Volume 8, Issue 1 | 2017

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Volume 8, Issue 1 | 2017

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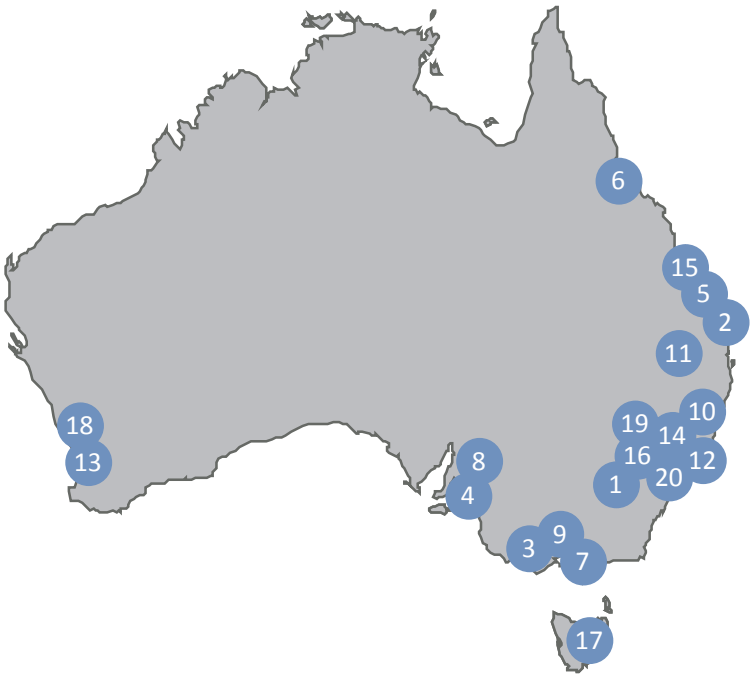

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Editor's welcome

Swaranjali Jain
Editor-in-Chief, AMSJ

Welcome to Volume 8, Issue 1 of the *Australian Medical Student Journal* (AMSJ). In this issue, we are proud to showcase the research and perspectives of medical students and junior doctors around Australia. We are privileged to include discussions on a wide array of topics, spanning the breadth of medicine, surgery and global health and providing snapshots into developments in these continually changing fields. We hope you will find the following articles of interest and take some inspiration on how you can also push the boundaries of medicine to improve patient care, the patient experience, and public health.

We are honoured to include the insights of doctors who are changing the face of medicine in Australia and abroad in our guest articles. Dr Stewart Condon, the current President of *Médecins Sans Frontières* Australia, writes of his unique journey in humanitarian and remote medicine and discusses the value in challenging yourself and expanding the possibilities of what you can achieve in your career to make a meaningful difference to those in need.

We also feature outstanding guest commentaries from clinicians with decades of research experience and leaders in their respective fields on the increasing importance of practicing evidence-based medicine, given the continuing rapid expansion of research and technology. Professor Frank Bowden provides an entertaining insight into how doctors can use EBM to navigate modern medicine and make sense of information overflow to truly determine what is best for our patients. Professor Ian Harris AM writes from a surgical perspective on how surgical practice needs to have rigorous scientific underpinnings, which is sometimes sadly lacking for many surgical procedures even today. Professor Rakesh Kumar invites clinicians to carefully consider their rational use of diagnostic investigations, particularly pertinent for all medical students to consider as they transition into becoming junior doctors, accountable to not only their individual patients but also the health system at large.

The AMSJ is a national peer-reviewed journal open to all medical students across Australia and once again, we are proud to highlight articles covering a range of issues. Sarah Yao, in her review article, looks ahead to the rise of big data in clinical research and the challenges and rewards associated with its inevitable use in the future; issues all future clinicians and researchers should be aware of. Dr Grace Leo in an original research article conducted in her medical student years provides a scholarly discussion on the impact of acquired brain injury in childhood. Our feature articles provide a range of moving perspectives on palliative care, empathy in medicine and the challenges faced in global health, and we thank our authors for contributing their perceptive insights and personal stories that we are sure will motivate and inspire you to consider the impact we can have on our patients and on a broader level as well.

Finally, on behalf of the AMSJ team, we would like to thank all of our authors, contributors, peer reviewers and sponsors who have contributed to making this issue possible. Their efforts, dedication, tenacity and generosity in volunteering their time are truly invaluable and we are most appreciative of their support. Thank you also to those working behind the scenes – our AMSJ team consisting of volunteer medical students who work tirelessly to edit, proof-read, publish, promote and finance each issue. Lastly, thank you to you, our readers – we hope you enjoy this issue and are inspired to engage in research, discussion and collaboration, so you too can push the boundaries of medicine now and throughout your careers in the future.

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Lacklustre performance: drugs targeting β-amyloid in Alzheimer's disease

Ross Penninkilampi
Associate Editor
4th Year Medicine

The Alzheimer's Association International Conference (AAIC) is the largest gathering of the Alzheimer's disease (AD) research community in the world, and provides a unique forum for the discussion of ideas and dissemination of knowledge. One of the key concepts grappled by the AD research community at AAIC 2016 in Toronto, Canada, was the validity of the amyloid hypothesis.

It is generally accepted that the accumulation of β-amyloid (Aβ), particularly $Aβ_{40-42}$, in the extracellular spaces around neurons as amyloid plaques is central to the pathogenesis of AD. This idea is expressed in the 'amyloid cascade hypothesis' [1,2]. It thus follows that by reducing the production of Aβ or eliminating the amyloid plaques from the brain, the progression of disease could be slowed, halted, or even reversed [3]. Alzheimer's disease is the most important cause of dementia, which affects a staggering 40 million people worldwide, a number which is predicted to double every 20 years until 2050 [4]. Therefore, achieving prevention, or even just slowing of disease progression, would have a significant impact on morbidity, mortality, and burden on healthcare systems worldwide.

Hence, significant funding has been directed by both public research institutions and private pharmaceutical corporations towards the development of drugs that target Aβ. Aβ is produced by two steps of enzymatic processing: first by β-secretase, and then by γ-secretase [5]. The latter has been targeted by drugs collectively known as γ-secretase inhibitors, most prominently avagacestat and semagacestat. Both of these drugs failed in Phase 2 and 3 trials, and notably were associated with cognitive decline, an increased risk of skin cancers, and an overall increased risk of serious adverse events [6-10]. It was suspected that the failure of γ-secretase inhibitors, particularly with regards to the adverse events profile, was due to off-target inhibition of Notch, a receptor that is involved in a signalling pathway that is particularly prevalent in the skin and gastrointestinal system [9-11]. However, tarenflurbil, a γ-secretase modulator that spared the active site of γ-secretase and hence spared Notch, also failed to be clinically efficacious, as measured by changes in cognitive indicators such as the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale – cognitive component (ADAS-cog), and the Clinical Dementia Rating – sum of boxes (CDR-sb) [12,13]. Hence, drug development has largely moved away from inhibition of γ-secretase, and β-secretase (BACE) inhibitors are now in early development as a potential alternative.

Active and passive immunotherapeutic agents targeting Aβ have also been tested, with mixed results. While bapineuzumab was successful in lowering amyloid concentrations in two Phase 3 trials, it did not cause any clinical improvement, compared to placebo, and was associated with the development of amyloid-related imaging abnormalities (ARIA) [14-17]. ARIA comprise two separate changes: vasogenic oedema and cerebral microhaemorrhages. These changes may occur due to destabilisation of amyloid in vascular walls [18,19]. While often asymptomatic, in combination with a lack of clinical efficacy this was sufficient to halt the development of bapineuzumab. Another immunotherapeutic, solanezumab, was underwhelming in its Phase 3 trial performance, but was better tolerated than bapineuzumab and showed some cognitive improvement in patients with mild AD [20-22]. Aducanumab [23], crenezumab [24], and gantenerumab [25] have all also shown promise and currently have Phase 3 trials in planning or underway. Hence, it appears that immunotherapy may be a more viable modality for the treatment of AD than inhibition of γ-secretase.

It is possible that all trialled therapeutics have targeted AD too late in the disease course, when clinical features such as memory decline and functional impairments have become frankly apparent. Hence, some trials have now shifted towards targeting AD earlier in its disease course. Mild cognitive impairment (MCI), also known as prodromal AD, is the accepted early pre-AD stage in which it is now believed the greatest improvements can be made, by preventing further decline [26]. Another stage prior to this, subjective cognitive impairment (SCI), in which patients report some cognitive changes but their scores on the MMSE and other indicators are unchanged, is also being recognised and may soon be targeted by therapeutic or preventive strategies [27].

It is also possible, of course, that the current paradigm of the amyloid cascade hypothesis is wrong. Perhaps the drugs have failed to show clinical efficacy, despite reducing cerebrospinal fluid Aβ levels, because Aβ is not actually central to disease pathogenesis. Another player in the game is tau – a protein that accumulates intracellularly in the classical neurofibrillary tangles. It was originally thought that tau accumulation occurred later in the disease course than that of Aβ and was in some way triggered by Aβ, supporting the role of Aβ accumulation as the primary mediator of disease progression. However, it is now being argued that tau may actually develop concurrently and independently of Aβ, and hence this may prove to be a viable target for pharmaceuticals in the future. What is certain, however, is that the pathogenesis of AD is complex, and it is unlikely that engaging with a single target will be sufficient for prevention or a cure [28].

Next year, when AD researchers congregate for AAIC 2017 in London, it is likely that the amyloid cascade hypothesis will further be tested by results from clinical trials of drugs targeting Aβ, particularly those of immunotherapeutic agents. Whether there is a significant paradigm shift in terms of our understanding of AD pathogenesis, or a reorientation of our efforts towards prevention over treatment, will largely depend on these results over the next decade. It is certainly important that significant progress is made in the near future, lest pharmaceutical companies that fund drug development put AD in the 'too hard' basket and move on to simpler challenges.

Conflicts of interest

None declared

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A different path: taking medicine beyond borders

Dr Stewart Condon
President, Médecins Sans Frontières Australia

Dr Stewart Condon is a medical doctor with extensive experience working in Australia and around the world. After completing his degree and junior years in Sydney he worked in remote Aboriginal communities in the Northern Territory as a rural medical practitioner.

Soon after he began his work with Médecins Sans Frontières (Doctors Without Borders) travelling to Sudan, Indonesia, Pakistan, Sri Lanka and Bangladesh. In 2014 he was elected President of Médecins Sans Frontières Australia.

In recent years, Stewart has diversified his clinical experience in emergency departments, prisons and remote area clinics with non-clinical roles. With experience in the public sector, the corporate environment and the non-government organisation (NGO) arena, Stewart has a unique perspective on medicine. His specialties include medical assistance, telehealth, rural and remote medicine and medical/humanitarian work.

I have been interested in humanitarian work since high school. I was always looking for a career that allowed me to help people, using the combination of science and communication. Medicine seemed to fit perfectly.

By the end of my medical degree I was thinking about how I could start working in the humanitarian sector. I liked the idea of taking my skills around the world, to places like South Sudan or Pakistan. We had a field worker come and talk to our Medsoc at a symposium around "travelling with your degree". This inspired me and showed me that I didn't have to take a standard path in becoming a specialist or a GP, living and working in Australia for the rest of my life. Alternate possibilities were out there.

It was at this time I also started orienting my work towards building skills that would be useful overseas. Paediatrics stood out for me – being able to treat sick or injured kids in third world contexts was always going to stand me in good stead. I worked my PGY3 as a paediatric resident at Sydney Children's Hospital at Randwick, and then half the year at Wollongong Hospital in general paediatrics. Having my diploma of paediatrics gave me a sense of confidence.

Working out bush

The next step was to get experience in remote medicine. I had lived in Sydney for all of my study years, and aside from a couple of years in the Illawarra, I'd remained city-based as I started to work. I needed to get out, and an opportunity to work in the centre of Australia came at almost the perfect time. I headed out to the Northern Territory for six months to work in the Yuendumu community, with the Warlpiri people.

Dr Stewart Condon attending an MSF refugee camp awareness raising campaign in Martin Place Sydney. Copyright: MSF

Dr Stewart Condon

Many Australians who work with Médecins Sans Frontières have experience working remotely, particularly with the Indigenous communities in Australia. Working within these remote communities is a challenge, for so many reasons. It's about resources, distance but perhaps most importantly a different concept of health and disease.

These circumstances exposed me to the idea that you cannot have access to everything that you need all the time, and at times it is necessary to trust your clinical gut to make a decision. You learn to be able to look at a patient and decide whether they need an urgent test today, in which case you can organise an immediate evacuation to hospital, or whether it's something you can keep an eye on. Working in the bush gave me the confidence to be able to do that, as well as the ability to work unsupported – an essential skill in remote areas.

Working remotely also opened my eyes to those patients who live in truly difficult circumstances and don't get the care they need. I knew about other organisations that did similar work to MSF but I was attracted to MSF because it worked right on the frontlines of international humanitarian crises, treating those patients that weren't being reached.

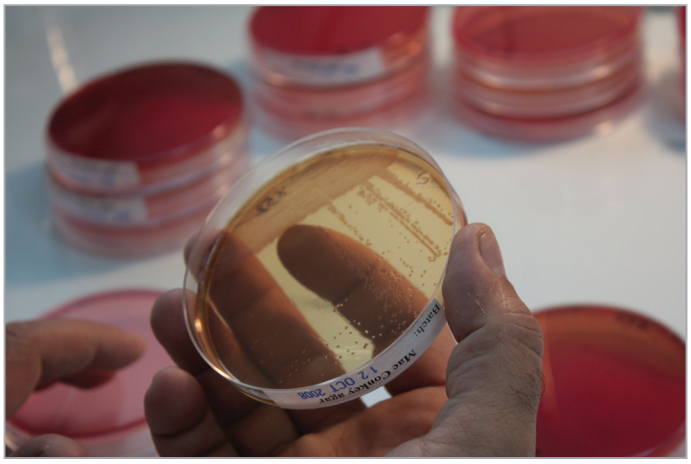
It was this experience in the Northern Territory that really prepared me for my first field assignment with MSF in Bentiu, in what is now South Sudan. It was 2004 and there were only three medical doctors at our project- two were international staff, including myself, and one

Sudanese doctor. We had very basic medical resources, no access to tests and some very sick patients who you had to take care of, quite often on your own. It was here I was able to challenge myself and recognise I had been taught what I needed to know - how to examine and treat a patient, and how to make a diagnosis. In modern medicine we often rely on a full battery of blood tests, x-rays, scans and specialist opinion. But from my experience in the Northern Territory I knew I could make a clinical judgement, and that not having the tests did not necessarily mean that patient care was compromised.

Dr Stewart Condon on his first field assignment with MSF in Bentiu, (now South Sudan) 2004. Copyright: MSF

My time in South Sudan gave me a taste for this humanitarian side of medicine, but it was really my second assignment in Aceh, Indonesia following the devastating tsunami in 2004, that opened my eyes up to the humanitarian issues around the patients we were seeing every day. It was in Aceh that I began to recognise that it was not just about the patients that we were seeing nor the medical care, it was just as much about humanitarian need. It was at that point I realised I was interested in becoming a Coordinator, rather than solely a doctor. During my next assignments in Pakistan, Sri Lanka and Bangladesh I took on roles as

MSF, Amman Hospital - 2016
This man is a 23 years old Syrian. he used to study law in Damascus. He was among the first revolutionaries in Deraa, in the ASL brigade. This is the third time he is wounded, a bomb took his leg away.
Amman hospital reconstructive surgery project is meant for the wounded of Jordan's surrounding countries that undergo war, armed conflict or violence. The reconstructive surgery hospital offers integrated care and sophisticated surgical operations, physiotherapy and psychological support. All patients admitted are considered being "impossible to treat" in their original country, because of either access problems or technical complexity. Since the opening of the structure, MSF has been taking care of 3 600 patients.
Photographer: Chris Huby



Examination in the laboratory of the hospital of Souleymanieh, October 2008. In the medical bacteriological laboratory teams prepare culture media and reagents in order to carry out the bacteriological analysis.
Photographer: Jean Baptiste Ronat

Project Coordinator and Country Medical Coordinator. In these roles I was able to work together with other humanitarian organisations, as well as government authorities. It gave me a sense of other parts of MSF that I could give value to, beyond medicine.

Attacks on hospitals

I have been President of MSF Australia for nearly three years and on the board since 2011. The most important part about being President is my responsibility to our field workers and patients. One of the most alarming trends we have faced in the last couple of years is the attacks on hospitals and medical facilities. In Afghanistan, South Sudan, Yemen and Syria we have seen our hospitals repeatedly attacked. Unfortunately, these are not isolated events and the normalisation of such attacks is intolerable. For us attacking hospitals and medical workers is a non-negotiable red line. International humanitarian law protects medical facilities, the people working in them, and the people receiving treatment.

Another challenge, more medical but no less critical, is antimicrobial resistance. Drug-resistant infections are a looming challenge for our humanitarian work. We see them in the war-wounded people we treat in Jordan, in newborns in Niger, and in our burns unit in Iraq.

Kunduz Hospital After the Attack
The remains of a bed frame in a room on eastern wing of the main Outpatient Department building. Burnt-out corridors, collapsed roofs, twisted metal and ash, is all that remains of many building at the MSF Trauma Centre in Kunduz, northern Afghanistan, following the 03 October US airstrike on the facility which killed more than 20 MSF staff members and patients.
Photographer: Andrew Quilty

Central laboratory of Koutiala hospital.
End of 2013, MSF initiated the restructuring and renovation of the central laboratory of Koutiala hospital, where MSF manages the pediatric unit. MSF has added a department of bacteriology, operational since March 2014, to improve the diagnoses made in the laboratory and meet the requirements of quality of medical care at the hospital. Through the department of bacteriology, MSF is now able to diagnose all bacterial diseases which are affected children.
Photographer: Aurelie Baumel

Haydan Hospital
Haydan Hospital, March 2016, after 5 months of air strikes.
Constant bombing , blocking of aid, non-observed truces ... In six months , the Yemeni conflict has claimed thousands of lives, including many hundreds of children, and reports of more than 1.5 million displaced.
Photographer: Atsuhiko Ochiai

Our medical staff are increasingly seeing people with infections that can only be treated with the last lines of antibiotics. When I was in Pakistan in 2006, post-earthquake, we recognised quite early on many patients were not improving after treatment. Some of these patients were already on very heavy antibiotics because in this particular community they had been given antibiotics for anything and everything. As a result, many had resistant bacteria on their skin which would then go into their bones, giving them bone infections. We were having to use heavy antibiotics (e.g. meropenem) that we are only now really starting to use in a similar way in hospitals in Australia.

There are many global challenges caused by antimicrobial resistance. Countries must do much more to better use existing antibiotics by strengthening health systems, human resources and laboratory capacity. There also needs to be improved access to existing medical tools, including reduced prices for existing vaccines to prevent infections, as well as research and development of new products that are patient-focused, affordable and appropriately available to all who need them. MSF is participating in global efforts to control drug-resistant infections by increasing our capacity to diagnose infections, improve the use of antibiotics, prevent the transmission of infections in hospitals and monitor rates of resistance, as well as supporting efforts to develop new, affordable diagnostic tools and treatments.

Northern Yemen, October 15 – February 16
A man clears debris revealing the Médecins Sans Frontières logo 29 October 2015 painted on the roof of MSF's hospital in Haydan, Yemen after an airstrike on the facility.
Photographer: Rawan Shaif

Ask yourself "why medicine?"

For those who are looking ahead to their future in medicine and are interested in working in the humanitarian sector my advice is very simple, get out and challenge yourself. Remove yourself from the big city hospitals and work remotely. You will not typically be provided this opportunity without asking. Ask your hospital for a rotation to a regional centre or request something a bit different. Take a leap and show up.

You need to be interested in things that are not strictly just medical. I am sure that you already are, of course! Working at MSF we look at so many issues outside of the first emergency response. It can be anything from access rights to medications, the humanitarian needs of a particular context, the effects of war on communities or what happens to women after a natural disaster. This information influences how we treat a patient and what kind of patients we see.

And most importantly make sure you're asking yourself the really important questions. Why are you studying medicine? What type of patients do you want to be treating in ten to fifteen years? Why do you think you will get a buzz out of being a doctor? Understanding your 'why' will help you understand how to get there and what your career will look like in the future.

Working in the humanitarian field can be dynamic and volatile. If you don't mind that lifestyle partnered with medicine, then it's the perfect job for you.

Conversational EBM

Professor Frank Bowden
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Medicine, to paraphrase LP Hartley, is a foreign country - they say things differently there [1]. When I started out, most of the anatomy, physiology, biochemistry and microbiology was, well, Greek to me. My undergraduate years were as much language lab as pathology lab but by the time I completed my final exams after 6 years of full immersion I was speaking Medicine in my dreams.

Then, in the 1990s, I met a tribe known as 'Clinical Epidemiologists' who spoke a medical dialect I had not previously encountered. Their words were familiar but the meanings were hard to exactly translate. I knew, for example, the common definition of 'sensitive' and 'specific', (indeed my wife said that at times I had too much of the latter and not enough of the former), but these strangers had something else in mind when they used the words. Some phrases seemed to be self-evident - what else could 'positive predictive value' be apart from the 'predictive value of being positive'? And what on earth was a 'meta-analysis' or a 'likelihood ratio'?

The Lancet, that bastion of all that is right and good in the medical world, wrote an editorial in 1995 expressing the view that the emerging EBM speakers were OK as long as they stayed 'in their place' [2]. Since then, two generations of medical students have learnt their trade in clinical environments that have only reluctantly and incompletely adopted EBM as the lingua franca. Some young doctors have entered the workforce truly bilingual but most have EBM as a second language. The paucity of native speakers in hospitals and general practices means that many doctors never have enough time to adequately practice their conversation skills. Some have forgotten even the most basic vocabulary.

Critics - and they are many [3] - argue that evidence based medicine focuses on groups and averages; that it is only about research and academia; that it is an excuse for cost-saving and external control and that it is not really about individual patients. But from the outset David Sackett, the father of EBM, defined his newborn as 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient' [4]. Take each of the words in that sentence seriously and I believe that it would be hard to find a better way to live a medical life.

Like most doctors I struggle to stay up to date even in my area of specialty. (If they change the name of one more bacterium or fungus I will scream!) Yet it is hard to convey to people younger than 30 how precious information was in the time before the interweb. It is not surprising then, that after we graduated, virtually the only source of education about new treatments and diagnostics came from the people who made and sold them. We read clever advertisements in journals and we listened, over fine food and wine, to well-dressed experts talking about new advances. There was no Cochrane database, anything that was in Harrison's textbook was unquestionably correct and Up to Date was something that we wanted to be, not log on to. Today we carry more information in our mobile phone than was ever imagined by Douglas Adams or Isaac Asimov.

But some things don't change: I have observed that doctors, as a species, hate bureaucracy, administration and any form of external

Professor Frank Bowden
Source: http://unihouse.anu.edu.au

control, yet we are naively open to the influence of experts that look or sound like us. If a colleague we like says something, we are inclined to believe them. Even if we don't like them, we tend to be more Mulder than Scully. If you think I'm exaggerating, consider the exponential rise of PSA testing in the 1990s [5], the explosion of thyroid cancer diagnoses in the last decade [6], the sunburst of unnecessary vitamin D measurement [7], the overuse and subsequent loss of every new antibiotic released in the last 50 years [8], the epidemic of unnecessary radiological investigations and the steely push for wider access to the unproven benefits of robotic surgery [8-10] - to name just a few examples. On the other hand, independent sources, such as the Australian Choosing Wisely program [11], almost exclusively recommend that we do fewer investigations and treat fewer people, rather than more.

If good medical practice is the offspring of a metaphorical marriage between expert, independent professionals and autonomous, informed patients, we have to acknowledge the risk that a third party presents to the relationship. My patients have the right to know where I get my facts and who is influencing my decision making.

So, how can doctors make sense of modern practice in a world that is overflowing with information, short on knowledge, long on potential for conflict of interest and sadly wanting for wisdom? Just teach them more evidence based medicine? That it were so easy… Sorting out the treatments that really do make a difference to our health and well being is much harder than it seems. If you want doctors who are able to tease out the complex arguments about the pros and cons of prostate or breast cancer screening [12], who can make an independent

judgement about the role of early thrombolysis in stroke [13], who can convey the difference between absolute risk and relative risk in a way that is understandable to the lay person, then EBM instruction has to be integrated into all levels of medical training.

I hate to admit this but I used to watch my students' eyes glaze over when I tried to teach them certain things in evidence based medicine. For example, and this will make the EBM purists cringe, it is very difficult to get undergraduate medical students excited about critical appraisal of research studies. It's not that it isn't important - understanding the fine details of clinical research methods is essential for doctors who are going to be creators of knowledge - it's just that the vast majority of us are consumers, not makers. The well informed consumer needs to know how to safely and effectively use the product they have, more than they need to know how to manufacture it. I worry that many medical students never learn the importance of EBM (and its parent - epidemiology) if the early focus of teaching is on the laborious dissection of the mechanisms of evidence-making rather than on a more general exploration of what evidence is and how it can be applied in the real world.

Medical facts change rapidly but the principles of EBM stay remarkably stable. The range of treatments that existed when I was a medical student was nothing like that which is available today and we can only guess at the progress that will occur over the next 30 years. Nevertheless, the design of the studies needed to prove the efficacy and safety of those new treatments will be almost identical to those of today and we will still use the tools of EBM to interpret the results.

Perhaps only a small group of doctors - the creators - need to be truly fluent in EBM. But the rest of us - the users - need to make the effort to learn the basics of the language of evidence. Those who don't may find that they have been left out of the conversation altogether.

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Surgery: art or science?

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Ian Harris is a Professor of Orthopaedic Surgery at the University of New South Wales and a clinician based at Liverpool Hospital and the Ingham Institute for Applied Medical Research. His research interests are in the evidence for surgery and he has produced clinical trials, systematic reviews, and cohort studies in the field of surgery. He has published approximately 150 peer reviewed articles and has been an investigator of grants worth over $16 million. He is a frequent critic of unsupported clinical practice and has summarised his objections to the observational nature of surgical practice in a book: Surgery, The Ultimate Placebo.

It's often said that surgery is more art than science. Rubbish. Too much emphasis is placed on surgeons' technical skills and not enough on the decisions behind them.

Any good surgeon can operate, better surgeons know *when* to operate and the best surgeons know when *not* to. Knowing when to operate and when to hold off relies on weighing up relative probabilities of success and failure between alternatives.

Good decision makers (and therefore good surgeons) base such decisions on quality evidence, and this is where science comes in. The evidence we seek is evidence of the true effectiveness of an intervention, and it is the scientific method that provides us with the most accurate and reliable estimate of the truth. Faced with alternatives, surgeons can sometimes make the wrong choice by being unscientific.

Surgeons often decide to do certain procedures because it's what's usually done, because it's what they were taught, because it *sounds* logical, or because it fits with their own observations. If the surgeon's perception of effectiveness and the evidence from scientific studies align, there is little problem. It's when the two conflict that there's a problem: either the surgeon's opinion or the evidence is wrong. Worse, sometimes there is no good quality evidence and we are left with the surgeon's opinion.

There is abundant evidence that surgeons overestimate the effectiveness of surgery, and considerable evidence of seemingly effective operations (based on observational evidence) turning out to be ineffective on proper scientific testing.

So what evidence should we rely on? Put simply, when you are trying to determine true effectiveness, the best method is the one that is least wrong, i.e., the method that has the least error. The scientific method is constructed to reduce error – we rarely know the truth, but we can increase the likelihood of our estimates containing the truth and we can make those estimates more precise by reducing error. In other words, we can never be certain but we can reduce uncertainty.

