



Australian Medical Student Journal

Editorial Recapturing compassion



- Editorial** ➔ Appraising laboratory-based cancer research for the medical student
- Feature** ➔ Exercising patient centred care
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




















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Australian Medical Student Journal

Volume 5, Issue 1 | 2014

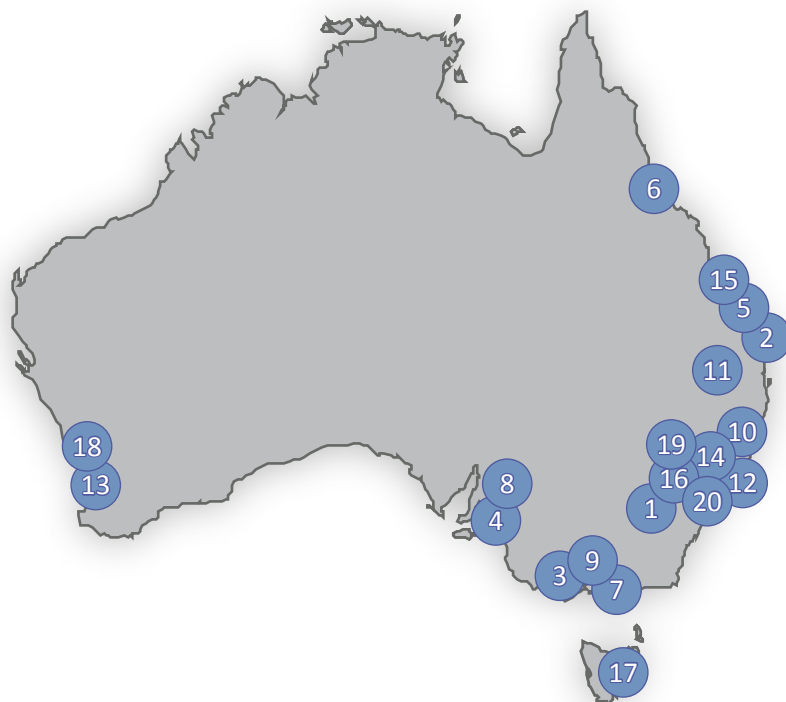
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A platform for research and endeavour

Saion Chatterjee

Editor-In-Chief, AMSJ

Welcome to Volume 5, Issue 1 of the *Australian Medical Student Journal* (AMSJ). The latest issue continues to showcase the vast breadth of medical student and junior doctor research, reviews, and opinions in a wide range of relevant and compelling articles.

This issue includes the latest trends in laboratory-based cancer research, covered in an editorial by Alison Browning, and provides a timely overview of this rapidly growing field. Grace Leo's editorial shifts our attention to the waning practice of compassion during patient care and ways in which this can be addressed.

Key guest articles include a piece by Professor Patrick McGorry which builds on the momentum placed on medical student mental health and wellbeing this year, offering new insights in this area in the wake of a 2013 beyondblue survey which highlighted some stark statistics on medical student and junior doctor mental health. Professor Stephen Leeder, the Editor-in-Chief of the *Medical Journal of Australia* (MJA) which is celebrating its centenary this year, navigates the overload of medical information that faces us now and into the future. The Australian Indigenous Doctor's Association provide an informative view into the future of Indigenous health in Australia, and draws on the need to train

culturally competent doctors to make inroads in this area.

Additionally, this issue has attracted an unprecedented number of original research submissions, testament to the growing popularity of research amongst students and the AMSJ's ongoing drive to publish early career research. Stephanie Barnes suggests a technique to anatomically localise functionally defined cortical areas using MRI, while a second research article in the field of radiology compares two key methods of identifying adrenal glands on computed tomography (CT). Public health measures to prevent skin cancers amongst men and women are assessed in a study of rural Australians, and the findings suggest that the measures are still not being heeded by some.

The review and feature articles again cover a diverse array of topics, with a spotlight on penicillin allergies, an overview of the history of modern anaesthesia, and reviews of cancer and psychiatric treatments.

The growing calibre of research submissions, as well as our staple review and feature articles, reflect the variety of interests and undertakings of Australian medical students and junior doctors. The AMSJ is currently in the midst of exploring potential partnerships with the Australian Medical Students'

Association (AMSA) and the MJA to bring more opportunities to students, encourage research, and promote medical editing and journalism. Keep an eye out on our website for more announcements. Furthermore, our presence on social media continues to strengthen and has played a strong role in increasing our readership, including to an emerging international audience.

The AMSJ is produced by an expanding team of volunteer staff of medical students which is now well and truly established across all states and medical schools in Australia. This year has been a time of transition at the AMSJ with many staff members completing their terms with us and handing over the reigns to a new team of enthusiastic editors, proof-readers, and other internal staff positions who bring with them a wealth of experience. I would like to thank past executive members and editors who have overseen the development of the AMSJ and to current staff who have worked tirelessly to publish this issue. I would also like to extend our thanks to the peer-reviewers who have provided us with invaluable feedback on articles and are central to the quality and success of the AMSJ.

Finally, I would like to thank our readers, authors and sponsors who continue to support the AMSJ. On behalf of the staff at the AMSJ, we hope you enjoy this issue.

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Appraising laboratory-based cancer research for the medical student

Alison Browning

Associate Editor, AMSJ

Increasingly clinicians are being asked to participate in translational research—working closely with laboratory scientists to help guide research goals and projects. The work that is done in the laboratory setting can sometimes fall outside the scientific grounding that most medical students and clinicians receive at university, making it difficult to assess the quality of techniques described in journal articles. This article aims to explore some of the most frequently utilised models and technologies in laboratory-based cancer research to ease the appraisal of such scientific papers for the budding clinician.

Statistical significance and biological significance

A recent publication in *Nature* demonstrating the limitations of the p value has highlighted how research results can be unintentionally misleading, [1] yet many studies still rely simply on this measure. Beyond the limitations of statistics, it is important to consider what a meaningful outcome is in the context of cancer treatment. A treatment may lead to a significant reduction in the levels of a certain protein or RNA transcript, but it is more important to measure how this ultimately affects an *in situ* tumour. Depending on the way these levels are measured, a small reduction in expression levels can appear statistically significant, but may not represent a large enough change to actually alter the behaviour of tumour cells. Small quantities of stimuli such as cytokines can sometimes have no effect on cancer cells. [2] Similarly, systems can reach an optimal concentration at which point even increasing doses by 10-fold will have no additional effect on cell growth. [2] It is therefore pertinent to consider not only whether a change can pass statistical tests, but also whether this change is altering the tumour environment through more functional experiments that can quantify proliferation, angiogenesis, cell death or apoptosis.

Culturing cancer cells

Many studies utilise *in vitro* cell culture work. It is a convenient way to look closely at the behaviour of cancer cells in response to various stimuli and treatments. There are, however, a number of limitations to this model. Human cancer cell lines originate from human tumours (the most famous being the HeLa cell lines - isolated from Henrietta Lacks, a cervical cancer patient from the 1950s [3]). Many are not sourced from primary tumours, but rather originate from metastases,

commonly from surrounding lymph nodes, but sometimes from such unusual and distal sites as a brachial muscle metastasis. [4] Cancer cells that metastasise are known to have different properties to primary tumours, [5] and although studying metastasis themselves is a valuable pursuit, applying the properties of these cells to a whole disease is flawed.

Furthermore, in order to culture cancer cells, an immortalisation process must be undertaken to allow continued growth outside of the body. [6] Although many cancer cells have already developed a way to avoid normal cell cycle regulation, this process inevitably introduces more oncogenic mutations that may not have been present originally. [7] It is also clear that over time in culture, these cells develop further mutations, leading to variability in results. The product of this is conflicting scientific articles: for example, eight years later and in a different laboratory, pancreatic cancer cells showed the opposite expression of a key oncogenic transcription factor. [8, 9]

Despite allowing scientists to look closely at the behaviour of cancer cells, *in vitro* studies have limited application to *in vivo* disease, demonstrating the need for *in vitro* studies to be confirmed with compelling disease models.

Models of disease

As a way of contextualising results seen in cells cultured in the laboratory, animal models of cancer are widely used to examine pathogenesis and management options.

Mice with genetic mutations

Specific augmentation of genes can lead to spontaneous development of tumours without other stimuli. [10] These models can be excellent for studying a range of disease processes, looking at specific oncogenes and other events (such as inflammation) that may result in the development of tumours. [10] Their relevance can sometimes be limited by this single mutation, as very rarely do endogenous or naturally occurring human tumours result from one single mutation. Additionally, tumours do not always mimic the disease course in humans, with atypical metastatic processes. [11]

Mice with inducible cancers

As gene modulation developed, a number of systems that allows organ- or cell-type-specific



genetic mutation have allowed more detailed study into the roles of specific proteins in the development of tumours.

A common inducible model is the *Kras* model. *Kras* is a gene that is mutated in approximately 90% of lung cancers. [12] This gene can be utilised to generate lung tumours in mice. Removal of a stop codon in the *K-ras* gene allows for expression and development of tumours, which can be done by administering a viral effector, *AdenoCre*. [12] Similar to mice with specific genetic mutations, this sort of targeted induction of mutation is not wholly representative of human disease.

Other forms of treatment can also be used to provoke dysplasia in animal models. An extremely widely used model for mimicking inflammation-associated colorectal cancer is the DSS-AOM model. This model has been highly variable, especially in regards to the role of the immune system in worsening or alleviating disease. [13-18] Much of this variation has been attributed to resident gut flora variation, highlighting its role in the development of inflammation-associated cancer, [16] but not assisting in providing a robust answer to the scientific questions posed in these individual studies.

Xenografts

An alternative to endogenous cancers, animals can be used to investigate the response of human tumours to therapies. The process of removing a tumour from a patient, and inserting it into an immunocompromised mouse is called xenografting. These can be very effective models for assessing, *in vivo*, the penetrance and effects of cancer therapy. [19-22] Unfortunately, these too have limitations. Many studies insert tumours in the subcutaneous tissue of the mouse flank – making tumour size easy to measure, both

for ethical and research outcomes. However, the limitations of this location are clear, as the tumour is not located in a place it would usually physiologically be able to access. Recently, an effort to establish xenografts in a most physiologically appropriate location has been made. [23, 24] This may yield more accurate results and improve the efficiency of translated treatments in clinical trials.

Xenografts could also potentially play a role in advancing personalised medicine. Studies have implanted an individual patient's

tumour into a colony of mice, who are then administered a range of chemotherapeutic agents to determine which regime leads to the greatest reduction in tumour burden. [25] This is an exciting frontier in personalised medicine that will hopefully lead to more effective treatment in the future.

Conclusion

Despite limitations in laboratory research, the future for cancer therapy lies, at least partially, in these laboratories. When paired

with a clear clinical goal and active attempts to translate ideas both from the bed to the bench and back again, promising breakthroughs can be made that will be valuable for researcher, clinician and most importantly, patient.

Conflict of interest

None declared.

Correspondence

A Browning: afbro1@student.monash.edu.au

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Recapturing compassion

Grace Sze Yin Leo
Senior Editor, AMSJ

John was wheeled into hospital on a Friday of a long weekend. He was elderly and frail, with severe Parkinson's disease. Many hospital staff attended to him – prescribing medications, delivering meals, and changing his sheets. Unfortunately, no one realised that John's limited mobility meant that he could not reach his drinking cup. Although the staff had performed their duties, the absence of compassion led John to become dehydrated and develop acute kidney injury.

When we first entered medicine, we pledged ourselves as model medical students. We spoke of our compassion for the sick and a dedication to helping our community. But as we progress through our studies into full time clinical work, putting such aspirations into actions becomes more challenging.

There are checklists for assessing practical skills – be it history taking and examination, inserting cannulas, or writing discharge summaries. Medical schools are honed to teach us to be competent; but do they teach us how to be compassionate?

Why should we care about compassion?

Compassion is derived from the Latin, 'compati', meaning 'to suffer with' other people. It also involves an active concern for and effort to alleviate that suffering.

Whilst as students we may initially see the best way to alleviate suffering is to 'cure' our patients with medicine, we soon come to realise that we cannot 'cure' all our patients. Indeed, over 7 million Australians suffer from chronic disease, which cannot be 'cured' completely. [1] But it is not just for these patients that the 'care' is just as, if not more important than the 'cure'. As Sir William Osler explains, 'The good physician treats the disease; the great physician treats the patient who has the disease.'

Patients want compassionate doctors. [2] Being compassionate can improve patient wellbeing and care. Compassionate doctors also help reduce patient anxiety. [3] A positive patient mindset is important, as several studies have linked optimism with better health outcomes. [4] When compassion enters the patient-physician relationship, it builds trust, aiding more accurate diagnosis and understanding of patient problems. [5] Through compassion, care is optimised. It transforms healthcare from being a system to a service.

Why do we struggle with being compassionate?

Although we may begin work with a good understanding of the necessity of compassion, stressors such as heavy workloads and limited time can harden our hearts towards our patients. [6] Bureaucracy and red tape takes time away from direct patient contact. We start to become wary as the list of people needing attention expands. It is possible to let faces blur and details melt away until we are treating 'the man with the ankle fracture' or 'bed 5's dehydration'. While we never intend to lack compassion, the current reality of medicine means that we are often pre-occupied with treating the patient, rather than caring for them.

In many instances, acting with compassion to a patient can be a challenge. In medicine, we see humanity at its best, but also at its worst. Patients are not always polite or easily satisfied. Sometimes, the most difficult keep coming back again and again. 'Frequent flyers' is a term applied to patients who commonly represent to hospital. Last year, 1,200 of these patients accounted for over 22,000 presentations to Victorian casualty wards between them. [7] One patient managed to visit Royal Melbourne Hospital 144 times alone. [7] Whilst some of these patients have legitimate health problems, others may be drug seeking, homeless, or hypochondriacs.

It is not surprising then that doctors are at high risk of 'compassion fatigue', resulting from the constant demand of caring for others. Compassion fatigue can lead to burn-out and compromise our ability to provide safe and effective patient care. It is concerning to look at the results of the 2008 Australian Health and Wellbeing Survey of junior doctors which found that 54 percent of respondents were at risk of secondary trauma or 'compassion fatigue'. [8]

How can we recapture compassion?

Perhaps we must begin by remembering to treat ourselves with compassion.

Having enough time for oneself is important in continuing to be a kind and functioning human being capable of showing others compassion. This includes addressing basic needs such as getting enough sleep, eating regular meals, and making time to refresh our bodies and souls. Unfortunately, it is common to see doctors neglecting on these things and



more. There are doctors who have abstained from drinking water to avoid bathroom breaks, and others who have even performed ward rounds with drips in their arms. Such exploits have been boasted about as personal achievements or as self-sacrifice for the sake of having more time with patients. But this is a misperception that is likely to do more harm to ourselves and our patients, as we are prone to make mistakes when tired and stressed. [9]

In fact, being compassionate does not necessarily require large amounts of time. One study compared two interviews in which the diagnosis of breast cancer was presented. In the second interview, the doctor was more compassionate and added two statements, which acknowledged the patient's difficulty of receiving such a diagnosis and expressing support. [3] Study participants evaluated the doctor as significantly more compassionate and they also had a reduced anxiety state compared to those exposed to the standard interview. Interestingly, the time difference between the two interviews was only 40 seconds. In the time that we might wait for a lift, it is possible to improve patient wellbeing by showing compassion.

Sometimes it seems difficult to know where we should start with being compassionate to our patients. It does not have to be a dramatic act, but may begin with pulling up a chair and four simple words, "Hello my name is...". This is the potent thought that Dr Kate Granger triggered across the world in her viral hashtag #hellomynameis. It was a call to address what she saw as an important gap in communication and patient care within the healthcare system. [10]

Dr Granger is a geriatrician. She is also a long-term patient diagnosed with sarcoma in 2011. During her illness she was startled to find that

many of the healthcare workers examining, treating, and looking after her went about nameless. They had missed an essential step to building relationship and trust – the introduction. [10] These experiences inspired her to start sharing her stories and encouraged reforms in Britain's National Health Service (NHS).

At the end of the day, we do not always need to feel compassionate or have vast time or strength for it. Instead, we choose

compassion in the little things and persevere in the remembrance that everyone has intrinsic worth. That is when we discover the simple truth – that what makes a compassionate doctor is the same as what makes a compassionate human being.

At the Australian Medical Student Journal, we provide a stepping-stone for medical student research and writing. We also hope to inspire not only more competent clinicians, but more compassionate ones too.

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Acknowledgements

I would like to thank May Whitbourn, Peggy Kuo, Linda Wu, Dr Michelle Johnston, Dr Natalie May and Dr Matthew Leung for their invaluable feedback and encouragement.

Conflict of Interest

None declared.

Correspondence

G Leo: gracesyleo@gmail.com

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Psychopathy: A disorder or an evolutionary strategy?

Dr. Kylie Cheng
BMed

Kylie graduated from the University of Newcastle in 2013 and is currently working as an intern at Campbelltown/Bankstown Hospital. She wrote this letter as a final year medical student. She is interested in mental health and aims to pursue a career in psychiatry.

I am writing to discuss an interesting construct in psychiatry often referred to as 'psychopathy'. In psychiatry there is often lively debate about how we should classify and define psychopathology, influenced by cultural factors as much as scientific advances. In this letter I wish to explore the somewhat controversial idea that, instead of being a disease or pathology, psychopathy can be viewed as a natural variant in human personality. In other words, psychopathy may be a phenotype resulting from various adaptive strategies occurring throughout evolution.

Psychopathy is a term describing a particular constellation of personality traits and behaviours, sometimes viewed by the medical community and society as a disorder or pathology. The Hare Psychopathy Checklist, Revised (PCL-R) is the traditional measure used to define and assess psychopathy.

Box 1. The Hare PCL-R defines psychopathy as a combination of key interpersonal and affective deficits (Factor 1) and socially deviant behaviours (Factor 2) [1]

Factor 1 traits

lying
conning
lack of guilt/remorse
lack of empathy

Factor 2 traits

high impulsivity
irresponsibility
poor behavioural control
criminal versatility

Although psychopathy is sometimes perceived as being synonymous with the DSM-5 diagnosis of antisocial personality disorder, this is largely incorrect. Antisocial personality disorder focuses more on outwardly observable criminal behaviours, whereas psychopathy takes into account personality traits that are less readily observable. These differences have been discussed elsewhere. [3]

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The concept of psychopathy as an adaptive strategy is well discussed by Glenn *et al.* [4] Unlike schizophrenia and other mental disorders that are clearly harmful or maladaptive for the individual, psychopathy is not so clear-cut. One can even argue that the greatest danger of psychopathy is harm to society, rather than harm to the affected individual. Certain traits associated with psychopathy (such as fearlessness and superficial charm) may have been beneficial to the individual in the ancestral environment, existing as a social strategy to increase survival and reproductive success. [4] Even in today's society, it seems that traits such as fearlessness and low stress reactivity may sometimes help a person to perform well in high-stress occupations (e.g. executive management, politics, military).

Psychopathy may be more common than we expect. The idea of 'successful' and 'unsuccessful' psychopaths further complicates the pathology vs. strategy debate. Most studies have been unable to find a clear correlation between psychopathy and intelligence. [5] According to Hare, 'successful' psychopaths are commonly described as intelligent, successful and high-functioning individuals, with no criminal convictions and variable integration into society. These individuals are usually more difficult to identify and study. [6] 'Unsuccessful' psychopaths typically describe the cohort encountered in forensic settings, individuals who regularly run into trouble with the law (and are hence easier to identify and study). [6] Consequently, it is this population from whom we derive the bulk of our knowledge and research on psychopathy. If we are only identifying a subset of psychopaths, psychopathy on the whole may be more ubiquitous in society than we think.

Further research is still required into many aspects of psychopathy. Whether the traits associated with psychopathy represent true pathology is still open to debate. Although



a diagnosis of psychopathy has the practical benefit of directing treatment in the forensic setting (e.g. towards behavioural change and control therapies instead of empathy and social skills training), [7] the psychopathy label carries considerable stigma and possible social, psychological and legal consequences for the individual. An example is the difference in criminal sentencing in certain countries. [8] For personality traits to constitute a disorder in the DSM-5, there must be significant distress or functional impairment caused to the individual. Although psychopathy is not a personality disorder in the DSM-5, it is interesting to note that 'successful' psychopaths may experience neither of these.

In conclusion, the aim of this article was to put forth an alternative view on psychopathy. Rather than to comment on management or the correctness of any particular viewpoint, I hope to have highlighted some of the complexities surrounding human personality and behaviour through this brief discussion on psychopathy.

Conflict of interest

None declared.

Correspondence

K Cheng: c3108437@uon.edu.au

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About Helen Caldicott's guest article

Dr. Mark Foreman

Associate Professor

Nuclear Chemistry/Industrial Materials Recycling
Chalmers University of Technology, Sweden

Dr. Foreman is an associate professor of industrial materials recycling who has since 2001 held an interest in the chemistry of radioactive materials. His research interests include the chemistry of both radioactive waste and serious nuclear reactor accidents.

A university academic whose professional interests include the chemistry of serious reactor accidents I disagree with many of the statements made by Helen Caldicott in her recent article "The impact of the nuclear crisis on global health". While she is an iconic figure for many people it is important that her statements are critically assessed, in the interests of public health neither statements made by the opponents or supporters of any technology should be accepted blindly. For reasons of brevity I am unable to address all my concerns about her article, so I will focus on a few of the errors I believe she has made. Helen claims that the low level exposure that the general public experienced caused symptoms of "radiation sickness". This claim is at odds with what I have been taught during the radiological health and safety training I have had and I would like to point out that to induce the acute radiation syndrome in humans a dose of at least 1 to 2 Gy needs to be delivered over a short time. The doses which the public had during the accident were far too small. If radiation is as able as she claims to induce the acute effects (blood and GI disturbances) then surely these effects would be commonly seen after moderate medical exposures such as CT scans and diagnostic nuclear medical procedures.

I would like to challenge her claim that all radioactive elements bioconcentrate as they pass through a food chain. While some radionuclides can pass through food chains with ease, others do not do so, for example,

the human digestive system is unable to absorb into the blood more than a small fraction of any plutonium that is swallowed. A classic test to determine if a worker has inhaled plutonium dust is to measure the plutonium content of their faeces. If the digestive system were a good absorber of this element then this test would be impossible.

It is noteworthy that the biokinetics of tritium and cesium are not compatible with the idea that it will bioconcentrate in all food chains; the biological half-life of cesium in humans and farmyard animals is in the range of one to three months. As a result, after a short exposure to cesium most of it will be gone in less than one year. During a protracted constant exposure to cesium-134 or 137 an equilibrium will be set up within months which will prevent the further accumulation of cesium; the majority of the cesium ingested will be excreted before it is able to undergo radioactive decay. The common form of tritium (HTO) has an even shorter biological half-life in humans, as a result it is one of the least toxic radioisotopes.

Helen claims that iodine-131 is a potent carcinogen in humans, while I advocate exercising great care when working with any radioactive substance I note that a Swedish medical scientist (L.E. Holm) was unable to find any evidence that this radionuclide is able to cause thyroid cancer in humans. He could see no excess of thyroid cancer in a population of people exposed during diagnostic medical procedures. However data



associated with Chernobyl and atom bomb tests strongly indicates that radioactive iodine causes thyroid cancer. L.E. Holm suggested that the shorter lived higher beta energy iodine radioisotopes from bombs / Chernobyl may have been the main carcinogen. While I do not know if L.E. Holm's short-lived iodine hypothesis is right, based on the current evidence it is not a certainty that iodine-131 is a potent carcinogen.

I hold the view that people are equally entitled to hold antinuclear or pronuclear views. However, any scientific argument either for or against nuclear power should be correct and good quality science.

Conflict of interest

None declared.

Correspondence

M Foreman: foreman@chalmers.se

The α_5 subunit-containing GABA_A receptor: a target for the treatment of cognitive defects

Abhishta Pierre Bhandari

Fourth Year Medicine (Undergraduate)

James Cook University

Abhishta Bhandari did a year of BSc majoring in Chemistry before entering into medicine. He is interested in research that looks at novel ways to target existing problems.

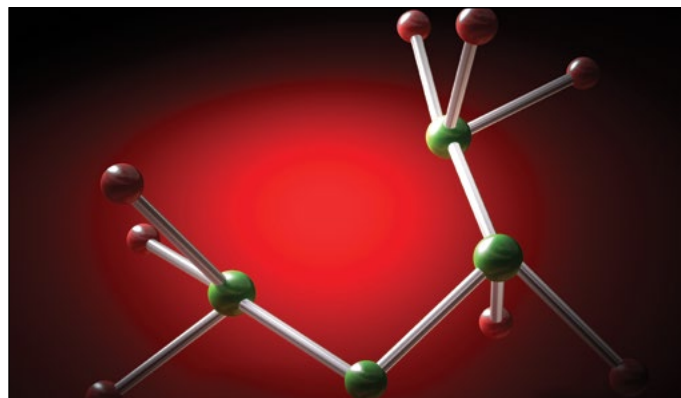
Amnesic effects of benzodiazepines are in part the result of the activity of α_5 -subunit containing GABA_A receptors (GABRA5). Negative modulators at this receptor could improve cognition. In order to explore this beneficial effect, this article reviews the evidence on the effects of GABRA5 negative modulators and searches potential uses for such drugs. A literature search found a number of GABRA5 negative modulators. These drugs generally improve hippocampal-dependant learning via an increase in long-term potentiation (LTP) in the hippocampus. Passive avoidance learning was also improved. In addition, the compounds examined demonstrated minimal side effects partly due to lack of binding to different alpha subunit-containing GABA_A types. Due to its beneficial properties, there is potential for such a drug in treating Alzheimer's, alcohol-related amnesia and Down syndrome. Despite the myriad animal studies that utilised GABRA5 negative modulators, only three human studies were found. Due to its cognitive enhancing properties and minimal side effects, further human trials should be conducted in order to ascertain the potential of such drugs in treating cognitive deficits.

Introduction

γ -aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain and is responsible for regulating neuronal excitability. There are at least three different receptors that it targets — GABA_A, GABA_B and GABA_C. [1] The GABA_A receptor is the main target for the popular class of drugs, the benzodiazepines. This receptor is an ionotropic membrane receptor, which facilitates the movement of chloride into cells. In neurons, this increases the threshold needed to excite them. [2] Benzodiazepines are positive modulators at this receptor and exert their effects by binding to the interface between the γ_2 and α subunits on the GABA_A receptor. [3] Since they are modulators and not agonists, they do not work in the absence of GABA. [4] They only bind to the receptors containing the α_5 , α_3 , α_2 , and α_1 subunits. [5] Each of these subunits mediates different effects. In knockout mice, the α_1 subunit has shown hypnotic/sedative effects, whilst the α_3 , α_2 and α_5 subunits have anti-anxiolytic effects and these have been exploited for therapeutic use. [6]

Despite their uses in treating various conditions, traditional benzodiazepines have numerous side effects. The main side effects associated with therapeutic use are amnesia, confusion, impaired coordination and dizziness. There may be tolerance due to rapid escalation in the dose needed to provide the required effect. There are also long-term issues with dependence. In acute overdose the most life-threatening effect is respiratory depression, especially when combined with alcohol. [7]

Interestingly, it is thought that positive modulators at the α_5 subunit-containing GABA_A receptors (GABRA5) produce the anterograde amnesia associated with benzodiazepine use. [7] Most of these receptors are found in the hippocampus (a brain region associated with memory) and provide tonic inhibition in this region. [8] The exploitation of this receptor has led to the increasing use of the infamous 'date rape' drug flunitrazepam, which is a positive modulator at the GABRA5 in addition to its other functions. Because of its amnesic effects, victims are unable to recall events following intoxication and this provides a major challenge for prosecutors. [7] Despite these negative properties, by using a GABRA5 negative modulator the opposite effect might



be achieved and cognition improved. The use of such a drug could potentially improve the quality of life for those living with cognitive defects and could also counteract drug-induced amnesia (for example, alcoholic 'blackout'). However, this must be balanced with the inverse activity of non-selective negative modulators which could produce convulsant or anxiogenic effects. [4]

Based on the premise that a GABRA5 negative modulator could improve cognition, the aim of this literature review was to review the evidence on (1) the effects of GABRA5 negative modulators on cognition; and (2) investigate the potential of GABRA5 negative modulators in managing conditions involving cognitive defects.

Effects of GABRA5 selective negative modulators

A number of GABRA5 negative modulator compounds were examined. Many of the studies used animals as subjects. Studies in animals provide a solid starting platform for understanding the various physiological changes that a drug induces. [9] Of particular importance is the avoidance of potential side effects as a result of non-selective actions at other GABA_A receptors. Side effects could include an increase in anxiety, aggressiveness, motor impairment, inability to sleep and proconvulsant effects. [7] Ultimately, the knowledge gained from animal experimentation can be used to conduct safe and effective clinical trials.

Dawson *et al.* [10] examined a compound named $\alpha 51A$ (3-(5-Methylisoxazol-3-yl)-6-[(1-methyl-1,2,3-triazol-4-yl)methoxy]-1,2,4-triazolo[3,4-*a*]phthalazine), which has selective negative modulator effects at GABRA5. The authors found that $\alpha 51A$ reversed the inhibiting effects of GABRA5 in the hippocampus in rats and mice. This resulted in an increase in performance in a memory test named the "delayed matching-to-position version of the Morris water maze", which is a hippocampus-dependant cognitive test. [11] In addition, 'long-term potentiation' (LTP), which is thought to underlie the synaptic changes that take place during memory formation, was found to be enhanced in the hippocampus. [11,12] Benzodiazepine (agonist) effects and non-selective GABA_A negative modulator effects were also examined. The authors found no anxiogenic, convulsant, withdrawal or motor-impairing effects from the drug. [10]

Only certain components of memory have shown to be improved by GABRA5 negative modulators. Collinson *et al.* [13] extrapolated on the results obtained by Dawson *et al.* [10] and looked at the effect of a modified version of $\alpha 51A$, $\alpha 51A-II$. They separated memory into three components — encoding, consolidation (conversion into long-term

memory) and recall. Results were obtained by measuring performance in the delayed matching-to-position (DMTP) version of the Morris water maze in rats. The authors found that the compound improved encoding and recall but not consolidation in this hippocampal-dependant memory test. [13]

The effect on cognition by another selective GABRA5 negative modulator was examined by Ballard *et al.* [14] This was done by the use of an imidazo-triazolo-benzodiazepine compound named RO4938581. The effect of this compound on cognition was examined in rats. [15] This compound demonstrated similar effects to those found by Dawson *et al.* [10] in that they found no convulsant or anxiogenic effects. In addition, similar to Dawson *et al.* [10], there was an increase in hippocampal LTP. The authors also found that working memory was enhanced since RO493881 reversed scopolamine-induced working memory impairment. [14] This was shown by an increase in performance in the DMTP task, which is used to assess spatial working memory. [14,15] It also reversed diazepam-induced spatial impairment. This was demonstrated by an increase in performance in the Morris water maze task. [14]

'Moderate' GABRA5 negative modulators improve passive avoidance learning but generally have no effect on active learning. [16] This was shown by an experiment conducted by Savic *et al.* [16] in which they examined effects of PWZ-029 (a 'moderate' GABRA5 negative modulator) on passive and active learning avoidance in rats. The result was obtained through various shuttle-box based behavioural experiments. This experiment proved that even at 'moderate' efficacy a GABRA5 negative modulator can induce memory formation. The compound also had no effect on muscle tension and anxiety (non-selective side effects). [16] Although promising, this study was limited by the fact that the compound only had 'moderate' negative modulator activity at GABRA5 so using a more efficient compound may display different effects on avoidance learning. Despite this limitation, this shows that the use of a 'moderate' GABRA5 negative modulator would be beneficial in the treatment of disease due to its limited side effects and its memory-enhancing properties. [16]

Application in management

The compounds examined in this review show that selective GABRA5 negative modulators have nootropic effects without any serious side effects, which are seen in non-selective negative modulators at the alpha subunit of the GABA_A receptor. [17] Thus, there is strong potential for the use of GABRA5 negative modulators in healthcare settings. One major limitation is that most of the data obtained for this review was from animals. Further human trials need to be conducted to ascertain the potential of this drug. Drawing on the literature, possible future uses for a GABRA5 negative modulator are detailed below.

GABRA5 negative modulators could be used to treat Alzheimer's disease since GABRA5 is preserved in Alzheimer's disease patients. [18] Alzheimer's disease is commonly characterised by the gradual worsening of ability to remember new information. [19] Administration of a GABRA5 negative modulator could help with the 'encoding' and 'recall' of this information. [8] It could also be used to treat mild cognitive impairment (MCI), which is a risk factor for later developing the disease. [20] Administration of such a drug to patients may provide relief to older caregivers, who often show signs of sleep detriment. [21]

A review by Attack [22] in 2010 found two human trials on the GABRA5 negative modulator $\alpha 51A$ and one trial on MRK-016. Since then no human trials were found and this could be an area of future research. The first study found that a potential application of GABRA5 negative modulators is the treatment of alcohol-induced amnesia. Nutt *et al.* [23] found that pre-treatment reduces alcohol's amnesic effects in humans. This was measured by word list learning which is linked to hippocampal processing. Alcohol-induced amnesia has been shown to predict future alcohol-related injury. [24] Therefore, the use of a GABRA5 negative modulator may help in reducing this risk. In addition, it may also reduce alcohol-related stress since it has been found

that amnesic episodes related to alcohol have resulted in moderate psychological stress. [25]

Unfortunately, GABRA5 does not improve age-related cognitive defects. In fact it has been found that $\alpha 51A$ significantly impairs cognition in the elderly despite having positive effects on the young. Attack [22] found that young subjects (mean age 22 years) performed much better than older subjects (mean age 72 years) on the paired associates learning test, which is sensitive to age-related cognitive decline. Therefore, this trial showed no potential in reversing age-related cognitive decline. This demonstrates that careful consideration based on age should be taken in to account when using this drug.

MRK-016 (3-tert-butyl-7-(5-methylisoxazol-3-yl)-2-(1-methyl-1H-1,2,4-triazol-5-ylmethoxy)-pyrazolo[1,5-d]-[1,2,4]triazine) is another negative modulator and showed greater LTP in rat hippocampal slices than $\alpha 51A$. It also enhanced performance in the DMTP and Morris water maze tasks, which are used to test spatial memory. In humans, it was well tolerated in young adults with a maximum tolerated dose of 5 mg with 75% occupancy. In elderly subjects, however, it was poorly tolerated even at 10% of the maximum dosage in young adult males. Therefore, this particular drug has been precluded for development. [26]

Recent trials of GABRA5 agonists, in particular L-655,708 and MRK-016, have focused on restoring post-anaesthetic cognitive deficits. Lecker *et al.* [27] found that L-655,708 and MRK-016 reduced the potentiation of GABRA5 post-inhalation of isoflurane and sevoflurane. A further study by Zureck *et al.* [28] found that short-term memory assessed by the novel object recognition task was fully reversed by L-655,708 after isoflurane anaesthesia. This demonstrates the potential use of L-655,708 in reducing post-anaesthetic amnesia. However, further studies which include those performed on humans are needed to validate the potential of MRK-016 and other GABRA5 negative modulators in reducing post-anaesthetic amnesia.

The use of GABRA5 negative modulators could help with treating cognitive deficits related to Down syndrome. A recent review by Martínez-Cué *et al.* [29] investigated this specific application. It identified two studies that examined the effects of a GABRA5 inverse modulator on a Down syndrome mouse model (Ts65Dn). Braudeau *et al.* [30] found that acute treatment with the GABRA negative modulator $\alpha 51A$ improved learning deficits in the Morris water maze task. The second study also showed that chronic administration of a similar drug, RO4938581 has also been shown to have memory-promoting effects in the Morris water maze task on Ts65Dn mice. [31] In a practical sense, administration of such a drug could improve performance in learning a wide range of functional skills in those living with Down syndrome. For example, in children this may include learning how to use the toilet and administering self-care. [32]

Conclusion

The literature supporting the use of a GABRA5 negative modulator in the treatment of cognitive deficits is promising. GABRA5 negative modulators exert their actions by enhancing hippocampal dependant memory formation. There are minimal side effects as no withdrawal symptoms, convulsant, anxiogenic or motor-impairing effects were found. There is great potential for the use of GABRA5 negative modulators as they have been shown to reduce alcohol-related amnesia and may have potential in the treatment of Alzheimer's disease. They could also treat cognitive deficits in Down syndrome patients, increasing the speed at which they learn functional skills. Due to these favourable findings, there is an increased need for human clinical trials in order to validate the potential for this important receptor target.

Acknowledgements

A/Prof Zoltan Sarnyai, for reviewing this article when I submitted it as an assignment.

Conflict of interest

None declared.

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Correspondence

A Bhandari: abhishta.bhandari@my.jcu.edu.au

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A review of early intervention in youth psychosis

Dr. Helmut C Y Yu
BE (Hon I), PhD, MBBS

Prior to his medical degree, Helmut completed a Bachelor of Engineering (photonics) at UNSW followed by a PhD in photonic engineering at The University of Sydney.

Dr. Nimenka Ramanayake
BSc (Hons), MBBS, PhD

Nimenka completed a MBBS/PhD conjoint degree at The Australian National University in 2013. Her PhD was in the field of cellular and molecular biology. She is currently working as an intern at The Canberra Hospital. She hopes to pursue a career that combines both clinical medicine and cellular/molecular research.

Dr. Vivek Baskaran
BSc, MBBS

Vivek is a graduate of The Australian National University Medical School Class of 2013. He is currently an intern at The Canberra Hospital, ACT.

Dr. Hannah Hsu
BMedSci, MBBS

Hannah is a graduate of The Australian National University Medical School Class of 2013. She is currently an intern at Blacktown Hospital, NSW.

Dr. Jennifer Truong
BMedSci, MBBS

Jennifer is a graduate of The Australian National University Medical School Class of 2013. She is currently an intern at The Canberra Hospital, ACT.

Dr. Geoffrey Balean
BSc, MBBS

Geoffrey is a graduate of The Australian National University Medical School Class of 2013. He is currently an intern at The Canberra Hospital, ACT.

Early intervention in youth psychosis has been a topic of contentious discussion. In particular, there is a lack of consensus regarding how early to treat patients with a psychotic disorder. There has been a recent push to provide treatment early in the development of psychosis, specifically to patients in an ultra-high risk or prodromal stage. There is also debate about the types of interventions that should be used, such as psychoeducation, psychotherapy and pharmacotherapy. In Australia, these uncertainties have been reflected by the production of conflicting guidelines by key stakeholders in this area. There are significant arguments both for and against the practice of early intervention. This article explores these arguments and reviews current practices in Australia. A number of updated recommendations are also set out in accordance with the findings of this article.



use, depression) are recognisable in advance and can be acted upon. [2]

Introduction

Psychotic disorders are characterised by the presence of symptoms that reflect an excess or distortion of normal functions. For example, hallucinations, delusions, thought disorder and disorganised behaviour are symptoms characteristic of psychosis. Patients diagnosed with schizophrenia must demonstrate positive symptoms or severe negative symptoms (e.g. flattened affect, social withdrawal) in addition to deterioration in their social and vocational functioning. [1] Hence, the diagnosis is typically made after the onset of significant symptomology.

