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The role of CT pulmonary angiography in patients with suspected pulmonary embolism admitted to general medicine
P Chin, M Hurrell, D McGregor, L Beckert

This audit, performed at Christchurch Hospital, reviewed how effective computed tomography (CT) lung scans were for patients admitted to General Medicine with suspected blood clots (pulmonary emboli) in the lungs. After some consideration, these scans are usually done using a risk-scoring system based on symptoms, blood tests (D-dimer), and plain lung X-rays. This audit shows that blood tests (D-dimer) and plain radiographs were used appropriately but there is room for improvement in the use of the scoring systems. Indeed, the management of suspected pulmonary emboli could be improved; and it is likely that after-hours CTs could be reduced.

Aggressive acts by patients against general practitioners in New Zealand: one-year prevalence
C Gale, B Arroll, J Coverdale

We asked New Zealand general practitioners (GPs) if they had experienced aggression from patients in the previous year (2002). We found that 15% had been verbally abused, 11% had been intimidated, 7% had harassment by means of a formal complaint, 6% had been sexually harassed, 3% had been physically attacked, 1.9% had been stalked, and 0.8% had been injured. Men were more likely to be assaulted, and women were more likely to be sexually harassed. In the week prior to completing our survey, 35% of GPs had a symptom of distress, but less than 1% had severe distress. We suggest that these types of events are workplace hazards for GPs.

Psychosocial variables as prognostic factors in metastatic cancer: a brief review
C Paton, D Perez

Many people believe that survival from cancer can be influenced by psychological or social (i.e. psychosocial) factors. This review examines whether psychological coping style, psychosocial interventions, social ties, and quality of life can influence outcome in patients with advanced cancer. Studies suggest that medical factors exert a stronger influence on survival than psychosocial factors. However it is noted that psychosocial interventions can improve the psychological health of patients. Limitations of previous studies and directions for future research are also discussed.
Using the COPE assessment tool with informal carers of people with dementia in New Zealand
H Roud, S Keeling, R Sainsbury

Following the development of the COPE (Carers of Older People in Europe) Index, this Christchurch study explores the value of health practitioners using the Index to initiate discussions on how family carers of older people with dementia perceive their own health and wellbeing as well as sources of support. The study concludes that the COPE Index is an easily administered and generally acceptable tool that may be useful for initiating more comprehensive assessment of dementia carers’ needs. It is hoped that improved communication between informal carers and health service providers will support public policies, which promote “ageing in place”.

Atypical antipsychotic use for adult outpatients in New Zealand’s Auckland and Northland regions
A Wheeler

With regards to people attending community mental health centres in Auckland and Northland in 2004, this paper outlines the prescribing patterns of antipsychotic medications that are used to treat their mental health problems such as schizophrenia. Most people were treated with a single antipsychotic, and the newer atypical antipsychotics (risperidone, olanzapine, quetiapine, and clozapine) were the preferred treatment. They were being used primarily for psychotic disorders such as schizophrenia. (Atypical antipsychotics medications have less severe side effects than the older medications.) Clozapine, which is used for people who have not responded to other antipsychotics, was prescribed for a third of people with schizophrenia, which is in line with estimates of treatment-resistant illness. In summary, this study found that antipsychotics are being prescribed in a way that is consistent with clinical practice guidelines.
When does a specialist assume the “duty of care” for a patient? The significance of Case 04HDC13909

Frank Frizelle

According to a recently realised decision by the Health and Disability Commissioner (HDC) on the care of a urology patient at Southland Hospital, a specialist assumes the “duty of care” for a patient when they receive the referral letter.

This aspect of care has now been clearly defined, and it is important to most doctors practising clinical medicine. The Commissioner’s report states:

It is well recognised within the health sector that there is insufficient public funding to meet the immediate health needs of all New Zealanders. It is inevitable that not all patients who require treatment will be able to be seen, and some patients may spend a significant time period waiting to be assessed and treated in the public sector. In this environment, it is essential that patients waiting for assessment and treatment in the public sector receive appropriate care and management until such time as they are able to be seen.¹

He then goes on to say,

…[this decision] explores the responsibilities of providers in the management of patients waiting for a First Specialist Assessment (“FSA”) in the public system. In particular, it examines the relative responsibilities for the prioritisation and ongoing management of patients waiting for FSA appointments, and the systems that should be in place to ensure that patients do not fall through the cracks.¹

Many clinicians believe that the responsibility for not seeing the patient lies with the district health board (DHB) or Government for not providing the resources for the patient to be seen. They are right to a point, as the HDC report states:

…under the Ministry of Health national service specification, DHBs had a duty to develop, implement, and manage booking systems for all medical, surgical, and diagnostic services. If DHBs could not meet the ongoing demand for specialist assistance and advice within 6 months of referral; the specification required DHBs to prioritise referrals; notify referrers and patients of the ability or inability to provide services within the minimum standard of 6 months; and provide referrers with information that indicated the level of need or priority that could be serviced, together with referral or management guidelines to enable general practice to manage the patient’s plan of care and review or reassess the patient’s condition as appropriate.¹

However at the individual patient level the clinician has a responsibility that cannot be abdicated. This is what has been defined by the Commissioner in his report, when he states:

A clinician does not have to be in direct contact with a patient to owe that patient a duty of care, and a clinician can accept a patient into his or her care without ever seeing that patient, a specialist assumes responsibility for a patient for the purposes of establishing a duty of care when the information in the referral letter is considered, and a priority allocated.¹
The intriguing aspect of this HDC report is that the above statement is referenced to a discussion document released by Dr David Geddis—Aspects of a Doctor’s Duty of Care.² This controversial discussion document appears not to have been accepted by many professional groups. Dr Geddis wrote this document for the Medical Advisers Group as a private individual before he started work for the Ministry of Health. It was firmly rejected by the Council of Medical Colleges and the New Zealand Medical Association who were both sufficiently concerned about the document for the Chairman to inform the then Director General of Health, Dr Karen Poutasi.³ It is of great concern that this document, of uncertain status, has become a document of record because the Commissioner has used it as a critical part of his argument.

Of course the Commissioner is correct in going on to point out the reality of the system we work in with his comments:

Doctors have a responsibility to ensure that the process for assigning priority is appropriate. Referrals to a service with limited resources should be seen in order of priority and a patient should receive treatment in accordance with his or her assigned priority. Prioritisation systems should be fair, systematic, consistent, evidence-based, and transparent.

These comments are entirely consistent with the New Zealand Medical Council’s own statement on “Safe Practice in an Environment of Resource Limitation” of which some points are outlined below


- A service has a duty to ensure that only those referrals that can be seen within the resources available (including time, staffing, and physical resources) are accepted.
- As far as possible, assessment should fairly establish the patient’s priority for treatment compared to that of other patients.
- Doctors have a responsibility to ensure that the process of assigning priority is appropriate. Referrals to a service with limited resources should be seen in order of priority and a patient should receive treatment in accordance with his or her assigned priority. Prioritisation systems should be fair, systematic, consistent, evidence-based, and transparent.
- Doctors making a referral to a service he or she knows to be constrained should try to ensure that the referral contains all the information needed to ensure a fair assessment of the patient’s priority.
- A doctor who receives a referral which does not contain the information required to make a fair assessment, should request the relevant information or return the referral to the referrer with a request for more specific information.
- All referrals must be met with a timely and appropriate response.
- A service or team making a decision about the management of a patient is responsible for the effects of making that decision.
- A doctor who has a patient in a booking system for treatment, should advise that patient, to the best of their ability, how long they could expect to wait for
treatment and must notify the patient if his or her priority changes. It is
acknowledged that managing acute services in conjunction with elective services
can sometimes make this difficult. The booking system must be accurately
portrayed and must not be misused to shift patients from a doctor’s care.

However it now appears that the waiting-list situation may have deteriorated to the
point where, despite patients being correctly prioritised, patients with significant
degrees of illness can’t get treated in the public sector in reasonable timeframes.

The previous Minister of Health stated in the NZMJ\textsuperscript{4}:

\begin{quote}
If DHBs are not providing timely services, they need to account to the Ministry of
Health and the Minister for the reasons. Sometimes, for example, workforce
shortages or industrial action make it more difficult, but DHBs are expected to take
all action to meet their signed agreements with the Minister. At times, this can
include use of the private sector…the Minister and Ministry can only take rapid
action to address problems if they are kept informed of the latest issues…(The
Minister) is keen for DHBs to be more proactive in terms of identifying potential
problems so they can be averted.\textsuperscript{4}
\end{quote}

With this in mind, one of the most significant activities of the DHBs has been to
remove patients from the waiting lists. A total of 8108 patients were removed from
surgical waiting lists between January 2005 to January 2006.\textsuperscript{5} In the last few months
there have been many more reports of the removal of large number of patients from
waiting lists. However the DHBs do not seem to be responsible on an individual
patient basis—the doctor is—and a DHB’s response is to remove people from the
waiting list to fulfil the ministerial agreements about achieving manageable waiting
lists.

The only time DHBs appear to become involved with individual patient care is when
the patient complains via the media, their Member of Parliament, or the Minister of
Health.

So, in summary, doctors have been made responsible for a job, without being given
the tools to do it.

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Improving the use and interpretation of diagnostic tests in pulmonary embolism

Sarah Aldington, Geoffrey Robinson, Richard Beasley

The investigation of patients with suspected pulmonary embolism (PE) is fraught with difficulties, with clinical assessment and diagnostic tests often inadequately used and interpreted as evident from a recent New Zealand study.¹ It is likely that the difficulties are mainly due to a lack of understanding and familiarity of the principles of diagnostic tests in clinical practice.

In this editorial we briefly consider an evidence-based approach to the use and interpretation of diagnostic tests,²-⁴ using PE as an example.⁴-⁶

This approach requires an understanding of:

- Properties of diagnostic tests;
- Bayesian theory;
- Decision analysis; and
- Integration into an algorithm (their application to clinical medicine)

Properties of diagnostic tests

The properties of a diagnostic test in terms of sensitivity and specificity are traditionally shown as in Figure 1,⁵ from which the following observations can be made:

- There is an inherent trade-off between sensitivity and specificity; a cut-off point is usually chosen which is considered most appropriate to guide decision-making.
- Different cut-off values (to define “normal” or “abnormal”) may be used depending on whether one attempts to confirm a disease through a positive result (high specificity) or to rule out the disease via a negative result (high sensitivity).
Figure 1. The properties of plasma D-dimer measurements in the diagnosis of pulmonary embolism

The numbers in brackets represent different D-dimer level cut-off values. In patients presenting with symptoms of pulmonary embolism (PE), a D-dimer cut-off value of 500 µg/L has high sensitivity (a value <500 µg/L effectively rules out PE) but low specificity (less than half of patients with a value >500 µg/L have a PE). Using higher cut-off values improves the specificity but at the expense of sensitivity to the extent that the D-dimer test loses its clinical utility [reproduced from reference #5].

Bayesian theory

The application of Bayesian theory to clinical medicine requires that the results of any test are not considered in isolation but are interpreted in conjunction with all other information that is available concerning the patient. In practice, this requires an estimation of a pre-test probability from the pre-existing patient information and knowledge of the disorder under consideration. The test is then undertaken, from which a post-test diagnostic probability is calculated based on the pre-test probability and knowledge of the properties of the test.

The results of Bayesian analysis are usually expressed in graphic form, as shown in Figure 2.
Figure 2. Relationship between pre- and post-test probability for (a) lung scan → (b) D-dimer → (c) ultrasound through graphic representation of Bayesian theory

The probability of a pulmonary embolism is determined by the pre-test clinical probability and the results of the different tests, for which the properties are known. A single test result will yield different probabilities in patients with different pre-test probabilities.

The shaded area in each diagram represents the range of post-test probabilities for which pulmonary angiography should be performed, if the test under consideration is the only available test, or the last in a sequence of tests. This range has been determined by decision analysis from which it has been calculated that the test threshold is around 5% and the treatment threshold is around 45%.

In this example, a patient with suspected PE (moderate clinical probability estimated 50%) is investigated initially with a V/Q scan which is low probability, yielding a post-test probability of around 30%. This becomes the pre-test probability for the next test (D-dimer) which is positive, resulting in a post-test probability of around 40%. This becomes the pre-test probability for the next test (ultrasound) which is negative, resulting in a post-test probability of around 20%.

Through decision analysis it is evident that the preferred approach is to now undertake pulmonary angiography as the probability is sufficiently low not to warrant treatment and sufficiently high not to be able to rule out a PE. [Reproduced from reference #6]
Several observations can be made:

- The same test result may lead to an entirely different post-test probability of a diagnosis, depending on the pre-test probability—i.e. it is necessary consider the test results in conjunction with the clinical situation.

- In a situation of very high or very low pre-test probability, a test is unlikely to be informative—i.e. if there is either no real clinical suspicion for undertaking the test or if the diagnosis has essentially been confirmed, a further diagnostic test is unlikely to be helpful.

- It is not possible to properly interpret results of tests without knowing their basic properties.

**Decision analysis**

Once the post-test probability has been determined, the next step is to decide whether the probability is sufficiently high to confirm the diagnosis and treat (treatment threshold), sufficiently low to exclude the diagnosis (test threshold), or intermediate in which case a further diagnostic test is required. This involves the process of decision analysis in which the preferred course of action has been calculated mathematically, and made available to the clinician.

The test and treatment thresholds are dependent on a balance between the severity of the untreated disease, the efficacy of treatment, the risks associated with both the treatment and invasive tests, and the properties of the test. These factors need to be considered when clinicians assess the requirement for further investigation or treatment.

As shown in Figure 2, the use of decision analysis enables the post-test probability to be used in a meaningful way as the basis for deciding the best approach for further investigation and treatment of a patient with suspected PE.

**Integration into an algorithm**

Finally, the properties of diagnostic tests, their application through Bayesian theory, and decision analysis can be brought together in the format of an algorithm. An algorithm presents a practical diagnostic and treatment pathway. The algorithm currently in use at Wellington and Kenepuru Hospitals for the assessment and management of PE or DVT is shown in Figure 3.

Doctors need to understand the basic principles presented in this review to ensure that they use and interpret investigations appropriately. These principles are particularly helpful in the investigation of patients with suspected DVT or PE.

We recommend the implementation of an assessment and management algorithm for suspected DVT and PE in emergency departments in New Zealand.
Figure 3. The algorithm for the investigation and management of patients with suspected DVT or PE used at the emergency departments at Capital & Coast District Health Board

1. If radiology is unable to provide the required investigations acutely, the patient can be managed as an outpatient if they have a DVT, are clinically stable, have received the first dose of LMWH and follow-up has been arranged.
2. A VQ scan is an alternative to CTPA if the chest X-ray is normal.
3. If the symptomatic limb is abnormal on ultrasound, then the other limb should also be investigated.
4. This algorithm should not be used as a substitute for a thorough history, examination and clinical judgement.
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The role of CT pulmonary angiography in patients with suspected pulmonary embolism admitted to general medicine

Paul Chin, Mike Hurrell, David McGregor, Lutz Beckert

Abstract

Background CT pulmonary angiography (CTPA), D-dimer testing, and pre-test probability scoring have greatly improved the ability to manage patients with suspected pulmonary embolism. International guidelines suggest combining these investigations for the best yield. We have been investigating the use of CTPA in patients with suspected pulmonary embolism (PE) admitted to the Department of General Medicine at Christchurch Hospital, New Zealand.

Methods A retrospective audit of 100 patients with suspected pulmonary embolism who had a CTPA performed between October 2003 and April 2004.

Results CTPA was positive for PE in 31% of admissions. The pre-test probability was documented in only 4% of admissions. All patients with PE had a significantly elevated D-dimer (> 499 ng/mL). Wells score calculated by the investigators showed 59 (59%) to have a low, 33 (33%) a moderate, and 8 (8%) a high risk for PE. Of these, PE was diagnosed in 9 (15%), 15 (45%), and 7 (88%) respectively; 93% of patients had a blood gas performed, yet only 77% had the D-dimer measured. No patient with a measured and negative D-dimer had a diagnosis of a PE; 32 CTPAs were performed on 32 patients out of hours.

Conclusion There was a very low uptake of the formal use of pre-test probability scores by medical registrars. This audit confirms that, in patients with low or moderate risk of PE and a negative D-dimer, an alternative diagnosis should be considered. The management of suspected venous thromboembolism (VTE) could be improved; it is likely that after hours CTPA could be reduced.

Computed tomographic pulmonary angiography (CTPA) has become the imaging modality of choice for investigation pulmonary embolism (PE).1 It is widely available on a 24-hour basis and allows recognition of alternative diagnoses when PE is excluded. One disadvantage of CTPA is the need for intravenous contrast, especially in the setting of renal failure in compromised or dehydrated patients. In addition, it has recently been highlighted that diagnostic imaging contributes to the risk of developing cancer.2 Measurements of D-dimer can risk stratify patients suspected of PE as part of a clinical algorithm. A level of less than 250 ng/ml has been shown to exclude clinically important venous thromboembolism (VTE) in a low-risk group population.4 A multi-detector helical CTPA interpreted as part of a clinical algorithm in conjunction with a pre-test probability score and D-dimer can make the diagnosis of a clinical relevant VTE in 98% of all cases.1 However when used on its own it has been
shown to have a sensitivity of 70%, and a specificity of 91% with a true positive rate ranging from 65% to 100% depending on the location of the embolus.\(^3\)

The CTPA is a revolution in diagnostic strategies and most hospitals describe an almost exponential increase in the request for CTPA.\(^1,5\) The Department of General Medicine in Christchurch Hospital is the primary referral service for patients presenting with a clinical suspicion of PE. We are examining the use of CTPA in our department.

This study has two aims:

- To audit the adherence to local and international management guidelines in requesting CTPAs; and
- To comment on the possibility of a more cost effective and efficient way to use a CTPA in patients with suspected PE.

**Methods**

**Setting**—This study was performed on patients admitted to the Department of General Medicine in Christchurch Hospital, New Zealand—a tertiary level institution with 600 beds, serving a population of about 500,000. About 600 CTPAs are performed each year. During the period of this audit, CTPAs were performed using a single-slice helical CT scanner (High Speed Advantage CT/I scanner, GE systems, Milwaukee, USA) with 150 ml of Ultravist 300™ contrast medium.

The Instrumentation Laboratory (IL)-test D-dimer is used in Christchurch Hospital. It is an automated quantitative latex enhanced immunoassay, which provides a rapid quantitative measurement of D-dimer that has been shown to correlate well with ELISA methods.\(^6,7\)

We have recently shown that the cut-off of 250 ng/ml using the IL D-dimer measurement system is a safe cut-off for patients to be discharged from the Emergency Department.\(^4\) Clinically the 250 ng/ml level using the IL D-dimer system is equivalent to 500 ng/ml utilising the VIDAS system.

**Subjects**—Our index test was a CTPA. A computerised radiology database (COMRAD) was searched to identify all CTPA requests in that time period. Clinical notes were then reviewed and patients included in the analysis if they had been admitted to General Medicine with suspicion of PE. We analysed 100 consecutive CTPA requests from the Department of General Medicine at Christchurch Hospital from October 2003 to April 2004.

Analysis included the collection of demographics, presenting symptoms, and documentation pre-test probability score. We noted whether D-dimer was requested and the results. CTPA results, time of scanning, clinical diagnosis, outcome, treatment, and any complications of the CTPA were also recorded. Out-of-hours CTPA was defined as that occurring during weekends and public holidays, and between 2300 and 0700 during weekdays—during these hours a radiographer and nurse are off site unless called in, while a radiology registrar is always on site.

**Audit design**—We noted how often the Geneva or Wells scores were documented in the hospital records. When neither the Geneva nor Wells score were documented, the investigators used the information recorded in the medical records and computerised results system (Éclair version 3.6) to calculate a score. We subsequently analysed the results of formal pre-test probabilities and D-dimer results against CTPA results.

**Results**

In our institution, the number of CTPA performed has increased significantly over the last 5 years (Figure 1).
Figure 1. Number of CTPAs performed at Christchurch Hospital (by year)

The 100 admissions consisted of patients with a mean age of 60 years, and 58 were females; 32 of the 100 analysed scans were performed after hours. Eighty-seven CTPAs were performed within 24 hours of presentation. Common presenting complaints included pleuritic chest pain (39%), dyspnoea (30%), and collapse (16%).

CTPA was positive for PE in 31% of admissions; 87 patients had a CTPA performed within 24 hours of admission. None of the patients primarily diagnosed with PE died during the index admission. One patient had a contrast reaction. This was labelled as mild by the treating physician: a slight rash and swelling around the eyes with itchy neck and throat that developed shortly after having contrast; it was completely resolved by the following day.

The pre-test probability was rarely documented, with only 4% of admissions documenting a Geneva or Wells score. Blood gas was measured in 93, and D-dimer was requested in 77 admissions.

100 admissions had a calculable Wells score. A stratification of these patients by score, D-dimer result, and presence of PE on CTPA is shown on Figures 2 and 3; 59 (59%) patients were calculated to have a low, 33 (33%) a moderate, and 8 (8%) a high risk for PE. Of these, PE was diagnosed in 9 (15%), 15 (45%), and 7 (88%) respectively.

No patient with a negative D-dimer had a diagnosis of a PE (Figure 4). However, CTPAs were performed in the low pre-test probability group in 2 patients with a negative D-dimer and in 10 patients without a D-dimer measurement. In the moderate group, CTPAs were performed on 2 patients with a negative D-dimer and on 10 patients without D-dimer measurement; 7 of these 24 patients had CTPA out of hours.
Ninety-three admissions had a measurable Geneva score. Of these, 53 (57%) were calculated to have a low, 33 (35%) a moderate and 7 (8%) a high risk for PE. Pulmonary embolism was diagnosed in 10 (19%), 15 (45%) and 5 (71%) respectively (Figure 4).

No patient with a negative D-dimer had a diagnosis of a PE. However, CTPAs were performed in the low pre-test probability group in 3 patients with a negative D-dimer
and 11 without a D-dimer measurement. In the moderate group CTPAs were performed on 12 patients without D-dimer measurement. 6 of these 26 patients had CTPA out of hours.

Figure 4. Stratification of 93 admissions into pre-test probability groups using Geneva score

![Bar chart showing stratification of admissions into pre-test probability groups using Geneva score.]

All patients with PE had a significantly elevated D-dimer (> 499 ng/mL) if this was measured.

Thirty-two CTPAs were performed out of hours. Only three of these patients had a high pre-test probability (D-dimer was measured and was positive in two patients) using the Wells score. With the Geneva score, two CTPAs were performed out of hours in high pre-test probability patients (neither with D-dimer measured).

**Discussion**

The recent British Thoracic Society (BTS) guidelines suggest using three diagnostic steps in making a diagnosis of pulmonary embolism: pre-test probability testing, D-dimer measurement, and imaging (CTPA or V/Q-scan) interpretation. The guidelines emphasise requesting and interpreting CTPA in the context of these pre-test probability assessment. Reliable methods of determining the pre-test probability of PE prior to imaging have been derived and, in combination with D-dimer measurement, have been shown to reliably exclude PE with an error rate of 1–2%. 

9,10
All scoring methods categorise those investigated for PE into low, moderate, and high risk for PE prior to imaging investigations. The Geneva score\(^\text{10}\) includes questions about age, risk factors, together with the presence of tachycardia and the findings on arterial blood gas measurement. This score has the advantage of objectivity but it is reliant on arterial puncture.

The Wells method\(^\text{9}\) includes tachycardia, haemoptysis, symptoms suggestive of deep vein thrombosis (DVT), and risk factors—together with the question “Alternative diagnosis less probable than PE?” The score has a high inter-observer variation because of this last question.\(^\text{11}\) Both scoring system are being used in our institution; the clinical utilities of these scores have been evaluated in our institution against empirical assessment and among junior and senior staff.\(^\text{11}\)

This study shows that a large number of CTPAs are requested by the General Medicine service, with approximately one-third requested after hours. Almost a third of scans will be positive. This result is in keeping with other hospitals in our region. We are performing a similar number of CTPAs for the size of our population and have a comparable rate of positive diagnosis compared to some reports.\(^\text{12–16}\)

Our study has the recognised limitations of any audit. There might be a conceptual problem with using pre-test probability scores retrospectively relying on clinical notes. It is possible that the Wells score may be particularly influenced by bias, as the D-dimer value might have been available to the reviewer prior to scoring the Wells score. This is the principle problem when reviewing data and applying prospective scores \textit{post hoc}.

In clinical practice, the D-dimer may also often be available to the clinician prior to calculating pre-test probability scores. In our cohort, the D-dimer when measured was negative in four patients.

As a result of the retrospective nature of the review of clinical records, we assume that absence of documentation implies the absence of scoring. Thus it is possible that we have underestimated the proportion of admissions where a Geneva or Wells score was calculated by the admitting team.

For example, a CTPA may have been requested primarily to search for underlying pulmonary disease, with PE thought unlikely but needing exclusion. This complexity of thinking would not be apparent in a retrospective review. However, we would argue that this probably should not lead to a CTPA performed after hours in an emergency setting, but rather planned after senior staff review. The number of cases reviewed is numerically small. However, as they encompass 7 months of admissions under General Medicine, they are likely to be representative of all patients with a suspicion of PE admitted to this department in Christchurch Hospital.

We cannot comment on potentially missed PE in cases where CTPAs were not requested when current guidelines would suggest a need for such a scan. Finally, these results are only applicable to Christchurch Hospital, and should be interpreted with great caution in other settings.