There are two types of error: random error and systematic error. Random error is easy to understand. If you toss a coin ten times, you may get seven heads, but that doesn't mean the coin is unbalanced. Toss it 100 times and if you get 100 heads then you have reduced random error (the play of chance in generating such a result) and it is now very likely (and we are more certain) that the coin is unbalanced.

Systematic error (bias) is when we consistently get the wrong answer because we are doing the experiment wrong. There are many causes of bias in science and many go unrecognised, like confirmation bias, selective outcome reporting bias, selective analysis bias, measurement bias, and confounding. Systematic error is poorly understood and a major reason for the difference between the true and the apparent effectiveness of many surgical procedures.

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The best way to test the effectiveness of surgery and overcome bias (particularly when the outcome is subjective, such as with pain) is to compare it with a sham or placebo procedure and to keep the patients and those who measure the effectiveness 'blinded' to which treatment was given. Yet such studies, common in the drug world, are rare in surgery.

In a study that summarised the research that has compared surgery to sham or placebo procedures, it was shown that the surgery in most such studies was no better than pretending to do the procedure [1]. And in the studies where surgery was better than placebo, the difference was generally small.

It's not always necessary to compare surgery to a sham - sometimes comparing it to non-surgical treatment is sufficient. This is particularly the case for objective outcomes (survival, recurrence of disease, anatomic corrections) where blinding is less important. But you still have to compare it to something – to merely report the results of an operation with no comparator provides no reference for effectiveness beyond some historical control (of different patients, with possibly different conditions, from another place and another time). Journals are littered with case reports showing that most people got better after receiving treatment X but such reports tell us nothing about what would have happened to the patients if they did not receive treatment X, or received some other treatment. These types of non-comparative studies continue to sustain many quack therapies as well as common medical and surgical therapies, just as they sustained the apparent effectiveness of bloodletting for thousands of years.

However, even when comparative studies are done, they are not always acted upon. In a study looking at the evidence base for orthopaedic surgical procedures, it was found that only about half of all orthopaedic procedures had been subjected to tests comparing them to not operating [2]. And for those procedures that *had* been compared to not operating, about half were shown to be no better than not operating, yet the operations were still being done. The other surgical specialties are unlikely to be much better.

So there are two problems in surgery: an evidence gap in which there's a lack of high quality evidence to support current practice, and an evidence-practice gap where there's high quality evidence that a procedure doesn't work, yet it's still performed.

Part of the problem is that operations are often introduced before there's good quality evidence of their effectiveness in the real world. The studies comparing them to non-operative treatment or placebo often come much later – if at all.

Surgical procedures should not be introduced or funded until there's high quality evidence showing their effectiveness, and it should be unethical to introduce a new technique *without* studying its effectiveness. Instead, the opposite is argued: that high quality comparative studies (placebo controlled trials) are unethical.

Often, procedures that surgeons consider to be obviously effective are later shown to be ineffective. In the US in the 1980s, a new procedure that removed some lung tissue was touted for emphysema. Animal studies and (non-comparative) results on humans were encouraging. So the procedure became commonplace. A comparative trial was called for but proponents argued that this would deprive many people of the benefits of the procedure, the effectiveness of which was obvious.

Medicare in the US decided only to fund the surgery if patients participated in a trial comparing it to non-surgical treatment. The trial was done and the surgery was found wanting. This cost Medicare some money, but much less than paying for the procedure for decades until someone else studied it. This type of solution should be considered in Australia – only introduce new procedures if they are being evaluated as part of a trial.

The current practice of surgery is not based on quality science. If you got a physicist from NASA to look at the quality of science supporting current surgical practice they would faint. But it is getting better. It is getting better because of advancements in our understanding, because of the spread of evidence based medicine (in teaching and in journal requirements, for example), and because surgeons are understanding science better. The trials are getting better, but the incorporation of the results of those trials into practice is slow and often meets resistance because of suspicions that stem from a lack of understanding of science and the biases that drive current practice.

Billions are spent worldwide on surgical procedures that may not be effective because in many areas of surgery we still rely on surgical opinions based on biased observations and tradition. It is time for surgery to be a real science and to rely on the kind of evidence on which other scientific endeavours rely; the kind of evidence that we demand of other medical specialties and of non-medical practitioners. It's not too hard. It's not unethical. It's right, and it's time.

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Evidence-based medicine and the rational use of diagnostic investigations

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Professor Rakesh Kumar has worked in Pathology at UNSW since 1977. He completed a PhD in 1981 and was a Fogarty International Research Fellow at the US National Institutes of Health in 1987. Professor Kumar has received a number of awards and honours for his enthusiastic teaching of Medicine and Science students, as well as of postgraduate health professionals. His particular interests in education include methods of assessment and the appropriate use of information technology. His experimental research, focusing on mechanisms of inflammation in chronic lung diseases, has been supported by grants from NHMRC and ARC.

Every senior medical student and young doctor want to be able to keep up with the latest advances in medicine. However, the output of published literature keeps rising, so that we are all in danger of drowning in data. It's difficult enough to keep up with the latest in clinical practice, let alone in basic research.

To at least some extent, evidence-based medicine can help, because it offers approaches that help to turn the data into knowledge which can actually be applied. Notably, these include systematic reviews and meta-analyses, which yield evidence-based practice guidelines that can inform clinical decision-making. Of course, one must remember that guidelines are only generalisations. Achieving the best outcomes for any given patient requires a combination of:

- skilled clinical observation
- appropriate investigations
- application of knowledge and expertise gained by experience
- the best scientific evidence from the literature.

In this article, I will focus on the appropriate use of investigations. This is an important issue with respect to the care of individual patients, because unnecessary and inappropriate investigations may have adverse effects, while false-positive results may prompt further needless investigation. It is also important with respect to utilisation of resources, particularly in Australia where costs to the health care system are substantially borne by the taxpayer. Over the past decade, the use of laboratory tests has seen a modest annual increase of approximately 3% to 6% [1]. At the same time, requests for diagnostic imaging investigations have increased at approximately 9% per year, so that these services now account for approximately 15% of all Medicare outlays [2].

When looking at evidence-based medicine in the context of the rational use of investigations, it is easy to get lost in the arithmetic of predictive values, probabilities and likelihood ratios. An alternative simpler approach is to rely on the maxim "Only request a laboratory test if the result will change the management of the patient" [3]. This may be an oversimplification in that among other things, investigations are relevant to establishing a diagnosis, excluding differential diagnoses, assessing prognosis and guiding management. Nevertheless, focusing on investigations that matter is sound advice, which is unfortunately all too often ignored.

The quality of the evidence around overuse of diagnostic investigations is relatively low. In hospital settings, however, it has long been recognised that as many as two-thirds of requests for some common Pathology tests may be avoidable, in that they fail to contribute to diagnosis or management [4]. Senior medical students and junior medical officers need to be especially aware of this, because most hospital Pathology test requests are submitted by junior doctors. Among factors that contribute to the uncritical overuse of investigations by JMOs are inexperience, lack of awareness of the evidence base for using a particular investigation and lack of awareness of the cost of the test. Other significant factors are the desire to anticipate the expectations of one's supervisor and the fear of missing something important. Perhaps the supervisors of PGY1/2 trainees themselves need to drive cultural change and better model the appropriate use of diagnostic investigations!

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Some strategies targeted at the test-requesting behaviour JMOs appear to be effective in at least some settings, for example restricting the range of tests that junior doctors may request in emergency departments [5,6]. More generally, management systems with budgetary controls, as well as online systems with decision support, have been promoted [7]. Importantly, education also has a valuable role to play [8].

With funding support from the Commonwealth Department of Health, my colleagues and I developed an open-access website to educate JMOs about the rational use of diagnostic investigations. As a user, you interact with simulated cases and can request investigations as you attempt to establish a diagnosis, while being presented with a running tally of the costs of the tests sought. At the end of each case, you receive feedback via comparison with what an expert would have done. Try it by self-registering, without cost, at http://investigate.med.unsw.edu.au/. The largest collection of cases is targeted to JMOs, but are also likely to be of interest to senior medical students. In addition, there are cases for trainee GPs, plus a few specifically created for advanced trainees in Respiratory Medicine. However, all cases are accessible to all users.

We have evidence that this educational approach can work: in a trial at a large Sydney hospital, we demonstrated that in the period immediately following active engagement of the cohort of junior doctors with this website, there were significant hospital-wide cost savings and an encouraging reduction in the number of blood samples

collected from patients [9]. Unfortunately, in agreement with other studies of educational interventions, these changes in test-requesting behaviour were not sustained over the following months. However, there is additional evidence that routine requests for diagnostic investigations can be reduced if junior doctors are provided with cost data at the time of submitting a request [10]. We think a good case can be made for integrating this information into online systems in hospitals, to provide reinforcement.

Meanwhile, I encourage you to have a look at one of the few collections of guidelines about the use of investigations, available on the Australian Choosing Wisely website at http://www.choosingwisely.org.au/resources/clinicians?displayby=MedicalTest. These guidelines are supported by a number of specialist medical colleges, notably including the Royal College of Pathologists of Australasia and the Royal Australian and New Zealand College of Radiologists. Also well worth reading is a thoughtful reflection on the "big picture" of overuse and the Choosing Wisely initiative, published late last year and targeted specifically to medical students and trainee doctors [11].

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Healthcare in Australia must continue to be freely available for all Australians

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Universal healthcare is a privilege and a right that we must protect to ensure the healthy future of Australia. As medical students and doctors, we are more than simply practitioners of medicine. We hold more responsibility than solely the management of disease. A key responsibility of our profession is advocacy for the health of our patients, the health of our nation, and the protection of our public health system.

The recent election has highlighted the fragility of our public health funding, and the willingness of both sides of politics to use Medicare and public healthcare as a political tool to serve their own agenda. This short-term and selfish thinking has the potential to abolish equal and fair access to healthcare; this is something that is, and should continue to be, a universal right for every Australian. The opportunity to live a long and healthy life should not be decided by our wealth. As it stands, the health gap between those from upper and lower socioeconomic backgrounds is significant [1]. The ramifications of freezing or removing funding to Medicare and public healthcare will be widespread. The current policy of a "freeze" on Medicare will increase out-of-pocket costs to all patients, impacting patients from lower socioeconomic backgrounds significantly. The effect of this freeze will be two-fold, with the added effect of increased practice costs in areas where patients cannot afford to pay out-of-pocket fees [2]. In turn, this will impact practice viability, and in lower socioeconomic areas, some practices may be forced to close, leaving vulnerable groups with limited access to healthcare [2].

The result of increased out-of-pocket fees will be an increasingly privatised healthcare system, and one does not need to look far to see the detrimental effect of such a system. In America, the healthcare system screams of inequality. It is a system where doctors are often placed in tremendously difficult situations, and are often left with no option but to turn away patients who are unable to afford healthcare [3]. America has a per capita healthcare expenditure that far exceeds that of other developed nations, however, public spending only covers 34% of residents in the United States, compared to every resident in Australia and the UK [4]. What is most damning about these statistics is that despite exorbitant healthcare expenditure, predominantly at a cost to patients or their insurers, the life expectancy American citizens languishes at 31st in the world, well below that of Australia, which is ranked fifth [5]. But that is not where the inequality stops. The privatised, self-funded system in America also stakes claim to the highest infant mortality rate amongst all developed nations, and a higher prevalence of chronic disease than that in developed nations with a universal public healthcare system [4]. If we are to preserve the health of Australians, we must take on the responsibility to advocate for healthcare as a universal right for all Australians.

In the lead up to, and in the days following the recent election, the Australian Medical Association (AMA) and the Royal Australian College of General Practitioners (RACGP) have been highly outspoken regarding their concerns about the inequality of funding cuts to Medicare. This advocacy, along with campaign material centred on Medicare, led to a strong response from the Australian public at the election, making it evident that Australians value free universal healthcare. However, this has not led to a response from parliament about the freeze on Medicare funding. Without a change in this policy, 57% of GPs have said they will increase out-of-pocket expenses, and 30% have said they will stop bulk billing [2]. This will directly affect patient access to healthcare, and has the potential to have a detrimental impact on Australian health outcomes, similar to health outcomes seen in America. As medical students and doctors, we are on the frontline of these changes, and it is our responsibility to protect our universal healthcare system. It is an issue that needs all of our support.

As a highly educated and privileged group, we need to ensure that governments understand the ramifications of cutting funding to Medicare and public healthcare. Universal healthcare needs to remain a priority in Australia and a right for all Australians, young and old. The health of our nation reflects the spirit of our nation, and it is the role of all medical professionals to advocate for equality in healthcare. Our advocacy need not make headlines in newspapers or fill prime-time television slots. Through simple conversation we can raise awareness about the importance of universal healthcare. It is our role to ensure that Medicare and public healthcare remains a priority, not just for the next election cycle, but for the long-term, so that future generations of Australians can enjoy long, prosperous, and healthy lives, just like the Australians of today.

Conflicts of interest

None declared.

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What's in a Name: what MD really means for us

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I feel like a dying breed. A dinosaur, if you will. At the outset of my studies I knew this and I still think about it occasionally, still wonder if I made the right decision at the naïve age of 17.

I'm talking of course about my name. Specifically, what's going to appear after it in just a few years' time — MBBS. That cultural UK tradition drawn from the fusion of Physicians (Bachelors of Medicine) and Surgeons (Bachelors of Surgery), who at some point decided it was all the same stuff, and that MBBS was more attractive than BM, BS.

In Australia, and in my university, we're seeing a relatively new kid on the block — the Doc-tor of Medicine (typically MD). The roots of this seem to come from across the pond, where at some stage Americans decided to silently disagree once again with the conventions of Eng-land. In fact, I am the last cohort of MBBS in my university – many of the students below my year boast their superior would-be qualification, and I've heard it time and again from universities that already have it. But is MD a new degree, or just a new name? Is this really a new breed of Doc that will one day uniformly scoff at me, a dinosaur from the age of MBBS?

I set about this question in a number of ways. There are the facts and figures, the institutional requirements that fall under the Australian Qualifications Framework (AQF) and the Australian Medical Council. And then there are the perceptions — much more difficult to grasp, but no less important for a degree so public as medicine, where your qualifications guide your job opportunities, your patient trust, and ultimately the ability to help people.

So to the facts. The AQF guides the ability of universities and other tertiary providers to name programs. This is a 10-step ladder, available in an interactive website provided by the AQF [1]. It runs from Level 1 - a Certificate 1, through to Level 10 - a PhD. In Australia, universities are self-accrediting higher education providers, and are overseen by the Tertiary Education Quality and Standards Agency, a Commonwealth Government department. Although I can't admit to knowing the exact process of application and oversight, the simple fact remains: In Australia, your primary medical degree can be Level 7, Level 8 or Level 9.

Level 7 is a Bachelor degree – there are several broad expectations of someone having attained this level of degree, which is summarised on the AQF website as the following:

"Graduates at this level will have broad and coherent knowledge and skills for professional work and/or further learning" [1].

That seems pretty good to me. Medicine is a profession that I want work in, and I'm very open to further learning – such as a specialty or a research higher degree.

Level 8 is a Bachelor degree with Honours, something provided by many of the universities that still offer MBBS. Although it must be noted that at some universities, Honours is given only to those who undergo extensive research on top of their studies, while at other universities, the requirements seem far less stringent. Level 9 qualification is where MD comes in — according to the AQF levels it is a single Masters degree. The summary of graduates of this level is:

"Graduates at this level will have specialised knowledge and skills for research, and/or professional practice and/or further learning" [1].

This doesn't seem to mean much to me as a medical student. Surely "specialised knowledge" is gained in postgraduate vocational training, as per the system of Australian Specialist Medical Colleges, in turn overseen by the Confederation of Postgraduate Medical Councils and the AMC [2]? And in terms of research, does that mean I can't complete useful medical research, with my measly BSc/MBBS?

Maybe the Australian Medical Council could straighten things out for me, and tell me how much I'm worth. The AMC is ultimately responsible for the training of all medical students and doctors in Australia, as dictated by the Medical Board of Australia [3]. This is a huge responsibility – and with medicine changing more and more rapidly over the past 50 years, it's impressive that they could keep up!

In fact, there is no difference in the AMC accreditation level of university medical graduates. Quite the opposite – the AMC regards all medical students as having had a comparable experience in medical school to make them safe enough for an Australian internship. For the University of Melbourne, the first university to offer the MD in Australia, there was a re-accreditation process with the AMC before the degree could be offered [4]. Likewise, the University of Western Australia overhauled their program, entirely changing the number of years of medical school [5]. But every other medical school in Australia that has switched or is considering switching has not required extensive re-accreditation beyond the normal re-quirements that exist year-to-year [6-7].

On the ground, what does this mean for students? Are students becoming better doctors and better scholars, or are they not? My personal feeling is the latter. I have peer-tutored at my university for the year below me, and they do not seem to be a new breed at all. Like me, they wish they started cramming a week earlier with each coming semester. Like me, they whinge when the School makes small program changes that they don't agree with, or schedules lectures that they think are useless. Like me, they attend Evidence-Based Medicine with a somewhat silent resentment, not because it's not important but because it's not exciting.

The School has made some changes; I suppose to be in line with AQF standards. All MD students at my university now write a research protocol – as I understand it, a report on how they might do some research. It's not revolutionary, it's not PhD-worthy, and in fact, it's a lot less than the research required to get an Honours in my current program.

But more than all the facts and figures, I do care about the perceptions. I do wonder if a pa-tient one day will take a look at my name-tag and ask me what an MBBS is, and why they're not being seen by a real doctor. I wonder if the applications office at RACP or RACS will one day look at my name and think less of me. I wonder if I should have chosen to be the last of the MBBS cohort at my university, or done an extra year of science and slipped into the first MD class. These are worries that can't easily be put to rest – especially when my juniors already think themselves superior in some way. As though somehow, their research protocol made them able to pick the diagnosis when I would have missed it.

Many students at my university are from overseas, and eventually become fully registered doctors in countries like the US. There, MBBS means nothing, and MD sits in a strange qualifications level that we don't have in Australia. In many states of America, you can, for a nominal fee, apply to legally change from MBBS to MD after your name, and many of my colleagues will do so [8]. This may be a potential solution to my worries down the track, should they ever really arise.

I decided at the end of the day, that MD is much more about business than health. It was attractive for the University of Melbourne to pioneer a new name, and now each new medical school that "gets the MD" can call themselves on par once again. Unfortunately, the restrictions for Domestic Full-Fee Places in universities do not apply to postgraduate courses such as Masters, which legitimately poses a financial threat to new students, and added strain to the internship crisis [4]. For now, I'm content in the hope that most people don't care what's in a name. A medical degree by any other name would doctor just as well. And after all, the Australian National University now provides their students an MChD and nobody seems to complain [9]!

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Conflicts of interest

None declared.

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Big data in clinical research

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Sarah is a third year medical student at Monash University. She has come to appreciate that she has various interests in medicine and surgery, but is particularly interested in paediatrics, medical education, and research.

Abstract

Background: Medicine is an ever evolving field of knowledge, new practice, and research. There are various clinical research methodologies; the clinical researcher may actively collect patient information, or retrospectively obtain patient data from traditional datasets, such as hard-copy patient records. In more recent years, clinical research has seen the emergence of 'big data'.

Big data are large electronic databases characterized by the four V's- volume, variety, veracity and velocity. The rise of big data suggests that there are advantages to its use. One advantage of big data is easy accessibility, which allows information to be obtained and analysed in a short period of time. However, there are shortcomings of using big data in clinical research, mainly with regards to sampling bias and validity. Nonetheless, big data are here to stay in today's digitised age of medicine, and the researcher must consider the appropriate contexts for the use of big data in clinical research.

Aim: The aim of this paper was to define 'big data' in medicine and examine its use in clinical research.

Methods: A literature review was conducted on Ovid MEDLINE to identify relevant literature. The PRISMA statement was used to screen and select articles that would be reviewed for the paper.

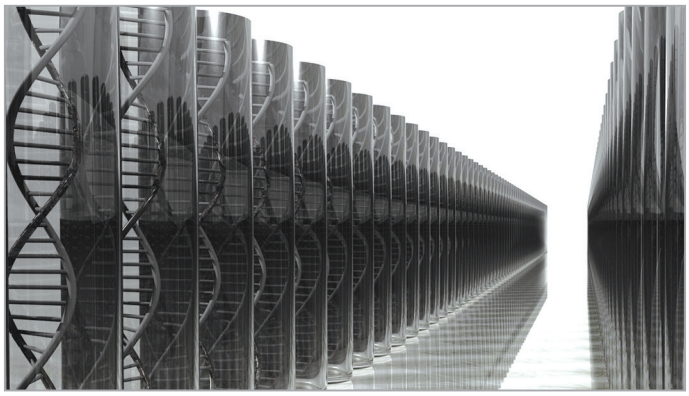
Conclusion: The future of big data is promising, with the allure of low-cost, immediate, and comprehensive data, but it is important that clinical researchers understand how to utilise these well for research and knowledge translation.

Introduction

The future of medical practice is shaped by the outcomes of today's clinical research trials. Medicine is an increasingly data-intensive field reliant on clinical research [1]. For decades, the clinical research industry has conducted large amounts of research by either actively collecting patient data or retrieving it from hard-copy patient records [2]. However, recent years have seen the emergence of 'big data' as the key source of data for clinical trials and observational clinical research alike [3,4]. Big data algorithms in medicine broadly refer to the aggregation of individual medical datasets into large, electronic databases that are readily available for data analysis in clinical research [3,5]. The rise of big data in clinical research suggests that there are obvious advantages of its use. However, there are also challenges in optimising its use in clinical research due to the risk of bias [6]. The aim of this paper was to define 'big data' in medicine and examine its use in clinical research.

Methods

This literature review examined recent literature that focused on the use of big data in clinical research. This included researching its validity, reliability, advantages, and disadvantages. Recent literature was defined as articles published from 2005 until 2016.



A literature search was performed on Ovid MEDLINE using the following query:

("validity" OR "reliability" OR "advantages" OR "disadvantages")

AND

("administrative data" OR "database" OR "big data" OR "electronic health records" OR "electronic medical record" OR "clinical database")

AND

("clinical research" OR "healthcare")

The PRISMA statement was used when selecting articles for this review (Figure 1). A total of 164 publications were identified through the database searches. One additional record was identified through the bibliography of one of the articles retrieved from the database search. The abstracts of these articles were manually reviewed for relevance to the topic, excluding 119 articles. Full-text screening excluded a further 23 articles due to inappropriate topic focus and repetition. This paper subsequently focused on reviewing 23 articles. These articles were primarily original research articles and systematic reviews.

What is big data?

(i) Defining big data in a medical context

Big data in medicine is characterised by the four V's – volume, variety, veracity, and velocity [7]:

a. Volume refers to the large amounts of patient information being collected over time and stored, as suggested by the term 'big data'. Various elements incorporated into big data include patient demographics, history, investigations, diagnoses, and length of stay [8]. Big data are available in the form of registries and patient databases. Registries gather disease- or population-specific information, while patient databases document patient information throughout the course of an illness [8].

b. Variety of data can be broadly discussed as structured or unstructured data. Structured data is information that is easily stored, searched, retrieved, edited, and analysed digitally, as

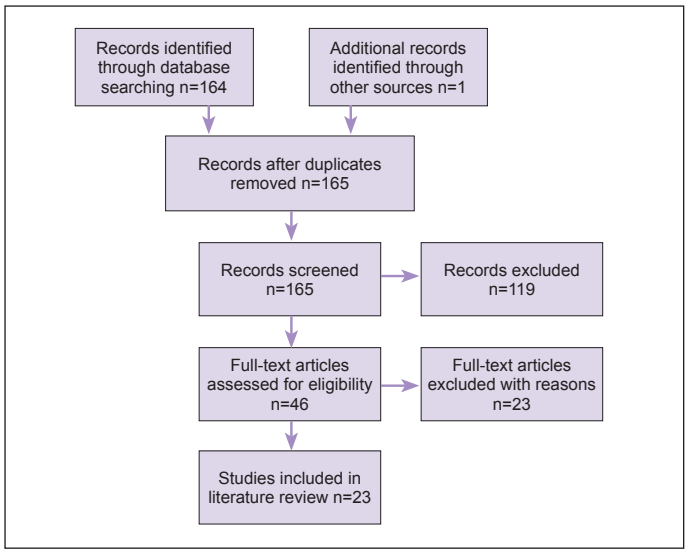


***Figure 1**. PRIMSA flow diagram demonstrating search strategy.*

in keying in patient ID numbers into electronic medical records to access patient information [7]. In contrast, unstructured data include traditional print records, electronic free text, radiographic films, or survey data collected from patients [9].

c. Veracity concerns the true representativeness of the data. It refers to the goal of achieving validity and credibility in the data set [7].

d. Velocity represents the rate at which data is recorded and generated to allow timely retrieval for analysis and decision-making [7].

Advantages of using big data

(i) Accessibility and availability

Big data are readily available [10]. Patient records, such as admission history, investigations, diagnostic results, and medications, are all electronically documented on hospital databases. As these hospital databases are installed on staff computers in the hospital, health professionals working in these hospitals are able to easily access this data for review or, increasingly, for clinical research. The integration of multi-pathway patient records[1] in big data provides a convenient, comprehensive pool of information available to researchers [11]. This integration facilitates retrospective cohort studies and therefore aids researchers to identify patterns in disease progression and compare the effectiveness of treatments [11].

(ii) Cost- and time-efficiency

Given the convenience of data collection using electronic patient registers, the process of obtaining information needed for clinical research is shortened, in comparison to the more time-consuming alternative of manually collecting patient data [12]. Big data are useful in minimising logistical impediments in prospective and retrospective, longitudinal, population-based studies [13,14]. Researchers who require large sample sizes can also easily extract information from the available pool of data in these databases, potentially increasing the study power of their research [13]. The added benefit of being able to use computerised techniques to analyse unstructured data within big data also means that finer data acquisition can be performed, compared to data acquired by laborious, manual extraction from traditional datasets [14]. In addition, this information is available at a low cost, if not free, to clinical research staff, bypassing potential additional costs that might be incurred through manual data collection [15].

Challenges of Big Data

Kaplan *et al.* [16] suggests that several biases can arise when analysing big data, including, but not limited to, sampling bias and lack of scope in the information recorded. Secondly, the validity of big data is highly dependent on the context in which it is being used [17]. Lastly, minor data security issues may arise from the utilisation of big data.

(i) Sampling bias and lack of scope

Sampling bias of big data can be discussed in terms of its standardisation and completeness. Completeness of data encompasses both its comprehensiveness and whether it is a good representation of the population of interest [17]. Clinical research often requires data collection from a large sample size of patients. As every patient will have different investigations, diagnoses, and treatment plans, every patient will have varying types and amounts of clinical documentation and to differing degrees of detail. There will, therefore, be difficulty in standardising a method for data collection across an array of available patient information to ensure completeness of the data. It is crucial to ensure that the data is complete, otherwise the research results could be subject to information bias [8]. Typically, the ideal method to achieve this is to conduct prospective data collection, minimising omissions [8]. However, as big data is retrospective, it is often difficult to agree upon a decision regarding inclusion of the data or methods to retrieve missing data when medical records are not available [8]. In those situations, the clinical researcher will be required to design algorithms to clean and correct the available data, however it is difficult to design an objective method to validate certain choices made in this process of data collection.

In addition, the coding of information is very much skewed towards documenting and following up the primary diagnoses [17]. As such, secondary diagnoses are often missed or poorly recorded, resulting in a lack of well-documented secondary patient information, such as co-morbidities.

(ii) Validity of big data

Joppe defines validity in quantitative research as a criterion that determines whether a research truly measures what it was initially intended to measure [18]. The validity of big data varies between different clinical specialties and the circumstances in which the data is being used [17].

