifferentiated patients, belief in added educational value in going to theatre, theatre attendance, career intention and primary trainer.¹

This questionnaire was distributed to house officers using SurveyMonkey (SurveyMonkey Inc.), an online survey development website. House officers undergoing surgical runs at all Auckland hospitals were included (Waitemata District Health Board, WDHB; Auckland District Health Board, ADHB; and Counties Manukau District Health Board, CMDHB).

86 of 183 (46.99%) house officers working in surgical attachments responded, of which 84.88% had attended a case in theatre by the end of their attachment with 81.40% having completed ASTEEM as well. There were equal numbers of male and female respondents with postgraduate year one (PGY1) house officers making up the largest proportion (47.67%) followed by PGY2 house officers (39.53%).

84.88% of respondents attended the operating theatre during their run with 87.21% believing that there was added educational value in going to theatre. The mean overall score of the ASTEEM was 68.76% which compared similarly to previous surgical theatre educational environment measures.²⁻⁶ See Table 1.

Table 1. ASTEEM results

Subscales	Score	Questions
Good surgical operating experience	56.2%	Before the operation my trainer discusses the surgical technique planned 3.19/5 I get enough opportunity to assist 3.27/5 I am usually too busy doing other work to go to theatre 1.97/5
Friendly atmosphere in theatre	75.7%	My trainer is enthusiastic about teaching 4.17 The theatre staff are friendly 3.85/5 There are enough theatre sessions per week for me to gain the appropriate experience 3.25/5 The atmosphere in theatre is pleasant 3.81
Discrimination against me	81.3%	The anaesthetists put pressure on my trainer to operate himself to reduce anaesthetic time 3.47 I feel discriminated against in theatre because of my gender 4.29/5 I feel discriminated against in theatre because of my ethnicity 4.44/5
Questions from the full STEEM		I get on well with my trainer 4.33/5 The nursing staff dislike it when I operate as the operation takes longer 2.91/5 My trainer's surgical skills are very good 4.53/5 I get bleeped during operations 1.89/5 When I am in theatre, there is nobody to cover the ward 2.14/5

A Mann-Whitney test was then performed to compare ASTEEM scores between house officers with surgical versus non-surgical career intentions. In total there were 31 house officers who had surgical career intentions and 39 house officers who had non-surgical career intentions. House officers interested in surgery rated their surgical educational environments significantly higher overall (72.43% versus 65.84%, p=0.006) as well as in the ‘friendly atmosphere in theatre’ subscale (80.95% versus 71.55%, p=0.002). See Table 2.

Table 2. ASTEEM scores comparing house officers with surgical career intentions versus non-surgical career intentions

Variable	Surgical n=31	Non-surgical n=39	P-value
Total score	72.43%	65.84%	0.006
Good surgical operating experience	58.93%	54%	0.185
Friendly atmosphere in theatre	80.95%	71.55%	0.002
Discrimination against me	83%	80%	0.521

A high percentage of surgical house officers achieved the New Zealand Curriculum Framework procedural learning outcomes of: managing common complications (95.35%), monitoring and managing patients postoperatively (94.19%) and being able to explain indications and contraindications for common procedures (90.70%). However procedural skills including wound dressing, simple skin lesion excision and wound debridement were very poorly achieved at 37.21%, 25.58% and 20.93% respectively.¹

Our study suggests that attending the operating theatre is perceived as beneficial by most house officers irrespective of career intention and that the operating surgical theatre environment is positive to their learning experience. It should be noted that our sample size precludes subgroup analysis and that we have no validation of our modified ASTEEM. Nevertheless, our results compare favourably to previous STEEM and mini-STEEM studies suggesting reliability.²⁻⁶

<http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2015/vol-128-no-1411/6486>

In addition, it was noteworthy that while 84.88% attended theatre, New Zealand Curriculum Framework procedural learning outcomes of managing common complications, monitoring and managing patients postoperatively and being able to explain indications and contraindications of common procedures were met by over 90% of respondents.

Educational environments should be monitored regularly and this survey provides a simple method to audit the effects of any interventions implemented.⁷ It is also the first house officer-focused tool for assessing the operating theatre educational environment to our knowledge.

(Ethics approval for this study was granted by the Auckland District Health Board Ethics Committee.)

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Appendix 1. Survey (page 2); including 15 Likert-scale type questions (questions 12–26)

Please continue only if you have attended a theatre case during this run. If not, you may stop here, thank you for your participation.

11. When in theatre, who provided you with the most 'training'?
 Consultant
 Fellow
 Registrar

Please indicate whether you strongly agree (SA), agree (A), unsure (U), disagree (D) or strongly disagree (SD) with each of the statements below by circling the appropriate response. Your answers should reflect the situation in the operating theatre at your current post. 'My trainer' in the statements below refers to the consultant, fellow or registrar who provided you with the most 'training'.