There was a very low uptake of the formal use of pre-test probability scores by medical registrars, as only 4% of all patients had a formal pre-test probability score recorded. D-dimer testing was also probably under-utilised. In our cohort, a blood gas was requested in 93%, but a D-dimer in only 77 of admissions.
BTS guidelines suggest that (in patients with a high pre-test probability score) the D-dimer need not be measured, but in our audit this excuse for not measuring D-dimer could only be used in a small number of cases, raising the possibility of inappropriate CTPA requests. Indeed, a CTPA was requested in 24% of cases with a low or moderate pre-test probability without measuring a D-dimer.

The observation that CTPAs were requested in a cohort of patients with a low or moderate pre-test probability and a negative D-dimer is not in keeping with best evidence. Finally, one-third (34) of all the 100 CTPAs occurred after hours and approximately a quarter (7) of low or moderate risk admissions had CTPAs performed out of hours.

We conclude that there is room for improvement in CTPA requests in General Medicine at Christchurch Hospital, both in terms of the use of D-dimer measurement and application of pre-test probability scores. With more appropriate requests, both in terms of case finding and timing, resources might be utilised more efficiently and patient management improved.

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Aggressive acts by patients against general practitioners in New Zealand: one-year prevalence

Christopher Gale, Bruce Arroll, John Coverdale

Abstract

Aim There is limited data about aggressive or violent acts that patients or their relatives commit against general practitioners (GPs). We aimed to estimate the one-year period prevalence of violence, harassment, and complaints, and the current level of psychological distress from the event perceived as causing the most distress.

Method An anonymous, postal, national survey was sent to all vocationally registered general practitioners in New Zealand, in 2002.

Results In one year, 15.4/100 GPs were verbally abused, 11.5/100 were intimidated, 7.1/100 received a complaint, 6.2/100 were sexually harassed, 3.5/100/yr were assaulted, 3.0/100 had property damaged, 1.9/100 had been stalked, 1.7/100 were inappropriately touched, and 0.8/100/yr were injured. Men were more likely to be assaulted, and women were more at risk of sexual harassment. Thirty-five percent described some distress, and 27 GPs were severely distressed by these events. The context of the most distressing event mentioned was related to either requests for drugs, sexually inappropriate comments, and complaints.

Conclusions The rate of violent acts reported depends in part on the action. Aggression may not be limited to attack and sexual harrassment. These events continue to cause distress. There is a poor association between commonly used interventions to prevent attacks and any reduction in risk. Informing GP trainees of such acts would be useful.

Previous surveys of aggressive acts towards general practitioners (GPs) were based in Great Britain and Ireland. Specifically, Hobbs\(^1\) surveyed 1093/2094 GPs (40.6% response rate) and found 687 (62.9%) had suffered some form of aggression from patients within the previous year; 91.3% of these events being verbal abuse or threats with no direct physical act.

O'Connell and Bury\(^2\) (N=622, response rate 98%) found that 21% of GPs had experienced a violent event during their career, and 7% of those events led to injury to the practitioner. Ness and others\(^3\) (N=390, 91% response rate) found that 54% of respondents had been verbally abused, 28% had received (specific) threats, 6.3% had been attacked, and 1.6% had been injured by patients.

These surveys did not enquire about events such as sexual harassment, inappropriate touching, threats to family, or stalking. In addition, no previous survey attempted to measure the psychological impact of these events on GPs.

Given the limitations of the previous GP surveys, we designed a survey to determine the one-year period prevalence of patient-initiated violent events among vocationally (specialist) registrationed GPs in New Zealand.
Method

During August to October 2002 we sent an anonymous postal survey to all vocationally-registered GPs on the Medical Council of New Zealand (MCNZ) database.

We asked if general practitioners had experienced any of the following 10 events listed on the survey form: verbal abuse or threats; threats to their family; non-verbal intimidation; having their (or their practice’s) property damaged; sexual harassment; sexualised touching; attempt to hit; being hit; being injured; being followed or stalked; and having complaints made against them. We defined complaints as “being harassed or persecuted by means of a formal complaint.” We asked if the event had happened within (the previous) one year.

To preserve GPs’ confidentiality, few demographic details were kept. We asked GPs to describe (in their current workplace) whether there were any preventative factors commonly reported in a previous survey of mental health managers— including security guards, panic buttons, or personal alarms. In addition, we asked if GPs had received training on self-defence or management violence and whether the workplace had policies on reporting and debriefing (after incidents).

We asked for details about the most distressing incident in each GP’s career and then used the Impact of Events Scale (IES) to measure distress about that event. (The IES instrument measures stress in the week prior to the assessment. In previous work in traumatised populations, an impact of events score over 40 has been associated with a diagnosis of post-traumatic stress disorder (PTSD).)

During the initial tabulation and visualisation of the results we noted that some of the subgroups were quite small. We therefore tested for correlations using either the Chi-squared (χ²) test or Fisher’s exact test (which also gave odds ratios). All tests were performed using R version 1.6.0.

Results

We identified 2308 GPs and received 1205 responses (52.2% response rate). The respondents were more likely to be male and were predominantly middle-aged (35.5% female; 32.5% aged 36–45, 42.2% aged 46–55, 13.8% aged 56–65, and 6.0% aged over 65 years). The distribution of workplaces was as follows: in group practices 70.6%, solo practice 20.4%, and capitated practices 3.7%.

The one-year period prevalence is reported in Table 1. The rate of events varied from 15.4 per 100 practitioners per year (for verbal threat) to 0.76 per 100 per year (for assault requiring medical attention—i.e. injury).

<table>
<thead>
<tr>
<th>Act by patient</th>
<th>Number in 1 year</th>
<th>Prevalence in 1 year (%)</th>
<th>Confidence interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal threat</td>
<td>184/1190</td>
<td>15.4</td>
<td>14.7–16.2</td>
</tr>
<tr>
<td>Threat family</td>
<td>20/1185</td>
<td>1.69</td>
<td>1.59–1.78</td>
</tr>
<tr>
<td>Intimidation</td>
<td>136/1186</td>
<td>11.5</td>
<td>10.9–12.0</td>
</tr>
<tr>
<td>Damage property</td>
<td>36/1188</td>
<td>3.03</td>
<td>2.86–3.20</td>
</tr>
<tr>
<td>Sexual harassment</td>
<td>73/1184</td>
<td>6.16</td>
<td>5.84–6.50</td>
</tr>
<tr>
<td>Inappropriate touching</td>
<td>20/1186</td>
<td>1.67</td>
<td>1.60–1.78</td>
</tr>
<tr>
<td>Assault</td>
<td>41/1188</td>
<td>3.45</td>
<td>3.26–3.81</td>
</tr>
<tr>
<td>Injury</td>
<td>9/1186</td>
<td>0.76</td>
<td>0.70–0.81</td>
</tr>
<tr>
<td>Vexatious compliant</td>
<td>84/1188</td>
<td>7.07</td>
<td>6.70–7.44</td>
</tr>
<tr>
<td>Stalking</td>
<td>22/1184</td>
<td>1.86</td>
<td>0.53–1.96</td>
</tr>
</tbody>
</table>

Male GPs were at greater risk of being verbally threatened (OR 1.34; 95% CI 1.03–1.72), or being attacked (OR 1.69; 95% CI 1.19–2.43). Female GPs were more likely to be subjects of sexual harassment (OR 3.55; 95% CI 2.64–7.68), as were younger...
practitioners ($\chi^2=21.2; \text{df}=4; p=0.00028$). There was no correlation of age and inappropriate sexualised touching, but female practitioners were again at higher risk (OR 2.41; 95%CI 1.52–3.82).

Women were less likely to have property damaged (OR 0.59; 95%CI 0.40–0.86), or to be harassed by patients through complaint system(s); that is, experience complaints (OR 0.71; 95%CI 0.51–0.95). There was no correlation of gender and attack causing injury (OR 0.93; 95%CI 0.41–1.96). We could not identify any risk or preventative factors relating to patients stalking GPs.

Of the 1205 survey respondents, 867 (72.0%) could estimate how recent the most distressing event was, and 860 (71.4%) were able to describe the event. In the group who could give a time for an event, 157 (18.1%) stated that the event had occurred in the previous 12 months.

Within the entire survey group, the most common contexts for patient-initiated violent events were request for drugs (218/860—25.3%), sexually-inappropriate comments (194/860—20.9%), complaints (92/860—10.6%), certification (e.g. sickness from work, benefit forms; 79/860—9.2%), and management of psychosis (77/860—8.9%).

Male gender (OR 1.34; 95%CI 1.03–1.72), younger age ($\chi^2=13.5; \text{df}=4; p=0.009$), the presence of an emergency management team (OR 1.79; 95%CI 1.03–2.09) and training in de-escalation (OR 1.47; 95%CI 1.02–2.16) were correlated with an increase risk of being verbally threatened.

The association of various preventative actions are summarised in Table 2. The availability of panic buttons (OR 1.60; 95%CI 1.04–2.46), personal alarms (OR 2.03; 95%CI 1.06–3.69), emergency management teams (OR 2.15; 95%CI 1.02–4.24), security guards (OR 1.99; 95%CI 1.07–3.57), training in de-escalation (OR 1.75 (1.01–2.94), and training in management of violence (OR 1.93; 95%CI 1.08–3.32) were associated with increased risk of threats to the practitioner’s family.

Intimidation of practitioners was associated with panic buttons (OR 1.34; 95%CI 1.03–1.75), security guards (OR 1.67; 95%CI 1.18–2.41), training in de-escalation (OR 1.68; 95%CI 1.18–2.41), and training in management of violence (OR 1.49; 95%CI 1.01–2.19). Women were less likely to have property damaged (OR 0.59; 95%CI 0.40–0.86). Training in de-escalation (OR 1.60; 95%CI 1.02–2.46), and management of violence (OR 1.79; 95%CI 1.12–2.83) was associated with increased risk to property.

Women practitioners were more likely to be subjects of sexual harassment (OR 3.55; 95%CI 2.64–7.68), as were younger practitioners ($\chi^2=21.2; \text{df}=4; p=0.00028$). There was no correlation between age and inappropriate sexualised touching, but female practitioners were again at higher risk (OR 2.41; 95%CI 1.52–3.82).

Male practitioners were at a higher risk of assault (OR 1.69; 95%CI 1.19–2.43), as was a GP in rural-based practice was (OR 1.61; 95%CI 1.03–2.46). Attack causing injury was associated with increasing age ($\chi^2=9.57; \text{df}=4; p=0.048$). There was no correlation between gender and attack causing injury (OR 0.93; 95%CI 0.41–1.96).
<table>
<thead>
<tr>
<th>Incident</th>
<th>Panic button (95% CI)</th>
<th>Personal alarm (95% CI)</th>
<th>Emergency team (95% CI)</th>
<th>Security guard (95% CI)</th>
<th>Training in self-protection (95% CI)</th>
<th>Training in de-escalation (95% CI)</th>
<th>Training in management violence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal threat</td>
<td>1.31 (0.99–1.72)</td>
<td>1.46 (0.90–2.36)</td>
<td>1.79 (1.02–2.09*)</td>
<td>1.47 (0.94–2.34)</td>
<td>1.07 (0.76–1.53)</td>
<td>1.47 (1.02–2.16*)</td>
<td>1.46 (0.98–2.22)</td>
</tr>
<tr>
<td>Threat to GP’s family</td>
<td>1.60 (1.04–2.46*)</td>
<td>2.09 (1.06–3.69*)</td>
<td>2.15 (1.02–4.24*)</td>
<td>1.99 (1.07–3.57*)</td>
<td>1.21 (0.06–2.10)</td>
<td>1.75 (1.01–2.94*)</td>
<td>1.93 (1.08–3.32*)</td>
</tr>
<tr>
<td>Intimidation</td>
<td>1.34 (1.03–1.75*)</td>
<td>1.88 (1.20–2.96**)</td>
<td>1.49 (0.89–2.51)</td>
<td>1.67 (1.07–2.58*)</td>
<td>0.88 (0.62–1.25)</td>
<td>1.68 (1.18–2.41**)</td>
<td>1.48 (1.01–2.19*)</td>
</tr>
<tr>
<td>Damage to property</td>
<td>1.31 (0.91–1.86)</td>
<td>1.21 (0.66–2.11)</td>
<td>1.62 (0.84–2.96)</td>
<td>1.17 (0.66–2.01)</td>
<td>1.14 (0.71–1.78)</td>
<td>1.60 (1.02–2.46**)</td>
<td>1.79 (1.12–2.83*)</td>
</tr>
<tr>
<td>Sexual harassment</td>
<td>0.93 (0.68–1.29)</td>
<td>1.56 (0.96–2.51)</td>
<td>1.58 (0.89–2.73)</td>
<td>0.97 (0.57–1.59)</td>
<td>1.39 (0.94–2.04)</td>
<td>1.33 (0.89–2.11)</td>
<td>1.38 (0.89–2.11)</td>
</tr>
<tr>
<td>Inappropriate touching</td>
<td>0.99 (0.59–1.63)</td>
<td>1.20 (0.51–2.50)</td>
<td>1.79 (0.75–3.81)</td>
<td>0.94 (0.38–2.03)</td>
<td>1.41 (0.76–2.49)</td>
<td>0.97 (0.47–1.86)</td>
<td>0.74 (0.30–1.59)</td>
</tr>
<tr>
<td>Assault</td>
<td>1.13 (0.80–1.58)</td>
<td>0.84 (0.44–1.49)</td>
<td>1.56 (0.84–2.77)</td>
<td>0.88 (0.48–1.51)</td>
<td>0.82 (0.51–1.29)</td>
<td>1.01 (0.63–1.58)</td>
<td>1.29 (0.80–2.04)</td>
</tr>
<tr>
<td>Injury</td>
<td>1.10 (0.48–2.35)</td>
<td>1.77 (0.52–4.75)</td>
<td>1.42 (0.27–4.75)</td>
<td>2.02 (0.67–5.11)</td>
<td>0.52 (0.10–1.72)</td>
<td>0.79 (0.20–2.30)</td>
<td>0.71 (0.13–2.31)</td>
</tr>
<tr>
<td>Complaints</td>
<td>1.05 (0.76–1.43)</td>
<td>1.46 (0.89–2.35)</td>
<td>1.37 (0.76–2.40)</td>
<td>1.16 (0.71–1.87)</td>
<td>1.08 (0.71–1.60)</td>
<td>1.11 (0.73–1.67)</td>
<td>1.23 (0.78–1.89)</td>
</tr>
<tr>
<td>Stalking</td>
<td>1.14 (0.64–1.66)</td>
<td>1.33 (0.61–2.62)</td>
<td>1.37 (0.55–2.98)</td>
<td>1.51 (0.75–2.86)</td>
<td>1.01 (0.52–1.80)</td>
<td>0.83 (0.40–1.57)</td>
<td>0.83 (0.37–1.66)</td>
</tr>
</tbody>
</table>

*p<0.10; **p<0.05.
Women were less likely to be harassed by patients through complaint system(s); that is, experience vexatious complaints (OR 0.71; 95%CI 0.51–0.95). Rural practitioners were at greater risk of such complaints (OR 1.69; 95%CI 1.09–2.45). We could not identify any risk or preventative factors relating to patients stalking GPs.

The majority of participants (1500/2308; 65.8%) had no symptoms on the impact of events scale. Although the median IES score was zero, the mean total IES score was 5.18, the mean intrusion score was 2.72, and the mean avoidance score was 2.45. The range of IES (total) scores was 0 to 65, the intrusion subscale range was 0 to 35, and the avoidance subscale range was 0 to 40; 27 (1.8%) of participants had an IES (total) score of over 40, which could indicate clinically significant distress in the previous week.

Discussion

This study is a national sample of GPs. It is also the first study of GPs to include questions on complaints and stalking. We directly asked about the timing of events. The response rate is lower than in other surveys. By using an anonymous survey were relying on self-report. We do not know about the nature or adequacy of the response by the persons to whom incidents were reported, or why some incidents were not reported. We do not know about the coping styles of the GPs, and we do not know about the consequences to patients of the incidents reported, or whether patients were charged for criminal behaviour.

The literature on patient-initiated aggression has concentrated on the hospital, assault, and harrassment. In general practice, we found a broader range of events. Although verbal threats and intimidation were the most frequently reported types of patient initiated aggression, both complaints and sexual harrassment were more common than assault or injury. We found that female practitioners may be less likely to be physically attacked, or have complaints. However, they are at a much greater risk of being subject to sexualised incidents.

Most practitioners have not been distressed, but 1.8% of practitioners reported distress that has been associated with PTSD. As the impact of events scale only asks about distress in the last week, this distress was either ongoing or precipitated by the survey. Subjectively, some practitioners expressed this by writing extensively on the form—not only about the event itself but about the perceived lack of support that they experienced.

Unlike previous surveys, there has been an attempt to correct for the length of career by estimating the one-year period prevalence. By using vocational registration, we controlled (in part) for variation in experience within the New Zealand workplace. This survey attempts to also measure the current distress to general practitioners from the most distressing event.

After this survey was planned, a systematic review of the management of violence was published that concentrated on the one-year period prevalence. A paper surveying doctors who had been investigated within New Zealand suggested that the process of investigation by statutory led to ongoing distress to the doctor who received the complaint.
We suggest that patient-initiated aggression needs to include verbal, physical, sexual, and administrative (or legal) methods of causing distress or harm. It may be that qualitative exploration of the meaning and impact of such events on GPs could lead to the development of better tools to assess these events and the impact on them. If such events are reported by GPs, other staff in the general practice may also be at risk, and this needs to be quantified.

Although one should be cautious about drawing conclusions from associations, the association of commonly suggested interventions (to prevent experiencing an act of violence) underscore the need to test interventions to prevent and mitigate the effects of patient aggression within general practice.

Although only a minority of GPs reported distress, support may be needed for doctors who have been attacked or harassed: some models could be generated by comparing the risk of distress following assault between various specialties or between professional groups (which have different methods of re-accreditation). Such models should also be tested before general implementation.

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**Acknowledgements:** This paper was supervised in part by Roger Marshall. In addition, Ora Pellett provided assistance with research.

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**References:**

Psychosocial variables as prognostic factors in metastatic cancer: a brief review

Claire Paton, David Perez

The extent to which psychosocial variables influence prognosis in metastatic cancer is a topical issue which many people hold opinions on. Since the 1950s, numerous studies have investigated the relationship between psychosocial variables and the progression of cancer. The resulting literature has notably been characterised by contradictory findings. 1, 2

Previous reviews relating psychosocial variables to cancer survival have combined studies of metastatic and non-metastatic cancer patients in their analyses. 2–4 However as stage of disease is a significant medical prognostic factor, the two groups of patients should be analysed separately. This review examines the association between psychosocial variables and survival in patients with metastatic disease.

Methods

Many psychosocial variables have been associated with cancer prognosis. This report covers four categories of variables: psychological coping style, psychosocial interventions, social ties, and health-related quality of life (HRQoL). The first three have been prominent in the literature for a number of years. The relationship between HRQoL scores and prognosis is an area of increasing interest.

PUBMED (1966-January 2005), PsycINFO (1967-January 2005), and EBM (1970-2004) databases were searched for published English language studies and review articles. Keywords included cancer, metastatic cancer, advanced cancer, cancer survival, psychological coping, psychotherapy, social support, social ties, marital status, health-related quality of life, and culture.

Inclusion criteria were:

- A study group of adult patients with metastatic or advanced (i.e. incurable) cancer; and
- Survival or mortality as specified outcomes. Both experimental and observational investigations were included for review.

Results

Psychological coping style and metastatic cancer

Background—It is a popular lay belief that mental attitude can influence survival from cancer. 3 However academic opinion diverges widely. Research interest originated from a 1979 observational British study 5 that analysed the psychological responses of 69 women with early-stage breast cancer. Recurrence-free survival at 5 years was significantly more common among patients who responded with denial or “fighting spirit” than among those with attitudes of stoic acceptance or feelings of “helplessness/hopelessness”. At 10- and 15-year follow-up, the results remained significant. 6, 7 More recently, the authors attempted to replicate these findings in a cohort study of 578 early-stage breast cancer patients, controlling for prognostic factors and using self-administered questionnaires to assess psychological response instead of a structured interview.
At 5 years, there was a significantly increased risk of death in women with high scores for helplessness/hopelessness. However, fighting spirit was not associated with improved survival. At 10-year follow-up, only helplessness/hopelessness had a continuing effect.

Studies in metastatic disease—Three early studies examined psychological coping in women with metastatic breast cancer. Derogatis and coworkers assessed 35 patients at their second appointment for treatment of recurrent disease. Using t-tests, short-term survivors displayed lower levels of hostility and higher levels of positive mood. Long-term survivors demonstrated higher levels of negative mood states.

There was no reported assessment of lymph-node status and short-term survivors had received more previous chemotherapy. Levy et al attempted to replicate these findings, testing 36 women at diagnosis of first recurrence. Cox regression analysis found that positive mood at baseline predicted longer survival. Hostility and negative mood states were associated with shorter survival.

Jamison et al assessed 49 women at the beginning of treatment. Using t-tests, there were no significant differences between short-term versus long-term survivors on disease-related variables, and no consistently significant differences on any of the personality variables examined.

More recently, Butow et al assessed psychologic variables in 125 metastatic melanoma patients soon after diagnosis. Regression analysis (controlling for disease and demographic predictors) indicated that patients who viewed the aim of treatment as curative or for long-term prolongation of life, who minimised the impact of cancer on their lives, and who expressed more anger about their illness lived the longest. When the authors replicated their study with 99 metastatic breast cancer patients, they found that women who minimised the impact of cancer survived longer (a median of 29.1 versus 23.9 months after study entry, p<0.01). These studies may not be representative as participating patients were less ill than non-participants.

Earlam and colleagues assessed 50 patients with colorectal liver metastases and reported no statistically significant survival difference between high and low scorers on tests of baseline anxiety and depression.

Using Cox regression analysis, Naughton et al found that higher baseline depressive symptoms were of borderline significance for shorter survival in small-cell lung cancer patients (n=70). Faller and Schmidt assessed 59 patients with Stage III or IV lung cancer within 3 days following diagnosis. Cox regression analysis showed that a depressive coping style (p=0.034), but not depression, predicted shorter survival.

Studies combining a variety of advanced cancers in their analyses have found that baseline assessments of helplessness/hopelessness were not associated with survival up to 8 years later, and that within the context of palliative radiation therapy, pessimism was a risk factor for mortality among younger (rather than older) adult patients.

Conclusion—On the basis of these reports, the predictive value of psychological coping style for patients with metastatic cancer remains inconclusive. However
minimisation has been reported as a significant prognostic factor in studies of two different types of cancer.

Psychosocial interventions and metastatic cancer

Background—Since the late 1970s, reports have been published exploring the role of psychosocial interventions in alleviating psychological distress among cancer patients. Designed for individuals and for groups, interventions have been categorised as education, coping, emotional support, and psychotherapy.

Two intervention studies, conducted by Spiegel et al and Fawzy et al, reported significant increases in survival of patients with metastatic breast cancer and malignant melanoma. Since then, the view that psychosocial interventions can help to prolong survival has been examined in academic literature and presented in several popular books. Therefore, some cancer patients have high expectations of such therapies.

Studies in metastatic cancer—There have been six published reports on interventions with metastatic cancer patients: five randomised controlled trials (RCTs) and one qualitative/quantitative study:

Randomised controlled trials—All RCTs included in this review have assessed women with metastatic breast cancer. An earlier trial of men with mixed metastatic cancers is excluded because patients were dying of end-stage cancer, and survival was not expected to differ between groups.

At 10-year follow-up, Spiegel reported an average survival advantage of nearly 18 months for patients who had participated in 90 minutes of weekly supportive-expressive group therapy for 1 year (n=50), as compared with no intervention (n=36). This was not accounted for by differences in medical treatment. Although less advanced staging at initial diagnosis favoured intervention patients, statistically this did not account for survival differences. The study was generally recognised as being methodologically sound, but has been criticised for the small number of control cases and for the delay between metastatic diagnosis and study entry. Goodwin et al attempted to replicate Spiegel’s results, randomising women to either weekly supportive-expressive group therapy for at least one year (n=158) or no intervention (n=77). After 201 deaths, multivariate analysis showed that the intervention had no significant effect on survival. Although there were imbalances between the two groups at baseline for some prognostic factors, only progesterone receptor status was associated with improved survival, thus favouring the intervention group. Including this factor in multivariate analysis increased the hazard ratio for death, thereby decreasing the likelihood of a beneficial effect of the intervention on survival.

Cunningham and colleagues randomly allocated patients to either a weekly intervention for 35 weeks (n=30) or a control group (n=36). The intervention comprised both supportive-expressive and cognitive behavioural group therapy, as well as a weekend of training in specific coping skills. The control group received a home study cognitive behavioural package. Groups were
balanced for the disease variables measured. Five years after study commencement no significant difference in survival was found between the groups.

Edelman et al.\(^{29}\) randomised women to either 8 weekly sessions of group cognitive behaviour therapy and a family night, followed by 3 more monthly sessions (n=60) or a no-intervention (n=61) control group. The groups did not differ significantly on assessed clinical factors. There was no survival advantage associated with the intervention five years after its commencement.

Meta-analyses of RCTs—A Cochrane Library systematic review of psychological interventions for women with metastatic breast cancer\(^{26}\) conducted meta-analyses of survival data for the above studies at 1, 5, and 10 years of follow-up. The authors concluded that, although there is evidence of heterogeneity in the data, no clear evidence exists of survival benefit from group psychological interventions for women with metastatic breast cancer. Furthermore, they noted that data insufficiencies did not permit assessment for some potential effect modifiers such as the extent of disease at initial diagnosis.