McGorry *et al.* [2] argue that late-stage diagnosis of a psychotic illness leads to delayed and inconsistent management of these patients. The concept of “early intervention” refers to appropriately managing patients in the early stages of psychotic disease, to minimise long-term negative social and psychological outcomes. As such, it represents a secondary prevention strategy and a paradigm shift in the way schizophrenia and other psychotic disorders are viewed; rather than being seen as illnesses with an inevitably poor social and functional outcome, they are viewed as conditions whose course can be altered by recognition of the early warning signs and application of timely intervention. [2] The proponents of early intervention argue that many of the recognised risk factors for the development and progression of a psychotic disorder (e.g. disrupted peer and family networks, substance

The clinical staging model [3] proposes that psychiatric illnesses should be viewed as a sequence of stages that increase in disease severity. Employing the appropriate treatment modality at a particular stage would allow regression of the disease to an earlier stage. The clinical stages of early psychosis include the ‘ultra-high risk’ stage, the ‘first psychotic episode’ stage and the ‘first 5 years after diagnosis’ stage. [2]

The ‘ultra-high risk’ stage is the stage preceding the first psychotic episode. Although the first psychotic episode is often the first recognised sign of a psychotic illness, retrospective analysis reveals many changes occur in an individual’s thoughts and behaviour in the period preceding the psychotic episode. This is known as the ‘prodromal phase’. To intervene at this stage, it is clearly necessary to be able to identify this period in advance, and a considerable research effort is being focused on developing prospective criteria for this purpose. Two tools currently in use are the Positive and Negative Syndrome Scale (PANSS) or Attenuated Positive Symptoms (APS) approach and the Basic Symptoms (BS) approach. [4] The PANSS is a 30-point questionnaire with a 7-point rating for each question. It covers positive symptoms (e.g. delusions, hallucinations), negative symptoms (e.g. social withdrawal, blunted affect) and general symptoms of psychopathology (e.g. depression, poor insight, feelings of tension). [5] The Basic Symptoms approach focuses on subtler, self-experienced subclinical symptoms such as

thought interference, disturbance of receptive language, inability to divide attention between tasks and derealisation. [6]

Intervention at the 'first psychotic episode' stage is largely aimed at reducing the duration of untreated psychosis (DUP), as a high DUP has been shown to result in poorer outcomes. Some authors have argued that untreated psychosis can lead to irreversible brain damage. [7,8] Although this theory has yet to receive widespread support, the personal, social and societal consequences of untreated psychosis can have a tremendous impact on the patient's ability to recover from the episode. [2] Functional MRI brain imaging studies have shown decreased memory encoding in patients with schizophrenia and interestingly, decreased posterior cingulate activity in patients with ongoing first-episode psychosis compared to those showing remission at one year. [9] Such alterations in brain activity in patients more likely to proceed to a significant psychotic illness has exciting implications for the use of fMRI as a tool in screening for patients most likely to benefit from early intervention.

The 'first 5 years after diagnosis' stage is a crucial period that determines a patient's long-term outcome. It is the time most likely to result in suicide, disengagement, relapse, [2] long-term treatment resistance and the break down and accumulation of disabilities in personal, social and occupational settings. [10] Mason *et al.* [11] suggest that the level of disability accumulated in the first 2 years of psychosis may in fact 'set a ceiling for recovery in the long term'. Hence, intervention at this period is important. Maintaining a steady support structure especially tailored towards young people receiving a diagnosis of psychosis is likely to maximise chances of engagement with mental health care, life-style modifications, and adequate family involvement. [2]

Current Practice

There are currently a number of different practices/guidelines in Australia relating to early intervention in youth psychosis. The Royal Australian and New Zealand College of Psychiatrists (RANZCP) has produced clinical practice guidelines for schizophrenia, which include recommendations for patients at ultra-high risk (UHR). [12] Orygen Youth Health and *headspace* have also developed guidelines, called 'The Australian Clinical Guidelines for Early Psychosis', which are now in the second edition. [13]

Australia has established the first clinical and research clinic in the world for individuals considered to be at imminent risk of psychosis. The Personal Assessment and Crisis Evaluation (PACE) clinic was established by Orygen in Melbourne in 1994. [14] The clinic receives referrals from general practice, school counsellors and various health services. [14] They facilitate case management and provide a variety of in-house support services to families and carers including group programs, vocational and educational assistance, and occupational therapy. [15] Orygen, in conjunction with the Australian General Practice Network, the Australian Psychological Society and the Brain and Mind Research Institute also established *headspace*, which is a national youth mental health foundation. [16] The aim of *headspace* was to facilitate early intervention by increasing community awareness, clinician training and taking a youth-specific approach to management, as well as utilising multidisciplinary care. [16,17] Another service available is the Early Psychosis Prevention and Intervention Centres (EPPIC). In the 2010-11 and 2011-12 budgets, the Federal Government allocated \$247m to the establishment of a network of 16 of these centres across Australia, modelled upon Orygen's EPPIC centre in Melbourne. [18] A more detailed summary of the current guidelines/practices existing in Australia for youth psychosis is listed in Table 1.

Table 1. Current practice (guidelines and health services) in Australia for youth psychosis.

Guideline	Recommendations
RANZCP Clinical Practice Guidelines for the Treatment of Schizophrenia and Related Disorders (2005) [12]	Assessment and close monitoring every 2-4 weeks along with the provision of information to the patient and their family about the risk and likelihood of progression. Other techniques such as cognitive behavioural therapy (CBT), stress management and vocational rehabilitation should be employed depending on any concurrent psychosocial difficulties. Antipsychotics are only to be prescribed when the patient has been frankly psychotic for over a week, or in cases when milder symptoms are associated with a risk of self-harm or aggression (however, patients without such a history are often treated regularly with antipsychotics and the primary concern here is that they may have a delirium or physical illness, which should be excluded first). [12]
The Australian Clinical Guidelines for Early Psychosis [13]	Commencement of CBT for all patients identified as being at ultra-high risk is recommended. Family, vocational, educational and accommodation support should also be provided as required in a low stigma setting. Antipsychotic medication should only be considered once full threshold psychotic symptoms have been sustained for over a week, or if there is rapid deterioration accompanied by psychotic-like symptoms. [13]
Health service	Nature of service provided
The Personal Assessment and Crisis Evaluation (PACE) clinic	PACE provides information to individuals and their families about what it means to be at risk of psychosis. [14] They facilitate case management and provide a variety of in-house support services to families and carers including group programs, vocational and educational assistance and occupational therapy. [15] Specific treatment is largely in the form of voluntary participation in clinical trials, such as those looking at antipsychotic use or CBT in ultra-high risk individuals. [14]
Headspace	These centres for 12-25 year olds combine specialist mental health, drug and alcohol and primary care services, vocational services and training, and employment support within a youth and family-friendly environment. [16,17] <i>Headspace</i> centres are also tasked with developing awareness campaigns for their local community and providing training for primary care and other workers using an evidence-based approach. [16]
Early Psychosis Prevention and Intervention Centres (EPPIC)	Provide comprehensive in-patient and mobile components and aim to identify patients as early as possible and deliver phase-specific best-practice interventions to psychotic individuals between the ages of 15 to 24. [19] This model has also been adopted widely around the world, including in the UK [20] and the US. [21]

The early intervention model has also been subject to some criticism. The major basis for this is a lack of evidence, especially with regard to the use of anti-psychotics in the prodromal stages of psychotic illness and the significant cost associated with creating a clinical infrastructure for patients who may never proceed to a long-term psychotic illness.

Results and Discussion

Evidence for early intervention

There is evidence from several small studies that psychotherapy such as CBT [22] and pharmacotherapy [3,23] can reduce the progression of ultra-high risk individuals to first episode psychosis.

Wyatt *et al.* [8] reviewed 22 studies, of varying study designs, which included contemporaneous control group studies, cohort studies, mirror image studies and early intervention studies. In these studies, patients with schizophrenia were either given or not given neuroleptics at a specific time during the course of their illness. 19 of the studies, in particular, looked at patients who were experiencing their first psychotic episode. After re-analysing the data, Wyatt *et al.* [8] showed that early intervention with a neuroleptic in first-break schizophrenic patients improved the long-term course of the illness, commonly assessed based on re-hospitalisation and relapse rates. It was also shown that with the use of neuroleptics, the length of the initial psychotic period was reduced. In addition, when neuroleptics were discontinued, it resulted in poorer outcomes as the patients were not able to return to their previous level of functioning and relapses occurred more frequently. Neuroleptic medication has the strongest support for relapse prevention in schizophrenia and is the basis of most interventions.

It has been suggested that the duration of untreated psychotic episodes directly correlates with less complete recovery, a higher rate of relapse and increased levels of compromised functioning, since these episodes have a toxic effect on the brain. [7,8,24-26] These studies, both retrospective and prospective, suggest that a longer DUP in the early stage of schizophrenia is associated with a longer time to remission, a lower level of recovery, a greater likelihood of relapse and a worse overall outcome.

Studies have shown that raising public awareness and using mobile outreach detection teams to identify candidate patients [27] has significantly reduced DUP, leading to beneficial outcomes. In particular there has been a reduction in negative symptoms in schizophrenic patients.

Arguments against early intervention

There are certain groups who are against early intervention. One of the arguments against early intervention relates to whether it is cost effective, as resources may be diverted from treatment programs for patients who already have an established diagnosis of psychosis. In addition, they argue that the great majority of high-risk patients do not in fact progress to frank psychosis. There is also the argument that some patients seeking early intervention may not have 'true prodromal' features, thus inflating the numbers of those who actually require early intervention. These arguments are discussed in more detail below.

Economic cost of early intervention may be infeasible

Those against early intervention believe the increased attention and funding given to early intervention diverts funding away from treatment in those with established psychosis. [28-30] They also argue that proponents of early intervention have touted the cost-effectiveness of early intervention as such programs utilise more outpatient resources compared to inpatient resources, thus reducing overall healthcare costs (with outpatient services being much cheaper than inpatient treatment). However, critics of early intervention have pointed out that implementation of a cost-effective treatment actually increases total costs [31,32] since cheaper treatment would have a much higher uptake compared to an expensive alternative, thus raising the total cost of treatment. In addition, Amos argues that total healthcare costs are further increased since in-patient costs are not reduced with early intervention. [33] This is because 80% or more of hospital costs are fixed costs and by shifting psychosis treatment to largely outpatient settings in the community, community costs increase but hospital costs are not reduced. [33] This is corroborated by previous studies, which

show an increase in total costs when hospitalisation rates had been reduced. [34,35]

Most high-risk patients do not progress to frank psychosis

One possible explanation for this is that a subset of adolescents whom are identified as being UHR may just be odd adolescents that become odd adults with few progressing to a frank psychosis. The prominent child psychiatrist Sula Wolff was the first to describe these odd adolescents in her book, *Loners: The Life Path of Unusual Children*. [36] Her research has shown that while odd qualities such as those found in schizoid and schizotypal disorders are found pre-morbidly in patients with schizophrenia, very few children with such personality traits/disorders go on to develop schizophrenia. For example, in 1995 Wolff undertook a records survey of all psychiatric hospital admissions in Scotland. Overall, 5% of schizoid young people were affected by schizophrenia in adulthood compared to a population prevalence rate in the UK of 0.31-0.49%. [36] These numbers suggest that while the risk for schizophrenia in schizoid children is higher than that of the general population, it is still low. To reiterate, there may be a proportion of patients who are flagged as being prodromal but whom actually have qualities consistent with schizoid personality disorder that will never progress to psychosis.

Recently, there has been a decline in the proportion of patients at high risk of psychosis actually progressing to frank psychosis

This decline has important ramifications for the practice of early intervention. A decline in the transition rate of patients identified as UHR has been reported within the PACE clinic (Melbourne, Australia) and in other UHR clinics as well. [37,38] As an example, The PACE clinic has reported that each successive year between 1995-2000 had a rate equal to 0.8 of the previous year. [38] The reported decline in transition rate was not due to differing patient characteristics across the years, such as gender, age, family history, baseline functioning and degree of psychopathology and psychiatric symptoms. [38] Additionally, the UHR criteria remained unchanged in the PACE clinic between 1995-2000. [38]

There are a number of possible explanations for the declining transition rate to psychosis. Firstly, UHR patients are being detected more quickly than in the past (the duration of symptoms prior to detection is getting shorter). [38] However, it is unclear whether the resulting decline in transition rate is due to earlier treatment (which may be more effective than delayed treatment), the identification of increased numbers of false positives (those who are not going to progress to psychosis) or a combination of both. [38] There may also be an effect from clinicians becoming better at managing UHR patients. [38] Additionally, it has been noted that the decline in transition rate was more prominent for patients who met two of the UHR inclusion criteria simultaneously compared to those who met only one of the criteria. [38] This could have been due to the increased emphasis which was placed on detection of patients who met both criteria, both in the UHR clinic and from referrers, thereby leading to earlier detection and treatment. [38] This is also in keeping with the wider community shift and preoccupation towards early psychosis and its recognition, and the increase in available referral pathways.

The decline in transition rate also raises questions about the validity of intervention approaches, such as pharmacotherapy and psychosocial treatment, on patients who may not ultimately transition to psychosis. [38] Such intervention may be harmful and therefore unjustified in this context. The UHR concept, which is used extensively in psychosis research, may also have to be re-visited if many of the identified patients are not transitioning. [38]

Due to the uncertainties regarding the basis for the declining transition rate, a review of the role of UHR clinics may be warranted. [38] It may be necessary to initially monitor patients and treat conditions such as depression, substance use problems and anxiety disorders while withholding antipsychotic treatment until features suggestive

of transition occur, such as worsening of sub-threshold psychotic symptoms. [38] This may be prudent in the context of detecting increasing numbers of patients who were never destined to transition to psychosis. In any case, further research is needed to clarify the ongoing uncertainties in this area.

Bias in patient selection

Specialised teams set up to treat early psychosis engage with anyone who is seeking help. However, Castle [39] believes that this would skew the treatment group, as it would engage those with help-seeking behaviours rather than prodromal psychosis. Furthermore, it also raises the issue that those seeking help may have signs and symptoms of what is a normal developmental process or a 'psychosis proneness', which is part of a normal distribution within the general population. [40] Thus, these individuals may not require treatment for psychosis at all as they would either grow out of 'psychotic proneness' or would stabilise and never develop psychosis.

Prescribing anti-psychotics to a population that is not psychotic: An ethical implication

The potential dangers of psychotropic drugs on young people are outlined in the United Nations Convention on the Rights of the Child, where children are recognised as being particularly deserving of protection from unnecessary exposure to psychotropic substances. [41] However, much of the research into early intervention includes administration of a low dose of antipsychotics as a crucial and efficacious treatment option. [42] Furthermore, antipsychotics are known to have serious side effects including sedation, weight gain, mild sexual dysfunction and disconcerting extrapyramidal symptoms (EPS) such as pseudoparkinsonism, akathisia, acute dystonia, and tardive dyskinesia. [43] While these effects have a stronger association with first generation antipsychotics, there is increasing evidence suggesting that second generation antipsychotics (SGA) are associated with significant side effects such as weight gain, hyperprolactinemia and EPS in the adolescent population.

Summary and recommendations

In view of the currently available literature, the authors make the following summary and recommendations with regards to early intervention in psychosis.

- Psychosis is a highly disabling condition with detrimental impacts on patients' relationships and occupational and social functioning
- Possible interventions that delay or prevent transition from the prodromal period to psychosis are important, both clinically and economically
- A systematic review by the Cochrane Database found limited evidence about interventions to prevent psychosis. Despite this, early intervention facilities such as *headspace* are widespread in Australia

Our recommendations

1. We do not recommend the use of antipsychotics in children and adolescents who have been identified as at increased risk but who have not yet progressed to frank psychosis. Exposing children and adolescents to the serious side effects of antipsychotics is both unethical and inappropriate considering a proportion of these patients will not progress to psychosis.
2. We recommend more research into safer, less harmful interventions such as omega-3 fatty acids and psychotherapy.

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Table 2. Summary of the evidence supporting and arguments against early intervention in psychosis.

Evidence supporting early intervention	Evidence from small studies showing psychotherapy such as CBT and pharmacotherapy can reduce the progression of ultra-high risk individuals to first episode psychosis. Studies show that raising public awareness and using mobile outreach detection teams to identify candidate patients significantly reduces the duration of psychosis.
Arguments not in favour of early intervention	The economic cost of early intervention may be infeasible. Most patients identified as being high risk do not progress to frank psychosis. Treatment teams for early psychosis may disproportionately target patients with "help seeking behaviour" and thereby treat more patients who simply display signs and symptoms of a normal developmental process or "psychosis proneness". The negative ethical implications associated with prescribing antipsychotics to a population that is not psychotic.

For omega-3 fatty acids, evidence suggests a beneficial effect on transition rates compared to placebo. [44] However, this evidence comes from a single trial with few participants. A replication study with a larger sample size is needed to more definitively ascertain the merit of this intervention.

3. As previously discussed, preliminary evidence shows that CBT may reduce the transition rate to psychosis. Further research should be undertaken to conclusively establish the benefit of psychotherapy in high-risk individuals. Further research should include investigation of the cost-effectiveness of psychotherapy as an early intervention for youth psychosis. In addition, research should aim to identify any detrimental effects associated with providing psychotherapy to patients who do not progress to psychosis.
4. Patients identified as being at risk of developing psychosis should be monitored closely by a multi-disciplinary team. Team members may include a general practitioner, social worker, psychiatrist and psychologist. By closely monitoring at-risk patients, their progression into frank psychosis can be detected earlier and appropriate treatment given in a timely manner. Prompt detection and treatment of psychosis is crucial, as delayed untreated psychosis has been shown to result in poorer outcomes.

Acknowledgements

The authors would like to thank Professor Jeff Cubis and Professor David Harley for their guidance and expert opinion on the matter.

Conflict of interest

None declared.

Correspondence

H C Y Yu: u4788941@anu.edu.au

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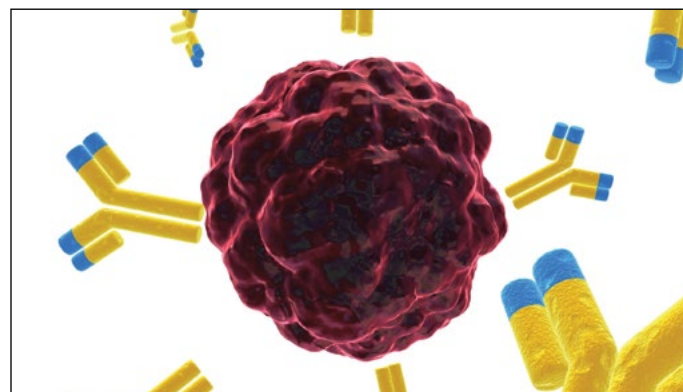
Insights into the application of evolutionary and ecological concepts to cancer treatment via modelling approaches

Kok-Ho Ho

Third Year Medicine (Graduate)
University of Sydney
BSc (Hons) & ARCS in Microbiology

Kok-Ho's interest lies in infectious diseases and oncology as well as the application of novel theoretical concepts to the development of better cancer treatment strategies. Kok-Ho's primary motivation in medicine is to find a novel therapy for cancers with poor prognosis so that patients who are incurable now may have a new lease of life in the near future.

Therapeutic resistance has been shown to result in poorer clinical outcomes in cancer treatment. It has been proposed that evolutionary adaptations of cancer cells to therapy result in the development of resistance with the rate of adaptive change correlating with the heterogeneity of the tumour. These concepts can help overcome therapeutic resistance and have been exploited by Gatenby and others in promising evolutionary double-bind simulations. It was further suggested that tumour vasculature contributes to intra-tumoural heterogeneity through the development of substrate gradients. Increasing analogy between natural ecosystems such as riparian habitats and the tumour environment may allow us to devise novel treatment strategies. This review will briefly examine some of these evolutionary and ecological concepts and how they can be applied to cancer treatment.



Introduction

Carcinogenesis is the process by which normal cells in the body acquire mutations and form tumours. In the 1970s, Peter Nowell characterized this transformation in terms of evolutionary change and this concept has been well accepted by the scientific community. [1] He proposed that genetic instability and mutations form the basis for heritable changes required for natural selection and clonal growth of single cancer cells. Cells are selected for desirable characteristics such as survival and proliferation in response to changes in their immediate environment. [1] Surprisingly, evolutionary principles have seldom been used in the treatment of cancer. Aktipis and colleagues did an analysis of over 6000 papers focusing on therapeutic resistance and cancer relapse and revealed that 'evolution' has been used in only 1% of all papers. [2]

As evolution is influenced by changes in the environment, it is possible to view the tumour microenvironment as an ecosystem consisting of heterogeneous populations of cancer cells interacting with one another, and with other cells of the microenvironment. These complex interactions have much in common with ecosystems in nature and consist of analogous abiotic and biotic components which provide novel treatment targets to circumvent therapeutic failure.

Failure of chemotherapy can be attributed to cancer resistance which can be inherent or acquired. Inherent resistance may occur due to over-expression of drug metabolism pathways such as the excision repair cross-complementing 1 gene (ERCC1 — a nucleoside excision repair gene) in resistance against platinum agents while acquired resistance can be caused by altered membrane transport as in the case of the P-glycoprotein transport protein encoded by the multi-drug resistance-1 gene (MDR-1). [3]

Evolutionary game theory

Hypoxia and acidosis within the tumour can exert selective pressures on individual cancer cell populations. These populations may adapt to these conditions through different phenotypic strategies arising from genetic instability and genotypic variations. Gilles and colleagues proposed that these interactions can be understood through the evolutionary game theory. In this theory, the evolutionary rate of a phenotypic strategy is dependent on the amount of phenotypic diversity and the fitness of cancer cell populations. [4] Cancer cell

populations will evolve rapidly in the presence of a harsh tumour environment or when cell populations are phenotypically diverse. Selective pressures originating from perturbations outside the tumour microenvironment can also promote further phenotypic diversity. [4,5] Alteration of the tumor environment by chemotherapy can potentially encourage cancer cell populations to diversify and become heterogeneous via *de novo* mutations arising from therapy or selection of existing chemotherapy-resistant cells in the tumour. [5]

The evolutionary game theory therefore predicts that the probability of the existence and/or emergence of resistant cells correlates with the level of tumour heterogeneity. It also suggests that chemotherapy will inadvertently lead to resistance if chemo-resistant cells (such as cancer stem cells) are already present in the tumour. [4,5] These predictions appear to correlate with clinical findings as advanced cancers which are less responsive to therapies usually exhibit high levels of heterogeneity while the use of high-dose chemotherapy improves survival but seldom cures epithelial cancers. [6]

High-dose chemotherapy regimens were first conceptualized mathematically through the Norton-Simon model. It is hypothesised that administering the maximum tolerated dose (MTD) over a short time period would achieve a high cancer cell kill rate and a low probability of therapy-induced evolution of resistant clones. [7] This model, however, does not account for pre-existing chemo-resistant cells which clonally proliferate and result in cancer relapse after initial treatment. By recognising that resistant cells potentially pre-exist in tumours and that they correlate positively with tumour heterogeneity, certain strategies can be devised. These include controlling the heterogeneity of the tumour to prevent the occurrence of chemo-resistance and, exploiting our ability to predictably alter the adaptive strategies of cancer cells through various treatment modalities.

Controlling tumour heterogeneity: induction of evolutionary bottlenecks and achieving an evolutionary 'double-bind'

Intra-tumoural heterogeneity is minimal in early neoplasms and the use of low-dose chemotherapy may be sufficient to eliminate early cancers with less risk of resistance. [7] This formed the basis of metronomic chemotherapy where low doses of chemo-drugs were given in frequent intervals. [8] However, intricate strategies involving circumvention of therapeutic resistance would be required as a cancer progresses.

Resistant cells favour tumour progression in a treatment setting but

many forms of resistance incur phenotypic costs. If the phenotypic cost is low, for example, due to the ability of the cancer cell to adapt to therapy through up-regulation of xenobiotic mechanisms or usage of a redundant signaling pathway, control of cancer cell proliferation will be less effective. [9] Conversely, if the phenotypic cost is high, for example, due to competition from co-existing cancer cell populations with different proliferative characteristics and biological therapies, robust and long-lasting control may be achieved because cancer cells can only survive by diverting resources away from proliferation. The latter creates an evolutionary double-bind where the only way tumour cells can evade the deleterious effects of treatment is by compromising its fitness attributes, thereby inhibiting its proliferation or ability to develop resistance. [9]

An evolutionary double-bind in a combination therapy setting would require anticipating the adaptation of cancer cell populations to a specific treatment and then targeting the adapted phenotype by a follow-up treatment. [4] In a study by Hunter *et al.*, treatment of glioblastoma multiforme tumours with the alkylating agent temozolomide (TMZ) resulted in hypermutations in the MSH6 mismatch repair gene. [5,10] These mutations were not present in untreated tumours and suggest that chemotherapy selected for MSH6-mutant cells. A clonal selection process was thought to create an evolutionary bottleneck where the majority of the cells were MSH-6 mutants while cancer cells with the wild-type MSH6 gene were eliminated. [5,11]

The transient decrease in genetic heterogeneity following TMZ administration provides a therapeutic window when cancer cells are most susceptible to a secondary treatment. [5] An *in vivo* study investigating the effects of the oral poly(ADP-ribose) polymerase (PARP) inhibitor ABT-888 on xenograft models of human tumours found that this PARP inhibitor not only synergistically maintains and potentiates the cytotoxic effects of TMZ on different tumours but also overcomes TMZ resistance. [12] ABT-888 and other similar PARP inhibitors may therefore have a role as a secondary treatment in combination therapies as they can eliminate most of the residual chemo-resistant cell populations. A schematic diagram of a two-step evolutionary double-bind is shown in Figure 1.

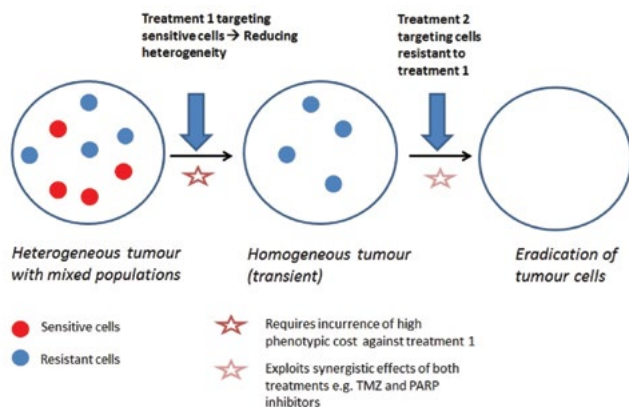


Figure 1. Evolutionary double-bind. For simplicity, tumour cells can be sensitive (neutral or susceptible) or resistant to a treatment. A two-step setup would involve the first treatment reducing heterogeneity of the tumour by imposing a high phenotypic cost on tumour cells. The second treatment works synergistically with the first treatment, such as in the case of PARP inhibitors and TMZ, to eradicate initially resistant cell populations.

Chemotherapy-based combination therapies

The widespread use of chemotherapy necessitates a scrutiny of its synergistic and antagonistic effects in cancer treatment. Basanta and colleagues examined the use of an evolutionary double-bind in a combination therapy consisting of the p53 vaccine and chemotherapy. [13] Using a mathematical framework derived from the evolutionary game theory, they found that the p53 vaccine and chemotherapy work synergistically to exert robust anti-tumour effects. Interestingly, depending on whether the p53 vaccine or chemotherapy was used as

the first treatment, different effects were observed.

Application of chemotherapy before the p53 vaccine was found to be more effective than using the p53 vaccine initially followed by chemotherapy. [13] This was attributed to a commensalistic relationship between vaccine-resistant cells and other cell populations. Eliminating vaccine-resistant cells in the first instance disrupts the protective effect and results in other cell populations (e.g. chemo-resistant and fully susceptible) being susceptible to immune mechanisms mediated by the p53 vaccine. In other words, ecological interactions between different cell populations of a tumour appear to determine the effectiveness of an evolutionary double-bind.

Although application of the p53 vaccine before chemotherapy had a diminished anti-tumour effect, the effectiveness of this approach can be increased with longer exposure to the p53 vaccine. [13] Indeed, both approaches appeared to be most effective when the first treatment was applied for a longer period. This reflects the importance of the first treatment as a limiting factor in combination therapy. Prolonged exposure to the first treatment widened the therapeutic window and acted as a barrier against therapeutic resistance most likely by reducing tumour heterogeneity through the creation of an evolutionary bottleneck.

Ecological interactions (e.g. commensalism or competition) between cancer cell populations are important and we can further characterize these interactions by considering the fitness of different cancer cell populations through phenotypic costs. [4] In the absence of treatment, resistant cells are likely to be less fit and have a slower rate of proliferation as compared to sensitive cells since they have to devote more resources to surviving. [4] These cells are most often found in the inner regions of a solid tumour where harsh conditions such as hypoxia and acidosis cause necrosis of tumour cells but favour the selection of resistant clones. Conversely, sensitive cells will be located at the outer rim of the tumour where a close proximity to the vasculature and expression of pro-survival proteins allow them to proliferate easily. [14] We can therefore predict that sensitive cells will be more susceptible to chemotherapy due to their proximity to the blood supply whereas resistant cells are highly affected by metabolic changes.

Silva and Gatenby proposed an evolutionary double-bind strategy consisting of the glucose competitor 2-deoxyglucose (2-DG) and chemotherapy. This was an attempt to reduce the fitness of both sensitive and resistant cell populations as well as stabilize tumour growth through competition via *in silico* simulations. [15] Different combinations of 2-DG and chemotherapy were modeled mathematically and the combination of 2-DG→chemotherapy was suggested to have the most potent anti-tumour effect. Efficacy was predicted to be lower in chemotherapy→2-DG and lowest in the synchronous administration of 2-DG and chemotherapy. The results become intuitive when we consider tumour cell populations in terms of inner region and outer rim populations. For the 2-DG→chemotherapy approach, the inner region populations are 'pulverized' by 2-DG due to their sensitivity to glucose depletion and this increases the surface area for chemotherapy to eliminate the outer rim cells. [15] Furthermore, 2-DG created a 'pulverized' morphology where a barrier of cells exists between the outer rim and inner region cells. This potentiates glucose depletion because glucose cannot diffuse effectively from the outer rim to inner region.

Interestingly, 2DG→chemotherapy mirrors the effectiveness of the p53 vaccine→chemotherapy approach. [13] This is probably attributed to the initial targeting of chemo-resistant cells and also the maintenance of a higher proportion of sensitive (and presumably fitter) cells as compared to resistant cells. The latter implies that sensitive cells can impede proliferation of resistant cells via competition for resources. Indeed, the chemotherapy→2-DG approach most likely had a better anti-tumour effect than synchronous administration because, even though the chemo-sensitive outer rim cells were targeted first, the introduction of a break or 'drug holiday' between chemotherapy

sessions in the study's protocol allowed the sensitive cells to recover and maintain a sizeable numerical advantage over resistant cells. [16] A similar effect was also noted in previous studies with different treatments. The chemotherapy→2-DG approach fared worse than 2-DG→chemotherapy as glucose can readily diffuse from the outer rim to inner (i.e. allowing chemo-resistant cells to survive) while the synchronous approach was least effective as the outer-rim was readily destroyed by chemotherapy; therefore reducing competition between sensitive cells and resistant cells. [15] Moreover, poor diffusion of chemotherapeutic drugs to areas deeper within the tumour meant that the inner region cells only received sub-lethal doses which favour the development of chemo-resistance.

Out of the three strategies, only the 2DG→chemotherapy approach managed to achieve an almost complete eradication of cancer cells when a bolus of MTD chemotherapy was applied while the other two strategies resulted in chemo-resistance. This result has two implications: firstly, it reflects the point that eradication of tumour cells is possible if tumour heterogeneity is targeted in the first instance and, specifically here, the chemo-resistant population. Secondly, it also implies that delineation of tumour cell populations into sub-groups based on location and proximity to key tumour structures such as the vasculature may be therapeutically significant. In fact, there is evidence that populations of tumour cells often exhibit a convergent phenotype despite genotypic differences between individual cells. [17] Thus, targeting this phenotype may be a more practical option since natural selection acts on phenotypes rather than genotypes.

Riparian ecosystems as an ecological framework for human tumours

Tumour vasculature can contribute to intra-tumoural heterogeneity by creating disparities in substrates such as oxygen and glucose through blood flow gradients, which then select for different populations of cancer cells. [17,18] Alfarouk and colleagues proposed that growth of cancer cell populations can be understood in the context of plant species in a riparian habitat. [18] A riparian habitat is the interface between land and a river stream and two distinct regions of plants can be identified depending on their distance from a river. The mesic region contains lush, tall vegetation which are adjacent to and well nourished by the nutrients from the river. This is followed by an abrupt transition to a xeric region containing sparse, short vegetation which, due to their relatively long distance away from the river, develop adaptations that allow them to conserve water and survive in arid conditions. [19] The rivers and regions of vegetation in a riparian habit are analogous to the vasculature and cancer cells in a tumour respectively.

Tumour cell populations can be broadly separated into 'mesic' and 'xeric' cells depending if they are adjacent or distal to a blood vessel. [18] Mesic tumour cells and their proximity to blood vessels would render them highly susceptible to angiogenesis inhibitors by systemic administration. Since the 'lush' mesic region is expected to contain many tumor cells, a drastic reduction in tumour volume can be achieved. [18] However, the elimination of mesic tumour cells favours unprohibited proliferation of xeric tumour cells and an early treatment directed against the xeric region would be necessary. Phase I and II trials have shown that pro-drug carriers (containing chemotherapeutic drugs) based on 2-nitromidazoles can target hypoxic regions of a tumor and have shown strong anti-tumour effects. [20,21] Combining pro-drug carriers with an intra-tumoural route of administration may improve the accuracy of this approach. Considering the scarcity of xeric tumour cells, prolonged early treatment may be extremely effective. A summary of the different strategies described above is shown in Figure 2.

Discussion and conclusion

Tumours are resilient in nature because they consist of a heterogeneous system of cells locked in a constant state of feedback. [22] Any perturbations in the environment of these cells may simply reinforce tumorigenic processes which restore overall tumour fitness.

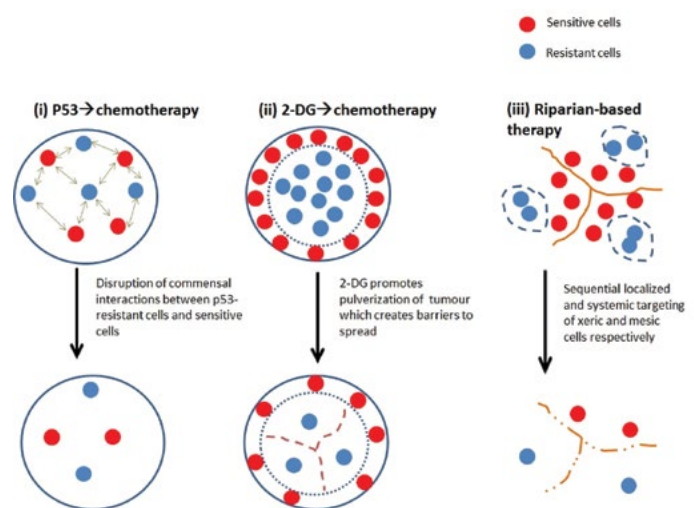


Figure 2. Best predicted outcomes in evolutionary and ecologically enlightened strategies. (i) *In silico* studies suggest that p53-resistant cells and p53-sensitive cells exist in a state of commensalism. The initial introduction of p53 eliminates vaccine-resistant cells and predisposes all remaining cells to destruction by chemotherapy. A greater effect is seen with prolonged p53 administration. (ii) 2DG targets and 'pulverizes' resistant cells, creating physical barrier between resistant cells but retains an outer-rim chemo-sensitive cells that inhibits cancer spread. (iii) Riparian-based therapy may achieve maximal tumour cell death through a localized targeting of mesic cells by hypoxia-based strategies followed by targeting of xeric cells by angiogenesis inhibitors.

Although all therapies inherently disturb this fragile equilibrium, *in silico* studies have demonstrated proof of principle that a well-designed strategy such as an evolutionary double-bind can control and potentially eradicate most tumour cells. While modelling methods may not translate to immediate clinical benefits, they are an inexpensive way of exploring theoretical concepts in a controlled situation and provide a sound framework for further *in vivo* studies and clinical trials. The models described here can also readily be modified to study other forms of combination therapy, illustrating their flexibility and broad applicability to the clinical environment. One limitation, though, is that the parameters used in models have to be as realistic as possible and this can only occur through close cooperation between experimentalists and clinicians.

Key features highlighted here such as the need for prolonged initial treatment to reduce intra-tumoural heterogeneity, enhancing competition between resistant and sensitive cells and combining systemic and localized approaches are intuitive and feasible options that can be readily applied to existing treatment protocols. High-dose chemotherapy is no longer considered as a first-line approach except occasionally as salvage treatment for relapsed disease. This is not surprising in light of possible selection for chemo-resistance and increasing preference for low-dose maintenance and adaptive regimens. [6] The examples discussed in this review focused primarily on solid tumours due to easy visualisation and amenability to mathematical modelling. However, treatment of haematological malignancies would also benefit from a double-bind approach as evident from the restoration of drug sensitivity by second-generation tyrosine kinase inhibitors in treatment-resistant chronic myelogenous leukemia. [23]

There are several potential areas for further research. Firstly, we need to understand why natural selection appears to control cancers but does not eliminate them. In fact, a parallel exists with infectious diseases and high fitness costs and the tendency for organisms to evolve tolerance mechanisms may account for this phenomenon. Secondly, we should consider maximising the potential of new treatment modalities such as immunotherapy in evolutionary double-binds. [24] The limited efficacy of immunotherapy appears to contradict observations in natural ecosystems which indicate that biological control incurs higher phenotypic costs and achieves robust control of pests. This implies that

inappropriate immune targets are being selected and, therefore, a true double-bind cannot be achieved. [4,23]

In conclusion, therapeutic resistance is a major obstacle to the optimisation of cancer treatment. Evolutionary and ecological principles may appear far-fetched concepts with little direct relevance to oncology but a closer inspection of the evolutionary origins and the spatial organisation of cancer cells reveal strategies that can improve clinical outcomes. Under-utilisation of these concepts is most likely a

reflection of an inability to change our mindset rather than an issue of practicality. These encouraging modelling results provide a sound foundation for further translational research.

Conflict of interest

None declared.

Correspondence

K Ho: koho2292@uni.sydney.edu.au

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Glibenclamide therapy as tertiary prevention of melioidosis for Type 2 diabetics

Raelene Aw-Yong

Third Year Medicine (Undergraduate)

James Cook University

Raelene is a medical student with a strong interest in international, tropical, rural and remote health particularly in the field of infectious disease.

Background: Melioidosis is a relatively high-incidence, high-mortality tropical infectious disease caused by *Burkholderia pseudomallei*. To date, the few prevention and management strategies in practice have failed to reduce mortality from septic shock in patients with severe melioidosis. Up to 60.9% of patients also have pre-existing type 2 diabetes mellitus (T2DM), the most significant risk factor for melioidosis. An effective tertiary prevention strategy against melioidosis for these diabetic individuals would impact significantly on the burden of disease. Glibenclamide, a drug belonging to the sulfonylurea class and commonly used as an antidiabetic, may have the potential to be one such strategy. **Aim:** To examine the underlying inflammatory cause of morbidity and mortality in melioidosis and to assess the potential for glibenclamide to ameliorate these causes. **Results:** Bacteraemia with *B. pseudomallei* leads to widespread infection. Multi-organ damage and loss of function results from both direct bacterial damage and an excessive inflammatory response, the latter of which also causes potentially fatal septic shock in 21% of cases. Massive cellular infiltration of the lungs is particularly damaging. The immunomodulatory effects of T2DM further exacerbate the deleterious immune response into a dysregulated, hyperinflammatory state. On the other hand, the several anti-inflammatory effects of glibenclamide have been demonstrated to significantly reduce mortality from septic shock in melioidosis. **Conclusion:** For diabetics living in regions where melioidosis is endemic, choosing glibenclamide over other sulfonylureas and metformin for antidiabetic treatment could be a promising tertiary prevention measure against melioidosis.