12. I get on well with my trainer	SA	A	U	D	SD
13. My trainer is enthusiastic about teaching	SA	A	U	D	SD
14. The anaesthetists put pressure on my trainer to operate himself to reduce anaesthetic time	SA	A	U	D	SD
15. The nursing staff dislike it when I operate as the operation takes longer	SA	A	U	D	SD
16. Before the operation my trainer discusses the surgical technique planned	SA	A	U	D	SD
17. My trainer's surgical skills are very good	SA	A	U	D	SD
18. I get enough opportunity to assist	SA	A	U	D	SD
19. I feel discriminated against in theatre because of my gender	SA	A	U	D	SD
20. I feel discriminated against in theatre because of my ethnicity	SA	A	U	D	SD
21. The atmosphere in theatre is pleasant	SA	A	U	D	SD
22. The theatre staff are friendly	SA	A	U	D	SD
23. There are enough theatre sessions per week for me to gain the appropriate experience	SA	A	U	D	SD
24. I get bleeped during operations	SA	A	U	D	SD
25. I am usually too busy doing other work to go to theatre	SA	A	U	D	SD
26. When I am in theatre, there is nobody to cover the ward	SA	A	U	D	SD

Thank you for completing this survey

Appendix 2. Survey (page 1)

The Auckland Surgical Theatre Educational Environment Measure

1. Are you?
 Male
 Female

2. Level of training
 PGY1 HO
 PGY2 HO
 PGY3 or above HO - please specify year: _____

3. District Health Board
 Waitema DHB
 Auckland DHB
 Counties Manukau DHB

4. Current run
 Cardiothoracic Surgery
 General Surgery
 Neurosurgery
 Orthopaedic Surgery
 Otolaryngology Head and Neck
 Plastic and Reconstructive
 Urology
 Vascular Surgery
 Obstetrics and gynaecology
 Paediatric Surgery
(specify subspeciality below)
 Other - please specify: _____

5. Have you previously completed this run as a house officer?
 Yes
 No

6. Which of the following proposed NZCF (New Zealand Curriculum Framework for Prevocational Medical Training) procedural and interventional learning outcomes for PGY1 and PGY2 were you able to achieve during this run?
 Explain indications and contraindications for common procedures
 Monitor the patient and provide appropriate aftercare
 Identify and manage common complications
 Administration of local anaesthesia
 Scrub, gown and glove
 Simple skin lesion excision
 Surgical knots and simple wound suturing
 Suture removal
 Wound debridement
 Wound dressing

7. On this run I had the opportunity to review an undifferentiated patient new to my service
 Frequently
 Occasionally
 Never

8. Do you believe that there is added educational value in going to theatre over and above performing ward work, going to clinic etc?
 Yes
 No
 Please explain:

9. Did you attend a theatre case during this run?
 Yes
 No

10. Career intention - tick one only
 Medicine/specialty medicine
 Surgery/specialty surgery
 General practice
 Mental health
 Emergency
 Intensive care
 Anaesthetics
 Radiology
 Paediatrics
 Pathology
 Don't know
 Other - please specify: _____

2 of 3

100 YEARS AGO

WW1: Prices of Drugs

Editorial published in *NZMJ* 1914 September;13(55):323–324.

WELLINGTON, SEPTEMBER, 1914.

THE widespread ramifications of the war are perhaps in no respect more marked than in the effect that they are having, and are likely to have, on the supplies and prices of many varieties of drugs and other surgical requisites which form an indispensable part of the equipment of hospitals and dispensaries.

The needs of the large armies now operating in Europe have already had the effect of greatly curtailing the supplies of many drugs, required for both surgical and medical purposes. Statements criticising the action of wholesale druggists in advancing the prices of certain drugs have recently been published, and a reply to those has been made by the manager of one of the Auckland wholesale establishments. "There are hundreds of lines which have not been advanced more than 10 per cent," a *Herald* interviewer was informed, "but there are many other lines of which fresh supplies cannot be obtained. These naturally have become very valuable, and high prices are being paid for them. We do not think that the retail chemists have quite grasped the seriousness of the position, or that they realise on how many drugs the embargo of the prohibition of export has been placed by the Imperial Government. Our firm spent about £100 in cables to London, America, and Australia in endeavouring to secure drugs which are urgently needed, and to obtain the latest information from the source of supplies."

One of the cablegrams which we received from London states that the export of cotton wool, lint, cellulose wadding, bandages, gauzes, and fine chemicals has been prohibited. Another London cable states that the export of the following articles has also been prohibited:—Iodides and bromides of potassium, soda and ammonia, salts of morphia, cocaine, formalin, chloroform, carbolic acid, citrates, mercurial salts, bismuth preparations, opium, belladonna, nux vomica, and quinine.