Chow’s meta-analysis of the four intervention trials also found no significant difference in overall survival at 1 and 4 years.\(^{30}\)

Qualitative/quantitative study—A second study, by Cunningham et al.,\(^{31}\) longitudinally investigated the psychological factors associated with length of survival in 22 patients with mixed metastatic cancers who were receiving weekly group psychotherapy for up to 1 year. While acknowledging the limitations on interpretation associated with correlative study design, the authors reported an association between longer survival and degree of involvement of patients in psychological self-help activities.

Conclusion—There is no conclusive evidence showing that group psychosocial interventions prolong survival in patients with metastatic cancer. However RCTs have not explored possible effects of individual psychotherapy on prognosis, nor assessed online group support facilities.\(^{26}\) In addition they have focused almost exclusively on women with metastatic breast cancer.

Social ties and metastatic cancer

Background—The literature on social ties and prognosis in cancer provides some evidence for an association between social involvement/support and survival,\(^{32}\) but the relationship between marital status and prognosis is unclear.\(^{33}\)

Studies in metastatic disease—Studies of patients with metastatic melanoma,\(^{13}\) metastatic breast cancer,\(^{14}\) and advanced lung cancer\(^{16,34}\) have not found social support/ties to be predictive of length of survival.

Being married has been associated with longer survival in metastatic lung cancer\(^{35}\) and metastatic melanoma,\(^{13}\) but was not predictive of survival in studies of metastatic breast cancer patients.\(^{14,28}\)
Conclusion—Social support does not appear to be predictive of longer survival in patients with metastatic cancer. Marital status is inconsistently related to prognosis.

Baseline health-related quality of life scores and prognosis in metastatic cancer

Nowadays, health-related quality of life (HRQoL) is regarded as a useful endpoint for measuring the impact of cancer therapies. Most cancer-specific HRQoL instruments measure global quality of life, a variety of functional domains (e.g. physical, role, social, emotional), as well as symptoms of the disease and its treatment.

Some key studies in metastatic or advanced melanoma, breast, lung, colorectal, bladder, and esophagogastric cancers suggest that baseline HRQoL scores may have a prognostic role for length of survival in metastatic cancer. Generally speaking, the global HRQoL score, physical functioning, or physical symptom scores seem to be the most common predictors of survival. Scores obtained on the psychological or social domains tend to be less predictive. This is in keeping with the findings presented in the previous sections.

Discussion

Overall, studies reported in this brief review provide little evidence for a positive association between psychological coping style, psychosocial interventions, or social ties and survival from metastatic cancer. The most reliable indicators of prognosis appear to be baseline HRQoL scores. However, the review is not comprehensive. Unpublished and non-English language studies were not included. Some studies meeting inclusion criteria may have been unintentionally overlooked, and the methodological strengths and weaknesses of the individual reports were not assessed in detail.

Furthermore, the literature base is small and tends to be dominated by studies of women with metastatic breast cancer, thereby limiting the generalisation of findings to other cancers and to men. As far as psychological coping and/or psychosocial interventions are concerned, some authors have called for large-scale studies with well-matched patients (to allow assessment of a possible small effect), and for future studies to explore the possible mechanisms underlying longer survival.

It is suggested that more attention should be paid to the potential influence of culture as a mediating variable for survival in metastatic cancer. Butow’s study of patients with metastatic breast cancer reported that fewer Australian-born women than non-Australian women minimised the impact of cancer on their lives implying “that adoption of this coping style may be more sanctioned in some cultures than others” Cultural factors may also influence the acceptability of interventions. Certainly, the relationship between culture and cancer remains under-researched in New Zealand.

In conclusion, despite the widely held public belief that psychosocial variables can influence prognosis in metastatic cancer, published scientific studies suggest that medical factors predominate. Nonetheless, the literature does provide evidence of psychological and emotional health benefits for patients involved with psychosocial...
intervention programmes. Indeed, as these programmes improve the quality of life for people with cancer they should remain an important component of patient care.

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**References:**


Using the COPE assessment tool with informal carers of people with dementia in New Zealand

Helen Roud, Sally Keeling, Richard Sainsbury

Abstract

Aims To evaluate the validity of the COPE index (CI) carer assessment tool within a study exploring perceptions of carer support, health, and wellbeing.

To assess the utility and acceptability of the CI with health practitioners and informal carers of people with dementia, following the European COPE protocol.

Methods Research interviews (one pre- and two post-CI assessment) recorded demographic characteristics of carer (n=45) and care recipient, formal (service) and informal support use and satisfaction, self-reported health, the General Health Questionnaire (GHQ-30), Burden Interview, Caregiver Competence, and Personal Gain. COPE Index assessment was undertaken by referring health practitioners (n=12).

Results Construct validity of the CI compared positively with findings reported in the literature. Psychological morbidity in carers (33%) was often undiagnosed; 19% of carers presented a more positive perception of their health to the health practitioner than to the researcher; diagnosis of care recipients was not always clear to carers (25%). COPE Index assessment improved both communication and understanding of carers’ needs and was evaluated positively by most carers and health practitioners.

Conclusions The COPE Index is an easily administered and generally acceptable tool that may be useful for initiating more comprehensive assessment of dementia carers’ needs.

Carers of frail older people (especially dementia carers) have high levels of psychological morbidity, burden, and health service utilisation but in the past their own health and support needs have not been formally assessed by health professionals.

In New Zealand, there is an emphasis on ‘ageing in place’ which means that frail older people and those with dementia are increasingly likely to be cared for in the community. Opie described patterns and experiences of informal care which share the family-based and gendered features described internationally.

Although investigators have examined both negative and positive constructs of caregiving, a better understanding is needed of the biopsychosocial factors contributing to poor health outcomes as well as of the needs of caregivers for information, support, and assistance with coping, to enable health practitioners to address these needs.

In a study exploring the health and wellbeing of carers of people with dementia in the community, Roud concluded that carer screening (including health and support
requirements) should become standard procedure at dementia patient general practitioner (GP) visits.

Evidence-based guidelines on assessment tools for older people have been developed in New Zealand, but local evaluation of standardised carer assessment tools in primary care settings has yet to be undertaken. Additionally, there is limited international data available on the comprehensive assessment of carers’ needs.

The COPE (Carers of Older People in Europe) Index, a brief, first-stage assessment instrument developed and evaluated through a European Commission-funded project, has been shown to be useful in increasing understanding of the role perceptions of older carers. The theoretical model on which the instrument is based emphasises the carer’s subjective perceptions of both negative and positive aspects of caregiving.5

Using the COPE Index with a sample of carers of older people with dementia could offer insight into how the Index components vary as a function of caring for older people who differ in their care needs. The conceptual model of Alzheimer’s caregivers’ stress11 is used as a framework for the current study.

Methods

People identified as the primary carer of someone with dementia were approached (n=59) and recruited (n=45) from two psychogeriatricians and 10 general practitioners (GP) working in four urban health centres.

Health practitioners were selected from health centres which reflected a local cross-section of patient socioeconomic groups. A primary carer was defined as the person who is primarily responsible for the day-to-day care/oversight of a person with dementia. Participants were the primary carers of a person over 50 years old, with dementia symptoms of at least 3 months’ duration. Formal diagnosis of the dementia was not required. The primary investigator (Helen Roud) conducted the three structured interviews (one pre- and two post- COPE Index assessment) in participants’ homes or a place convenient to them. The study design is shown in Table 1.

Table 1. Study design

<table>
<thead>
<tr>
<th>Weeks 1–2</th>
<th>Week 3</th>
<th>Week 5</th>
<th>Week 7/8 &amp; Week 28/29</th>
<th>2 weeks after final COPE assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-assessment interview (HR) (n=42)</td>
<td>COPE Index (CI) assessment (GP or psychiatric geriatrician): (n=45)</td>
<td>CI Evaluation Questionnaire mailed to carers (n=43)</td>
<td>Post-assessment interviews (HR) 1 mth–6 mth post (n=41) (n=21)</td>
<td>CI Evaluation Questionnaire mailed to GP or psychiatric geriatrician (n=12)</td>
</tr>
<tr>
<td>Carer questionnaire</td>
<td>COPE Index</td>
<td>COPE Index carer evaluation</td>
<td>Carer questionnaire</td>
<td>COPE Index health practitioner evaluation</td>
</tr>
<tr>
<td>Caregiving competence</td>
<td>–</td>
<td>–</td>
<td>Caregiving competence</td>
<td>–</td>
</tr>
<tr>
<td>Personal gain</td>
<td>–</td>
<td>–</td>
<td>Personal gain</td>
<td>–</td>
</tr>
<tr>
<td>Burden interview</td>
<td>–</td>
<td>–</td>
<td>Burden interview</td>
<td>–</td>
</tr>
<tr>
<td>GHQ-30</td>
<td>–</td>
<td>–</td>
<td>GHQ-30</td>
<td>–</td>
</tr>
</tbody>
</table>

Measures in the Carer Questionnaire included demographic characteristics of carer and care recipient, formal (service) and informal support use and satisfaction, health visits, and medication use. The formal support service use question was a modified version of the questionnaire used by Collins and Jones.12
Information on use of services (e.g., respite care, meals on wheels, home help) over the previous 2 months was collected. Similar questionnaires have been used in other dementia-carer studies.\textsuperscript{13,14} Informal support for carers was assessed in three areas: confidante, practical and emotional, following the format of questions used in the Mosgiel Longitudinal Study of Ageing.\textsuperscript{15,16} Also included was a single-item self-report health question shown to correlate highly with physician ratings of health\textsuperscript{1} and used in other caregiver studies.\textsuperscript{8,10,17} This self-report health question is also included in the COPE assessment.

The General Health Questionnaire (GHQ) – 30 item,\textsuperscript{18} the two subscale version of the Burden Interview,\textsuperscript{20} and measures of Caregiver Competence and Personal Gain,\textsuperscript{11} were included both as comprehensive descriptors of caregiver well-being and for comparison with COPE Index subscales.

In scoring the GHQ-30, both bimodal and Likert methods were used to enable both the prevalence of psychological morbidity (depressive symptoms) and the level of distress (anxiety) to be assessed.\textsuperscript{20} The GHQ-30 has been used in other dementia carer studies.\textsuperscript{21–23}

The Burden Interview consists of the 12-item Personal Strain subscale, which measures how personally stressful the caregiving experience is—e.g. “Do you feel you have lost control of your life since your relative’s illness?”; and the six-item Role Strain scale which measures stress due to overload or role conflict—e.g. “Do you feel stressed between caring for your relative and trying to meet other responsibilities?” A Likert scale (0=Never to 4=Nearly always) is used to score items.

The four-item Caregiving Competence and Personal Gain scales represent two of the four dimensions of self-concept included as a measure of intrapsychic strain following the conceptual model of Alzheimer’s caregivers’ stress.\textsuperscript{11} The competence scale (each phrased in positive terms) asks carers to rate their adequacy in the caregiving role, while the personal gain scale measures positive aspects of inner growth which may be perceived by the caregiver as a result of their role. Each measure has been included in other dementia caregiver research.\textsuperscript{8,24}

The 15-item COPE Index\textsuperscript{10} includes six Negative Impact items—e.g. “Do you feel trapped in your role as a caregiver?”; and five Positive Value questions—e.g. “Do you feel you cope well as a caregiver?” These eleven items are summed to give an indication of how well the carer is coping with the caregiving relationship. There are no threshold scores, but for guidance, <15% of the older carer population are expected to score above 12 for Negative Impact or below 12 for Positive Value (personal communication, 2000).\textsuperscript{25}

Three quality of support items (e.g. “Do you feel well supported by health and social services?”) and one regarding financial difficulties associated with caregiving are included in the COPE Index. A cover page records demographic information and the single-item self-report health question. Assessment, which took 10–15 minutes per carer, was undertaken by the referring health practitioners within 2 weeks of the initial research interview.

GPs, psychogeriatricians, and carers were asked to evaluate the acceptability and usefulness of the COPE Index. Evaluation questionnaires were mailed to carers within 2 weeks of their assessment, and to practitioners within 2 weeks of their final COPE Index assessment. Carer evaluation items cover both use and content. Evaluations include items on utility (11)—e.g. “Improved communication between myself and the carer”; and format (7)—e.g. “The COPE Index had too many questions”. The practitioner questionnaire also asked whether practitioners would be happy to use the COPE Index as part of their future assessment of carers’ needs.

Simple descriptive statistics were used to characterise participants and the people they were caring for. Internal consistency of the COPE instrument was assessed by use of Cronbach’s alpha.

Construct validity was assessed by an independent instrument developed as part of the COPE protocol (the COPE Index Carer Evaluation Questionnaire). Evaluation of construct validity was undertaken by determining associations between the COPE instrument subscales and the other measures of carer health and well-being, using Pearson’s product-moment correlation analyses. Finally, the utility of the COPE Index for clinicians was evaluated by a semi-structured Practitioner Evaluation Questionnaire administered to recruiting practitioners.

The Canterbury Ethics Committee approved the study.

**Results**

**Response rates and demography**—The initial participation rate was 76%. Forty-five of the 59 carers initially identified completed the COPE Index with their referring
practitioner (15 with psychogeriatricians/30 with GPs), and 43 completed the COPE evaluation questionnaires within the study protocol. Ten practitioners completed evaluation questionnaires.

Table 2. Participant baseline demographics and caregiving characteristics

<table>
<thead>
<tr>
<th>Carer characteristics:</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>15</td>
<td>(33)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>30</td>
<td>(67)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>(60)</td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>(40)</td>
</tr>
<tr>
<td>Marital Status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>38</td>
<td>(84)</td>
</tr>
<tr>
<td>Other (widowed or separated or never married)</td>
<td>7</td>
<td>(16)</td>
</tr>
<tr>
<td>Occupational status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>32</td>
<td>(71)</td>
</tr>
<tr>
<td>Employed</td>
<td>7</td>
<td>(16)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>6</td>
<td>(13)</td>
</tr>
<tr>
<td>Relationship to person cared-for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Husband</td>
<td>13</td>
<td>(29)</td>
</tr>
<tr>
<td>Wife</td>
<td>16</td>
<td>(36)</td>
</tr>
<tr>
<td>Daughter</td>
<td>10</td>
<td>(22)</td>
</tr>
<tr>
<td>Son</td>
<td>5</td>
<td>(11)</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>Living situation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With care-recipient</td>
<td>29</td>
<td>(64)</td>
</tr>
<tr>
<td>Care hours per week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>16</td>
<td>(35)</td>
</tr>
<tr>
<td>20–160</td>
<td>7</td>
<td>(16)</td>
</tr>
<tr>
<td>24 hours per day</td>
<td>21</td>
<td>(47)</td>
</tr>
<tr>
<td>Not known</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>Duration of care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 years</td>
<td>12</td>
<td>(27)</td>
</tr>
<tr>
<td>2–5 years</td>
<td>15</td>
<td>(33)</td>
</tr>
<tr>
<td>5+ years</td>
<td>16</td>
<td>(36)</td>
</tr>
<tr>
<td>Not known</td>
<td>2</td>
<td>(4)</td>
</tr>
<tr>
<td>Perceived health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good/very good</td>
<td>29</td>
<td>(69)</td>
</tr>
<tr>
<td>Fair</td>
<td>13</td>
<td>(31)</td>
</tr>
<tr>
<td>Poor/very poor</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Care-recipient characteristics:</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–74</td>
<td>12</td>
<td>(27)</td>
</tr>
<tr>
<td>75–84</td>
<td>16</td>
<td>(35)</td>
</tr>
<tr>
<td>85+</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>Not known</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26</td>
<td>(58)</td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>(42)</td>
</tr>
<tr>
<td>Dementia diagnosis (carer report)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>9</td>
<td>(20)</td>
</tr>
<tr>
<td>Multi-infarct</td>
<td>4</td>
<td>(9)</td>
</tr>
<tr>
<td>Lewy Body</td>
<td>4</td>
<td>(9)</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>(31)</td>
</tr>
<tr>
<td>Not known/not diagnosed</td>
<td>11</td>
<td>(24)</td>
</tr>
<tr>
<td>Not reported</td>
<td>3</td>
<td>(7)</td>
</tr>
<tr>
<td>Cognitive-enhancing medication use:</td>
<td>14</td>
<td>(31)</td>
</tr>
</tbody>
</table>

Participant demographics and caregiving characteristics are presented in Table 2. Care-recipient diagnoses reported by carers in the category ‘other’ included dementia, short-term memory loss, memory loss/confusion, Parkinson’s disease-related, and diffuse degenerative neurological condition.
COPE Index responses—Of the 45 COPE Index assessments completed, 3 carers (7%) had a low positive value score (less than 12); 7 carers (16%) had high negative impact scores (greater than 12); Only 1 carer scored in both low positive and high negative categories.

A majority of carers reported that caregiving never caused difficulties with family, friends or finances. For all other items, the majority of carers reported sometimes, often, or always experiencing caregiving in the way described (Table 3). Descriptive statistics for both Positive Value and Negative Impact scores (Cronbach’s alpha=0.59 and 0.68 respectively) are reported.

Table 3. Participant response to COPE Index items

<table>
<thead>
<tr>
<th>Items</th>
<th>Response categories</th>
<th>Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
<th>n/a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Impact Items: n=45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean 19.13 (range 13-24); SD 2.47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you find caregiving too demanding?</td>
<td>8 17.8</td>
<td>27 60</td>
<td>7 15.6</td>
<td>3 6.8</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Does caregiving cause difficulties in your relationship with friends?</td>
<td>26 57.8</td>
<td>14 31.1</td>
<td>2 4.4</td>
<td>3 6.8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Does caregiving have a negative effect on your physical health?</td>
<td>15 33.3</td>
<td>25 55.6</td>
<td>5 11.1</td>
<td>0 0</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Does caregiving cause difficulties in your relationship with your family?</td>
<td>28 62.2</td>
<td>16 35.6</td>
<td>1 2.2</td>
<td>0 0</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Do you feel trapped in your role as a caregiver?</td>
<td>13 28.9</td>
<td>23 51.1</td>
<td>6 13.3</td>
<td>3 6.7</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Does caregiving have a negative effect on your emotional well-being</td>
<td>8 17.8</td>
<td>27 60</td>
<td>10 22.2</td>
<td>0 0</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Positive Value: n=45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean 16.16 (range 10–20); SD 2.74</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you feel that anyone appreciates you as a caregiver?</td>
<td>4 8.9</td>
<td>12 26.7</td>
<td>15 33.3</td>
<td>14 31.1</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Do you feel you cope well as a caregiver?</td>
<td>0 0</td>
<td>13 28.9</td>
<td>16 35.6</td>
<td>16 35.6</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Do you find caregiving worthwhile?</td>
<td>0 0</td>
<td>8 17.8</td>
<td>13 28.9</td>
<td>24 53.3</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Do you feel well supported by your family?</td>
<td>2 4.4</td>
<td>9 20</td>
<td>10 22.2</td>
<td>24 53.3</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Do you have a good relationship with the person you care for?</td>
<td>0 0</td>
<td>3 6.7</td>
<td>11 24.4</td>
<td>31 68.8</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does caregiving cause you financial difficulties?</td>
<td>37 82.2</td>
<td>3 6.8</td>
<td>4 8.9</td>
<td>1 2.2</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Do you feel well supported by your friends and/or neighbours?</td>
<td>9 20</td>
<td>10 22.2</td>
<td>12 26.7</td>
<td>14 31.1</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Overall do you feel well supported in your role of caregiver?</td>
<td>2 4.4</td>
<td>10 22.2</td>
<td>15 33.3</td>
<td>18 40</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Do you feel well supported by health and social services?</td>
<td>2 4.4</td>
<td>10 22.2</td>
<td>11 24.2</td>
<td>22 48.9</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Construct validity—

Health measures—At baseline interview, 14 carers (33%) had current depressive symptoms (GHQ-30 score >5) and 17 (40%) had high anxiety scores (GHQ-30 score >28). Of those carers with current depressive symptoms, six were on antidepressant
medication and eight were not diagnosed. GHQ-30 scores were higher for carers describing their health as fair than for those describing it as good (Table 4).

Table 4. Carers’ baseline GHQ-30 scores for anxiety and depressive symptoms

<table>
<thead>
<tr>
<th>Measure</th>
<th>Good health (n=31)</th>
<th>Fair health (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (lower to upper quartile)</td>
<td>Median (lower to upper quartile)</td>
</tr>
<tr>
<td>GHQ-30 Depression</td>
<td>2 (0–5.5)</td>
<td>7 (3–11)</td>
</tr>
<tr>
<td>GHQ-30 Anxiety</td>
<td>23 (19.5–30)</td>
<td>32 (22–37)</td>
</tr>
</tbody>
</table>

Over the course of the study, 18 carers (43%) were identified as having depressive symptoms. At final interview, five carers were taking antidepressant medication and 10 carers continued to have depressive symptoms.

The Pearson product-moment correlation coefficients between the COPE Index negative impact and positive value scales and the psychological morbidity, burden, competence, and personal gain measures from initial research interview are recorded in Table 5. No significant association was demonstrated between negative impact and positive value (r=0.24, n=42).

Table 5. Associations between negative impact and positive value scales and standard comparative measures

<table>
<thead>
<tr>
<th>COPE Index Subscales:</th>
<th>Outcome measures:</th>
<th>Burden Interview:</th>
<th>Intrapsychic Strain:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>General Health Questionnaire (GHQ-30):</td>
<td>Personal Strain</td>
<td>Personal Gain</td>
</tr>
<tr>
<td>Depression</td>
<td>Depression</td>
<td>42 0.46** 42 -0.18</td>
<td>41 0.04 41 0.31*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Anxiety</td>
<td>42 0.32* 42 -0.17</td>
<td>41 -0.09 41 0.16</td>
</tr>
</tbody>
</table>

There were significant associations demonstrated between the COPE negative impact subscale and both psychological morbidity and burden measures. While the COPE positive value subscale demonstrated a significant association with personal gain, a negative association was demonstrated between positive value and personal strain.

A comparison between carers’ self-reported general health at COPE assessment and at initial research interview demonstrated a significant association (Pearson, r=0.58, p<0.01). However, 16 carers reported a different health status to their GP than to the research interviewer. Of the 9 differences not explained by time lag or recorded changes in health, 8 reported a better health status to their GP.
**Carer support**—At first interview, participants were in contact with between one and 11 formal support services (median=4). Use of support services was significantly correlated with time spent caring (r=0.42, p<0.01). The most commonly used support services were GP and home help. A small group of carers (19%) reported not being fully satisfied with their care-recipient’s GP. Low use was made of daycare and respite care (5–19%). The COPE assessment found that 33/45 carers (73%) reported feeling well supported by health & social services (always or often).

Sixty-three percent of carers affirmed at baseline interview that they had access to someone who could provide help with daily tasks, instrumental or practical support. When asked “Could you have used more support?” of this type, 50% said yes. Carer response to Cope Index item 5 (the negative effect of caregiving on physical health) was associated with reported access to, and expressed need for more practical support (both r=0.34, p<0.05). This effect was also associated with self-rated health (r=0.45, p<0.01) and psychological morbidity (r=0.38, p<0.05).

The majority of carers (81%) reported that they have ‘one special person’ to whom they could turn - a ‘confidante’. Seventy-two percent had access to emotional support but 49% said they could have used more. Family members (daughters, sons, spouses, and siblings) were the most frequently identified as providing emotional support. In the COPE assessment, 75% of carers reported feeling well supported by family (always or often).

**Utility of COPE Index**—At least half the carers responded positively on all five Utility questions exploring their response to the COPE Index (Figure 1).

Six of the 43 carers offered additional comment on the COPE Index. In one case, a spouse carer reported that in working through the Index with the GP, the practitioner (who had seen her husband recently) had encouraged her to reassess the situation more realistically than she had been indicating by her COPE Index responses, which she had found helpful. In contrast, another carer said “It begged the direct question—‘How are you feeling about things at the moment?’ at the end of the questionnaire.” In a similar vein, one carer stated “(The COPE Index) Questions don’t get to the heart of the matter…Not sure that acceptable support would be available when needed. Discussing needs not difficult—getting the message through to supply something practicable is the difficulty.”
Figure 1. COPE Index evaluations by carers

All health practitioner evaluations agreed that using the COPE Index made carers feel that the practitioner was interested in their needs, and 7 of the 10 considered that the COPE Index improved their understanding of carers’ needs (Figure 2). Six agreed that the COPE index both improved the assessment process, and improved communication between them and the carer.

Figure 2. COPE Index evaluations by health practitioners
In practitioners’ comments, there is an indication of a more guarded response to the COPE Index—e.g. “The questionnaire was very general” and “Useful as a systematic springboard for discussion…responses in terms of frequency often inappropriate.” Eight out of 10 practitioners reported that they would ‘possibly’ use the COPE Index for future assessment, while 2 said that they would ‘definitely’ use it.

Discussion

Our observations in this exploratory study are mixed. Researcher and practitioner assessments of the diverse carer (and care recipient) group revealed findings which at times differed between the perspectives of the carers, and those of their health practitioners.

The more negative self-appraisal of carer health disclosed by some study participants to the researcher (when compared with that disclosed to the health practitioner) might support an observation of Robinson and Austin. They suggest that the under-reporting of caregiver problems is due both to denial and lack of awareness of the effects of caregiving on their physical and mental health.

In the current study, time and depth of research interview was far greater than the practitioner’s COPE Index assessment. Furthermore, in one-quarter of cases, carers indicated that their care recipients had not (to their knowledge) been diagnosed clearly, and psychological morbidity in carers was often undiagnosed and more prevalent than in the general population. (It is acknowledged that a high score on the GHQ-30 does not necessarily mean that depression is present.)