Occasionally, big data may contain incomplete data sets, or even incorrect data, due to errors in transcription or abstraction [8]. There have been instances when data is misclassified during the recording of data during the data coding process [17]. These may occur when a patient undergoes a procedure that treats more than one condition, or in recording a patient's hospital admission based on presenting complaint [17]. These systematic errors are hence potentially misrepresentative of the data [17]. A literature review by Talbert and Lou Sole [8] in 2013 found that there has been substantial research suggesting that administrative databases, a subset of big data, have only moderate sensitivities and specificities for correct data coding and may underreport procedures [8].

The increasing trend of activity-based funding of hospitals in some countries, such as the United States and Australia, may also influence the information recorded in big data at discharge [19]. Activity-based funding is a policy intervention targeted at restructuring incentives across healthcare systems through a fixed

[1]Multi-pathway patient refer to a thorough documentation of a patient's journey from admission into the emergency department, referral to various specialties and notes from allied health. These include documentation on the patient's presentation, treatment, progress and recovery.

funding allocation for each episode of care administered to each patient, regardless of their duration of stay and resources used [19]. Obvious benefits include reduced hospital costs and shorter hospital stays, however, hospitals may misuse the system to increase revenue by up-coding diagnoses, or focusing on profitable patients and procedures [19]. As a result, the diagnoses and procedures included in the discharge coding within big data may misrepresent the actual situation in the hospital.

It is crucial to note that electronic medical records adapted for clinical research serve the purpose of a clinical care record and are not designed for research [20]. Electronic inpatient databases document the clinician's case notes, which often focus on treating the patient's current illness and respond to the individual clinician's concerns. These may not always correspond with the aims of future clinical researchers. As such, the available information on the patient may not necessarily be as comprehensive as required by the clinical researcher [12].

Analysis of inaccurate data may cause incorrect conclusions to be drawn. In situations where researchers simply use whatever big data are provided to them, the validity of the clinical research is compromised as the data collected and analysed may not truly reflect the research aims.

(iii) Data security

Griebel *et al.* [1] suggest that users who lack experience in using big data and third party users could potentially pose a threat to data confidentiality. Such circumstances may occur when healthcare providers work with commercial corporations and outsource the information to a commercial cloud [1]. However, mitigation strategies, such as the implementation of high-security data authentication protocols to limit access, can be put in place to ensure data security [1]. Examples of high-security data authentication protocols include advanced firewalls to prevent access by unauthorized users and setting up a digital certificate, which requires the user to identify himself or herself [5]. There are also newer techniques, such as obfuscation, where patient data is stored in an encrypted form and decryption is only allowed through authorised privacy manager software [5].

Choosing appropriate contexts to utilise big data in clinical research

Big data are beneficial to clinical research in providing the following information:

(i) Patient demographics and risk factor profile for disease

Big data are highly applicable in the field of patient profile analytics [2]. Big data can be used to identify relationships between patient demographics and disease or treatment outcomes. By routine monitoring and documentation of patient flow and outcomes, big data allow the incidence and prevalence of diseases, as well as the overall outcome amongst selected patient groups, to be estimated [17]. Furthermore, big data are ideal for developing predictive analytic models based on risk factor profile. As big data capture patient demographics, they help the clinical researcher pinpoint patient risk factors specific to certain diseases, draw links with disease progression and hence, has the potential to be used in developing prediction models [17]. Moreover, risk factors can also be prognostic, and highlight the possibility of a future health outcome [17]. When advanced analytics are applied to these patient profiles and patients at risk of developing specific diseases are identified, there is the opportunity to intervene and provide preventive care to the selected group of patients [2].

(ii) Patient treatment outcome

Additionally, by combining both structured and unstructured data across multiple disciplines—medical and surgical clinical data, financial and operational data, and genomic data—to match treatments with outcomes, big data can also predict treatment effectiveness for patients [2]. Collectively, these suggest that big data can be useful in calculating the risks and benefits for various outcomes of both a disease and treatment in different patient groups, hence enabling the clinician to provide more efficient and cost-effective care [2,15].

The future of big data

Improvements in big data organisation and an increasing familiarity with using big data will allow clinical researchers to better utilise the data to their advantage. For instance, researchers are progressively able to model inclusion criteria to obtain relevant data [21]. Up and coming technological infrastructure can be expected to springboard the potential of big data in medicine. For example, cloud computing allows big data to be bigger, better and faster. Cloud computing has the potential to provide researchers with multi-scale data integration tools that will help highlight relationships between discrete data entities [22,23]. Cloud computing will also enable researchers to customise personal networks and virtual servers to increase data security of the electronic resources being used [1].

Beyond clinical practice, there is also potential for big data in other healthcare areas [2]. Big data have the potential to integrate population clinical data sets with genomics data, facilitating pharmaceutical development [2]. There is also a role for big data to play in public health surveillance. Big data can aid in analysing and tracking disease patterns, which is of utmost importance in delivering effective and efficient healthcare responses during disease outbreaks [2].

Conclusion

Big data are a useful and efficient source for obtaining patient information. It offers immediate access to large amounts of patient data with high convenience, low cost and easy accessibility. However, big data may be a poor source for immediate causal inference in data analysis as it lacks randomisation. Yet, there is much potential for big data in clinical research and clinical researchers must improve their utilisation of big data in knowledge translation and data analysis. Appropriate handling of big data through well-designed algorithms and data analysis must be done to overcome its limitations. Nonetheless, with its allure of low-cost, immediate, and comprehensive data, the rise of big data is promising. It is here to stay.

Conflicts of interest

None declared.

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Hepatocellular carcinoma: the potential for an effective genetic screening test

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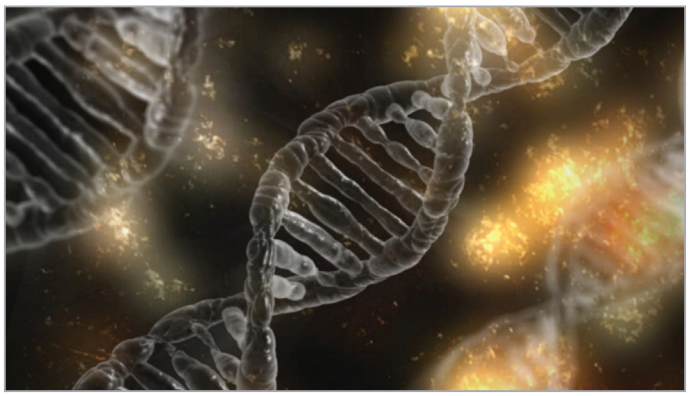
Tobias is a third year medical student at UWA, with broad interests in medicine and surgery. He previously completed a degree in Biomedical Science, specialising in cellular and macromolecular biochemistry. Tobias is passionate about the role of evidence-based research in medicine and plans on being heavily involved in research throughout his medical career.

Abstract: Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide contributing to approximately 600,000 deaths each year with this number on the rise in the developing world. The aetiology of HCC has been well characterised, including chronic hepatitis B and C infection as well as alcoholic cirrhosis. Current screening programs for patients at high risk of developing HCC, including ultrasound and alpha-fetoprotein analysis, are neither sufficiently sensitive nor specific to detect early HCC. This reduces the likelihood of detecting HCC when curative treatment is effective. One genetic marker which has been shown to be associated with HCC carcinogenesis is the p16 INK4a/ARF locus. If further research confirms this mutation as a common step in early hepatocarcinogenesis then this maker could be utilised to screen for early HCC lesions in at risk populations. Further research in this area could facilitate the early diagnosis of HCC, improving the efficacy of treatment.



Introduction

Liver cancer is the sixth most common cancer worldwide and the second largest cause of cancer mortality [1]. It has several subtypes including hepatocellular carcinoma (HCC), bile duct cancer, hepatoblastoma, and various other liver sarcomas and carcinomas [2]. Of those subtypes, HCC is the most common, comprising about 78% of all liver cancers [1,2]. HCC is unequally distributed globally with over 80% of cases occurring in either Sub-Saharan Africa or Eastern Asia; predominantly in China [3,4]. When considering Western countries, there is strong evidence from the United States that the incidence of HCC is rising, with nine cancer registries reporting via the National Cancer Institute that there has been a 41% rise in mortality from primary liver cell cancer and a 70% rise overall in incidence between 1980 and 1995 [5].

A similar rise in HCC incidence and death rates in Australia have also been identified; possibly linked to the increased prevalence of Hepatitis B and Hepatitis C infection in Australia [6,7]. Moreover, there is evidence that HCC incidence rates in Australia may be up to two-fold higher than the rates reported by cancer registries such as the Victorian Cancer Registry [8]. A higher rate of HCC has also been reported in Aboriginal and Torres Strait Islander populations; estimated at 2% and 8% in urban and rural areas, respectively, compared with less than 1% for the total Australian population [9].

The aetiology of HCC is well documented in the literature with high rates linked to both hepatitis B and hepatitis C exposure [9]. Other significant causes that may cause patients to present include alcoholic liver disease, non-alcoholic steatohepatitis as well as hereditary conditions such as haemochromatosis, alpha-1 antitrypsin deficiency, and autoimmune disorders (Figure 1) [10,11]. These conditions result in significant parenchymal loss, increased fibrogenesis and inflammatory signalling resulting in cirrhosis; a condition associated with 70-90% of all detectable HCC cases [10,11].

The natural history of HCC growth begins as small asymptomatic nodules which can often take years to develop depending on the aetiological exposure [5]. Small HCCs at detection have relatively long tumour doubling times with tumours of less than five centimetres associated with a survival of 81-100% at one year, and 17-21% at three years without therapy, which suggests that early diagnosis may allow for a greater intervention window [5].

These features make HCC an insidious and difficult disease to clinically detect and investigate. Patients who develop HCC are usually asymptomatic, mostly displaying symptoms related to their chronic liver disease which can become modified with disease progression [6,12]. Examples of this include signs of decompensation such as ascites, encephalopathy, jaundice, and variceal bleeding [12]. Advanced lesions also can present more conspicuously causing obstructive symptoms such as jaundice, diarrhoea, weight loss, and fatigue [13]. These signs are a result of local tumour invasion and growth inside the liver. However, systemic signs can also occur as a result of metastases which can develop in the lung, portal vein, periportal nodes, bone or brain [13]. As a result of these features, HCC is typically diagnosed late in its course with a median survival following diagnosis of 6 to 20 months, and a five-year survival ranging from 12% in those outside major cities and 17% within major cities in Australia. [13,14].

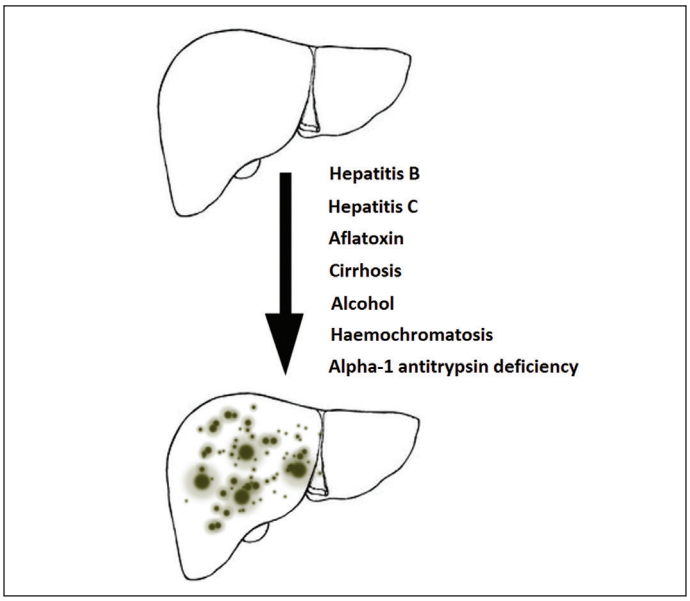


Figure 1. *Aetiology of hepatocellular carcinoma*

Screening and detection of HCC

Accordingly, screening programs for HCC in at risk groups, those with chronic liver disease or chronic hepatitis infection, is recommended with specialist review forming part of a 6-12 monthly management plan [15]. These programs involve using alpha-fetoprotein (AFP) and ultrasound to screen for the presence of cancer lesions.

AFP is a widely studied screening test marker for HCC with a level above 400 ng/mL regarded as diagnostic [5]. However, two thirds of HCCs less than 4 cm have AFP levels less than 200 ng/mL and up to 20% of HCCs do not produce AFP even when they are very large [5]. Moreover, there is evidence that fluctuating levels of AFP in patients with cirrhosis might reflect flares of HBV or HIV infection or liver disease exacerbation rather than HCC development [16]. Some studies investigating the clinical utility of AFP have suggested it lacks the sensitivity to be useful, with one study suggesting it rarely assisted in a diagnosis [5,17,18]. As a result of this, it has been suggested that AFP testing alone should only be used if ultrasound is unavailable, with the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommending it not be used at all [16,18,20]. This therefore limits the use of AFP as a reliable test to screen for HCC in at risk groups. Due to these limitations, other serum markers which include plasma microRNAs such as miR-122 and miR-192, des-gamma-carboxy prothrombin, AFP isoforms and glypican-3 are currently being investigated and evaluated for future use [19,20].

Another modality that is used in HCC screening is ultrasound. Ultrasound can detect large HCCs with high sensitivity and specificity; however, it is less able to reliably identify smaller lesions, which are required if more effective therapy is to be offered [6,19,20]. Ultrasound has been shown to detect 85-95% of lesions 3-5 cm in diameter, but can only achieve a 60-80% sensitivity of 1 cm lesions [5]. A large meta-analysis investigating this in 2009 found similar results demonstrating that surveillance with ultrasound showed a limited sensitivity (64%) for early HCC detection [19]. Combined use of AFP and ultrasound has been shown to increase detection rates, but had a raised combined false positive rate of 7.5% compared to AFP and ultrasound alone at 5.0% and 2.9% respectively [18]. Despite the limitations of these tests, the Royal Australian College of General Practitioners guidelines suggest that patients with chronic liver disease or chronic hepatitis infection should be considered for 6-12 monthly AFP and ultrasound screening [15]. The Asian Pacific Association for the Study of the Liver also recommends surveillance for HCC with both AFP and ultrasound every 6 months [21].

The importance of early HCC detection cannot be understated. The natural history of early tumours is poorly known as most are treated upon diagnosis; however, surgical resection, tranplantation and ablation offer high rates of complete responses and a potential cure in all patients with early HCC [22]. Advanced course HCC has a survival of less than six months without treatment with prognostic factors for survival including anatomical extension of the tumour, performance status and functional hepatic reserve based on the Child-Pugh Score [22-24]. It is from this that researchers are currently investigating superior screening techniques which can identify tumours earlier and with greater sensitivity and specificty to enable earlier intervention and better treatment outcomes.

Cancer biology as the pathway for a HCC screening test

One approach that is currently being investigated in the medical literature focusses on the biology of HCC hepatocarcinogenesis to develop a sensitive early screening test that can guide and detect treatment before the cancer can extend and spread. Mature hepatocytes have an average lifespan of between 200-400 days and rarely proliferate unless stimulated by acute injury [25]. The observation of normally quiescent hepatocytes and cholangiocytes proliferating after partial hepatectomy has highlighted the significant regenerative ability of the liver after acute insult [26]. If this regenerative capacity is compromised, the liver has liver progenitor cells (LPCs) which can expand and regenerate the chronically damaged liver [27,28]. LPCs can propagate and differentiate into two types of liver epithelial cells; hepatocytes and cholangiocytes [27]. These cells have been defined as stem cells because they are clonogenic, with a high growth potential and are able to be induced to differentiate into both types of liver cells and have shown capability in repopulating the liver on transplantation [27-30].

The proliferation and differentiation of LPCs into hepatocytes render them a target population for hepatocarcinogenesis [30]. LPCs have been traced to hepatocytes and are markedly elevated in chronic liver disease [28]. Recent laboratory experimentation has shown a link between induced liver damage in mice and the development of HCC, suggesting a tenable link between LPCs and HCC development [31,32]. LPCs have also been documented in chronic human liver pathologies, such as chronic hepatitis C, which is highly associated with hepatocarcinogenesis [29,33-35]. Analysis of premalignant lesions in HCC have also identified the presence of LPCs, with up to 50% of developed HCCs being shown to express markers of progenitor cells including CK7, CK19, OV6 [35-38] These findings have also been found in further studies on both human and mouse liver cells [38,39]. These results suggest a significant link exists between LPCs and HCC carcinogenesis.

From a molecular analysis of HCC progression, it has been shown that hepatocarcinogenesis is a multistep process that is heterogeneous and not well understood [40]. Progressive genetic alterations have been shown to cause a spectrum of cellular changes starting from cell hyperplasia, proliferation to dysplasia and eventually cancer [28,40]. This model is widely accepted and has been applied to many types of cancer, including HCC [28]. Multiple studies have demonstrated that two tumour suppressor pathways are important in controlling cell proliferation including the retinoblastoma protein pathway and the p53 pathway [28,41]. Most human tumours have genetic mutations, deletions, deregulated methylation or alterations in microRNA signalling in their Retinoblastoma and p53 pathways; making these genes likely candidates in the transformation of non-tumourigenic LPCs to tumourigenic LPCs [42-44].

Future HCC screening with the marker p16 INK4a/ARF

One gene involved in the p53 tumour suppressor pathway which may play a crucial role in hepatocarcinogenesis is the INK4a/ARF locus. Studies have identified variable rates of inactivation of the p16 INK4a/ARF gene in HCC with inactivation ranging in the literature from 35-82% of HCCs depending on the aetiology [45-50]. Studies on HCC mouse models have highlighted the important role of INK4a/ARF in tumourigenesis with concomitant loss of p53 and INK4a/ARF accelerating tumourigenesis and the progression to metastatic lung lesions [51-53]. Furthermore, tumours lacking both p53 and INK4a/ARF demonstrated strong migration and invasion capabilities. This was not demonstrated when p53 itself was inactive; suggesting that INK4a/ARF inactivation may be a critical step in HCC development (Figure 2) [52,53]. Significant evidence suggests that INK4a/ARF are important tumour suppressors encoded at 9p21 [9,46,52-54]. Kaneto *et al.* suggested that the methylation of the INK4a/ARF locus promoter is an early event in hepatocarcinogenesis, making this gene an ideal candidate for further study in the pursuit for an accurate diagnostic tool for HCC [46].

The nature of how genes are inactivated in tumourigenesis is biologically complex. The INK4a/ARF gene can be affected by many different forms of inactivation notably mutations, homozygous deletions or gene methylation [54]. Tannapefel *et al.* showed that of 71 carcinomas

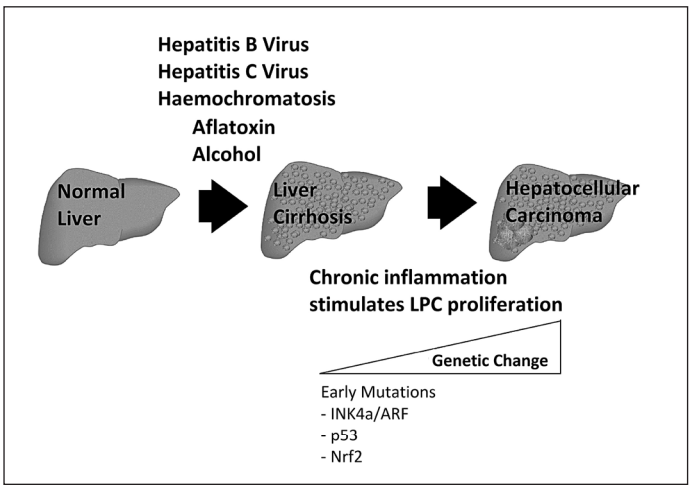


***Figure 2**. Stages of hepatocellular carcinoma development*

examined, 59% showed aberrant methylation of the INK4a gene [54]. Another recent review suggested that as many as 40-70% of HCCs demonstrate an INK4a methylation resulting in the downregulation of protein expression [55]. The pathogenesis of the ARF gene in HCC was not as clear, with studies finding ARF gene methylations in non-cancerous liver tissue as well as low rates of ARF methylation in human HCC samples [54,55]. Despite this, evidence of promotor methylation has arisen from investigations into the cause of INK4a/ARF inactivation in other tumours such as human cutaneous squamous cell carcinoma and colorectal carcinomas [56,57]. These studies provide evidence that the methylation of the INK4a/ARF gene may be an important step in the hepatocarcinogenesis of HCC and therefore could be an effective clinical marker for the identification of HCC development in at risk patients.

Conclusion

While it is clear from this review that further research needs to be conducted to better understand the role of the INK4a/ARF gene locus in HCC development, the potential for a clincial application remains a potent driver for further research in this area of molecular medicine. While the current screening methods using AFP and ultrasound are considered to be clincially useful in detecting HCC, there exists a space for more accurate modalities to detect early HCC lesions. If future research shows that the INK4a/ARF gene is a common early mutation in HCC hepatocarcinogenesis, then future tests may be developed which can sample high probability sites in the liver or the blood to investigate for DNA which contains this mutation. This could potentially improve the prognosis of patients with HCC development and allow early directed treatment with the possibility of cure.

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Conflicts of interest

None declared.

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Imatinib resistance in chronic myeloid leukaemia caused by Bcr-Abl kinase domain and non-Bcr-Abl mutations: a comparison and review

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Sam is in his fourth year of undergraduate medicine at James Cook University and is thoroughly enjoying his time there, especially his university's focus on rural health. He has also published with JCU's Vascular Biology Unit in the field of peripheral artery disease. This review has taken Sam out of his comfort zones of emergency and cardiovascular medicine and into the world of molecular oncology.

Abstract

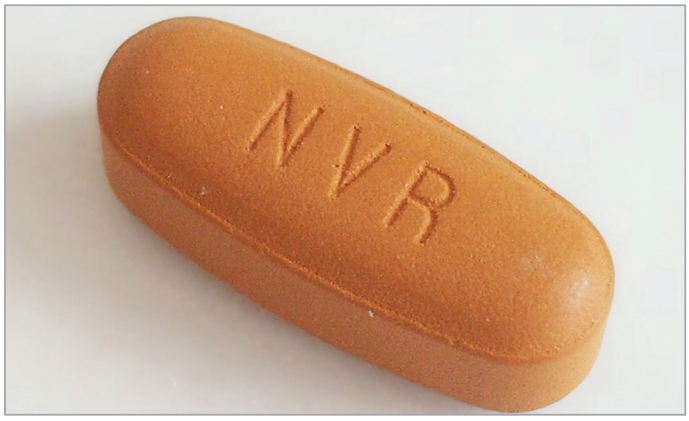
Chronic myeloid leukaemia (CML) is a myeloproliferative disorder caused by BCR-ABL1 fusion encoding for a tyrosine kinase oncoprotein. Since the introduction of the tyrosine kinase inhibitor (TKI), imatinib, in 2000, CML survival rates have increased, to the point where life expectancy is equal to that of the general population. One obstacle patients face is imatinib resistance. Literature about resistance has mainly focussed on mutations in the Bcr-Abl kinase domain (KD), which have been well described. Areas that have not been as well established include the origin of KD mutations and resistance from mechanisms outside of KD mutations. This review focuses on how KD mutations arise and their mechanisms of resistance and the roles of BCR-ABL1 gene amplification, Erk1, and Lyn kinase in creating resistance outside of the KD. Experimental therapies to combat imatinib resistance are also mentioned. Using database searches to obtain the current literature, this review attempts to determine the current consensus on these topics and highlight areas where research could be beneficial. While the origin of KD-mutations and non-KD resistance is not entirely clear, the many possible causes that have been elucidated thus far have already paved the way for new therapies.

Introduction

Chronic myeloid leukaemia (CML) was the first cancer where the pathological chromosomal abnormality was identified, and is one of the most understood and well-managed cancers [1,2]. CML is a clonal disorder of pluripotent stem cells that results in over-proliferation of mature myeloid cells [3]. Constitutive and aberrant tyrosine kinase activity is responsible for pathological cell proliferation in CML [4]. Before the advent of tyrosine kinase inhibitors (TKIs), 5-year survival rate for patients aged 20-44 was 40%, and less than 20% for patients over 65 years. For patients aged 15-44 diagnosed in 2000, this jumped to 71.6%, increasing to 86.4%, if diagnosed in 2005 [5]. Responsible for these leaps in survival was imatinib mesylate, a TKI approved in 2001 [6]. Imatinib antagonises tyrosine kinase activity by competing with ATP binding to the Bcr-Abl protein, reducing unchecked cell-cycle progression [3]. Imatinib resistance undermines therapy, putting patients at risk, and occurs in approximately 25% of patients [1]. Hence, it is important for doctors and medical students alike to understand that resistance occurs, some of the mechanisms behind resistance and how new pharmacotherapies can combat these. This review summarises the pathophysiology of CML and synthesises the literature around competing theories of imatinib resistance.

Pathophysiology of CML

CML is a myeloproliferative disease caused by a reciprocal translocation between chromosome 9 and 22 (9;22)(q34;q11.2)[1,7]. This creates an abnormal chromosome 22 called the Philadelphia (Ph) chromosome, named after the city it was discovered in in 1960 [2,8]. The oncogenic



effects of this translocation are caused by 5' exons of the BCR (breakpoint cluster region) gene fusing to the 3' exons of *ABL1* (Abelson tyrosine protein kinase 1) [3]. This creates the *BCR-ABL1* oncogene on the Ph chromosome encoding for Bcr-Abl tyrosine kinase, or $p210^{BCR/ABL}$ [9-11]. Retroviral insertion of $p210^{BCR-ABL}$ in murine models induces a myeloproliferative disorder similar to CML [11]. However, in less than 10% of cases, gene fusion occurs in different exons creating kinases p190 or p230 depending on where the fusion occurs [12,13]. Bcr-Abl has constitutive tyrosine kinase activity, causing modulated gene transcription, proliferation, and enforced survival of myeloid progenitor cells [14]. Unregulated cells grow and enter the S-Phase of the cell cycle independently of physiological growth factors and avoid apoptosis [8,14,15]. Abl and Bcr-Abl are non-receptor tyrosine kinases that travel between the nucleus and the cytoplasm and phosphorylate proteins via SH2 and SH3 domains [16].