Introduction

Melioidosis, a tropical infectious disease, is a significant cause of death and illness in northern Australia and Southeast Asia. Its non-specific prodrome and clinical presentation makes early detection difficult. [1] Yet, timely diagnosis is critical because responsiveness to treatment declines with progression of the disease over time. [2] Morbidity and mortality remains high despite aggressive antibiotic treatment. As of yet, no vaccine is available for primary prevention and novel developments such as granulocyte colony-stimulating factor (G-CSF) and corticosteroid therapy lack evidence as good measures of tertiary prevention. Considering the significant population health threat, any effective prevention strategy would be of value. This article suggests the potential use of glibenclamide, an antidiabetic sulfonylurea, for tertiary prevention of melioidosis in diabetics. Because diabetics are approximately 13 times more likely to contract melioidosis, [3,4] this strategy may have widespread application.

One of the major and dangerous end-stage complications of melioidosis is septic shock. Especially in settings such as Northeast (NE) Thailand where melioidosis is endemic but intensive care is unavailable, morbidity and mortality from septic shock are unacceptably high. Systemically-spread *B. pseudomallei* stimulates massive release of cytokines into the blood, this event being instrumental in the immunopathogenesis of septic systemic vasodilation, hypotension, vascular hyperpermeability, and disseminated intravascular coagulation (DIC). Furthermore, poor glycaemic control in diabetics increases the risk and severity of these events by precipitating a compensatory, dysregulated, and hyperinflammatory response to bacterial immunogenic stimuli. Demanding particular attention is the stimulated production of cytokine IL-1 β because it promotes excessive



neutrophilic recruitment to the lungs and bacterial persistence inside cells. Fortunately, there is strong evidence that glibenclamide acts protectively against IL-1 β -mediated damage by targeting IL-1 β production directly as well as multiple upstream components in the IL-1 β production pathway. The result of glibenclamide use for diabetics is a significantly reduced morbidity and mortality from melioidosis septic shock compared with diabetics not taking the drug.

Epidemiology of melioidosis

Melioidosis is endemic in Southeast Asia, northern Australia, India, Hong Kong, southern China and Taiwan. [5,6] Isolated sporadic cases have also appeared in Central America, the Caribbean, New Caledonia, Mauritius, Africa, and the Middle East. [7] Of particular concern are the hyperendemic hotspots – NE Thailand and the Top End of the Northern Territory of Australia. A 2006 NE Thailand study that gathered results from four large hospitals reported the region experienced an estimated minimum annual incidence of 21.3 cases per 100,000 people and case fatality rate of 40.5%, melioidosis locally being the third highest infectious cause of death and second most common pathogenic cause of community-acquired bacteraemia. [8,3] From 2004 to 2009, according to data collected at Royal Darwin Hospital (RDH), the annual incidence in the Top End was 21.6 per 100,000 people and average case fatality rate plateaued at 9% having decreased from 30% since 1989. The lower fatality rate in Darwin is attributed to greater access to intensive care unit (ICU) supportive care and early sepsis management that prolongs life in the event of fatal septic shock, a complication that develops in at least 21% of cases. [9]

Type 2 diabetes mellitus (T2DM) is the largest risk factor for melioidosis. 48% and 60.9% of individuals with melioidosis were confirmed to have T2DM at RDH and in NE Thailand respectively. [10,11] The 2006 Thai study reported that the relative risk (RR) of melioidosis in adult diabetics compared with non-diabetics was 12.4. [3] In the Top End region, combining diabetes with the additional risk factor of Indigenous ethnicity raised the RR from 13.1 to 20.6. Other notable risk factors associated with a significant RR are chronic lung disease (RR 4.3), age ≥ 45 years (RR 4.0), chronic renal disease (RR 3.2), Indigenous ethnicity (RR 3.0), male sex (RR 2.4) and hazardous alcohol consumption (RR 2.1). [6]

The presence of any of these risk factors in infected individuals also dramatically increases their chance of developing septic shock (RR 4.5) and death (RR 9.2), the risk factors with highest independent association with death being age ≥ 50 years (RR 2.1) and chronic lung disease (RR 1.5). Malignancy (RR 1.9) and rheumatic heart disease and/or congestive cardiac failure (RR 1.7) are statistically insignificant risk

factors for death. Clinical presentations most likely to result in death are septic shock (RR 11.2) and, out of the non-septic shock cases, the presence of neurological infection foci (RR 4.7). [9] Additionally, case fatality during the peak rainfall months of December through February is 1.6 times greater than it is during other months. [9]

Immunopathogenesis and pathophysiology

Melioidosis is caused by Gram-negative bacterium *B. pseudomallei*, found in contaminated soil, rodents, food, water, and excretions, are transmitted via inhalation, ingestion, or percutaneous inoculation – usually direct contact with open skin lesions. [12,13] Post-inoculation, *B. pseudomallei* can invade most human cell types. Employing Type 3 Secretion System (TTSS) clusters, bacteria enter non-phagocytic cells. If bacteria are phagocytosed, TTSS enables exit from intracellular phagocytic endosomes such that degradation is evaded. Once escaped into the cytoplasm of cells both phagocytic and non-phagocytic, bacteria replicate and self-induce polarised actin filamentation that confers motility, facilitating spread to neighbouring cells by forcing host-cell membrane protrusion and fusion. [14]

B. pseudomallei possesses highly immunogenic factors that trigger a strong host immune reaction essential to the host for early bacterial containment. [15] *B. pseudomallei* expresses pathogen-associated molecular patterns including lipopeptides, peptidoglycan, lipopolysaccharide, flagellin, TTSS, and DNA. They are recognised by host cell toll-like receptors (TLR) and NOD-like receptors (NLR). TLRs and NLRs are expressed by immune cells both professional – macrophages and dendritic cells – and non-professional – epithelial cells, endothelial cells, and fibroblasts. [16]

Activation of NLRC4 or NLRP3 induces binding of caspase-1, Asc (apoptosis-associated speck-like protein containing CARD) and NLRC4 or NLRP3 to form an inflammasome. The NLRC4 inflammasome in infected macrophages triggers pyroptosis, serving to limit intracellular *B. pseudomallei* growth and proliferation, while the NLRP3 inflammasome performs proteolytic activation of pro-IL-1 β and pro-IL-18 into their mature forms for secretion. [17] IL-1 β recruits neutrophils to infection site(s). However, excessive recruitment is often deleterious because neutrophils, lacking NLRC4, fail to pyroptose and instead provide a favourable intracellular environment that sustains chronic bacterial persistence. In the lungs, persistence leads to damaging pulmonary abscess formation and acute respiratory distress syndrome. [17,18] In contrast, elevated IL-18 production correlates with survival and immunoprotection because IL-18 induces IFN- γ production. [17,19] IFN- γ activates macrophages, stimulating their direct antimicrobial processes – phagolysosomal fusion and toxic reactive nitrogen species synthesis that produces nitrosative stress. [20] The cytokine also facilitates macrophage antigen processing and presentation, recruits leukocytes to infection site(s), upregulates Th1 CD4+ cell population, enhances natural killer cell function, regulates B cell anti-lipopolysaccharide antibody production and isotype switching. [21]

TLR activation upregulates secretion of principal inflammatory mediators including type 1 interferon, chemokines, antimicrobial proteins, and pro-inflammatory cytokines. [22] Elevated expression of TLR1, TLR2, TLR3, TLR4, TLR5, TLR8, and TLR10 has been demonstrated in patients with septic melioidosis. [16] In particular, stimulation of the TLR2-mediated signalling pathway is a principal step in recognising the immune challenge of *B. pseudomallei* and initiating early inflammatory processes. [23] TNF- α and IL-6, along with IL-1 β , increase vascular permeability, induce acute phase protein production, and recruit leukocytes to the site of infection. [24] TNF- α and IL-6 also activate the complement and coagulation cascades that are key defense mechanisms of the innate response. [25] However, excessive inflammatory cytokine production induced by widespread bacteraemia often leads to septic shock characterised by systemic vasodilatory hypotension, vascular hyperpermeability causing major cellular and

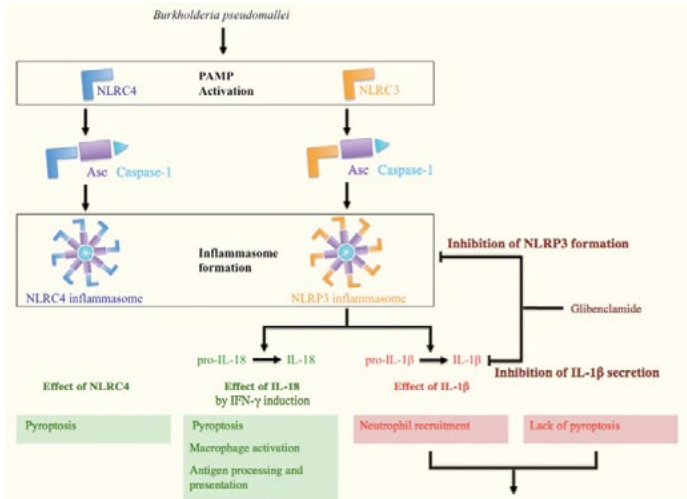


Figure 1. NLRC4 inflammasome leads to immunoprotective effects while NLRP3 inflammasome produces both protective and deleterious responses. Glibenclamide works by inhibiting NLRP3 inflammasome formation and its deleterious effects.

fluid leakage from the intravascular to extravascular compartments, DIC, and death in the absence of immediate treatment. [26]

Through the establishment of bacteraemia, *B. pseudomallei* spreads from primary foci of infection to other body tissues, usually the lungs, genitourinary tract, skin, joints, bones, liver, spleen, skeletal muscles, prostate, parotid gland, and nervous system. Multi-organ spread leading to impaired organ function and failure is the main source of morbidity and mortality in melioidosis. [27] Thus, a rapid but non-deleterious inflammatory response is critical before *B. pseudomallei* establishes an intracellular niche that enables its persistence and protection against eradication by a subsequent immune attack. Paradoxically, subsequent immune attacks may cause further damage to the host.

Effect of Type 2 diabetic state on host response

Diabetics, due to their generally immunosuppressed state, compared with non-diabetics, are more susceptible to developing sepsis from most organisms, [28] with the most common source of systemic spread being respiratory, followed by urinary and abdominal. [29] Gram-positive bacteria have become the leading cause of sepsis since the 1980s, and sepsis due to causes other than *B. pseudomallei* actually affects diabetics more commonly than melioidosis. [29,30] However, it is still of significance that diabetics are particularly vulnerable to pathogens such as *B. pseudomallei* and *Mycobacterium tuberculosis* because immune defence against these intracellular bacteria is highly macrophage-mediated – a function that is critically impaired in poorly-controlled T2DM. [31]

T2DM, especially if poorly controlled, causes marked immunomodulation that produces *B. pseudomallei*-induced immune responses that are damaging and yet insufficient to offer host protection. Morris *et al.* created an *ex vivo* whole-blood assay using human peripheral blood to compare inflammatory responses to *B. pseudomallei* between diabetics and non-diabetics. Immune insufficiency was worst in poorly controlled diabetics, the assay detecting: elevated serum IL-10 (an anti-inflammatory cytokine); reduced CD11b on polymorphonuclear leukocytes (PMNs) leading to decreased PMN function with reduced activation, adhesion, transmigration, and migratory capacity towards IL-8; reduced endotoxaemia-induced upregulation of ICAM-1; and defects in phagocytic detection and response to the bacteria. [32] *In vivo* and *in vitro* models using streptozotocin (STZ)-induced, leptin deficiency, leptin receptor deficiency, and diet-induced diabetic mice found similar immune impairments. [31,33-35] Transcriptional analysis of STZ-diabetic mice responses over the first 42 hours of *B. pseudomallei* exposure attributed delayed defence and splenic dysfunction

(permitting uncontrolled bacterial replication intracellularly causing susceptibility to sepsis) to diminished TLR2 recognition of the bacterium. [34]

Incompetence of the early inflammatory response to contain an initial infection precipitates a compensatory, dysregulated, hyperinflammatory response to the spreading infection. The intensity of this ensuing reaction is exacerbated by chronic low-grade inflammation and increased oxidative stress, both characteristic of T2DM. Morris *et al.* found poorly controlled diabetics to have the most elevated levels of pro-inflammatory markers ESR, CRP, TNF- α , IL-1 β , IL-6, IL-8, IL-12p70, MCP-1, and MPO (which indicates increased oxidative burst activity in PMNs). At focal infection sites, there was extensive infiltration with PMNs and greater risk of tissue damage, as well as generalised endothelial dysfunction and vascular inflammation. [32]

Hyperglycaemia is a major link between T2DM, immune derangement, and susceptibility to sepsis. The supra-physiological hyperosmolarity of hyperglycaemic blood directly potentiates TLR4-mediated cytokine production, as well as dampening phagocytic responses and granulocyte oxidative burst. [36] Activation of the RAGE pathway by advanced glycation end-products formed secondary to hyperglycaemia perpetuates inflammation and worsens survival in septic mice. [37] Furthermore, in the event of sepsis, poor glycaemic control allowing for periods of hyperglycaemia in both diabetics and non-diabetics correlates with longer hospital stay, greater morbidity, and possibly decreased survival. [38] In addition to immunomodulatory effects, hyperglycaemia exacerbates hypotension in septic shock by promoting glycosuric diuresis and cardiac hyperresponsiveness to cholinergic stimulation and the baroreflex. [39] Elevated risk of myocardial infarction, stroke, and venous thromboembolism is associated with the prothrombotic effect of acute hyperglycaemia that is further potentiated by hyperinsulinaemia or an inflammatory stress state. [40]

Prevention and management

No human vaccine is available. [41] CDC prevention guidelines recommend avoiding contact with soil and stagnant water in endemic regions. [42] High-risk individuals should stay indoors during heavy wind and rain in endemic regions due to possible bacterial aerosolisation that greatly facilitates transmission. [43]

Treatment involves two weeks of intravenous antibiotics – ceftazidime, meropenem, or imipenem, in combination with trimethoprim-sulfamethoxazole – followed by 3 months of oral eradication therapy to prevent recrudescence. [44] However, even with early antibiotic administration, case fatality from septicaemia remains at 37% in Thailand. [45] The development of septic shock is an indication for ICU supportive care usually involving invasive monitoring, fluid resuscitation, renal replacement therapy, and vasopressor, inotropic, and mechanical ventilatory support. [46,47]

Adjunctive use of recombinant G-CSF holds no clinical utility for improving sepsis from melioidosis and other aetiologies. Both animal and human trials – including prospective, multicentre, randomised, double-blind, and placebo-controlled studies – confirm this. [47-49] In fact, G-CSF may cause increased hepatic dysfunction and higher peak troponin I levels. [50] Other immunomodulatory adjuncts such as corticosteroids do not improve survival. [46] In light of the paucity of effective evidence-based prevention strategies and adjunct therapies for underserved populations, we turn to a novel potential for tertiary prevention.

Glibenclamide and its protective effects

Glibenclamide is a sulfonylurea used in the management of diabetes. It antagonises ATP-dependent potassium (K_{ATP}) channels in pancreatic β -cells, stimulating insulin release. The salient risk associated with glibenclamide is accidentally developing hypoglycaemia, an event of varying seriousness in patients who are not critically ill but a great

predictor of mortality in acute sepsis. Furthermore, recent studies comparing glibenclamide with metformin and other sulfonylureas elucidated its significant adverse effects in addition to severe hypoglycaemia, such as increased risk of malignancy and mortality from cardiovascular disease due to interference with ischaemic preconditioning. [51,52] Despite glibenclamide still being a popular choice, a trend in medical opinion has arisen against its use in favour of alternative sulfonylureas. [53,54]

However, for T2DM individuals living in regions endemic with melioidosis, choosing glibenclamide over other antidiabetic drugs has an additional benefit that clinicians must consider. In a 5-year prospective cohort study from 2002 to 2006, Koh *et al.* followed 1160 adult patients with culture-confirmed melioidosis for 28 days during and after their admission to a major NE Thailand hospital. 71.3% of diabetic individuals taking glibenclamide survived from melioidosis after 28 days, while only 50.7% of diabetics not taking glibenclamide and 47.0% of non-diabetics survived (survival of patients discharged from hospital within 28 days were assumed to have survived). Using a logistics regression model, glibenclamide treatment reduced case fatality with an adjusted odds ratio (AOR) of 0.34 when compared to diabetics not taking glibenclamide and an AOR of 0.47 compared to non-diabetics. Incidences of hypotension (AOR 0.48) and respiratory failure (AOR 0.50) were also reduced in these patients. [55] Therefore, this protective effect must be factored into the drug's risk-benefit comparison with metformin and with other sulfonylureas. If it informs clinicians' drug choices for glycaemic control in management of T2DM, glibenclamide can contribute to tertiary prevention of melioidosis.

Although preventing hyperglycaemia in sepsis improves patient outcomes, glibenclamide does not rely on its glucose-lowering effect. [56] Using a mouse model, Koh *et al.* attributed the mechanism of glibenclamide's protective effect to two main anti-inflammatory pathways. Firstly, glibenclamide reduces IL-1 β secretion, attenuating IL-8 production and neutrophilic and monocytic influx into the lungs (without completely ablating the neutrophilic response). [55,57] *In vitro* evidence suggests that glibenclamide does this by partially blocking NLRP3 inflammasome formation and/or by directly inhibiting the secretion of mature IL-1 β (Figure 1). [57-59] Glibenclamide may also attenuate transcription and translation of caspase-1, NLRP3, and IL-1 β genes. [57] Secondly, by reducing systemic vasodilation and maintaining normal peripheral vascular resistance, glibenclamide restores systemic mean arterial pressure in the event of septic shock. K_{ATP} channels in vascular smooth muscle preferentially open during sepsis. [60] When they do, they hyperpolarise the cell, inhibiting Ca^{2+} influx (via voltage-dependent Ca^{2+} channels) and causing muscular relaxation. Glibenclamide opposes this effect by blocking the K_{ATP} channels. However, the only evidence for this is found in animal models. [61,62]

Conclusion

Melioidosis remains a significant public health concern due to its high incidence, mortality and case fatality rates particularly in the Top End of Northern Territory and NE Thailand. T2DM is the largest risk factor for melioidosis. The antidiabetic drug, glibenclamide, reduces morbidity and mortality from melioidosis-induced septic shock and so plays a potential role in tertiary prevention of melioidosis. In the debate over glibenclamide use, consideration of the drug's protective effect for diabetics living in melioidosis-endemic regions, particularly those that are resource-limited, is critical.

Conflict of interest

None declared.

Correspondence

R Aw-Yong: raeleneaw@gmail.com

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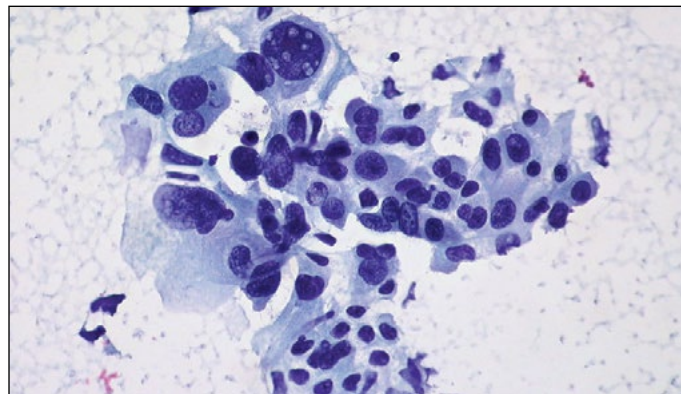
Resistance to epidermal growth factor receptor inhibitors in non-small cell lung cancer and strategies to overcome it

Bernard Chua

Fifth Year Medicine (Undergraduate)
Monash University

This article was written as part of Bernard's written assignment for his overseas elective rotation in Clinical Oncology at The Christie's NHS Trust in Manchester, U.K. Bernard is hoping to pursue Medical Oncology in the future and has also participated in research projects in uropathology with Professor John Pedersen. Bernard is also a trumpet player in the Monash Medical Orchestra.

The War on Cancer has been a particularly long, drawn-out one ever since the National Cancer Act was put into legislation by then U.S. President Richard Nixon. While we attempt to reveal the mechanisms that sustain the uncontrolled growth of cancer cells, the biology of cancer constantly changes and adapts to evade our treatment modalities. The discovery of imatinib, which is a tyrosine kinase inhibitor (TKI) and treats a subset of chronic myelogenous leukaemia, heralded a new generation of drugs that would specifically target cancer cells and reduce toxicity to normal cells. Erlotinib and gefitinib are two epidermal growth factor receptor (EGFR) TKI's that have been developed for the treatment of patients with EGFR-mutation-expressing non-small cell lung carcinoma. However, in recent years, resistance to EGFR TKIs has been described in the literature. While the promise of a new treatment modality has been short-lived, this has also sparked interest and research efforts to understand the mechanisms of resistance to EGFR TKIs in a bid to discover strategies to overcome them and to further drug development. Well studied mechanisms include T790M mutation, loss of balance in the PI3K/Akt/mTOR pathway and MET amplification amongst many others. This article reviews the current literature regarding various mechanisms of resistance to EGFR TKIs and their potential for translation into new therapeutic agents and treatment strategies.



intracellular signaling. [6,8] There is evidence to suggest that EGFR TKIs have led to significant extension of progression-free survival as a second or third line treatment in patients with advanced NSCLC with positive EGFR status. [6,9,10] Promising results have also emerged in recent years for the use of EGFR TKIs as first line treatment for NSCLC patients exhibiting EGFR mutations in Phase III trials. [10-13]

Lung cancer is the 5th most commonly diagnosed cancer in Australia with poor 5-year survival rates of around 14%. [14] Specifically, NSCLC accounts for 60% of all cases of lung cancer. [15] According to the guidelines for lung cancer treatment in Australia, the role of EGFR TKIs (erlotinib), remains primarily in the treatment of Stage IV inoperable NSCLC. [16] It is not recommended for first-generation EGFR TKIs like gefitinib or erlotinib to be used in combination with standard chemotherapy regimens. Erlotinib plays more of a role as a first-line maintenance therapy after standard chemotherapy, as a second-line therapy instead of chemotherapy or as a third-line therapy after having failed two lines of treatment and for patients with poor performance status.

In 2010, Jackman *et al.* proposed a definition of acquired resistance to EGFR inhibitors to help standardize investigations into this topic. [17] They have found that about 70% of NSCLC patients with positive EGFR mutation status will experience tumour regressions whilst on either gefitinib or erlotinib. However, most initial responders develop acquired resistance to EGFR TKIs, [6] usually occurring about after 12 months of treatment. [18,19] Therefore, much effort has been dedicated to understanding and rediscovering the different mechanisms of EGFR inhibitor resistance-both intrinsic and acquired-in order to develop strategies to overcome them.

Areas of interest

There are numerous hypotheses as to how NSCLC patients develop resistance to EGFR TKIs. However, mechanisms of EGFR TKI resistance that have been more extensively studied and show the most potential for translation into clinical practice will be highlighted in this article.

T790M – The 'gatekeeper mutation'

The mechanism of resistance that is most commonly identified in recent work is an acquired mutation in the EGFR gene at position 790 (T790M) in exon 20. This involves a threonine to methionine substitution and it is present in 50% of patients with acquired resistance to EGFR TKIs. [6,7,9,20] This substitution mutation causes steric interference with the binding of EGFR TKIs to the ATP binding site. [21] It is also hypothesized that this mutation leads to increased ATP affinity,

Background

One famous discovery of a targeted drug treatment is imatinib, a tyrosine kinase inhibitor (TKI) used to treat a subset of chronic myelogenous leukaemia expressing the Philadelphia chromosome. This discovery has triggered a series of research efforts, shedding light on topics such as tumourigenesis and cell signaling pathways, leading to the development of many new drugs which target these specific mechanisms. However, it has been documented that resistance to these drugs can develop, therefore reducing their treatment potential [1,2] This is also true for a similar group of TKIs known as epidermal growth factor receptor (EGFR) inhibitors, which have been used as part of the treatment regime for a subgroup of lung cancer patients with non-small cell lung carcinoma. This article will review the mechanisms of intrinsic and acquired resistance to EGFR inhibitors and strategies to overcome them.

Introduction to EGFR inhibitors

The work of Stanley Cohen and Rita Levi-Montalcini in Epidermal Growth Factors has revolutionized cancer research and treatment, having been awarded the 1986 Nobel Prize for Medicine. [3] Their work has triggered further research, eventuating into the approval of gefitinib in 2003 and erlotinib in 2010 by the Food and Drug Administration (FDA) for use in patients with NSCLC. [4-6]

The overexpression and over-activation of EGFR (independent of any ligands) has been found to be involved in the tumour progression of many different types of cancers. [7] Aberrant activation of this oncogene leads to a cascade of complex downstream signaling that contributes to tumourigenesis. [8] The understanding of EGFR's role in tumourigenesis assisted in the development of gefitinib and erlotinib as first generation TKIs to target and block EGFR activity to retard cancer growth. They bind reversibly to the ATP binding pocket of EGFR, preventing receptor phosphorylation and subsequent downstream

conferring drug resistance. [6,21] This allows for phosphorylation of EGFR despite the administration of TKIs due to its restored affinity for ATP, allowing the cancer cell to grow unchecked once again with the restoration of EGFR activation. Of interest, some studies have found T790M mutations occurring at low frequency in the germ line of TKI-naïve patients, [6,22,23] indicating potential intrinsic resistance. This mutation can also be found in NSCLC patients expressing wild-type EGFR before treatment, possibly explaining that the T790M mutation may be a contributing factor to intrinsic resistance to TKIs. [7]

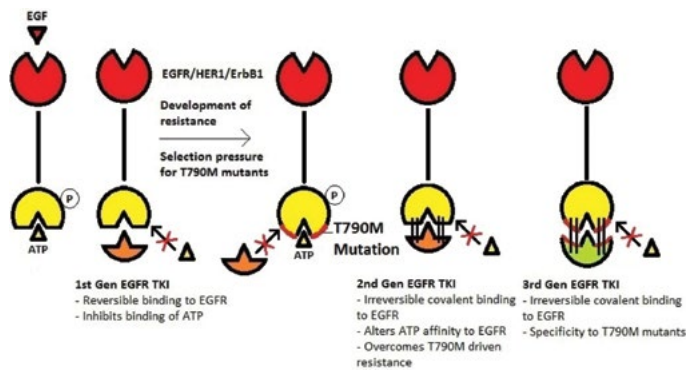


Figure 1. T790M driven drug resistance and mechanism of action of different generations of EGFR TKIs.

Loss of PTEN expression and PIK3CA mutation in the PI3K/Akt/mTOR pathway

A complex network of signaling pathways interacting via various molecules are involved in cancer cell growth independent of EGFR activity. These signaling pathways are usually downstream of an EGFR and can potentially bypass loss of EGFR activation due to administration of TKIs such as gefitinib and erlotinib. One important pathway is the PI3K/Akt/mTOR signaling pathway. Sustained activation of Akt can potentiate resistance to chemotherapy and radiotherapy in general. [24,25] For EGFR-expressing NSCLC patients, Akt is strongly activated to maintain the survival of cancer cells. Activation of Akt always involves membrane recruitment for phosphate transfer. This is regulated positively by phosphoinositol-3-kinase (PI3K) and negatively by phosphatase and tensin homologue (PTEN), a tumour suppressor gene product. Therefore, loss of PTEN expression, via a deletion on chromosome 10, leads to uncontrolled phosphate transfer and activation of Akt, which is commonly observed in NSCLC patients with EGFR TKI resistance. [7,26] On the other hand, a PI3K catalytic alpha (PIK3CA) oncogene mutation is also observed in a small minority of advanced NSCLC patients. [27] This mutation enhances the positive regulation of the pathway via PI3K, thereby leading to heightened activation of Akt. As it is noted that PIK3CA mutations are commonly found in treatment naïve lung adenocarcinoma [6] with concurrent driver mutations in EGFR, KRAS or BRAF, PIK3CA mutation is likely to be a secondary, acquired mutation contributing to resistance. [28] By targeting these mechanisms, a patient's response to EGFR TKIs can potentially be restored.

Insulin-like growth factor 1 Receptor – Parallel EGFR independent pathway

Like EGFR, Insulin-like growth factor 1 receptor (IGF-1R) is a tyrosine kinase that can trigger similar downstream signaling events. Blockade of EGFR pathways with TKI administration has led to compensatory or adaptive upregulation of downstream signaling via the IGF-1R pathway which eventually leads to sustained activation of the PI3K/Akt/mTOR pathway. [29] Gefitinib-resistant cancer cells are also found to have reduced expression of IGF binding proteins, [8] which modulates the activity of IGF-1R by binding to IGF ligands such as IGF-1 and IGF-2. Loss of these binding proteins leads to higher levels of IGF-1 and IGF-2, which increases constitutive activation of the IGF-1R tyrosine kinase and its downstream targets.

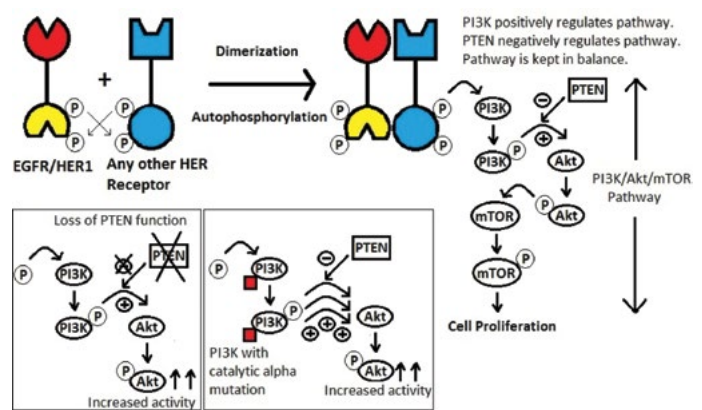


Figure 2. PI3K/Akt/mTOR pathway.

MET pathway amplification

EGFR is an important member of a class of four ErbB receptor tyrosine kinases – EGFR/HER1/ErbB1, HER2/ErbB2, HER3/ErbB3 and HER4/ErbB4. Dimerization of any two of this class of receptors (homodimerization or heterodimerization) will lead to phosphorylation and eventual downstream signal cascade. MET (Mesenchymal-Epithelial Transition) is a receptor tyrosine kinase that binds to hepatocyte growth factor (HGF) and is found to undergo amplification in the presence of TKIs. The extensive crosstalk between the HGF/MET pathway and the PI3K/Akt/mTOR pathway strongly reactivates downstream signals through HER3/ErbB3 phosphorylation, resulting in similar downstream events as EGFR phosphorylation, despite TKI administration. [6,9,18,30] Another interesting observation is that both MET and EGFR have loci on chromosome 7 and EGFR mutation positive NSCLC patients commonly have polysomy of chromosome 7. [19,31] This could be a contributing factor to the presence of intrinsic resistance to EGFR TKIs as targeting EGFRs does not negate the effect of co-existing MET amplification on the PI3K/Akt pathway.

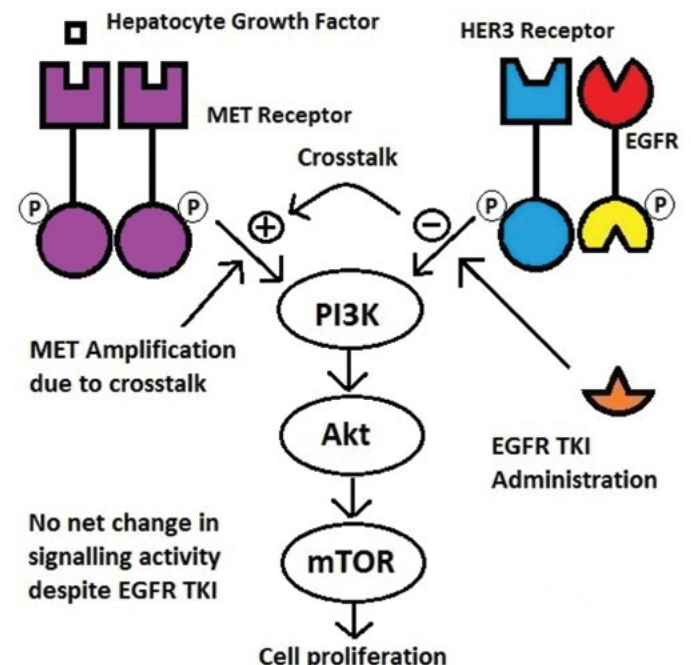


Figure 3. MET amplification.

Others

The vascular endothelial growth factor (VEGF) pathway, which plays a key role in angiogenesis, is another signaling pathway that can be targeted. This is based on the principle that multiple oncogenic targets can contribute to the malignant phenotype. By targeting multiple oncogenic targets, such as inhibition of both EGFR and VEGF, it is hoped that this would circumvent development of resistance to EGFR TKIs, maintaining treatment efficacy. [32]

Sequist *et al.* observed that a histological transformation from NSCLC to small cell lung cancer (SCLC) can occur with TKI treatment. [33] This was found in 14% of EGFR-expressing NSCLC patients who have acquired EGFR TKI resistance. The significance of this is that the histological transformation has now given the patient a chance of a good response with standard SCLC chemotherapy regimens. More investigations regarding this are necessary to understand the mechanism of the transformation as it can potentially be a novel strategy for the treatment of NSCLC patients.

Novel Therapies being investigated to overcome EGFR TKI resistance

2nd Generation Irreversible Tyrosine Kinase Inhibitors

Through understanding how the T790M mutation changes binding of first generation TKIs to EGFR, second generation irreversible TKIs have been developed and are being investigated in various trials. These second generation TKIs such as neratinib and afatinib bind irreversibly to the ATP binding site of EGFR via the formation of a covalent bond. They have been shown to be able to overcome T790M driven acquired resistance. [6,34,35] Also, these TKIs can target not only EGFR/HER1 tyrosine kinase receptors, but also other members of the same class that potentiate similar downstream signaling. For example, afatinib targets EGFR/ErbB1 and ErbB2 tyrosine kinase receptors. [35] Dacomitinib is shown to be a pan-HER TKI, targeting all members of the same class, and is found to be effective against tumours harbouring T790M mutations, however, phase III trials have yet to be completed. [20,36] There are also concerns regarding the higher toxicity profile of these drugs with a narrower therapeutic window. Work on third generation EGFR TKIs are also in progress, binding covalently to the ATP site of mutant EGFR with particular specificity to the T790M mutant. [6,37]

Specific T790M inhibitors

A new class of drug that specifically targets and inhibits the T790M mutant has also been developed. [38] It is thought that targeting cancer cells which have the mutation would spare cells without the mutation and therefore remain susceptible to TKIs. Hence, mutated cancer cells with acquired resistance to TKIs can now be targeted, and the efficacy of TKIs on TKI-susceptible cancer cells is maintained.

Altering the PI3K/Akt/mTOR pathway

There is great promise in creating drugs to target this pathway as we know that levels of molecules involved in signal transduction are tightly regulated by multiple factors via many interactions. However, because this pathway is present in both cancer cells and many normal cells as well, there are concerns that drugs which alter its activity would result in pharmacological toxicities. PI3K (LY294002) and Akt inhibitors are currently being studied both as a monotherapy and as a concurrent treatment with EGFR TKIs. [39]

Another drug that has been used with great experience as an immunosuppressive agent, everolimus, is being studied for its effect on advanced NSCLC. [40] Another PI3K/mTOR inhibitor, XL765, is currently undergoing early phase trials against erlotinib alone and in combination with erlotinib. [41]

MET receptor – inhibiting amplification

Observation of the crosstalk between the HGF/MET and PI3K/AKT/mTOR pathways has led to the hypothesis that co-administration of MET inhibitors can restore sensitivity to EGFR TKIs in resistant tumours displaying MET amplification. [42,43] In a phase II randomized trial, progression free survival (PFS) was higher when erlotinib was given with tivantinib (an agent targeting the MET receptor) as compared to erlotinib given with placebo. [44] Although this finding was not statistically significant, phase III trials are currently ongoing to explore its efficacy and related toxicities. [45]

Onartuzumab, an anti-MET receptor monoclonal antibody has shown increased PFS and overall survival when given with Erlotinib as

compared to placebo. [46]

A phase I study of cabozantinib (XL184), a drug which targets both VEGF and MET receptors, has shown promise after preliminary analysis. [9]

Others

Multiple targets with great potential are currently being investigated. Blockade of IGF-1R receptors with antibodies or molecular substrates can potentially alter downstream signaling that promotes cancer growth. [29] This can also be achieved by administration of recombinant IGF binding proteins to reduce circulating levels of IGF-1R ligands. Inhibition of the nuclear factor κ B pathway is also of particular interest.

Different approaches to the treatment of EGFR positive NSCLC patients

Sensitizers

With the observation of histological transformation as a mechanism of acquired resistance to overcome EGFR inhibition, [37] it is hypothesized that under the therapeutic stress of EGFR TKIs, the cancer cells can be encouraged to adopt this resistance mechanism and transform from a NSCLC to SCLC. Administration of EGFR TKIs can then 'sensitize' the cancer cells to be susceptible to platinum and etoposide based chemotherapy (standard regimen for SCLC), that would otherwise be ineffective for NSCLC.

Alternating Treatment/Different Dosing

A review by Oxnard [37] has found that although some cancer cells can acquire the T790M mutation in the presence of a EGFR TKI, this mutation becomes undetectable after a period of discontinued EGFR TKI therapy. It is explained that the T790M mutation causes suboptimal growth profile in the absence of EGFR TKIs and therefore through the notion of 'survival of the fittest', they are removed from the cancer population when EGFR TKIs are discontinued. This dynamic change in cancer cell profile now allows the cancer to once again be susceptible to EGFR TKI treatment. Thus, there is a biological rationale to create a dosing schedule with intervals of EGFR TKI treatment and intervals without. This would hopefully maximize cancer cell kill and improve patient outcomes.

Combination/Polytherapy

There is a lot of potential in targeting specific parts of the complex signaling network in cancer treatment, but this runs the risk of the development of acquired resistance via compensatory pathways. Therefore, a different approach of combining multiple drugs targeting different receptors and different parts of the signaling pathway at the same time may provide a synergistic effect in limiting cancer cell growth. This can be achieved with various classes of drugs such as TKIs, downstream signal molecule inhibitors, monoclonal antibodies targeting receptors involved, immunosuppressants such as everolimus and even chemotherapy. However, trials do require adequate time, participants and investments. More effort and investigation must be performed before the best combination can be identified.

Selection of Patients

Demographically, it has been found in many articles that patients who are most likely to respond to EGFR TKIs are of Asian background (mainly Japanese), female, never-smokers and have NSCLC of the adenocarcinoma histology. [6,8,19,20,39] Presence of mutant KRAS is also found to be a strong predictor of lack of response to EGFR TKIs in NSCLC patients. [6,47,48] It is also discovered that low expression of nuclear factor κ B inhibitor was predictive of poor clinical outcome for patients receiving erlotinib without a T790M mutation, indicating its potential in predicting response to EGFR TKI therapy. [18] PTEN inactivation is also a predictor of resistance to EGFR-family antagonists, implying that this subset of patients would not be amenable to long term EGFR TKI therapy. [39] These predictors not only enable us to select patients who are more likely to benefit from EGFR TKI therapy, but also help to prevent exposure of unnecessary toxicities to poor responders. With further validation of these predictors through

studies, it might be even possible to develop a nomogram or scoring system to predict the success of EGFR TKIs in NSCLC patients.