Accordingly, improved communication between practitioners and carers through regular and (when necessary) comprehensive carer assessment is recommended. Informal feedback from general practitioner groups confirmed that they find dementia-carer communication and support a challenging field of practice.

The larger than suggested proportion of carers with high COPE Index negative impact scores (16%) in this study supports reported findings of greater negative effect in dementia-carers when compared with non-dementia carers. The negative impact scale was correlated in the expected direction with the GHQ scores and both role and personal strain scores from the Burden Interview. In contrast, the small proportion of carers (6%) with low positive value scores suggests that, although stressful, the caregiving role is satisfying for many carers.

The positive value scale correlated with personal strain and personal gain in the expected directions, although the absolute size of the correlation was more modest. The lack of significant association between positive and negative item subscales also supports previous findings as described by McKee et al.

The association between carers’ positive perception of caring and utility of the COPE Index assessment is interesting. This observation may suggest that carers who express role satisfaction (and are likely to feel well supported) have a greater capacity to appreciate the assessment process, which (in turn) affirms their role. Conversely, for carers with greater support needs, the outcomes of the assessment process may influence their evaluation of its utility.
When considering whether the COPE Index is acceptable and useful to health practitioners, our results support a cautiously positive response. Interestingly, while half the practitioners noted that the Index helped them identify areas in which carers needed support, only one practitioner reported that it helped in planning more effective support.

Given that nearly three-quarters of the carers reported that they felt well supported by health and social services, and could also identify a source of emotional support, perhaps this is not surprising. At the same time, reported support service use was only moderate, and 50% of carers indicated in their research interviews that they could have used more practical and emotional support in previous months. This illustrates disparities between carer support needs, practitioner understanding and response, and service availability and acceptability. Indeed, while carers evaluated the COPE Index positively, appreciating the opportunity to discuss issues important for them, there was also for some, a sense of frustration with regard to these issues.

Interestingly, while formal support use was generally greater, carers’ reported levels of informal support were markedly lower, and levels of expressed need higher than those recorded by Keeling\textsuperscript{15} for older people living in the community. (This may reflect the different needs and perceptions offered by older people generally, compared with the carers of older people.)

In contrast, reported levels of support (overall, by family, by friends and/or neighbours) in the COPE Index assessments were higher in this study when compared with European participant responses reported by McKee et al.\textsuperscript{10} and reported difficulties in relationships with family and friends were lower. The internal consistency and descriptive statistics reported in Table 3 reflect these differences, with positive value scores and reliability within the range reported in the literature, but negative impact descriptors lower than those reported by McKee et al.\textsuperscript{10} Despite these differences construct validity analyses were positive.

The limitations of this study need to be recognised. Although the diverse characteristics of this small dementia-carer sample are similar to previous local study samples, generalisation to the wider population is not possible. Given the small sample size, statistical tests need to be interpreted with caution. Individual tests for correlation may have been underpowered, however, initial examination of scatterplots supports the pattern of associations reported here.

In conclusion, the GP is by far the most frequently accessed formal support for carers and their care recipients. Moreover, a significant minority of carers carry a high, changing and often undiagnosed health burden which impacts on their need for, and use of support services. A deliberate and ongoing assessment of carers’ needs in the context of care planning for people with dementia may assist both carer and practitioner in more comprehensive consideration of support needs and health care.

This study and its conclusions represent an initial approach to carer assessment evaluation with a small health practitioner sample. Further carer research in both primary and secondary care settings (such as that currently being undertaken by Keeling and Roud in 2005/2006) will provide more comprehensive and conclusive results. Our preliminary results suggest that the COPE Index is an easily administered tool, which may be acceptable and useful for initiating carer-practitioner dialogue.
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Acknowledgement: This study was funded by the Canterbury Medical Research Foundation.

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8. Roud H. Living with Dementia: Evaluation of an education course for family members. MHealSc Thesis, Dept of Medicine, Christchurch School of Medicine, University of Otago, New Zealand; 2000.


25. Philp I. (Personal communication) Protocol for further validation of the COPE Index (May 2000) and revised protocol (September 2000).


Atypical antipsychotic use for adult outpatients in New Zealand’s Auckland and Northland regions

Amanda Wheeler

Abstract

Aim To outline the prescribing patterns of atypical antipsychotics for adult mental health outpatients in Auckland and Northland in 2004.

Methods All community files were reviewed retrospectively (n=6165). Patient characteristics, diagnosis, and antipsychotic and concurrent medication were recorded and analysed.

Results Overall, 71.3% of outpatients were prescribed an antipsychotic, of which 82.5% were atypicals: oral risperidone (30.9%), olanzapine (30.3%), quetiapine (17.1%), clozapine (26.3%), and depot risperidone (0.4%). Psychotic disorders accounted for 73.2% of outpatients on atypicals, and schizophrenia was the most common disorder overall (62.5%). Combination antipsychotic treatment occurred in 13.5% of those prescribed atypicals; 4.8% had another atypical and 8.7% had a typical co-prescribed. Clozapine was least likely to be combined with a typical antipsychotic. Those receiving combination typical and atypical antipsychotics had a greater likelihood of being prescribed an anticholinergic medication.

Conclusions Atypical antipsychotics are the preferred treatment for outpatients with psychotic illness and are being prescribed in a manner consistent with clinical practice guidelines. Co-prescribing of antipsychotics was low, but may be causing unnecessary adverse effects and risks.

Antipsychotics are the primary pharmacological treatment in psychotic disorders such as schizophrenia, but also have a role in the treatment of psychoses commonly seen in more severe episodes of depression or mania in the secondary care setting.

The atypical antipsychotics (clozapine, risperidone, olanzapine, and quetiapine) have been introduced into clinical use in New Zealand in the past 10 years. Generally they have comparable efficacy with typical antipsychotics in reducing positive psychotic symptoms and a growing body of evidence suggests increased efficacy for negative and neurocognitive symptoms.\(^1\)

Clozapine has been shown to be more effective in people who have not responded to other antipsychotic treatments and has a specific indication for treatment-resistant schizophrenia.\(^2,3\) Atypical antipsychotics are less likely to cause distressing extrapyramidal symptoms (particularly akathisia and tardive dyskinesia), however they do cause other unwanted effects such as weight gain and metabolic changes in lipids and glucose.\(^1\)

Emerging evidence shows that atypical antipsychotics are better tolerated and impact positively on quality of life compared to the typical antipsychotics, although well-designed controlled studies are still lacking.\(^4\)
Australasian clinical practice guidelines recommend the use of atypical antipsychotics as the treatment of choice for most patients with schizophrenia, especially for first episode psychosis, and that clozapine should be used as soon as resistance to two antipsychotics has been observed. Combination antipsychotic treatment is not recommended except for periods of switching between agents.  

The National Mental Health Plan (1997) for New Zealand, set objectives and targets to meet the goals outlined in Looking Forward: Strategic Directions for the Mental Health Services (1994).  One such objective was “to prescribe new antipsychotic medication to people who are newly presenting or who can benefit most from changing from older style antipsychotic medications (including those who currently suffer intolerable side effects).”

Additional funding was approved for this express purpose, based on the assumption that by 2001 the newer antipsychotics would be prescribed as first line treatment for psychosis throughout New Zealand. Until 1999, access to clozapine, risperidone, and olanzapine treatment had been limited because outpatient funding was restricted to discretionary use from hospital budgets. Consequently, in an attempt to meet the access targets set in the National Mental Health Plan, the three medications became fully funded on the Pharmaceutical Schedule in 1999, with the addition of quetiapine in 2001.

Ongoing funding restrictions exist for both quetiapine, which requires prescription endorsement, and for olanzapine, which requires special authorisation prior to starting treatment. A long-acting injectable atypical antipsychotic (risperidone depot) became available in New Zealand in 2003, however it has only been funded on the Pharmaceutical Schedule with special authorisation from October 2005.

Initially the funding of atypical antipsychotics was for the treatment of schizophrenia and related psychoses, however a growing body of evidence has led to changes in their registered indications to include use in other psychiatric illness including acute mania (for risperidone, olanzapine, and quetiapine), long-term treatment of bipolar disorder (risperidone and olanzapine), and behavioural problems in dementia, conduct and disruptive disorders for risperidone. Funding is not however necessarily aligned with all changes to the registered indications.

Although the Pharmaceutical Management Agency (PHARMAC) reports that spending has increased dramatically for the oral atypical antipsychotics, indicating they are being widely used, little is known about how they are actually being prescribed in clinical practice in the New Zealand community adult mental health setting.

This study investigated atypical antipsychotic prescribing for all adult outpatients treated at community mental health centres in Auckland and Northland in October 2004.

Methods
This study is a retrospective review of atypical antipsychotic prescribing in October 2004 in the four District Health Boards of Auckland and Northland (2001 catchment population 15–64 years, 872,718 people). Data were collected from clinical files for all adult outpatients treated with an antipsychotic, including demographic information (gender, age, and ethnicity), working diagnosis (DSM IV documented at the most recent medical review), antipsychotic prescribing (type,
administration route, and dose) and co-prescribed medication. The study received approval from the Auckland Regional Ethics Committee.

Data were entered into a Microsoft Access database and statistical analyses were conducted using SPSS (version 12) software. Statistical differences between groups were investigated with Chi-squared ($\chi^2$) tests for categorical values and analysis of variance for continuous variables. Post hoc comparisons were conducted using Dunnett’s T3 test. When sample distributions did not satisfy assumptions of normality (e.g. antipsychotic dose), the variable was log-transformed for analysis. Statistical significance was set at $p<0.01$.

**Results**

6165 outpatients attended community mental health services in October 2004, of whom 71.3% were prescribed an antipsychotic (n=4398). The median age of this treated population was 39 years, 59% were male, 53% identified as European, and 53% had a diagnosis of schizophrenia (Table 1).

**Table 1. Antipsychotic treatment population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2599</td>
<td>59.1</td>
</tr>
<tr>
<td>Female</td>
<td>1799</td>
<td>40.9</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>39.4 (11.6)</td>
<td>-</td>
</tr>
<tr>
<td>Median (range)</td>
<td>39 (17-80)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>2367</td>
<td>53.8</td>
</tr>
<tr>
<td>NZ Maori</td>
<td>1039</td>
<td>23.6</td>
</tr>
<tr>
<td>Pacific Nations</td>
<td>673</td>
<td>15.3</td>
</tr>
<tr>
<td>Asian/Other</td>
<td>319</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychoses</td>
<td>3228</td>
<td>73.4</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>2336</td>
<td>53.1</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>442</td>
<td>10.1</td>
</tr>
<tr>
<td>Other psychoses*</td>
<td>450</td>
<td>10.2</td>
</tr>
<tr>
<td>Mood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar</td>
<td>634</td>
<td>14.4</td>
</tr>
<tr>
<td>Depression</td>
<td>335</td>
<td>7.6</td>
</tr>
<tr>
<td>Other mood†</td>
<td>36</td>
<td>0.8</td>
</tr>
<tr>
<td>Anxiety</td>
<td>71</td>
<td>1.6</td>
</tr>
<tr>
<td>Other</td>
<td>94</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4398</td>
<td></td>
</tr>
</tbody>
</table>

*Other psychoses includes delusional disorder, brief psychotic disorder, schizophreniform disorder, substance-induced psychotic disorder, psychotic disorder not otherwise specified and secondary to a general medical condition.
†Other mood disorders includes dysthymic and, cyclothymic disorders, substance-induced mood disorder, mood disorder not otherwise specified and secondary to a general medical condition.

**Antipsychotic prescribing**—The majority of antipsychotic-treated outpatients were prescribed one antipsychotic (n=3829/4398; 87.1%). There were 542 (12.3%) prescribed two and 27 (0.6%) prescribed more than two antipsychotics concurrently. Atypicals were prescribed for 82.5% of this treated population (n=3629/4398).
Typical antipsychotics were prescribed for 26.3% (n=1156/4398); 8.7% typical oral (n=381) and 17.6% typical depot treatment (n=775).

**Atypical prescribing**—Within the outpatient group prescribed atypicals (n=3629), the most common medications were risperidone (n=1120;30.9%) and olanzapine (n=1099;30.3%). Fifteen outpatients (0.4%) were prescribed the atypical depot risperidone and one was prescribed aripiprazole via a clinical trial.

Table 2 shows the distribution of oral atypical antipsychotic use and doses prescribed by diagnosis. Most of the outpatients prescribed an atypical antipsychotic had a diagnosis of a psychotic disorder (n=2655;73.2%); the most common disorder overall was schizophrenia/schizoaffective disorder (n=2268;62.5%). The atypicals were also being used for other disorders; 23.6% (n=856) for mood disorders, including 14.4% with bipolar disorder (n=522), 8.4% for depression (n=305), and 3.3% (n=118) for ‘other’ disorders (including anxiety, substance-related, adjustment, cognitive and Axis II disorders). The average dose for risperidone, olanzapine and quetiapine was significantly higher for those outpatients with psychotic disorders (Table 2 footnotes).

Table 2. Oral atypical antipsychotic prescribing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Clozapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>1120 (30.9)</td>
<td>1099 (30.3)</td>
<td>619 (17.1)</td>
<td>954 (26.3)</td>
</tr>
<tr>
<td>Dose (mg/day)</td>
<td>Mean (SD) Median (range)</td>
<td>Mean (SD) Median (range)</td>
<td>Mean (SD) Median (range)</td>
<td>Mean (SD) Median (range)</td>
</tr>
<tr>
<td>Psychoses</td>
<td>751 (21) 3.3 (1.8)</td>
<td>818 (22.5) 16.4 (7.6)</td>
<td>299 (8.2) 395 (289)</td>
<td>924 (25.5) 371 (152)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>494 (13.6) 3.6 (1.9)</td>
<td>545 (15) 17.3 (7.5)</td>
<td>178 (4.9) 410 (290)</td>
<td>811 (22.3) 375 (150)</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>89 (2.5) 3.3 (1.8)</td>
<td>125 (3.4) 16.4 (7.7)</td>
<td>57 (1.6) 377 (312)</td>
<td>100 (2.8) 340 (173)</td>
</tr>
<tr>
<td>Other Psychoses</td>
<td>168 (4.6) 2.7 (1.4)</td>
<td>148 (4.1) 13.3 (6.8)</td>
<td>64 (1.8) 370 (270)</td>
<td>13 (0.4) 308 (131)</td>
</tr>
<tr>
<td>Mood</td>
<td>316 (8.7) 2.4 (1.5)</td>
<td>265 (7.3) 13.3 (7.8)</td>
<td>269 (7.4) 318 (227)</td>
<td>29 (0.8) 318 (156)</td>
</tr>
<tr>
<td>Bipolar</td>
<td>172 (4.7) 2.6 (1.6)</td>
<td>205 (5.6) 13.9 (7.9)</td>
<td>134 (3.7) 270 (246)</td>
<td>26 (0.7) 318 (164)</td>
</tr>
<tr>
<td>Depression</td>
<td>136 (3.7) 2.0 (1.3)</td>
<td>53 (1.5) 10.9 (6.5)</td>
<td>120 (3.3) 197 (196)</td>
<td>3 (0.1) 317 (76)</td>
</tr>
<tr>
<td>Other Mood</td>
<td>8 (0.2) 2.6 (1.6)</td>
<td>7 (0.2) 15.4 (8.2)</td>
<td>15 (0.4) 198 (242)</td>
<td>- -</td>
</tr>
<tr>
<td>Other</td>
<td>53 (1.5) 2.6 (1.8)</td>
<td>16 (0.4) 11.6 (6.6)</td>
<td>51 (1.4) 316 (302)</td>
<td>1 200</td>
</tr>
</tbody>
</table>

Note: Some patients are prescribed more than one antipsychotic; *Risperidone dose log transformed F2,1117=18.53, p<0.01; †Olanzapine dose log transformed F2,1096=8.12, p<0.01; ‡Quetiapine dose log transformed F2,616=26.96, p<0.01; §Clozapine dose log transformed F2,951=0.67, p= 0.04.

The proportion of outpatients prescribed oral atypical antipsychotics within the treated population for the three major disorders of schizophrenia (including schizoaffective disorder), bipolar, and depression is shown in Figure 1. Clozapine is mainly being prescribed for its registered indication of schizophrenia. For the schizophrenia group, it is the most frequently prescribed atypical antipsychotic. Olanzapine is the most commonly used atypical for bipolar disorder, and risperidone is the most commonly used atypical for those outpatients with a primary diagnosis of depression.
Figure 1. Proportion of treated outpatients by atypical antipsychotic and diagnosis

![Proportion of treated outpatients by atypical antipsychotic and diagnosis](image)

Note: Some patients are prescribed more than one antipsychotic.

**Antipsychotic co-prescribing**—For those outpatients prescribed an atypical agent, 86.5% (n=3138/3629) were prescribed antipsychotic monotherapy. The type of co-prescribing for each of the five atypical formulations is shown in Table 3.

Co-prescribing with another atypical occurred for 4.8% (n=175/3629) and in combination with a typical antipsychotic for 8.7% (n=316/3629) of outpatients. When a single oral atypical was prescribed in combination with a typical antipsychotic (n=311/3436), clozapine was found to be the least likely agent (n=24/869;2.8%), compared with risperidone (n=117/999;11.7%), olanzapine (n=102/1037;9.8%), and quetiapine (n=68/531;12.8%) ($\chi^2=60.22$, df=3, p<0.01).

**Anticholinergic co-prescribing**—Co-prescription with an anticholinergic medication occurred for 404 (11%) outpatients prescribed an atypical. Anticholinergics were significantly more likely to be prescribed for outpatients concurrently prescribed combination atypical and typical therapy (n=116/316; 36.7%) compared to both atypical monotherapy (n=269/3138;8.6%) and two atypicals (n=19/175;10.9%) combined ($\chi^2=229.75$, df=2, p<0.01).

In comparison, the rate of anticholinergic co-prescribing for those outpatients prescribed typical antipsychotic treatment only (typical monotherapy or a combination of typical antipsychotics) was 31.5% (n=242/769).
Table 3. Atypical antipsychotic co-prescribing

<table>
<thead>
<tr>
<th>Co-prescribed Antipsychotic</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Clozapine</th>
<th>Depot Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>-</td>
<td>20</td>
<td>39</td>
<td>58</td>
<td>-</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>20</td>
<td>-</td>
<td>31</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>39</td>
<td>31</td>
<td>-</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>Clozapine</td>
<td>58</td>
<td>7</td>
<td>18</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Depot Risperidone</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Typical Oral

| Chlorpromazine               | 17          | 11         | 5          | 6         | -               |
| Haloperidol                 | 6           | 8          | -          | 1         | 1               |
| Methotrimeprazine           | 1           | 2          | -          | 2         | -               |
| Penfluridol                 | -           | -          | 1          | -         | -               |
| Thioridazine                | 7           | 2          | 2          | 1         | -               |
| ThiOTHIXINE                 | 2           | 1          | 1          | -         | -               |
| Trifluoperazine             | 3           | 5          | 2          | 3         | -               |
| Zuclopenthixol              | -           | 1          | 1          | 1         | -               |

Typical Depot

| Flupenthixol                | 37          | 42         | 24         | 3         | -               |
| Fluphenazine                | 18          | 6          | 6          | 1         | -               |
| Haloperidol                 | 10          | 5          | 11         | -         | -               |
| Pipothiazine                | 6           | 6          | 8          | -         | -               |
| Zuclopenthixol              | 3           | 5          | 4          | -         | -               |

2+ Antipsychotics           | 11          | 10         | 2          | 3         | -               |

Total 238 (21%) 164 (15%) 156 (25%) 109 (11%) 3 (20%)

Discussion

This study of outpatient antipsychotic treatment found the majority of patients were treated with a single antipsychotic. Atypical antipsychotics were the preferred treatment prescribed by community mental health services. They are being used primarily for psychotic disorders such as schizophrenia.

The expansion of registered indications for treatment is reflected in the study findings for clinical use of these agents for disorders beyond psychosis. Despite the fact that the study found little ‘off-label’ use in clinical practice, some prescribing for atypicals may be outside of approved funding.

Risperidone and olanzapine were prescribed equally often, similar to United Kingdom and United States prescribing reviews—and in contrast with Australia where olanzapine accounted for 65% of atypical prescriptions. Similar use of risperidone and olanzapine in New Zealand practice may reflect the impact of PHARMAC funding restrictions rather than prescriber preference alone.

The lower rate of quetiapine usage in this study possibly reflects its later entry into the New Zealand market, as little difference in efficacy has been reported between risperidone, olanzapine, and quetiapine in the management of schizophrenia and other psychotic disorders. They are each generally well tolerated but have different adverse effect profiles.
Within the treated group with schizophrenia, 33% were prescribed clozapine, which is in line with estimates of treatment-resistant illness. An internationally recognised conservative estimate of treatment resistance is 30%.\(^{17}\) The mean and median doses for all four atypical antipsychotics are consistent with international practice.\(^{14,18}\) The mean doses were consistently higher in the treatment of psychotic disorders, in particular schizophrenia, which is also in line with other community practice.\(^{14}\)

Combinations of an atypical plus another antipsychotic were observed in 13.5% of outpatients, however the best-practice recommendation in the Australasian guidelines for use of combinations is only for transitioning from one antipsychotic to another.\(^{5}\)

Atypical and typical combinations are especially contentious, as they are likely to reduce the major advantages of the atypical group (particularly the risk for extrapyramidal and secondary negative symptoms). Anticholinergic medications are primarily used in psychiatry to treat extrapyramidal symptoms (with the exception of clozapine-induced hypersalivation).

This study found that anticholinergics were more likely to be prescribed when atypicals and typicals were combined. The rate was very similar to that found when typical antipsychotics were prescribed alone, thus indicating extrapyramidal symptoms were a problem (but were not necessarily worsened by the combination), and a major advantage of atypical treatment had been lost.

Other disadvantages of anticholinergics include new or additive adverse effects (e.g. dry mouth, blurred vision, and constipation), which may further reduce quality of life and complicate medication regimens and adherence for outpatients.

Little evidence supports antipsychotic combinations, but (in exceptionally difficult situations) evidence supports augmentation of clozapine with another antipsychotic, particularly sulpiride\(^{19}\) (not available in New Zealand) and risperidone\(^{20}\).

Antipsychotic polypharmacy is included in an American clinical practice guideline for patients with resistant illness (including combinations when clozapine is contraindicated, e.g. history of agranulocytosis or patient refusal).\(^{21}\)

Just over half of the instances of co-prescribing with clozapine in this study were with risperidone, however it was beyond the scope of this study to examine the clinical indications for co-prescribing practice. Despite this rationale for co-prescribing, certain practices observed in this study have no evidence to support their use, including multiple (more than two) antipsychotics and combinations of clozapine and depot antipsychotics. (The latter should be avoided because of the risk of prolonged bone marrow suppression.)

The findings of this study represent ‘real-world’ prescribing for all adult community mental health patients in Northland and the three Auckland District Health Boards (Counties Manukau, Auckland, and Waitemata). It reflects the total antipsychotic regimen that the prescriber intended the patient to take at the time of the review however the study did not explore adherence to treatment or the clinical effects of treatment.

The study methodology employed data collected retrospectively from clinical files, which confers a limitation regarding accuracy and completeness of the information.
Wherever possible, the researchers attempted to clarify ambiguous or missing data with clinicians involved in the patient’s care. Treatment data was recorded from the medication chart, confirmed with duplicate copies of prescriptions if these were filed and in the body of the clinical notes for the audit period. For example, ‘prn-if required’ medication was only recorded in the study if it was clearly documented that the prescriber had intended the outpatient to be taking this medication at the time of the audit and/or a prescription had been provided.

The findings may not be generalisable to other outpatient settings such as elderly and child and adolescent services or primary care, however the study reflects antipsychotic prescribing for about one-third of adult community mental health patients in New Zealand by more than 50 prescribers.

In summary, this study found that atypical antipsychotics are the preferred treatment for outpatients with psychotic illness. They are generally being prescribed in a manner that is consistent with clinical practice guidelines. The use of combinations of antipsychotics, whilst encouragingly low, may be causing unnecessary levels of adverse effects and risks for patients and increasing the cost of care.

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Quetiapine and citalopram: aetiological significance in serotonin syndrome

Karl Marlowe, Dorothea Schirgel

Abstract

The use of atypical antipsychotic medication is increasing, with an increase in reported side-effects. The first reported case of quetiapine and citalopram-associated serotonin syndrome is discussed with reference to a Medline, Embase, and PsycINFO literature search. The putative aetiological mechanism is supersensitivity of 5-HT(1A) receptors (quetiapine) within an environment of increased synaptic available serotonin (citalopram). The symptom profile of serotonin syndrome overlaps with neuroleptic malignant syndrome, but can be reliably differentiated using a time and toxicity scale.

Quetiapine is a second generation atypical antipsychotic with both dopaminergic and serotonergic receptor antagonism. Specific mesolimbic D2 and weak 5-HT(2A) antagonism is hypothesised for the lack of extrapyradimal side-effects compared to typical antipsychotic medication.

At high doses, there is greater 5-HT(2A) antagonism, which leads to an increase in synaptic availability of both dopamine and serotonin, and to 5-HT(1A) hyperactivation.\(^1\) It is the 5-HT(1A) agonist action which has aetiological relevance to a serotonin syndrome.\(^2\) There are no reported cases of quetiapine associated with serotonin syndrome on a MEDLINE, EMBASE, and PsycINFO database search.