Targets of increased phosphorylation that have proliferative effects include insulin-like growth factor receptor 1 (IGF-1R) [17], Ras [16], p27Kip [18], and others. This review will focus on a selection of the most well-known pathways (Figure 1). Bcr-Abl regulates *IGF-1R* expression via Stat5, which enhances IGF-1R gene expression [19,20]. IGF-1R tyrosine kinase stimulates haematopoietic stem cells and CML patients show higher than normal levels of *IGF-1R* mRNA [17]. When CML cells were treated with an inhibitor of tyrosine kinase phosphorylation of IGF-1R, the cells underwent apoptosis, cell-cycle arrest, and decreased cell proliferation, illustrating how IGF-1R and CML are linked [17]. One protein both IGF-1R and Bcr-Abl stimulate is Ras [21]. Ras is a well-studied oncoprotein that regulates several downstream pathways that increase cell proliferation including PI3/AKT and JAK/STAT [16]. The importance of Ras in CML pathophysiology was confirmed when association of Bcr-Abl and Ras was blocked and subsequent attempts to induce a CML-like disorder failed [22]. P27Kip is a cyclin dependent kinase (cdk) inhibitor and decreases cdk2 activity, thus inhibiting G1/S-phase progression. In CML, while the amount of $P27^{Kip}$ is unchanged, 80% of $P27^{Kip}$ is relocated to the cytoplasm, where it cannot interact with nucleic cdk2, allowing unregulated cell-cycle progression [18]. This is caused by Bcr-Abl interfering with cytoskeletal proteins such as β1-integrins [23]. These three pathways highlight that Bcr-Abl is central

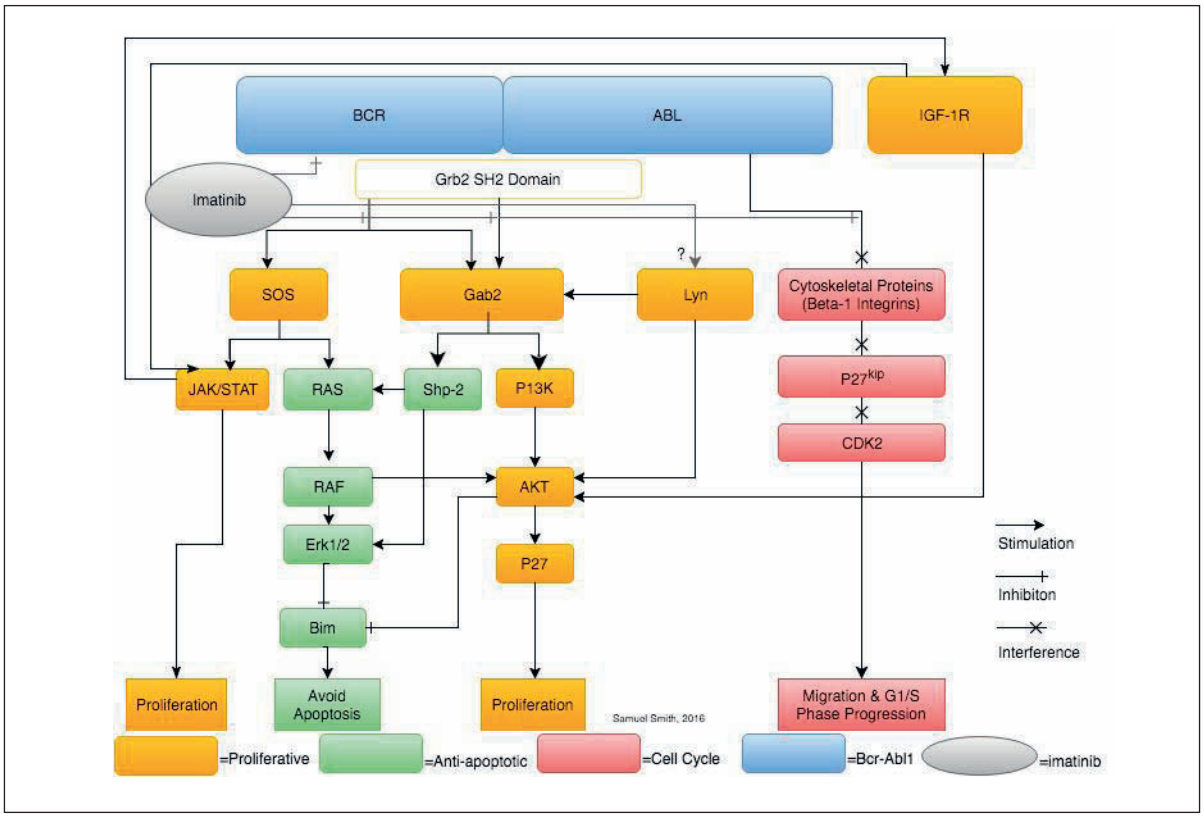


Figure 1. *Intracellular pathways influenced by Bcr-Abl Kinase [24,25,26].*
A synthesis and simplification of selected pathways (JAK/STAT, Gab2, Lyn kinase, IGF-1 and β-1 integrin) showing the leukaemogenic downstream effects of Bcr-Abl signalling. Imatinib is shown solely inhibiting Bcr-Abl, however, research shows imatinib therapy also affects Lyn kinase expression and activity.

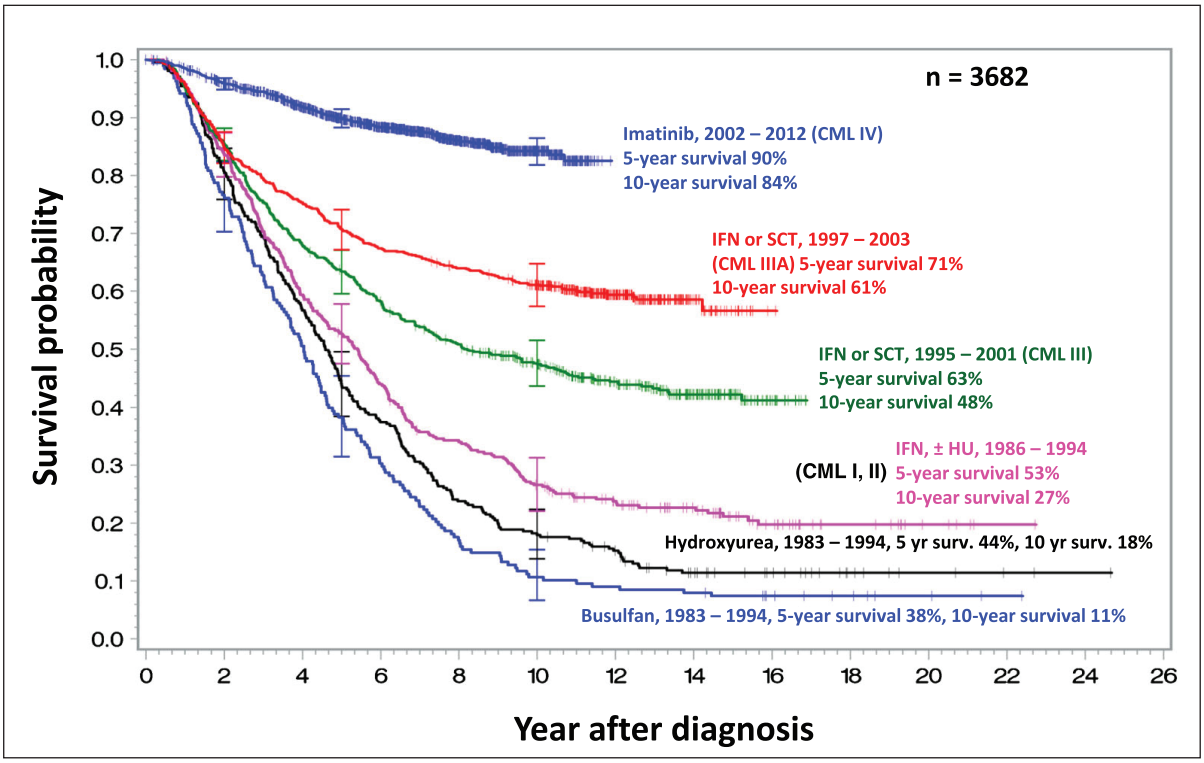


Figure 2. *Survival with CML over time [29].*
This figure from the German CML-Study group shows patient survival probability as a function of time after diagnosis in five consecutive randomised treatment optimisation studies. HU = hydroxyurea; IFN = interferon; SCT = stem cell transplantation. Survival with chronic myeloid leukaemia (CML) as observed in five consecutive randomised treatment options suties of the German CML Study Group 1983 - 2014. Kindly authorised by R Hehlmann.

Table 1. *Measurements of CML therapy outcome [1,32]*

Parameter	Definition	Strengths	Weaknesses
Complete Haematologic Response (CHR)	Leukocyte count <10 x 10^9/L, basophils <5%, platelets <450x 10^9/L, absence of immature granulocytes, impalpable spleen	Can be undertaken in routine medical exam	Not as accurate as other measures Slower detection of relapse
Complete Cytogenetic Response (CCyR)	0% Ph^+ metaphases seen in bone marrow using chromosome banding analysis (CBA)	Highly accurate Can detect new chromosomal abnormalities	Requires bone marrow sample Cost
Major Molecular Response (MMR)	BCR-ABL1:ABL1 ratio <0.1% International Scale (IS) using RQ-PCR (using an international standard of sensitivity)	Compares patient to international standard-more reliable results Uses PCR	No prognostic value over CCyR
Complete Molecular Response (CMR)	Undetectable BCR-ABL with PCR assay sensitivity >4.5	Gives a good prognostic indicator (equivalent to 0.01% BCR-ABL)	Normally not achieved until 12 months of therapy or later
Molecular Response 4.5 (MR4.5)	(<0.0032% *BCR-ABL1*^{IS}) using PCR	Achievement is associated with better long-term outcomes Uses IS and PCR	Not universally adopted Cost

to CML pathology[11]. As a consequence, pharmacotherapy targeting Bcr-Abl has been developed in the form of imatinib.

Imatinib

Imatinib is a TKI hailed as a conceptual breakthrough in targeted chemotherapy, and is the first line treatment in CML, while also being used in Ph^+ acute lymphocytic leukaemia and some gastric cancers [27]. In early evaluation studies, it was found to specifically inhibit cellular proliferation and tumour formation of Bcr-Abl expressing cells by 92%-98% [28]. Imatinib is effective when compared to other early treatments for CML, increasing the likelihood of survival at ten years by 20% when compared to the closest alternative therapy (Figure 2) [29]. The current parameters to measure successful treatment outcomes are listed with definitions in Table 1. In the International Randomized Study of Interferon and STI571, it was found that complete haematological response (CHR), complete cytogenetic response (CCyR), and major molecular response (MMR) scores were superior in imatinib-treated patients compared with interferon-treated patients [30]. Additionally, in the original trials for imatinib approval, three phase II studies involving 1027 patients showed over 90% of patient leukocyte counts returned to normal, and when combined with interferon, 100% of evaluable patients achieved CHR [31].

Mechanism of action

Bcr-Abl has an activation loop, a P-loop with an ATP binding site (in the kinase domain) and substrate anchoring SH2 and SH3 domains [33,34,35]. Imatinib binds specifically to the ATP-binding sites of Bcr-Abl, c-kit, and platelet-derived growth factor receptors, and inhibits their tyrosine kinase activity by both preventing ATP binding and stabilising the activation loop in an inactive conformation [34,36,37]. When Bcr-Abl tyrosine kinase activity is inhibited, there is no downstream signalling and treatment is successful in 77% of all patients [1] and virtually 100% of patients treated in the early stages of the disease [34]. The European LeukemiaNet (ELN) 2013 guidelines use MMR as the marker to indicate success of TKI therapy [32], however, Thompson *et al.* [1]. have argued that MMR overestimates the number of patients with treatment failure.

Treatment considerations and mechanisms of Imatinib resistance in CML

Failure of TKI therapy is caused by a number of factors, including inappropriate drug choice, patient non-adherence, and drug resistance. There are a number of opinions as to what constitutes treatment failure, but the definition used by this paper is the one put forward by the ELN and European Society for Medical Oncology. Treatment failure depends on which measurement is used; using haematological parameters (testing peripheral leukocyte counts), treatment failure is defined as no haematological response by three months, or any loss of CHR. Using cytogenetic response, however, treatment failure is no cytogenetic response within six months, no CCyr by 18 months, or any loss of CCyr, as detected by CBA [38]. Finally, a sub-optimal molecular response is defined as no MMR by 18 months or loss of MMR at any point using PCR for *BCR-ABL1* transcripts [38]. While this review focuses on imatinib (the gold standard in CML therapy) [30], second generation TKIs such as nilotinib, ponatinib, and dasatinib are now also used, both as first line agents and for use in imatinib resistant patients [1,27]. Which TKI to use and at what dose depends on a number of factors, including imatinib sensitivity and which disease phase the patient is in. CML is staged into chronic phase (CP), accelerated phase (AP), and blast phase (BP) (Table 2) [39]. For instance, a patient in AP who has never had a TKI is still treated with imatinib, but if they have taken imatinib and then progressed to AP, a second generation TKI is used [1]. Using imatinib inappropriately could cause treatment failure, while immediately using a second generation TKI or increasing TKI dosages has been found to limit adherence, as well as side effects (Table 2), especially for patients who require more potent TKIs and higher doses [40].

The most serious complication in CML treatment is resistance to therapy. This occurs most frequently in the AP and BP stages of the disease22. Traditionally, resistance is thought to occur from point mutations in the Bcr-Abl kinase domain (KD) [1,15,34,43]. There are several mutations that can cause mutations in this setting (Table 3). Bcr-Abl KD mutations can be intrinsic (primary) or acquired (secondary) and interfere with TKI therapy in a number of ways [1]. The most common mechanisms are by directly interfering with TKI binding via amino acid substitutes in the ATP binding site or by preventing the activation loop from adopting the inactive conformational state [34]. Although Abl KD mutations causing TKI resistance were first induced in laboratory cell lines in 2000 [44], and detected *in vivo* clinically in 2001 [45], novel mutations are continually being discovered, with two new mutations conferring resistance sequenced in 2014 [46]. The discovery and sequencing of mutations has led to individualised therapy and a more accurate prognosis for specific mutations, for instance the T315I mutation. In this common mutation, threonine-315 is replaced with

Table 2. *Stages of CML with respective treatment options and side effects[1,27,41,42].*

Stage	Definition	Treatment2	Prognosis
Chronic phase (CP)	CML without AP or BP progression	Imatinib 400mg/d Dasatinib 100mg/d NIL also front line in CP-CML	If imatinib sensitive, equal life expectancy to general population.
Accelerated phase (AP)	15% or more blasts in bone marrow, 20% basophils in circulation or platelet counts <100,000 µL	Imatinib 600mg/d Nilotinib 400mg/d Dasatinib 140mg/d	If Imatinib sensitive: 80-90% CCyR. Lower response rates and inferior event free survival if patients have resistance.
Blast phase (BP)	30% or more blasts in peripheral circulation, clusters of blasts in bone marrow or extramedullary disease with blasts	Imatinib 800mg/d Nilotinib 800mg/d Dasatinib 180mg/d If two TKIs have failed, Allo-stem cell transplant (AlloSCT) should be considered	Dasatinib: Achieves CCyR 26%-46% of patients (depending on progrsssion) Ponatinib (not yet approved) has 55% 1-year survival

Table 3. *Sample of $p210^{BCR/ABL}$ kinase domain mutations known to cause resistance [1,34,49-51].*

Location	Mutation	Mechanism	Incidence*	Resistant To:
Imatinib Binding Site	T315I	Alters drug binding site	1.17%	All TKIs
	F317L	Alters drug binding site	0.31%	Imatinib, dasatinib
P-Loop	G250E	Alters protein conformation	0.63%	Imatinib
	Q252H	Alters protein conformation	0.55%	Low dose imatinib
	E255K	Alters protein conformation	1.25%	Imatinib, nilotinib
	Y253H	Alters protein conformation	0.47%	Imatinib, nilotinib
Activation Loop	L384M	Alters protein conformation	0.08%	Low dose imatinib
	H396R	Alters protein conformation	0.26%	Low dose imatinib
Catalytic Domain	F359C/V	Alters drug binding site	0.86%	Imatinib, nilotinib
	M351T	Alters Drug Binding Site	1.17%	Imatinib

*Incidence based off Ursan *et al.*'s meta-analysis of a total of 1,698 patients. Overall mutation rate for imatinib was 9.7% [50].

isoleucine, effectively removing a hydrogen-bonding site required for TKI binding resulting in enormous treatment difficulty [34]. Only one TKI has any activity in $T315I^{+}$ patients and that is the highly potent ponatinib. However, this drug is not used as a front line therapy as it has a higher rate of arterial thrombosis and pancreatitis when compared to imatanimb [1]. A novel drug that binds to a nearby site not affected by the mutation, HS-438, is being investigated for use in $T315I^{+}$ CML and has shown success in pre-clinical trials [47]. Another drug, ABL001, also acts at another molecular site and thus avoids the resistance caused by KD mutations. ABL001 mimics the autoregulating region of ABL1 that is lost upon fusion of *BCR*, restoring negative regulation, and has been shown to remain effective against clinically significant mutations in an in vivo model [48]. This example highlights how sequencing mutations can provide valuable, individualised prognostic information and guide future research.

How these mutations arise is not clear; in some patients with secondary resistance pre-therapeutic samples revealed the same KD mutation detected at relapse, consistent with selection of pre-existing resistant clones during therapy giving an evolutionary advantage [52,53]. There is some contention as to whether these stem cell mutations can cause primary resistance or whether KD point mutations can only cause secondary resistance and relapse. Previous studies have concluded that Bcr-Abl KD mutations are a rare cause for primary resistance, however, more recent research found KD mutations in 56% of patients with primary resistance [54,55]. This discrepancy may be explained by the more recent study utilising more sensitive technology and patients who had CML for a longer period of time, which has been linked to mutagenicity [28]. KD resistance in Bcr-Abl1 CML differs from other diseases in that unlike traditional drug resistance, where treatment resistance arises via positive selection of tumour cells with mechanisms to avoid DNA damage, in CML resistant cells there is a tendency to accumulate more rather than less DNA damage [56]. The mechanism behind this is unknown, but it is an example of how the malignancy directly causes resistance. Nevertheless, the evidence suggests that pre-existing KD mutations in cancer stem cells are more likely to be responsible for secondary resistance.

Other research suggests that BCR-ABL1 has the ability to cause self-mutagenesis. Mutation rate and advanced disease phase were

correlated, consistent with mutations being related to exposure time to Bcr-Abl activity [34]. One suggested mechanism is production of reactive oxygen species causing genomic instability, shown in vitro and in murine models, but beyond the original studies, no further research has been undertaken [34,57]. While KD mutations are a highly researched area in CML therapy (over 60 unique point mutations have been identified), there remains an information deficit, for example, the prevalence of mutations in specific populations, or randomised controlled trials for TKI choice following imatinib failure [1,58].

Non Bcr-Abl kinase domain mediated resistance

Recent research adds complexity by suggesting there are a number of mutations and events occurring outside of Bcr-Abl KD that impact drug resistance [43].This includes mutations of Bcr-Abl1 outside of the kinase domain, such as *BCR-ABL1* amplification, and causes outside of the Bcr-Abl1 protein altogether, such as mesenchymal cells, drug transporters and bypass molecular pathways. Increased *BCR-ABL1* expression via gene amplification is found in most TKI resistant cells, whether the mutations are primary, secondary, KD, or non-KD, implying a link between increased expression and resistance [59]. However, increased expression is not the sole cause of non-KD mediated resistance as studies have shown that increasing imatinib concentration in non-mutated, sensitive cells with induced *BCR-ABL1* amplification still reduces Bcr-Abl activity, whereas some resistant cells without KD mutations remain resistant at any dose [60].

Extracellular Signal-Regulated Kinase 2 (Erk2) is a Mitogen Activated Protein Kinase (MAPK) and has been implicated in both primary and secondary resistance (i.e. immediate resistance to therapy and resistance that builds over time)[60,61]. In a study of non-KD mutated resistant cells treated with imatinib, Erk2 was found in the nucleus of resistant cells only, and inhibiting Erk2 caused damage to resistant cells [60]. Mechanisms for how Erk2 could cause primary resistance were then elucidated. To achieve this, mutated Ras (which activates Erk2), was virally transduced into sensitive cells that were cultured and treated with imatinib. Using proliferation assays to determine cell survival, it was discovered activating Erk2 gave previously sensitive cells resistance without any prior exposure to imatinib. Erk2 is a key regulator of the pro-apoptotic molecule Bim and it is proposed interactions between Erk2 and Bcr-Abl over-stimulate Erk2 and reduce CML cell apoptosis [62]. Research in 2016 by Wong *et al.* [63] extended these results to create a pharmacotherapy inhibiting Erk2, showing areas outside of the KD can cause primary and secondary resistance and can be targeted.

Lyn kinase

Lyn kinase is a non-receptor tyrosine kinase regulated by Bcr-Abl. Imatinib resistant but Bcr-Abl KD-mutation negative cells were found to overexpress Lyn kinase following treatment with imatinib [64]. In cell lines from these patients, while imatinib effectively inhibited Bcr-Abl activity, Lyn kinase phosphorylation continued, allowing proliferation to continue. Interestingly, prior to imatinib therapy, there was no consistent difference in Lyn expression between sensitive and resistant cells, but afterward there were consistent distinctions in their control of phosphorylation. This implies imatinib treatment uncouples Lyn expression from Bcr-Abl, leading to resistance. Lyn overexpression can induce a three to fourfold resistance, equal to some KD mutations, yet the mechanisms of its overexpression and how it worsens CML are not yet known [65]. One theory is that because silencing of Lyn kinase induces apoptosis in CML cells, overexpression causes cell survival, signalled through via Gab2 [66,67]. The fact that this effect is not seen in imatinib-naïve CML patient cells supports the idea that Lyn kinase only causes acquired resistance, leaving the mechanisms behind primary resistance a mystery.

Drug transporters

Alterations in drug transporters are yet another mechanism by which medication resistance can occur and will be mentioned briefly. A drug must both reach the target organ in sufficient amounts and be present at an effective therapeutic concentration for it to exert and effect, and both influx and efflux transporters can interfere with these pharmacokinetics [27]. Radiolabelled imatinib assays have determined that the level of kinase inhibition is dependent on the level of uptake and retention of imatinib achieved [68]. Imatinib enters the circulation from the gastrointestinal tract by a member of the organic cation transporter (OCT) family, OCT-1, thus mutations in OCT-1 are thought to contribute to treatment failure [68]. Conversely, imatinib leaves the cell via the p-glycoprotein multidrug resistance protein-1 (MDR1 or ABCB1) [69]. In other drugs, MDR1 overexpression has been confirmed to cause drug resistance by increasing efflux before a therapeutic concentration can be reached, and this is a relationship currently under investigation in CML.

Non-Bcr-Abl KD resistance is not a well-studied area and much research is yet to be undertaken. Two recent CML mutation reviews by Jabbour *et al*. and O'Hare *et al*. only provide a brief mention of non Bcr-Abl mutations causing resistance, even though these mutations cause from 10%-40% of TKI resistance [3,70]. In addition, there was much disagreement among researchers concerning molecular pathways to resistance. Erk2 is part of a super-family of MAPKs, other members such as Erk1, Erk5, and P38MAPK, have been considered in imatinib resistance [71,72]. Aceves-Luquero *et al*. carried out knock-out studies of MAPKs, which identified only Erk2 as having a resistance-inducing effect [52]. Extremely resistant patients require potent TKIs or stem-cell transplantation, both of which greatly affect quality of life, which could be avoided if mechanisms behind resistance were uncovered and targeted treatment developed1.

Limitations

While $p210^{BCR\text{-}ABL}$ accounts for 90% of cases of CML, other Bcr-Abl variants were not examined despite their different treatment responses, limiting the applicability of this review. Furthermore, the diagram in Figure 1 is a simplified representation of the pathways associated with Bcr-Abl, especially in the case of JAK/STAT. Only pathways that have been clearly implicated in CML and imatinib resistance by research literature were included. Systematic database searches were used to carry out this review. Spelling and terminology variations that influence search results, for example, "myeloid" and "myelogenous", were a limiting factor.

Clinical implications

This article holds a number of clinical implications for all medical students, not just the aspiring oncologist. For instance, the prevailing view in oncology is that mutations that confer imatinib resistance occur in the kinase domain. With the explosion of advances in genome sequencing, it is becoming possible to prospectively genetically screen patients to determine whether resistance will occur. If the current wisdom regarding CML resistance prevails, then mutations outside the kinase domain (that have been reported to cause between 10% - 40% of resistance) could be ignored, potentially putting patients at risk of ineffective treatment which could cost them their lives [2]. By investigating and becoming aware of the role of non-KD mutations, doctors could also give more accurate prognoses to patients with these mutations and begin studies looking at the best treatment for these cases (for example, randomised controlled trials comparing current therapy to higher doses of imatinib, or new pharmacological agents altogether). This review also provides a general overview into CML pathophysiology, imatinib pharmacology and chemotherapy resistance, topics every medical practitioner should be very familiar with.

Conclusion

Imatinib is a TKI that revolutionised leukaemia treatment and increased the length and quality of life of CML patients. While it has been known for many years that primary and secondary resistance to imatinib exist, the mechanisms have not been fully explained. While mutations in the Bcr-Abl KD account for the majority of resistance and are well known, what remains unclear is the origin of these mutations, and how resistance occurs without KD mutations. Stem cell mutations and self-mutagenesis are possible explanations for how KD mutation occurs, and gene amplification, Lyn kinase and Erk2 for resistance occurring outside of the KD. Further research identifying key events in downstream pathways will offer new approaches for overcoming all forms of imatinib resistance.

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Conflicts of interest

None declared.

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MicroRNA-34a: a novel treatment approach for hepatocellular carcinoma

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Abstract

Aim: To ascertain the function of miRNA-34a in hepatocellular carcinoma (HCC) and to assess its use as a therapeutic agent through the analysis of pre-clinical and clinical trials.

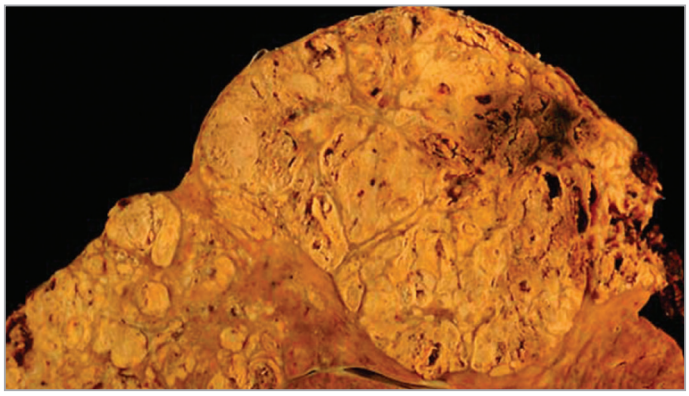
Discussion: Multiple studies found that miRNA-34a was down-regulated in the majority of human HCC samples and subsequently had a tumour suppressor role via the inhibition of a number of target genes essential for carcinogenesis. MRX34, a miRNA-34a mimic, is currently in an ongoing phase I clinical trial. Interim data has indicated that this therapy has a manageable safety profile, with a partial response observed in one patient. The combination of miRNA-34a with other agents has also proven to exert enhanced anti-tumour effects. Conversely, many studies have reported that miRNA-34a was up-regulated in HCC samples, particularly in those with activation of the beta-catenin pathway.

Conclusion: Pre-clinical studies have shown promising results in the use of a miRNA-34a mimic in HCC as a single agent or as a combination therapy, however, the results from the phase I trial are yet to be fully established. The mechanisms of miRNA-34a in HCC remain to be elucidated, with further research required into its proposed oncogenic role, especially relating to the clinical implications of this interaction.

Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related deaths worldwide and is the most common form of liver cancer, accounting for between 85% and 90% of primary liver cancers [1]. The major risk factors for hepatocellular carcinoma include hepatitis B (HBV) or C virus (HCV) infection, smoking, alcohol, and aflatoxin [2]. Currently the prognosis for HCC is poor with Australian statistics indicating that the five year relative survival rate for primary liver cancers is only 16% [3]. The non-specific tyrosine kinase inhibitor sorafenib currently represents the only effective treatment against HCC [4]. This poor prognostic outlook and the limited availability of targeted molecular agents for HCC has led to the development of new therapies such as microRNAs (miRNAs).

miRNAs are short (19-24 nucleotides), non-coding RNA molecules that are post-transcriptional regulators of gene expression. Initially, miRNA is transcribed as primary miRNA (pri-miRNA), which is processed into precursor miRNA (pre-miRNA). This is then transported from the nucleus into the cytoplasm where it is processed into its mature form by the enzyme Dicer. The mature miRNA forms part of the RNA-induced silencing complex (RISC), which is responsible for regulating the output of protein-coding genes. These miRNAs interact with the 3' untranslated regions (UTRs) of the protein-coding genes to result in a decrease in protein output via mRNA degradation or translational repression [5]. Alternatively, miRNAs can result in post-transcriptional stimulation of gene expression via a multitude of direct and indirect mechanisms [6]. It is estimated that a single miRNA can target hundreds to over one thousand different mRNAs, ultimately resulting in miRNAs being responsible for the regulation of around 20-30% of all protein-encoding genes [7]. These miRNAs have been reported to



have key roles in cancer initiation, progression, and metastasis [8]. Oncogenic miRNAs are miRNAs that are up-regulated in cancer cells and promote carcinogenesis via the inhibition of tumour suppressor genes. Conversely, the miRNAs that are decreased in cancer cells are known as tumour suppressor miRNAs, as they normally inhibit proto-oncogenes to prevent cancer from developing [9]. The mammalian miRNA-34 family consists of miRNA-34a, which is encoded via its own individual transcript, and miRNA-34b and miRNA-34c, which possess a common primary transcript [10]. Due to the promising and extensive research conducted on miRNA-34a, this review article focused specifically on this particular isoform. Dysregulation of miRNA-34a has been implicated in a wide variety of cancers, including prostate, colon [11], and HCC [12]. The purpose of this review is to analyse the specific role of miRNA-34a in HCC, including addressing contradictory findings and investigating the recent clinical trials.

The tumour suppressor role of miRNA-34a in hepatocellular carcinoma

A range of studies established that in the majority of human HCC samples, miRNA-34a expression was decreased in comparison to the surrounding non-cancerous liver tissue (Table 1) [12-16]. A murine model of hepatocarcinogenesis induced by a methyl-deficient diet also resulted in the down-regulation of miRNA-34a [17]. Low expression of miRNA-34a in HCC samples has been correlated with a shorter overall [13-15] and disease-free survival [14], as well as higher recurrence rates [13] when compared with samples that displayed up-regulation of miRNA-34a. The decreased expression of miRNA-34a is thought to be caused by genetic alterations such as deletions, point mutations, or chromosomal translocations of its genomic region 1p36 [18], which is common in HCC [19, 20]. Alternatively, this decreased expression has been linked to inactivating mutations of the p53 gene [18], as the induction of miRNA-34a is correlated with p53 status [21]. Furthermore, epigenetic silencing of miRNA-34a has been implicated with these decreased expression levels in multiple forms of cancer, via abnormal CpG methylation in its promoter region [22].

The administration of a miRNA-34a mimic (MRX34) has been shown to cause inhibition of a number of genes within multiple oncogenic pathways such as Wnt/ beta-catenin, c-MET, VEGF, hedgehog, and MAPK (all of which have been implicated in hepatocarcinogenesis), as well as stimulating multiple genes of the p53 pathway [23]. Daige *et al.* explored a diverse range of HCC related pathways, demonstrating how miRNA-34a exerts its anti-cancer effects by modulation of a

Table 1. *Percentage of human HCC samples with decreased miRNA-34a expression compared to surrounding non-cancerous liver tissue.*

Author of study	Number of HCC samples with decreased/low miRNA-34a expression	HBV+/HCV+ positive rates
Li *et al*. [12]	76% (19/25)	80% HBV
Xu *et al*. [13]	69% (52/75)	76% HBV, 6.7% HCV
Lou *et al*. [14]	71.4% (10/14)	92.9% HBV
Yang *et al*. [15]	50% (15/30)	76.7% HBV
Dang *et al*. [16]	83 participants, relative expression found to be decreased in HCC tissues	Not reported

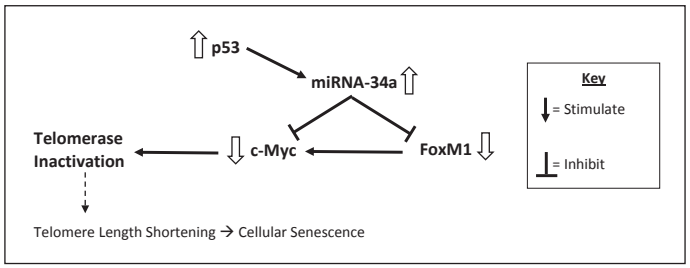


Figure 1. *Telomere dependent pathway of miRNA-34a induced cellular senescence* (adapted from Xu *et al*. [13]). High levels of miRNA-34a, which is regulated by p53, results in the inhibition of FoxM1 and c-Myc, causing the inactivation of telomerase, leading to telomere shortening and subsequently cellular senescence.

number of genes responsible for processes such as metastasis, cellular proliferation, cell cycle regulation, apoptosis, and cellular senescence [23].

miRNA-34a and cellular proliferation, cell cycle regulation, and apoptosis

A number of cell culture studies investigated the effects of ectopic expression of miRNA-34a in the HepG2 cell line, with contradicting results [12,16,18]. Ectopic expression of miRNA-34a caused significant inhibition of cellular proliferation at 72 hours [18] and 96 hours [16] post- transfection. In addition, miRNA-34a was demonstrated to regulate the cell cycle via inducing G1 arrest [18]. Furthermore, it has been found that miRNA-34a can induce apoptosis, as determined by increased caspase 3/7 activity [16]. In contrast, other reports claimed that there was no effect on cellular proliferation, G1 arrest, or apoptosis, [12,18], highlighting the conflicting information within the current literature. The discrepancies between these three studies could partially be explained by the varying methods used to express miRNA-34a, and the different measurement times post-transfection (48, 72 or 96 hours) [16]. Additional research has found that miRNA-34a induces apoptosis in HCC cells via binding to the 3' UTR of the Bcl-2 mRNA, causing inhibition of its translation [15]. Over-expression of miRNA-34a has also been correlated with a decreased expression of Bcl-2 in a number of other HCC studies [14,24].

miRNA-34a and metastasis

Down-regulation of miRNA-34a expression has been associated with metastatic HCC [12,16,25]. Multiple studies have established that the ectopic[1] expression of miRNA-34a in the HepG2 cell line inhibits tumour cell migration and invasion via silencing of the c-Met gene, which subsequently decreases the c-Met-induced phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) [12,16]. Cheng *et al.* also proposed that miRNA-34a prevents tumour migration, invasion, and metastasis by decreasing cathepsin D [18], a protease that contributes to the degradation of the basement membrane [26]. Furthermore in the HCC cell line Hca-F (high lymphatic metastatic potential) it was determined through *in vitro* and *in vivo* studies in mice that the ectopic expression of miRNA-34a caused a reduction in the metastatic potential [27].

miRNA-34a and cellular senescence

Earlier studies showed that miRNA-34a induced cellular senescence via cell cycle arrest in pathways that were telomere-independent [13, 28]. Recently, miRNA-34a over-expression has been shown to induce senescence in HCC cells in a telomere-dependent manner, regulated by p53. This cellular senescence occurs by the inhibition of FoxM1 and c-Myc, which causes the inactivation of telomerase activity, resulting in telomere shortening (Figure 1) [13].

[1] *The introduction into a tissue in a location where the target gene is not normally expressed for its effects to be studied*

miRNA-34a delivery methods

There is a vast array of delivery systems, both viral and non-viral, that are used to increase miRNA expression. Both mechanisms are associated with advantages and disadvantages [29]. Rubone and MRX34 are two prominent non-viral delivery methods that have been investigated in HCC studies [23,24]. Rubone is a small molecular modulator of miRNA-34a that was shown to induce miRNA-34a expression selectively in HCC cells (although only those with wild-type or mutant p53, not with p53 deletion), causing inhibition of tumour growth both *in vitro* and *in vivo* in the HepG2 xenograft mouse model. Xiao *et al.* also found that this miRNA-34a modulator displayed similar or even greater anti-HCC activity than sorafenib, the current treatment for advanced HCC [24]. MRX34 is a double-stranded miRNA-34a mimic that is delivered by liposomes [30]. The systemic delivery of this molecule resulted in tumour regression during *in vivo* studies in two different xenograft mouse models (Hep3B and HuH7) of liver cancer [23]. An oncolytic adenoviral vector that co-expressed miRNA-34a and IL-24 has also been studied in a HCC model. This was found to cause increased anti-tumour activity both *in vitro* and *in vivo*, predominantly via the downregulation of SIRT1 and Bcl-2 [14].

Clinical trials

Currently there is an ongoing phase I trial of MRX34 [31], which commenced in April 2013 and was originally indicated for patients with primary liver cancer or cancers with metastasis to the liver [32]. It was then gradually expanded to include patients with other advanced solid tumours (with or without liver metastasis) and haematological malignancies (lymphoma and multiple myeloma) [31]. There were 75 patients with advanced solid tumours enrolled in this study and 30 of these had HCC [33]. This trial's data revealed that partial responses to the treatment, as per the RECIST guidelines (Table 2) [34], were observed in one patient with HCC, one with melanoma, [33] and

Table 2. *Revised RECIST guidelines [34]*

Response	Criteria
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	>30% decrease in sum of longest diameters of all target lesions
Progressive Disease (PD)	At least 20% increase in sum of diameters of all target lesions Appearance of 1 or more new lesions
Stable Disease (SD)	Neither adequate shrinkage for PR or adequate increase for PD

one with advanced renal cell carcinoma [35]. Furthermore a number of patients in this trial were found to have attained a stable disease state [35]. This interim phase I data also determined that MRX34 has a manageable safety profile [33]. A recent press release from MIRNA therapeutics has indicated that phase II clinical trials will commence by the end of 2016 and will consist of two studies, one on renal cell carcinoma and the other on melanoma [35]. In terms of HCC-specific trials with MRX34, the future direction is currently unclear and with limited data available at the present time it is difficult to draw any definitive conclusions.

Combination therapy

Yang *et al.* demonstrated that ectopic expression of miRNA-34a resulted in the sensitisation of HCC cells to sorafenib-induced apoptosis and toxicity via inhibiting expression of Bcl-2 [15]. Additionally, the administration of miRNA-34a was found to sensitise HCC cells to chemotherapy (cisplatin) *in vitro* through the AXL pathway [36]. The combination of a miRNA-34a mimic and C-met inhibitor also resulted in a greater inhibition of cell growth and induction of apoptosis *in vitro* than either of these two therapies alone [16]. However, to establish more definitive results, further research is required in this field, particularly in regards to clinical trials.

The oncogenic role of miRNA-34a in hepatocellular carcinoma

Conversely, a number of other studies have shown increased expression of miRNA-34a in both murine and human HCC tissues [37-41], suggesting it may have an oncogenic role in addition to its tumour suppressor role. A recent article has investigated these claims and found that miRNA-34a displays oncogenic properties in liver tumours with beta-catenin activation [40]. Increased beta-catenin activation is most commonly caused by mutations in the CTNNB1 gene (the gene encoding beta-catenin), and this is estimated to occur in 20-40% of HCCs [42]. Gougelet and colleagues demonstrated using Apc^{KO} mice (Apc^{KO} causes activation of the Wnt/beta-catenin pathway [43]) that administration of a miRNA-34a inhibitor (LNA-34a) caused increased expression of hepatocyte nuclear factor 4a. This leads to increased apoptosis predominantly via caspase 2 activation and decreased cell proliferation through inhibition of cyclin D1 (Figure 2). This theory was then postulated to complement the data of the studies listed in Table 1, by accounting for those samples that showed up-regulation of miRNA-34a expression. The disparity in results between studies is thought to be due to the varying causes of HCC [40]. For example, the majority of HCC samples from the studies in the Table 1 were HBV+, and this was found to be associated with a lower frequency of CTNNB1 mutations [44]. Conversely HCC resulting from HCV infection has been shown to have a higher rate of CTNNB1 mutations [45]. However, these findings contradict the theory that miRNA-34a has a tumour suppressor function, and with relatively limited research on this oncogenic pathway, further investigation is required. Studies investigating the concept of miRNA-34a having a tumour suppressor or oncogenic function depending on the cause of the tumour would also be important, as well as an investigation of the clinical implications of this relationship.

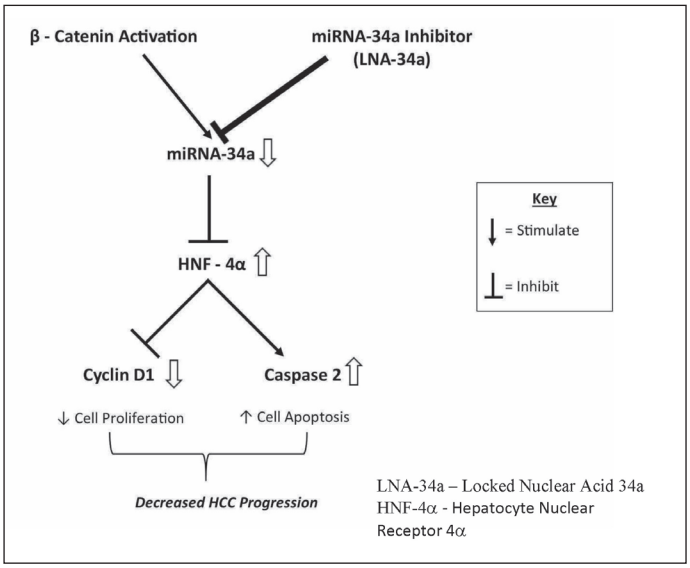


Figure 2. *Role of miRNA-34a inhibitor in counteracting the oncogenic action of miRNA-34a in HCC with beta-Catenin activation (*Adapted from Gougelet *et al*. [40]). The miRNA-34a inhibitor LNA-34a causes a reduction in β-catenin induced miRNA-34a expression which leads to an increased expression of HNF-4α. Subsequently cyclin D1 levels are reduced, leading to decreased cell proliferation and increased caspase 2 levels, leading to increased apoptosis. The combined effects of these two actions then leads to the decreased progression of the hepatocellular carcinoma.

Limitations

A number of limitations were identified within this review, particularly relating to the conflicting information and the limited availability of clinical trial results. Contradictory information was noted on a number of occasions, especially with the use of a miRNA-34a inhibitor for HCC, making it difficult to evaluate a clear clinical benefit to this potential therapy. The data surrounding the clinical trial was also restricted as the trial is ongoing. Subsequently, all the data had to be sourced from press releases and abstracts from presentations at conferences, which were all funded by MIRNA therapeutics; thus a potential conflict of interest was noted.

Conclusion

Results have indicated that miRNA-34a has a tumour suppressor function in HCC and is responsible for the down-regulation of a number of genes involved in carcinogenesis. There is, however, contradicting information described in studies investigating these parameters, highlighting the complexity of this topic. Rubone and MRX34 are two prominent miRNA-34a delivery systems that were shown to exert anti-tumour activity in pre-clinical models. Additionally, MRX34 has been commenced in a clinical phase I trial that is still currently ongoing, with a partial response already observed in one patient. However, the future of HCC-specific MRX34 trials remains unclear as limited information is currently available. Based on the promising results of miRNA-34a as a combination therapy, this is an area that requires further investigation through clinical trials. Conversely, other sources have found that miRNA-34a plays an oncogenic role in HCC, particularly in those with beta-catenin activation. Subsequently, it was demonstrated that miRNA-34a inhibitors should be used in these instances. Further research is necessary in order to ascertain the clinical implications of using a miRNA-34a mimic or inhibitor depending on the beta-catenin mutation status of the patient.

Conflicts of interest

None declared.

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Effects of subchorionic haematoma on pregnancy outcomes

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Abstract:

Introduction: Subchorionic haematoma (SCH) is the most common ultrasound abnormality found in women with symptoms of threatened miscarriage. It refers to a collection of blood between the chorionic membrane and the uterine wall. Depending on the time the haematoma is formed, it may appear as either hypoechoic or hyperechoic on the ultrasound. The cause of SCH may be related to poor placentation. Although SCH is common, the effects of SCH on pregnancy outcomes are unclear. The review aims to provide an overview of the effects of SCH on pregnancy outcomes and identify prognostic factors that may predict adverse pregnancy outcomes in women with SCH.

Methods: To identify the relevant literature, electronic databases (PubMed and EMBASE) were searched using the search terms: "subchorionic haematoma" and "subchorionic hemorrhage". Exclusion criteria include multiple pregnancy, ectopic pregnancy, Breus mole, review articles, case reports, and studies that did not focus on the effects of SCH on pregnancy outcomes.

Results and conclusion: Women with SCH have an increased risk of placental abruption. Studies are conflicting on the risk SCH poses on pregnancy loss. There are only limited studies on other adverse pregnancy outcomes such as preterm delivery, small for gestational age, pre-eclampsia, and chorioamnionitis. Factors that may predict an increased likelihood of adverse pregnancy outcomes in SCH include: large haematoma size, fundal or retroplacental location, early gestational age of diagnosis (before 9 weeks), and severity of symptoms. Persistent SCH is rare but it carries a high risk of complications, including chorioamnionitis.

Introduction

Up to 25% of pregnant women experience symptoms of threatened miscarriage, namely first trimester per vaginum (PV) bleeding with or without uterine contractions [1]. The most common ultrasound abnormality in these women is a subchorionic haematoma (SCH) [2]. SCH is a collection of blood between the chorionic membrane and the uterine wall [2]. Typically, it appears as a crescenteric hypoechoic lesion around the gestational sac [2]. According to a 2014 retrospective cohort study from Turkey, the reported incidence of SCH in women with symptoms of threatened abortion is 18.2% [3]. In the general obstetric population, the incidence of SCH varies between 1.7% to 3.1% [4,5].

Pathophysiology

The exact pathophysiology of SCH is still unknown. Nevertheless, the underlying cause of SCH is believed to be poor placentation [3,6]. Poor placentation can impair angiogenesis and lead to the formation of weak vessels that tear easily [3,6]. In SCH, it is postulated that the marginal utero-placental veins tear and cause low pressure bleeding [7]. The blood then tracks around the gestational sac to form a cresenteric haematoma between the chorionic membrane and the uterine wall [7]. In contrast, the bleeding in placental abruption is usually high pressure bleeding from ruptured spiral arterioles [8]. Results from a recent Japanese study appear to support the theory that SCH is caused by poor placentation [9]. The study found that SCH is more common in

women with risk factors for poor placentation such as multiparity and pregnancies conceived through in-vitro fertilisation, especially those using a frozen-thawed embryo transfer [9].

Clinical presentation

While some SCH are asymptomatic, most can present with first trimester PV bleeding with or without uterine contractions [5,10]. In most cases (up to 70%), PV bleeding of varying degree, ranging from spotting to heavy bleeds, can continue intermittently for 1 – 3 months after the diagnosis of SCH [11]. The symptoms usually resolve spontaneously during the second trimester [11]. However, a small minority of women (0.46% of all obstetric patients) can have a persistent SCH that remains symptomatic until delivery [11].

Diagnosis

SCH is diagnosed using ultrasound (Figure 1). The characteristic sonographic finding is a hypoechoic cresenteric lesion between the chorionic membrane and the uterine wall [2]. The haematoma may appear hyperechoic initially but with time, it becomes hypoechoic [2]. Possible differential diagnoses for this sonographic finding include chorioamniotic separation and twin gestational sac [2].

Rationale and aims

Although SCH is very common in women with symptoms of threatened miscarriage, the effects of SCH on pregnancy outcomes are unclear. This review aims to provide an overview of the effects of SCH on pregnancy outcomes. It also aims to identify prognostic factors that may predict adverse pregnancy outcomes in women with SCH.

Methods

To identify the relevant literature, electronic databases (PubMed and EMBASE) were searched using the search terms: subchorionic haematoma and subchorionic hemorrhage. The search was limited to English-language human studies published between January 1981 and June 2016. A total of 192 studies were identified from the database search and an additional 14 studies were identified from manual review of bibliographies. After removing the duplicates, studies were excluded for reasons such as multiple pregnancy (n = 2), ectopic pregnancy (n = 2), Breus mole (n = 11), review articles (n = 2), case reports (n = 4) and different study focus (n = 82) (Figure 2). For this review, 28 studies discussing the effects of SCH on pregnancy outcomes were included.

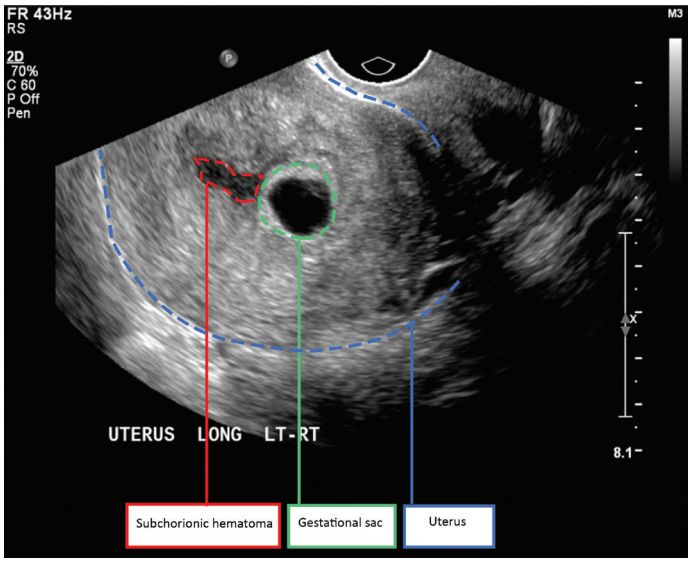

Figure 1. *First trimester subchorionic haematoma.*

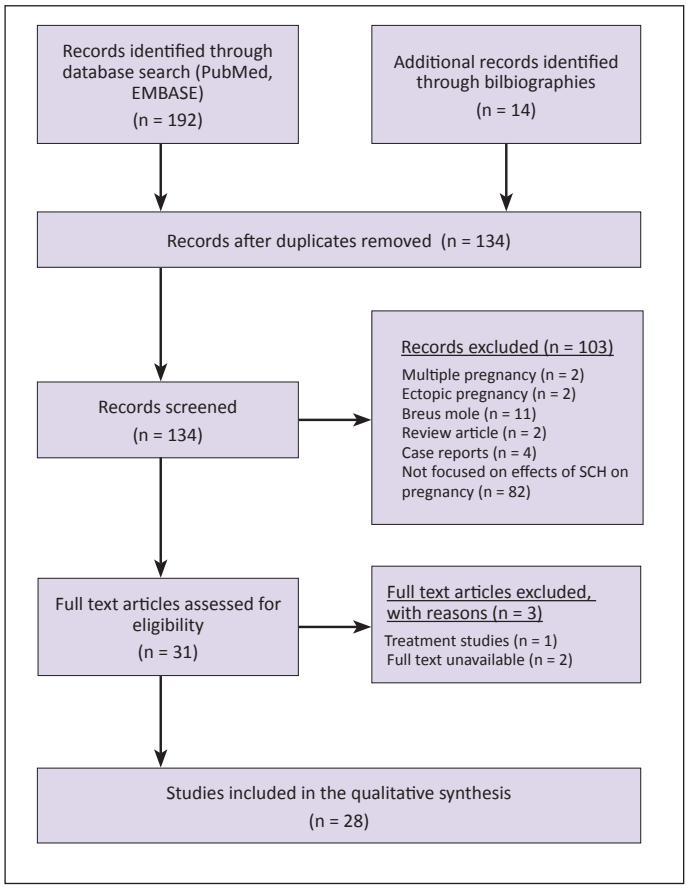

Figure 2. *PRISMA study flow diagram.*

Effects on pregnancy outcomes

Adverse pregnancy outcomes that may be associated with SCH include early and late pregnancy loss, placental abruption, preterm delivery (PTD), preterm premature rupture of membrane (pPROM), small for gestational age (SGA) and chorioamnionitis. The pathophysiological mechanisms behind how SCH might contribute to these adverse pregnancy outcomes remains unclear. It is thought that SCH may cause pregnancy loss through either a direct mechanical effect or an indirect inflammatory response [12]. As for placental abruption, studies suggest that the underlying cause of SCH – poor placentation - also predisposes the patients to placental abruption [5,13].

Early and late pregnancy loss

In several studies, SCH is associated with an increased risk of miscarriage (pregnancy loss before 20 weeks) and stillbirth (pregnancy loss after 20 weeks). In a recent study, Sukur *et al.* [3] reported that the miscarriage rate was significantly higher in women with SCH compared to those without (29.5% versus 12.6%). A similar finding was obtained by Kurjak *et al.* [14]. According to Ozkaya *et al.* [15], the risk of miscarriage was six times higher in women with SCH (OR = 6.29, 95% CI 1.43 – 37.7). In a separate study, the risk of miscarriage remained significantly higher in cases of SCH even after PV bleeding has stopped [16]. Stillbirths are also more common in women with SCH compared to women without SCH [13]. Ball *et al.* [13] found that the risk of stillbirth was significant when compared to women both with and without PV bleeding. From a meta-analysis performed in 2011, SCH doubled the risk of miscarriage and stillbirth (OR = 2.18, 95% CI 1.29 – 3.68 and OR = 2.09, 95% CI 1.20 – 3.67, respectively) [6]. Based on the meta-analysis, for every 11 women with SCH, there was one additional miscarriage [6].

However, some studies had contrasting results. Two small studies (n = 22, n = 62) of SCH did not find that SCH increases the miscarriage rate [17,18]. In one of these studies, there were no miscarriages in all 22 cases of SCH studied [17]. Tower and Regan [19] studied the effect of SCH in a population with recurrent miscarriages. They found that SCH did not increase the miscarriage rate for these patients [19]. Based on a 2003 prospective study, women with SCH also did not have a significantly higher risk of stillbirth [5]. In a large retrospective study, the risk of stillbirth in women with SCH was not significant after adjusting for ethnicities, PV bleeding, chronic hypertension, pregestational diabetes, and smoking [4].

The mixed results from different studies suggest that the effect of SCH on pregnancy loss is complicated. Not all cases of SCH have an equal risk of miscarriage and stillbirth. The likelihood of pregnancy loss in SCH may depend on several prognostic factors, such as the size and location of haematoma.

Placental abruption

Unlike the risk of pregnancy loss, the risk of placental abruption in women with SCH is well established. When SCH is present, the risk of placental abruption increases from 0.6% to 3.6% (aOR = 2.6, 95% CI 1.8 – 3.7) [4]. This finding is echoed by several other studies [5,13,20]. From a meta-analysis that pooled together the results of four different studies, SCH increased the risk of placental abruption by more than fivefold (OR = 5.70, 95% CI 3.91 – 8.33) [6]. The number needed to harm was only 34 [6]. Given that studies have consistently reported that women with SCH have a higher risk of placental abruption, SCH most likely has a true effect on the risk of placental abruption.

Preterm delivery (PTD)

Studies also found that women with SCH have a significantly higher risk of PTD [4,5,20,21]. In 2003, Nagy *et al.* [5] reported that SCH doubled the risk of PTD (RR = 2.3, 95% CI 1.6 – 3.2). In their study, 43% of these PTD cases occurred before 34 weeks and 10% occurred before 28 weeks [5]. This result was corroborated by a large retrospective cohort study from 2010, which included more than 1000 cases of SCH [4]. More recently, Palatnik and Grobman [20] carried out a multivariable regression analysis and showed that SCH increased the risk of PTD independent of mid-trimester cervical length. There were several studies that did not find a correlation between SCH and preterm delivery [3,13,14,18,19]. However, these studies were smaller in size, with only one of the studies having more than 100 cases of SCH [13]. Nevertheless, more studies are required to confirm the risk of PTD in women with SCH.