Future Directions

As investigative techniques such as genotypic assessments, new assays, cell lineage tracing, chemical genomic profiling studies, next generation sequencing and proteomics develop, more information regarding tumorigenesis will be revealed. Ongoing research in other cancers may also provide insight to the pathogenesis of NSCLC. As more drugs are being released for clinical use, further research must be done to determine the short and long term side effect profiles of these drugs, whether used on their own or in combination. The fundamental principles of beneficence and non-maleficence should not be forgotten. No matter how novel or promising a drug can prove to be, its value for clinical application becomes limited when its toxicity profile causes more harm than good to patients.

It is also interesting to note that tumour signaling profiles are in a dynamic rather than static state. Mutations can be gained and lost, depending on patient's biology, genetics and treatment received. This could mean that gathering information regarding the cancer may have to be a continuous activity rather than just prior to treatment. Patients may have to be regularly biopsied at different stages of chemotherapy or EGFR TKI treatment.

Knowing that every patient with NSCLC can have subtle differences in the biology of the cancer, future research may warrant the need to create a tumour bank where cancer cells are profiled and sequenced, both before and after treatment. This information will then be stored in a database where researchers can retrieve information from, and

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possibly access cell samples if required.

With the development of deep analytic systems such as the IBM supercomputer Watson, who is 'learning' about lung cancer at the *Memorial Sloane-Kettering Cancer Centre*, information from the tumour bank can be rapidly processed to generate meaningful data. Such information sharing will require an international effort, enhancing the development of targeted, higher-powered and multi-centred trials. This can drive down the high costs of drug discovery, reducing wastage of precious resources into unfruitful studies that seek to answer poorly formulated clinical questions.

Conclusion

The idealistic imagination of cancer cure will come in the form of personalized medicine where cancer cells are analyzed through a machine which puts together a concoction of molecules to create a single, simple tablet that will destroy the tumour entirely without side effects. As research becomes more focused into the little details of each signaling molecule in every pathway, the cumulative understanding of cancer will be heightened tremendously. The content and amount of research done is no doubt exciting and promising, but, as a clinician, our focus remains ultimately on the patient and not merely on the cancer.

Conflict of interest

None declared.

Correspondence

B Chua: bjchu2@student.monash.edu

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Aripiprazole as first-line treatment of late-onset schizophrenia: a case report and literature review

Tasciana Gordon

Final Year Medicine (Undergraduate)
James Cook University

Tasciana is a final year medical student at James Cook University. She is the Cairns Co Chair for Rural Health in Northern Outback. In third year she was in the winning team for JCU in the Emergency Medicine Challenge at the AMSA convention in Sydney. She is interested in many aspects of medicine and hopes to have a successful career in the field of her choice.

Introduction: Guidelines for the first-line treatment for late-onset schizophrenia (LOS) in the elderly patient have not been established. The current recommended treatment of schizophrenia in younger age groups has been extrapolated to those in the older age groups. This report considers the effects of medication specific to this demographic. **Case study:** BB, a 73-year-old male, presented to the Mental Health Unit following a request and recommendation in response to concerns from family and friends, with a history of increasing paranoia and paranoid delusions. He was managed under an involuntary treatment order and was prescribed aripiprazole 10 mg once daily. **Methods:** A literature review was conducted using UpToDate, Medline, PsychOnline and Ovid databases with limits set to exclude articles that were not written in English, published before the year 2000 or which were not available as full text. Articles were found using a combination of the search terms "late onset schizophrenia"; "risperidone AND mechanism of action"; "aripiprazole AND mechanism of action"; "paraphrenia"; "schizophrenia AND Australian therapeutic guidelines"; and "atypical antipsychotics pharmacology". Results: The literature review confirmed the efficacy and safety of aripiprazole in the elderly patient with LOS. Studies identified fewer side effects with aripiprazole, such as cerebrovascular and cardiovascular events, than with risperidone. There were no studies identified that directly addressed the question of whether aripiprazole should be used as first-line management of LOS instead of risperidone. **Conclusion:** Aripiprazole may be considered as first-line management for patients with late-onset schizophrenia.

Case study

BB is a 73-year-old Caucasian male who presented to the Mental Health Unit (MHU) following a request and recommendation (under the *Queensland Mental Health Act 2000*) in response to concerns from family and friends. BB presented from a nursing home with paranoid delusions that incorporated persecutory themes with thoughts that the nursing staff were poisoning his food in order to kill him. He also presented with auditory hallucinations complaining of hearing people through a speaker telling him they were going to cut off his toes and genitals. BB expressed suicidal ideation to escape, however, no previous attempts at suicide or self-harm had been made. When BB was further questioned about a suicidal plan he stated that he would like to do it cleanly with towels around him so there was no mess but no instrument or method was established. There was no history of substance abuse.

BB is retired and lives in a nursing home. His wife died three years prior to this presentation.

On assessment, BB was well groomed, sitting on a hospital bed, clutching his legs in a curled up manner. Mr. BB maintained a paranoid and untrusting manner throughout the presentation, with poor eye contact. Therefore, rapport with mental health staff was difficult to establish. His speech was agitated and consistent with anxiety. Affect was restricted and he appeared apprehensive towards the interviewer. His mood was difficult to establish because of his paranoid state. He had no insight into his mental illness and judgement was poor. BB was assessed to have a moderate risk of violence.



A Mini-Mental State Examination was carried out on admission to the MHU. BB scored 30/30 and combined with further assessment in the MHU dementia-related psychosis was excluded.

BB had a one-week admission to the MHU four years previously following the death of his wife. He had neurovegetative symptoms: not eating or sleeping and not carrying out activities of daily living. He required diazepam to assist with sleep and a nasogastric tube for enteral feeding. He was later discharged with family support. BB has a medical history of hypertension, dyslipidaemia and ischaemic cardiomyopathy.

After a request and recommendation for assessment, BB was diagnosed with late-onset schizophrenia in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria and managed under the *Mental Health Act* (involuntary treatment order) for three weeks for this presentation.

BB was commenced on aripiprazole 5 mg once daily (OD). His auditory hallucinations and paranoid delusions persisted with no reduction in their severity. Aripiprazole was then increased by 5 mg after four days until clinical improvement was achieved at 10 mg OD.

Throughout the admission, BB's auditory hallucinations and paranoid delusions resolved significantly and there was an improvement in his mental state. Pharmacotherapy combined with repetitive cognitive assessment resulted in a good initial prognosis.

Following aripiprazole 10 mg daily for two weeks, BB reported no auditory hallucinations or paranoid delusions. There had been no side effects of aripiprazole. BB was discharged with aripiprazole 10 mg OD and returned to Old Persons' Mental Health Services in the community for support.

Introduction

Schizophrenia is characterised by various symptoms including delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour and negative symptoms (including loss of motivation, poverty of words and affective flattening). [1,2]

The average age of onset of schizophrenia is 18 in men and 25 in women. Late-onset schizophrenia (LOS) is a separate category of patients whose onset is after 45. Very late-onset schizophrenia (VLOS) occurs after 60 years of age. Australian diagnostic criteria do

not separate LOS and VLOS. [2] Therefore, in the case study, Mr. BB is diagnosed with LOS.

Late-onset cases present with some differences to early-onset schizophrenia. The clinical presentation of LOS includes more persecutory delusions and hallucination, as evident in the case study, and is less likely to include disorganised behaviour and negative symptoms. [1] LOS has been demonstrated to have an increased response to pharmacotherapy (anti-psychotics) in lower doses, resulting in an improvement in symptoms compared with early-onset schizophrenia. [2]

If smaller doses can be administered the possibility of side effects is reduced.

Aim

The current recommended treatment of schizophrenia in younger age groups has been extrapolated to those in the older age groups. This article is a review of the literature, supplemented with a case study, and outlines the evidence that is available for the effectiveness of aripiprazole as first-line management of LOS. Aripiprazole is compared with risperidone, which is the current first-line management for schizophrenia in the younger population. Risperidone has been used for this review rather than olanzapine and quetiapine as it is more frequently prescribed as initial management in the elderly population. [3]

Data collection

To address the management of LOS, a literature search was conducted

using the search terms “late onset schizophrenia”; “risperidone AND mechanism of action”; “aripiprazole AND mechanism of action”; “paraphrenia”; “schizophrenia AND Australian therapeutic guidelines”; and “atypical antipsychotics pharmacology”. The databases UpToDate, Medline, PsychOnline and Ovid were used with limits set to only include articles written in English and available as full-text journals. Articles published before the year 2000 were excluded from this study. Articles including meta-analyses (Level I evidence) as well as randomised controlled trials (Level II Evidence) were reviewed. No study was found comparing the use of risperidone as first-line management for LOS with the use of aripiprazole.

Current first-line management

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) Clinical Practice Guidelines for the treatment of schizophrenia (inclusive of LOS) and related disorders since 2005 include psychotherapy and pharmacotherapy. [3]

Guidelines for the introduction of pharmacotherapy recommend:

- Notification of patients and families of the benefits and risks of drug therapy. Where it is not possible to fully discuss the choice of agent as is the case in most acute episodes, oral atypical agents are used. Risperidone, olanzapine and quetiapine are regarded as the treatments of choice in the first episode of psychosis. [3]
- Evaluation of the efficacy of treatment subjectively as well as objectively by the clinician with regular Mental State Examinations and reviews of the patient. [3,4]
- Titration of the dose of risperidone as appropriate for the patient. [5]

	Risperidone [5]	Aripiprazole [6]
Route of entry	Oral or IM	Oral or IM
Mechanism of action	Dopamine antagonist	Partial dopamine agonist
Half life/elimination time/steady state	Well absorbed <u>Absolute oral bioavailability</u> : 70% <u>T_{1/2}</u> : 3 hours in extensive metabolisers and 20 hours in poor metabolisers <u>Elimination</u> – eliminated in the urine, to a lesser extent via faeces <u>Steady state concentrations</u> of risperidone are reached in 1 day (good metabolisers) to 5 days	Well absorbed <u>Absolute oral bioavailability</u> : 87% <u>T_{1/2}</u> : 75 hours in extensive metabolisers and 146 hours in poor metabolisers <u>Elimination</u> – eliminated in the faeces, to a lesser extent via urine <u>Steady state concentrations</u> of aripiprazole are attained within 14 days
Main side effects	Parkinsonism Extrapyramidal side effects are more prominent	Sedation
Cost	Consumer cost undetermined; on the PBS since 1993 Average dose 4–6 mg; RISPERDAL [®] 4 mg [60]: Authority streamlined PBS: \$219.45	Consumer cost undetermined; on the PBS since 2003 ABILIFY [®] 5 mg [30] pack: Authority streamlined PBS: \$156.44
Drug Interactions	Medications co metabolised by the enzyme cytochrome p450 2D6	Medications co metabolised by the enzyme cytochrome p450 2D6

Table 1. Comparison of anti-psychotic medications.

*PBS = Pharmaceutical Benefits Scheme

Discussion

Aripiprazole is the proposed first-line management of LOS versus risperidone.

Dosing

The recommended starting dose for aripiprazole is 10 mg to 15 mg OD. [6] Intramuscular injection has a therapeutic benefit from 10 mg to 30 mg. There is no evidence showing oral medication being more effective above 15 mg OD. It is advised that dose increases should not be more frequent than twice weekly as this is the time needed to achieve a steady state. [6] In contrast, recommended initial risperidone dosing is 2 mg with titration in increments of 1–2 mg per day as tolerated by the patient to a recommended dose of 4 to 8 mg. For schizophrenia, efficacy with risperidone has been evident from 4 mg to 16 mg.

Mechanism of action

Aripiprazole acts as a partial dopamine D₂ receptor agonist in the limbic system. It also acts as a partial agonist at serotonin 5-HT_{1A} receptors but an antagonist of 5-HT_{2A} receptors. [6,10] This is compared with risperidone, which acts as a dopamine D₂ antagonist and low-affinity antagonist of serotonin type 2 receptors. [5,8]

Efficacy

In review of the Cochrane database, aripiprazole was compared with other antipsychotics for schizophrenia. One hundred and seventy four randomised control trials (RCTs) were compared involving 17 244 participants. [10] The RCTs comparing aripiprazole against risperidone demonstrated an increase in efficacy through an improvement in mental state measured by the Brief Psychiatry Rating Scale when using aripiprazole. Additionally, for patients using aripiprazole there was also a significant increase in the quality of life. Despite these demonstrations of efficacy these RCTs do not compare the use of these medications in the elderly population, limiting their applicability to LOS.

Comparison of side effects

Aripiprazole has minimal extrapyramidal side effects. [11] Sedation is a dose-related side effect (most prominent at 30 mg) which seems to decrease with time. [7,12] Monitoring is important in the elderly because of the potential for increased falls and, subsequently, possible fractures and head injuries.

In several controlled trials aripiprazole-induced extrapyramidal side effects were reported to be reduced compared to dopamine antagonists such as risperidone. [13–16] However, aripiprazole-induced akathisia was reported as higher (approximately 20%) in patients with schizophrenia. Anticholinergic agents may be used to treat

parkinsonism and dystonia but are ineffective in treating akathisia. Beta-blockers and benzodiazepines are effective in reducing akathisia. Risperidone has been reported to have increased extrapyramidal side effects including parkinsonism, akathisia, dystonia and tremor. [5,16] Cerebrovascular side effects include stroke and altered cardiac conduction, potentially causing life-threatening arrhythmias. Nausea, constipation, dyspepsia, salivary hypersecretion, abdominal discomfort, and diarrhoea were also recorded. Prolactin inhibition may result in reduced libido, caused by reduction in levels of testosterone and oestrogen. In long-term therapy low testosterone and oestrogen levels may lead to osteoporosis, which is especially relevant for older adults.

It is important to note that there is an absence of controlled studies of risperidone in the elderly, thus making assessment of the LOS side-effect profile impossible. Nevertheless, based on the known side-effect profile of risperidone, it is contraindicated for Mr. BB with a medical history of hypertension, dyslipidaemia and ischaemic cardiomyopathy.

Conclusion

Aripiprazole may be considered as an option for the first-line pharmacotherapeutic management of LOS. In trials comparing aripiprazole against risperidone, aripiprazole has higher efficacy in the management of the symptoms associated with schizophrenia. Additionally, aripiprazole produces fewer cardiac conduction abnormalities, gastrointestinal side effects, and extrapyramidal side effects than risperidone. Consequently, those on aripiprazole have a reduced risk of cardiovascular and cerebrovascular events, both of which are more common in older age groups.

Despite the indirect evidence for the use of aripiprazole in LOS, there is a paucity of studies directly comparing aripiprazole and risperidone in LOS. Further controlled studies (ideally double-blinded, placebo-controlled) should be performed to assess the efficacy, side-effect profile and drug interactions in older-age patients.

Consent declaration

Informed consent was obtained from the patient for the original case report.

Conflict of interest

None declared.

Correspondence

T Gordon: tasciana.gordon@my.jcu.edu.au

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The future of Indigenous health in Australia

Dr. Tammy Kimpton

BMed FRACGP

President

Australian Indigenous Doctors Association

Tammy Kimpton completed her FRACGP in 2013 and currently works part-time in rural General Practice. She is the president of the Australian Indigenous Doctors Association (AIDA) and has been a member since its inception. Over the years, she enjoyed contributing to many important roles in AIDA.

Dr. Rob James

Past Student Director

Australian Indigenous Doctors Association

Robert James is a Torres Strait Islander man who currently lives in Melbourne, Victoria. While working at the Bone Marrow Transplant unit of Royal Children's Hospital as a research officer, he was inspired by a paediatric oncologist to pursue medicine. He graduated with an MBBS from the University of Melbourne in 2013.

In 1866 the first Indigenous Canadian doctor completed her training and in 1899 the first Maori doctor graduated from medical school in the United States. Professor Helen Milroy, a founding member of the Australian Indigenous Doctors' Association (AIDA), graduated from the University of Western Australia as Australia's first Aboriginal doctor 84 years later in 1983. The number of Aboriginal and Torres Strait Islander medical graduates has increased to 180 with a further 261 Indigenous medical students studying at universities. In 2011 the intake of first year Indigenous medical students at Australian universities reached a new high of 2.5 per cent, matching the percentage of Australia's Aboriginal and Torres Strait Islander population.

AIDA is the peak representative body for Indigenous doctors and medical students, and strives to achieve the vision of Aboriginal and Torres Strait Islander people having equitable health and life outcomes. We do this by: providing a unique medical and cultural perspective on Aboriginal and Torres Strait Islander health; maintaining links between traditional and contemporary medicine; and growing and supporting current and future Aboriginal and Torres Strait Islander doctors. This vision is central to the work that AIDA undertakes and is embedded in our advocacy and policy work.

AIDA also recognises the role of traditional healers who preceded contemporary medicine and to this day still remain active in Aboriginal and Torres Strait Islander communities throughout Australia: "The knowledge, wisdom, and skill of our traditional healers is becoming increasingly recognised within Australia as well as internationally... not only for the direct benefit of the community but to ensure that health practitioners are being educated in understanding and working with traditional healers to improve physical health and mental health outcomes." [1] We are proud to have a strong relationship with the traditional healers who act as teachers, guides and leaders to our organisation.

In order to consider the future of Indigenous health in Australia, it is imperative that all Australians understand the current health status of the population. In 2011 Aboriginal and Torres Strait Islander people comprised 2.5 per cent of the total Australian population, with 669,736 people recorded in the 2011 census. [2,3] New South Wales had the largest Indigenous population (208,364) and Northern Territory had the highest proportion of Indigenous people (29.8 per cent), with the majority of Aboriginal and Torres Strait Islander people living in major cities. [3] A major observation in the Australian Demographic Statistics was that in 2011 one third of the Indigenous population were aged 15 years or below and only four per cent were above the age of 65. [2] The Aboriginal and Torres Strait Islander population is younger and dying earlier compared with our non-Indigenous counterparts. The life expectancy for Aboriginal and Torres Strait Islander peoples was estimated to be 11.5 years lower than that of the non-Indigenous populations for males (67.2 compared with 78.7 years) and 9.7 years lower for females (72.9 compared with 82.6 years). [4] The leading causes of Aboriginal and Torres Strait Islander deaths in 2006-2010 were cardiovascular disease (including heart attacks and stroke), cancer, and injury/trauma (including transport accidents and self-harm). [4] Also, the incidence of type II diabetes has risen exponentially,



Source: www.aida.org.au

leading to various chronic health issues in communities. It is also important to note that 75 per cent of the deaths mentioned previously are preventable, therefore it is achievable to alter the statistics for the better. [4]

The inequality of health in Australia was brought to the wider public's attention by the former Aboriginal and Torres Strait Islander Social Justice Commissioner, Dr Tom Calma AO, in the 2005 Social Justice Report. Subsequent to this report the Close the Gap Coalition was formed and the Close the Gap Campaign was launched. Close the Gap has raised the awareness of Indigenous health to all Australians and provides an opportunity for individuals to advocate for improvements in health. AIDA is a member of the Close the Gap Steering Committee and is also a signatory of the Close the Gap: Statement of Intent (2008) between the Australian Government, the opposition party, and peak Indigenous and non-Indigenous organisations. [1] To ensure targets within the Statement of Intent are achieved there need to be systematic processes to ensure Aboriginal and Torres Strait Islander people have control over their own health. An emphasis on Indigenous people being a part of the decision making process and having access to culturally safe health services are examples of such processes.

The Council of Australian Governments (COAG) has demonstrated support for the Close the Gap Campaign by keeping Indigenous health on the agenda of Commonwealth and State Governments. This commitment has led to the COAG Closing the Gap targets, they are: closing the life expectancy gap within a generation (by 2031); halving the gap in mortality rates for Indigenous children under five within a decade (by 2018); ensuring access to early childhood education for all Indigenous four year olds in remote communities within five years (by 2013); halving the gap in reading, writing, and numeracy achievements for children within a decade (by 2018); halving the gap for Indigenous students in year 12 attainment rates (by 2020); and halving the gap in employment outcomes between Indigenous and non-Indigenous Australians within a decade (by 2018). These targets highlight the importance of health, education, and employment all of which are

crucial for improving the health and wellbeing outcomes of Aboriginal and Torres Strait Islander people.

Another critical factor in improving health outcomes for Indigenous people is an Aboriginal and Torres Strait Islander workforce. The Australian Human Rights Commission addressed this in a recent summit: "The Indigenous medical workforce is integral to ensuring that the health system has the capacity to address the needs of Aboriginal and Torres Strait Islander peoples. Indigenous health professionals can align their unique technical and sociocultural skills to: improve patient care; improve access to services; and ensure culturally appropriate care in the services that they and their non-Indigenous colleagues deliver." [5] One approach AIDA is using to develop and strengthen an Indigenous medical workforce is building meaningful partnerships. The partnership approach should be based on mutual respect and commitment to joint-decision making, priority setting and constant learning, and reflection. An example of the partnership approach includes AIDA's Collaboration Agreements established with the Medical Deans of Australia and New Zealand, the Confederation of Postgraduate Medical Educational Councils, and more recently with the Committee of Presidents of Medical Colleges. [6] Partnership with peak medical training organisations ensures that Indigenous health remains on the agenda across the medical training spectrum. The incorporation of outcomes in the Collaboration Agreements such as increasing the support for and retention rates of Indigenous medical students, trainees and fellows, and promoting medical education and training policy reform indicates a genuine commitment from the peak medical training bodies to support the Indigenous medical workforce at all levels. Building a culturally safe health workforce, both in numbers and competence, and culturally safe workplaces, are crucial to delivering high quality and sustainable health services to Indigenous people.

Although we must strive to ensure that the Indigenous medical workforce continues to grow, collaboration with and commitment from our non-Indigenous medical colleagues is vital if we are to improve the health status of Indigenous people. One example of collaboration between Indigenous and non-Indigenous health professionals is the Inala Indigenous Health Service Southern Queensland Centre of Excellence for Aboriginal and Torres Strait Islander Primary Health Care, in Brisbane, QLD. In 1994 the centre only had 12 Indigenous people registered as clients, since implementing a number of strategies informed by the local community; it now has 10,000 registered Indigenous patients, 8,000 of whom are regular users. Strategies implemented by the service include: employing more Indigenous staff; creating a culturally safe waiting room; staff cultural awareness training; disseminating information to the Indigenous community; and promoting intersectoral collaboration. [1] AIDA commends the work done by Associate Professor Noel Hayman and the team at Inala Indigenous Health Service Southern Queensland Centre of Excellence for Aboriginal and Torres Strait Islander Primary Health Care, for demonstrating effective collaboration and providing a good practice case study.

Partnership within the Indigenous health sector between peak health organisations is integral if we are to build strong and sustainable improvements in Indigenous health. AIDA is a member of the National Health Leadership Forum (NHLF), an entity within the National Congress of Australia's First Peoples that involves the collaboration of peak Indigenous health organisations. The NHLF provides Indigenous leadership in the health sector and provides a strong voice to ensure that Aboriginal and Torres Strait Islander health remains on the agenda of Government. The NHLF is a strong example of how the strength of a collective can inform the development of collaborative policy, such as the 2013-2023 National Aboriginal and Torres Strait Islander Health Plan ("The Plan"), and more importantly advise and monitor the implementation of The Plan. [7]

Within the National Aboriginal and Torres Strait Islander Health Plan culture is central, and it is important to acknowledge and value the

link between Indigenous culture, and health and wellbeing. The vision of The Plan is that "The Australian health system is free of racism and inequality, and all Aboriginal and Torres Strait Islander people have access to health services that are effective, high quality, appropriate and affordable." Together with strategies to address social inequalities and determinants of health, this provides the necessary platform to realise health equality by 2031. [8]

Long term approaches to progressing improvements in Indigenous health need to also target the next generation of Indigenous health workforce with a focus on pathways into health careers for Indigenous youth. The age profile of the Aboriginal and Torres Strait Islander population is significantly younger than that of the non-Indigenous population. In 2011, around 36 per cent of the Indigenous population was aged less than 15 years, compared with 18 per cent of the non-Indigenous population. [9] With regards to the education attainment of Indigenous people, 25 per cent of the population had completed year 12, compared with 52 per cent of non-Indigenous people, and 4.6 per cent of Aboriginal and Torres Strait Islander people had achieved a bachelor level degree, compared to 20 per cent of non-Indigenous people. [9] If we are to develop an appropriate future Indigenous health workforce, greater attention will need to be given to developing the skills of the younger Aboriginal and Torres Strait Islander generation so that they are ready and able to pursue a career in the health sector.

In April this year, under the auspice of AIDA, and in partnership with the following peak Aboriginal and Torres Strait Islander health organisations: National Aboriginal Community Controlled Health Organisation; Indigenous Allied Health Australia; Congress of Aboriginal and Torres Strait Islander Nurses and Midwives; National Aboriginal and Torres Strait Islander Health Worker Association; Indigenous Dentists' Association Australia; and the Australian Indigenous Psychologists Association, the inaugural Murra Mullangari: Pathways Alive and Well Health Careers Development Program was launched. Murra Mullangari: Pathways Alive and Well is targeted at addressing a critical area of need in the health industry, which is engaging young people with health careers; with a specific focus on Aboriginal and Torres Strait Islander youth who have expressed an interest in establishing a career in this sector. The Murra Mullangari: Pathways Alive and Well Program involved two components, the first being a residential workshop, held in Canberra. This component saw 30 Indigenous secondary students experience university life, be advised on a range of health career prospects and hear first-hand from Indigenous health professionals across a variety of health disciplines. The second component involved mentoring for participants, who are matched with an Indigenous professional in the health career of their interest.

As future members of the medical profession we encourage all medical students to build their knowledge of, and engagement with, Aboriginal and Torres Strait Islander health. It is important to understand that cultural safety is not simply a module that can be completed as a part of your medical degree; it requires continuous learning and experience, maintenance of strong clinical skills, and the ability to understand patients holistically. This could be done through volunteering in Indigenous communities, placement at an Aboriginal Community Controlled Health Organisation, or associate membership with AIDA.

It is important to build on the momentum developed through key collaboration agreements such as AIDA's agreements with the Medical Deans of Australia and New Zealand, Confederation of Postgraduate Medical Education Councils, and the Council of Presidents of Medical Colleges. These partnerships enable a continued focus on the recruitment, retention, and graduation of Indigenous medical students, alongside support for trainees and fellows which is critical for the development and retention of a strong Indigenous medical workforce.

The development of medical practitioners, Indigenous and non-Indigenous, who are culturally and clinically competent and passionate about social justice are integral to the health outcomes of Australia. The

way you practice medicine in the future could facilitate generational change within the health sector and lead to health equity in Australia.

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This change could be you and your peer's legacy; the only thing left to consider is what part you will play in delivery this outcome.

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Days of miracle and wonder

Professor Stephen Leeder AO

FAA, FRCPA

Editor-in-Chief, *The Medical Journal of Australia*

Stephen Leeder has been the Editor-in-Chief of The Medical Journal of Australia since 2013. He has a long history of involvement in public health research, educational development and policy, and is Professor of Public Health and Community Medicine at the University of Sydney and immediate past Director of the Menzies Centre for Health Policy. He is also Chair of the Western Sydney Local Health Network Governing Council.

My youngest son, James, is an undergraduate in his third year at the University of Sydney. His world is more like yours, dear reader, than mine. It differs from mine in the depth of experience and knowledge he has acquired at a young age, his international travel formerly for music and now for debating, his less guilt-ridden ethics, and his friends' and his own profound concerns about the future of the planet. These differences distinguish him from me even now, but more dramatically, they separate us, especially when I compare his life at present with what mine was like as a serious young medical student in the 1960s. Search as I might, I can find nothing – *not a thing* – that marks out my experience in my twenties as superior to his.

The outstanding technological advances that form our environment are based largely upon information science. James and his friends are in constant contact electronically as I guess you are with your colleagues. Information communication technology revolutionises teaching and learning: Who knows where massive open online courses (MOOCs) will lead us? And it *has* been a revolution.

Imagine this: When I moved from Newcastle University to the gigantic Westmead Hospital in 1986, I asked for a fax machine for our Department of Community Medicine that I was then to direct. The hospital authorities questioned my request because, they said, "there is already a fax in the hospital." Debate was occurring as to whether a big central computer was the way to go or whether we would support desktops. Now the paperless hospital is upon us. This was not many years ago: in functional terms it feels like a century.

This new electronically-informed and supported environment has its problems, one of them being information overload. This year, *The Medical Journal of Australia* is celebrating its centenary and in defining its future we must take into account the avalanche of information, comprised of original studies, syntheses, synopses (Cochrane Reviews) and computerised decision support systems. The sheer volume of information means that new skills are needed to navigate through, and around, the avalanche in search of signs of life. Journals such as yours and ours must respond. As I wrote in the centenary editorial, the amount of information we generate each day is stupendous:

Given the exponential rate of electronic evolution, Eric Schmidt, executive chairman of Google, claimed that humans now create as much information every 48 hours as we made from the dawn of civilisation to 2003 – that's 5 exabytes of data, or five billion gigabytes, in 2 days.

Where can we go for help? We must learn from radio astronomers who have wrestled with massive data sets and also from the stupendous advances occurring in the management of big data by enterprises such as Google. Big data can yield astonishing results, reducing the need for sampling when conducting population studies, providing rapid answers to questions about infectious disease transmission and providing early warning of epidemics, for example. We will find our way, I am confident, but we will need to be active searchers.

J. Craig Venter, the leader of the private enterprise team that sequenced



the human genome in parallel with Francis Collins and the publicly-funded team in 2001, has not slowed down and heads a major biotech company and institute in La Jolla, California. He depends heavily on ICT and sees the future of medical research to be completely intertwined with the future of information technology.

It is now possible, he has shown, to sequence the complete genome of a bacterium or fungus, reduce it to binary code, transmit it at the speed of light to another laboratory and synthesise a new genome from the data, insert it into a life form from which the genetic material has been removed and bingo! You have regenerated life. Hence the title of his recent book, *Life at the Speed of Light*.

Mars, Venter claims, has swapped lots of material with earth over the past millions of years, in the form of meteorites, and he reasons that life on the two planets may well have a common origin. He has a dramatic imagination. Here he promotes an idea that may become a reality during your lifetime.

Venter asks us to consider sending a rover to Mars capable of drilling to reach deep subterranean lakes. If analysis of the water yields a life form that contains genetic material, the rover, which is fitted with a genetic sequencer, would translate the genome into binary code and radio it back to Earth where the Martian bacterium, or whatever, would then be synthesised.

Think for a moment where you are with regard to the unravelling of dark medical mysteries such as dementia - you are so much further ahead than I was at your age and possess so much more scientific power to progress a positive, health-promoting agenda.

As singer Paul Simon says in his 1986 song, *The Boy in the Bubble*, "These are the days of miracle and wonder!" Old frontiers in medicine have disappeared; new horizons beckon. You are entering a fabulously exciting world. Make certain you document your progress and publish it – in your journal or ours!

Minding the mental in health...

Professor Patrick McGorry

AO, MD, PhD, FRCP, FRANZCP

Executive Director

Orygen Youth Health Research Centre

Centre for Youth Mental Health

University of Melbourne

Patrick Dennistoun McGorry is Professor of Youth Mental Health at the University of Melbourne. He is also executive director of Orygen, The National Centre of Excellence in Youth Mental Health and founding editor of Early Intervention in Psychiatry published by the International Early Psychosis Association. McGorry also advocated strongly for the establishment of Headspace, previously known as National Youth Mental Health Foundation.

"There is no health without mental health"—David Satcher, US Surgeon General, 1999

As Australia's future doctors, you are facing the challenges of finishing your training and establishing yourself within your chosen career pathway in a profession that offers unique opportunities, but also significant stressors, all at a uniquely vulnerable time of life. Many of the stressors associated with a career in medicine have a disproportionate impact on students and junior doctors. These include the high workloads and demanding training requirements—often within difficult clinical environments—that young doctors face in the early stages of their careers, along with the need to find a balance between the demands of professional and personal responsibilities, among others. In this context then, it should come as no surprise that medical students, and doctors, report substantially higher rates of psychological distress and suicidality than other professionals, or the general public.

The recent national survey of doctors' and medical students' mental health by beyondblue presents some sobering statistics; but first, some crucial demographic data. [1] The majority (80%) of the 6,658 medical students who took part in the survey were under 25 years of age, with 32.5% in the preclinical and 67.5% in the clinical stages of their training. Strong epidemiological data tells us that 75% of those who suffer from a mental illness experience their first episode by the age of 25 years, with a peak in new onsets in the late teens and early twenties. [2,3] Thus, most medical students, along with other tertiary students, are in the peak age group in terms of risk for developing mental ill-health.

Disturbingly, 9.2% of medical students reported very high levels of psychological distress, a rate double that of intern doctors (4.4%) and triple that of the general population (3.1%). Rates of depression and anxiety were also significantly higher in medical students than the general population, but similar to those in the broader university student population. Of even greater concern, the rate of suicidal ideation and suicide attempts by medical students was almost ten-fold higher than those of the general population, with almost one in five medical students reporting thoughts of suicide and approximately 4% an actual suicide attempt within the last year. [1]

Clearly, medical students are not immune from mental ill-health: this should come as no surprise, given our developing understanding of the chronology and epidemiology of the mental illnesses. Adolescence and early adulthood—better described as emerging adulthood—is a time of great developmental significance, when young people are establishing their psychological, social, and vocational identities and pathways as part of the transition to independent adulthood. [4] This transition occurs against the background of the highly dynamic changes in brain architecture that occur at this time of life, driven by a series of maturational processes that result in the refinement of the neuronal circuitry and a recalibration of the inhibitory/excitatory balance, particularly in the frontal cortex. [5] Because these biological and social changes coincide, they combine to create a unique 'window of vulnerability' to the onset of mental illness.

Without doubt, undertaking the extremely demanding training that medical school requires contributes to the developmental and social stresses that impact all young people, and more so for those who



Source: www.monash.edu.au

are already vulnerable to mental ill-health. In this regard, the most commonly reported sources of stress for medical students were largely related to the demands of study, the university-related workload, conflict between study/career and family/personal relationships, keeping up to date with knowledge and fear of making mistakes. Along with their psychological symptoms, students also reported extremely high rates of burnout and exhaustion, with over half reporting emotional exhaustion, and around a quarter reporting high cynicism and low professional efficacy. [1]

Encouragingly, the majority of medical students (56%) who felt seriously depressed or who had received a diagnosis of depression sought treatment, while 40% of those who felt seriously anxious or had been diagnosed with an anxiety disorder sought treatment. [1] These figures are almost double the national average for young people, [6] although they are in keeping with medical students' status as a group that is aware of mental health issues. However, the fact that around half of those at least with a need for care are not seeking or accessing it. The nature and quality of such care is another issue altogether. The most common sources of professional help were GPs, followed by psychologists or counsellors, and then university counselling services, while family and friends were the most common personal sources of support. Significantly, the most common coping strategies used by students who felt anxious or depressed were positive, and the rates of harmful drinking were half that of their student peers, while other substance use rates were low. While many medical students do seek help for mental health concerns, and at higher rates than their peers, only 20% of students reported feeling comfortable this, with almost half the cohort citing embarrassment, fears regarding confidentiality/privacy or not wanting help from others as the main barriers to seeking help. [1] The level of engagement seems poor and the skill levels of the professionals remains unclear.

This brings me to the crux of this article: stigma and the lack of parity between physical and mental health care. Would 80% of young people—medical students or not—feel uncomfortable about seeking care for a physical ailment, say a broken bone, or diabetes, or flu? I strongly suspect not. Stigma is institutionalised in our health care system from the level of funding—although mental illness accounts for 13% of the burden of disease in Australia, mental health care receives about 7.7% of the total health budget [7]—to the quality of physical and mental health care that those with serious mental illness receive. [8] The 'lethal discrimination' that results in those with serious mental illness dying on average 20 years earlier than their peers, largely as a

result of cardiovascular disease or suicide, is an ongoing disgrace that we are yet to address. [9]

The beyondblue report presents some very disturbing statistics on medical students' attitudes to doctors with mental health issues that are particularly salient here. Medical students believed that the medical community holds stigmatising attitudes towards doctors with a mental illness, with approximately 50% of students reporting the belief that doctors considered that experiencing depression or anxiety was a sign of personal weakness, while 41.5% believed that doctors with a history of depression or anxiety were less likely to be appointed. Even more disturbing was the fact that 60% of medical students with a current diagnosis felt that other doctors thought less of doctors who have experienced depression or anxiety, and over half thought that doctors with a mental health history were less competent than doctors with no history of mental illness. [1] This endemic stigma within the medical profession affects not only the way we interact with colleagues who are experiencing mental health issues, but also our patients. It also acts a major barrier to help-seeking among students who worry not only about their self-image but also their future prospects and reputation.

What are the lessons to learn here? Firstly, and as the report recommends, a wider discussion needs to be held about doctors' mental health and wellbeing within the medical community. Education is the key to reducing stigma, and better education regarding the prevalence of mental health issues within the medical community and the importance of seeking help early is an excellent first step here. Why should seeking help for a mental health complaint be any different to seeking help for a physical illness, even for doctors? Vulnerability is after all part of what makes us human, and often makes us better doctors. Recognising our own vulnerability to mental health issues will enable us to better recognise our patients' difficulties and deal with them constructively. Normalising, rather than stigmatising, mental

illness is the first step towards parity in health care. With the lifetime prevalence of mental ill-health approaching 50%, [2] mental health issues, just like physical health problems are hard to avoid, are after all very 'normal' as a challenge to be faced, and will touch almost all of us at some point.

In concrete terms, what can we do to address the immediate issues? Firstly, training could also be provided regarding stress minimisation and positive coping strategies, from medical school on, and all doctors and medical students should be encouraged to have their own youth-friendly GP outside their workplace setting to minimise concerns over privacy and confidentiality, as well as self-prescribing. Secondly, issues related to workplace stress need to be addressed. This will involve reducing the workload expected of doctors, particularly junior staff who are still in training, and promoting a better work-life balance. Extra support and expert clinical care for those who are struggling, either through specific mental health services, supportive mentoring, and training in stress management, could also be provided. Thirdly, medical students themselves have shown great leadership in getting this issue on the agenda and should be heavily involved in a redesign of student health and mental health care on campuses around Australia. Tertiary students in general report significantly higher rates of mental ill-health than their age matched peers, [10] and hence the tertiary sector and government has a serious responsibility to provide health services that appeal to students and that recognise their needs, including their mental health care needs.

As Australia's doctors of the future, you have the opportunity to help move our health care system out of the past and into the present; firstly, by valuing your own mental wellbeing, and that of your colleagues. Recognising the importance of mental health to overall wellbeing is central to providing quality health care, and is a long overdue step that we need to take on the road to system reform.

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Medication-induced acute angle-closure glaucoma: a case study

Allister Howie

Final Year Medicine (Graduate)
University of Tasmania

Allister Howie is a final year medical student at the University of Tasmania. He is keenly interested in the eyes, previously completing medical electives at Moorfields' Eye Hospital in London, and at the National Eye Centre in Dili, Timor Leste.

Acute angle-closure glaucoma, is an uncommon condition. It is an emergency associated with the potential for significant vision loss and unilateral blindness if not diagnosed and treated promptly. This case describes a classic presentation of angle-closure glaucoma, highlighting the potential of certain medications to precipitate acute angle-closure glaucoma in at-risk individuals. Although the incidence is uncertain, it is thought that a significant number of cases may be medication-induced, and so it is important to be aware of what medications may precipitate acute angle-closure and have a plan for assessing and managing this small but real risk. In addition, patients should be warned of possible ocular symptoms and advised to seek urgent medical attention if they occur. In a presentation of acute angle-closure glaucoma, the key management is urgent reduction of intraocular pressure and ophthalmology referral.