Citalopram is a selective serotonin re-uptake inhibitor (SSRI), which increases the synaptic availability of serotonin. The potential for citalopram to cause serotonin syndrome on monotherapy is reported to increase on combination therapy with other psychotropic medications.\(^3\)\(^-\)\(^6\)

Case report

A 42-year-old Caucasian woman, with a 5-year history of bipolar affective disorder—and taking 40 mg of citalopram, 800 mg of quetiapine, and 1.25mg of alprazolam per day—took an extra 200 mg of quetiapine in the morning. Within 12 hours, on that day, she was delirious and agitated. She remembered “explosions in my head,” was incontinent of urine, disorientated, and unable to drive.

She presented with hyper-reflexia, muscle rigidity, and dehydration with abnormal blood creatine kinase (CK=3005) on admission. The initial treatment consisted of IV fluids, discontinuation of previously prescribed medications, blind IV antibiotic (pre-antibiotic blood cultures were negative), and oral benzodiazepines.

After 48 hours of treatment, low-dose risperidone was initiated as prophylaxis for psychosis, and was increased to 2 mg per day within 1 week. By 1 week, she had made a full physical recovery (with a normal range of routine blood levels) and she reached a stable mental state.
Maintenance treatment consisted of risperidone and alprazolam (reducing dose), with a continued remission at 10 weeks’ follow-up. This case presentation is idiosyncratic, but the validity and aetiological mechanism for serotonin syndrome can be explored in this context.

**Discussion**

With the exclusion of anti-dopaminergic medication, exclusion of medical conditions, and with the consumption of serotonin agent, serotonin syndrome can be classified into three stages on the basis of clinical severity—with (1) mild state of serotonin-related symptoms, (2) full-blown serotonin syndrome, and (3) toxic states.\(^7\)

The Hunter Serotonin Toxicity Criteria incorporates this variation in severity with a clinical differentiation of neuroleptic malignant syndrome (NMS).\(^8\) Criteria for differentiating NMS from serotonin syndrome are summarised in Table 1.

**Table 1. Differentiating increasing severity of serotonin syndrome from neuroleptic malignant syndrome**

<table>
<thead>
<tr>
<th>Serotonin syndrome: acute onset within 24 hours, with rapidly increasing severity</th>
<th>Neuroleptic malignant syndrome: delayed onset of days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restlessness</td>
<td>As for serotonin syndrome, plus early evidence of:</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>• Muscle hypertonicity</td>
</tr>
<tr>
<td>Tremor</td>
<td>• Increased CK and WCC</td>
</tr>
<tr>
<td>Shivering</td>
<td>• Autonomic dysfunction prominent</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Longer duration of symptoms, up to 1–2 weeks of stopping medication</td>
</tr>
<tr>
<td>Temp greater than 38°C</td>
<td>Differential diagnosis includes catatonia or encephalitis</td>
</tr>
<tr>
<td>Hyper-reflexia</td>
<td></td>
</tr>
<tr>
<td>Elevated CK level</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
</tr>
<tr>
<td>Seizure activity</td>
<td></td>
</tr>
<tr>
<td>Rapid improvement within days of stopping medication</td>
<td></td>
</tr>
</tbody>
</table>

CK=Creatine Kinase; WCC= White Cell Count.

The putative mechanism for serotonin syndrome is of increased brainstem and spinal cord 5-HT(1A) receptor modulation occurring with 5-HT(2A) receptor antagonism. It is this synaptic system, which is the association for atypical antipsychotics and serotonin syndrome.

In the comparison of atypical antipsychotic medication on the 5-HT(2A) and 5-HT(1A) systems, quetiapine has theoretically the lowest risk. This is due to significantly less receptor binding, with 100 to 200 times less receptor potency at 5-HT(2A)—compared to risperidone, olanzapine, and clozapine.\(^9\)

This case report would, however, indicate that even with quetiapine having moderate 5-HT(2A) receptor antagonism, there is still clinical significance at the upper dose range. Ziprasidone, which has direct 5-HT(1A) receptor agonism has, conversely, the greatest theoretical potential for serotonin syndrome.
The only temporal change prior to the manifestation of symptoms in the case presented, was of an increase in quetiapine rather than a change in citalopram dose, and this would strengthen the hypothesis of 5-HT(2A) and 5-HT(1A) receptor mediation. A total dose of 1000 mg per day of quetiapine is not particularly unusual clinically, but the increased sensitivity may occur from the increase of synaptic serotonin with the co-prescription of citalopram 40 mg per day.

The initial management of serotonin syndrome is to discontinue the suspected serotonergic agent and the institution of supportive measures. Broad 5-HT receptor antagonists may also play a role, with short-term prescription of cyproheptadine or propranolol in severe toxic states. Treatment in toxic hyperthermia with seizure activity, includes intubation, anticonvulsant, and antihypertensive management.

The early detection of serotonin syndrome can decrease the morbidity before rapid progression of severity. Once treatment is instituted, the physical syndrome typically resolves within 24 hours, but confusion can last for days. In the case presented, after 48 hours, risperidone was initiated with a successful prophylactic outcome at 10 weeks’ follow-up. Furthermore, it needs to be noted that the introduction of another atypical antipsychotic (5-HT(2A) receptor antagonist) may resemble a worsening psychosis due to mild serotonin toxicity.

Conclusion

The aetiological significance with the combination of a selective serotonin reuptake inhibitor (SSRI) and atypical antipsychotic medication increases the risk of serotonin syndrome—even if there is very low affinity for either 5-HT(2A) or 5-HT(1A) receptors.

Despite the findings of this case report, quetiapine (at normal dose) has the lowest theoretical risk of serotonin syndrome compared to other atypical antipsychotic medication. This case indicates the possible increase in risk if specifically co-prescribed with citalopram. The treatment of serotonin syndrome shows rapid improvement, and can be differentiated from NMS with high specificity using a high index of suspicion and reliable criteria.

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Spontaneous recovery in a case of Miller-Fisher syndrome presenting as polyneuritis cranialis

Subhasis Roy Chowdhury, Partha Chakraborty, Shounak Majumder, Dipanjan Bandyopadhyay, Ananya Chattopadhyay, Krishna Basu

Guillain-Barré syndrome (GBS), or acute inflammatory demyelinating polyneuropathy (AIDP), is typically characterised by rapidly evolving areflexic motor weakness.

Miller-Fisher syndrome (MFS) is a rare variant of GBS characterised by the triad of ophthalmoplegia, ataxia, and areflexia. Unlike GBS, MFS has an excellent prognosis; hence early clinical recognition may save the patient from costly therapy.

Case report

A 52-year-old male developed (10 days prior to presentation at our hospital) acute onset drooping of both eyelids (Figure 1), followed by gradual progressive inability to move his eyeballs in any direction. Furthermore, he reported unsteadiness of gait, dribbling of food from both the corners of his mouth, slurring of speech, and aches and pains over his entire body. His symptoms were without any diurnal variation. One month earlier, the patient reported having an episode of sore throat with fever.

Figure 1. Bilateral ptosis, complete external ophthalmoplegia, and bilateral lower motor neurone (LMN) facial palsy at presentation

(This photograph is reproduced with kind permission from the patient)
The patient had slurred speech, bilateral ptosis, and complete external ophthalmoplegia with dilated, sluggish-reacting pupils and bilateral lower motor neurone (LMN)-type facial palsy.

The tone and power of all limbs were normal without any obvious atrophy or fasciculation. Plantar responses were flexor. Deep tendon reflexes could not be elicited, even on reinforcement. All modalities of sensation were preserved.

Although coordination of his lower limbs were impaired, other tests for cerebellar functions were normal. He could stand without support but tended to fall to either side while attempting to walk. Examination of the other systems was normal.

There was no detectable abnormality on the brain CT scan. Cerebrospinal fluid (CSF) analysis, performed 7 days later, revealed 5 cells/cmm with protein 102 mg/dL. Electrophysiological studies documented reduced sensory nerve action potential (SNAP) and slightly diminished motor nerve conduction in peroneal nerves with normal F-latencies. A Tensilon test was also performed, which was negative.

We diagnosed a case of Miller-Fisher variant of Guillain-Barré syndrome. He recovered completely in 10 weeks.

**Discussion**

The usual case of GBS/AIDP is readily identified. However, characteristic absence of proximal weakness with the clinical triad of ophthalmoplegia, ataxia, and areflexia is an important pointer to the diagnosis of MFS. Neuropathological studies in MFS have documented peripheral demyelination,\(^1\) thus confirming it to be an unusual variant of GBS.

Patients may present with or without ptosis but are characterised by preservation of motor strength, as in our case. Deep aching pain is common in GBS.\(^2\) A mismatch between proprioceptive sensation and kinaesthetic input, from muscle spindles and joint receptors respectively, accounts for the ataxia.\(^3\)

Patients presenting with rapid onset of symmetrical, multiple cranial nerve palsies (most notably bilateral facial palsy) may be a characteristic of this syndrome.

Our patient had bilateral oculomotor, trochlear, abducens, and facial nerve involvement. Other aetiologies of multiple cranial nerve palsy were excluded by appropriate investigations. CSF analysis showed increased protein, but normal cells (albuminocytological dissociation), and electrophysiological studies were consistent with a diagnosis of MFS.

In 1992, an association of MFS with antiGQ1b antibodies was suggested by Chiba et al.;\(^4\) it is currently documented in over 90% of cases. However, we could not estimate the titres due to cost constraints.

Lastly, we would like to highlight that, in spite of an alarming onset, most patients with MFS (including our patient) recover completely in 8–12 weeks, even without immunoglobulin treatment.\(^5\)
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Electroconvulsive therapy in New Zealand: terrifying or electrifying?

Pamela Melding

Abstract

Electroconvulsive therapy (ECT) is viewed by many patients as a ‘terrifying’ treatment. A petition to ban ECT presented to the House of Representatives in 1999 resulted in the commissioning of a comprehensive review of efficacy and safety of the treatment in New Zealand as well as a requirement for the Ministry of Health (MOH) to collect annual statistics on ECT use.

Although the systematic review found that ECT was a safe and effective treatment for depression and some other serious mental illnesses, it still attracted adverse comments from opponents. Almost immediately following its publication, another petition was presented to Parliament, this time requesting that ECT be banned for young people, pregnant women, and older people.

Compared to similar countries, New Zealand has a low rate of use for ECT overall, with wide regional variance. There are many misconceptions about ECT in New Zealand that are not in keeping with current standards of practice and may be limiting its use in some areas. However, access to resources for the treatment of depression may be a major limiting factor. ‘Electrifying’ new research emanating from neurobiological and magnetic resonance imaging (MRI) studies is challenging traditional notions of depression, and is providing more explanations on how ECT and other antidepressant treatments might work. These new findings demonstrate that cognitive deficits and structural brain changes play important roles in serious depression and suggest that early and adequate treatment of major depression should be paramount.

Background

In 1999, a petition presented to Parliament requested that the House of Representatives ban electroconvulsive therapy (ECT)—a treatment option for severe depression—stating that the treatment is “degrading and inhumane” and “the scientific fact is that ECT always causes brain damage including memory loss.”

The Health Select Committee, after hearing many submissions on both sides of the argument, made several recommendations. Amongst them was the commissioning of an independent review of the efficacy, safety, and legal aspects of ECT in New Zealand, and a request to the Ministry of Health (MOH) to collect and publish annual statistics on ECT use in New Zealand.

Previous meta-analytic systematic reviews of properly conducted current controlled trials had concluded that ECT was an effective and safe treatment but a New Zealand-specific review was sought by the Health Select Committee. The reviewers were Professor Craig Anderson (a neurologist and expert in evidence-based medicine), Professor Peter Skegg (a lawyer), and Ms Ranui Wilson (a consumer
consultant). To ensure impartiality, neither a psychiatrist nor a member of the anti-ECT lobby were included as reviewers. An expert reference group of stakeholders advised the Review Group on the practice of ECT together with cultural and social issues directly relevant to New Zealand.

The Review Group evaluated over 400 scientific papers using the guidelines methodology of the New Zealand Guidelines Group (NZGG) and the Scottish Intercollegiate Guidelines Network (SIGN). They also appraised the various Acts of Parliament and regulatory documents concerning ECT in New Zealand and similar nations, and they undertook focus groups meetings to incorporate the views of consumers.

The Review Group concluded that ECT is an effective treatment for depression and some other serious mental illnesses and stated that the treatment should not be banned. However, they stated that there was a lack of randomised evidence that could inform definitive statements about the efficacy and safety of ECT given to the special population groups of young people, pregnant women, and older people. They were also concerned about the adequacy of legal provisions regarding informed consent.

Despite the comprehensiveness of the review, the petitioners and opponents of ECT described the review as “flawed,” and they questioned the impartiality and integrity of the reviewers by suggesting their independence could have been “compromised” because they were “hand-picked” by the MOH.

A few weeks later, a new petition was presented to Parliament requesting that ECT be banned for those special groups of patients highlighted by the Review as lacking randomised evidence.

Simultaneously with the review’s publication in March 2005, the first year’s raw statistics were prematurely posted on the MOH website. The data collection was very basic and showed that there was wide variation in its use across the country. They indicated that a considerable number of patients were being treated under the provisions of the Mental Health Act, people over 60 years received 45% of treatments and that two-thirds of ECT was given to women. Despite the statistics being removed within hours of posting, an immediate media reaction ensued (with articles, radio interviews, and press releases).

The raw statistics were described as “appalling” and “shocking” in the press release of one prominent member of Parliament. Precipitate and ill-informed interpretations in the media of the unpublished data gave the impression that district health boards (DHBs) had been exposed in a nefarious use of a terrifying treatment. This reaction was a very good example of how simplistic data can be easily over-interpreted. The 2003–4 statistics, together with those for the latest year of 2004–5, will be officially published shortly. We can expect a similar media response on their release.

**Rates of use**

The new petition is currently before the Health Select Committee and once again puts ECT into the spotlight. The use of the treatment in New Zealand needs to be put into perspective with use in similar nations. ECT is not a major treatment option in New Zealand, and currently we have a mean rate of 8 courses per 100,000 adult population (MOH statistics).

In contrast, Scotland recently reported a rate of 19.7/100,000, Wales a rate of 22 patients per 100,000, and the Australian state of Victoria an adult rate of 44/100,000
in the public sector. Rates of ECT use in Australian psychiatry private practice averages 22/100,000, with a range across the states from 34/100,000 in Queensland to 14/100,000 in Western Australia. Furthermore, ECT use in Australian private practice has been steadily increasing each year since 1991.

The number of individual ECT courses done also needs to be seen in the context of the prevalence of severe depression in our communities. The Christchurch epidemiology study found the 2-week prevalence of major depressive episodes was 3.7%. This suggests that in any 100,000 population, 3700 individuals could, theoretically, have the most severe forms of depression needing clinical management. Of these individuals, clinical trials indicate that 70% could be expected to respond to each class of antidepressants, thus controlling symptoms for about 90%.

In New Zealand, ECT is only considered as a last resort treatment for people who have usually failed at least two (sometimes more) trials of different classes of antidepressants, each trial taking several weeks to months. Thus, the 10% (theoretically 370 people) who don’t respond to two antidepressants are the patient population for whom ECT might be indicated. Consequently, even the highest rate of 22 patients per 100,000 given ECT in some DHBs indicates that only 0.6% of potentially seriously depressed patients in their catchments are actually treated with ECT.

The large range in the rates of use of ECT across the nation, from 22–1/100,000, is intriguing and there could be many factors contributing. However, an important contributor could be access to treatment for serious depression. As individuals having ECT are at the very severe end of the depressive spectrum, they are often unable to look after themselves or maybe acutely suicidal, and they usually require hospitalisation for their course of ECT. Access to inpatient bed resources also vary markedly throughout the country and it is interesting to note that the DHBs with more inpatient beds per unit of population also do more ECTs than those with proportionally fewer beds.

The decline of ECT as a treatment in New Zealand has probably less to do with its efficacy as a treatment (or negative public opinion) and more to do with lack of access to treatment facilities for adequate treatment of depression.

The unpublished Ministry data indicates that a higher number of women are receiving ECT. Whilst this seemed sinister to some critics, there are reasonable explanations. There is a female preponderance in the epidemiology of depression, and women more commonly present to mental health services and are admitted to inpatient facilities.

Critics of ECT argue that the treatment is more commonly given to older people. However, the MOH data shows that there are slightly more people under 60 years having ECT (55% in 2003/4 and 53% in 2004/5) than over 60 years. This is despite the fact that older people have more co-morbidities, which makes the prescribing of all classes of antidepressants problematic in terms of side effects, and they have fewer options for the treatment of depression.

There is also increasing good evidence (from meta-analyses of random controlled trials [RCTs] and good quality non-RCT research) that ECT is an effective treatment for late-life depression and its severest form melancholia. This latter
condition is not only more common in older people but can be life-threatening due to poor nutrition and hydration.

Consent

The ECT Review\textsuperscript{7} was quite justifiably concerned with issues of consent for ECT, as this is a major issue for some critics. As one report put it, \textit{Treatment without patient consent is interpreted by some as the arrogance of the medical profession versus the powerlessness of the patient.}\textsuperscript{20}

When the MOH data indicated that a considerable number of patients having ECT were also under the Mental Health Act (24\% in 2003/4), opponents to ECT in New Zealand quickly assumed that, \textit{our regulatory controls are insufficient to prevent excesses}.\textsuperscript{8}

Most patients are capable of informed consent,\textsuperscript{21} but for some, the most important issue is not their willingness to consent but their ability or competency to make decisions concerning their treatment. As ECT is usually indicated only late in a patient’s illness (at its most severe after failure of conventional treatments), they are often extremely mentally unwell, depressive thinking rendering them incapable of weighing up relevant information or making decisions about ECT or any other treatment.

Use of the regulatory controls for patients who are incapable of giving informed consent (because of severe illness) indicates that the Mental Health Act is working and that patients having a controversial procedure are being protected by a defined legal process that requires two consultant psychiatrists to approve the treatment. The provisions of the Mental Health Act make sure that if individuals are incapable of, or passively consenting without understanding, there is an oversight process set in motion. Furthermore, a treatment order under the Mental Health Act does not necessarily mean the patient did not voluntarily consent to the procedure.

Misconceptions about ECT

There are many misconceptions held by the general public about ECT. The stories of former patients appear frequently in the media, with the implication that their experiences would be as true today as they were half a century ago. These influences, despite the patients lacking knowledge of modern day practice, are pervasive on politicians and even health professionals.\textsuperscript{22}

Kerr et al\textsuperscript{23} identified four sources from which the public form their impressions about ECT. These were (in order of frequency) a friend; films and television; a doctor; and newspapers and magazines. In the twenty-first century we should add the Internet as a primary source, which has many websites perpetuating terrifying myths about ECT.

Kerr found that subjects whose information had come from a doctor had significantly fewer misbeliefs but those who identified films and television or a friend as a source of information held significantly more erroneous views and were more afraid of ECT.

Recent research from two Scottish universities, on the views of patients following ECT, found that the patients considered ECT helpful for 73\% having the treatment voluntarily, and also helpful for 81\% of the patients who had not consented.\textsuperscript{24} Other studies\textsuperscript{25,26} showed similar results. People exposed to the treatment for themselves,
family, or friends have far fewer misconceptions and more positive attitudes. But, for others, the misconceptions continue. Whilst the technology, techniques, and practice of ECT have progressed in keeping with other medical practice, the public perception is still rooted in the 1950s and 1960s with ideas kept alive by sensationalist media and Internet articles, more interested in perpetuating the misbeliefs than reporting clinical evidence.

The original petition cited the misconception that ECT is “degrading and inhumane”. Current practice is no more degrading or inhumane than is any other procedure requiring anaesthesia. Is it the epileptic seizure, which occurs during treatment that is perceived as inhumane, despite it being barely noticeable in today’s clinical practice, or is it the notion that having severe depression that fails to respond to treatment is degrading?

The interesting issue of ‘brain damage’

The over-riding concern of ECT opponents is the scientific fact that ECT always causes brain damage including memory loss. However, this assertion is simply not true and completely ignores the evidence-based medical approach. Indeed, much of the ‘scientific’ evidence cited to support the ‘fact’ is anecdotal, outdated, and some of it discredited.

A popular misconception is that all memory loss, transient or prolonged, during or following ECT, is a result of the treatment. Certainly, patients can and may experience declarative and episodic memory loss during their course of ECT. For the majority, this is transitory, improving within a few weeks, sometimes to a much better level than it was before the treatment began. These temporary memory disturbances are thought to be caused by the various neurochemical changes that occur with the ECT induced seizure. In animal experiments, these changes reverse after about 40 days, with return of memory functions.

Depression and cognitive deficits

Significantly, depression itself causes memory loss. Porter et al assessed depressed drug-free adults, not having ECT, on a range of neuropsychological instruments and found the patients had impairments across a range of cognitive domains, including attention/executive function and visiospatial learning and memory. Other workers have found similar results with elderly depressed people.

Importantly, for some adult and older patients, cognitive impairments, including memory losses, can persist despite clinical recovery. The advent of the MRI scanner has started to clarify this phenomenon.

We now know that treatment-resistant depression and chronic psychological stress can cause structural loss of neurons in the limbic system, hippocampus, and frontostriatal regions of the brain (areas important for memory function), and that these changes increase with age. These findings are overturning traditional theories of the aetiology of depression, casting doubt on the notion that the cognitive impairment of depression is solely due to mood disturbance and/or neurotransmitter imbalance. Instead, this new research is pointing to structural brain changes playing an important role.
Seizures and ‘brain damage’

Opponents argue that inducing seizures causes brain damage. Several studies have shown that seizures can cause brain damage if they are prolonged or under conditions of hypoxia. Such conditions possibly did apply to some people in the days of unmodified ECT and, together with the now outdated use of sine wave delivery machines, they may explain many of the memory complaints patients from that time suffered.

In modern ECT, the brief-pulse seizures are highly controlled, lower in dose, and given under oxygenation and anaesthesia. Under these conditions, structural damage has not been shown despite several prospective MRI studies of the brain, or cerebrospinal fluid (CSF) and blood marker studies for products of neuronal breakdown.\(^{41,42}\)

In contrast, ‘cutting edge’ neurobiological research is revealing that both antidepressants and ECT cause an increase not only in neurotransmitters important in maintaining mood but also brain-derived neurotrophic factor (BDNF), and other neurobiological factors that actually enhance new neuronal growth.\(^{38,39,43–46}\) Furthermore, of all the antidepressant treatments, ECT seems to be the most effective method of inducing neurogenesis, at least in animal models.\(^{47}\) This rapidly-growing, exciting field of research is promising to identify the neurobiological changes underpinning observed clinical improvement,\(^{45}\) which in turn will lead to newer and better treatments for depression, including increasingly sophisticated brain stimulation techniques.\(^{48}\)

Conclusion

It was naïve to think that the Review Group’s comprehensive review would resolve the controversies about ECT for New Zealand. The people, who believe that they have suffered as a result of ECT in the past, and their supporters, are committed to seeing the treatment banned.

The latest petition\(^9\) will no doubt be followed by another, if the current one also fails to secure the opponent’s main objective. In the past, misuse and inappropriate use of ECT certainly occurred in New Zealand and overseas. However, the correct response to misuse is not to ban use but to make sure there is correct use. Current practice guidelines and high-level training requirements for ECT are designed to do just that.

Unfortunately the new petition on ECT is likely to focus attention onto this very small area of psychiatric practice, diverting (once again) from the much bigger issue of access to treatment for depression in New Zealand.

Inpatient facilities are at capacity treating major psychoses leaving few beds for treating depression. Furthermore, not enough people with depressive disorders can access treatment from primary care through to tertiary services. The struggle needs to be directed towards making sure there are sufficient resources to treat depression early and adequately.

For the few who do require ECT, the clinical evidence from controlled trials has clearly demonstrated its efficacy for treatment resistant depression and some other serious mental disorders. New research is giving us major insights into the
neurobiology of depression and its treatments and is signalling the importance of treating depression early and comprehensively.

ECT in New Zealand is well beyond its history, perceived as ‘terrifying’ by many, and ‘electrifying’ new research is confirming ECT’s place as an important option for the treatment of serious depression.

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**References:**


Quality improvement in healthcare in New Zealand. Part 1: what would a high-quality healthcare system look like?

Mary Seddon on behalf of EPIQ*

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Abstract

This Special Series attempts to define what a high-quality healthcare system would look like for New Zealand. The Series focuses on the dimensions of a quality service—safety, access, equity, effectiveness, efficiency, and patient centeredness—not only elucidating in plain language what these dimensions are, but how they might be measured and improved. The central premise is that clinicians need to become involved in measuring and improving the quality of healthcare provided.

To assist clinicians, the Series will cover ways to measure the effectiveness of care they provide with articles on clinical audit and clinical indicators, and also to examine the pros and cons of the measures of efficiency used by the funders—organisational performance indicators, and benchmarking. The Series will wrap up with a vision of how we might continue to improve quality through embedding clinical governance into District Health Boards, so that their performance is measured in both quality and fiscal terms.

On the 16 February 2006, the Quality Use of Medicines (QUM) group presented their strategic national plan¹ to the incoming Minister of Health, the Hon Pete Hodgson. He listened and asked pertinent questions, and used his experience as a veterinarian to empathise with how easy it was to make a ‘slip error’ with medications. However, during discussion he said something like I don’t know what quality is all about, no-one can define it clearly, and [seeing my raised hand] no I don’t want any more definitions.

While this might worry those of us who have been working in healthcare quality, it is probably an accurate reflection of not only the Minister’s frustration, but also the frustration of many others within the healthcare sector. Why is it so difficult to define what a high-quality healthcare system would look like?