Chorioamnionitis

Chorioamnionitis is a rare but severe complication in pregnancy that can cause life-threatening neonatal sepsis. Currently, the risk of chorioamnionitis in women with SCH is still unknown. There was only one study that extensively investigated the risk of chorioamnionitis in SCH [11]. In that study, Seki *et al.* [11] reported that chorioamnionitis was particularly common amongst women with persistent SCH. Six out of 22 women (27.3%) with persistent SCH had chorioamnionitis [11]. Half of these women had a miscarriage, while the other half delivered preterm [11]. In the study, persistent SCH was defined as a haematoma with clinical symptoms that lasted until delivery [11]. Recently, a study found that women with SCH had significantly different vaginal swab culture results [22]. Women with SCH had significantly higher prevalence of *coagulase-negative Staphylococcus* and Gardnerella vaginalis and lower prevalence of *Lactobacillus* on vaginal swabs [22]. The culture result is suggestive, though not diagnostic of bacterial vaginosis, a condition that has been associated with chorioamnionitis, pPROM, and PTD [22]. However, in that study, the swabs were only collected in the second trimester, which was temporally distant from the time SCH was diagnosed [22]. Hence, a direct cause and effect relationship could not be confirmed through the study [22]. The risk of chorioamnionitis in women with SCH warrants further investigation.

Small for gestational age (SGA) and pre-eclampsia

Given that SCH may be associated with poor placentation, it is important to also consider other adverse pregnancy outcomes typically associated with poor placentation such as SGA and pre-eclampsia. SCH was associated with a significantly higher risk of SGA in two studies [5,15] and and pre-eclampsia in one study [5]. However, the majority of the studies did not support a significant relationship between SCH and SGA [3,4,12,13,19,20]. SCH was also not associated with pre-eclampsia in multiple studies [4,12,19,20]. More importantly, in the two largest controlled studies on SCH (n = 512 and n = 1,081), SCH did not increase the risk of SGA or pre-eclampsia [4,20].

Preterm premature rupture of membrane (pPROM)

Limited studies recorded the incidence of pPROM in women with SCH. In a study by Palatnik and Grobman [20], pPROM was significantly more common in women with SCH compared to women without SCH (6.4% versus 4.0%). However, this finding was not reciprocated in two other studies [4,12].

Other adverse pregnancy outcomes

Interestingly, Nagy *et al.* [5] noted that women with SCH had significantly higher rates of an abnormally adherent placenta that required manual removal (13.9% versus 4.9%). Previously, two uncontrolled studies also noted that manual placenta removal was required in 7% and 11.1% of women with SCH [10, 23]. More controlled studies are needed to provide information about the risk.

Prognostic predictors

The likelihood of adverse pregnancy outcomes in SCH may depend on several prognostic factors. Differences in the size, location, and persistency of SCH, as well as, the gestational age of diagnosis and the severity of symptoms can all change how SCH affects pregnancy [24]. Examining these factors in closer detail can help clinicians clarify the risk of SCH.

Size of haematoma

The risk of adverse outcomes may be increased with larger haematoma size. In the original case series on SCH, Mantoni and Pederson [25] noted that SCH > 50mL occurring after 16 weeks gestation increased the risk of spontaneous abortion and PTD but SCH < 35 mL had a good prognosis. In one study, all women had SCH < 16 mL and none of them had a miscarriage [17]. In contrast, another study found that 81% of the pregnancies with SCH > 60 mL did not continue to term [21]. The rate of miscarriage appeared to be vastly different depending on the size of the SCH. *Ozkaya et al.* [15] used a receiver operating characteristic curve analysis (ROC) and determined that haematoma > 32 mL was 81% sensitive and 80% specific for predicting the risk of miscarriage. The size of haematoma was also shown to be an important factor for miscarriage in several other studies [23,26-29]. However, many studies did not observe an association between size and pregnancy loss [1,13,14,16,18,30,31]. Predicting the risk of miscarriage with the size of haematoma is controversial because of the mixed evidence. It has been suggested that size is not the best indicator of the extent of subchorionic bleeding [24]. This is because a larger haematoma can be caused by either an increase in subchorionic bleeding and a decrease in cervical drainage as PV bleeding [24]. This may explain why several studies did not find the size to be predictive of poor prognosis. While size may not correlate linearly with increased risk of miscarriage, haematoma above a certain volume may still confer a higher risk. This is because regardless of the cause, a larger haematoma can have more direct pressure-volume effect on the pregnancy. A significantly larger haematoma may also have greater placental involvement. Currently, the size of haematoma remains a controversial predictor of poor outcome.

Location of haematoma

Haematomas in certain locations may have a worse prognosis. Most SCH are located on the anterior aspect of the uterus and at the peripheries of the placenta [5,17]. Haematomas that were retroplacental or fundal had significantly higher rates of pregnancy loss according to several studies [14,29,30]. A fundal haematoma was four times more likely to cause a miscarriage compared to supra-cervical haematoma (27.5% versus 6.6%) [14]. While retroplacental location was a significant risk factor, Nyberg et al. [29] found that ultimately, it was the degree of placental involvement that best predicted foetal mortality. Using a multiple logistic regression analysis, *Nyberg et al.* [29] showed that the location was no longer significantly associated with foetal mortality after adjusting for placental involvement. Without any placental involvement, foetal mortality was only 8% [29]. When 20 – 50% of the placenta was involved, foetal mortality climbed to 20%. Greater than 50% of placental involvement resulted in a 75% foetal mortality rate [29]. Based on the current evidence, greater placental involvement and retroplacental or fundal location of haematoma may all be important risk factors for the poorer prognosis amongst women with SCH.

Persistency of haematoma

Most SCH will self-resolve in the second trimester but some can remain symptomatic until the delivery. This persistent SCH is rare and was only present in 0.46% of the general obstetric population [11]. Persistent SCH may carry a worse prognosis. *Seki et al.* [11] studied 22 cases of persistent SCH and found that while the miscarriage rate was not particularly high (13.6%), most women with persistent SCH experienced preterm labor (77.3%), half of which occurred before 32 weeks. There was also a high prevalence of chorioamnionitis amongst women with persistent SCH (27.3%) [11]. *Aoki et al.* also found that there is a higher rate of complications, including PTD, SGA, and neonatal lung disease in ten cases of persistent SCH [32]. Although there were no other studies on haematoma that persisted until delivery, several studies observed that haematoma that was slow to resolve or was associated with prolonged PV bleeding had higher rates of pregnancy loss [1,10,23,27]. The evidence is limited but persistent SCH appears to be associated with higher complication rates.

Gestational age of diagnosis

An earlier gestational age of diagnosis of SCH has been found to be a risk factor for worse outcomes in several studies. From a 2005

observational study, SCH diagnosed before 9 weeks has a significantly higher risk of pregnancy loss and an adverse outcome compared to SCH diagnosed after 9 weeks (aOR = 18.29, 95% CI 2.36 – 41.46 and aOR = 2.22, 95% CI 1.13 – 4.40, respectively), even after adjusting for other factors such as haematoma size and maternal age [33]. The study also showed that the risk of pregnancy loss increased from less than 2% to 20%, if the diagnosis occurred before 9 weeks [33]. Similar results were obtained by *Bennett et al.* [26]. However, the studies were not clear on when the symptoms of PV bleeding occurred in relation to the diagnosis of SCH. Furthermore, many other studies did not agree that an earlier gestational age of diagnosis was a significant prognostic factor [16,27,29,34]. In one study, an earlier gestational age of diagnosis was strongly associated with preterm labor but not pregnancy loss [29]. Yet, according to a 2003 study, there was no significant correlation between gestational age of diagnosis and risk of PTD [34]. Based on the current evidence, gestational age of diagnosis is not a clear risk factor for worse outcomes. A probable mechanism on how an earlier gestational age of diagnosis leads to adverse outcomes is also lacking in the existing studies.

Severity of symptoms

Asymptomatic SCH are common and benign [13,23,35]. In women with SCH, those that experienced PV bleeding were more likely to have PTD than those who were asymptomatic (OR = 4.8, 95% CI 1.2 – 15.9) [34]. Based on a study by Abu-Yousef et al. [27], most women (83%) with moderate-to-heavy PV bleeding had an unfavorable outcome. In contrast, most women (75%) with light PV bleeding had a favorable outcome [27]. The risk of an adverse pregnancy outcome is higher with more severe symptoms in SCH.

Management

Despite the effects SCH might have on pregnancy, there is no specific management guideline for SCH. This is partly because there are only limited studies on how to manage SCH. Currently, most women with SCH are regularly monitored using ultrasound until the haematoma resolves. Otherwise, women with SCH are managed similarly to other women with threatened miscarriage, with advice on bed rest and supplementary progestogen. However, bed rest is not considered to be beneficial for women with threatened miscarriage based on the results of a Cochrane review [36]. There was one non-randomised controlled trial that showed a lower miscarriage rate in women with SCH that had bed rest (6.5% versus 23.3%) [37]. However, given that the study lacked randomisation and was performed retrospectively, the evidence is weak and inconclusive. In terms of progestogen, a Cochrane review of four randomised controlled trials found that it reduced the rate of spontaneous abortion in women with threatened miscarriage significantly (RR = 0.53, 95% CI 0.35 – 0.79) [38]. The beneficial effects of progestogen may be related to its immunomodulatory properties. Progestogen increases the production of progesterone-induced blocking factor, which favors T-helper cell type 2 response [39-41]. Besides that, progestogen may also help by promoting implantation and inhibiting uterine contraction and cervical dilation [39,41]. In several trials, progestogen was beneficial for women with SCH [40,41]. Pandian reported that dydrogesterone given as 40 mg/day stat. followed by 10 mg twice daily until 16 weeks gestation reduced the miscarriage rate by 15.9% (OR = 0.36, 95% CI 0.172 – 0.756) [41]. In another study, taking 40 mg of oral dydrogesterone daily until 16 weeks gestation resulted in maintenance of pregnancies for 93% of women with SCH [40]. Although the results are encouraging, more studies are needed to confirm the benefits of progestogen. Patients and clinicians should weigh the cost and benefits carefully, before starting on progestogen treatment.

A novel drug, called vaginal alpha lipoic acid (ALA), is currently being investigated for its potential use in SCH management [42]. A randomised controlled trial has shown that women taking 10 mg of vaginal ALA had faster resorption of SCH compared to women taking 400 mg progesterone and women without any medication [42]. ALA is thought to be beneficial because of its immunomodulatory properties [42]. However, the trial was a small pilot study with only 76 patients [42]. It is not powered to detect a change in the clinical outcome of miscarriage rate (3/27 in ALA group and 6/27 in progesterone group) [42]. It is still unclear whether faster resorption of SCH would improve clinical outcomes.

Learning points for medical students

For women with symptoms of threatened miscarriage, SCH is the most common ultrasound abnormality detected. It has been suggested that the cause of SCH may be poor placentation, which leads to formation of weak marginal uteroplacental veins that tear and bleed. SCH significantly increases the risk of placental abruption but studies are still conflicting on whether it increases the risk of pregnancy loss and other adverse outcomes including PTD, SGA, pre-eclampsia, and chorioamnionitis. Predictors of poor outcomes include the size of haematoma, location with greater placental involvement, persistency of haematoma, earlier gestational age of diagnosis, and severity of symptoms. Management of SCH involves regular ultrasound monitoring. There are potential benefits with bed rest and supplementary progestogen in some studies but the evidence is still limited. Vaginal ALA is a novel treatment option that is still under investigation. In the future, larger controlled studies that measure all the various prognostic factors will help provide better information on the risk posed by SCH.

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Conflicts of interest

None declared.

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Educational outcomes for children with moderate to severe acquired brain injury

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Abstract

Background: Acquired brain injury (ABI) in childhood can have serious physical, cognitive, and social consequences, although its specific impact on schooling attendance and provision of aid for children is often uncertain. We described educational and neuropsychological outcomes for a population of children with moderate to severe ABI.

Methods: A retrospective cohort study of children with moderate to severe ABI attending a paediatric brain injury service at The Children's Hospital at Westmead between January 2003 and December 2007 was performed. The children were aged 8-16 at time of injury and information on school attendance, provision of aide, and neuropsychological test results were collected at 6, 18, and 30 months post-injury. Children with previous moderate to severe ABI, neurological disorders or learning difficulties were excluded.

Results: 104 children were included (mean age 12.4, 62.5% male). 48 had severe ABI (Glasgow Coma Scale ≤ 8 or Post Traumatic Amnesia ≥ 7 days). The proportion having returned to full time schooling improved from 56% to 89.7% between the 6 and 30-month follow-up. A majority of children had an impairment recorded on neuropsychological testing. Regression analysis found that severity of injury and language deficit were predictors of attendance in the first six months post-injury. During the 30-month follow-up, 18% of children attended special classes or received a classroom aide.

Conclusion: Time is important in recovery from ABI in children. Neuropsychological deficits influence delivery of classroom aides or modified curricula. Children with severe injury are more likely to have poorer cognitive and educational outcomes.

What is already known about this topic

- Acquired brain injury can lead to serious physical, mental, and social problems for school-aged children
- These deficits can often extend years after the initial injury
- Severity of injury is correlated with poorer outcomes

What this paper adds

- An Australian perspective of educational outcomes for children with moderate to severe brain injury
- Information on deficits experienced by children over two-and-a-half years of follow-up
- A better understanding of the importance of time, neuropsychological deficits, and physical injuries in transition back to school

Introduction

Acquired brain injury (ABI) includes a range of disabilities affecting the brain after birth including traumatic brain injury and haemorrhage. Children with moderate to severe ABI often experience long-term physical, cognitive, or behavioural impairments [1,2]. During discharge planning for these children, families often want to know what to expect from the future. In particular, they worry about the transition from hospital to the home and school environment [3]. Schooling is an important forum for childhood learning, as well as emotional and social development [4]. As such, parents often worry about how and when their children may return to school [5]. These concerns are important to address but are difficult to answer due to the great heterogeneity of outcomes following ABI.

Research has indicated that transition of children with ABI back into school is a challenging time for families. After brain injury, students may need to change their educational and vocational goals to accommodate changes in their abilities [6]. Interviews with children returning to school after ABI raise many issues, including social isolation, missed schoolwork, difficulties adjusting to physical and cognitive changes, and the support provided by schools [7]. Children find it more challenging to participate in school activities than at home and this may be due to the familiarity and greater support provided by the home environment [8].

It has been clearly established by prospective longitudinal studies that severity of injury is associated with poorer physical or cognitive outcomes [1,9-11]. Younger children are also more vulnerable to ongoing consequences of brain injury due to their larger head-to-body ratio, ongoing brain tissue myelination, and their thinner cranial bones [12]. Other factors such as type of injury, socioeconomic status, and provision of family support are also known to affect outcomes following childhood ABI [1,5,7]. Time plays a particularly important role in recovery from ABI however it is useful to note that some deficits may also become more apparent over time.

Neuropsychological testing may also be an early predictor of educational performance and special education requirements: in a study by Kinsella *et al.*, severity of injury and verbal memory and fluency at three months post-injury was a predictor for requirement

of special education at 24 months post-injury, Similar findings of the importance of verbal memory influencing educational performance at two years post-injury were made by Catroppa and Anderson as well as Miller and Donders [13,14]. Arnett also found that measures of executive functioning and verbal memory predicted educational competency but did not find these measures predictive of provision of special education [15]. Many studies regarding educational and schooling outcomes for children with ABI do not look specifically at school attendance. Studies of educational outcomes are also limited by small patient numbers and limited follow-up [16].

This study aims to use retrospective data to provide a better understanding of specific neuropsychological and schooling outcomes for children with moderate to severe ABI over a two-and-a-half-year period of follow-up. In particular, the study looks at providing a picture of time for return to schooling and the likelihood of requirement for an aide in the classroom or special education. It also seeks to explore whether neuropsychological factors such as attention, memory, information processing, and executive function, and whether co-morbidities such as fatigue and motor capacity may influence return to school and provision of an aide. This information may enable parents of children with ABI to have a better understanding of what to expect and could improve school engagement in the rehabilitation process [7].

Methods

Participants

Eligible cases were identified from the 2003-2007 database of a paediatric brain injury service at The Children's Hospital at Westmead, New South Wales, Australia.

Inclusion criteria were age at injury of 8-16 years, moderate or severe ABI, and admission to hospital for ABI. Moderate ABI was defined as Glasgow Coma Scale (GCS) ≤ 12 or Post Traumatic Amnesia (PTA) ≥ 1 day. Severe ABI was defined as GCS ≤ 8 or PTA ≥ 7 days [17]. There were eight cases which were judged as representing moderate or severe ABI but there was unclear GCS and PTA data. These cases were included in order to more accurately represent the patient population and were classified as "undefined" in severity.

Exclusion criteria were previous moderate or severe ABI, previously documented behavioural or developmental difficulties, or previously documented special education support.

Medical records were searched and data extracted from neuropsychological and brain injury clinic reports, discharge summaries, and other hospital records. Data were collected for 0-6, 6-18, and 18-30 months post-injury. Data on educational outcomes of school attendance, provision of classroom aide, and whether children changed school were collected. Data on neuropsychological outcomes was taken from reports written by clinical neuropsychologists at the service. Patient demographics were taken from medical notes. Information on co-morbidities was collected primarily from brain injury clinic reports.

Measures

The neuropsychological testing variables measured were attention, memory, information processing, and executive functioning. Neuropsychological profile was considered intact when reported as "low average" or above. Where terms such as "difficulty", "reduced", "borderline", or "impaired" were used as descriptors in reports they were coded as a deficit. In cases where children had no deficit on initial neuropsychological testing and were subsequently discharged without further testing, it was assumed that they would not develop deficit later on.

This research also collected data on variables concerning other sequelae of ABI including mood/behavior, fatigue, gross and fine motor deficit, receptive and expressive language deficit, visual impairment, and hearing impairment. These deficits were determined by whether they were mentioned as ongoing issues in clinical letters and other medical notes during the set follow-up periods.

Statistical analysis

Quantitative analysis was undertaken using STATA 11 SE. Where possible, variables were coded dichotomously for analysis using Fisher's Exact Test to look for a relationship with attendance at school or provision of aide. Ordered logistical regression examined which variables (severity, neurological findings, or co-morbidities) were predictive of school attendance.

Ethics approval

Ethics approval was obtained from the Services Improvement Unit at The Children's Hospital at Westmead, NSW, Australia, approval number: QIE-2011-02-09.

Results

Participant demographics (Table 1)

Of the 158 identified cases, 104 cases met the inclusion criteria. Age at time of injury was between 8-16 years, with the mean age at time of injury being 12.4 years. There were 48 children with severe injury, 48 with moderate injury and 8 with non-traumatic injury, mostly haemorrhage from rupture of arteriovenous malformations. 62.5% were male and three quarters came from urban residencies. 37.5% of injuries were due to falls and 31.7% of children were involved as passengers or pedestrians in motor vehicle accidents. CT and MRI data was collected for 85.6% patients, of which 82% showed abnormalities.

Outcomes

Neuropsychological deficit (Table 2)

Sex and age at onset were not associated with any significant differences in neuropsychological outcomes. As expected, severe ABI has a trend towards more deficits as compared to moderate ABI. Children often had deficits in more than one domain, and children with severe injuries had higher rates of reported deficits. Almost all cases of children who had no deficits on neuropsychological testing were children with moderate ABI. Over time, there was improvement in the numbers of children with reported deficits across attention, memory, information processing, and executive functioning. There was no increase in incidence of deficits over time. Many children with deficits recorded at 0-6 months recovered by 18 or 30 months of follow-up.

Co-morbidities

The most common complaints reported were headache, fatigue, and dizziness. From 0-6 months, 62 children reported fatigue. Mood and behavioural problems were also common, with 61 children reporting problems between 0-6 months, 38 at 6-18 months, and 25 at 18-30 months. Persistence of mood and behavioural problems discussed by parents and children at rehabilitation clinics even two-and-a-half years after injury reflects the ongoing difficulties faced by children with ABI even after physical injuries have healed.

Fine motor deficits were slightly more common than gross motor deficits. For gross motor deficits, from 0-6 months, there were a greater number of children with impaired mobility requiring aid, than those without aide, but between 6-30 months, the majority of children with impaired mobility were able to walk without an aide. Over a fifth of children had initial reports from brain injury clinic reviews describing receptive or expressive language problems, but two thirds of these

Table 1. *Patient demographics of children with moderate to severe acquired brain injury.†*

Demographic		Moderate	Severe	Undefined	All
Number (N)		48	48	8	104
Age at injury: years, mean±SD		12.5±2.3	12.4± 2.4	12.4± 1.9	12.4
Gender, males N, (%)		32 (66.6)	29 (60.4)	4 (50)	65 (62.5)
Traumatic Injury					
MVA	Passenger N, (%)	5 (10.4)	10 (20.8)	1 (12.5)	16 (15.4)
	Pedestrian N, (%)	5 (10.4)	12 (25)	0 (0)	17 (16.3)
Falls N, (%)		2 (4.2)	18 (37.5)	1 (12.5)	39 (37.5)
Sport N, (%)		7 (14.6)	0 (0)	0 (0)	8 (7.7)
Other Traumatic N, (%)		5 (10.4)	3 (6.3)	0 (0)	8 (7.7)
Non Traumatic Injury N, (%)		5 (10.4)	5 (10.4)	4 (8.3)	14 (13.5)
Urban Residence N, (%)					78 (75)
Language (English only) N, (%)					90 (86.5)
CT/MRI Pathology N, (%)					73 (82.0)

† Note that information is only reported for those cases where it was available. Undefined cases are cases that were clinically moderate to severe but GCS and PTA were not clearly recorded.

Table 2. *Number of children with moderate to severe acquired brain injury with neuropsychological deficits at follow up.†*

Neuropsychological outcomes	Moderate	Severe	Undefined	Total children with deficit present (%)		Total
Intellectual deficit						
0-6 months	7	14	2	23	(31.9)	*n=72*
6-18 months	3	4	1	8	(12.9)	*n=61*
18-30 months	0	1	0	1	(1.7)	*n=58*
Attention deficit						
0-6 months	6	21	3	30	(41.1)	*n=73*
6-18 months	2	8	1	11	(22.2)	*n=59*
18-30 months	1	1	0	6	(10.5)	*n=57*
Memory deficit						
0-6 months	7	18	3	28	(38.4)	*n=73*
6-18 months	4	9	1	14	(22.2)	*n=63*
18-30 months	3	3	0	4	(7.1)	*n=56*
Information processing deficit						
0-6 months	5	16	4	25	(36.8)	*n=68*
6-18 months	3	6	1	10	(17.2)	*n=58*
18-30 months	1	2	1	2	(3.8)	*n=53*
Executive function deficit						
0-6 months	6	26	2	34	(45.9)	*n=74*
6-18 months	1	16	2	19	(31.7)	*n=60*
18-30 months	0	6	1	7	(13.5)	*n=52*

† Non-traumatic cases had consequences considered to reflect moderate to severe ABI but there was insufficient information on GCS for status to be clearly defined. Note that information is only reported for those cases where it was available. This table therefore does not report on the entire sample of 104. Undefined cases are cases that were clinically moderate to severe but GCS and PTA were not clearly recorded.

Table 3. *Frequency of co-morbidities reported for children with moderate to severe ABI at follow-up.†*

Co-Morbidities	N (%)	
Mood/Behavioural problems		
0-6 months	61	(70.1)
6-18 months	38	(52.8)
18-30 months	25	(47.2)
Fatigue		
0-6 months	59	(67.8)
6-18 months	40	(55.6)
18-30 months	17	(32.1)
Gross motor deficit		
0-6 months	11	(12.6)
6-18 months	8	(11.1)
18-30 months	3	(5.7)
Fine motor deficit		
0-6 months	13	(14.9)
6-18 months	15	(20.8)
18-30 months	10	(17.0)
Receptive or expressive language deficit		
0-6 months	18	(20.7)
6-18 months	13	(18.1)
18-30 months	5	(9.4)
Vision impairment		
0-6 months	7	(8.0)
6-18 months	6	(8.3)
18-30 months	4	(7.5)
Hearing impairment		
0-6 months	7	(8.0)
6-18 months	8	(11.1)
18-30 months	2	(3.8)
Total		
0-6 months	**87**	
6-18 months	**72**	
18-30 months	**53**	

† Note that information is only reported for those cases where it was available for all co-morbidities. This table therefore does not report on the entire sample of 104.

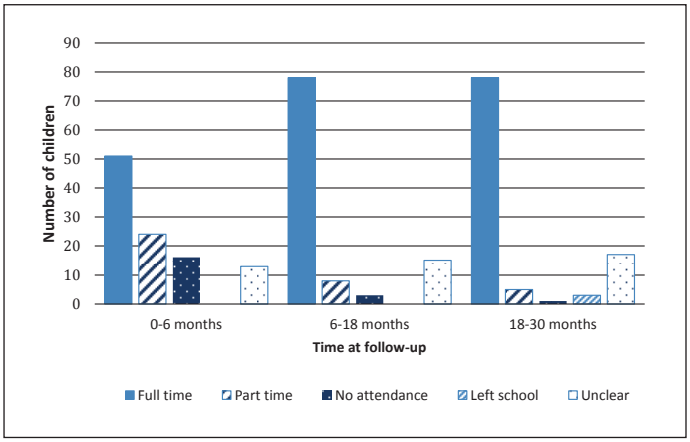

Figure 1. *School attendance for 104 children with moderate to severe brain injury over follow up.*

Table 4. *Ordered logistical regression of attendance 0-6 months for 63 children with moderate to severe ABI.†*

Attendance 0-6 months	Odds Ratio		z	P>|z|
Severity [95% CI]	.2281	[.0878-.5922]	**-3.04**	**0.002**
SE	.1110			
Language Deficit 0-6 months [95% CI]	.1059	[.0350-.3204]	**-3.97**	**0.000**
SE	.0598			

† SE = Standard Error.
Likelihood Ratio chi2(2) = 24.58 Prob > chi2 = 0.0000
Log likelihood = -52.060058 Pseudo R2 = 0.191

were resolved by 30 months follow-up. Between 2-8% of children experienced vision or hearing problems after ABI. Except for fine motor deficits, co-morbidities were most frequently recorded during the first 6 months. The frequencies of co-morbidities were recorded at each of the follow-up time points (Table 3).

School attendance

Attendance improved over time; most part-time students transitioned into full-time schooling by 18 months (Figure 1). At the end of 18-30 months follow up, 6.9% (n = 87) remained unable to return to full-time schooling.

Ordered logistic regression was performed to identify predictors of school attendance. As expected, injury severity was negatively associated with full-time school attendance at 0-6 months post-injury. A child with severe ABI was five times less likely to attend school within six months post-injury than a child with moderate ABI (Table 4). There was a significant difference in school attendance at 18 months post-injury for children with moderate versus severe injury ($p < 0.05$). No relationship was found at 30 months ($p > 0.2$). No significant statistical impact of individual neuropsychological measures and attendance of schooling was found.

Of the co-morbidities measured, it was found that injury severity and language deficit (independently and in combination) were negatively associated with full-time school attendance at 0-6 months post-injury. A child with a receptive or expressive language deficit was ten times less likely to attend school within six months post-injury than a child without a known language deficit.

School aide and change of school

Classroom aide was received by 3.3% of children at 0-6 months follow-up, by 12.8% at 6-18 months, and by 13.4% at 18-30 months. There was a significant difference according to injury severity for provision of a teaching aide at 18-30 months ($p < 0.03$). Special classes or educational programs were provided for 1.1% of children at 0-6 months follow-up, by 5.3% at 6-18 months, and by 7.2% at 18-30 months. There was some overlap with children receiving both aide assistance and attending a special class. During follow-up, seven children required a change of school for reasons relating to their ABI. Of these children, five had experienced severe ABI.