Case

A 65-year-old female presented to her general practitioner with a painful, red left eye associated with blurred vision and nausea. She had commenced paroxetine for management of depression three weeks prior. On examination, best-corrected visual acuity was 6/19 in the left eye, 6/6 in the right. The left pupil was mid-dilated and fixed. Examination was otherwise normal. An urgent ophthalmology review was organised and a diagnosis of acute angle-closure glaucoma was made.

Though uncommon in Australia, acute angle-closure glaucoma (AACG) is a medical emergency that requires rapid diagnosis and reduction of intraocular pressure to prevent permanent vision loss. [1,2]

Discussion

Epidemiology

Glaucoma is the second leading cause of vision loss worldwide, with an estimated 79.6 million people to be affected in 2020. Though approximately 74% of cases worldwide are open-angle glaucoma, it is projected that 5.3 million people will be legally blind due to AACG in 2020, comparable to the 5.9 million estimated to be blind due to open-angle glaucoma. [2]

Pathogenesis

Overwhelmingly, the most common cause of angle closure crisis is pupillary block. Aqueous humour normally flows between the pupil and lens, from the posterior chamber to the angle of the anterior chamber of the eye, where it then drains across the trabecular meshwork. When the pathway between the lens and iris is blocked, aqueous accumulates behind the iris, pushing it anteriorly and blocking the trabecular meshwork, thus preventing aqueous drainage. [3] When this occurs, intraocular pressure (IOP) rapidly becomes elevated, frequently reaching pressures greater than 60 mmHg, rapidly causing glaucomatous optic neuropathy if untreated. [4] Eyes with pre-existing anatomic narrow angles are predisposed to acute angle-closure.

Medication-induced angle-closure

Medication-induced angle-closure has been reported to cause a significant proportion of AACG cases in developed countries. [5] Consequently, it is important to be aware of the risk when prescribing implicated medications. The underlying mechanism may be due to pupil dilatation (mydriasis) as a medication side effect, or due to

choroidal effusion, causing swelling of the ciliary body and forward movement of the lens and iris towards the chamber angle. [4,6]

Ophthalmic mydriatics are a well-known precipitant of angle-closure crisis, but other medications with mydriatic effects also carry risk. Importantly, this includes several classes of antidepressants: selective-serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants and serotonin–noradrenaline reuptake inhibitors. [7] Visual disturbance has frequently been a cause of SSRI withdrawal and it has been suggested that SSRI-induced intraocular pressure elevation may be underestimated. [8]

Any medication with sympathetic or anticholinergic effects has theoretical potential to precipitate angle-closure in at-risk eyes. Other drugs implicated include phenothiazine antipsychotics, antihistamines, benzhexol, over-the-counter medications containing phenylephrine, nebulised ipratropium bromide and salbutamol. [4,9]

Topiramate, an anticonvulsant commonly used to treat epilepsy and for migraine prophylaxis, has commonly been reported as a precipitant of AACG in the literature due to choroidal effusion. A report suggested topiramate may be the most common cause of AACG in individuals under the age of 40. [11] The risk is thought to be due to the sulfur component of the drug. Other sulfur-containing medications, including acetazolamide, have been reported as precipitants, though only rarely, so should therefore not be used to treat topiramate-induced angle-closure. [6,9,10]

Drug-induced acute angle-closure usually develops soon after initiation of treatment, and generally within 30 days. Whilst AACG classically presents with a unilateral red eye with pain and reduced vision, bilateral presentations may occur and are more common in medication-induced cases. If symptoms are consistent with angle-closure crisis, a high index of suspicion must be maintained. [11,12]

Clinical implications

Clinicians should be aware of medications associated with increased risk of angle-closure glaucoma, and consider and warn the patient of this small possibility when initiating these medications. [13] The risk of causing angle-closure when dilating pupils is very low (estimated 1 in 20 000) and mydriatics should always be used when performing a complete fundus examination. A good choice of medication to minimise risk is tropicamide 0.5%. [14]

It would be impractical for an ophthalmologist to review every patient

before prescribing many of the associated medications, however, a brief history of ocular symptoms should be taken and the risk profile of the patient stratified. [9]

Acute angle-closure risk factors include:

- Advanced age
- Asian ethnicity
- Severe hyperopia (beware of the patient wearing thick glasses)
- Known shallow anterior chamber, or occludable angle
- Family history of blindness suspicious for angle-closure glaucoma

The oblique flashlight test, a simple way to estimate anterior chamber depth, should be performed (Figure 1). A light is shined onto the temporal iris. If the anterior chamber is deep, the iris will be uniformly illuminated. Shadowing of the nasal iris indicates the anterior chamber may be shallow, increasing risk of anterior chamber angle occlusion. The test is only 45.5% specific, but is 82.7–91.7% sensitive and may be performed rapidly. [15,16] Patients should be warned of ocular symptoms and their significance at first prescription of implicated medications, particularly if identified to be at high risk. If at high risk, an ophthalmology referral should be considered to evaluate the degree of openness of the angle that is prone to angle-closure. [9,13] On review after initiating implicated medications, it is important to ask patients whether they have experienced any ocular symptoms. [17]

It is important to note that open-angle glaucoma is a separate condition and patients with this condition should not be denied medications associated with angle-closure glaucoma. [18]

Treating angle-closure glaucoma

Immediate treatment goals are rapid reduction of intraocular pressure and symptomatic relief. Intravenous mannitol 5–10 mL/kg of 20% solution, given over 30 minutes, will cause a rapid, temporary reduction in intraocular pressure. [19] Intravenous or oral acetazolamide may also be required. Topical medications, including timolol, prednisolone, and brimonidine, may be used. [10] A miotic, such as pilocarpine, is used to constrict the pupil. This will pull the peripheral iris away from the angle, thereby opening drainage through the trabecular meshwork. Antiemetics and analgesics should be given as needed, and the patient

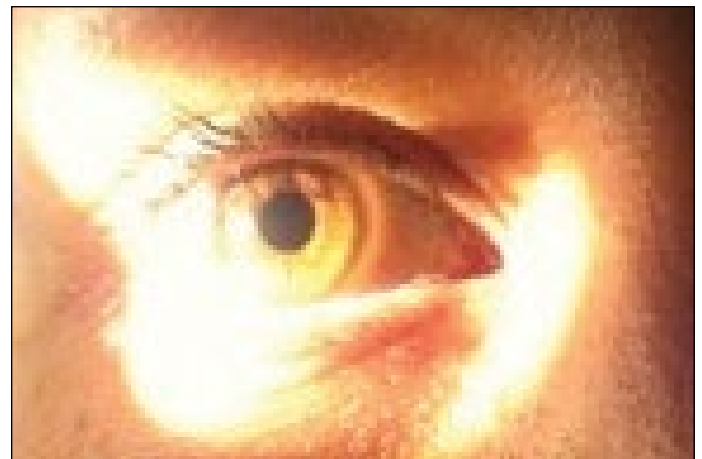


Figure 1. Oblique Flashlight Test. Uniform illumination of the iris indicates a deep anterior chamber. should be supine, in an attempt to prevent further anterior movement of the lens. Any medications possibly contributing should be ceased. [5,12]

Definitive treatment is laser iridotomy, performed by an ophthalmologist. An opening is made in the peripheral iris, allowing free flow of aqueous between posterior and anterior chambers, allowing equilibration of pressure between the chambers, thus preventing the occurrence of pupillary block. Both eyes are treated, even in unilateral presentations, as the fellow eye is likely to have the same narrowed angles, which increases the risk of angle-closure. [3,11]

Consent declaration

Informed consent was obtained from the patient for publication of this case report. Informed consent was obtained from individuals photographed for the purposes of this report.

Conflict of interest

None declared.

Correspondence

A Howie: ahowie@utas.edu.au

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Comparison study of two methods of identifying the adrenal glands on computed tomography

Timothy Yong Qun Leow

Third Year Medicine (Undergraduate)
University of Western Sydney

Timothy is a third year medical student at the University of Western Sydney. He is developing an interest in oncologic imaging, surgery, and medical education.

Dr. James Boon Kheng Khoo

MBBS, FRCR, FAMS
Head, Department of Oncologic Imaging
National Cancer Centre Singapore

Dr James Khoo is a senior consultant radiologist from the National Cancer Centre in Singapore. He is also Adjunct Associate Professor in the Duke-NUS Graduate School of Medicine and a member of the Specialist Training Committee for Diagnostic Radiology in Singapore.

Background: The adrenal glands (AG) are common sites for metastases in cancer patients. Identification of the AG on computed tomography (CT) is complicated by surrounding anatomical structures of similar radiological density, and may be difficult for non-radiologists. **Aim:** This study compared the accuracy of two landmarks commonly used to identify the AG on CT. **Methods:** 1,112 consecutive patients attending a comprehensive cancer centre received CT scans of their abdomen or chest over a one-month period. Scans were retrospectively analysed on a PACS workstation by a radiologist. The distance between the AG and two easily identifiable CT landmarks were measured. The landmarks included the upper pole of the kidneys (UP) and the coeliac axis (CA). **Results:** CT scans were analysed to find the distance (using axial slices) between the AG and the landmarks. When they occurred on the same slice, the distance was given a value of zero. The CA and the right AG occurred at the same level in 65% of patients, and the CA and the left AG in 88% of patients. For the right UP, the right AG was at the same level in 42% of patients; and the left UP, at the same level as the left AG in 58% ($p < 0.001$). The mean distance of the CA from the right and left AG was 4.45 ± 7.14 mm and 1.15 ± 3.59 mm respectively. The right and left UP were at a mean distance of 8.05 ± 9.42 mm and -4.30 ± 5.94 mm respectively from the AG. Paired t-test showed a significant correlational difference between the CA and UP as landmarks for the AG ($p < 0.0001$). **Conclusion:** This study showed that the CA was closer to the AG than the UP. The CA may provide an accurate landmark for identification of the AG on CT scans.



them more difficult to identify without a stable landmark. [9,18,19] Finally, a paucity of intra-abdominal fat can hinder identification of the AG. Generally, the right AG is easier to identify than the left AG owing to its different anatomy and surrounding structures. [20]

There is limited research available to compare the different methods for identifying the AG. [7,12] Known methods use different landmarks: most commonly the UP and possibly the coeliac axis (CA). [18,21] These landmarks are used to aid in the identification of the AG, and are especially useful for medical professionals not trained in cross-sectional radiography. [1,12] While the UP are frequently used landmarks, [18,21] the CA, a major branch of the abdominal aorta that gives rise to the hepatic and gastric arteries, is suggested to be an accurate landmark as it is present in most patients. [22,23] Although the hepatic and gastric branches move with respiration, the origin of the CA (which comes off the aorta) demonstrates minimal movement with respiration. It is currently unclear whether the CA is an accurate landmark for identification of the AG. Accordingly, we conducted a cross-sectional study with the aim of comparing the distances of the CA and UP from the AG on CT scans.

Methods

Patient Population

Consecutive patients ($n=1,112$) attending a comprehensive cancer centre over a one-month period underwent CT scans of their abdomen or chest as part of their routine medical management. CT images and clinical data were reviewed retrospectively in accordance with Institutional Review Board (IRB) and ethics approval. Patients were excluded if they had medical conditions that were thought to significantly alter the location of the AG ($n=75$). This included patients with surgery adjacent to the AG ($n=9$), splenomegaly ($n=1$), renal lesions ($n=27$), massive adrenal nodules ($n=7$) and massive adrenal metastases ($n=31$). Patients who had not received IV contrast ($n=74$) were not excluded from the study.

CT acquisition and analysis

Patients were scanned on a LightSpeed © 64-Slice VCT CT system, manufactured by GE Healthcare (Little Chalfont, Buckinghamshire, UK). Contiguous axial 0.6 mm slices were obtained and the images

Introduction

The adrenal glands (AG), locoregional lymph nodes, and the liver are common sites of metastases in cancer patients, with more than half of adult malignancies from renal cell carcinomas affecting the AG. [1-3] The majority of AG metastases are identified on computed tomography (CT) imaging. [1,4-8] Occasionally, one may encounter primary adrenal tumours such as adrenal adenomas and rarely, adrenal carcinomas. [3,6] It is important for clinicians to be able to accurately identify the AG in cancer patients to allow early identification and subsequent management of metastases. [9-12] As there are often delays in the time for CT scans to be assessed by a radiologist, early diagnosis of adrenal metastases by physicians may be of benefit in terms of earlier treatment and cost savings. [4,13] Furthermore, physicians who are able to quickly identify adrenal lesions on CT and provide detailed information to their patients in clinic may aid their patients in the understanding of their illness. This may potentially improve treatment outcomes, especially for patients with metastatic cancer. [13-16]

Identification of the AG on CT can be difficult for a number of reasons. Firstly, surrounding anatomical structures can complicate the diagnosis of adrenal lesions by superimposing upon the AG, or mimicking an adrenal mass (pseudotumour). [1-4,7] Secondly, the AG may cover the upper pole of the kidneys (UP) or be pressed up against the crus of the diaphragm. [17] Thirdly, the AG may move with respiration, making

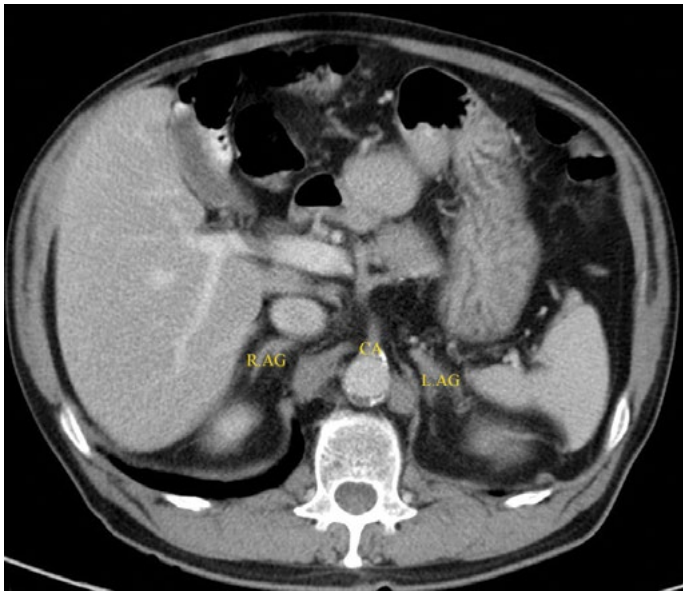


Figure 1.a. A CT scan reveals the coeliac axis (CA) on the same slice (and level) to the right (R.AG) and left adrenal gland (L.AG).

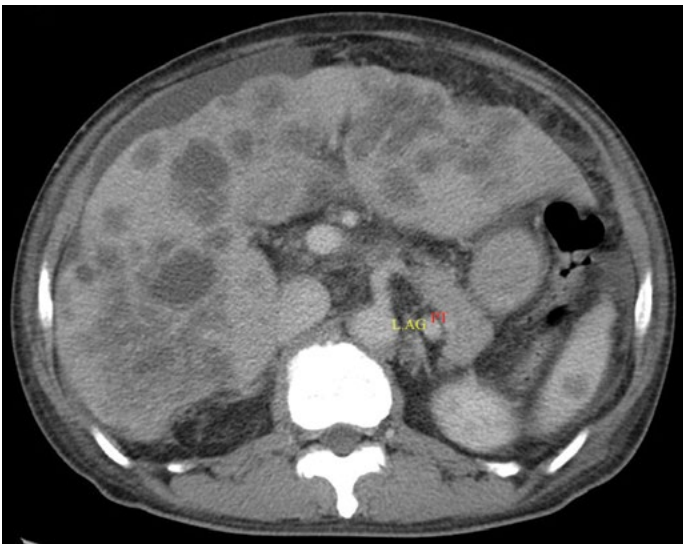


Figure 1.b. A CT scan that demonstrates the tail of the pancreas (PT) interfering with the left adrenal gland (L.AG) and the right adrenal gland is absent from the image.

were reconstructed at 5 mm intervals for viewing on a Carestream PACS v10.2 workstation (Carestream Health, Rochester, NY, USA). All images were reviewed by a radiologist with over 20 years of experience in cross-sectional imaging.

Two methods were studied to determine the more effective method of land marking and identifying the AG. The first and more commonly known method involved the identification of the UP, following it slice by slice superiorly until reaching the mid-level of the AG. The second method employed the CA, as the landmark (Figure 1.A). [22] For this study, the mid-level of the AG was identified, and its position was noted in relation to the upper margin of the respective UP and to the CA. Distances between the AG and landmarks were calculated by counting the number of axial slices between the structures and converting this to millimetres (craniocaudal distance). Each CT DICOM had a slice thickness of 5 mm (Table 1). A distance of 0 mm indicated that the landmark and AG were present on the same slice. Positive values indicated the AG were superior to the landmark and negative values indicated that the AG were inferior to the landmark.

Statistical analysis

Results were analysed using IBM SPSS® version 20 (Armonk, NY, USA). The distance between the AG and the defined landmarks were compared using paired t-tests. A p-value of <0.05 was considered to be statistically significant.

Results

In total there were 1,037 patients with a median age of 60 years (Inter-quartile range: 52-68 years) and male to female ratio of 527:510. Twelve (1.2%) of the patients in the study had non-massive adrenal lesions and 74 (7.1%) of the patients had not received IV contrast. The images without IV contrast were scrutinised in greater depth because it was more difficult to distinguish the CA on non-contrast CT, but it did not markedly affect the identification of normal AG. [12,21,24] The results below provide an overview of the relational distance between AG and landmarks, calculated by slice levels that were numbered and converted to millimetres (Table 1). Graphical representation of the mean distances of the AG to the landmarks are shown in Figure 2. Statistical assessment of differences between landmarks are shown in Table 2 and Figure 3.

	N=1037		Number of cases, level to landmark (n, %)*		Median, IQR (mm)	
	CA	UP	CA	UP	CA	UP
Right AG	668 (65%)	430 (42%)	0 [0,10]	5 [0,15]		
Left AG	906 (88%)	593 (58%)	0 [0,0]	0 [0,10]		
Both AG †	605 (58%)	242 (23%)	0	0		

Table 1. A comparison of the distance between the adrenal glands and their respective landmarks (coeliac axis and upper poles of the kidney). IQR, inter-quartile range; CA, coeliac axis; UP, upper pole; AG, adrenal gland.
* The number of cases in which the AG were on the same slice (0 mm, level=0) as the respective landmarks, with the valid percentage included.
† Both the right and left AG and their joint relationship with the landmarks, CA and UP.

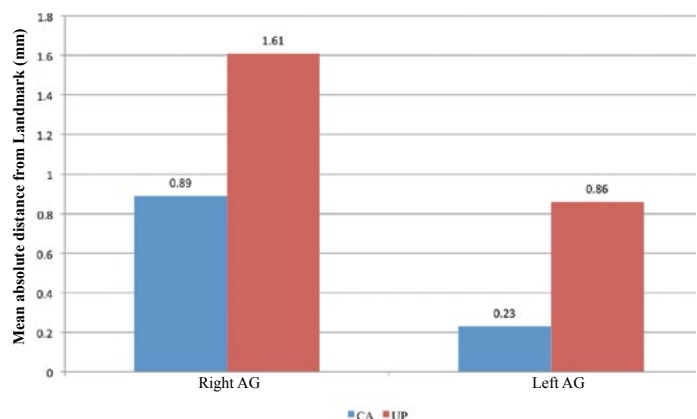


Figure 2. A comparison of the mean absolute distance of the adrenal glands from the respective landmarks. The AG to CA (blue), and AG to UP (red).

Pair 1 is the comparison of the mean distance between the right adrenal gland and its landmarks, the coeliac axis and the upper pole of the right kidney. Pair 2 is the comparison of the mean distance between the left adrenal gland and its landmarks, the coeliac axis and the upper pole of the left kidney. Differences are expressed as mean and standard deviation.

The CA and the right AG occurred at the same level in 65% of patients, and the CA and the left AG in 88% of patients. For the right UP, the right AG was at the same level in 42% of patients; and the left UP, at the same level as the left AG in 58% (p-value<0.001). The median distance for the CA to the right AG (0 mm) was less than the median distance between the right UP and right AG (5 mm). The left AG had the same

N=1037	Paired Differences (mean, std. deviation)	Pearson Correlation	p-value
Coeliac axis – Right upper pole of kidney	-0.72 ±2.46	-0.088	<0.0001
Coeliac axis – Left upper pole of kidney	-0.62 ±1.39	-0.006	<0.0001

Table 2. Paired *t*-tests samples show a significant decrease in distance within individual patients when using the coeliac axis as a landmark.

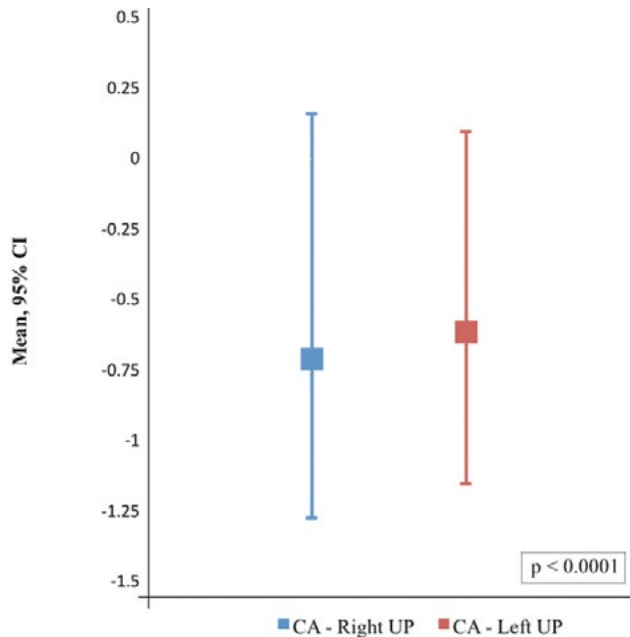


Figure 3. Paired *t*-test analysis demonstrates significant difference between coeliac axis and left and right adrenal glands. Distance reported as mean and 95% confidence interval.

median distance from the CA and the left UP (0 mm). The CA also had smaller interquartile ranges, 0–10 for the right AG and 0–0 for the left AG, compared to the UP with interquartile ranges, 0–15 for the right AG and 0–10 for the left AG. Pair 1 compared the right UP with the CA, and Pair 2 compared the left UP with the CA. Both Pair 1 (the distance of the right AG from the CA and right UP) and Pair 2 (the distance of the left AG from the CA and left UP) indicated that the CA distance to AG was closer to 0 mm than the UP distances to AG ($p < 0.0001$; Table 2).

Discussion

The main finding of this study was that the AG could be more accurately identified on CT images when the CA was used as the reference landmark as opposed to the conventional method of using the UP as a landmark. The distance between the AG and the CA was significantly shorter than the distance between the AG and the UP. Furthermore, the CA was more likely to be located on the same axial slice as the left and right AG than the UP. This study also showed that the CA was a less variable landmark than the UP, with smaller interquartile ranges. These findings support the belief that the CA does not move with respiration, providing one explanation why the CA appeared to be a more accurate landmark.

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Anatomical landmarks play an important role in medical imaging. Identifying a landmark proximal to the target organ can reduce distance-related errors that may occur when analysing CT images. [25] As Gunderman [26] said, "By far the most important role of imaging in the evaluation of the AG lies in the detection, characterization, and staging of adrenal tumours." There are a limited number of studies available that explore different methods of identifying the AG, however, many studies have been undertaken assessing other radiological landmarks in the body. [7,12,27-31] For a landmark to be accurate, it must include the following general characteristics: Firstly, having a close measurable distance relationship to the target structure (preferably less than 10 mm). Secondly, the stability of the landmark should allow clinicians to accurately estimate the location of the target structure, and avoid the over- or underestimation of the target structure's location from the landmark. [25,28-30] Thirdly, pattern approach CT imaging interpretation requires the more accurate landmark to be easily recognizable to the viewer. [28-32]

This study has several limitations. First, data was gathered from a sample of cancer patients, which is a subset of all patients that receive CT scans of the abdomen. Consequently, the results of this study may not be a true representation of the general population. Second, IV contrast was not administered to all 1,037 patients included and enhanced images may have allowed for easier identification of the CA. [12,21,24] Finally, CT images were analysed by an experienced academic radiologist. The findings may have been different had they been analysed by junior doctors or other non-radiologist physicians. This study could be improved by including a number of non-radiology clinicians as the primary readers. The data described here was from a cancer centre in Southeast Asia only. This study could be further improved with an international patient pool allowing comparison of different ethnic groups. Patients with massive renal and adrenal pathology, such as adrenal metastases, were excluded from the study. A larger study is required to investigate the impact of such pathology on the identification of AG on CT. Further research could be done to determine the possibility of reducing the time taken to identify and diagnose the status of the AG, when using the CA as a landmark. The technique of using the CA as a landmark may also be applied to the identification of primary or secondary carcinoma, and further study could aid with the locating and identification of abnormal AG.

Conclusion

The CA is an easily identifiable landmark that is closer to the adrenal gland than the UP. This landmark may be applied by clinicians to facilitate timely detection of the AG on CT scans.

Acknowledgements

Professor John Morley and Associate Professor Noel Young for their assistance in proof-reading the abstract. Eric Martin and Diane Premnath for their patience and kindness in reviewing the paper. Jeremiah Schmidt for his aid with the statistics. Michelle Ng, Sophie Kobuch, Chatwin Lee, Lisa Leow, Corinne Fulford, Simon Chow, and Karlene Zhu for their patience in proof-reading the paper.

Conflict of interest

None declared.

Correspondence

T Leow: yong.qun@gmail.com

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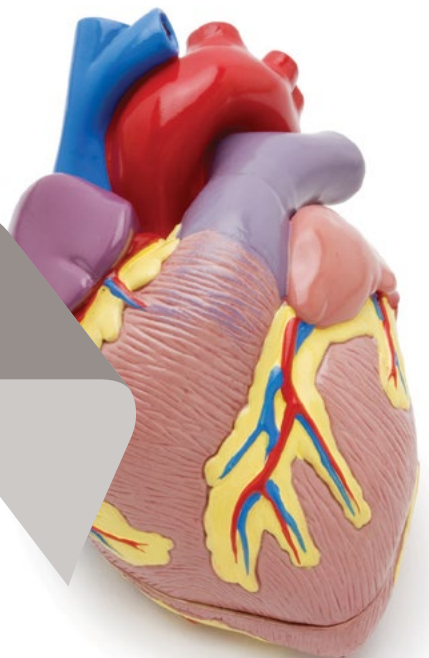
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Test-retest reliability of isometric hip muscle strength measured using handheld dynamometry: a pilot study

Thomas P. Denton

BPhty, BHSc (Hons)

Second Year Medicine (Postgraduate)

Deakin University

Thomas is a graduate physiotherapist. He completed his thesis in 2009 and continued his involvement in research in this field, co-supervising an honours student. He continues to practice physiotherapy and has a keen interest in general practice and sports medicine.

Mark A. Jones

BS (Psych), Cert Phty, Grad Dip Advan

Manip Ther, MAppSc (Manip Ther)

Program Director of postgraduate physiotherapy at the University of South Australia

Mark has been a member of the academic teaching staff at the School of Health Sciences at the University of South Australia for 25 years. He is currently the director of the post-graduate physiotherapy program. He edited the books 'Clinical Reasoning in the Health Professions' and 'Clinical Reasoning for Manual Therapists'. He has supervised numerous honours and PhD students.

Dr. Steven W. Saunders

PhD, BAppSc (Phty)

Director of Sports Science and Medical Services at North Melbourne Football Club

Steven has completed his PhD in lumbo-pelvic motor control. He has continued his role in research through his position at the North Melbourne Football Club, numerous university affiliations, and as supervisor of numerous honours and PhD students.

Introduction: Hip muscle weakness has been shown to be associated with lower limb pain and (re)injury. A reliable means of assessing hip muscle strength is required to assist sports physicians, orthopaedic surgeons, and physiotherapists in assessing injury risk and applying preventative measures such as appropriately prescribed and monitored exercise intervention. This study aimed to determine the relative and absolute test-retest reliability of a testing procedure assessing the isometric strength of hip flexors, extensors, abductors, adductors, internal rotators, and external rotators using handheld dynamometry. **Methods:** 10 healthy subjects with an average age of 25.5 years (\pm SD 6.0 years) had the isometric strength of their six hip muscle groups measured by one tester using a handheld dynamometer. Subjects were tested on two separate occasions with an average interval of 5.7 days. Intra-class correlation coefficients (ICC) and the standard error of measurement (SEM) were used as measures of relative and absolute reliability respectively. **Results:** All six hip muscle groups demonstrated 'excellent' test-retest relative reliability (ICC 0.86–0.97). Absolute reliability ranged from 3.3–7% and 0.03–0.13 Nm/kg as a measure of unit strength. **Discussion:** This protocol demonstrates excellent test-retest reliability for analysis of the isometric strength of all six hip muscle groups using a handheld dynamometer. This protocol serves as an important reference for clinical assessment of hip muscle function.



testing experiences. A more quantitatively accurate measure of muscle strength can be obtained using dynamometry. Dynamometry measures the force produced on a maximum voluntary contraction and in contrast to MMT it provides an objective unit measure of strength. Many laboratory dynamometry stations used previously [11,12] have poor clinical utility as they are expensive and lack easy portability. In contrast, handheld dynamometry is an inexpensive and portable means of measuring strength amenable to clinical use.

Reliability is also an important component of clinical utility. Relative and absolute reliability have been identified as two distinct measures. [13] Relative reliability assesses the level of agreement between values. [14] It provides information about the association between test-retest data but not the proximity of the values. [13] Absolute reliability measures the variability between test-retest data, with less variability representing greater reliability. [13] A number of studies have assessed the reliability of handheld dynamometry on hip muscle strength testing. [7,15–20] A small number have established reliability using a handheld device for all six hip muscle groups. [2,21,22] These studies have included strength testing positions where the tester is required to stabilise the subject or hold the non-test limb during testing, leaving only one arm available to counteract the force produced by the hip muscles. Given the magnitude of force produced by the hip muscles [18] and that reliability is affected by the tester's ability to apply sufficient counteracting force, [23] it is important that for a reliable strength testing procedure, positions are chosen to facilitate stability for not only the subject but also the tester.

There is no single, universally accepted testing protocol for all six hip muscle groups. Previous investigations have included testing positions that have required the tester to stabilise the subject. More stable

Introduction

Adequate hip muscle strength is required to control the alignment of the lower limb and therefore limit exposure of distal structures to potentially damaging forces. [1] Deficits in hip muscle strength have demonstrated an association with pain and (re)injury in the hip, [2,3] knee, [4,5] and ankle. [6] Consistent with these observations, strengthening of hip muscles through exercise interventions has been shown to reduce lower limb pain and injury, [7,8] improve lower limb landing alignment, and minimise potentially injurious positions. [9] Given this well established link between hip muscle strength impairment, pain, and (re)injury; a reliable, clinically applicable means of measuring hip muscle function is necessary to assist clinicians in the development and monitoring of interventions aimed at minimising pain and (re)injury, and improving patient function.

In the clinical setting, strength is conventionally assessed using manual muscle testing (MMT). MMT provides only a rated score (ranging from zero to five) of strength [10] and relies on clinical judgement of strength relative to the contralateral limb and/or previous strength

testing positions are required to account for the magnitude of force produced by the hip musculature. The purpose of this pilot study was to therefore assist in establishing the test-retest relative and absolute reliability of a strength testing protocol for hip flexion, extension, abduction, adduction, internal rotation, and external rotation using handheld dynamometry.

Methods

Subjects

Approval for this study was obtained through the University of South Australia Human Research Ethics Committee. Five healthy male and five healthy female subjects were recruited via a convenience sample through an Adelaide Physiotherapy and Sports Medicine clinic. The means and standard deviations of height ($1.72\text{m} \pm 0.09\text{m}$), mass ($71.7 \pm 9.9\text{kg}$), and age (25.5 ± 6.0 years) were established. Subjects were included if they had no history of pain or clicking/clunking sensations from either hip joint. Subjects were excluded if they reported pain during the strength assessment period that would limit the production of a maximum voluntary contraction. Furthermore, to limit error in the measures that may be due to strength gains from exercise training, subjects were excluded if they were participating in regular lower limb strengthening exercises. Strength was assessed by the same tester on two separate occasions with an average test-retest interval of 5.7 days (range 5–7 days). All subjects were graded as performing at a 'sufficient' level of physical activity measured using the Active Australia Survey. [24]

Strength Assessment

Strength of the six hip muscle groups was measured using a Nicholas handheld dynamometer (HHD) (Lafayette Instruments, Lafayette, IN, USA). Strength data was recorded in kilograms (kg) and then converted to torque values with the force in Newtons (N) (where $1\text{kg} = 9.81\text{N}$) multiplied by the action length in metres (m), giving a unit of Newton-metres (Nm). The action length is the perpendicular distance from the axis of rotation to the line of force (i.e. the placement point of the dynamometer). The action length for flexion, extension, abduction, and adduction was measured as the distance from the greater trochanter of the femur to the lateral femoral epicondyle, and for rotation from the lateral femoral condyle to the base of the lateral malleolus. Each action length was recorded as the average of two measures for each measured action length based on the protocol for measuring limb length validated by Beattie and colleagues. [25] To account for the confounding effect of body size on strength, [26] data was normalised to body mass, which was measured in kilograms (kg) using the same scales (Hanson, Croissy-sur-Seine, France) for each subject.

Subjects were tested on the same height adjustable plinth. Strength was assessed using the 'make' test where the subject's isometric muscle action is matched by the tester. [17] To ensure the dynamometer force plate was maintained in a perpendicular position relative to the test limb, the tester's arm was positioned with elbows locked in extension. Pillows were used as required to achieve and maintain subject positions with the hip joint in a neutral orientation in reference to adduction, abduction, internal rotation, and external rotation for all positions (Figure 1). Participants were given instructions including a description and passive demonstration of the action required, the movements to avoid, and the instruction to "push as hard as you can". They were asked to give one sub-maximal contraction of 50 percent effort, followed by three tests of maximal effort (consistent with previous methodologies used [15]) separated by a 5 second rest. Tests were initiated and ceased with a single beep and not the tester's verbal commands. Given that isometric muscle strength has been shown to be influenced by motivational states, [27] this method was employed to limit the tester's influence over the subject's performance through varying volume or verbal inflections that can differentially affect subject effort. Therefore no encouragement was offered during tests. The strongest of the tests was recorded. If the last test produced the strongest result the subject was retested to ensure improvements in strength were

not a result of habituation and the subject's best effort or maximum had been achieved. Subjects were retested if they reported failure to achieve maximum effort, or if stabilisation of the device and/or subject during testing was inadequate. The dynamometer limited tests to five seconds, to allow enough time for the generation of maximum tension. [17] The maximum force produced within the five second test period was recorded by the dynamometer. Because several muscles within the hip contribute to more than one hip joint movement, the order of strength assessment was randomised between participants. The tester was blind to strength data from the first test session until retest data was gathered.

Subject Positioning

Hip flexion was measured in sitting, with the hip and knee flexed to 90° (Figure 1a). The plinth height was standardised for each subject as the height of two fingers between the plantar-flexed foot and the floor, hence feet were not in contact with the ground, eliminating compensation by calf muscles. For the remaining muscle groups the plinth was adjusted to be as low as possible. The HHD was positioned on the surface of the skin immediately proximal to the superior pole of the patella (as shown previously [15]). Hip extension was measured in prone with the hips in neutral (Figure 1b) and legs supported by a foam wedge. The dynamometer was placed on the surface of the skin of the posterior thigh two centimetres proximal to the femoral epicondyles. [21,28] Participants were instructed to lift their thigh from the table without bending or straightening their knees, or pushing their shin into the foam wedge. Hip abduction and adduction were measured in side lying (Figure 1c, d). The subject was instructed to lift their test limb into the air while keeping their pelvis and knees straight and not to rotate their thigh in or out. The dynamometer was placed immediately superior to the lateral (abduction) and medial (adduction) femoral epicondyles. [21] Internal rotation and external rotation were assessed in side lying with the subject instructed to rotate their thigh by lifting the ankle of their test limb into the air (Figure 1e, f). The dynamometer was placed two centimetres proximal to the lateral (internal rotation) and medial (external rotation) malleoli. [21]

Data Analysis

Histograms and values of skewness demonstrated all data to be distributed normally. Bland-Altman plots were used to determine if there was a relationship between magnitude and measurement error (heteroscedasticity) present within the data. [29] Paired t-tests were used to determine the presence of systematic bias. [29] A probability level of 5% ($p < 0.05$) was assumed to be significant. Relative reliability was established via intra-class correlation coefficients (model 2,1) (ICC) and were interpreted as excellent (> 0.75), fair to good (0.40 to 0.75), or poor (< 0.40) according to classifications by Shrout and Fleiss. [30] Absolute reliability was assessed using the standard error of measurement (SEM) and was calculated by the equation: $[\text{SEM} = \text{SD} \times \sqrt{1 - \text{ICC}}]$, where SD is the standard deviation of the strength data from all subjects for each muscle group. [14] The SEM was presented as a unit of strength (Nm/kg) and as a percentage of the average of test and retest means of each muscle group as per previous methods. [22] A threshold beyond which a true change in strength is said to have occurred was determined for each muscle group. This is termed the minimum detectable change (MDC) and was calculated by multiplying the SEM by the square root of 2 (to account for error associated with repeated measures) and the z-score of 1.64 to establish a 90% confidence interval. [16] This confidence interval was dictated by the sample size. All data was analysed using SPSS for Windows 17.0 (SPSS, SPSS Inc., Chicago, IL, USA).

Results

Paired t-tests showed no differences ($p > 0.05$) between repeated measures for all muscle groups. Bland-Altman plots showed no heteroscedasticity present within the data. ICC values, as a measure of relative reliability, ranged from 0.86 – 0.97 (Table 1), which is classified as 'excellent' reliability by Shrout and Fleiss. [30] The lower



(a)



(b)



(c)



(d)



(e)



(f)

Figure 1. Subject positioning for strength testing of (a) flexion, (b) extension, (c) abduction, (d) adduction, (e) internal rotation, (f) external rotation.

boundary of the 95% confidence interval fell below this classification for hip flexion only (Table 1). As a measure of absolute reliability, the SEM represented as a unit of strength ranged from 0.03 Nm/kg to 0.13 Nm/kg and as a percentage from 3.3% to 7% (Table 1). MDC data ranged from 0.070 Nm/kg to 0.302 Nm/kg (Table 1) and represented the minimum change required in subsequent testing to reason with 90% confidence that a true change in strength has occurred and that differences are not a result of measurement error.