Partly this difficulty derives from the different ‘player’s’ perspectives and responsibilities. The Minister is responsible for the entirety of the health sector from the individual care provided in the primary sector, through the complex decisions around funding expensive drugs in secondary care, right onto planning for a possible bird-flu pandemic. He also has responsibility to see that care is provided in a fair, equitable way without reference to whether someone lives in Southland or Auckland, or on their ability to pay for care.

Furthermore, he must address those large health promotion issues such as smoking and the ‘obesity epidemic.’ Of course, advocates for each of these areas have been making time to speak with the Minister to put their particular point of view and push
for increased resources for their subset of the health sector. The Minister must balance these ‘demands’ with his need to take a population view and be cognisant of making the best use of the available resources.

His working definition of healthcare quality will necessarily be different from that of the front-line clinicians whose responsibility for quality revolves around the individual/clinician interface. The concern here is primarily around technical excellence—‘doing the right thing’ (appropriate care based on the best available evidence) and ‘doing it right (delivering safe, timely care).’

Patients will have a different definition depending on whether they are awaiting elective surgery (where access and timeliness might be the main indicator of quality), or whether they have a chronic disease (where coordination of care might be the most important).

However, these different ‘quality worldviews’ should not deter us from defining what a high-quality healthcare service would look like. We could ask learned committees to come up with definitions. One of the most often quoted comes from the American Institute of Medicine which defines healthcare quality as:

...the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.3

While this definition touches all the right buttons—highlighting healthcare quality for both individuals and populations, focusing on desired outcomes (presumably ‘desired’ by patients) and evidence based medicine—it is a little difficult to operationalise.

As discussed, the definition of quality depends on where in the health sector each player sits and one approach to defining healthcare quality is to customise the definition from these different viewpoints. Another way forward is to break down ‘quality’ into the dimensions that would define a high-quality healthcare system.

Using this approach and incorporating the different player’s perspectives a framework for Quality Improvement (Figure 1) was developed by the National Health Committee4 and has since been included into the Ministry of Health’s Improving Quality strategy.5

For the clinician and the clinical team perhaps the two most important dimensions are safety (“first do no harm”) and effectiveness. Safety (or the lack of it) in healthcare has become a cause celebre since the Institute of Medicines’ 2000 publication, To err is human: building a safer health system.6

The analysis of the previous decade’s work on the incidence of harm from medical management (adverse events) estimated that between 44,000 and 98,000 Americans died as a result of the care they received. Even if the lower estimate is closer to the truth, this would make deaths from adverse events the seventh leading cause of death, higher than the deaths due to motor-vehicle crashes, AIDS, or breast cancer. And no, this is not a problem peculiar to the United States of America—similar studies in the United Kingdom, Australia, and New Zealand confirm the universality of the issue.5–9

The New Zealand study estimated that 12.9% of hospital admissions were associated with an adverse event—around 14,000 patients per year—and that a third of them were preventable. A fuller investigation of the safety dimension, the causes of unsafe care, and efforts to improve it, will be the subject of the next article in this Special Series.
Effectiveness can be defined as making appropriate decisions based on the best available evidence, avoiding ‘overuse’ (providing care of no proven benefit or in situations where the benefits are outweighed by the risks) and ‘underuse’ (failing to provide care of proven benefit). The third article in this Series will explore the effectiveness dimension of quality in greater depth and outline the role of clinicians in measuring the effectiveness of the care that they provide. It will specifically cover clinical audit and then the fourth article will look at how to best use clinical indicators. The central premise of these articles is that the involvement of clinicians in the measurement and management of quality is essential to improve the quality of care delivered.

Many doctors have been sceptical of the various quality improvement mantras, but critically analysing how effectively we deliver care is actually embedded in our professional ethos, and while there may be reasons why some have lost sight of this (i.e. little patient-free time, ever-expanding work commitments, little teaching in quality improvement measures, cumbersome administrative demands), it is now essential that clinicians take a lead in quality improvement—otherwise they risk imposition of measures by those removed from the realities of the ‘shop-floor.’

The fifth article in the Series will focus on those global measures that District Health Boards (DHBs) and the Ministry of Health demand to assess the efficiency of the healthcare system. Efficiency is predicated on a service delivering an effective service so that it can make the best use of available resources. This article will therefore outline the pros and cons of outcome indicators and the use of benchmarking.

There is of course no point in having a safe, effective, and efficient healthcare system if patients are unable to access it. Timely and equitable access to care has been a political focus since the 1980s. In 1992, the National Advisory Committee on Core Health and Disability Support Services (the Core Services Committee) tried to develop a nationally explicit set of core services to which all New Zealanders would have access. It eventually rejected the concept of a ‘core service’ arguing that few treatments were ineffective in all patients, and exclusion of whole services would be
unfair to the patients who may benefit.\textsuperscript{11} It suggested an ‘individual benefit’ approach to determine resource allocation and from this has come the Clinical Priority Assessment Criteria for a number of surgical operations. The success (or otherwise) of this innovative approach to healthcare quality is still to be evaluated—we do not yet even have reliable systems to measure the number of operations that we do in the public sector,\textsuperscript{12} and equity of access is still a political ‘hot-potato’.

The sixth article in the Series will explore the ‘patient-centred’ dimension of quality. Although not explicit in the Ministry of Health framework the importance is seen with the centrality of the patient in the diagram. In addition, the Treaty of Waitangi principles have been added, including the concepts of partnership, participation, and protection. This is apt given the growing interest in patients (and their families) taking control of their care, being active partners in decision-making, and ensuring provision of acceptable care. It is perhaps embodied by Don Berwick’s (Institute for Healthcare Improvement) statement, \textit{nothing about me without me}.\textsuperscript{13}

The final article in the Series will explore how clinical governance might be used to improve healthcare quality and to ensure that any gains are held. Clinical governance in essence charges healthcare executives with not only being fiscally responsible but also responsible for the quality of the clinical care provided—a point noted in the Bristol Inquiry.\textsuperscript{14}

We hope that this series of articles will guide the Hon Pete Hodgson (and NZMJ readers) as to what a high-quality healthcare system would look like, and provide some tools for clinicians to achieve such a system.

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\textbf{References:}


Sacral teratoma

This case report was written by W. R. Stowe, M.D., Palmerston North, and published in the New Zealand Medical Journal 1906, Volume 5 (19), p52

The following case may prove of interest to your readers: Twelve months or so ago I was delivering a child and met with unexpected obstruction after the shoulders and thorax were born; the breach refused to pass the outlet, and it was only by passing a towel round the thorax and pulling on it that I could complete delivery.

A large tumour lay between the rectum and the sacrum, was generally soft, cystic in three places, but for the most part fleshy.

When the child was a month old Dr. G. Wilson removed the tumour en masse. The operation was beset with difficulties, especially the detachment of the upper part of the tumour, which was intimately connected with the bowel and other structures anterior to the first part of the sacrum. The child left the table alive, however, and made good progress. It is now in perfect health.

Dr. A. A. Martin and I dissected the tumour. It consisted of soft fibrous tissue with a few cysts. A largish cyst in the centre contained foetal remains—i.e., pelvic bones, a vertebra with a canal though which passed a rudimentary cord, a small portion of large(?) intestine distended with fluid, and a few odd bony fragments which we were unable to identify.

Teratomata in the pelvic cavity are apparently very rare, as I can find no mention of such in the literature I have at my command. Bland Sutton mentions their existence in the abdomen and thorax and on the posterior surface of the sacrum.

Sacral teratoma
Demographic and physiologic profiles of patients undergoing videofluoroscopic swallowing studies (VFSS). Michael Dimov\textsuperscript{1,2,3}, Maggie-Lee Huckabee\textsuperscript{1,2}, Irene Hudson\textsuperscript{1,4}, 1) Van der Veer Institute for Parkinson’s and Brain Research, Christchurch; 2) Department of Communication Disorders, University of Canterbury, Christchurch; 3) Watford and Three Rivers Primary Care Trust, Watford, United Kingdom; 4) School of Mathematics and Statistics, University of South Australia, Australia

The videofluoroscopic swallowing study (VFSS) is recognised as the primary diagnostic technique for swallowing impairment. This retrospective study was designed to characterise demographics, physiologic swallowing profiles, and healthcare outcomes in 498 patients who had undergone VFSS from 1993-2003 at two regional healthcare centres in New Zealand. To describe the patient population, data were collected from the medical record regarding gender, aetiology, age and health care setting at time of swallowing evaluation. Records were further scrutinised for healthcare outcomes, including survival, dietary prescriptions, use of alternative feeding and morbidities such as respiratory infection. VFSS were evaluated using Subscale 1 of the New Zealand Index for Multidisciplinary Evaluation of Swallowing (NZIMES) to gather information regarding physiologic profiles. Inter- and intra-rater reliability was high (ICC = 0.81 and 0.94 respectively, based on 20% of cases). NZIMES ratings revealed that 16.3% of patients received a rating of ‘normal’ on all physiologic features of swallowing; 48.8% of patients demonstrated no physiologic rating score above ‘mild’ in any category. However, despite the over-representation of non- or mildly impaired individuals, a normal diet level was recommended for less than 10% of patients. The average survival length post VFSS was 644.4 days; however 21.5% of acute patients survived less than 30 days and 51.8% survived less than 6 months post their examination. Other outcomes’ data will be reported and discussed. Given existing data on the prevalence of dysphagia, this study suggests a need to carefully evaluate referral patterns for the VFSS and management of the dysphagic patient.
Flow mediated dilation of the brachial artery: methods development and effects of exposure to diesel exhaust on endothelial function. Fiona N. Sands¹, Alon Peretz¹, Joel D. Kaufman¹,², Daniel F. Leotta³, Edward A. Gill⁴, Jeffery H. Sullivan¹, Marla Paun⁵, Carol A. Trenga¹, Sara Jarvis¹, Heidi Curtiss¹, Mary R. Aulet¹ ¹) Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington, USA; ²) Department of Medicine, University of Washington, Seattle, Washington, USA; ³) Department of Surgery, University of Washington, Seattle, Washington, USA; ⁴) Department of Medicine, Division of Cardiology, University of Washington, Seattle, Washington, USA; ⁵) Applied Physics Laboratory, University of Washington, Seattle, Washington, USA

To evaluate the mechanism by which particulate matter might cause cardiovascular health effects, endothelial function was assessed through ultrasonographic measurement of brachial artery reactivity. The hypothesis that exposure to inhaled diesel exhaust (DE) will result in concentration-related changes in endothelial homeostasis as reflected in flow mediated dilation (FMD) was evaluated using two method development pilot studies and a main study. Two of the studies used controlled inhalation exposure to DE particulate as a model with healthy subjects exposed to 2 hours of filtered air (FA), 100, and 200 µg/m³ PM₂.₅ DE followed by assessment of endothelial function. The third study assessed variability of FMD with varying cuff placement in repeated measurements (no exposure).

Data from the first pilot study and the main experiment (n = 10) were combined to examine controlled exposure to DE. The percent change in FMD for upper arm cuff placement suggested a trend to increased FMD after exposure (14.99% at FA, 16.88% at 200 µg/m³). The percent change in brachial artery diameter for the subjects in which a pre-exposure measurement was made (n=5) were -0.47% for FA and -5.32% for 200 µg/m³.

The variability of FMD with upper versus forearm cuff placement was assessed using data from the repeated measurements pilot and FA exposures from the main experiment (n = 26). FMD was larger for upper arm (16.2 ± 1.2%) compared to forearm (7.3 ± 0.9%) cuff placement (p<0.0001). Upper arm cuff placement was also found to be more variable (2.4%; 95% CI 0.5-4.3; p=0.013).

In summary, the effect of DE on FMD requires further exploration. However, distal cuff placement was determined to have statistical advantages over proximal as a method to assess endothelial function and should be used in further studies.

Sex steroids and vasoactive factors in endothelial cells. Lachlan J Pearson¹, Timothy G Yandle², M Gary Nicholls², John J Evans¹ ¹) Department of Obstetrics and Gynaecology, Christchurch School of Medicine & Health Sciences, Christchurch; ²) Department of Medicine, Christchurch School of Medicine & Health Sciences, Christchurch

It is well documented that there are gender differences in the patterns of cardiovascular disease, but the reasons are unclear. Endothelial cells on the inner lining of blood vessels are in direct contact with circulating factors, and are also in contact with the smooth muscle layer. We hypothesised that sex steroids may modulate the secretions of these endothelial cells, which then may affect the activity
of the smooth muscle layer by paracrine processes. The effects of sex steroids on the percentage of vascular endothelial cells that secrete the vasodilator peptide, adrenomedullin, and on the adrenomedullin-stimulating action of angiotensin-II were investigated using the cell immunoblot method. Cells were incubated with selected concentrations of angiotensin-II, oestradiol, and testosterone alone and in combination. The percentage of adrenomedullin-secreting cells was increased by angiotensin-II (100pM-10µM) in a concentration-dependant manner (p<0.001). Testosterone (3.5nM-3.5µM) at physiological concentrations was observed to increase the number of adrenomedullin-secreting cells (p<0.001) whilst oestradiol (3.7pM-3.7µM) had no effect. Testosterone and angiotensin-II together elicited a less than additive increase in the number of cells secreting adrenomedullin compared to the sum of their separate effects. It is concluded that testosterone increases the percentage of endothelial cells secreting adrenomedullin and augments the stimulating action of angiotensin-II. These results reveal another action of testosterone on vascular endothelial cells.

Postural hypotension in the mechanism of transient ischaemic attacks.

Elna Ellis¹, David Jardine¹, John Fink² ¹) Department of General Medicine, Christchurch Hospital, Christchurch; ²) Department of Neurology, Christchurch Hospital, Christchurch

Postural hypotension (PH) is thought to be a rare contributing mechanism in the aetiology of transient ischaemic attacks (TIAs). However PH is common in the elderly and has recently been associated with stroke. We suspect that PH is frequently missed in TIA patients and so may be under-recognised in the pathophysiology of this condition.

The aim of this study is to undertake tilt-testing on patients presenting to Christchurch Hospital with anterior circulation TIAs; to determine the incidence of PH during head-up tilt; and to assess the association between tilt-induced hypotension and their TIA symptoms.

Patients over 60 years of age with anterior circulation TIAs were recruited from the emergency department, medical wards and neurology clinics. After consenting, patients were asked to fill out a questionnaire which included recent neurological symptoms, postural symptoms and medication. Patients underwent 60-deg head-up tilt testing with continuous systolic blood pressure (SBP) monitoring using digital plethysmography. After 15 minutes of tilt, nitroglycerine spray (GTN) was administered. Patients remained tilted and were observed carefully for focal neurological signs as SBP fell. Patients were returned rapidly to the horizontal position in the event of focal neurological changes or impending syncope.

To date, 15 patients (7M/8F), mean age 77.4 yrs (range 65-85) have been tilted. 13 patients were taking anti-hypertensive medication. Patients underwent 60-deg head-up tilt testing with continuous systolic blood pressure (SBP) monitoring using digital plethysmography. After 15 minutes of tilt, nitroglycerine spray (GTN) was administered. Patients remained tilted and were observed carefully for focal neurological signs as SBP fell. Patients were returned rapidly to the horizontal position in the event of focal neurological changes or impending syncope.

To date, 15 patients (7M/8F), mean age 77.4 yrs (range 65-85) have been tilted. 13 patients were taking anti-hypertensive medication. Mean SBP values (with ranges) were: Resting horizontal 138 mmHg (113-194); at 5 minutes tilt 149 mmHg (112-230); and when symptomatic (at BP nadir) 70 mmHg (48-114). TIA symptoms and signs were reproduced in 3 patients. SBP returned to baseline rapidly following tilt back to the horizontal and focal neurology normalised within 5 minutes.
Despite nearly all patients taking hypotensive medication, PH was not seen during early tilt. However hypotension reproduced TIA symptoms in 3 patients (20%), consistent with our hypothesis that some TIAs may occur secondary to a low flow, rather than an embolic mechanism. These preliminary findings also support previous studies that have found tilt-testing (with GTN challenge) to be safe in elderly patients with cerebrovascular disease.

Formation of foam cell from human monocyte-derived macrophages in the absence of modified low density lipoprotein. Zunika Amit, Steven Gieseg. Free Radical Biochemistry Laboratory, School of Biological Sciences, University of Canterbury, Christchurch

Foam cells are lipid loaded macrophages full of cholesteryl esters and are the dominant cells in atherosclerotic plaques. Most studies generate foam cells in vitro by feeding oxidised low density lipoprotein (OxLDL) to either cultures of animal macrophages or immortal macrophage-like cell lines. The exact nature of the foam cell formed in plaque or human monocytes in tissue culture is poorly defined.

This study aimed to develop foam cells from human monocyte-derived macrophages purified from human blood. Macrophages were incubated for up to 10 days in RPMI 1640 media containing 10% heat inactivated human serum with varying concentrations of LDL, OxLDL, aggregated LDL (AggLDL) or aggregated OxLDL (AggOxLDL). Changes in cellular cholesteryl ester concentration (as quantified by gas chromatography (GC) and high-performance liquid chromatography (HPLC)) and lipid staining using oil red-O was used to assess the degree of foam cell formation. All experiments condition were carried out in triplicate and all experiments were conducted on at least three different cell preparations.

Microscopic examination of oil red-O stained cells showed accumulation of lipid droplets during differentiation into macrophages. Treatment with modified LDL failed to change the oil red-O staining morphology of the cells. This was surprising as studies with non-human macrophages showed distinct changes in oil red-O staining after treatment with OxLDL. Measurement of lipid levels by GC, showed no significant different in free or total cholesterol levels of the control and modified LDL treated human macrophage cells. A more sensitive HPLC analysis showed an increased in cholesteryl esters levels of the macrophages only when the macrophages were incubated with AggLDL, OxLDL or AggOxLDL. This study suggests that modified LDL uptake is not required for the development of the foam cell morphology.

Something smells fishy: preserving the nutritional value of aquacultured fish. Nicholas Tuckey1,2, Steven Gieseg1,2, Malcolm Forster1,2 1) Free Radical Biochemistry Laboratory, School of Biological Sciences, University of Canterbury, Christchurch; 2) Higher Value Seafoods, Seafood and Marine Extracts, Crop and Food Research, Nelson

Harvesting procedures may play a role in reducing the quality and nutritional benefit of aquacultured seafood. Oxidation, particularly of the unsaturated fatty acids that make salmon a food source of high nutritional value, has long been thought to play a
role in tissue degradation. Oxidized lipids are the primary source of the foul odour associated with degraded fish flesh and their consumption has been implicated in a number of diseases including atherosclerosis. Fillets from salmon harvested in a rested state using the aquatic anaesthetic AQUI-S and fillets from salmon that were exhausted and stressed prior to harvest, were exposed to normal atmospheric conditions and maintained at 15°C for up to 96 hours. Protein carbonyls began to increase immediately in the exhausted fillets and after a 6 hour delay in the rested fillets. This increase was reasonably linear over the entire 96 hours with a total carbonyl increase of 300 nmol/g tissue. Both lipid peroxides (TBARS) and uric acid concentrations began to increase in the exhausted group after 30 hours, reaching a final concentration of 65 nmol TBARS/g tissue and 212 nmol/g tissue for uric acid. No significant increase in lipid peroxides or uric acid was seen in the fillets from the rested animals over the entire incubation. Vitamin E concentrations reduced slowly but did not change significantly despite the oxidation that was evident in the tissue. This work has shown that salmon harvested in a rested state with AQUI-S are less prone to lipid oxidation and potentially of a higher nutritional value.
Proceedings of the 183rd Scientific Meeting of the Otago Medical School Research Society, Thursday 6 July 2006

Low proliferation is an indicator of poor outcome in colorectal cancer. A Anjomshoaa¹, Y Lin¹, A Chatterjee¹, H Lin¹, J McCall², M Black¹ and AE Reeve¹. ¹Cancer Genetics Laboratory, Department of Biochemistry, University of Otago, Dunedin. ²Department of Surgery, Auckland Public Hospital, Auckland.

Cell proliferation is an indicator of tumour aggressiveness and clinical outcome in some malignancies. In colorectal cancer, however, discordant results have been reported and the prognostic impact of tumour cell proliferation is unclear. As the conclusions on tumour cell proliferation are mostly based on a single proliferation marker, we used oligonucleotide microarrays to overcome this limitation.

Starting with a cell line model including ten colorectal cell lines, a proliferation signature consisting of 32 proliferation-related genes was defined with over-expression in proliferating cells. This in vitro-derived proliferation signature was then applied to the gene expression profiles of 73 primary and 28 unpaired liver metastatic colorectal tumours to evaluate the relative proliferation rate of tumours. Up-regulation of the proliferation signature in primary tumours compared with liver metastases indicated that the liver metastases were less proliferative than their primary counterparts. The proliferation signature was then used to identify two distinct classes of primary tumours with different cell proliferation rates. Non-parametric tests and gene list comparison analysis were then applied to detect any possible associations between proliferation activity and clinicopathologic parameters. Clinicopathologic parameters associated with poor survival (Dukes stage, lymphatic invasion and lymph node involvement) were inversely associated with the expression level of proliferation signature \( (P < 0.005) \). Furthermore, both overall and recurrence-free survival were significantly shorter in patients with low proliferative tumours. (Log rank test \( P=0.03 \) and 0.04, respectively).

We conclude that proliferation activity of colorectal cancer is reduced during the progression from localised to disseminated tumours. Moreover, in colorectal cancer, a low proliferation rate is associated with some unfavourable histopathologic parameters and poor clinical outcome. These findings contradict the long-held belief that rapidly dividing cancer cells are a harbinger of poor prognosis.

Murr1/COMMD1 colocalises with delta epithelial sodium channel (δENaC) and regulates its ubiquitination. T Chang, FJ McDonald. Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin.

The epithelial sodium channel (ENaC) is a key regulator of salt homeostasis and hence blood pressure. The classic ENaC consists of three subunits: \( \alpha \), \( \beta \) and \( \gamma \), which are highly expressed in epithelial tissues such as kidney, colon and lung. Despite close similarity, a fourth ENaC subunit called δENaC is highly expressed in brain, ovary,
testis, and pancreas. A δENaC binding partner called Murr1/COMMD1, which is a regulator of intracellular copper concentration, was identified from a yeast-two hybrid screen. A Xenopus oocyte functional assay showed that Murr1 downregulates the channel activity of δENaC, and that direct interaction between δENaC and Murr1 is necessary for the inhibition. The present study investigates the underlying mechanism of Murr1-mediated δENaC downregulation.

Three kidney cell lines, COS-7, HEK293 and MDCK, were utilised as models to study the interaction between δENaC and Murr1. Immunocytochemical studies and confocal microscopy suggest that both δENaC and Murr1 are expressed in the cytosolic compartments in cultured cells. This was further supported by a subcellular fractionation study. With the utilisation of organelle markers, it was found that δENaC and Murr1 are primarily colocalised in the recycling/early endosomes, suggesting that Murr1 might be a regulator of δENaC intracellular trafficking. Ubiquitination assays suggest that Murr1 might downregulate δENaC channel activity through enhanced ubiquitination of δENaC, which might lead to a decrease in δENaC surface expression.

Together, these findings propose that Murr1 downregulates δENaC by altering its intracellular trafficking, and inducing δENaC ubiquitination.

Fetal oncoproteins, PAX2 and PAX8, activate telomerase in glioma. Y Chen, AW Braithwaite, MR Eccles, JA Royds. Department of Pathology, Dunedin School of Medicine, University of Otago, Dunedin.

Telomeric DNA cannot be fully replicated by the conventional DNA replication machinery, hence cancer cells activate a telomere maintenance mechanism (TMM) to solve this “end replication problem”. We previously reported that TMM has prognostic significance for glioblastoma multiforme (GBM), and also that paired box (PAX) developmental genes are frequently expressed in this cancer. We have now investigated the expression of PAX genes in glioma and their role in TMM.

We analysed nine human glioma cell lines and 29 GBMs of known TMM, for mRNA expression of PAX2, 5 and 8 by real time PCR and for protein expression of the active form of PAX2, 5 and 8 using immunohistochemistry (IHC). Increased levels of PAX2, 5 and 8 mRNA were detected in 38% (11/29), 3% (1/29) and 66% (19/29) of gliomas, respectively, and 66% (21/32) of GBMs demonstrated more than 50% cells immunopositive for PAX by IHC. The level of PAX8 mRNA correlated with telomerase activity ($r^2 = 0.7$) ($P = 0.003$). Analysing the basal promoter of human catalytic subunit of telomerase (hTERT), we found there are potential binding sites for PAX2. Luciferase assays showed both PAX2 and PAX8 are able to activate hTERT in U87MG, A172 (wild type $TP53$), LN18, T98G and SF268 (mutant $TP53$) glioma cell lines. However in vivo, only gliomas carrying wild type $TP53$ had high levels of PAX8 expression ($P = 0.0075$) suggesting that PAX8 is important only in a subset of GBM during gliomagenesis. PAX8 had a stronger effect than PAX2 in the luciferase assay. By Western blotting and telomerase PCR ELISA, PAX8 was also found to upregulate both hTERT protein and activity.
These results reveal for the first time that oncofetal proteins, PAX2 and PAX8, have a novel role in TMM regulation and that they regulate telomerase. GBMs utilising different TMMs possibly originate from different pathways.

**Development of sexually dimorphic kisspeptin neurons in the preoptic area in relation to puberty. J Clarkson, AE Herbison. Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin.**

One key unanswered question in reproductive neurobiology is how gonadotropin-releasing hormone (GnRH) neurons are activated to initiate puberty. A novel neuropeptide, kisspeptin, was discovered to be indispensable for puberty, as deletion or mutation of its receptor, GPR54, prevents puberty resulting in infertility. Additionally, kisspeptin potently stimulates the reproductive axis in a developmentally regulated manner, suggesting an important role in GnRH neuron activation and modulation. The present study investigated the pubertal development of kisspeptin neurons and kisspeptin projections to GnRH neurons in the mouse brain.