Discussion

This study describes the pattern of children in accessing schooling and special education or aide support following ABI. Extended absences from school are one of the initial challenges facing children after ABI; 17.6% of children in our study population did not attend school in the first six months post-ABI. Whilst hospital and home schooling were sometimes available, this represents a considerable time difference in which children with ABI may fall behind their peers. This study found that a combination of severity of injury and language deficit were found to be predictive of attendance in the first six months after injury. The involvement of language as a predictive factor is important, as it is modifiable. Language is important to complex learning and adaptation and contributes to understanding shared meanings in contexts such as school [18,19]. Language intervention programs may be able to facilitate earlier transition back to school. This study shows that the great majority (93%) of children with moderate or severe ABI will be able to return to full-time schooling. It also shows that the majority of these children are not given provision of classroom aides, special classes, or educational programs.

Attention to classroom instructions, reasoning and expression of ideas, and self-monitoring are all important features of good reintegration to schooling [20]. Children with severe ABI accounted for a greater proportion of neurological deficits in every domain measured (intellect, attention, memory, executive function, and information processing), and 44 of the 45 children with no reported neuropsychological deficits on testing had only moderate ABI. Our study reinforces that there is great variability in the way that ABI affects children, but severe ABI generally has a poorer prognosis and such children may experience greater challenges when returning to school. It is reassuring to note that time can help reduce the burden of ABI, with prevalence of neuropsychological deficits generally improving during follow-up. Longer-term studies suggest that intellect and personality problems may resolve by adulthood, but that reduced quality of life in relation to education and employment can persist [1]. Further long-term follow-up of these patients may be valuable in investigating this. Our study also found that attendance also improves with time, as 89.7% of children were able to resume full-time schooling by 30 months post-injury.

The presence of a classroom aide and modified learning programs is important in exploring whether the ongoing needs of children with ABI are met by schools. Our study found that 13% were provided with classroom aide during 30 months of follow-up. The provision of aid was found to increase over time. This may be accounted for by the inability of children with severe injuries to return to school early but another possible explanation is that there is a delay in the processing and provision of aid.

Quality of aide provision and the satisfaction children and their families had with the schooling system were not measured in this study. This is a possible avenue for future research, as general school educators

and also special education teachers often do not have specialised training for working with children with ABI. TBI Consulting Team and BrainSTARS are two promising models currently available for improving professional development of educators in caring for children with ABI, but both require further studies to show objective improvement [21].

In our study, some children reported needing to repeat a year of school. Grade repetition is known to be a de-motivating process that can affect homework completion and predict greater amounts of school absence [22]. A possible direction for future research would be to examine how common grade repetition is amongst the ABI population.

Strengths and limitations of this study

This study addresses the need for a better understanding of educational outcomes for children with moderate to severe ABI. The follow-up time of 30 months also provides a clearer understanding of how outcomes change over time. Additionally, this study deals specifically with school attendance and provision of aide time, two outcomes which are often overlooked in studies describing participation of children in the community following ABI.

The study also provides important information regarding predictors of attendance in the first six months of schooling. Whilst severity has been a known predictor, language has not been a focus for research previously. This new information may help guide health and education professionals in providing appropriate resources to ensure the best educational outcomes for children with ABI [23].

This study had a number of methodical limitations. Due to the highly variable nature of ABI and the small sample size, subgroup analysis was limited. As the study was retrospective there were a number of missing data fields. The results may underestimate true incidence of neuropsychological deficits as standard clinical practice does not comprehensively test children at all points of follow-up if no changes are expected or testing is not necessary. A larger, prospective study of educational outcomes would provide more data for studies with larger patient cohorts to be undertaken in order to confirm our results [24].

The study did not include a control group so confounders were minimised by excluding children with previous intellectual deficits, moderate to severe brain injury, schooling problems, or behavioural difficulties.

This study was unable to detect differences for children who were previously above average, but dropped into an average category on neuropsychological testing. Unfortunately, pre-morbid capabilities are difficult to quantify without formal testing. This study would not consider these children to have a deficit even though they have experienced a change in abilities. Any changes in abilities should not be discounted as they can still negatively impact the expectations and lifestyle of children and their families.

Conclusion

Children with moderate to severe ABI experience a wide range of neuropsychological and physical co-morbidities that can persist for at least 30 months following injury. Greater severity of injury and presence of language deficit are predictive of school attendance of children in the first six months following ABI. 13% of children required additional aide support or involvement in special classes. Over a third of children still reported fatigue and behavioural problems at 30 months follow-up. This study shows that whilst patients and families experience a long and difficult process of recovery, they may be able to expect improvements over time, and children are very likely to have returned to full-time schooling by 30 months post-injury.

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Conflicts of Interest

None declared.

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Perspectives on Alzheimer's disease

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Abstract: Alzheimer's disease is a commonly encountered patient case by medical students. However, many students struggle to see the person beyond the disease. This essay offers a different perspective into Alzheimer's disease, a deeper understanding that is crucial towards fostering more empathetic, attentive and compassionate patient interactions.

Since the start of my medical studies, I have found the disease process of Alzheimer's disease an emotional and physiological enigma. However, it is the case of Clarice that profoundly impacted a deeper insight into the complexity of a life lived with Alzheimer's disease.

Clarice has been living with Alzheimer's disease since the death of her husband eleven years ago. Her family helplessly witness as she gradually loses any semblance of order and familiarity in her life. At first, she disguised her confusion through a veil of phrases, covering up her forgetfulness with laughter "Of course I knew that, I was only joking." Alzheimer's disease drowned Clarice within waves of confusion, muddling up her thoughts and blending the faces she was surrounded by all of her life with faces of strangers as she tried to tread water in the relentless current. She always wore a smile and came accompanied with jokes and quirky musings. She became known by eccentric catch phrases "How do you spell *nachas* (happiness)?" that she asked of her grandchildren. To which they answered melodiously "C L A R I C E". At every family gathering, she tapped her glass with a fork and announced, "with tears in my eyes, I just want to say how special it is to be here, no itching or bitching, just all together, as a family." As she left, she gathered everyone together and departed with famous final words "Go well, go shell, but don't go to hell".

"Go well, go shell, but –",
"Don't ring the bell!"
"Don't say farewell!" her family tried to interject.
"No." she confirmed with a cheeky grin, "Don't go to hell!"

At Friday night meals, Clarice's thirteen grandchildren said the Jewish blessing over food in chronological order from eldest to youngest. With much humour, Clarice would exclaim "Our Father, the holy spirit…" and proceed to tap out the cross on her body, reminding them of her rich childhood. Having attended a Catholic boarding school as a young Jewish girl, the daily prayers and hymns have stayed with her into old age. Her family loved her Zulu exclamations *"saqua bona wena",* to which they replied in their own made up language, matching the sounds of her youth.

As her cognition declined, her honesty and humour sharpened and the kindness, love, and compassion that overflowed from her heart amplified. At times, her honesty was brutal, revealing hidden layers about the people surrounding her. No longer aware of social cues or the importance of privacy, she pointed out the sad man sitting by himself, or the distressed woman lost in thought. While sometimes uncomfortable, such honesty only exposed her caring and sensitive nature. She was apt at identifying someone's hidden sadness,

unbeknownst to anyone else, and quick to enquire why, offering her ear and heart.

If her family had visitors at their weekly *Shabbat* meals who showed signs of fragility, Clarice was the first to get up and help. "Can I help you up from the table?" "You stay put and I'll get your food for you, what would you like?" The irony of such moments was heartrending, her ability to help those who were physically unwell when she wasn't able, nor was anyone else, to help the illness that overwhelmed her mind.

As time gradually undid the threads that held together the clarity of Clarice's mind, her sentences slipped into nonsensical musings. Moments of her childhood featured more frequently as she lost track of time. She referred to herself as a little girl, telling her adult children that she had to go home lest her parents worry where she was.

Yet, there were moments of pure happiness that peaked out occasionally. Her genuine awe as she watched the sunsets that showered her balcony and the raw happiness and surprise she had when her granddaughters kissed her on the cheek for a 'selfie', were moments of bliss. Her family learnt what made her happy and was able to tap into such experiences to change solemn moments into happier ones. The more they became desensitised to the tragedy of her illogical talk and the more they learnt how to laugh with her rather than cry, the more they were able to find joy and beauty in her quirky musings and disjointed sentences. The more they distanced themselves from her disease, the more they appreciated her presence, her warmth, and her unconditional love.

Clarice is not and never has been my patient. She is my grandmother, my *Bobba*. At the same time that I was dealing with the sudden deterioration of my Bobba's cognition, I started my geriatrics placement at the hospital. The internal struggle that I felt as I grappled with my Bobba's decline gave me a new perspective of the patients I met during that term.

Patient labels transitioned from 'the demented old lady with delirium secondary to constipation' to 'the retired teacher and grandmother of seven suffering with …'. I found myself with a newfound depth of empathy and patient centered care. This gave me a greater understanding of the underlying disease processes of the patients as

my passion for their wellbeing led me to deeper investigations of their conditions. The lessons I learnt from communicating with my Bobba, especially in her moments of stress and confusion, enabled me to connect to the geriatric patients with greater patience, tolerance, and appreciation. I found that I was able to implement the 'tricks' I learnt from soothing my Bobba to soothing distressed, agitated, and scared patients. The timing of my geriatrics placement was no coincidence but a treasured journey that transformed the blanket of grief, loss, and regret that plagued my mind, with acceptance, gratitude, and understanding. It was emotionally draining to be confronted with the exact challenges that I tried to distance myself from in my personal life every day at placement. Nonetheless, witnessing so many people in the same circumstance as my Bobba and my family also brought solace and comfort.

One moment I will never forget was walking into a very disorientated woman's room; she was 63 years old and had early onset Alzheimer's disease. She lay in bed with her 40-year-old daughter, who cuddled her while stroking her hair and placating her with kind words "Don't worry mum, I'm here, everything's going to be alright". I left hospital that day and went straight to my Bobba's home. Although I sensed that she didn't know exactly who I was that day, I felt her love for me and as we sat together cuddled up on the couch, I found pleasure in the complex simplicity of love and togetherness that persists, and perhaps even strengthens, in the face of suffering and adversity.

Just like the 40-year-old daughter, I remember my own mother placating my Bobba by likening her confusion to a car ride, telling her that she can simply shut off, relax, and enjoy the ride, knowing with confidence that she was being looked after. That although she was in the passenger seat, she could trust in the fact that the driver had planned the journey meticulously ahead with love and care. When my mother suffered herself, overwhelmed by hopelessness and pain, I remember my aunty, my mother's younger sister, telling her that it was better to laugh, to simply shut off, relax, and enjoy the ride herself. As my aunty so aptly put it, "we have to laugh, for if we don't laugh, then we'll just cry."

We chose to ignore the ugliness of the disease and to find joy in the benevolent absurdity of my Bobba's behaviour. We laughed in the lift of crowded people when my Bobba interrupted the silence singing 'Ba Ba Black Sheep'. We laughed when my Bobba plaited my friends' hair together as they sat on the couch. We laughed when my Bobba walked up to the stranger engrossed in her book to sit down beside her and engage in conversation as if they were lifelong friends. We laughed so much with my Bobba until we laughed so much that we cried. And I thought of all those times we ran around as small children, my Bobba warning us "too much laughter ends in crying". Yet, now we reversed this, we turned all our crying into laughter. And we were so much happier.

Alzheimer's disease teaches us to savour every minute spent with those we love. It sensitises us to those extraordinary moments of pure joy. It clears out the complexity of the recent past and future to make way for the serenity of the present. It peels away the shell of the mind only to reveal the perfection of the soul - what a beautiful force to be around.

Conflicts of Interest

None declared.

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The changing face of cancer in Australian medical schools

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Abstract: A multitude of changes are revolutionising the study and practice of oncology worldwide. Despite the undeniable importance of cancer education, there is currently no consensus amongst Australian medical schools as to what should be taught regarding oncology practice, nor have the best ways of teaching and learning about cancer been fully elucidated in the literature, or in the clinical realm. There is a lack of important cancer knowledge amongst graduating medical students and variation exists amongst individual Australian medical faculties, between states as well as individual universities from the same state. Furthermore, there is very little teaching here in Australia in relation to emerging genomic technologies within oncology, and in particular, the ever-increasing role of personalised and preventative medicine in cancer care today. Ultimately, there is a clear need for an integrated, overarching national oncology curriculum, embracing a patient-centred approach; national evaluation and assessment; supplementary courses; utilisation of self-directed learning and reflective practice activities; and greater emphasis on emerging technologies. With more research focus on this area, in future there may be a larger evidence-base targeted at providing improvements in Australian Oncology education, assisting graduates in gaining adequate understanding and appreciation of cancer-related scenarios and cancer care. More effective teaching and learning facilitation, with better overall Australian training outcomes, will lead to advancement in cancer diagnosis, treatment, and management as well as ensuring more insightful and valuable patient interactions in the future.

Introduction

A multitude of changes are revolutionising the study and practice of oncology worldwide. The ways in which oncology and cancer care are incorporated into medical school curricula in Australia is thus of particular interest. Despire the undeniable importance of cancer education, there is currently no consensus amongst Australian medical schools as to what should be taught in regards to oncology practice, nor have the best ways of teaching and learning about cancer and cancer care been fully elucidated in the literature or in the clinical realm [1-4].

In Australia, there is considerable variation in undergraduate and postgraduate teaching of oncology amongst individual medical faculties [8,9] and a lack of important cancer knowledge amongst graduating medical students, between states and between individual universities from the same state [8,9,10]. This inconsistency is compounded by the nature of oncology as a multidisciplinary specialty, with overlap in numerous fields including pathology, surgery, histology, radiology, anatomy, genetics, communication skills, and palliative care [1].

Further, there is very little teaching here in Australia in relation to emerging technologies within oncology and in particular, the ever-increasing role of personalised and preventative medicine in cancer care today. Educators are now presented with the inevitable task of addressing all foundational educational needs in our generation of medical graduates. They must also ensure to incorporate pertinent aspects of such a rapidly progressive field of medicine as it relates, for example, to genetic testing and counselling, the rise of personalised or 'precision' medicine, and ongoing development in cancer immunotherapies [11-14].

Variation in oncology education in Australia is compounded by the lack of literature on this subject, which is predominantly qualitative in nature and overall, more difficult to evaluate [30]. Whilst cancer is the number one cause of death in Australia, oncology itself is still not a subscribed part of the medical curriculum, nor is an oncology rotation compulsory in Australian medical schools. There is an ongoing lack of literature regarding oncology-specific teaching and learning methods, as well as a lack of evidence in the effective implementation of compulsory curricula or rotations to engage with foundational and emerging aspects of oncology or palliative care.

The importance of this issue resonates with students, recent graduates, and educators as all medical students will at some point in their career play a role in the management of a cancer patient [5], whether as a resident on an oncology rotation, as a general practitioner at the stage of diagnosis, during long-term follow-up of a cancer survivor [6], as a fully-qualified oncologist, or as a clinical geneticist. Furthermore, with our ageing Australian population, there will be greater numbers of individuals diagnosed with and treated for cancer than ever before as well as an increased number of survivors, making cancer a chronic illness to be managed by a multidisciplinary team [7].

How did we get here?

In 1993, the General Medical Council published a detailed review of medical education [15], which led to a major overhaul of medical school oncology training in the United Kingdom, and worldwide [1,16]. A survey of European universities showed that 95% indicated the need for increased cancer education and there was an overwhelming interest in a common European oncology curriculum [17].

In 1999, and again in 2007, the *Ideal Oncology Curriculum (IOC) for Medical Students* was released here in Australia [18], produced by the Oncology Education Committee of the Cancer Council Australia and endorsed by the Union for International Cancer Control (UICC). It provides an unparalleled example of the evidence-based recommendations required for medical school cancer education, including prescribed clinical experiences and knowledge attainment,

which necessitate a patient-centred approach to training methods. In each section, there is detail of prerequisite knowledge, as well as a list of representative questions that illustrate the 'required depth of knowledge' for graduating medical students, with attached example answers and multiple-choice question-answer options.

Focus is on the patient rather than the discipline, with topics ranging from public health and cancer biology, to patient management, diagnosis, communication skills, and clinical experiences [18]. More recently, it has been supplemented by a detailed e-Book entitled "Clinical Oncology for Medical Students", which may be utilised alongside the recommended experiential learning, and acquisition of technical oncology skills, for a more robust understanding of the prescribed *IOC* material [19].

Moreover, the World Health Organisation and UICC recommend that cancer education be incorporated into oncology modules within an undergraduate curriculum and that medical students spend a minimum of two weeks in oncology training [4,5]. However, despite the superlative example given by the *IOC*, there has been minimal uptake in Australia, which may be linked to the current lack of a national curriculum, the dearth of literature on effective educational strategies, or the historical absence of oncology content in Australian medical school curricula. This lack of implementation and an inadequate evidence-base makes the feasibility and effectiveness of oncology rotations or uptake of the *IOC* guidelines incredibly difficult to ascertain, let alone, achieve.

Oncology teaching and learning methods

Internationally, there has been a push for an overarching pre-clinical oncology curriculum for medical students incorporating medical knowledge, psychosocial aspects, communication skills training, and utilisation of a variety of teaching methods such as interviews, discussion, reflection, and lectures [1,2,7,20].

There is increased emphasis on a patient-centred approach to teaching [11,13] and learning in oncology education [22,23]. This should extend from the use of standardised patients teaching examination skills to medical students, to the involvement of cancer patients in communication skills teaching and portfolio learning [1,24].

Self-directed learning (SDL) is the educational strategy considered most likely to produce medical graduates who are prepared for lifelong learning and who are able to meet the needs of their patients [26,30]. SDL activities include problem-based learning (PBL), discovery learning, task-based learning, experiential and reflective learning, portfolio-based learning, small group or project-based learning, and peer evaluation with learning contracts [26]. Results from numerous studies have indicated a trend towards improved student performance from SDL assessment, as with the follow-up of a cancer patient over an extended period of time [1,21,23-25]. The use of portfolio assessment and learning journals is also championed as a tool of successful oncology training and for lifelong education [25]. An array of methods may thus be employed in undergraduate oncology training whilst utilising the SDL approach [26-27].

The PBL approach, more specifically, as one of the major aspects of SDL, facilitates a deeper learning style [28] and involves an active search for understanding based on a given scenario. This technique is linked to better clinical problem-solving skills in medical students with higher levels of motivation and stimulation found [27] and superior outcomes in students tested [9,29].

Regarding format, some have argued that an independent block style is more effective in presenting an oncology curriculum [20]. This is as opposed to an integrated model of teaching into other system modules and would be relevant within an Australian-based system. In block format, the curriculum may be presented through oncology-specific technology-based lectures, team-based communication, and clinical skill exercises supplemented by lectures paired with relevant clinically-based scenarios and other activities posted online to be worked through independently [20].

Computer-aided learning [1,21,22,30] may itself have a role to play as supplementation to oncology study though technology-based approaches are not necessarily superior to other learning techniques [1]. Here in Australia, a number of medical schools are already utilising the e-Learning Undergraduate Modules for Australian Medical Schools, accessible via The e-Learning Portal, which is provided by The Australasian College of Dermatologists [31]. This is highly applicable on a national level when considering skin cancer rates in Australia [32]. Overseas, an 'eDerm' online curriculum [33] provided to 252 medical students in the United States significantly improved the diagnosis and management of pigmented skin lesions by medical students [33].

In regards to communication skills, suboptimal communication can lead to adverse psychological effects in patients. It can compromise a physician's ability to treat patients, as well as impacting patient satisfaction, medication compliance and overall clinical outcomes [34]. The use of group presentations, small-group communication skills practice [35], and reflective self-awareness exercises have been shown to improve communication skills. This is particularly true with the use of patient-actors in simulated clinical situations as opposed to role-play alone. There is overwhelming proof that communication skills can be taught and should be delivered through experiential learning methods, which are ultimately more effective than instructional modes to address communication skills development in oncology [36].

Moreover, a primary skill that any medical student can bring to an oncology experience, or rotation is their presence and their time. Medical student training in this burgeoning field [11] must facilitate the development of essential communicative abilities: to be able to listen to a cancer patient's story during their clinical journey, to be able to connect with this experience, and communicate effectively in response to this scenario [18,34-36].

Lessons from abroad

At the University of Wales' College of Medicine, medical students followed a patient along their cancer journey over a six-month period and were assessed during patient interactions and through a final portfolio. Overall, students found the project rewarding and reported gaining unparalleled insight into the cancer experience [22].

A three-day intensive oncology course has been piloted in Israel, with students feeling more comfortable with cancer-related issues, less afraid of dealing with death, and better able to cope with uncomfortable cancer-related emotional situations as a result [7]. Psychosocial and ethical aspects were presented through student-led presentations and discussions, a psycho-oncology session led by a psychologist, and two presentations by cancer patients describing their personal experiences and offering advice on aspects such as the doctor-patient relationship [7].

In Poland, attempts have been made to improve cancer education through the National Program for Combating Neoplastic Diseases [16]. This was done with a course incorporating computer-learning modules, online tests, portfolio learning, summer school, modules taught by cancer patients, and attachments in oncology and palliative care. Observations highlighted that the introduction of these courses better prepares students for delivering cancer care [16].

Finally, in a novel Brazilian experience, students staffed an oncology clinic, with 77% of students involved in this approach over a ten-year period rating it as the best activity of their course. Findings suggested that attendance at an oncology outpatient clinic can contribute significantly to the cancer education of medical students [24].

Future directions for Australian oncology education

There is a clear need for the following in cancer education:

1. An integrated, overarching national curriculum, with a patient-centred approach
2. National evaluation and assessment
3. Summer schools and supplementary courses
4. Embracing SDL & PBL, with reflective practice activities
5. Greater emphasis on emerging technologies

1. An oncology curriculum, with a patient-centred approach

A relevant, integrated oncology curriculum as detailed by the *IOC* [15,18] should be embraced by all Australian medical schools, with the aim of bringing together requirements regarding essential knowledge, skills, and attitudes about cancer and cancer-related care [2,8,9,10,17]. It should be well-rounded and ideally supported by a coordinating body, with an academic basis of professorships [2].

As detailed by the *IOC* [18], there is a need for increased emphasis on clinical interaction and greater time spent with patients [1,2,5,21,37]. As suggested [18], medical students need at least five cancer clinical experiences before graduating:

- Talking with and examining people affected by all stages of cancer;
- Talking with and examining people affected by all common cancers;
- Observing all components of multidisciplinary cancer care;
- Seeing shared decision-making between cancer patients and their doctors; and
- Talking with and examining dying people [2,15,18].

2. Assessment

As shown in Australian medical schools, assessment drives performance [2]. Thus, having decided upon a particular patient-centred approach, carrying out formal evaluation of student learning and course content is vital for enhancing training outcomes [18,38], and should inform the prescribed curriculum [2]. In future, this might include the introduction of national assessment, such as a national exit examination [40], with oncology-related scenarios aimed at testing core knowledge levels and ensuring standardisation is maintained across the country [9,39,40].

3. Supplementary courses

Regarding adjuncts to a proposed national curriculum and module [20] of oncology teaching, summer schools and extra courses [7,16] may be of great use here in Australia [1]. The Vienna Summer School, for example, receives high levels of praise and acceptance rates from European medical students. These students note that these supplementary courses provide them with a greater understanding of oncology and an appreciation of its' multidisciplinary character [15]. Summer schools may offer educational activities that fill the gaps of an otherwise disjointed oncology training program, as shown by the example of oncology summer schools in Europe [4].

4. Self-directed learning, problem-based learning and reflective practice

Learning in medical school is rarely fully autonomous, with students valuing pedagogic support and often relying on teachers as coordinators and facilitators of their learning environment [41]. Students should be encouraged to recognise the importance of evidence-based medicine, how to critically appraise literature, and the need to constantly update one's knowledge based on high-quality evidence and guidelines [18]. Furthermore, team-based learning through small scenario or discussion groups has a role to play in the application of basic science knowledge to real-world oncology-related scenarios [35]. This could lead to greater engagement with lecture content and its' application in daily medical practice.

There is increasing necessity for our medical curriculum to foster the development of sound communication skills. Furthermore, providing students at every level of their education with an opportunity for reflective practice, as individuals and in smaller groups, is also a must. This may serve as an important tool in supporting students who emotionally encounter negative experiences as a result of difficult or uncomfortable clinical encounters. Mentoring, as an extension of this pathway, may be of use in allowing reflection following hospital experiences. It may be of use for medical students to attach themselves to 'mentor' clinicians on rotation, staff whom they perceive to be effective teachers for coaching purposes, development of reflective practice, and consolidation of learning [42].

Moreover, students learn more effectively by being actively involved in a PBL strategy, as it facilitates epistemic curiosity through activation and elaboration of prior knowledge [22]. Reflection on experience, followed by evaluation, analysis, and appropriate action, may facilitate further learning and appreciation of curriculum content in the Australian context [1,4,18,21,22,23,25]. Portfolio learning [1,22,23] should thus be employed in a set teaching program [16,23], with reflective exercise and a compulsory portfolio-based experience, or assessment. This would to facilitate reflection and exploration of the patient experience along their cancer trajectory.

5. Emphasis on emerging technologies

Dramatic advances in genomic technology stand to revolutionise clinical cancer care [13,14]. Personalised (or 'precision') medicine is a banner term, describing the use of molecular tools to individualise healthcare through genetic testing, whole genome sequencing, exome, or transcriptome sequencing [13]. While there has been ample research in the area of genetic testing and its' implications for our future, very little is known about how best to encourage development in understanding of such technologies at the level of medical students or recent graduates.

In the realm of breast cancer in Australia, for example, an individualised cancer care approach is evidenced in the case of genetic testing for BRCA1/2 mutations, which reflect a specific predisposition toward breast and ovarian cancer [43]. About 5% of cases of breast cancer and 10% of ovarian cancer cases, are due to such inherited predisposition [44,45]. With progress towards a more personalised, family-centred model of oncological care in Australia, knowledge of ones' genetic and genomic information plays a crucial role, from screening and prevention, to individualised surgical treatment, and utilisation of targeted therapies based on a tumours' molecular signature [46].

In order to fully realise the effective application of personalised medicine into routine Australian cancer care, students and clinicians need a more comprehensive understanding of emerging technologies. In addition, an appreciation of the experiences, and attitudes of cancer patients, and their families is required. Evidence suggests that the majority of cancer patients are willing to undergo genetic and genomic testing during, or following, cancer treatment [11]. More work is needed in this area to provide graduates with a more refined appreciation of how best to communicate genomic concepts to a broad range of patients [11]. Medical graduates must have greater awareness of foundational genetics-based and personalised medicine pathways. This will allow them to alleviate patient misconceptions and ultimately, to empower patients to make more informed cancer care decisions [12-14]. Without this, there may be failure to adequately deliver genetically-guided cancer care, treatment, and management in the future. The issue our educators will now face is how to best integrate this information into a feasible medical student curriculum.

Conclusion

More effective teaching and learning strategies in oncology should be aimed at producing Australian medical graduates with adequate and relevant cancer-related knowledge, skills, and attitudes that best meet the needs of their society [2]. The *IOC* [18] does an exceptional job of demonstrating the requirements and expected knowledge to be attained through a prescribed oncology curriculum here in Australia.

Australian medical students need a well-rounded understanding of oncology concepts and appropriate examination and communication techniques to facilitate aspects of cancer diagnosis, referral, and management in future clinical practice [20]. There must be focus given to developing an awareness of emerging technologies in the realm of cancer care with emphasis on basic concepts related specifically to genetic testing, genetic counselling, and personalised medicine.

The foundational experiences provided by medical school training serve to shape one's entire career as a doctor. Those students more engaged in their learning through SDL, PBL and reflective practice strategies [26,27], and who have a greater understanding of key concepts are more likely to achieve superior assessment outcomes [2]. They are also more likely to be involved in successful clinical interactions overall [1].