Discussion

This study contributes to the establishment of a reliable isometric strength testing protocol for hip flexion, extension, abduction, adduction, internal rotation, and external rotation using handheld dynamometry. This protocol serves as an important reference for clinical assessment of hip muscle function. Both relative and absolute test-retest reliability were assessed, giving insight into both the level of agreement and variability between repeated measures. Overall,

findings were consistent with analysis of the present study's raw force data, indicating that the measurement of action length and body mass did not affect reliability. Relative reliability was examined using intra-class correlation coefficients. This method differs from previous studies, which calculated the level of agreement via Pearson's correlation coefficient, [2,21] a measure designed to assess the relationship between two variables rather than the same variable tested twice. [31]'Excellent' relative reliability [30] was demonstrated for the strength testing procedure for all six hip muscle groups (Table 1). This classification is comparable with analyses of the less clinically applicable 'gold standard' [32] laboratory dynamometry stations [11,28] and hand-held dynamometry investigations that assessed reliability from data gathered in the same test session, [21] where reliability may be overstated because the variable of subject setup is not tested twice. The use of two test occasions may leave the present study more exposed to systematic error. However, the absence of such error is supported by paired t-tests ($p > 0.05$) and normally distributed

Hip Motion	Mean test \pm SD	Mean retest \pm SD	Paired t-test	ICC (95% CI)	SEM (Nm/kg)	SEM (%)	MDC (Nm/kg)
Flexion	2.36 \pm 0.37	2.39 \pm 0.35	0.601	0.86 (0.53 – 0.96)	0.13	5.4	0.302
Extension	2.06 \pm 0.56	2.03 \pm 0.52	0.360	0.97 (0.88 – 0.99)	0.09	4.3	0.209
Abduction	1.92 \pm 0.42	1.95 \pm 0.38	0.520	0.97 (0.88 – 0.99)	0.07	3.3	0.162
Adduction	1.59 \pm 0.48	1.52 \pm 0.46	0.233	0.94 (0.79 – 0.99)	0.11	7.0	0.255
Internal Rot.	1.14 \pm 0.33	1.15 \pm 0.29	0.690	0.94 (0.78 – 0.99)	0.08	6.5	0.186
External Rot.	0.72 \pm 0.15	0.74 \pm 0.14	0.245	0.94 (0.77 – 0.98)	0.03	4.0	0.070

Table 1. The test and retest strength (Nm/kg) means and their standard deviations. Paired t-tests showed no difference between these means ($p > 0.05$). Also shown are the intra-class correlation coefficients (model 2,1) (ICC) and their 95% confidence intervals, the standard error of measurements (SEM) as units of strength (Nm/kg) and as a percentage of the average of test and retest means, and the minimum detectable change (MDC) (Nm/kg).

data. Absolute reliability was examined using the SEM. During repeated measures, some variability will be observed even if there is no reason to suspect a change in strength parameters. Given the SEM assumes an absence of heteroscedasticity, Bland-Altman plots were necessary as ratio data, such as that of the present study, is susceptible to an increase in measurement error as the measured value increases. [29]

The adductors had the largest SEM (7%); however, their ICC value indicated good agreement (0.94). The standard deviation observed in test and retest adduction means is consistent with heterogeneity that, where present, will inflate the ICC value. [13] The level of error demonstrated here by the SEM may be explained by the sensitivity of the area of the thigh where the HHD was placed. For subjects who consequently reported discomfort a hand towel was placed under the HHD to allow a maximum voluntary contraction. Nonetheless, this level of error is still comparable with previous investigations (7.8%) assessing hip adduction in this position, but with the HHD placed at the ankle. [22]

The hip flexors demonstrated the lowest ICC (0.86). Although these findings are in contrast to previous analyses of laboratory dynamometry (0.70–0.71), [11] the lower boundary of the ICC confidence interval (0.53) in the present study must be considered in the interpretation of this value. Given that the ability to counteract the force produced by the subject affects reliability, [18] it follows that the hip flexors, which generated the greatest torque, also demonstrated the lowest ICC. Furthermore, to prevent the subject from ‘cheating’ by the use of their calf muscles (see Methods), the plinth height was raised. As a result, the tester’s ability to position their upper body to provide sufficient counteracting force may have been compromised. As abduction and extension were tested with the plinth set as low as possible, this rationale is consistent with these muscle groups producing the next highest mean torque values, but also demonstrating the highest ICC (0.97). This ICC value is inconsistent with that demonstrated for abduction previously, [22] where the side-lying position was also adopted (ICC 0.74). Here the authors used one hand to hold the dynamometer and the other to stabilise the pelvis. While this aims to maximise subject stability, it may compromise the tester’s ability to counteract the force produced. Force being a vector, it has components of magnitude and direction. Changes in orientation of the HHD relative to the line of force of the hip motion may influence force transmission to the HHD (Figure 2). Using only one arm to hold the dynamometer may be insufficient to properly counteract both the magnitude and the direction of the force produced. Given that controlling for both these components of force is influenced by the tester, the present study chose positions that maximise not only the stability of the subject, but also that of the tester. These positions sought to permit the tester to position themselves and the HHD above and in line with the line of action of the test limb and were not dependent on the tester to stabilise the subject. Internal rotation and external rotation positions

were hence also dictated by this notion with both demonstrating relative and absolute reliability comparable with previous findings supporting their use as a potential alternative to the more commonly utilised sitting position. [5,15,16,21,22]

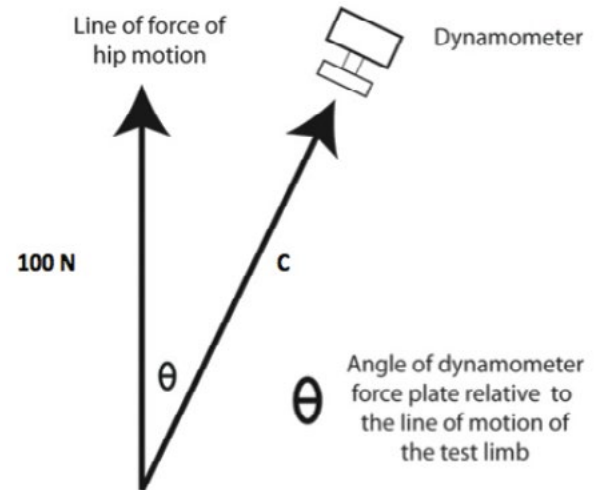


Figure 2. The effects of changes in the angle of the dynamometer force plate relative to the line of motion of the test limb on force recorded during strength testing. Here the dynamometer is no longer in line with the line of force of the hip motion, (i.e. the angle has increased from 0°). If θ is equal to 30°, and a subject produces 100 Newtons (N), then 116.3 Newtons will be transmitted to the dynamometer ($C = 100 \text{ Newtons} / \cosine 30^\circ$).

Although this study demonstrates excellent test-retest reliability, the limitations must be acknowledged. The nature of this investigation as a pilot study dictated the sample size and while the reliability established is comparable with previous studies of larger samples (e.g. Pua *et al.* [16]), further analysis may be needed to investigate the lower boundary of the confidence interval of the flexion ICC. Secondly, the MDC data offer clinicians guidelines as to when ‘real’ changes in strength have occurred which will assist in interpreting and monitoring data before and after intervention. However, given this study did not assess reliability between multiple testers, MDC data is based on the assumption that the clinician uses the dynamometer reliably and they therefore have sufficient strength to match those being tested, as is assumed to be the case in the present study given the findings. Finally, the action length will not have fully represented the length from the centre of the axis of rotation. However because of the deep location of the hip joint, the greater trochanter was reasoned to be a more reliable landmark to measure from.

Conclusion

The present study’s protocol demonstrates excellent test-retest reliability, hence supporting its use as a measure of hip muscle

function. Application of this measure can assist clinicians such as sports physicians, orthopaedic surgeons, and physiotherapists with clinical examination of injuries associated with hip muscle function, exercise prescription, and the monitoring of strength changes associated with intervention. Furthermore, this protocol offers a reliable means of measuring strength deficits and therefore injury risk as well as a reliable means of measuring performance at a strength-based level in sports where hip muscle function is important.

Future Directions

This study has established a reliable strength testing protocol for the assessment of strength of all six hip muscle groups. In contrast to

previous methods, the protocol offers positions, which aim to maximise subject stability to allow the tester to counteract both the magnitude and direction of force produced by the hip musculature.

Acknowledgements

The authors wish to acknowledge Saunders Sports and Spinal for the use of their facilities for subject testing.

Conflict of interest

None declared.

Correspondence

T Denton: tpdenton@gmail.com

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In vivo anatomical and functional identification of V5/MT using high-resolution MRI: A technique for relating structure and function in human cerebral cortex

Dr. Stephanie Barnes

University of Sydney
MBBS (Hons), BSc (Adv)

Stephanie is a recent graduate with an interest in neurology and neuroimaging. She completed this research as part of her honours degree.

Prof. Gary Egan

Monash Biomedical Imaging &
School of Psychological Sciences,
Monash University

Gary is an NHMRC Principal Research Fellow and the Professor and Director of Monash Biomedical Imaging.

Prof. John Watson

Sydney Adventist Hospital
University of Sydney

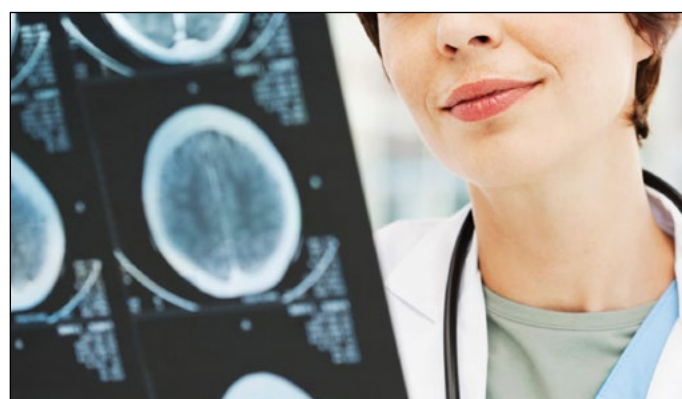
John is a consultant neurologist, Professor of Medicine and Associate Dean of the Sydney Medical School Clinical School at the Sydney Adventist Hospital.

Previous *in vivo* neuroimaging studies have clearly demonstrated the functional specialisation of the human cerebral cortex. However, precise anatomical localisation of functionally defined cortical areas is an ongoing challenge due to the poor spatial resolution of functional imaging techniques and significant inter-individual differences in the complex morphological structure of the human cortex. This study used high-resolution magnetic resonance imaging (MRI) to identify V5/MT in three subjects based on its distinctive magnetic resonance (MR)-visible myeloarchitectonic structure. Consistent with previous studies, V5/MT was localised to the junction of the ascending limb of the inferior temporal sulcus and the lateral occipital sulcus. This anatomically defined location of V5/MT was shown to correspond with its functionally defined location, identified using functional MRI in one subject. Structural MR images with high spatial resolution were acquired in this study by combining increased MR field strength, a multi-channel phased-array head coil for image acquisition and signal averaging across a series of T1-weighted images. This study confirmed that MR contrast can be used to resolve intracortical lamination known to be present on a histological level, enabling cortical substructure to be visualised *in vivo*. It provided proof of concept in a single human subject; therefore, further validation of this novel technique for identification of V5/MT and other functionally defined cortical areas is required. Application of this methodology in its own right, or integrated with other MR-based neuroanatomical mapping techniques, will facilitate structure-function correlation throughout the neocortex in living human subjects.

Functional specialisation of the human cerebral cortex has been demonstrated *in vivo* using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). [1] Current research is aimed at precise anatomical localisation of functionally defined areas. However, accurate localisation of active regions is an ongoing challenge given the poor spatial resolution of functional imaging and inter-individual variability in the complex morphological structure of the cerebral cortex. [2,3] Consequently, location of cortical areas must be examined within an individual to obtain precise structure-function information.

Various techniques have been developed to indirectly correlate structure and function in the cerebral cortex. Post-mortem human brain analysis, following functional imaging, would be ideal for precise anatomical localisation of functional regions within an individual; however, this is not readily available. Consequently, novel techniques were required to enable structure-function correlation in living humans.

Early research relied on presumed homology between human and non-human primate brains. Unfortunately, comparative variations



in brain size, complexity, orientation and potential rearrangement of cortical areas between species makes comparison of functional anatomy difficult. [4]

Brain atlases developed using traditional histological techniques to provide standardised coordinates for neuroanatomical landmarks have also been widely used. However, significant inter-individual variation in brain topography limits their usefulness in precisely identifying functional regions. For example, Talairach and Tournoux's [5] atlas is based on one brain's structure, over which Brodmann's [6] cytoarchitectonic map was projected. Given that functionally defined areas can vary in location by centimetres, such an atlas can provide only gross localisation. Additionally, Brodmann's two-dimensional map contained no data about the intrasulcal surface, two-thirds of the cortical surface, so we can only estimate these borders. [7,8]

Humans who have had a stroke, tumour, or traumatic brain injury also provide localisation information. Correlation of lesion location and subsequent neurological deficits provides information about the damaged region's role. However, this technique's usefulness is limited because (1) lesions are often extensive, so accurately locating the area responsible for the missing function is difficult and (2) rarely is only a single function lost, because lesions tend to incorporate areas performing a range of roles. [9]

Recent studies have revealed a successful new method of achieving precise anatomical localisation of functionally identified areas. Co-registration of structural MR with functional images from the same individual enables functionally defined regions to be mapped onto the specific morphological structure of each subject. [10-13] This approach to structure-function correlation relies on distinct anatomical features, in particular MR-visible cortical myeloarchitecture, e.g. the densely myelinated stria of Gennari, which demarcates the primary visual cortex. [14,15] These techniques were used here to identify the visual motion area, V5/MT.

V5/MT is readily identifiable histologically because of its characteristic myelination. Clarke and Miklosy [16] first identified putative V5/MT in post-mortem brains at the occipito-temporal junction featuring distinctive myelination. These MR-visible myelin bands in layers I, IV and V (the latter two, the external and internal bands of Baillarger) and radial fibres crossing layers VI to IV help anatomically localise putative V5/MT at the junction of the ascending limb of the inferior temporal sulcus (ALITS) and lateral occipital sulcus (LOS) in the parieto-temporo-occipital cortex. [11,13] This is largely consistent with functional results, showing that this functionally defined area also has anatomical identifiers.

V5/MT has been studied in non-human and human primates. Its location and role in non-human primates is similar, although not identical, to humans, [17,18] as expected given the limitations of such studies, discussed above. Research in brain-damaged humans also supports V5/MT's role in visual motion detection [19-22]; however, lack of imaging or post-mortem analysis has prevented accurate lesion localisation. Even using transcranial magnetic stimulation to mimic deficits experimentally [23,24] is limited by the extensive area such lesions encompass, likely responsible for a range of functions. Thus, structure-function correlation based on MR imaging in healthy humans represents significant progress in the field.

Recent studies have produced a robust, non-invasive method of identifying functionally defined cortical areas in living humans. [e.g. 11] However, acquiring MR images with sufficient spatial resolution to precisely characterise underlying microarchitecture is an ongoing challenge. Our approach focused on improving resolution by applying advanced technology and analysis now available.

Precise anatomical localisation of functionally defined cortical areas relies on correlation of functional and structural images. Visualisation of cortical lamination requires a minimum MR resolution of 200-300 μ m, since the thickest myelin band is 250 μ m thick. [9] Standard T1-weighted images are generally acquired at 1-1.5mm³ resolution – it would take several hours to acquire a single T1-weighted image of 200-300 μ m³ with equivalent signal intensity and signal-to-noise ratio (SNR). It is clearly unfeasible to expect subjects to remain stationary within the scanner for this time.

Several ways of increasing spatial resolution of T1-weighted images without relying on long scan times were used here. Firstly, the scanner's magnetic field strength was increased from 1.5 to 3 Tesla (T), nearly doubling available signal, producing a corresponding SNR improvement, [25] thus enhancing resolution. Secondly, a multi-channel phased-array head coil was used for image acquisition, increasing SNR using radiofrequency coils and combining multiple coils with individual receiver channels into an array covering the same volume as a larger coil with slight sensitive volume overlap. This produced a signal of equivalent amplitude but greatly reduced noise. [26] This improvement in SNR is particularly evident in surface regions, [27] such as V5/MT. Thirdly, averaging signal across a series of T1-weighted images significantly reduced noise, improving SNR and enhancing visibility of fine architectonic detail, [27] a technique validated by Walters *et al.* [11] Additionally, voxel oversampling during averaging due to jitter from small inter-scan head movements increased signal and reduced partial volume error of single scans, improving neuroanatomical detail. [28]

The current study thus applied a well-established methodology of non-invasive *in vivo* structural identification of functionally defined cortical areas developed by Walters *et al.* [11] to the precise anatomical localisation of V5/MT. We aimed to (1) validate this technique and (2) use technological advances to enhance MR images and to improve microarchitecture detection. It was hypothesised that this would produce improved spatial resolution of structural MR images, enhancing visualisation of cortical lamination within V5/MT.

Methods

Experiment 1: Identification of cortical microarchitecture using high-resolution MRI

Subject recruitment

Ethical approval was obtained. Three healthy male subjects (mean age 52) participated with informed consent.

Structural MRI

Twelve to sixteen high-resolution T1-weighted part brain images and three to four whole brain images were acquired over several sessions on a Siemens Trio 3T scanner using a 32-channel phased-array head coil (Siemens AG, Germany). Part brain parameters: three-dimensional magnetisation prepared rapid gradient echo (3D MP-RAGE) sequence: slices = 144; thickness = 0.75mm; field of view (FOV) = 220mm; in-plane resolution = 0.5x0.5mm²; echo time (T_e) = 3.41ms; repeat time (T_R) = 1800ms; inversion time (T_i) = 900ms; flip angle (FA) = 9°; number of excitations (NEX) = 1. Whole brain parameters: 3D MP-RAGE sequence: slices = 256; thickness = 0.60 mm; FOV = 265 mm; in-plane resolution = 0.6x0.6mm²; T_e = 2.81ms; T_R = 1900ms; T_i = 900ms; FA = 9°; NEX = 1. Raw images were transferred via a DICOM client program (Digital Jacket, Hewlett-Packard, CA), composed into contiguous volumes, and saved in Analyze (Radiological) format (Biomedical Imaging Resource, Mayo Foundation, MN).

Data analysis

Images were analysed using tools from Oxford Centre for fMRI of the Brain (FMRIB) Software library [29,30] and MRICro. [31] T1-weighted images were cropped at rostral spinal cord using MRICro and automatically segmented to remove non-brain tissue using the FMRIB Brain Extraction Tool (BET). [32] Each image was resampled at half the acquired voxel dimensions, producing volumes with voxel dimensions of 0.25x0.38x0.25mm³ for part and 0.30x0.30x0.30mm³ for whole brain images.

One part brain with minimal motion artefact was made the template for each scanning session. All images obtained in that session were registered to the template using a rigid body model with six degrees of freedom with the FMRIB Linear Image Registration Tool (FLIRT). [33] Template images for each session were then registered to the template for session one. Transformation matrices were concatenated and applied to each image. Transformed images were averaged using fslmaths, [29] producing a mean high-resolution image.

A single whole brain T1-weighted image was acquired in each scanning session. Each of these images was registered to that acquired in session one. Transformation matrices were applied to each and transformed images averaged using fslmaths, [29] producing a mean high-resolution image. SNR was calculated prior to and following image co-registration, with regional intensity measured using ImageJ version 1.45 [34].

V5/MT's site was estimated based on its postulated location at the ALITS and LOS intersection. Slices through this region were identified and two-dimensional cortical lamination analysis conducted. Intensity line profiles were manually generated using ImageJ version 1.45. [34] The number, intensity and relative location of each stationary point or point of inflection between cortical surface and grey-white matter boundary were calculated. These measurements were used to generate a cortical lamination map and enabled comparison of lamination between subjects.

Experiment 2: In vivo structural identification of V5/MT using high-resolution MRI

Subject recruitment

Subject 2 was previously involved in Walters *et al.* [11]

fMRI

fMR data for subject 2 was obtained from Walters *et al.* [11] Images were acquired on a 1.5T scanner (Signa Echospeed, General Electric). Subjects observed a moving checkerboard stimulus. [13] Further details available in Walters *et al.* [11]

Data analysis

Functional analysis was carried out by Walters *et al.* [11] using FLIRT [33] and SPM99. [35,36] High-resolution T1-weighted anatomical image obtained from subject 2 was aligned with the average greyscale-normalised surface coil T1-weighted image acquired by Walters *et al.* [11] The functional activation map was overlaid and used to identify functionally defined V5/MT for comparison with the location of anatomically defined putative V5/MT from Experiment 1.

Results

Experiment 1: Identification of cortical microarchitecture using high-resolution MRI

Figure 1 shows three T1-weighted MR slices from subject 2. Figure 1(i) shows the raw T1-weighted MR image, prior to de-skulling. The second panel (Fig 1(ii)) is from a single T1-weighted MR image; the third panel (Figure 1(iii)) shows the effect of co-registering multiple T1-weighted MR images within and across scanning sessions. The

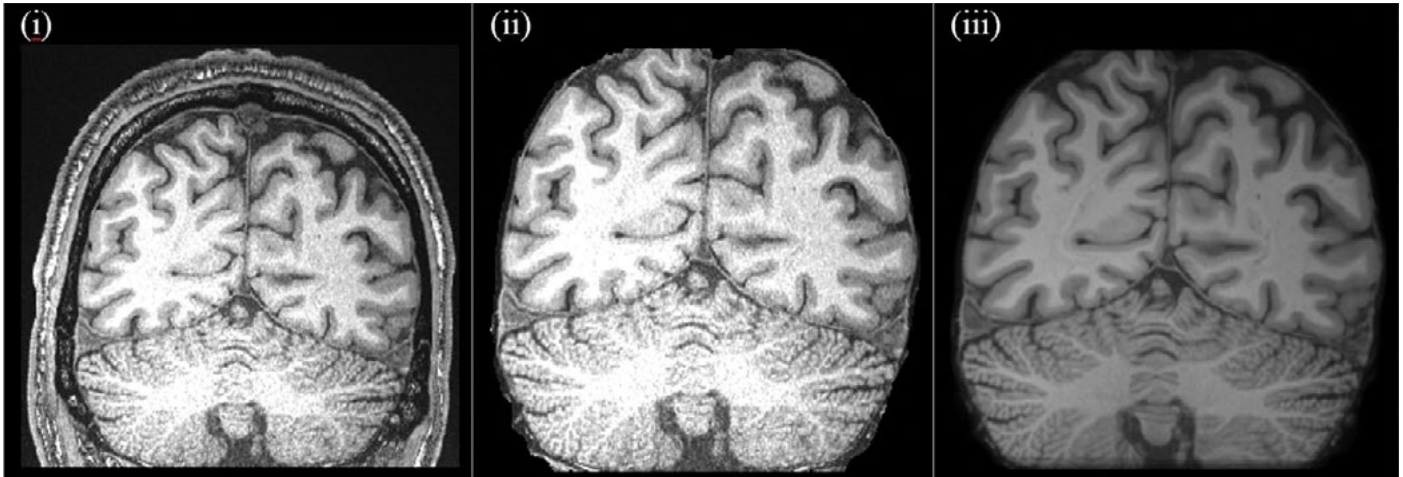


Figure 1. The effect of de-skulling then signal averaging across multiple T1-weighted MR images for subject 2. (i) A coronally-oriented slice from a single T1-weighted image prior to de-skulling. (ii) The same coronally-oriented slice from a single T1-weighted image after de-skulling using BET. (iii) An equivalent coronally-oriented slice from subject 2's average T1-weighted part brain image, derived by co-registering multiple T1-weighted MR images using a linear algorithm using FLIRT.

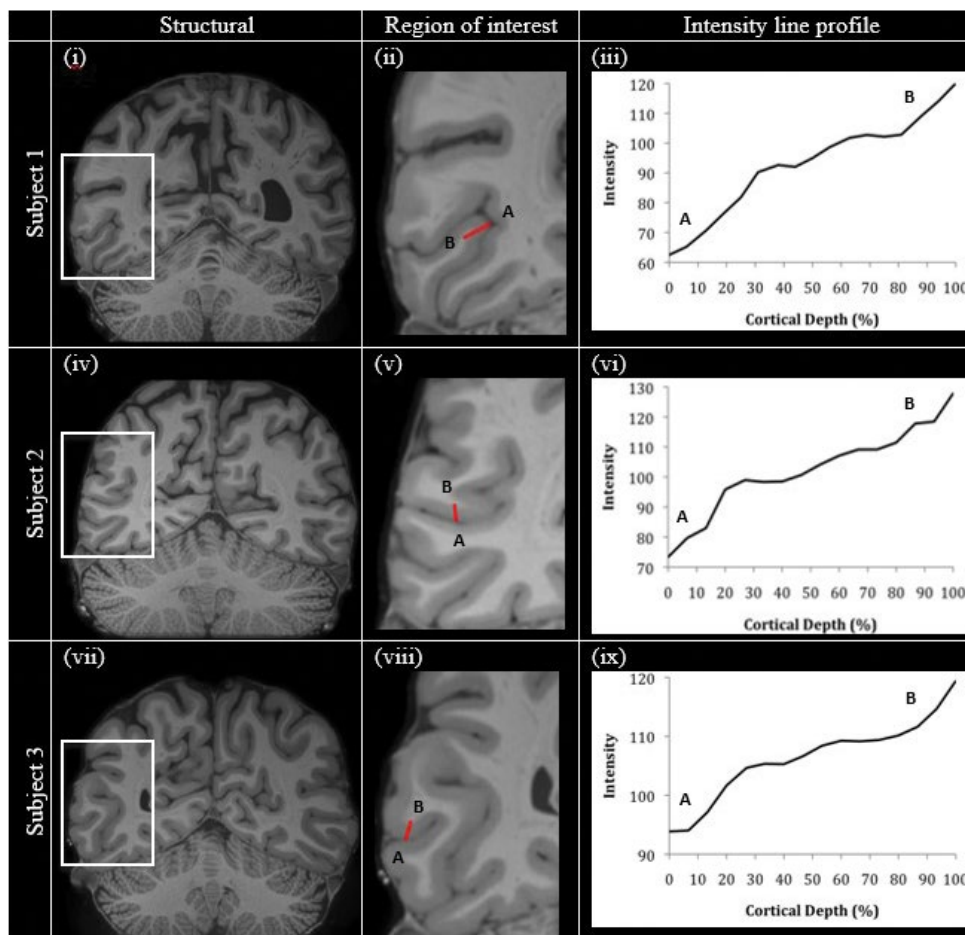


Figure 2. In vivo structural MR results from subjects 1 (left hemisphere), 2 (left hemisphere) and 3 (left hemisphere). The left column shows coronally-oriented slices through putative anatomically defined V5/MT in subjects 1 (i), 2 (iv) and 3 (vii). The region of interest has been highlighted (white boxes). The middle column shows an enlarged view of the highlighted area in (i), (iv) and (vii) for subjects 1 (ii), 2 (v) and 3 (viii) with a red line (AB) through the one of the banks of the sulcus, indicating the site of cortical lamination analysis. The right column shows intensity line profiles along the red line AB of (ii), (v) and (viii), showing two intensity maxima for subjects 1 (iii), 2 (vi) and 3 (ix), with an additional point of inflection at 90% cortical depth for subject 2. Cortical depth is normalised to 0-100% from the outer cortical boundary to the grey/white matter junction.

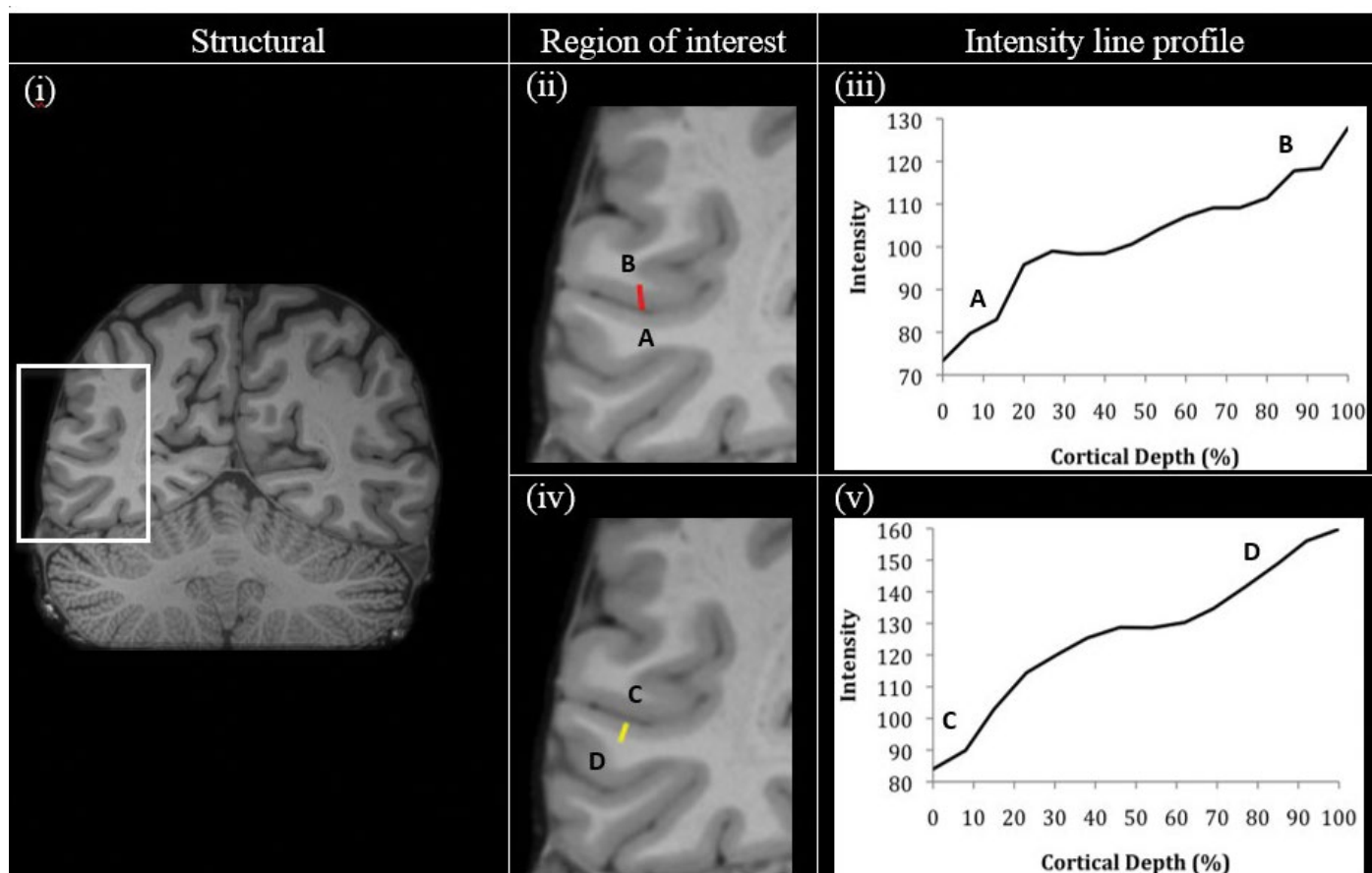


Figure 3. In vivo structural MR results from subject 2 (left hemisphere). (i) Coronal slice through putative anatomically defined V5/MT. The region of interest has been highlighted (white box). (ii) Enlarged view of the highlighted area in (i) with a red line (AB) through the upper bank of the sulcus, indicating the site of cortical lamination analysis, as in Figure 2 (v). (iii) Intensity line profile along the red line AB of (ii), showing two intensity maxima, as in Figure 2 (vi). Cortical depth is normalised as described in Figure 2. (iv) The same coronally-oriented slice as in (ii) with a yellow line (CD) through the lower bank of the sulcus, indicating the site of cortical lamination analysis. (v) Intensity line profile along the yellow line CD of (iv), showing a single intensity maximum.

significant increase in spatial resolution produced by averaging is clearly evident. Quantitatively, this reflects a 34% improvement in SNR due to co-registration.

Slices through putative anatomically defined V5/MT in the co-registered high-resolution structural T1-weighted MR images for all subjects are shown in Figure 2 (left). Visual examination of the areas of interest (Figure 2, middle) showed two horizontally-oriented bands within the cortical ribbon. Intensity line profile analysis through putative V5/MT at this point (AB) is also shown in Figure 2 (right). This enabled quantification of the location of these bands. The first was close to the cortical surface, at 30% grey matter depth, while the second was at 65% cortical thickness. The intensity line profile for subject 2 (Figure 2 (vi)) also suggested a third band near the grey-white matter junction (90% depth), consistently identified as either a local maximum or point of inflection.

Intensity line profiles of putative V5/MT are clearly different to the surrounding cortex. The opposite sulcal bank is characterised by a single wide peak at 45% cortical thickness (Figure 3).

Experiment 2: In vivo structural identification of V5/MT using high-resolution MRI

Functionally-defined V5/MT for subject 2 was identified on the high-resolution structural T1-weighted MR image acquired in this study using functional data from Walters *et al.* [11]. This region sits at the junction of ALITS and LOS. Other areas of activation correspond largely with lower order visual areas; there are also areas of parietal activation. Figure 4(i) shows a high-resolution slice through subject 2's brain with overlaid foci of functional activation. Figure 4(ii) is an enlarged view of the region, with functional activation overlying the location of putative V5/MT identified in Experiment 1. These functional results correlate

strongly with the spatial location of putative V5/MT. Characteristic intensity line profiles are thus effective anatomical identifiers for V5/MT.

Discussion

This study employed a well-established methodology of non-invasive *in vivo* identification of functionally defined cortical areas to determine V5/MT's precise location. Efficacy of the technique pioneered by Watson *et al.* [13] and extended to fMRI by Walters *et al.* [11] was confirmed. High-resolution structural MR images were successfully acquired and intensity line profiles drawn through putative V5/MT. Co-registration of functional data from Walters *et al.* [11] with new high-resolution structural data confirmed the putative anatomical location of V5/MT at the junction of ALITS and LOS in subject 2, consistent with previous studies [10,11,13].

Intensity line profile analysis has been used previously [11,37] to quantify cortical lamination. Current results are consistent with previous findings, demonstrating light-coloured bands at 30% and 65% cortical depth. Subject 2's data suggest a third band near the grey-white matter junction. The first two likely correspond to the heavily myelinated internal and external bands of Baillarger identified in putative V5/MT in post-mortem brains. [11] The origin of the third band may correspond with radial fibres traversing lower cortical layers, also described in post-mortem specimens. These results thus confirm V5/MT's characteristic T1-weighted MR appearance. Intensity line profiles distinguish putative V5/MT from the surrounding cortex. Profiles of the opposite sulcal bank are characterised by a single, wide peak at 45% depth (Figure 3), consistent with lamination described by Walters *et al.* [11].

There is a strong correlation between putative V5/MT's spatial

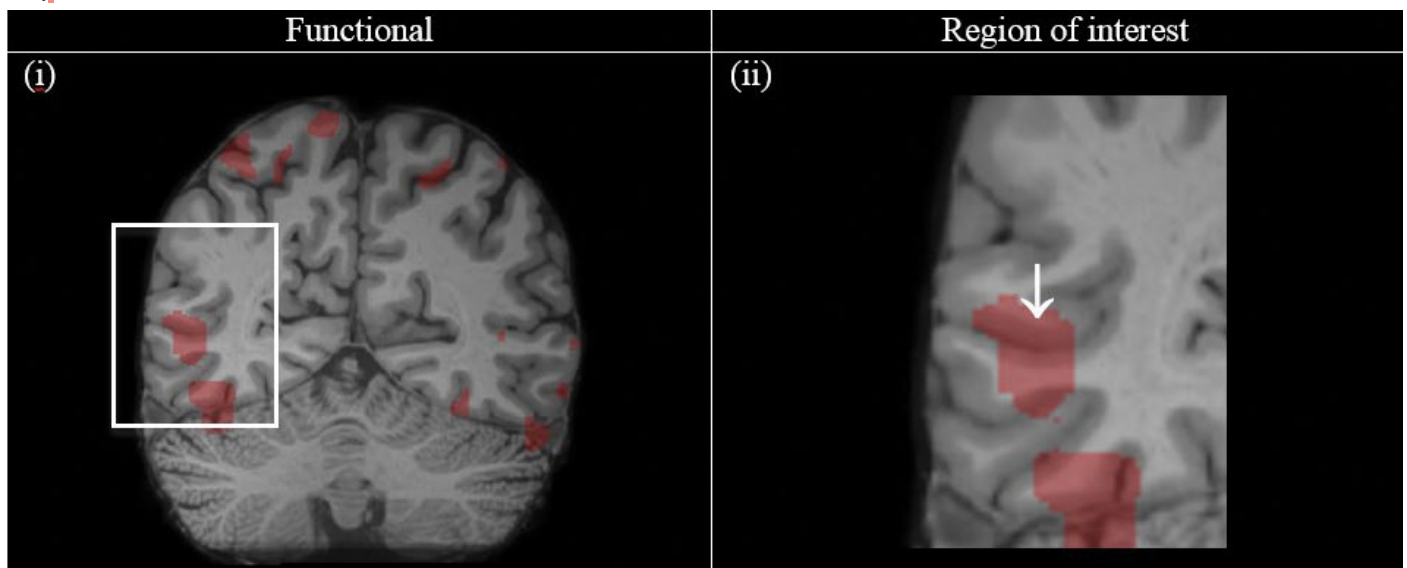


Figure 4: *In vivo* structural MR and fMR results from subject 2 (left hemisphere). (i) Coronal- oriented slice through high-resolution MR image with overlaid functional activation map. The region of interest has been highlighted (white box). (ii) Enlarged view of the highlighted area in (i) showing co-localisation of functional activation and putative anatomically defined V5/MT identified in Experiment 1 (white arrow).

location and functional results for subject 2. This confirms that the characteristic intensity line profiles from this region are distinctive anatomical identifiers for human V5/MT, verifying Walters *et al.* [11] Quantitative comparison of the intensity of line profile maxima through V5/MT here and in Walters *et al.* [11] was not possible due to different techniques used to derive cortical lamination maps. Qualitatively, however, the peaks of local maxima (Figure 2) are less well defined than those previously obtained. This reflects reduced SNR with the present paradigm.

On a whole brain level, high-resolution T1-weighted MR images acquired in this study clearly have superior spatial resolution compared to those in Walters *et al.* [11] However, this overall improvement in resolution is at the expense of reduced SNR at the site of interest, i.e. putative V5/MT. This is reflected qualitatively as less well-defined maxima on intensity line profiles. In comparison, images obtained previously have high resolution at V5/MT, but lower resolution across the remaining cortex. This represents a significant benefit of using surface coils placed directly over the cortex compared to the current paradigm. The potential for concurrent use of these techniques warrants exploration.

This novel approach to improving MR spatial resolution combined technological advances with innovative image analysis. MR scanning hardware is improving rapidly with improved access to high magnetic field strength scanners and multi-channel phased-array head coils. The technique of signal averaging across images from successive sessions is also relatively recent. We demonstrated that these new tools can be successfully applied to produce T1-weighted MR images with high SNR, enabling detection of cortical lamination.

The application of this new approach to *in vivo* structure-function correlation in the human cortex requires further validation. This study provides proof of concept in a single subject. High-resolution structural MR images obtained for two other subjects clearly demonstrate the efficacy of this approach in enabling visualisation of cortical microarchitecture; unfortunately, functional identification of V5/MT in these subjects was not possible. Future extension of this study will help resolve this issue.

Imaging techniques used here significantly reduced analysis complexity. Twin surface coil arrangements used by Walters *et al.* [11] with narrow fields of view resulted in complicated signal attenuation requiring correction prior to registration. This processing step was not required here. Furthermore, use of a multi-channel phased-array head coil also enabled examination of subcortical microarchitecture since high SNR is

not restricted to cortical surface. Acquisition of images with high SNR over a larger field of view represents significant progress.

As suggested by Walters *et al.* [11], this technique can be broadly applied to identification of cortical architecture in living humans. Its usefulness has not yet been fully explored with studies restricted to V1 and V5/MT [11,12,14]. Given the strong contribution of myeloarchitecture to MR signal, further studies investigating non-visual cortex should focus on Flechsig's [37] fields of increased myelination to maximise initial success.