Single-label chromogen immunocytochemistry (ICC) for kisspeptin and double-label fluorescent ICC for kisspeptin and green fluorescent protein (GFP) were performed on free-floating brain sections from male and female GnRH-GFP mice aged postnatal-day 10 (PND10), PND25, PND31, PND45 and PND60 (n = 4-8). Groups were compared using ANOVA and post-hoc Newmann-Keuls tests. Kisspeptin cell bodies were identified in the periventricular (PeN) and dorsomedial nuclei with kisspeptin fibres found abundantly in the rostral-preoptic area (rPOA) and arcuate nucleus. The number of kisspeptin cell bodies in the PeN increased from PND 10 to 60 in males and females (P<0.01) with adult-like levels attained at puberty in both sexes. However, a major sex difference was observed in the PeN with females having more than 5-fold greater numbers of kisspeptin neurons than males. The development of kisspeptin projections to GnRH neurons was examined by determining the number of GnRH neurons with kisspeptin-immunoreactive fibre appositions. The number of kisspeptin fibres in close apposition to rPOA GnRH neurons was sexually dimorphic (4-fold greater in females) and increased across postnatal development in both sexes (P<0.01).

These observations suggest that kisspeptin neurons located in the PeN represent a direct, sexually dimorphic input to GnRH neurons that develop around the time of puberty, implying an important role for kisspeptin in the activation of GnRH neurons at puberty.

**Serum fatty acids as biomarkers of dietary fat intake predict serum total cholesterol concentrations in New Zealanders. FL Crowe¹, CM Skeaff¹, TJ Green¹, AR Gray². ¹Department of Human Nutrition, ²Social and Preventive Medicine, Otago School of Medical Sciences, University of Otago, Dunedin.**

Results from dietary intervention trials indicate that the amount and type of dietary fat are important determinants of serum total cholesterol concentrations. However, the results from large observational studies show little association between saturated or polyunsaturated fat intake and serum cholesterol. Serum fatty acids are objective biomarkers of dietary fat and may overcome some of the limitations of dietary...
assessment. The objective was to assess whether serum fatty acids are associated with serum cholesterol concentrations in New Zealand adolescents and adults.

The fatty acid composition of serum cholesterol ester, phospholipid and triacylglycerol was measured in 2793 New Zealanders aged 15 years or older who took part in the 1997 National Nutrition Survey – a cross-sectional population-based survey. The results of the regression analysis after adjusting for sex, age, ethnicity, body mass index and smoking, revealed a one standard deviation increase in myristic acid (C14:0) in serum cholesterol ester, phospholipid and triacylglycerol that was associated with an increase in serum cholesterol of 0.19, 0.13 and 0.10 mmol/L, respectively. The mean difference in cholesterol concentrations between individuals categorised in the highest and lowest quintile of myristic acid in serum cholesterol ester was 0.48 mmol/L ($P < 0.001$). A one standard deviation increase in the proportion of linoleic acid (C18:2n-6) in serum cholesterol ester, phospholipid and triacylglycerol was associated with a decrease in serum cholesterol of 0.07, 0.07 and 0.05 mmol/L, respectively. The difference in mean serum cholesterol between the highest and lowest quintile of linoleic acid in serum cholesterol ester was 0.18 mmol/L ($P = 0.019$).

Saturated and polyunsaturated fat intake, as measured using fatty acid biomarkers, are important determinants of serum cholesterol concentrations in New Zealand. Therefore, population strategies for reducing elevated cholesterol concentrations should continue to focus on decreasing saturated fat, particularly dairy fat intake.

Quil-A containing lipid implants as a potential delivery system for subunit cancer vaccines. J Myschik, WT McBurney, F Eberhardt, T Hennessy, M Phipps-Green, T Rades, S Hook. School of Pharmacy, University of Otago, Dunedin.

Vaccine technology has seen a trend towards subunit protein or peptide vaccines. Subunit vaccines, whilst being safe, are less immunogenic and require multiple immunisations. Formulation technology allows the preparation of systems which deliver vaccines in a sustained manner, potentially removing the need for multiple injections. The aim of this study was to formulate a CD8 T cell stimulating, biodegradable lipid implant which releases antigen as a particulate, and to investigate \textit{in vivo} the immune response of mice to this vaccine.

Implants prepared from cholesterol, phosphatidylcholine and the adjuvant Quil-A (QA) released colloidal structures demonstrated by transmission electron microscopy. Fluorescently labeled ovalbumin (FITC-OVA, pFITC-OVA and PE-FITC-OVA) was incorporated into 2% or 30% w/w QA implants. The entrapment efficiency for each ovalbumin construct was $6.2 \pm 2.2\%$, $26.0 \pm 1.7\%$, $39.9 \pm 3.5\%$ for the 2% QA implants and $13.6 \pm 0.1\%$, $19.9 \pm 0.6\%$, $36.7 \pm 1.8\%$ for the 30% QA implants. Release of pFITC-OVA, investigated over ten days, demonstrated slow release (9\% total antigen in 24 h) for the 2\% QA implants and a burst release (84\% total antigen in 24 h) for the 30\% QA implants. \textit{In vivo} experiments using the 2\% QA formulation were performed in C57Bl/6 mice after adoptive transfer of T cells from OVA-specific transgenic mice. Mice received either injectable vaccines containing 10 \( \mu \)g pFITC-OVA given in two doses, or an implant containing 20 \( \mu \)g pFITC-OVA (n = 3). Expansion of CD8 T cells recognising an OVA-specific peptide [4.54\% (2\% QA
implant), 2.17% (2% QA injectable), 0.56% (alum control)] was observed. Immune response developed towards the implant vaccine was equivalent to two immunisations by injections.

Expansion of CD8 T cells is significant as these cells are required for killing tumours or virus infected cells. This research holds promise for future applications of subunit cancer vaccine delivery.

The ankyrin repeat proteins of Orf virus are a novel class of F-box proteins and associate with components of the cellular ubiquitination system. S Sonnberg, SB Fleming, AA Mercer. Department of Microbiology and Immunology, Otago School of Medical Sciences, University of Otago, Dunedin.

Most chordopoxviruses encode multiple ankyrin repeat proteins with unknown functions. The ankyrin motif mediates protein-protein interactions in cellular proteins. We have identified an additional potential protein interaction domain at the C-terminus of most poxviral ankyrin repeat proteins, the F-box domain. Cellular F-box proteins function as adaptor proteins in the multisubunit ubiquitin ligase S-phase kinase associated protein 1 (Skp1), Cullin1 (Cul1), F-box protein (SCF1) complex of the ubiquitin-proteasome system. F-box proteins are specificity factors that recruit substrate proteins to the SCF1 complex for polyubiquitination and degradation by the proteasome. The interaction between F-box proteins and the SCF1 component Skp1 is mediated by the F-box domain. In this study we carried out a functional analysis of the hypothesis that the poxviral ankyrin proteins contain an F-box domain and interact with the cellular ubiquitination system.

We used a co-immunoprecipitation approach to investigate the possible interaction between the 5 ankyrin repeat proteins of the parapoxvirus orf virus and the SCF1 components Skp1 and Cul1. Each of the orf virus proteins and either Skp1 or Cul1 were transiently expressed in HEK293 cells and the SCF1 components immunoprecipitated. The samples were analysed by Western blotting which showed that each orf virus ankyrin protein co-precipitated with Skp1 or Cul1. An F-box deletion construct of one orf virus ankyrin/F-box protein did not co-precipitate with either Skp1 or Cul1 showing that the interaction of the full-length protein is F-box-dependent.

Our results indicate for the first time a likely function for the large class of poxviral ankyrin proteins by identifying them as F-box proteins. We propose that poxviral ankyrin/F-box proteins associate with cellular proteins through their ankyrin repeats and use their F-box domains to target those proteins to the SCF1 complex. The large number of ankyrin/F-box proteins encoded by poxviruses suggests diverse cellular proteins in multiple pathways may be targeted.

The orf virus protein ORFV125 is a potent inhibitor of apoptosis. D Westphal¹, SB Fleming¹, EC Ledgerwood² and AA Mercer¹. ¹Department of Microbiology and Immunology, ²Department of Biochemistry, Otago School of Medical Sciences, University of Otago, Dunedin.

Apoptotic cell death forms part of the host defence against virus infection. It is therefore not surprising that numerous viral inhibitors of apoptosis have been
identified. The aim of this study is to characterise ORFV125, a proposed orf virus inhibitor of apoptosis, which localises to the mitochondria. The mitochondrial pathway of apoptosis is initiated by the release of cytochrome c into the cytosol leading to the activation of caspases, which can be inhibited by the cellular apoptosis regulator Bcl-2.

To quantify cytosolic cytochrome c after induction of apoptosis by UV irradiation (UVC, 80 Joules/m²), cytosolic and mitochondrial fractions of TK143B cells stably transfected with ORFV125, Bcl-2 or vector-only expression constructs were produced and analysed by Western blot. Cells carrying the empty vector showed cytochrome c in the cytosolic fraction at 4 h after UV irradiation, which increased up to 3-fold at 8 h. Within this time frame UV irradiation did not cause cytochrome c release in cells expressing ORFV125 or Bcl-2.

To measure the activation of caspases, cells carrying the ORFV125, Bcl-2 or vector-only expression construct were treated with UVC light for 7 h. Cell lysates were prepared and analysed for caspase activation using the fluorescent substrate Ac-DEVD-AMC. UV treatment induced a significant increase of caspase activity in cells expressing the empty vector (27 ± 4 pmol/min, mean ± SD, n = 3, Anova multiple comparison test) compared to untreated cells (2 ± 0.5 pmol/min, P < 0.001), which was completely inhibited in cells expressing ORFV125 (3 ± 1 pmol/min, P < 0.001) or Bcl-2 (3 ± 1 pmol/min, P < 0.001).

Taken together, the results clearly show that ORFV125 alone can completely inhibit UV-induced cytochrome c release and caspase activation. These features are comparable with the anti-apoptotic properties of the apoptosis regulator Bcl-2, indicating that ORFV125 may act in a similar manner.

Trochanteric bursitis: common or overdiagnosed? S Woodley¹, H Nicholson¹, S Mercer². ¹Department of Anatomy and Structural Biology, Otago School of Medical Sciences, University of Otago, Dunedin. ²School of Biomedical Sciences, The University of Queensland, Brisbane, Australia.

Trochanteric bursitis, or inflammation of the bursa associated with the greater trochanter of the femur, is implicated as a cause of lateral hip pain (LHP). Hence, the trochanteric bursa is of interest when performing palpation, injections and radiological imaging. Detailed knowledge of the anatomy of this bursa is fundamental to such techniques, as is its role in the pathogenesis of LHP. Given the dearth of information regarding both of these factors the aims of this study were to (a) clarify the morphology of the ‘trochanteric bursa’ and (b) investigate trochanteric bursitis as a cause of LHP.

Using macro-dissection and histological techniques, the bursae deep to gluteus maximus and the fascia lata were examined in 21 embalmed human hips (9 male, 12 female; mean age 78 (SD 9.4) years). Morphological associations, size and positions of the bursae were recorded. In addition, forty consecutive patients (37 female, 3 male, mean age 54.4 (SD 9.5) years) with unilateral LHP underwent magnetic resonance (MR) imaging. The images of each hip were analysed separately by three radiologists (blinded to symptomatic side) for signs of bursitis and other pathologies.
In the cadaveric hips, 72 bursae in four different locations were identified beneath gluteus maximus. As detected on MR imaging, trochanteric bursitis was diagnosed in 57.5% (47/80) of hips, being similarly prevalent in the symptomatic (24/40, 60%) and asymptomatic (23/40, 57.5%) hips. Isolated cases of trochanteric bursitis were uncommon (14/80, 17.5%). Instead, this type of pathology was typically found in combination with abnormalities of the subgluteus medius and minimus bursae, the gluteal tendons and osteoarthritis of the hip joint.

Taking these results together, clinicians need to be aware that several bursae are intimately associated with the greater trochanter, and that in many instances, pathologies other than trochanteric bursitis are responsible for, or contribute to, symptoms of LHP.

**Caspase-3 activity is elevated in differentiated myoblasts and during secondary myogenesis in rat hind limbs.** N Yoon, ASJ Lee, M Zhang. Department of Anatomy and Structural Biology, Otago School of Medical Sciences, University of Otago, Dunedin.

Activity of the key apoptotic serine protease, caspase-3, plays an important role during myogenic differentiation as it promotes myoblast fusion and myotube formation. Myogenic differentiation is significantly elevated at the late stage of myogenesis during which nearly 90% of skeletal muscle fibres are formed. The developmental stages of myoblasts are regulated by the sequential expression of primary (e.g. MyoD) and secondary (e.g. myogenin) myogenic regulatory factors (MRFs) and their upstream transcription factors, Pax3/7. The aim of this study was to investigate the correlation between caspase-3 activity and different myoblast populations in the early and late stages of myogenesis in vivo.

Isolated cells from rat hind limb muscles at embryonic days (E)15 and E18 were prepared for immunocytochemistry and Western blot analysis. Caspase-3 activity was detected using anti-caspase-3 (active) antibody in conjunction with anti-Pax7, MyoD and myogenin antibodies to mark proliferating, differentiating and differentiated myoblasts, respectively.

We found that the proportion of caspase-3\(^{+}\) cells in the sampled muscles significantly increased from 6.2 \(\pm\) 0.4% at E15 to 31.1 \(\pm\) 2.3% at E18 (mean \(\pm\) SEM; \(n = 9, P < 0.01\); ANOVA Single Factor). However, the level of caspase-3 activity in different myoblast populations underwent different changes during myogenesis. The proportion of caspase-3\(^{+}\) cells among Pax7\(^{+}\) (11.2 \(\pm\) 1.9%) or MyoD\(^{+}\) cells (22.2 \(\pm\) 3.3%) at E15 was nearly doubled at E18 (26.5 \(\pm\) 3.9% for Pax7\(^{+}\) and 38.3 \(\pm\) 3.1% for MyoD\(^{+}\) cells; \(n = 3, P < 0.05\) for both cases), whereas caspase-3\(^{+}\) cells among myogenin\(^{+}\) cells remained unchanged (29.4 \(\pm\) 6.3% at E15 and 27.6 \(\pm\) 1.4% at E18; \(n = 3, P > 0.05\)).

These results confirm that caspase-3 is actively involved in myogenesis in vivo. Such activity may be required for both myogenic differentiation and apoptosis, which is coordinately regulated temporally and numerically.
A fragile adolescent

Jubbin Jacob, Suceena Alexander, Nihal Thomas

A 17-year-old boy presented with history of fracture of the left humerus sustained on minimal trauma (Figure 1). There was previous history of multiple episodes of pathological fractures with deformities since childhood. Radiological survey of the patient revealed multiple expansile lesions in various long bones (Figures 2 & 3). Physical examination revealed a dark brown hyperpigmented lesion over the upper back with irregular borders (Figure 4).

Question—What is the diagnosis?
**Answer**

The radiographs show multiple lucent lesions in the metaphysis of the long bones, with endosteal scalloping and bone expansion. This bone lesion is characteristic of fibrous dysplasia. Fibrous dysplasia is a skeletal developmental anomaly of the bone-forming mesenchyme that manifests as a defect in osteoblastic differentiation and maturation.¹

The skin lesions in Figure 4 are called café au lait spots.² The presence of polyostotic (multiple sites) fibrous dysplasia and café au lait skin pigmentation confirms the diagnosis of McCune-Albright syndrome. In its classic form the triad includes autonomous endocrine hyperfunction in addition to the above two lesions. The presence of any two features among the three warrants a diagnosis of McCune-Albright syndrome (MAS).

The most common form of autonomous endocrine hyperfunction in this syndrome is precocious puberty, but affected individuals also may have hyperthyroidism, hypercortisolism, pituitary gigantism, or acromegaly.³

McCune-Albright syndrome is the result of a somatic mutation in the gene coding for the alpha subunit of the stimulatory G protein (Gsa).⁴

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**References:**

More (or less) about the economy class syndrome

The link between long-haul air travel and venous thromboembolism is the subject of continuing debate. Immobilisation, dehydration and possibly the reduced cabin pressure and oxygen tension in the airplane cabin may enter the equation. Apparently at cruising altitude during a long-haul flight, cabin pressure is typically equivalent to that at an altitude of 1524 to 2134 m and this may lead to a decrease in our arterial oxygen saturation to about 93%.

In this study, 73 healthy volunteers were subjected on alternate weeks to hypobaric hypoxia equivalent to atmospheric pressure at an altitude of 2438 m. Various tests were done comparing their normobaric and hypobaric haemostasis status. The researchers found no prothrombotic alterations in the blood during the hypobaric periods. So keep hydrated and keep the legs moving.

JAMA 2006;295:2251–61

Platensimycin versus drug-resistant hospital superbugs

Drug-resistant bacteria are an increasing problem—particularly in hospital practise. The two major villains being methicillin-resistant Staphylococcus aureus (MRSA) and Enterococcus. We need new antibiotics and one may be on the way. Researchers at Merck Research Laboratory have reported the discovery of platensimycin, a previously unknown class of antibiotics produced by Streptomyces platensis. It demonstrates strong, broad-spectrum Gram-positive antibacterial activity by selectively inhibiting cellular lipid biosynthesis in these bacteria. Not absolutely unique, as isoniazid works by the same method in killing the tubercle bacillus. But hold on—so far very effective in animals, but a long way from clinical practise. It usually takes several years to reach the clinic. Nevertheless, a pat on the back for Merck.

Nature 2006;441:358–61 & 293–4

Fractured neck of femur and death

Fractured neck of femur (NOF) is common in the elderly and not uncommonly is associated with death. Each year, about 60,000 hip fractures occur in the United Kingdom, with mortality 10–20% above that expected on the basis of age and sex. It would be a surprise if the New Zealand statistics were not similar. The question of whether a delay in the time of surgery affects mortality arises. This UK study reports on 129,522 admissions for fractured neck of femur in 151 trusts with 18,508 deaths in hospital (14.3%). The conclusion was that delay in operation was associated with an increased risk of death in hospital, which was reduced but persisted after adjustment for comorbidity. It must be borne in mind that delay of surgery might often (usually) be due to cardiorespiratory comorbidity needing to be stabilised.

BMJ 2006;332:947–50
Vascular disease, plasma homocysteine and folic acid, etc

More about the merits of folic acid supplements. Apparently in observational studies, lower homocysteine levels are associated with lower rates of coronary heart disease and stroke. As folic acid and vitamins B6 and B12 lower homocysteine levels, it seemed a good idea to use these supplements and see what happened.

Two recent randomised, placebo-controlled trials have addressed this matter—one for cardiovascular risks in general and the other in recent heart attack victims. Plasma homocysteine levels were reduced in both trials in the active treatments arms. Sadly this conferred no benefit in terms of cardiovascular risks, indeed there was a trend towards increased risk in the heart attack patients.

So, folic acid supplements are good for pregnant females and their babies, but no good for cardiovascular risk subjects.


Deal on malaria drugs

In a report in our column earlier this year (NZMJ 17 February 2006; http://www.nzma.org.nz/journal/119-1229/1869/) we discussed the rising tide of resistance to affordable antimalarial drugs. And a possible solution, artemisinin, a drug developed from a Chinese plant. The drawback—unless it is used in combination with other antimalarials—viz artemisinin combination therapy (ACT), it may also lose its effectiveness. We quoted Lee Jong-wook, the WHO’s Director General who said, “It is critical that artemisinins be used correctly. We request pharmaceutical companies to immediately stop marketing single drug artemisinin tablets and instead market artemisinin combination therapies only.” And Herwig Jansen, President of the Belgian company Dafra said, “It is not the function of WHO to insist on these things. This has to be worked out together with the academic experts and the industry.”

And then the bad news—Lee Jong-wook died. And the good news—13 firms agreed on 11 May to stop selling artemisinins individually, which can encourage resistance to develop. Instead, the firms will only sell the drugs in combinations.

New Scientist 2006;190(2552):7
Roche responds to the ‘Herceptin or deception’ article

Roche acknowledges that independent evaluations are required for fair and balanced consideration of the costs and benefits of Herceptin® for New Zealand women.

First results of independent assessments overseas have recently become public, with the National Institute for Health and Clinical Excellence (NICE) in the UK and the Scottish Medicines Consortium (SMC) recommending the use of Herceptin in early breast cancer on 9 June 2006.¹

These evaluations are based on transparency and the ability to ensure systematic critical appraisal of the results. However Martin Rosevar’s article published in NZMJ on 2 June 2006 (http://www.nzma.org.nz/journal/119-1235/2014) is limited in the information it provides, and a number of its cost estimates are based on inaccurate assumptions in regard to the funding review currently underway in New Zealand.

The Medsafe-approved indication is specifically for the use of the three-weekly administration regimen upon completion of chemotherapy² as used in the HERA trial.³ It is this three-weekly regimen with Piccart-Gebhart et al as the primary source of evidence, which PHARMAC has been asked to consider for funding. Three other trials (NSABP N9831, NCCTG B-31, BCIRG 006⁴) have been provided as supportive evidence. The paper by Romond et al reported the two-year combined results of NSABP N9831 and NCCTG B-31.⁵

The once-weekly administration schedule used in the NSABP N9831 and NCCTG B-31 studies forms the basis for the author’s simplistic evaluation. However the drug acquisition and administration costs are higher when Herceptin is administered once-weekly with chemotherapy, as is the rate of cardiotoxicity, (which will have associated treatment costs). The three-weekly regimen, as per the New Zealand indication, was considered by the NICE appraisal committee as better use of healthcare resource.¹

Rosevar also used the NICE 2001 cost/QALY estimate of £19–38k in metastatic breast cancer,⁶ which is not appropriate for early breast cancer. In the adjuvant setting, treatment with Herceptin significantly improves disease-free and overall survival.⁷ The costs associated with a patient being disease-free are minimal.⁸,⁹

The quality of life values have also been inappropriately adjusted by the author using the NICE metastatic breast cancer guidance, a significant decrease of 30–50%. The MEDTAP study commissioned by Roche UK and validated by the School of Health and Related Research (University of Sheffield) on behalf of NICE, adjusted the quality of life for the disease-free state after diagnosis of early breast cancer by 15%.¹⁰

Rosevar’s analysis over-estimates the costs for patients treated with Herceptin for HER2 positive early breast cancer. This is supported by the release of the draft NICE Guidance in the UK. Whereas the 2001 cost/QALY estimate for use of Herceptin in metastatic breast cancer was £19–38,000⁶, the estimate in early breast cancer is
between £2,387 and £18,000, with the upper limit assuming patients that go on to develop metastatic breast cancer would be retreated with Herceptin.\textsuperscript{1}

The public and medical support for the funding for Herceptin has been generated by the strength of the clinical evidence and the significant advance Herceptin offers women with HER2-positive early breast cancer.\textsuperscript{10}

It is important that the real benefit adjuvant Herceptin offers for women with HER2-positive early breast cancer does not get lost in the debate over the costs of providing this treatment.

Svend Petersen
Managing Director
Roche Products (New Zealand) Limited
Auckland

References:


2. Herceptin (trastuzumab) Data Sheet. 15 March 2006. Roche Products (New Zealand) Ltd. 8 Henderson Place, Auckland.


Martin Rosevear’s response

My article was one of a series which examined the ‘equity’ of PHARMAC’s funding for a range of new pharmaceuticals. The intent of these articles is to encourage rational debate and equity in our funding of health interventions, and we suggested that Herceptin® is expensive and we questioned whether it is affordable.

In summary:

- It is a promising new drug, but the evidence for its economic value is still being determined, although subsequent to my article the NICE group in the UK have found it is affordable in the UK setting for early breast cancer.

- If funded, Herceptin would have a significant budgetary impact, similar to the total funding of a small provincial hospital, and current budgets will struggle to cope with this.

The letters from Breast Cancer Advocacy Coalition and Roche raise valid issues on some technical details.

However the letters are mute on what we understand is the big issue of budgetary impact and our ability to fund such drugs. If new drugs such as Herceptin provide better value for money than other health interventions, then funding should be available to give patients access to these drugs. We are aware of a number of interventions provided routinely by hospitals where the $/QALY far exceed an agent such as Herceptin, according to our understanding, and the mechanisms to re-prioritise DHB funding between these ‘competing’ interventions are very weak. If existing funding mechanisms are getting in the road of good health governance, these structures should be changed.

As the respondents point out, the NICE findings suggest Herceptin is relatively affordable and our understanding of the final NICE findings is that they quote a base-case of approximately £18k ($55k) per QALY. However it should be noted that many of the assumptions in these findings are subject to debate and other interpretations would lower this value to £8k ($24k) per QALY.
As a result of new information received, I have revised the cost/benefit analysis in my original article, the details of which are set out in Figure 1:

**Figure 1. Herceptin survival estimates; hypothetical results**

![Figure 1](image-url)

The model above is simplistic and intended to capture the major issues in the debate. As we understand them, these issues are:

- The Chemotherapy arm has been generated based on a 10 year study of HER2 patients and adjusted to fit the survival data reported by Romond at four years+. We note that the Chemotherapy arm may give better survival advantage than nominally achieved in New Zealand since it includes the impact of taxanes which are not currently approved for use in New Zealand. Hence these findings are arguably conservative for local conditions.