A message from New York states that bromides of potassium, soda and ammonia are unobtainable, and that the stocks of carbolic acid are exhausted. Enquiries sent to Sydney produced replies stating that bismuth, ether, carbolic acid, bromide of potassium, salicylate of soda, salol, sulphonal, phenacetin, trional, vernal, novaspirin, protargol, and aspirin cannot be supplied from that source.

Enquiries addressed to New York did not produce encouraging replies. One message states that the price of peroxide of hydrogen, which is largely used for antiseptic purposes, had advanced 75 per cent., whilst a later message intimated that "the largest peroxide factory has closed down owing to its being unable to secure the raw material." This raw material is peroxide of barium, and Germany is its source of supply. Cables, it is stated, have been received in Sydney confirming this statement. A cablegram from the New York house of a well-known German chemical firm states that the chemicals manufactured by this firm can be supplied at an advance of from 100 to 300 per cent on ordinary prices.

Another message quoted, which came from London, also shows how greatly the war is affecting supplies of anaesthetics, creosote, olive oil, and disinfectants, the export of all of which has been prohibited. "No shipments from Marseilles during the war," is an addendum to this message. The same authority states that advices had been received to the effect that morphia, the supply of which was mainly dependent upon America, had advanced over 50 per cent. in price in America, and that it would probably advance much more.

No chloroform is obtainable in Australia, and it was stated that it was doubtful whether any more could be obtained from America. In the case of one particular drug it was stated by the informant that whereas his firm was recently selling it at 3s. 6d. a pound it was unable to obtain any in New Zealand even by offering to pay 14s. a pound for it. "The outlook in regard to the lines referred to," he added, "is certainly serious, and the only way in which we can protect ourselves and the medical profession if by husbanding our stocks and only allowing small supplies to go out to each customer. Doctors, of course, will have to be very careful in the use of these drugs."

METHUSELAH**Biodegradable stents and coronary artery disease?**

Despite rapid dissemination of an everolimus-eluting bioresorbable scaffold for treatment for coronary artery disease, no data from comparisons with its metallic stent counterpart are available. This multicentre international trial aims to compare these two techniques.

501 patients were randomly assigned on a 2:1 ratio to be treated with a bioresorbable scaffold stent (335 patients) or a metallic stent (166 patients). Both stents were associated with very low and similar mortality at 1 year. Three patients in the bioresorbable group had definite or probable scaffold thrombosis compared with none in the metallic stent group.

The researchers concluded that the everolimus-eluting bioresorbable scaffold showed similar 1-year composite secondary clinical outcomes to the everolimus-eluting metallic stent. An editorial commentator commended the study but noted that non-inferiority is not a powerful motivation to switch from the well tested and cheaper metallic stent.

Lancet 2015;385:10–12 & 43–54.

Effects of dietary education in treated gout patients

This study aims to investigate the influence of dietary education in patients with gout on a stable dose of urate-lowering therapy (ULT). Thirty patients with a history of gout who were receiving an appropriate and stable dose of ULT were randomised into two groups. The control group was advised on the importance of compliance with therapy and the benefits of weight loss. The intervention group received comprehensive dietary advice. The advice recommended: (i) reducing red meat intake, and avoiding offal, shellfish and yeast extract; and (ii) including low fat dairy products, vegetables and cherries and the potential benefit of coffee and vitamin C.

Serum urate estimations were done at baseline, 3 and 6 months. There was no significant difference in the urate levels of the two groups. Moreover, there was no difference in the incidence of clinical flares in the two groups.

Internal Medicine Journal 2015;45:189–194.

Preeclampsia in kidney donors

Each year, more than 27,000 persons worldwide become living kidney donors; the majority are women. Young female donors frequently ask whether kidney donation will affect future pregnancies. The evidence from previous studies has produced conflicting results.

This report concerns a retrospective cohort study of living kidney donors involving 85 women (131 pregnancies after cohort entry) who were matched in a 1:6 ratio with 510 healthy nondonors from the general population (788 pregnancies after cohort entry). The primary outcome was a hospital diagnosis of gestational hypertension or preeclampsia. Other maternal and fetal outcomes were noted.

Gestational hypertension or preeclampsia was more common among living kidney donors than among nondonors (occurring in 15 of 131 pregnancies [11%] vs. 38 of 788 pregnancies [5%]). There were no significant differences noted between the two groups in the rates of preterm birth or low birth rate. There were no maternal deaths, stillbirths or neonatal deaths in the donor cohort.

N Engl J Med 2015;372:124–133.