Development of imaging and analysis techniques enabling visualisation of cortical lamination opens up new research areas. For example, if functionally active areas are well-characterised microanatomically *in vivo* using high-resolution MR, major input and output cortical layers can be identified. This would require new task paradigms with multiple conditions activating a functional area in different ways, thus involving distinct pathways. [39] Additionally, anatomical localisation of functionally defined areas could guide medical therapy, like that achieved with deep brain stimulation in Parkinson's disease. [40] Further research in these areas is required.

Conclusions

This study confirmed that MR contrast can resolve intracortical lamination present histologically, enabling visualisation of cortical substructure *in vivo*. It employed improved MR hardware and analysis to validate Walters *et al.* [11], including V5/MT's characteristic MR profile, and identified further microarchitectonic detail. Further optimisation of techniques to improve lamination detection is required to maximise results. Application of this methodology alone, or integrated with other MR-based mapping, will facilitate structure-function correlation throughout the neocortex in living humans.

Acknowledgements

I am very grateful for the training in MR analysis provided by Jennifer Leech, Ayaka Ando, Alicia Dymowski and Dr. Marcus Gray, technical support from Sina Sadeghi and Dr. Neil Killeen, and assistance with MR imaging from Michael Kean. This research was supported by funds from the Florey Neuroscience Institutes, Melbourne. I was also grateful to receive the Dr. Charlotte Last Memorial Scholarship for Honours in Medicine from the Sydney Medical School, University of Sydney.

Conflict of interest

None declared.

Correspondence

S Barnes: stephaniebarnes01@gmail.com

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Skin cancer awareness in the Northern Rivers: the gender divide

Dr. Caydee Pollock

MBBS, BBiomedSc

Intern, The Tweed Hospital

Caydee is a recent graduate with an interest in emergency medicine and anaesthetics. This research article was inspired by a longitudinal placement in general practice she completed as a final year medical student.

Background: Australia has the highest incidence of skin cancer in the world. Despite decades of public health campaigns, these figures are rising, particularly within the male population. **Aim:** This study aimed to establish whether a gender divide exists in relation to skin cancer awareness, prevention and early detection in a rural area of Australia where skin cancer rates are high. **Methods:** Participants were recruited from two medical practices in the Northern Rivers region. Skin cancer awareness, knowledge and prevention were assessed through a qualitative questionnaire, with some questions having responses that used a modified Likert scale. Participant responses were scored for correctness and unpaired t-tests were used to compare scores between the genders. **Results:** Females scored higher than males in all three domains assessed, including awareness, knowledge and prevention. Knowledge surrounding skin cancer awareness was significantly higher ($p=0.03$) in females compared to males. Similarly, the frequency at which females performed skin self-examinations was significantly higher ($p=0.04$) than their male counterparts. Males were less likely than females to participate in a range of sun-protective behaviours, however, similar rates of sunscreen use were observed in both genders. **Conclusions:** Overall, our study demonstrated that females from the Northern Rivers, NSW were more knowledgeable about skin cancer than their male counterparts and are more likely to participate in sun protective behaviours and secondary prevention strategies, including skin self-examinations and clinical skin examinations by a medical practitioner. These findings of a gender divide are supported by several international studies and can perhaps provide an explanation as to why a discrepancy exists between Australian males and females with regard to the increased incidence of skin cancer.



2003 SCREEN project (Skin Cancer Research to Provide Evidence for the Effectiveness of Screening) in Northern Germany demonstrates the feasibility and effectiveness of systematic skin cancer screening. Over a twelve-month period, physicians carried out 360,288 skin checks and consequently identified 3103 melanomas resulting in a 34% increase in melanoma incidence for the year of the study. Five years after SCREEN, melanoma mortality was reduced by over 50%. [13] Northern Germany has a low skin cancer prevalence compared to Australia, thus the anticipated benefits of systematic skin cancer screening are likely to be even greater in Australia.

Current Australian clinical guidelines do not recommend systematic skin cancer screening, however, the Australasian College of Dermatologists recommends annual skin checks by a physician in individuals who are at an increased risk of developing skin cancer. [14] Risk factors for skin cancer include host factors such as Fitzpatrick skin types I and II, multiple melanocytic naevi or dysplastic naevi and melanoma in a first degree relative. [15] Environmental risk factors include excessive UV exposure and frequent sunburns, particularly from a young age. In addition to annual screening of high-risk groups, it is recommended that the general population perform whole body skin self-examinations (SSE) at least four times a year. [14] Previous surveys on the practice of SSE in Australia have indicated varying results, ranging from 6-60% of the population practising some kind of SSE depending on the population studied. [16] A survey of Queensland residents found that the rates of SSE were higher among females compared to males and there was an increased likelihood of SSE in individuals with a higher level of education. [17]

It has long been known that UV radiation is a significant factor in the development of skin cancer. As a result of this well documented link, the Australian government has launched numerous public health campaigns since the 1980's. [18] These sun safe media campaigns, including the well-known 'slip, slop, slap' campaign, aimed to increase community awareness. Despite these campaigns, the incidence of skin cancer in Australia has risen steadily over the past two decades. This rise can be partly explained by the increased diagnosis of small SCC's and BCC's that have previously remained untreated, however, it cannot solely be responsible for the increase in incidence.

A study by Staples *et al.* (2006), found that rates of BCC and SCC increased from 1985 to 2006, with 70% of men and 58% of women aged over 70 years having at least one skin cancer at the later time point. [19] Further, research into the cause of this increase identified that the rates of skin cancer in males may be the primary contributor to the rise. [19, 20] Skin Cancer Australia found that the incidence of melanoma in males has risen by 100% over the last 20 years. [20] The

Introduction

Australia has the highest incidence of skin cancer in the world, with two out of three Australians being diagnosed before the age of 70. [1] There are three types of skin cancer related to sun exposure: malignant melanoma (MM), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Malignant melanoma is the least common but the most serious, accounting for 75% of skin cancer related deaths. [2] Early melanomas are usually highly visible and previous studies have shown that early detection of thin lesions is associated with a high five-year survival rate. [3, 4] BCC is the most common skin cancer in Australia, followed by SCC. [5] Although the non-melanoma skin cancers rarely result in mortality, they are very common and have the potential to recur, disfigure and metastasise if not identified and treated in a timely manner. [6, 7]

The epidemiological literature concerned with predisposing factors for skin cancer emphasises the considerable influence of ultraviolet (UV) radiation on the incidence of skin cancer. [8, 9] Primary prevention efforts are aimed at reducing the risk factors for skin cancer, most notably sun exposure and sunburn, through environmental changes, social changes and behavioural modification. [5] This includes diverse activities to minimise exposure to the sun, such as adopting sun protection strategies such as using sunscreen, wearing protective clothing and avoiding midday sun. [10 11]

Secondary prevention efforts to reduce skin cancer, including the early detection through systematic skin cancer screening and excision of early precancerous or cancerous lesions, have an important impact on the morbidity and mortality associated with skin cancer. [12] The

exact cause of this increase in Australia is unclear.

It has traditionally been assumed that men have higher rates of skin cancer primarily because they are more likely than women to have outdoor jobs, which involve extensive sun exposure. This may be only one of the factors contributing to their higher risk. A recent American skin cancer foundation survey revealed that men are less likely than women to make an effort to protect themselves from the sun and are less knowledgeable when it comes to skin cancer prevention, awareness and early detection. [20] Furthermore, a qualitative study, which assessed skin cancer awareness, attitudes and sun protection behaviour among medical students at the University of Miami, Florida, found significant gender differences in sun protection and skin cancer knowledge. More women than men valued the importance of sun protection and acknowledged that sun exposure is the most important risk factor for skin cancer. [21]

A gap exists in the literature as to whether a similar gender divide is present in Australia, which could possibly explain the increased rates of skin cancers seen in the male population. Through the use of a qualitative questionnaire, this study aimed to:

1. Establish whether a gender divide in relation to skin cancer knowledge and prevention exists in the Northern Rivers region of NSW, an area close to the Queensland border, where the highest rates of skin cancer in Australia have been reported. [22]
2. Use these results as the basis for further studies that can better inform medical practice in relation to skin cancer awareness and prevention.

Methods

Participants and Study Design

Participants were recruited through information posters placed in the waiting rooms of two medical practices in the Northern Rivers region: the Goonellebah Medical Centre and the Lennox Head Medical Practice. Participation in the project was voluntary and anonymous, with participants returning the completed questionnaires to a secured box placed in the waiting room. There were no exclusion criteria other than participants needing to be aged 18 years or over. The study ran between December 2012 and February 2013 inclusive.

All participants completed the qualitative questionnaire, which was largely adapted from the Department of Health and Aging - Evaluation of National Skin Cancer Awareness Campaign [23] and previous UOW research. [24] Questions were constructed in such a way as to assess knowledge and attitudes towards skin cancer awareness, prevention and early detection. The questionnaire included questions on a modified Likert scale which were adapted from a previous study. [24] Demographic information including gender, age and level of education was also collected.

Ethics

This study received approval by the Human Research Ethics Committee (HREC) of the University of Wollongong, Australia (Ethics number: GSM12/055).

Statistical analysis

Descriptive statistical analyses were performed to establish the distribution of participants' characteristics. Responses either used a modified Likert scale or were scored for correctness (Appendix 1). Analyses of patients' sun protection practices, skin cancer awareness, skin cancer knowledge, frequency of skin self-examination and skin examination with a medical practitioner were completed using EXCEL, Microsoft (Redmond, Washington, U.S) software for Windows. Recorded information was then further analysed to establish whether responses varied between genders. Sample sizes for each analysis varied slightly due to incomplete questionnaires. Analysis was performed using unpaired t-tests, with the level of significance set at $p=0.05$.

Results

Demographics

In total, 91 patients from the two medical practices completed the questionnaire. There was an approximate 1.3:1 female to male ratio with a high representation of the older 55+ years age group. The age distributions of participants are shown in table 1. There is a sizeable difference in age distribution between males and females. This is largely due to the patient population seen at both medical practices. Level of education was relatively evenly distributed with 61% of females having tertiary education and 39% having secondary education compared to 58% and 42% respectively, for males.

Age	Females	Percentage	Males	Percentage
18-20	2	3.8	8	20.5
21-24	5	9.6	2	5.1
25-34	4	7.7	9	23.1
35-44	5	9.6	1	2.6
45-54	13	25.0	4	10.3
55+	23	44.2	15	38.5

Table 1: Age distribution of participants.

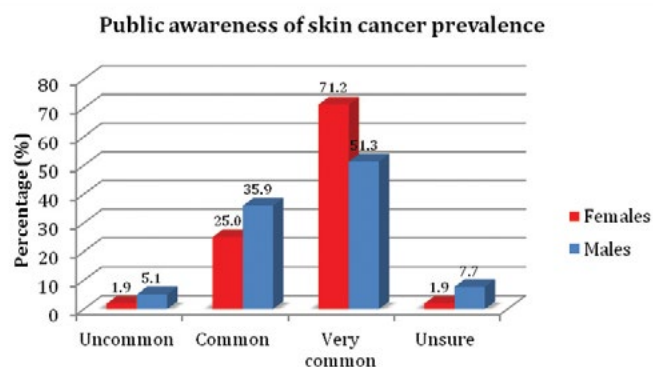


Figure 1. Compares the awareness of skin cancer prevalence in Australia between males and females.

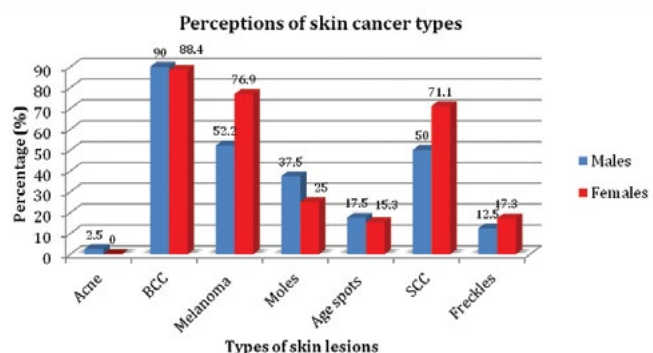


Figure 2. Perceptions of types of skin cancers between males and females.

Skin cancer knowledge

Skin cancer knowledge was assessed through three primary domains; awareness of prevalence of skin cancer within Australia (Figure 1), knowledge surrounding types of skin cancers (Figure 2) and awareness of sunburn as a primary contributory factor for the development of skin cancer (Figure 3). Females scored significantly higher in relation to prevalence of skin cancer, and sunburn risk compared with males (Table 2). The percentage of females who correctly identified key elements in the three domains was higher than males for skin cancer prevalence (71% females; 51% males), awareness of skin cancer types - SCC (71%

Knowledge	Females score	Male score	p-value
Prevalence	1.6 ± 0.5	1.3 ± 0.7*	0.03
Types of skin cancer	0.8 ± 0.4	0.7 ± 0.4	0.21
Sunburn	1.8 ± 0.4	1.6 ± 0.7*	0.03

Table 2: Comparison of skin cancer knowledge between males and females.
* = Significant males vs. females, $p < 0.05$, unpaired students t-test

females; 50% males) and melanoma (77% females; 52% males), as well as sunburn as a primary contributing factor (92% females; 76% males). The percentage of males and females who correctly identified BCC as a type of skin cancer was similar (88% females; 90% males).

Skin cancer prevention

Reported sun protective behaviours are shown in Figure 4. The most sizeable gender differences were that more females reported using wide brimmed hats, actively seeking shade and using sunglasses. Overall, only a small percentage of participants reported not engaging in any form of sun protective behaviour (males 3%, females 2%).

Skin cancer early detection

The frequencies of skin self-examinations are shown in Figure 5. Overall, the frequency at which females perform SSE was significantly higher than their male counterparts ($p=0.04$) when the response options were converted to a modified Likert scale of 0 - 3. Among females, 42% reported performing SSE frequently compared with 30% of males. The percentage of males who never (13%) or rarely (26%) performed a SSE was higher than females (8% and 6%, respectively).

The frequencies of skin examinations performed by a medical practitioner are shown in Figure 6. A substantial proportion of the male cohort (28%) reported to having never had their skin examined by a medical practitioner. This is higher than the corresponding female group (8%). Rates of reported examinations on a 6-12 month basis were much higher among the female population (38%) compared to the male population (17.9%). When these response options of frequency were converted to a modified Likert scale of 0-4, and compared using unpaired t-tests, there was no significant difference between males and females ($p = 0.111$).

Discussion

This population-based survey documents skin cancer knowledge, prevention and early detection in a Northern Rivers population (Northern NSW, Australia), an area close to the Queensland border, where skin cancer rates are high and rising rapidly particularly among the male population. The response rate obtained ($n=91$) was a satisfactory representation of gender (57% female, 43% male), but slightly weighted towards older age groups (>55 years). The predominantly elderly patient population seen at the two medical practices can explain this higher proportion of elderly participants.

In this population, females were significantly more knowledgeable than males in the identification of skin cancer prevalence ($p=0.03$) and were more likely to identify types of skin cancers, however, this difference was not significant ($p=0.21$). Despite Australia being a world leader in skin cancer incidence, only half (51%) of the male cohort compared to 71% of females correctly identified skin cancer incidence as being very common, occurring in 2 in 3 Australians. Given the higher prevalence of all skin cancer types within the male population, [20] this is an important finding as it suggests that perhaps skin cancer campaigns are not having as great of an impact on the male population in terms of education, and need to be more targeted in their approach.

A more perturbing finding was that males scored lower than females in relation to knowledge of the types of skin cancers that exist. Only half of the male cohort correctly identified melanoma (52%) and

Awareness of sunburn as a risk factor for skin cancer

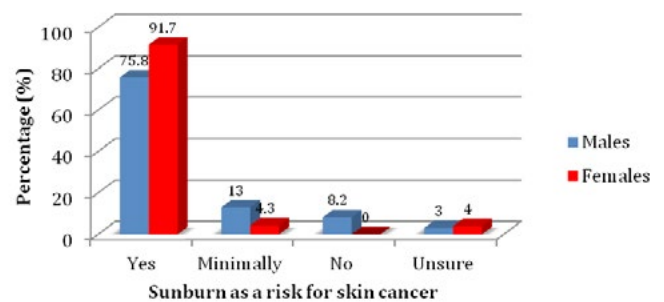


Figure 3. Awareness of sunburn as a key risk factor in the development of skin cancer.

Sun protective behaviours

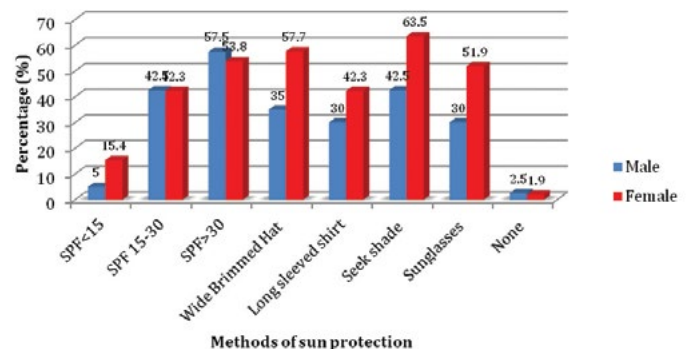


Figure 4. Reported sun protective behaviours by males and females.

Frequency of self skin examinations

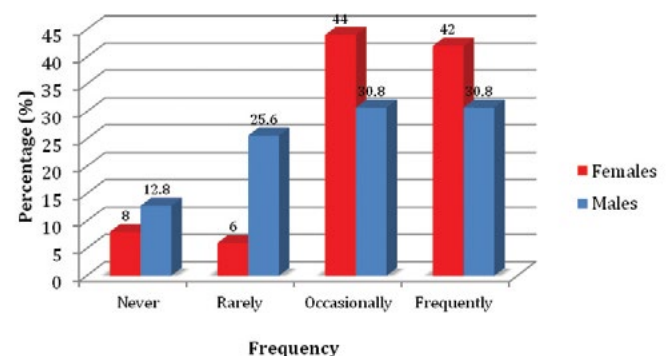


Figure 5. The frequency of self-skin examinations between males and females.

Frequency of skin checks by a doctor

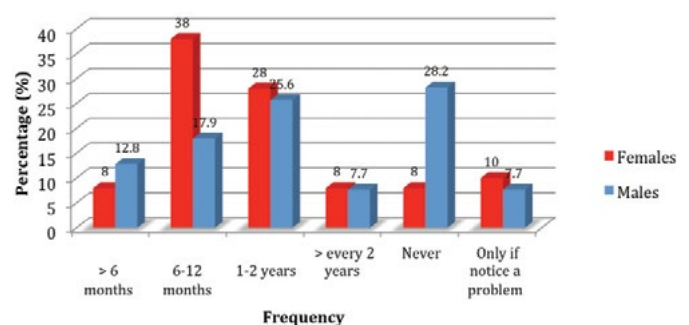


Figure 6. Frequency of skin examination performed by a medical practitioner.

SCC (50%) as skin cancers, compared to 77% and 71% respectively of the female cohort. These results are alarming given that melanoma is the fourth most common cancer in Australia and its incidence in the male population is 2-fold higher than that observed in females. [22] Surprisingly, and contrary to the former findings, 90% of male participants correctly identified BCC as a type of skin cancer, similar to females (88%). The exact cause of the higher identification of BCC as

a skin cancer is unknown, but may be attributed to the fact that BCC is the most common and prevalent skin cancer in Australia, and thus the male population may be more familiar with its presentation. [5] Interestingly, moles (37%), age spots (18%), freckles (13%) and acne (2%) were identified by a portion of the male population as types of skin cancers.

Despite demonstrating limited knowledge in terms of skin cancer incidence and types of skin cancers, the majority of the male cohort (76%) correctly identified excessive UV exposure and in particular recurrent sunburn as a key causative factor of skin cancer. This high response rate may be a reflection of the decades of public health campaigns the Australian public have been exposed to, which highlight the well-known link between sun exposure and skin cancer. Although the male score in this area was higher than that seen in the other two domains, it was still significantly lower ($p=0.033$) than that of the female cohort and once again demonstrated a gender divide concerning skin cancer knowledge.

Sunscreen was the most commonly used measure of sun protection by males with 57% of the male cohort reporting the use of SPF >30 sunscreen on a regular basis. This trend is in keeping with current literature, which reports that sunscreen is the most commonly used measure of sun protection in adults. [25] Stanton et al. report that females have a greater desire for a tan and have an increased perception that a tan is healthy and this translates into them using sunscreen at lower rates than the male population. [26] Our results demonstrate no such gender difference regarding this behaviour, and in fact our study demonstrates that females are more likely than males to participate in other sun protective behaviours such as wearing a wide brimmed hat, long sleeved shirt, actively seeking shade and wearing sunglasses. Overall, females were found to be more proactive when it comes to protecting themselves from the sun, however, on a whole, the level of sun protective behaviours in both cohorts were relatively low with just over half of the female population participating in some kind of sun protective behavior on a regular basis with lower rates seen in the male population. This finding is particularly relevant, as even though the majority of these participants were in their mid to late teens when the well known 'slip, slop, slap' campaign was launched, a large proportion of them are not necessarily adopting sun protective behaviours.

Secondary prevention strategies include clinical systematic skin examinations by a doctor and skin self-examinations. The current Australian clinical guidelines do not recommend clinical systematic skin examinations, however, due to the high incidence of skin cancer seen in Australia, the Australasian College of Dermatologists recommends annual skin checks by a physician in individuals who are at increased risk of skin cancer. [14] The College also recommended that all individuals perform SSE at least four times a year. Overall, females were more likely than their male counterparts to have their skin examined by a physician on an annual basis, however this difference was statistically insignificant ($p=0.11$). In addition, 28% of males reported to never having had their skin checked by a physician compared to only 8% of females. A similar trend was observed in the frequency of SSE. The reported frequency of SSE was significantly higher in females than males ($p=0.040$). Furthermore, the percentage of the male cohort that never (13%) or rarely (26%) performed SSE was much higher than the female cohort. The reasons behind this difference are not fully understood and are thought to be multifactorial, with some studies suggesting that men are less likely to get their skin examined by a doctor as they are less likely to identify themselves as at risk of skin cancer

and are less likely to recognise suspicious lesions which require further investigation. [27] As nearly one third of men had never had their skin examined by a doctor or rarely perform SSE, they are at increased risk of premalignant or malignant lesions going unnoticed and progressing to aggressive cancer. It is therefore important that treating physicians recognise that males are less likely to get routine skin checks and that they need to be opportunistic during a consultation and educate the patient regarding skin cancer awareness and prevention.

Strengths and Limitations

A key strength of this qualitative study is that it addresses an important clinical area where the evidence base is weak. Although the study included 91 participants, we acknowledge the limitation of recruiting from only two medical practices in the Northern Rivers region. Furthermore, the difference in the age distribution between males and females may have influenced results. There is a high representation of the 55+ age group and males in the 18-20 'risk taking' age group. This is representative of the patient population seen at the two practices but may not necessarily be a true representation of the patient population of the Northern Rivers Region. Future studies with a multivariate design to extract confounding factors of sun protective behavior and interactions between attitudes and knowledge should extend these findings to larger, more diverse samples.

Clinical implications

This study has implications for both primary care physicians and public health campaigns such as the National Skin Cancer Awareness Campaign. Many of the male participants were unaware or had limited knowledge around types of skin cancers, adopting sun protective behaviours and secondary prevention strategies. Our data suggests several key areas of skin cancer awareness that can be targeted in future research and health promotion on both a local and national level.

Conclusion

Overall, our study demonstrates that females from the Northern Rivers, NSW are more knowledgeable about skin cancer than their male counterparts and are more likely to participate in sun protective behaviours and secondary prevention strategies, including skin self-examinations and clinical skin examinations by a medical practitioner. These findings of a gender divide are supported by several other international studies and can perhaps provide an explanation as to why a discrepancy exists in Australia with regard to the increased incidence of skin cancer observed within the male population. Increasing awareness of skin cancer within the male population, encouraging them to readily adopt sun protective behaviors and encouraging them to take notice of any changing or newly appearing skin lesions with regular review and follow up by a physician, has the potential to reduce skin cancer morbidity and mortality in Australia.

Acknowledgements

The author would like to thank Dr Naomi Piyaratna for her contribution to survey development and data collection and Dr Theresa Larkin from the Graduate School of Medicine, Wollongong University for her expertise and assistance in producing this research article.

Conflict of interest

None declared.

Correspondence

C Pollock: caydeepollock@gmail.com

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Responses	Score
How common is skin cancer in Australia?	
Unsure	0
Uncommon (1 in 100)	0
Common (1 in 50)	1
Very common (2 in 3)	2
Does getting sunburnt increase your risk of skin cancer?	
Unsure	0
No	0
Minimally	1
Yes with each burn	2
Which of the following are types of skin cancers?	
Acne	0
BCC	1
Melanoma	1
Moles	0
Age spots	0
SCC	1
Freckles	0
Unsure	0
How often do you get your skin checked by a doctor?	
Never	0
Less than every 2 years	1
Every 1-2 years	2
Every 6-12 months	3
More often than every 6 months	4
How often do you perform a self-skin examination?	
Never	0
Rarely	1
Occasionally	2
Frequently	3

Appendix 1. Scoring for correctness of the modified Likert-type scale.

Exercising patient-centred care: a review of structured physical activity, depression and medical student engagement

Daniel Lowden

Second Year Medicine (Undergraduate)
James Cook University

Daniel is enjoying the challenges of second year medicine and coming to terms with pathophysiology.

Structured physical activity has a wide range of benefits that include improving mood and preventing chronic disease. Recently, there has been an explosion of research aimed at treating diseases such as depression using nothing more than exercise. This article presents an overview of research conducted into the use of exercise to treat depression. As a body of work, the literature finds it to be a practice that has significant clinical benefits; however, its implementation is not straightforward. Issues concerning exercise adherence have hampered studies and force us to ask whether prescribing exercise for sufferers of depression is indeed appropriate. Nonetheless, is there a role for medical students in encouraging physical activity as treatment? If we re-examine the use of exercise from a patient-centred perspective, medical students have an opportunity to engage with patients, promote exercise and possibly prevent depression.



Introduction

Structured physical activity has a wide range of health benefits that include the prevention of chronic diseases such as cancer, cardiovascular disease, diabetes and obesity. [1] There is also consensus that exercise has a short-term 'feel good' effect that improves mood and wellbeing. [2-4] Recently, converging interest in these two areas has spawned an explosion of research aimed at treating diseases such as depression using nothing more than exercise. [5-7] A 2012 meta-analysis of over 25 trials found that prescribing exercise to treat depression is on par with pharmacological and physiological interventions, and that exercise alone is moderately more effective than no therapy. [8] The study also highlights that prescribing exercise for depression is not straightforward. Poor patient attendance rates, along with issues including exercise adherence and the type, duration and intensity of exercise, all question whether prescribing exercise for sufferers of depression is indeed appropriate. The authors of the study admit the implementation is complex and that further study is required. Nonetheless, is there a role for medical students in encouraging physical activity as treatment? Can our skills in motivational interviewing and goal setting play a role? If we re-examine the use of exercise from a patient-centred perspective, medical students can promote exercise adherence and support those who are already exercising to stay exercising. In doing so, we can facilitate the prescription of exercise and possibly prevent depression. [5,7,9]

A background to depression

Depression affects a staggering 350 million people globally, with sufferers commonly reporting changes in emotional, cognitive and physical behaviour. [10] Depression also presents with high rates of comorbidity (the occurrence of more than one condition or disease). [11] More locally, a 2007 National Survey of Mental Health and Wellbeing found that almost half of the Australian population aged 18-85 (7.3 million people) had experienced a mental illness at some point in their lifetime. [3] A study by the Australian Bureau of Statistics (ABS) in the same year revealed that of those people suffering from mental illness, only 35% actually sought treatment, suggesting that within Australia there are 2.1 million potential patients going without much-needed assistance. [12]

Mental illness, while indiscriminate, has a higher incidence within certain sub-populations. Perhaps surprisingly, doctors and medical

students experience higher rates of depression and stress than the general population. Medical students report increased depressive symptoms as a result of medical school while a significant number of doctors report that they are less likely to seek treatment for depression despite their awareness of the condition. [13,14] With a reported 3668 students admitted to medical schools in Australia during 2013, these statistics highlight the importance for medical students to identify and understand depression. [15]

Pathophysiology and current treatment options

Therapeutic treatment options for patients who are depressed fall into two broad categories: psychological and pharmacological. Typically, people are treated using cognitive behavioural therapy (CBT), anti-depressant medication, or a combination of both. [4,16,17] Despite being able to treat depression, a simple pathogenesis is yet to be found. Current opinion centres on depression being a result of chemical imbalances within the brain, specifically the action of monoamine neurotransmitters, including dopamine, serotonin, and norepinephrine. [17] This approach has allowed the pharmaceutical industry to develop medications including selective serotonin reuptake inhibitors (SSRIs), which target neurotransmitter reuptake to help restore their usual balance and so reduce symptoms. [18]

One promising new development in the quest to understand the pathophysiology of depression concerns the emergence of inflammation as a mediator of depression. A recent meta-analysis of 24 separate studies found that depression is accompanied by immune dysregulation and activation of the inflammatory response system (IRS). [19] Specifically, when compared to non-depressed patients, sufferers of major depression were found to have significantly higher ($p < 0.001$) concentrations of the pro-inflammatory cytokines tumour necrosis factor- α and interleukin-6 in their blood. Once the increased cytokine signal reaches the brain, it is able to down-regulate the synthesis, release and reuptake of the very same monoamines targeted by antidepressant medications. [20] Understanding and preventing this interaction from occurring could lead to promising new treatments for depression.

Despite widespread prescription, the use of antidepressant medication is not without its drawbacks. Many patients experience unwanted side effects and stop taking their medication, while others simply do not want to take medicine that will make them feel worse. [21] Additionally, a 2012 report on Australia's overall health revealed that some patients who experience depression suffer worse health outcomes due to the social stigma associated with taking antidepressants. [22] As a result,

many patients choose to shun medication altogether, opting for alternative therapies such as acupuncture and yoga to help manage depression. [21] Viewed from the patient's perspective, the use of antidepressants can be seen as a choice between the lesser of two evils: treatment or depression.

Exercise and depression

The link between exercise and relieving depression has been a difficult one to make. A 2009 meta-analysis published by The Cochrane Collaboration evaluated the use of exercise, defined as "repetitive bodily movement done to improve or maintain ... physical fitness", in treating depression. [23] Initially, the Cochrane review pooled data from 25 trials and found a large clinical effect in the reduction of depressive symptoms when compared to a placebo or no treatment at all. However, in 2012, when the authors repeated the study, correcting for what they saw as errors and bias in the previous analysis, the data found only a moderate effect in relieving depressive symptoms. [8] Interestingly, in both studies, the data concerned with treating depression with exercise was found to be on par with the use of antidepressant medication. Nonetheless, despite the downgraded clinical effect, the authors of the study continue to find it reasonable to prescribe exercise to people with depressive symptoms; however, they caution to expect only a moderate effect at best.

Research into a preventative, rather than curative approach to depression is also being conducted. In a large-scale longitudinal study of depression, researchers hypothesised that an inverse relationship existed between the level of physical activity and depressive symptoms: those who were more active should not become depressed. [9] Researchers grouped exercise into three categories: light activity such as 'necessary household chores', moderate activity which included regular walks, and strenuous activity such as 'participation in competitive sports'. The study revealed that participants in the 'competitive sports' category reported less depressive symptoms than those in the 'necessary household chores' category – an unsurprising finding given the ability of exercise to lift mood. But perhaps more revealing is the finding that participants who decreased their activity from moderate to light, and from strenuous to light, reported the greatest increase in depressive symptoms, implying that exercise may act as a buffer against depression.

Exercising patient-centred care

While scientific analysis and treatment forms the foundation of modern health care, a focus on the patient as a person should be paramount. In 2010, the Australian government endorsed patient-centred care, a framework that enshrines the values and individual needs of the patient. Since then, patient-centred care has broadened to encompass 'an approach to the planning, delivery, and evaluation of health care that is grounded in mutually beneficial partnerships among healthcare providers, patients, and families'. [24] While relatively new, patient-centred care now shapes the delivery of health care in Australia. It has also reaffirmed the rights of the individual in developing and delivering health care.

Patient-centred care forces us to examine whether exercise as an intervention is at all appropriate for the depressed. While there may be some clinical benefit, is it really patient-centred? The Cochrane Collaboration study of exercise as a treatment for depression highlights low exercise adherence and high dropout rates amongst participants. [8] While the reasoning behind the dropouts was absent from the report, one could easily imagine the potential challenges in asking a person who is already lacking in drive and motivation to participate in an exercise program. Is it possible that in considering the prescription of exercise to the depressed we are violating key Hippocratic notions

including that of non-maleficence? Are we exposing an already vulnerable individual to a situation where they are likely to fail and experience a decline in their mental health as a result? [1] It would seem that when it comes to exercise and depression, the patient-centred perspective would advise against such risks. [24]

While it is clear that exercise is good for us, it is also clear that its prescription for depression is fraught with ethical issues. As medical students, how then can we engage in such an uncertain and potentially lethal landscape when we do not possess the skills to interact with depression in any therapeutic manner? If we re-examine the issue from a patient-centred perspective, we are able to view exercise as a preventative, rather than curative, approach to depression. This opens the door to medical student engagement. For example, we can use the motivational and goal-setting skills taught as part of the preclinical curriculum to help patients achieve and maintain their exercise goals. This could involve scheduling a progress telephone call to maintain the patient's motivation, a periodic home visit in an effort to reduce recidivism, or the discussion and identification of barriers that may prevent them from achieving their goals. Placements are the ideal environment for us to develop these mutually beneficial partnerships. Whatever the effort, promoting a healthier and more active lifestyle is a patient-centred perspective that all medical students should feel comfortable in advocating.

Conclusion

Re-examining the issue from a patient-centred perspective sees exercise as a multi-benefit, primary prevention tool that may also safeguard against developing depression. Moreover, this is wholly within our advocacy as medical students. Not only does this approach echo recommendations supported by the Australian Government to include collaborative, patient-centred care programs in undergraduate health programs, it also provides many practical opportunities for medical student engagement. For example, during placements in rural and remote areas, students often participate in community-based activities where we leverage the associative influence of our medical profession to promote the benefits of a healthier and more active lifestyle.

Despite reviews of studies inferring the protective effect of exercise against developing depressive symptoms, prescribing exercise as a treatment option requires skill and experiences beyond the scope of medical students. However, medical students do have skills in motivational interviewing and goal-setting strategies that enable us to promote exercise adherence. Therefore, if we consider exercise as a tool for disease prevention that may also safeguard against depression, patients will experience greater health outcomes and medical students can be active in its prescription.

If you or someone you care about is in crisis and you think immediate action is needed, call emergency services (triple zero – 000) or contact your doctor or local mental health crisis service, such as Lifeline (13 11 14).

Acknowledgements

I would like to thank the James Cook University Ecology of Health subject coordinators and Dominic Lopez for the valuable feedback provided in preparing this article.

Correspondence

D Lowden: danlowden@gmail.com

Conflict of interest

None declared.

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Penicillin allergies: facts, fiction and development of a protocol

Dr. John Floridis

BMBS (Hons), BPharm, GradCertClinEd,
AACPA
Intern, Royal Darwin Hospital

John was a final year medical student at Flinders University at the time of writing this paper. His interests include general medicine, acute care, nephrology and medical education.

Dr. Alison Ward

MBBS, FACHSHM
Consultant, Royal Adelaide Hospital

Alison is a consultant in sexual health medicine at Clinic 275, Royal Adelaide Hospital. She also plays an active role in the supervision and training of junior doctors and medical students.

Penicillins, a member of the beta-lactam family, are the most commonly prescribed antibiotic class in Australia. Beta-lactam agents are used in a sexual health setting for the management of syphilis, uncomplicated gonococcal infections and pelvic inflammatory disease. Patients frequently report allergies to penicillin, which can be protective but also counterproductive if it does not represent a 'true' allergy. Features of a reported reaction may be stratified as either high or low risk, which has implications for both re-exposure to penicillins; but also cross-reactivity to other members of the beta-lactam family such as cephalosporins. We reviewed the evidence surrounding penicillin allergies, in the context of developing a local protocol for penicillin-allergic patients at a sexual health clinic.



Case scenario

A 27-year-old male is referred to a sexual health clinic by a general practitioner (GP). He presents with a widespread maculopapular rash, fever and malaise for the past four days. Whilst he does not describe any other symptoms, he did notice a painless genital ulcer approximately four weeks ago. The ulcer resolved spontaneously; hence he initially did not seek medical advice. He does not have a stable sexual partner and mentions engaging in several episodes of unprotected sex with both women and men in the previous three months. Secondary syphilis is the suspected diagnosis given the widespread rash and preceding chancre, and testing confirms this with a positive syphilis enzyme-linked immunoassay (EIA) screening test, *Treponema pallidum* particle agglutination assay (TPPA), and a rapid plasma reagin (RPR) of 1:32. As part of a sexual health screen, he tested positive for rectal gonorrhoea by culture. The treatment regime includes 1.8 g intramuscular benzathine penicillin for syphilis, in addition to 500 mg intramuscular ceftriaxone and 1g oral azithromycin for gonorrhoea, all given as stat doses. Before signing the drug order, the clinician questions about any allergies. The patient mentions having an allergic reaction to penicillin when he was six years old but cannot remember any particular details. What is the plan now?

Introduction

This case presents a challenging scenario for the clinician. In this article, we hope to outline some of the facts surrounding penicillin allergies, dismiss some myths and provide a systematic approach to aid decision-making, especially in the sexual health setting where there are limited treatment options for gonorrhoea and syphilis.

The beta-lactam family of antibiotics are one of the most commonly prescribed antibiotic classes in medicine. The beta-lactam ring forms the structural commonality between different types of penicillins and this is also shared with other drug classes, such as the cephalosporins and carbapenems.

Penicillin allergy is the most commonly reported medication allergy, either by the patient or medical providers. [1] The implications of this 'label' can be either protective or counterproductive. For those patients with a severe previous reaction, such as anaphylaxis, this allergy is

important and re-exposure can prove disastrous and potentially fatal. However, for other patients with a minor or inconclusive reaction, not administering penicillin may be denying the patient first-line, efficacious treatment. Additionally, there are concerns that treating patients with alternative agents in this context contribute to the development of resistance, which is of public health concern. [2]

Whilst the use of beta-lactam antibiotics crosses many realms of medicine, this article is written in the context of developing a protocol for the management of patients with penicillin allergy in an urban sexual health clinic. It is not designed to provide guidance outside of this setting, nor to replace existing protocols in other clinical units.

Rationale for a protocol

Management of patients with penicillin allergy requiring beta-lactam treatment was reviewed as part of an overall revision of internal treatment guidelines. Sexually transmitted infections pose treatment challenges whereby certain conditions or patient sub-groups (e.g. pregnant women) have no equally efficacious or appropriate alternatives to penicillins. [3] For example, one acceptable alternative to penicillin for syphilis treatment is to administer oral doxycycline, however the potential harm associated with this treatment (permanent dental staining) contraindicates its use in pregnancy. [4]

Development process

Senior clinicians at the sexual health clinic provided the protocol brief in May 2013. This included, but was not limited to: reviewing existing guidelines for the management of penicillin-allergic patients both at a national and international level; reviewing literature about the incidence of penicillin allergy, and cross-reactivity rates in patients with a documented history of penicillin allergy; formulating a protocol, based on existing protocols and evidence which would be applicable for managing patients with a penicillin allergy; designing a flowchart which summarises the protocol in a clear manner, including clear decision making and referral points in addition to an estimation of risk; engaging senior nursing staff and the director to assess the usability and practicality of the protocol; and presenting a draft for consideration to medical and nursing personnel, with subsequent review, endorsement

and implementation.