- The default Herceptin arm has been generated by giving a 50% survival advantage to patients, based on disease free survival findings from HERA and overall survival results from Romond. Hence this line sits midway between the Chemotherapy arm and the average population.

- The persistence of Herceptin is perhaps the most important issue in the economic analysis. Does the 50% survival advantage observed in the trials last? Her2 patients tend to relapse within 5 years and given the action of Herceptin which prevents relapse to metastatic disease, it would seem reasonable to expect the impact of Herceptin on survival to be reasonably persistent. However uncertainties remain over long-term effects and the possible toxicity (especially in women with reduced cardiac capacity) which...
could reduce longer term survival. The NICE evaluation assumed no survival advantage after 5 years. Our model above is less conservative and uses a 10%/annum decline of persistence.

- Metastatic disease impacts approximately 40% of patients and Herceptin reduces its impact by 50%. The model does not account for the avoidance of this cost and suffering, hence our results are conservative.

- We have used treatment cost provided by Roche as a base-line. However we are aware that these are under negotiation and changes in clinical practice, especially in the duration of treatment, could change these.

- The quality of life adjuster has been set to 80% derived from Roche submission to NICE. Patients receiving Herceptin have generally had surgery and chemotherapy, and generally will have lost disfigurement and loss of quality of life.

- How many years should be used to estimate benefits? We have counted benefits up to them age of 70, since many other disease processes start impacting people over that age.

The life years gained is the area between the Chemotherapy arm and the options above (Herceptin with declining persistence and Herceptin with 100% persistence). These results are shown in Figure 2:

### Figure 2

<table>
<thead>
<tr>
<th>Item</th>
<th>20 years persistent</th>
<th>20 years declining</th>
<th>40 years persistent</th>
<th>40 years declining</th>
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<tr>
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<tr>
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<td>$30,625</td>
<td>$57,780</td>
<td>$17,853</td>
<td>$50,785</td>
</tr>
</tbody>
</table>

*Quality adjusted life year.

We have chosen to use the results over 20 years as our base-line results (ignoring the avoidance of metastatic disease):

- $31k per QALY (assuming persistent survival) to $58k per QALY (assuming 10%/annum decline in survival)

This result is lower than our original study. Furthermore we are aware of clinical developments which may lower these estimates further:

- Patient selection. An interview with Dr Piccart discusses work intended to improve the economic effectiveness by identifying sub-groups within the HER2 patient group who will respond more strongly to the drug.

- Shorter treatment. The Piccart interview above identifies trials where shorter duration treatments have been explored to find an ‘optimum’ treatment protocol which weigh up clinical effectiveness and cost.
We agree with the respondents that it is important for the real benefit of adjuvant Herceptin to be aired. But we also suggest that it is equally important to understand the challenges in funding these new treatments, and the need to re-prioritise interventions provided by the wider health system.

Martin Rosevear  
Director  
Outcome Management Services (a consultancy specialising in health and public sector economics)  
Wellington

References and endnotes:


7. See reference 2 above. We have been advised by Roche (personal communication) that the quality of life adjuster should be 85%, but at the time of writing we have not received the material supporting this, hence we have used 80% which is in the public domain.
Breast Cancer Advocacy Coalition responds to the ‘Herceptin or deception’ article

I write on behalf of the Breast Cancer Advocacy Coalition\(^1\) to express our disappointment at the publication of Martin Rosevear’s piece on trastuzumab (Herceptin\(^\circledR\)) in the 2 June 2006 issue of the New Zealand Medical Journal.\(^2\)

The analysis presented does little to help inform the debate. It does not accurately portray the latest or the most relevant clinical trial evidence for trastuzumab in early breast cancer. The analysis presented also takes an extremely superficial view of the economic outcomes associated with use of trastuzumab in early breast cancer. It further confuses the reader by presenting clinical outcomes and using assumptions derived from trastuzumab use in metastatic disease.

In marked contrast to this is the exhaustive process of evaluating clinical effectiveness and cost-effectiveness of trastuzumab in early breast cancer recently undertaken in the United Kingdom by the National Institute of Clinical Excellence (NICE).\(^3\) One input to the NICE appraisal was a review by authors from the School of Health and Related Research at the University of Sheffield (ScHARR).\(^4\) They concluded that trastuzumab in early breast cancer resulted in a statistically significant relative reduction in the hazard of all-cause mortality from 24% (HR 0.76, 95%CI 0.47 to 1.23, absolute risk reduction 0.5%) at a median follow-up of 1-year to 33% (HR 0.67, 95%CI 0.48 to 0.93, absolute risk reduction 1.8%) at median follow-up of 2 years.

The conclusion was that all studies at whatever schedule or length of follow-up showed a statistically significant relative difference (of about 50% in every case) in the hazard of recurrence or death from any cause (disease-free survival), favouring trastuzumab. These early results are considered unprecedented in the breast cancer field.

The cost-effectiveness analysis undertaken in the United Kingdom included not only the cost of trastuzumab (to which Rosevear’s analysis appears to have been limited) but also included other relevant health sector costs such as drug administration, laboratory costs, cardiovascular monitoring, ambulatory care, disease recurrence and adverse effects. The NICE analysis used a model that incorporated quality of life and survival based on the HERA trial (upon which the provisional MEDSAFE approval in New Zealand is primarily based) with rather conservative assumptions. This analysis resulted in an incremental quality-adjusted life-year (QALY) gain of 2.46 QALYs with trastuzumab compared with standard chemotherapy.

The conservative assumption in the analysis was that there was no further survival benefit after 5 years post-treatment. Nevertheless, the incremental cost per QALY for the United Kingdom analysis for trastuzumab in early breast cancer under this conservative assumption was £18,449. This analysis also assumed that all patients who progressed to metastatic disease would be treated with trastuzumab again. If this were not the case, then the incremental cost per QALY was £8,365. It is worthwhile noting that this analysis did not include any economic gains to society associated with improved survival of the women in whom recurrences are prevented or delayed. This
may be particularly important because HER2-positive breast cancers are more likely to affect younger women who can participate in the workforce after successfully completing their treatment.

The analysis by NICE led to a recommendation for trastuzumab as a clinically effective and cost-effective treatment option for women with early stage HER2-positive breast cancer. Only 2 weeks after its licensing in Europe, a recommendation was made for funding of this indication in the United Kingdom. It is apparent that this recommendation is based on a careful and exhaustive appraisal of all the available scientific evidence.

In New Zealand, MEDSAFE granted provisional approval for trastuzumab in March 2006 and we have yet to hear the outcome of a funding application made to PHARMAC in December 2005 by the manufacturer.

The issues that have been raised by Rosevear in relation to the cardiac toxicity of trastuzumab have been carefully considered in the medical literature and can be appropriately managed. The toxicity associated with trastuzumab is nothing new, as this drug has been available for metastatic disease in New Zealand since 2001, and the recommendations of Medsafe for trastuzumab use in early breast cancer deal with this appropriately. Such risks should clearly be the subject of discussion between women and their doctors when considering treatment with this option.

The public “pressure” for funded access to trastuzumab in early breast cancer is in fact based on a grass roots campaign, which was supported by 18,166 New Zealanders. This remarkable response was not the result of a “media campaign” by “well-resourced” people, as Rosevear incorrectly suggests, but the result of support by ordinary New Zealanders for a group of women who were forced to advocate for their own survival. In conclusion, it is unfortunate that the NZMJ chose to publish such an ill-informed and confusing piece on such an important issue.

Elisabeth P J Burgess
Chair
Breast Cancer Advocacy Coalition
Auckland

References and endnotes:

1. BCAC is a voluntary group of breast cancer survivors representing 12 organisations, with the aim of improving health outcomes for New Zealand women with breast cancer.


7. 2005/30 Petition to New Zealand Parliament of Anne Easter Hayden and 18,166 others.

Martin Rosevear’s response

My article was one of a series which examined the ‘equity’ of PHARMAC’s funding for a range of new pharmaceuticals. The intent of these articles is to encourage rational debate and equity in our funding of health interventions, and we suggested that Herceptin® is expensive and we questioned whether it is affordable.

In summary:

- It is a promising new drug, but the evidence for its economic value is still being determined, although subsequent to my article the NICE group in the UK have found it is affordable in the UK setting for early breast cancer.
- If funded, Herceptin would have a significant budgetary impact, similar to the total funding of a small provincial hospital, and current budgets will struggle to cope with this.

The letters from Breast Cancer Advocacy Coalition and Roche raise valid issues on some technical details.

However the letters are mute on what we understand is the big issue of budgetary impact and our ability to fund such drugs. If new drugs such as Herceptin provide better value for money than other health interventions, then funding should be available to give patients access to these drugs. We are aware of a number of interventions provided routinely by hospitals where the $/QALY far exceed an agent such as Herceptin, according to our understanding, and the mechanisms to re-prioritise DHB funding between these ‘competing’ interventions are very weak. If existing funding mechanisms are getting in the road of good health governance, these structures should be changed.

As the respondents point out, the NICE findings suggest Herceptin is relatively affordable and our understanding of the final NICE findings is that they quote a base-case of approximately £18k ($55k) per QALY. However it should be noted that many of the assumptions in these findings are subject to debate and other interpretations would lower this value to £8k ($24k) per QALY.
As a result of new information received, I have revised the cost/benefit analysis in my original article, the details of which are set out in Figure 1:

**Figure 1. Herceptin survival estimates; hypothetical results**

The model above is simplistic and intended to capture the major issues in the debate. As we understand them, these issues are:

- The Chemotherapy arm has been generated based on a 10 year study of HER2 patients and adjusted to fit the survival data reported by Romond at four years+. We note that the Chemotherapy arm may give better survival advantage than nominally achieved in New Zealand since it includes the impact of taxanes which are not currently approved for use in New Zealand. Hence these findings are arguably conservative for local conditions.

- The default Herceptin arm has been generated by giving a 50% survival advantage to patients, based on disease free survival findings from HERA and overall survival results from Romond. Hence this line sits midway between the Chemotherapy arm and the average population.

- The persistence of Herceptin is perhaps the most important issue in the economic analysis. Does the 50% survival advantage observed in the trials last? Her2 patients tend to relapse within 5 years and given the action of Herceptin which prevents relapse to metastatic disease, it would seem reasonable to expect the impact of Herceptin on survival to be reasonably persistent. However uncertainties remain over long-term effects and the possible toxicity (especially in women with reduced cardiac capacity) which
could reduce longer term survival. The NICE evaluation assumed no survival advantage after 5 years. Our model above is less conservative and uses a 10%/annum decline of persistence.

- Metastatic disease impacts approximately 40% of patients and Herceptin reduces its impact by 50%. The model does not account for the avoidance of this cost and suffering, hence our results are conservative.

- We have used treatment cost provided by Roche as a base-line. However we are aware that these are under negotiation and changes in clinical practice, especially in the duration of treatment, could change these.

- The quality of life adjuster has been set to 80%\(^7\) derived from Roche submission to NICE. Patients receiving Herceptin have generally had surgery and chemotherapy, and generally will have lost disfigurement and loss of quality of life.

- How many years should be used to estimate benefits? We have counted benefits up to them age of 70, since many other disease processes start impacting people over that age.

The life years gained is the area between the Chemotherapy arm and the options above (Herceptin with declining persistence and Herceptin with 100% persistence). These results are shown in Figure 2:

**Figure 2**

<table>
<thead>
<tr>
<th>Item</th>
<th>20 years persistent</th>
<th>20 years declining</th>
<th>40 years persistent</th>
<th>40 years declining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-years enhanced</td>
<td>2.23</td>
<td>1.18</td>
<td>3.82</td>
<td>1.34</td>
</tr>
<tr>
<td>Quality of life adjuster</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>QALY*</td>
<td>1.78</td>
<td>0.94</td>
<td>3.06</td>
<td>1.07</td>
</tr>
<tr>
<td>Cost per QALY ($NZ)</td>
<td>$30,625</td>
<td>$57,780</td>
<td>$17,853</td>
<td>$50,785</td>
</tr>
</tbody>
</table>

*Quality adjusted life year.

We have chosen to use the results over 20 years as our base-line results (ignoring the avoidance of metastatic disease):

- $31k per QALY (assuming persistent survival) to $58k per QALY (assuming 10%/annum decline in survival)

This result is lower than our original study. Furthermore we are aware of clinical developments which may lower these estimates further:

- Patient selection. An interview with Dr Piccart\(^6\) discusses work intended to improve the economic effectiveness by identifying sub-groups within the HER2 patient group who will respond more strongly to the drug.

- Shorter treatment. The Piccart interview above identifies trials where shorter duration treatments have been explored to find an ‘optimum’ treatment protocol which weigh up clinical effectiveness and cost.
We agree with the respondents that it is important for the real benefit of adjuvant Herceptin to be aired. But we also suggest that it is equally important to understand the challenges in funding these new treatments, and the need to re-prioritise interventions provided by the wider health system.

Martin Rosevear
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References and endnotes:


7. See reference 2 above. We have been advised by Roche (personal communication) that the quality of life adjuster should be 85%, but at the time of writing we have not received the material supporting this, hence we have used 80% which is in the public domain.
Response to Frank Frizelle’s editorial on the RMOs’ strike

In his editorial published in the 23 June 2006 issue of the NZMJ (Is it ethical for doctors to strike? http://www.nzma.org.nz/journal/119-1236/2037), Professor Frizelle raises some interesting issues with regard to the appropriateness (or not) of the recent resident medical officers’ (RMOs’) industrial action—particularly in relation to the international and historical aspects.

In his penultimate paragraph he refers to “doctors having a special contract with society.” Whilst this may have been the case in days gone by, and even when that assessment was made some 20 years ago, there was a subtle shift in how doctors were viewed by society when the Government of the day removed senior medical officers from the Higher Salaries Commission and made them form a union, now known as Association of Salaried Medical Specialists (ASMS).

It seems to me that “society” wants to have its cake and eat it too—i.e. wants us to behave like higher-minded, selfless individuals, but also wants to treat us like any other segment of the workforce.

“Society” needs to decide how it wants to manage the working conditions of its senior medical staff, and possibly its RMOs too. If it decides that it is appropriate to have us in a situation where we must bargain for the conditions under which we are employed then surely we must retain the ultimate right to withdraw our labour if unacceptable conditions of employment are forced upon us. Indeed, in the end, when it come to across the table bargaining, this is the only real bargaining tool available to us.

Reasoned argument does not go very far in the face of an entrenched view that there is “no money.”

Derek Snelling
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Anaesthesia and Pain Department
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Wellington South
Tyranny of democracies

It was great to read the 23 June 2006 editorial in the NZMJ (Frizelle F. Is it ethical for doctors to strike? http://www.nzma.org.nz/journal/119-1236/2037)

Support of junior doctors when trying to improve the position of patients (by being awake when caring for them) is always to be applauded. I would just like to raise another issue regarding the ethics of “strike action” however.

Apart from issues of the greater good, so eloquently put, there is also the idea of the democratic body representing the ideals and ethics of the majority. This has been true since first put forward in Athens by the Greeks in 508 BC.¹

It should also be remembered that the majority of Resident Doctors’ Association (RDA) members voted in favour of a strike. In relation to this, there is a question which has been raised several times during this industrial dispute: is it more “ethical” to undermine the very essence of democracy and “break” the strike by adhering to a personal code of ethics, or is it more ethical to abide by the rules of the land/union and support the democratic process?

Presumably if democracy is held is such low regard by those unwilling to strike due to personal ethics yet willing to call in the union when they personally feel threatened, then these people would also be willing to break the law of the democratic land whenever they felt it offended their personal ethics.

Of course, we should not forget the words of CS Lewis regarding the “tyranny of democracies.”² Some balance should always be found between the “moral high ground” of the democratic majority and the “personal ethics” of the individual.

Much like when negotiating a contract, one would assume.

Chris Wainwright
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Endnotes:

1. Wikipedia. History of democracy. Available online. URL: http://en.wikipedia.org/wiki/History_of_democracy Accessed July 2006. [Athens is among the first recorded and one of the most important democracies in ancient times; the word “democracy” (Greek: δηµοκρατία – “rule by the people”) was invented by Athenians in order to define their system of government, around 508 BC].

2. CS Lewis (1898–1963), essayist and novelist: “Of all tyrannies, a tyranny sincerely exercised for the good of its victims may be the most oppressive. It would be better to live under robber barons than under omnipotent moral busybodies. The robber baron's cruelty may sometimes sleep, his cupidity may at some point be satiated; but those who torment us for our own good will torment us without end for they do so with the approval of their own conscience.”
Cost of procedures on the New Zealand Mobile Surgical Bus

Bax et al (NZMJ 23 June 2006; http://www.nzma.org.nz/journal/119-1236/2025) claim in their analysis that the Mobile Surgical Bus performs procedures (1/3 of them dental) at a cost of $NZ 1900.00 each. However my arithmetic would suggest that $5 million dollars a year for 1000 procedures equates to $NZ 5000.00 per case. This is not including the cost of the bus itself.

For that budget I would be very happy to fly all of these patients to Auckland, accommodate family, have the operations performed with real rather than telepresence doctors, and include a limo to and from the airport.

John P Dunn
Director
Endoscopy and Laparoscopy Auckland
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Response

The 5-year Government contract for the Mobile Surgical Project is in three major parts: Mobile Surgery, Telepresence, and Rural Health Development. The article by Bax et al correctly states the amount allocated for day surgical procedures as $1.9 m. While the contract was for 1000 cases annually, for the last 3 years (with a lot of extra work by local hospitals’ management and staff) the average has been closer to 1500 cases each year for the same funding. This significantly drives the unit price down from $1,900 to around $1,300 per patient and would make it hard to implement Dr Dunn’s generous offer of family limousines.

The Government indicated last year it wished to extend the project contract to 2011, and will be evaluating requests by hospitals for more frequent visits and the need for a second bus.

Stuart Gowland
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Mobile Surgical Services
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(http://www.mobilesurgical.co.nz)
Long-acting beta agonists—prescribe with care

According to a recent consultation document, PHARMAC plans to increase the availability of the higher-strength long-acting beta agonists (LABAs), and to fund the salmeterol/fluticasone combination. Thus we are likely to see increased high-strength LABA use and increased prescribing of combination long-acting beta agonists and inhaled corticosteroids (ICS).

In many ways this is a positive move. The combination of long-acting beta agonists and inhaled corticosteroids have been shown in many studies to significantly improve day-to-day asthma management in mild to moderately severe asthma.\(^1\) Prescribing combinations of LABAs and ICS for suitable patients, is now a major component of asthma management around the World and firmly incorporated in evidence-based asthma management guidelines.\(^2\) But despite their advantages and widespread acceptance, there is a need for caution. Long-acting beta agonists are associated with a small but significant increased risk of life-threatening asthma attacks and asthma death.

While this has led to strong label warnings on all LABA containing medication in the US, it has received little publicity in New Zealand while both salmeterol and the formoterol/budesonide combination have been heavily promoted directly to patients on television.

Salmeterol was launched in the aftermath of the fenoterol controversy\(^3\) in the early 1990s and amid concerns about the use of beta agonists in asthma.\(^4\) Glaxo conducted a post-marketing safety study in the UK, published in 1993.\(^5\) The study (n=25,000) randomised patients 2 to 1 to salmeterol 50 \(\mu\)g twice daily or salbutamol 200 \(\mu\)g four times daily.

Asthma severity and concomitant therapy were well balanced between the treatment groups and 70% of patients were prescribed inhaled corticosteroids at entry to the study. There were 14 deaths due to asthma (12 in the salmeterol group, and 2 in the salbutamol group), a non-significant relative risk of 3.0 (95%CI 0.7–20). All deaths were in patients with severe asthma in the opinion of their GP or the independent consultants to the study, and 5 were on oral corticosteroids.

In the opinion of the consultants, 10 of the 14 patients who died might have been more appropriately treated with earlier or higher doses of inhaled corticosteroid. The authors concluded that severe or unstable asthma patients: “require stabilisation of their asthma with appropriate doses of inhaled or oral glucocorticosteroids (>1 mg per day of beclomethasone dipropionate or equivalent) as their main treatment.”

At the time of approval in the US, the Food and Drug Administration (FDA) asked GlaxoSmithKline to provide more safety data on salmeterol which led to a further randomised trial in the United States—the Salmeterol Multicenter Asthma Research Trial (SMART).\(^6\) This study commenced in 1996, consisting of 28 weeks of salmeterol 50 \(\mu\)g twice daily or placebo added to usual asthma care in subjects >12 years of age.
Unfortunately the warnings of the previous UK safety study were not followed, and there was no attempt to make sure that patients were stabilised before commencing salmeterol or even that they were using ICS. Following an interim analysis in 2003 with enrolment at just over 26,000 subjects, the study was terminated due to increased mortality in the salmeterol group. The full findings from this study were finally published earlier this year. There were 13 asthma deaths in the salmeterol group and 3 in the placebo group, a significant relative risk (RR) of 4.4 (CI 1.2–15.3).

For African Americans who had more severe asthma at baseline (twice the frequency of hospital admission and ED attendance for asthma and lower percent predicted peak expiratory flow rate [PEFR] than Caucasians) and were less likely to be receiving ICS at enrolment, the non-significant increased RR was 7.3 (CI 0.89–58.9).

For asthma deaths and life-threatening experiences, the increased relative risk was significant for the total study population RR 1.71 (1.0–2.9), and for African Americans RR 4.9 (CI 1.7–14.5). The number needed to harm for the total population and the African American sub group were 879 (CI 438–∞) and 158 (CI 97–429) respectively. Importantly, most of these adverse effects appeared to be reduced if ICS were prescribed at baseline, although the study was not powered to specifically answer this question.

The evidence that salmeterol increases the risk of death is now convincing; it has recently been further supported in a meta-analysis of studies of both salmeterol and formoterol with the authors concluding that both agents were associated with increased asthma hospitalisations, life-threatening asthma attacks, and asthma deaths in both adults and children and that ICS did not adequately protect against these effects. Indeed, in the US, these studies have led the FDA to place black box warnings (the strongest warning that the FDA issue) on all LABAS whether sold on their own or in combination with ICS.

However, despite widespread introduction and uptake around the World, there have not been any reported recent increases in asthma mortality. This is reassuring but perhaps surprising until one considers the unique way in which LABAs are generally prescribed and used, as twice daily regular treatment. Thus, there is little potential for LABAs to be used excessively in worsening asthma as happened during the fenoterol epidemic. The corollary of course is that LABAs increase the risk of death and life-threatening asthma at prescribed doses.

There have been recent calls for formoterol, which has a rapid onset of action, or the formoterol/budesonide combination to be used as a ‘one stop shop’ for maintenance and relief of acute asthma attacks. While these studies demonstrate improved asthma control, the benefits to the majority may well come at the cost of increased life-threatening attacks and deaths for a small minority.

What are the implications for New Zealand?

Firstly, long-acting beta agonists should not be used unless adequate doses of ICS are being taken regularly. Compliance with ICS is notoriously poor, being as low as 15% in some studies. The combination products will of course ensure this and for this reason should be encouraged. Secondly, LABAs should not be introduced when a patient’s asthma is deteriorating or poorly controlled. Particular care should be taken with patients who are using excessive amounts of short-acting beta agonists, who
have recently been admitted to hospital with acute asthma or have received frequent
courses of oral corticosteroids all of which may indicate poorly controlled and severe
disease.11 Thirdly, the lowest effective dose should always be used.

It is unfortunate that we still do not know how some short-acting beta agonists such as
isoprenaline and fenoterol or the long-acting beta agonists increase the risk of death in
severe asthma, but in the case of LABAs it appears to happen without excessive use.

New Zealand is a particularly sensitive barometer for the adverse effects of
bronchodilator treatment. For carefully selected asthmatic patients to reap the
symptomatic benefits of long-acting beta agonists combined with inhaled
corticosteroids (without a small but significant proportion of patients incurring serious
or fatal asthma attacks), they need to be prescribed judiciously and not be seen as a
panacea for asthma.

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Medical Benevolent Fund

NZMA Members, and families of deceased Members, may apply for aid when in situations of financial hardship or distress.

Applications should be directed through the NZMA:

Central Office
P O Box 156
Wellington
Tel: 0800 656161
An Introduction to Chinese Herbal Medicine: with Particular Reference to the Chinese Umbelliferae


This book describes a number of Chinese herbal medicines and discusses a fair amount of the literature and concepts of Chinese medicine. This is a huge topic. The author wrote the book primarily for herbalists and botanists rather than for a medical readership. However, some medical people may find this book interesting.

The book contains a major section on phytochemistry with modern analytic techniques including chromatography and mass-spectrometry that are used to characterise each constituent of herbs. Phytochemistry helps with botanical classification of the herb for the botanist and pharmacological understanding for the herbalist. The book then describes the classically documented herbs based primarily on the Chinese herbal the BEN CAO GANG MU.

Twenty-six herbal entities are described including the botanical aspects (description of plants, distribution and habitats, cultivation, and harvesting), traditional use in Chinese medicine, and biomedical information. The latter includes actions, biomedical applications, and phytochemistry. It also describes regional substitutes which are related herbs with similar properties.

Most current medical journals report scientific development and clinical trial findings. Evidence-based medicine is now generally accepted for most medical conditions. At the same time, there is also growing interest on “alternative” medicine. Even intangible healing methods (defined as widely practiced therapeutics without mechanistic explanation) such as praying have also been reported in scientific journals using controlled trial methods.

The book attempts to bridge the gap between traditional description of Chinese medicine (herbs) and scientific understanding of these biological compounds. As with Western medicines, it will be most interesting that individual Chinese herbs (or more specifically the individual constituents) are put into controlled clinical trials on specific medical conditions.

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