Use of penicillins and cephalosporins for treatment of sexually transmitted infections

Current protocols in the clinic suggest the use of beta-lactam antibiotics as first line treatment for the following conditions, in accordance with national guidelines [5,6]:

Syphilis

IM benzathine penicillin 1.8 g stat single dose for early syphilis (including early latent syphilis), 3 weekly doses for late latent syphilis

Uncomplicated gonococcal infections

IM ceftriaxone 500 mg stat (in conjunction with azithromycin 1 g orally)

Pelvic inflammatory disease (PID)

IM ceftriaxone 500 mg stat (in conjunction with doxycycline 100 mg BD for 14 days and metronidazole 400 mg BD for 14 days)

Mechanism of penicillin allergy and associated reactions

This article focuses on the main concern with penicillin allergy, which is the possibility of anaphylaxis, an IgE-mediated (type I) hypersensitivity reaction. However, the clinician should be aware that delayed type hypersensitivity reactions (type IV) can also occur, causing exanthema or other skin eruptions, such as morbilliform reactions. These are not determined by the beta-lactam ring or side chains of the antibiotics, but rather, the ability for a drug to act independently as a hapten and become antigenic in nature. [7] This antigenicity triggers an immune response through interaction with antigen-presenting cells (APC) and T-cells. [8]

The major determinant of anaphylactic reactions to beta-lactam antibiotics is the beta-lactam ring, which is shared amongst the penicillin class, as this binds to endogenous lysine proteins to form a hapten. [9] However, there is also evidence to suggest that an IgE-mediated reaction can occur with the minor determinants of the molecule, which is the R chain (acyl) side group of individual penicillins (Figure 1). IgE binding results in mast cell activation and histamine release, in addition to the release of inflammatory mediators.

In patients who develop an IgE-mediated reaction, there is subsequent risk of a more severe reaction on re-exposure. IgE-mediated reactions can have effects on the following body systems: dermatologic (urticarial rashes, angioedema, macroglossia), respiratory (asthma, bronchospasm, wheezing, laryngeal swelling), gastrointestinal (abdominal pain, vomiting, diarrhoea, cramping), and cardiovascular (hypotension, vascular collapse, altered consciousness, shock).

Whilst no universal definition exists for anaphylaxis, two commonly accepted definitions in Australia are: (1) the acute onset of illness, with typical skin features (urticarial rash, erythema/flushing, angioedema)

plus involvement of one other body system; or (2) the acute onset of hypotension, bronchospasm or upper airway obstruction with or without skin features. [10]

Incidence of penicillin allergy and cross reactivity with cephalosporins

Various early studies suggested the incidence of penicillin allergy to be approximately 2% per course, with anaphylaxis estimated in 0.05% of all penicillin courses. [1] However, a large retrospective cohort study in the UK, which looked at 3,375,162 patients prescribed subsequent courses of penicillin, found a much lower incidence of only 0.18%. [11] It must be noted when quoting these figures that the definition of an 'event' in this study did not include asthma or eczema; however, when included, the incidence increased from 0.18% to 9% which makes interpretation difficult as we consider asthma a feature of allergy in Australian definitions. [11]

It is difficult to accurately identify if a trend over time exists in patients having a penicillin allergy. Multiple protocols exist internationally about the diagnosis of penicillin allergy and subsequent testing. [12] Furthermore, an element of bias may be present from both the patient and the clinician as the label of an 'allergy' can be highly subjective, and a permanent feature on a health record without subsequent confirmation.

Many early studies have quoted 10% cross-reactivity between penicillins and cephalosporins. [13,14] Unfortunately, these original studies assessing cross-reactivity over three decades ago were flawed, poorly designed open studies, lacking control groups, and have consequently overestimated this figure. [15] Furthermore, it is also postulated that the original manufacturing processes of cephalosporins contributed to inflated allergy rates, due to cross-contamination with penicillin compounds. [15] Since manufacturing processes have been refined, there has been a reduced incidence in cross-reactivity. If studies past 1980 are exclusively considered, a patient with a confirmed penicillin allergy (by positive skin test) will react with a cephalosporin in less than 2% of occasions. [15]

There is further evidence to suggest that there is less cross-reactivity with newer cephalosporins (second generation and onwards). A recent review and meta-analyses have found that third generation cephalosporins, such as ceftriaxone, have a cross reactivity rate of only 0.8% in those patients who are confirmed to be penicillin-allergic by skin testing, compared to 2.9% with older cephalosporins such as cephalexin. [16,17] Furthermore, these papers established that the risk of anaphylaxis due to cephalosporin cross-reactivity is quite small, as there was a higher incidence of anaphylactic reactions to cephalosporins with a negative penicillin skin test, compared to positive skin test patients. [16] This demonstrates that anaphylaxis reactions are often unpredictable.

Assessing the type and severity of penicillin allergy

Evidence suggests that history from the patient, especially when vague or not documented, is insufficient for assessing the degree of penicillin allergy. [18] Furthermore, the potential for allergy changes over time, with 80% of individuals with a documented IgE-mediated reaction having no evidence of reactive IgE after 10 years from initial reaction. [19] Most IgE-mediated reactions occur within seconds (IV administration) or up to an hour if administered orally with food. [20] Reactions outside of this timeframe are less likely to be IgE-mediated.

Hence, when taking a history, specific information should be sought to identify the presence of low- or high-risk features of the previous penicillin-related reaction, and consequently stratify the risk of future allergic reactions to a penicillin or cephalosporin.

High-risk features include: reaction occurred within one hour of administration; reaction occurred within the last 10 years; well documented history of features suggestive of anaphylaxis; required hospitalisation; any features suggestive of anaphylaxis as defined

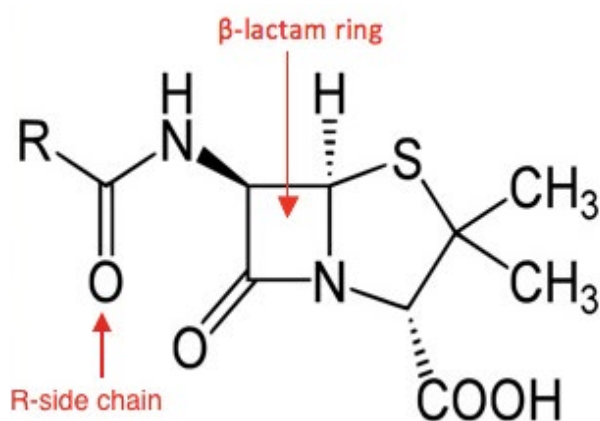


Figure 1. The beta-lactam ring is found in penicillins and several other closely related drug classes. Variants in the R chain are found within each drug class.

previously; and features of type IV hypersensitivity reactions including blistering, mucosal involvement, early onset desquamation (peeling), blood abnormalities such as derangements in liver function, renal function, or eosinophils. [15]

Low-risk features include: reaction occurred more than one hour after administration; reaction occurred more than 10 years ago; history is vague, unclear or poorly documented; localised reaction of mild severity involving one system only (rash not displaying any 'high-risk features' or stomach cramping); and a reaction that is not a true allergy; for example, an amoxicillin-Epstein Barr virus reaction. [10,15]

Role of the radioallergosorbent test, skin testing and desensitisation for penicillin allergy

In any patient with features of penicillin allergy, there should be consideration of referral for immunological skin testing and/or desensitisation, which can be performed quickly and is cost effective. The radioallergosorbent test (RAST) is more expensive, takes time to analyse and has poor positive predictive value. Desensitisation is performed in a supervised setting, can take 4-12 hours to complete in an acute setting, and results in a temporary reduction in immunogenic potential towards penicillins or associated medications. [21] Immediately following desensitisation, the first dose of penicillin is usually given. It must be noted that penicillin skin testing should also include testing against related beta-lactams such as cephalosporins, as a positive penicillin skin test cannot accurately predict cross-reactivity. [17]

Recommended drug choice in penicillin allergic patients

Based on the information outlined, and current existing guidelines, the following recommendations have been derived:

1. Any patient who has high-risk features on history should not receive a beta-lactam agent. [22] An alternative efficacious drug should be prescribed. If there is no efficacious alternative, or a cephalosporin is required, referral to immunology should occur for skin testing and desensitisation if needed.
2. In those patients who have only low-risk features on history, the following question must be addressed: 'which antibiotic

is required?' If a penicillin-based compound (i.e., benthazine penicillin) is required, the same precautions should be taken as mentioned above. However, if a cephalosporin such as ceftriaxone is required, the medication may be administered as the risk is less than 1% for third-generation cephalosporins. In this setting, the patient should be advised of the small but possible risk of an allergic reaction. [16]

Routine monitoring

Regardless of what antibiotic is prescribed, routine monitoring is advised as all serious allergic reactions need appropriate medical care. Observation facilities in addition to life support equipment and staff trained in first aid are essential in administering stat doses of antibiotics for the treatment of sexually transmitted infections. Signs and symptoms to look for during the observation period include the following: rash, swelling around the face/tongue/eyes, breathing difficulty, wheeze, vomiting, diarrhoea, abdominal pain, syncope or pre-syncope (low blood pressure), altered consciousness or shock. If any of these features are present or there is concern, refer to the local anaphylaxis and emergency protocols.

Case outcome

Although specific details of the previous allergic reaction could not be recalled by the patient, collateral history from his family suggested an urticarial reaction at the age of seven, with no other systemic features and not requiring hospitalisation. Consequently, the patient was deemed low-risk for a cross-reactivity allergic reaction towards ceftriaxone. He received the original prescribed treatment of 500 mg IM ceftriaxone and 1 g oral azithromycin without any adverse effects, or features of an allergic reaction. To treat his syphilis, he underwent a rapid desensitisation and subsequently received 1.8 g intramuscular benzathine penicillin, with no adverse effects.

Conflict of interest

None declared.

Correspondence

J Floridis: john.floridis@nt.gov.au

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The history of modern general anaesthesia

Dr. Richard Seglenieks
BMedSc(Hons), MBBS

Richard is currently undertaking his internship at the Royal Adelaide Hospital, having recently graduated from Adelaide University. He also completed an Honours Bachelor of Medical Science in Anaesthesia and Intensive Care.

Safe and effective anaesthesia is among the greatest advances in medical history. Modern surgery and the considerable benefits it brings would be impossible without the significant academic, pharmacological, and practical advances in anaesthesia over the past 200 years. At the forefront of these are the major developments in general anaesthesia and airway management. This article aims to provide a basic framework to understand the development of modern general anaesthesia.

A brief history of general anaesthesia

Anaesthesia is a relatively new field in modern medicine. Prior to its development, most surgical procedures were either minor or emergency operations. [1] It is clear that modern surgery and the considerable benefits it brings would be impossible without the significant academic, pharmacological, and practical advances in anaesthesia during the 19th and 20th centuries. First and foremost among these is the development of safe and effective general anaesthesia.

Carbon dioxide was first explored as an anaesthetic in the 1820s by the English physician Henry H. Hickman. By inducing partial asphyxiation, Hickman demonstrated that animals could be rendered unconscious for a prolonged period, enabling surgical procedures to be performed. [2] This was a major breakthrough, however the risks associated with hypoxic anaesthesia were too great to see the widespread adoption of carbon dioxide as an anaesthetic.

Diethyl ether, a solvent commonly referred to simply as 'ether', was first used clinically by American physician William E. Clarke for a tooth extraction in January 1842. [3,4] Several months later Crawford W. Long, an American surgeon and pharmacist, famously used ether as a surgical anaesthetic to remove a growth on a young man's neck. He published his findings after seven years, revealing that the patient felt nothing throughout the procedure. [5] The discovery of ether's clinical utility represented a significant advance in effective general anaesthesia, spurring a flurry of interest in potential anaesthetic agents.

Still used today for its anaesthetic properties, nitrous oxide was experimented with during the 19th century. Positive experiences by chemist Humphrey Davy lead to public gatherings, in which members of the public would inhale nitrous oxide for its exhilarating and pleasurable effects. [2] A medical student, Gardner Quincy Colton, made over \$400 profit from one such affair that attracted three to four thousand attendees. [6] These events were similar to those held for ether, known as 'ether frolics.' [2] Following the observation in these gatherings of nitrous oxide's analgesic and anaesthetic effects, it was formally tested in December 1844. Horace Wells, a dentist who had attended one of Colton's exhibitions, persuaded a colleague to extract one of Wells' teeth while Colton administered nitrous oxide gas. [7] The procedure was performed successfully, reportedly the first tooth ever removed painlessly. [8]

A former student of Wells, William T. G. Morton, was instrumental in the popularisation of ether as an anaesthetic. Morton performed a successful public demonstration of the anaesthetic capabilities of ether in October 1846 at Massachusetts General Hospital. [1] This event is often considered to mark the birth of modern anaesthesia, following which ether was widely adopted around the world. Later that year, Oliver W. Holmes, a writer and professor of anatomy, named the



process which Morton demonstrated *anaesthesia*, derived from the Greek for 'without sensation.' [2]

Scottish obstetrician James Y. Simpson was the first to adopt the organic compound chloroform to relieve the pain of childbirth in 1847. Chloroform anaesthesia grew in popularity around the world and was in wide use when Queen Victoria gave birth to Prince Leopold under its influence in 1853. The chloroform was administered by the famous physician and epidemiologist John Snow. [2] In the early 20th century, chloroform came to supersede ether as a general anaesthetic in light of its less offensive odour, and rapid induction and emergence.

Though the first intravenous injections took place in 1656, [9] the first intravenous anaesthetic, sodium thiopental (thiopentone), was not synthesised until 1934. [10] Thiopentone is a short-acting, rapid-onset barbiturate sometimes used for anaesthetic induction. Its earliest documented use in humans was later in 1934 by Ralph Waters, an American anaesthetist. [2] Intravenous anaesthesia allowed more precise dosing and a less confrontational experience for the patient, and thiopentone rapidly entered common usage. Although it remained popular for many years, thiopentone was gradually replaced by propofol as the preferred induction agent. Introduced in the late 1980s, propofol allowed rapid induction and emergence, reliable hypnosis, and has antiemetic properties. [1]

Significant advances were also made in the 20th century in developing better halogenated inhaled agents. The advent of improved volatile agents, in parallel with a rising interest and focus on patient safety, saw a shift from ether and chloroform anaesthesia to the use of newer intravenous and inhalational agents with more favourable characteristics. Routinely used today, these agents provide fast induction and emergence, and are ideally suited for maintenance of anaesthesia. After halothane and enflurane came isoflurane, then sevoflurane, and finally desflurane in the early 1990s. [1] These new volatile agents had a number of desirable properties including low solubility, minimal cardiorespiratory depression, and unlike ether, are non-flammable. In contrast to ether and chloroform however, they lack analgesic effects, necessitating the use of other agents such as opioids, local anaesthetics, or nitrous oxide to ensure adequate pain relief. Nitrous oxide saw a steady decline in use over the following years, in part due to the availability of these newer agents, but also because of concerns about potential toxicity and its link with postoperative nausea and vomiting. [1]

The introduction of muscle relaxants to clinical practice in the early 1950s allowed for major advances in anaesthetic techniques and thereby surgery. Curare, a natural alkaloid historically used on poison darts and arrows by aboriginal people across Africa, Asia, and the Americas, [11] was the first non-depolarising muscle relaxant used. Through the late 1970s to 1990s, quaternary ammonium muscle relaxants were developed, including vecuronium, atracurium, and rocuronium. These compounds brought several advantages, including more favourable cardiovascular effects and minimal release of histamine. [12] Due to their clearance by Hoffman elimination rather than renal excretion, atracurium and subsequently cisatracurium also possess the additional benefit of predictably rapid recovery with little cumulative effect following repeated administration. Suxamethonium, still in use today, was also developed in the 1950s. It is a depolarising neuromuscular blocking agent with fast onset and offset of action. It is considered by many as the agent of choice for rapid-onset neuromuscular blockade and has a short duration of action, although its side-effects of potassium release and increased intra-thoracic, intra-abdominal, and intra-cranial pressures will sometimes contraindicate its use.

Advances in monitoring have significantly impacted upon the practice of anaesthesia including the introduction of pulse oximetry and capnography in the 1980s. [1] The routinely used combination of these has contributed to a reduction in the proportion of anaesthesia-related complications that are preventable by monitoring from 39% in the 1970s to only 9% in the 1990s. [13] Other advances have included the measurement of inspired and end-tidal gases, including oxygen, nitrous oxide, and the volatile agents. The advent of 'depth of anaesthesia' monitors such as bispectral index (BIS) monitors has advanced our understanding of anaesthetic practice. Modern anaesthesia has achieved such an impressive degree of safety that the anaesthesia-related mortality in Australia is less than 3 deaths per million annually. [14]

A brief history of endotracheal intubation

In the late 19th century great advances were made in airway management for patients undergoing general anaesthesia. Without advanced airway support, the great safety and efficacy of modern anaesthesia would be impossible. The laryngeal tube had reportedly existed since at least 1791, and was used for a range of purposes including to facilitate breathing in oedema of the glottis, for direct delivery of medications to lung tissue, and for artificial respiration. [15]

Charles Trueheart of Texas published an account in 1869 describing a biphasic artificial respiration device, which included a laryngeal airway. However, the first successful delivery of endotracheal general anaesthesia was performed through tracheotomy by German surgeon Friedrich Trendelenburg in 1871. [16] Over the following decades, this technique was adapted in multiple settings to be delivered by oro-tracheal intubation and thus avoid the need for a surgical airway. [16,17]

A further breakthrough in intubation came in 1895, when German physician Alfred Kirstein performed the first laryngoscopy with direct visualisation of the vocal cords. [18] Previously, direct visualisation was thought impossible, and the glottis and larynx had been visible only by indirect vision using mirrors. Kirstein called his device the *autoscope*,

now known as a *laryngoscope*, and in the process of its development he established many of the principles of laryngoscopy which continue to be used in clinical practice. [18]

In 1913, Chevalier Jackson introduced a new laryngoscope blade with a light source at the distal tip, rather than the proximal light source used by Kirstein. [19] That same year, Henry Janeway expanded upon this, also including batteries in the handle, a central notch for maintaining the tracheal tube in the midline of the oropharynx, and a slight curve to the tip of the blade. [20] These changes were instrumental in popularising the use of direct laryngoscopy and tracheal intubation in anaesthesia, and the use of endotracheal intubation spread greatly following the First World War. [15]

Sir Ivan Magill went further with his invention, the Magill laryngoscope blade. The most significant features of this blade included a flat and wide distal end of the speculum, improving control of the epiglottis, and a slot on the side allowing the passage of catheters and tubes without obscuring vision. [21,22] He also developed the technique of awake blind nasotracheal intubation in 1928, along with a new type of angulated forceps (the Magill forceps) for nasotracheal intubation, and a new endotracheal tube. [21] The Magill laryngoscope blade remains in use today, however in 1943 Sir Robert Macintosh introduced the Macintosh blade, a curved model which is currently the most widely used laryngoscope blade. [23] Other specific blades may be used for certain patient subsets, such as straight laryngoscope blades in infants or the McCoy laryngoscope blade for difficult intubations.

The laryngeal mask airway (LMA) was first used in 1981 before being officially released in 1988. [24] The LMA revolutionised airway management – it provides a clear airway, forms an effective seal at the glottic inlet, and largely avoids the risk of trauma associated with intubation. [24] Endotracheal intubation remains an indispensable skill for the anaesthetist, with both LMAs and endotracheal tubes widely used.

A range of equipment for intubation is now available, including video laryngoscopes and fibre-optic bronchoscopes to aid in visualising the difficult airway, tubes with and without cuffs, reinforced tubes, and double-lumen tubes. Measurement of end-tidal carbon dioxide by capnometry has also provided a useful adjunct to direct visualisation for confirming correct placement of the endotracheal tube. [25,26] Despite these advances, the modern endotracheal intubation still relies heavily on the principles laid down by Kirstein and his successors.

Conclusion

Considerable progress has been made in the field of anaesthesia over the past two centuries. The development of safe, effective general anaesthesia is one of the most important advances in medical history, allowing the widespread expansion of surgery and the considerable benefits it brings. Significant advances beyond the scope of this article include the developments of local anaesthesia, regional anaesthesia, conscious sedation, and analgesia.

Conflict of interest

None declared.

Correspondence

R Seglenieks: richard.seglenieks@alumni.adelaide.edu.au

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Cutaneous manifestations of neonatal bacterial infection

Dr. Jazlyn Read
BPhty, MBBS

Jazlyn is an intern at the Royal Brisbane and Women's Hospital, and wrote this article while studying final-year medicine at Griffith University. In her spare time she enjoys travelling and languages.

Skin is a physical barrier that forms the first line of defence against potential pathogens. In the newborn, a range of cellular, immunological, and functional factors underpin an increased susceptibility to bacterial infection. This article reviews the structural and functional differences between newborn and adult skin, the innate immune system of the epidermis and dermis including the role of the cathelicidins, beta-defensins, and Toll-like receptors (TLRs) in neonatal skin defences, and the spectrum of neonatal cutaneous bacterial infections. *Staphylococci* and *streptococci* are the most common organisms responsible for cutaneous bacterial infections, and cause a wide range of clinical presentations depending on inoculation site, organism strain, and neonatal immunity. Premature neonates in particular are at increased risk of infection, due to an immature stratum corneum and impaired cutaneous barrier function. The emergence of multi-resistant strains highlights the importance of prevention measures and judicious antibiotic use, and will be of increasing significance in this 'post-antibiotic' era.

Introduction

Skin forms a dynamic interface with the external environment and is a complex organisation of cell types and associated structures that performs many essential functions. Although the stratum corneum of full-term neonates is analogous to that of adult skin, structural and compositional differences of the skin renders the newborn more susceptible to bacterial colonisation. Particularly for the preterm neonate, impaired cutaneous barrier function and an immature immune system reduce the capacity to defend against bacterial pathogens. The majority of cutaneous bacterial infections are localised to the skin and are easily treated, however, systemic bacterial infection and disseminated disease in the neonatal period may be life-threatening.

Differences in neonatal skin

Newborn skin is fundamentally different from that of the adult and adapts to the extrauterine environment during the first year of life through ongoing structural and functional changes. [1] Skin is a complex, selectively permeable membrane that performs a number of roles, including protection from infection and external stressors such as ultraviolet (UV) light damage, temperature regulation, sensation, and physical appearance. Protection against the external environment is primarily due to the most superficial layer of the epidermis, the stratum corneum, and recent advances in fluorescence spectroscopy and electron microscopy have helped elucidate the differences between adult and newborn skin. [1-3] The stratum corneum is a layer of lipid-depleted, protein-rich corneocytes embedded in a matrix of extracellular lipids, resulting from the continuous proliferation of keratinocytes in the basal epidermis. [3] Compared with adult skin, newborn skin produces smaller corneocytes, a thinner epidermis, and an increased density of microrelief grooves (Table 1). [1] The corneocytes of newborns also have a higher degree of irregularity and decreased organisation in both development and subsequent desquamation phases. [2] The change in neonatal skin pH from neutral, at birth, towards a more acidic mantle is also likely to impact on stratum corneum integrity, as incomplete skin surface acidification is linked to variable rates of desquamation. [3,4] Overall, decreased corneocyte size and a thinner, less cohesive stratum corneum has



negative implications for skin barrier function, as indicated by increased transepidermal water loss (TEWL) in newborn skin. [5]

Compared with full-term infants born at 37-42 weeks' gestation, preterm newborns do not develop the same level of protection provided by the stratum corneum until 2-4 weeks after birth. [6,7] The most significant difference is an increase in the stratum corneum from two to three cell layers at 28 weeks' gestation to the equivalent of adult skin with 15 layers by 32 weeks' gestation. [8] Due to the role of the stratum corneum in barrier protection, the premature newborn is at considerably greater risk of cutaneous complications.

Changes in TEWL, skin pH, and sebaceous activity all lead to the creation of a skin environment that promotes colonisation of certain microbial skin flora. [9] Colonisation of resident flora commences at birth, but newborns have a unique skin microbiome profile that develops throughout the first year of life and beyond. [9] The protection offered by resident commensal and mutualistic skin flora in the adult is therefore not immediately present in the newborn, leading to different patterns of subsequent infection.

Table 1. Differences between newborn and adult skin. [1,2]

	Newborn	Adult
Epidermis		
Stratum corneum	Thinner	Thicker
Corneocyte size	Smaller	Larger
Epidermal proliferation and desquamation rate	Higher	Lower
Dermis		
Distribution of dermal papillae	More homogenous	Less homogenous
Border between papillary and reticular dermis	Absent	Present
Function		
Transepidermal water loss	Higher	Lower

Skin defences and immune response of the newborn

Skin has antimicrobial function afforded by the innate immune system and antigen presenting cells (APCs) of the epidermis and dermis, as well as circulating immune cells that migrate into the dermis. This innate system works together with the adaptive immune system to defend against infection. In the newborn, innate immunity is the most important mechanism of defence, as this system is present at birth as a result of pattern recognition receptors encoded by germline DNA. This system responds to biochemical structures common to a number of pathogens, producing a rapid response with no residual immunity or memory. In contrast, adaptive immunity develops slowly and involves specific antigen receptors of T- and B-lymphocytes as part of a system that develops memory for faster successive responses.

Innate immune defences comprise the physical barrier formed by the skin itself, antimicrobial peptides (AMPs), complement pathways, and immune cells including monophages, macrophages, dendritic cells, and natural killer cells. [10,11] While the keratinocytes of the skin are typically considered to be static 'bricks' of the physical skin barrier, they are also dynamically involved in immunity by their secretion of cytokines and chemokines, AMPs, and complement components. AMPs secreted by keratinocytes are cationic proteins termed cathelicidins and defensins, and they appear to be particularly important in neonatal immunity, with selective bactericidal activity against common cutaneous pathogens. [12,13] Cathelicidins (LL-37) and beta-defensins (BD-1, BD-2, BD-3) are attracted to negatively charged bacteria, viruses, and fungi and exert their influence by membrane insertion and pore formation. [13] Neonates display higher baseline concentrations of cutaneous AMPs than adults, suggesting a greater role for these proteins in newborn skin defences. In the absence of specific antibodies, pattern recognition receptors such as TLRs play a pivotal role, with subsequent cytokine production changing with increasing age and correlating to age-specific pathogen susceptibility. [14]

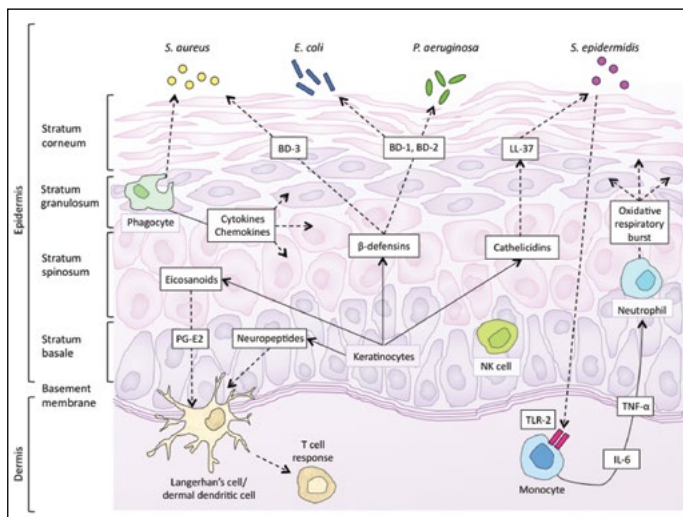


Figure 1. Innate immunity of the skin in the newborn.

Bacterial infections

Cutaneous staphylococcal and streptococcal infections cause a variety of clinical presentations depending on site of infection, strain of organism, and neonatal immunity. Impetigo is a superficial bacterial cutaneous infection that may present with or without bulla formation, as described by the conditions non-bullous and bullous impetigo. The bullae of bullous impetigo are invariably due to infection with *S. aureus* and the subsequent production of epidermolytic toxin, which is also responsible for the widespread bullae and desquamation in staphylococcal scalded skin syndrome (SSSS). Development of resistant strains, overcrowding, and poor infection control have been linked to nosocomial outbreaks of *S. aureus* and is of particular concern in neonatal intensive care units where neonates are more susceptible to

infection. [15]

Non-bullous impetigo

Both *Streptococcus pyogenes* and *S. aureus* are associated with the non-bullous form of impetigo, which presents as an erythematous macular rash before developing eroded lesions with a honey-coloured crust. [16] Isolated staphylococcal pustules and paronychia are also common in neonates. Although mild non-bullous impetigo has the capacity to self-resolve, treatment with topical mupirocin and fusidic acid limits the opportunity for disease to persist. [16]

Bullous impetigo

Localised cutaneous *S. aureus* infection presents with an erythematous vesiculopustular rash that preferentially affects the diaper area and skin folds, coalescing to form large flaccid bullae that rupture easily and appear as honey-crusted erosions. [16,17] Bacteria are present in the lesions, and the infection usually responds to first-line systemic flucloxacillin, which may be used in conjunction with topical fusidic acid. [16,17] Certain strains of *S. aureus* are associated with epidermolytic toxins, which facilitate pathogen entry beneath the stratum corneum and limit disease to the superficial epidermis. [18,19] The distinct bullae present in bullous impetigo are due to the toxin-induced cleavage of desmosomal cadherin proteins in the granular layer of the epidermis, which are normally responsible for maintaining functional adhesion between keratinocytes. [18] These same toxins are produced in SSSS.

Staphylococcal scalded skin syndrome

Haematogenous spread of *S. aureus* is facilitated by inoculation at a distant site such as the conjunctiva, umbilicus, or perineum, and the effects of bulla formation and desquamation are the direct result of circulating epidermolytic toxins. [20] This haematogenous spread results in a widespread infection that is more severe than the localised infection of bullous impetigo. Generalised erythema and skin tenderness are the initial clinical features, with evolution into large flaccid bullae and desquamation of the entire cutaneous surface. The Nikolsky sign is present, where blistering can be elicited by light stroking of the skin. [21] Bacterial cultures of cutaneous lesions are typically negative and *S. aureus* is only found at the distant sites of infection. Skin biopsy is considered the gold standard of diagnosis and is particularly relevant when considering toxic epidermal necrolysis (TEN) as a differential. In contrast to SSSS, TEN results in subepidermal blisters and keratinocyte necrosis rather than epidermal cleavage and typically involves oral mucous membranes. [20,21] Although biopsy is helpful in providing a definite diagnosis, neonatal biopsies are rarely performed due to the characteristic clinical presentation of both conditions. Despite the apparent polarity of the cutaneous and haematogenous forms of *S. aureus* infection, a handful of mild SSSS cases have been reported, lending support to a likely clinical spectrum ranging from a mild form to the classic severe disease. [22]

Omphalitis

After birth and separation of the umbilical cord, necrosis of the stump is followed by epithelialisation. The healing stump may become colonised, with the exposed umbilical vessels forming a potential portal of entry for pathogenic bacteria. [23] Omphalitis is characterised by stump erythema and periumbilical oedema, with or without discharge, and is frequently due to *S. aureus*. It is more common in developing countries, and the risk is increased in cases of protracted labour, non-sterile delivery, and prematurity. [23] A recent Cochrane systematic review identified significant evidence to support the use of topical chlorhexidine on the umbilical stump to reduce omphalitis and neonatal mortality in developing countries. However, this benefit could not be demonstrated in developed countries, possibly owing to reduced risk factors for omphalitis. [24]

Necrotising fasciitis

Infection of the fascia and overlying soft tissues is a rapidly progressive

neonatal emergency. Pathogens gain entry by cutaneous breaches such as omphalitis, birth trauma, and superficial skin wounds, with group A streptococci most commonly implicated as the causative organism. [25] Infection may also be polymicrobial, with a combination of organisms detected on wound cultures. [26] The infection follows the fascial plane, causing thromboses in the blood supply to overlying tissues and leading to tissue necrosis, and the skin becomes progressively more discoloured, tender, and warm. [26] While the initial presentation may not appear concerning, neonates rapidly become disproportionately tender and toxic. [26] Necrotising fasciitis has a high morbidity and mortality and requires immediate identification for surgical debridement. [25]

Ecthyma gangrenosum

Pseudomonas aeruginosa septicaemia is the most common underlying cause for this cutaneous manifestation, which typically presents with macules that progress via a necrotising vasculitis to form indurated necrotic ulcers with surrounding erythema. [27,28] Prematurity, immune deficiencies, and neutropaenia are the main predisposing factors, but lesions may develop in the absence of immunodeficiency when direct inoculation occurs through a breach in the skin barrier. [28]

Antimicrobial resistance and prevention

The treatment of neonatal bacterial infection depends on the pathogen and sensitivities to antibiotic treatments. In the Australian healthcare setting and internationally, antibiotic resistance poses a growing problem in this 'post-antibiotic' era. Methicillin-resistant *S. aureus* (MRSA) has become increasingly prevalent, particularly in the intensive care setting such as the neonatal intensive care unit (NICU). [29] As colonised neonates are continually admitted, the introduction of many

unique sources and various strains over time adds to the ongoing burden and is likely to contribute to difficulties in fully eradicating MRSA from the NICU. [30] Transmission of organisms such as *S. aureus* most commonly occurs secondary to direct contact with colonised caregivers, and this problem is compounded when hand hygiene and barrier protection is inadequate. Premature infants in the NICU are particularly susceptible, due to their immature immune systems and the increased risk of nosocomial infection with invasive monitoring and frequent healthcare worker contact. [31] The identification of previous treatment with third-generation cephalosporins and carbapenem as independent risk factors for the development of multidrug-resistant Gram-negative bacteraemia in the NICU highlights the issue of antibiotic resistance and underscores the importance of judicious antibiotic use. [32]

Conclusion

Skin is the first line of defence against invading pathogens, and there are a number of unique cellular, functional, and immunological factors that underpin an increased susceptibility to bacterial infection in the newborn. Premature newborns are at particular risk of infection, owing to potential deficits in cutaneous barrier function. Future practice in treating bacterial infections is likely to be influenced by the emergence of multi-resistant strains and may shift the focus toward improved prevention measures.

Conflict of interest

None declared.

Correspondence

J Read: jazlyn.read@griffithuni.edu.au

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The Emperor of All Maladies: cancer 101

Michelle Ong

Fourth Year Medicine (Undergraduate)
James Cook University

Michelle Ong is a 4th year medical student at James Cook University in Townsville. She recently completed an international placement in Singapore at various hospitals and GP clinics. She has a strong interest in rural and international health and aims to work with disadvantaged populations in her future career.

Mukherjee, S. The emperor of all maladies: a biography of cancer. London: Fourth Estate; 2011.

RRP: AU\$22.99

As medical students, we are experts in rare syndromes and exotic illnesses. However cancer, the second most common cause of death in the developed world, is still a total mystery. How do we explain to patients what so many of us don't understand? Where do we begin?

Dr. Siddhartha Mukherjee is an Indian-born American oncologist, researcher and Pulitzer Prize winner. In this captivating narrative, Mukherjee explores cancer, its complexities, changing personalities, nuances, pet-peeves and habits. Indeed, Mukherjee himself states that, 'it felt, inescapably as if I were writing not about something but someone.' The language, therefore, unlike the mere spouting out of facts like a medical textbook, draws one in, such that the reader feels that Mukherjee has blasted open a door and allowed us to enter a landscape of discovery.

Mukherjee describes cancer's existence thousands of years ago in Egyptian scripts, details the origins of the ongoing battle between cancer and physicians, and depicts his own clinical experiences with cancer patients, thus pouring insight, appreciation and a deeper understanding of this dreadful disease into the reader's mind. One cannot hope to pursue a discussion about the history of cancer without first explaining what it is. His brief explanation is easy to understand and strikes a happy medium between layman's terms and medical jargon, hence resonating perfectly with the mind of the medical student.

Cancer's story begins in Sidney Farber's lab in 1947, where leukemic cells were being studied. The utilisation of folate antagonists to treat leukemia can be credited to Farber's genius: 'If folic acid accelerated the leukemia cells in children, what if he could cut off its supply with some other drug – an antifolate?'. Thus, the idea of molecular targets and chemotherapy was born.

As chemotherapy grew in popularity, opportunities for combination therapy were explored. The author investigates the consequences of various clinical trials such as the catastrophic dips in white cell counts, the death toll rising with every turn of the page. He then leads us through the challenges of specific cancers, such as prostate and breast cancer.

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Mukherjee S. The Emperor of All Maladies: A biography of cancer. London: Fourth Estate; 2011.

Finally, Dr. Mukherjee arrives at the present day, detailing our new interests in gene therapy. Despite advancements, the true nature of cancer continues to elude us and with it, the cure consistently slips through our fingers. Dr. Mukherjee encapsulates this perfectly by advising us to, 'focus on prolonging life rather than eliminating death'. With cancer rates increasing, its presence is approaching a level of normality and this guidebook warns us not to underestimate 'the emperor of all maladies', an important lesson for all future doctors.

As a medical student, The Emperor of All Maladies is a great introduction into the world of oncology. It is an easy and fun read that is a refreshing break from the traditional textbooks we pore over daily. The reader is not only educated about the intricacies of cancer but also walks away with a great deal of empathy for the patients and families whose experiences are vividly narrated. Furthermore, in the journey from historical events to present day, Mukherjee's exciting and thrilling perspective of cancer is a useful timeline of the events of the past and what we, as medical students, can expect in the future of Oncology.

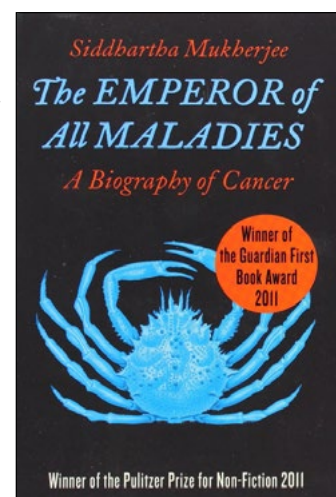
In summary, The Emperor of All Maladies is a roadmap of the places we have been, what we have done and where we still need to go. Cancer was, is, and will be the most challenging ailment that we, as future doctors will have to face. Hence, all medical students should take a note from cancer's biography and its master storyteller.

Conflict of interest

None declared.

Correspondence

M Ong: michelle.ong@my.jcu.edu.au





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Lina Hapoo
melbourne@amsj.org.au

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Sydney@amsj.org.au

Deakin University

Dan Hanna
deakin@amsj.org.au

University of Newcastle

Lukman Anderson
newcastle@amsj.org.au

University of Tasmania

Cecilia Xiao
tasmania@amsj.org.au

Flinders University

Agnik Sarkar
flinders@amsj.org.au

University of New England

Megan Grigg
une@amsj.org.au

University of Western Australia

Sarah Green
uwa@amsj.org.au

Griffith University

Grace Yeung
griffith@amsj.org.au

University of New South Wales

Denise Foo
unsw@amsj.org.au

University of Western Sydney

Chloe Boateng
uws@amsj.org.au

James Cook University

Tasciana Gordon
jcu@amsj.org.au

University of Notre Dame (Fremantle)

Mathew Jacob
fremantle@amsj.org.au

University of Wollongong

Sarah Chaudhry
wollongong@amsj.org.au

Monash University

Lewis Fry
monash@amsj.org.au

University of Notre Dame (Sydney)

Joe Wei
nd.sydney@amsj.org.au