With greater research focus on this area in future, there may be a larger evidence-base targeted at providing overarching improvements in Australian oncology education. This will assist graduates in gaining an adequate understanding and an appreciation of cancer-related scenarios and cancer care. More effective teaching and learning facilitation with better overall Australian training outcomes will ultimately lead to advancement in cancer diagnosis, treatment, and management outcomes as well as ensuring more insightful and valuable patient interactions in our futures [5,12].

Conflicts of interest

None declared.

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Opening the "die-logue" about palliation

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He was just about my age, but his face was pale, his cheeks cavernous, and there was a weariness in his every movement; he was too weak to speak or even swallow well. It was as if he had been drained of all his youth.

We spent the next three hours helping him get through a bowl of porridge, and I will forever remember it. He struggled with every spoonful, and watching that made me sad and angry at life for being so unfair to someone as young as him. There was also an odd sense of relief whenever he did not choke on a swallow, warmth whenever he mustered enough energy to smile at me, and the type of calm you feel when you watch the ocean waves. But instead, I was watching his bony ribcage heave up and down with every breath.

That was the first day of my first job as a teenager, as a carer at St Joseph's Hospice and Home in Singapore. I continued that job for four years and it inspired me to attend medical school. More importantly, however, those three hours were when I first discovered hospice and palliative care. Or rather, when it discovered me.

Since then, an aging population has become a major demographic trend worldwide and the topic of how to die well has garnered growing attention. Moreover, much focus has been directed to removing the taboo on death, a significant hurdle to the routine integration of palliative care into medicine [1]. As a fourth year medical student now, some deaths have inevitably left their marks on me, leading me to consider whether the palliative care we are offering to patients now really is the best. After all, in death, as in life, quality matters.

One of these deaths was that of a patient, Maggie, to whom I had provided care for a long time at St Joseph's. Maggie was a retired dance teacher. She was chatty and had always proudly shared the stories of her students with me. Even after I left Singapore to attend medical school in Sydney, I would visit her whenever I made a trip back home. Unfortunately, with each visit she grew frailer, and she was eventually placed in a wheelchair, where she was spent most of her time. Her frailty took away much of her independence, but she remained cheerful, nonetheless.

At this time, St Joseph's had begun working with a Singaporean philanthropic house, Lien Foundation, which conceptualised and pioneered the "Happy Coffin" palliative movement. The antithesis in the name of the movement captures its objective - to transform the coffin from a negative representation of death to a canvas for positive celebrations of life and expression of art. It is part of an initiative to lift the death taboo, encouraging hospice patients to share their lives, dreams, and wishes, which are interpreted and painted on a custom coffin by commissioned artists to liberate mind sets and open the "die-logue" [2]. Maggie was thus enrolled with Happy Coffin.

On my last visit to see Maggie, she showed me pictures of her coffin and described the drawings on them with a bright smile on her face. She said the lively children painted on it – her students - were the pride of her life. She seemed at peace with her condition and I felt genuinely happy for her. This seemed to reinforce what medical school had been teaching me: talking and planning for your death through palliative care really is the gold standard of dying.

A year later, I received news that Maggie has passed on. As one of the pioneer participants of the Happy Coffin experience, her death was highly publicised in the media, where she was positioned as the brave individual who confronted death optimistically, almost as the role model for all future deaths. Indeed, the moral strength of character of a patient who faces up to or denies death is always at stake whenever telling the story of death, and perhaps this is why we are fixated with open discussion of death and palliative integration [3]. They say she had a beautiful death.

However, the news of Maggie's passing arrived in my first clinical year of medicine, during my oncology placement, a time where I was becoming increasingly aware that not every death is – or can be like Maggie's.

There were many deaths in oncology, and thus many opportunities for palliative medicine to step in. While there were cases where palliation was seamlessly introduced into the care of terminally ill patients, I also witnessed many instances where palliative care implementation brought much distress and dilemmas in terms of medication choice, truth-telling, autonomy, and other treatment practises. Unlike what I had imagined, many patients were offended whenever death and palliation were mentioned, as some cultures believe that to speak of death is to invite it. In terms of pain management, different patients also had very different attitudes. Most doctors I met genuinely believed that pain relief is always the best option, although this can be quite controversial as many ethnic groups view pain tolerance as a form of strength. I particularly recall a Buddhist patient with staunch Confucian beliefs. Decision-making for his treatment was relinquished to his children, whose filial piety was, in turn, measured by their perseverance, both financially and emotionally, through curative therapies for their sick parent, even when efforts are futile. Such perseverance was a form of devotion and love. Palliation for this patient was, therefore, almost out of the question. On another occasion, I also observed a family get upset when the doctor had suggested for advanced care directives to be established - they saw it as prolonging autonomy when autonomy was not sought.

This set me thinking about the current model of palliation in medicine.

In medicine, we believe palliative medicine is the gold standard for dying, with the 2014 World Health Assembly prioritising the assimilation of palliative care and death planning into national healthcare systems [4]. The surge in this global palliative movement is understandably so, as palliation offers awareness and open communication, gradual acceptance of death, provision of pain relief, and continuity of a person's essence till death in the form of autonomy in decision-making and control in the dying process. Patients who have been palliated thus approach end-of-life with symptomatic pharmacological care, spiritual, and psychosocial relief to them and their family, abundant knowledge of their disease's natural history to manage expectations, and having their resuscitation status, medical proxies and advanced care directives established. Above all, confronting mortality empowers people to make the most of their time left, view life in wider perspectives, and live life it to the fullest [5].

However, amidst today's palliative hype, I wonder if the medical community may have created a singular definition of a "good death", forgetting that this definition may vary for different patients. Maggie's death was the first death I had encountered in a healthcare setting, and I had the privilege of understanding her and her palliation process; death was openly discussed with her, she had her advanced care directives prepared, curative therapies were stopped in place of symptomatic ones, and as a Catholic, she was attending weekly prayer support sessions from the church associated with the hospice. I saw how comfortable she was even in her last months, and I am convinced that this was the best possible death for her. However, is this enough reason for deaths like hers to be touted as the role model for all other deaths, especially in today's multicultural societies?

As our world becomes increasingly globalised and culturally diverse, our definitions of a "good" death will also diversify. This will inadvertently lead to provision of inappropriate end-of-life care to patients from diverse backgrounds and cultural misunderstandings. For example, a doctor's concept of a "good" death, which is likely to be influenced by their culture as well as their personal and professional experiences, may conflict with the desires of the patient [6].

In Australia, while we are a multi-cultural society, our ethical paradigm remains firmly rooted in Western philosophical traditions. This becomes apparent when examining the medical school curriculum- the dominant paradigm through which ethics is being taught is the Western bioethical framework. Medical students are taught to keep diagnoses confidential to the patient only, and to prolong patient autonomy as much as possible. Although, doctors may reflect the diverse cultural demographics of Australia, they are educated to uphold the Western set of ethical principles even whilst caring for patients from diverse cultural backgrounds [6]. Such education might have unintentionally created a culture of marginalising other modes of death in the pursuit of what we were taught is a "good" death.

Perhaps more flexibility in models of end-of-life care might allow us as a medical community to better accommodate the care preferences of people from diverse backgrounds. This can be achieved through a wider appreciation of different cultural notions of death. While it is not realistic for health professionals to understand the breadth of cultural beliefs in relation to illness, it is necessary to have a fundamental level of cultural competence and to understand when, and how, to consult further expertise when caring for people of different backgrounds.

It is as much the professional responsibility of the doctor as it is the moral responsibility of friends and family to ensure that a patient's death is in line with his/her wishes. Therefore, it really is time to open up this "die-logue" and examine how the different ideals of death seep through our current framework of palliative medicine, to decrease disparity in quality of death delivered to everyone. And who better to lead this "die-logue" than the medical community itself?

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Conflicts of interest

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The strengths and shortcomings of empathy in medicine

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Catharine is a student in the Doctor of Medicine program at the University of Melbourne. She previously studied French literature and is interested in research into the cause of type 1 diabetes. Past research experience has involved working with piglets at the University of Alberta and transforming mushroom DNA at the University of Guelph.

Abstract: Every day medical students and doctors are faced with challenging, ethical, and moral dilemmas. Caring for patients can be draining and bearing witness to their suffering can often take a toll on the mental and emotional health of practitioners. A key psychological component affecting how we react to these situations is empathy. Here, the effects of empathy on our health and relationships with patients as well as the benefits and challenges of using empathic practice are examined.

"Not even one's own pain weighs so heavy as the pain one feels with someone, for someone, a pain intensified by the imagination and prolonged by a hundred echoes."

— Milan Kundera, *The Unbearable Lightness of Being* [1]

Several times a day, if not more often, I see prescriptions for metformin on patient charts. Diabetes in hospital patients is almost as common as perfectionism in medical students; over 900,000 hospitalisations – or 9% of all hospitalisations – in Australia in 2013 were for management of diabetes as the principal or additional diagnosis [2]. Having lived with type 1 diabetes now for over 16 years, I have heard innumerable lectures on the pitfalls of chronic hyperglycaemia. With my last HbA1c falling in the "dangerously high" region at 12.9%, I am all too aware of how this can affect my long-term health. Yet, I cannot in good conscience stand at the bedside of patients with diabetes and lecture them on adherence to medication or better sleeping and eating habits when I myself struggle everyday with poor results. I often find myself torn between judging patients – and myself – for poor control, or letting poor control slide in acceptance of the human capacity for error. Rather than simply ruminating on my own shortcomings, the aim of this essay is to use my own as well as other patients' experiences to highlight the all-too-real dilemma of allowing empathy to guide us while still separating personal feelings from professional agendas in medicine.

Empathy is a complex phenomenon, involving cognitive and affective processes that affect our capacity to understand and respond to other people's emotional and mental states. Cognitive empathy can be defined as the awareness and understanding of another's emotion. Affective empathy refers to the vicarious experience of emotions consistent with those of the observed person and often results in *empathic concern*, which involves feelings of compassion or concern for another. A more problematic form of affective empathy is *personal distress*: personal feelings of discomfort and anxiety in response to another's suffering [3].

A recent popular article published in *Scientific American* explored the idea of empathy as being a double-edged sword [4]. The authors discussed the psychological construct of empathy's ability to overwhelm their clinical judgment, however they also underlined its importance in relating to patients and being a well-adjusted human being. The article concluded, "[the] key is knowing when empathy is called for and when it is detrimental. It should not be the goal of physicians, then, to be more empathetic. They should aim instead to find the right balance, the golden mean that optimises care."

Several studies have demonstrated that as clinical reasoning and experience in medicine widens, empathy decreases [5,6]. Reasons for this change are uncertain, however I question whether the inverse relationship between experience and empathy may be linked to the x-axis of time: the longer medical students spend exposed to the realities of medicine, the less able they become to expose their emotions to the harsh realities of patients' lives. We can't save everyone and often we can't even eliminate much of their burden of disease – so losing the ability to empathise so as to limit emotional and psychological burden is likely a factor here as well. The evidence for this decrease in empathy over time is elegantly demonstrated in a study by Newton and colleagues which revealed that medical students' empathy scores drop significantly between their first and third years [5]. This study used a standardised empathy scale to evaluate the same class of students every year between first and fourth year, and they found overall medical education was a determinant differentially affecting the vicarious empathy of students, with the greatest impact on male surgical specialties. The authors concluded, "the significant decrease in vicarious empathy is of concern, because empathy is crucial for a successful physician–patient relationship." Another study of American medical students demonstrated the drop in empathy scores to be most significant across the third year (their first clinical year), with no significant drop during basic sciences teaching [6]. They also reported greater feelings of psychological distress in students over this same period, which is consistent with Australian statistics from Beyond Blue that report one in five medical students have had suicidal thoughts in the past year [7].

While it is undoubtedly true that empathy is necessary for healthy doctor-patient relationships, I question whether there is an element of self-preservation involved in the gradual loss of empathy over the course of our clinical years. Throughout my childhood, my younger

sister was in and out of hospital for neurosurgeries involving a hard-to-access cyst in the pineal recess of her third ventricle. I was able to recite these words as a nine-year-old, and as a ten-year-old, I decided I wanted to be a doctor so that I could fix people like her. The problem was that I also hated hospitals; a normally well-mannered child, I would become hysterical after going to see her. In hindsight, I think that paediatric neurosurgery wards do this to a lot of people and in my case this was certainly caused by a vicarious empathetic response of personal distress. The immense suffering you see on these wards can make a bright day seem sombre, and it takes a special kind of nurse and surgeon to work in that environment day-in-day-out. If these people had not distanced themselves from their patients to a degree, the suffering they witnessed would almost certainly cause significant psychological distress. To preserve the emotional well-being of the medical staff on such wards, coping strategies such as intellectualisation, humour, and team support are essential [8].

There was one moment of kindness in that hospital which remains etched in my mind to this day. My sister was a bright child, and on the day before her surgery, unbeknownst to any of us, she secretly wrote a letter outlining her fears and questions for her surgeon. This man was the extremely busy head of neurosurgery and that morning, as usual, he charged into her room for rounds with his trailing procession of residents hanging on every word. After he had checked her over and turned to leave, my sister in a tiny voice announced she had something for him and thrust a piece of coloured paper at him. It was her list, carefully written out in crayon, of questions she wanted answered, number one being "Am I going to die?" He took it from her hand, glanced quickly at it, frowned, and left the room. My mother was appalled at his perceived indifference, while my father tried to soothe the situation with platitudes about how busy the man was. My sister was quiet and said little. Half an hour later we were surprised by the return of the surgeon, this time alone and with his white coat thrown over his shoulder. He walked in, nodded at my mother, and said to my sister, "Now that we've gotten rid of all those yucky doctors, let's take a look at this list." For the next ten minutes, he carefully went through each question with her and he told her the truth about everything. She calmly listened, occasionally asking more and when finished he rubbed his hands together and asked, "Are we good to go?" After she nodded, he smiled towards my parents and me and strode out of the room. Whether or not he was motivated by empathy I can only speculate, but it seems likely the surgeon recognised the suffering of my parents and sister and he demonstrated *empathic concern*: sympathy and compassion for others in response to their suffering. Whatever the case, I am thankful that this man was able to control his emotions without losing his humanity and I can only aspire to one day be able to do so as well.

I will conclude by making a case for using empathy in medicine. Empathy is derived from humanity and according to Hippocrates, "Wherever the art of medicine is loved, there is also a love of humanity" [9]. When a patient feels comfortable with a doctor, they are more likely to come forward with their true feelings and admit to forgetting to take prescription medications or to having sex without a condom, whatever the case may be. It is true that as future doctors we need to protect ourselves from feeling too deeply, but if we forget to open our hearts to the people we aim to help, we will risk losing their confidence altogether. Additionally, quite apart from the physician's need to take a patient's history to understand their affliction, the process of telling one's story can be therapeutic for patients [10] and may help facilitate the healing process. Finally, empathy is beneficial to physicians – other physicians have noted that doctors who are more attuned to the psychosocial needs of their patients are less likely to experience burnout [11].

As for myself, I no longer fear going into the hospital but there are still many days where, as a result of connecting with a patient, I feel the urge to cry on my walk home. I try to balance this by looking forward to the time when, as a doctor, I can improve patients' lives, just as the neurosurgeon did for my sister. I believe that empathy is a good tool to improve listening and understanding of the patient's perspective. Ultimately my goal is to have the attributes of an excellent physician and a compassionate human being without letting my awareness of the pain of others pain destroy my soul.

Conflicts of interest

None declared.

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Meditate to medicate: mindfulness meditation as a complementary therapy for surgical patients

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Abstract: Mind-body therapies such as mindfulness meditation (MM) are increasingly being studied and applied as legitimate medical therapies. Since becoming popular in the 1970s, MM has been shown to improve psychological states such as anxiety and depression. The scope of MM has expanded in recent years, and MM has been shown to have positive effects on pain, recovery time, and even wound healing after surgery. The number and types of surgery are increasing with the ageing population, and MM has potential as a non-surgical therapy to help hasten recovery, minimise analgesic consumption, and improve overall satisfaction after surgery. Training patients in MM before surgery may be implemented at low cost and up to 24 hours before admission. Given these benefits, complementary mind-body therapies such as MM have potential to improve a patient's surgical experience and outcomes. Despite the potential benefits, MM is not currently used routinely for patients undergoing surgery. The literature shows that there is a perceived suspicion of the practice's effectiveness, which appears to hamper its clinical acceptance. Critics cite concerns about patients' perception of meditation given its religious connotations and whether they would be encouraged to accept MM as a valid therapy. This essay explores the application of MM as a complementary therapy to expedite recovery from surgical admission and concludes that meditation may be as effective as medication in some circumstances

Introduction

"The part can never be well unless the whole is well." This epithet offered by Plato 2300 years ago refers to the symbiotic relationship between mental and physical health, and has increasingly been embraced by Western society [1]. The concept that psychological state can influence physical well-being has contributed to the acceptance and use of mind-body therapies and motivated research into their health benefits. Recent scientific enquiry has noted diverse benefits of meditation such as reduced anxiety and depression levels, improved cardiac health, heightened immunity, and fewer post-chemotherapy adverse symptoms among cancer patients [2-4]. Researchers have also established a strong link between mind-body therapies and pain attenuation [5]. These findings suggest that these therapies may have potential as treatment for elective surgery inpatients.

With the increased number and types of surgical procedures required by an ageing population, meditation has been proposed as a means of improving post-operative outcomes, particularly after elective surgery [6]. Despite reported benefits and potentially low implementation costs [7], traditional medicine has been slow in adopting these alternatives. Critics remain sceptical of the efficacy and practicality of meditation, whereas advocates suggest that the analgesic qualities indicate clinical potential. To reconcile these opposing views, one must consider the logistical, psychosocial, and therapeutic aspects of meditation in the surgical context.

Mindfulness meditation

Meditation is often defined as mental exercises and techniques designed to calm the mind through physiological processes [8-10]. Mindfulness meditation (MM) sometimes referred to as 'Vipassana practice' or 'insight meditation', was thought to have been conceived by Buddhist scholars over 2000 years ago in India and is inextricably linked with Buddhist theology [11]. It involves cultivating a focused psychological attention to the internal and external experiences occurring in the present moment [12,13]. In practice, MM requires attentiveness to simple physical sensations such as breathing, eating, or sitting. Technical applications of this approach vary. One popular methodology in a clinical setting involves using one's imagination to mentally scan the entire body for awareness of physical sensations without judgment, beginning with the head and progressing to the toes. This can be used for any duration and in many circumstances. MM may also incorporate 'guided imagery' techniques in a clinical context, in which the patient visualises his or her own healing process and affirms thoughts of positivity regarding the management of illness [14].

MM as a form of therapy

Despite its origins in antiquity, MM has recently been adopted by Western society [15], and today's incarnation is mostly secular [16]. One of the first occasions of mindfulness being introduced to Western medicine occurred in 1979 by Kabat-Zinn's Mindfulness Based Stress Reduction (MBSR) program at the Stress Reduction Clinic at the University of Massachusetts Medical Center [3,17]. The inaugural program described reduced self-reported scores for depression and anxiety in participants with psychological problems [11].

To implement MM as a therapeutic tool, Kabat-Zinn adapted the methodology. He anticipated that the introduction of an alternative medicine, particularly one with religious associations, would be denounced by orthodox medical practitioners as the work of charlatans or mystics [17]. Overcoming this prevailing medical stigma was integral to the wider acceptance of mindfulness today. Accordingly, Kabat-Zinn distinguished MBSR from its religious counterpart by exploring the curative potential of meditation and designed it to be used as a clinical tool that complemented rather than replaced conventional medical therapies.

The scope of clinical mindfulness has expanded greatly with wider acceptance of MM by the wider scientific community. Current programs include mindfulness-based cognitive therapy, acceptance and commitment therapy, and mindfulness-based relapse prevention [18,19]. There are now even smart phone applications, DVDs, and self-help books, which have propelled mindfulness concepts into the public domain.

The acceptance of mindfulness by the medical community is also evidenced by the recent interest in the scientific evaluation of mindfulness as a health promotion tool. For example, in the 2008-09 fiscal year, the US government funded hundreds of studies concerning the clinical applications of various meditative practices, at a cost of US $51 million [17].

MM and surgical outcomes

By influencing psychological states, MM may help address post-surgical complications such as pain and reduced functioning [20]. A systematic review of studies that evaluated psychological variables and surgical outcomes found that psychological state strongly correlates with early recovery, although differences in study design restrict the ability to confidently pool results [20]. Psychological factors have also been shown on occasion to be superior predictors of post-operative outcomes than the surgical intervention itself [14]. Despite continued technological innovation, today many patients endure moderate to severe negative post-operative outcomes [21]. For example, up to 40% of patients who undergo elective joint replacement surgery report suboptimal functional improvement, pain relief, and overall satisfaction after their procedure [22]. These issues suggest that there is a need for complementary therapies to support existing therapies in a surgical setting.

Mind-body therapies such as MM are being increasingly evaluated for their effects on post-operative psychological variables. The use of mind-body therapies as a nonpharmacological adjunct has been well studied in cardiac, abdominal, and orthopaedic surgeries [14]. In these contexts, MM is associated with improved levels of pain, anxiety, fatigue, and distress [14]. Reduced systolic blood pressure has been reported during the post-operative period in patients who have practised a guided-imagery protocol [23]. Other benefits include shorter hospital stay and promotion of wound healing in some studies [14,24].

MM has been shown to be useful for reducing reliance on analgesia in the post-operative period and beyond [14]. Analgesia consumption levels can be used as a proxy for pain control. Although analgesic use is essential for promoting surgical recovery, too great a reliance on pharmaceuticals increases the risk of adverse side effects such as nausea, respiratory depression, and lethargy [25]. Some analgesics can also predispose to long-term dependency if their use is not appropriately stewarded. Palmaro *et al.* [26] observed that one-third of patients undergoing orthopaedic surgery for carpal tunnel syndrome had persistent and increased consumption of anti-neuropathic and/or opioid analgesics for more than two months after surgery. Among this population, psychiatric disorders and subjective levels of pre-operative pain explained this increased use [26]. MM may positively affect these two variables and reduce medication use. An estimated 234.2 million surgeries are performed worldwide each year, many of these necessitating pain medications [27]. It would therefore make fiscal sense to reduce the amount of pharmaceuticals required after surgery through the use of nonpharmacological therapies such as MM.

Proposed mechanisms to explain the effects of MM on post-operative pain

Meditative practice has been shown to change brain structure and function [28]. These effects may be seen both immediately and from chronic practice as demonstrated via brain imaging modalities such as fMRI, SPECT and PET [28]. Firstly, the prefrontal cortex (PFC) is intensely active during meditation, specifically the lateral prefrontal regions [28,29]. The ventromedial areas of the PFC are responsible for the affective integration of sensory input, whilst the posterolateral regions are concerned with sensory appraisal without self-referential value [29]. It is proposed that a neuronal shift away from the ventromedial prefrontal regions to the posterolateral centres supports a more self-detached analysis of interoceptive and exteroceptive sensory events [29]. Secondly, additional neural correlates such as modulation of the limbic system contribute to meditative effects [28]. MM practice has been shown to reduce the activity of the amygdala, and broader limbic structures concerned with emotional reactions [28]. For example, after eight weeks of an MM intervention, arterial spin labelling functional MRI showed neuroarchitectural changes such as increasing grey matter concentration within the left hippocampus and amygdala [16]. These regions are associated with emotional regulation, which may account for reduced anxiety and improved coping reported after programs of a similar duration [30]. In addition to this, MM has been posited to exert influence on the hypothalamus, which by extension shifts autonomic nervous system function towards increased parasympathetic activity [28]. This hypothesis attempts to explain physiological reductions in heart rates, blood pressure and serum cortisol levels which all evidence relaxation experienced during MM [28].

Another potential benefit of MM as a surgical therapy is pain modulation. However the exact mechanisms through which MM regulates pain are unknown [3,31]. Zeidan *et al.* [5] suggested MM can attenuate post-operative pain, reporting a 40% reduction in pain intensity and 57% reduction in pain unpleasantness following mindfulness intervention in a laboratory setting. The authors posited that this phenomenon results from synergistic interactions of improved attentional control, expectation modulation, and a placebo effect. By exerting attentional control on physical sensations other than discomfort, MM is thought to dampen the saliency of nociceptive stimuli.

Although this explanation seems to be reductive at face value, it is consistent with knowledge about complex neurobiology. The influence of MM on neurological pain-modulating networks is only now being explored. The cognitive inhibition of pain has traditionally been attributed to opioidergic mechanisms [32,33]. This model proposes that endogenous opioids are secreted by regions of the brain with an abundance of opioid receptors [33] and that these natural opioids elicit analgesic effects. Opioid receptors are found in high concentrations in the anterior cingulate cortex, orbitofrontal cortex (OFC), and insula [34]. Pain relief attributed to a placebo effect, conditioned pain modulation, and attentional control mechanisms such as those involved in MM rely on opioidergic pain relief [35-37]. These analgesic effects can be reversed after administration with opioid antagonists such as naloxone [34]. Imaging studies have shown that MM-induced analgesia is associated with increased activation in these regions of the brain [34]. This suggests that opioidergic mechanisms may account for some of the analgesic effects associated with MM.

Pain attenuation by MM may be supplemented by non-opioidergic mechanisms because opioidergic and non-opioidergic brain regions work synergistically. In MM, the OFC projects synapses to the thalamic reticular nuclei (TRN) which, via further projections exerts inhibitory control over the thalamus, an area considered to be the 'gatekeeper' through which all sensory information must pass [38]. When the TRN is active (either through the OFC or distinct mechanisms) ascending information such as nociception may be filtered from triggering conscious awareness [38]. MM therapy responses might therefore be mediated by the interaction between the OFC and the TRN, which appears to inhibit nociception from reaching the conscious part of the brain, the cerebral cortex. Self-facilitated pain modulatory systems seem to be engaged by non-evaluative recognition of an unpleasant physical sensation such as nociception [38]. Pain reduction experienced during MM is also associated with thalamic deactivation, which suggests a pain-gating effect may be exerted by the limbic system [5]. This suggests that nociception is influenced by the complex interaction of expectations, emotions, and cognitive appraisals, and may be modulated by the meta-cognitive task of focusing on the present moment [5].

Delivery of MM therapy to elective surgical patients

MM-based interventions vary in format and administration. Group mindfulness interventions are often preferable in clinical and research settings, and have been shown to expedite improved socialisation, program participation, and skill acquisition [14].

Group therapy with a set number of sessions of prescribed length may be more cost-effective than individual one-to-one interventions [14]. In group formats, a health professional such as a psychologist, physician or nurse instructs participants and distributes supporting material such as books and audiotapes to reinforce the program rationale and encourage independent practice outside standardised sessions.

It may not be practical to offer group sessions for patients undergoing elective surgery because of the nature of elective admissions, which are typically non-emergency procedures and can be delayed or rescheduled at short notice. Patients requiring more urgent surgery would not have sufficient advance notice to begin preoperative group therapy. Therefore, viable program methodologies should be flexible in terms of participant admission or delivered on an individualised basis as part of pre-operative patient care.

Personalised instruction or a single session with a psychologist can be tailored to the patient's level of comprehension. Patients could also be given the opportunity for follow-up sessions to consolidate skills learned before admission.

Regardless of the mode of delivery, the rationale, advantages, and disadvantages of MM should be explained to the patient before surgery. The patient's cognitive capacity and psychological state should be assessed by the physician or psychologist to evaluate his or her suitability for MM intervention and provide baseline psychological scores for comparison.

The benefits of regular MM practice in clinical practice have been well documented, and these skills can be consolidated for life [17]. In the context of pre-operative MM programs, optimum duration and timing of MM programs should be considered. The MBSR program developed by Kabat-Zinn [13] spans an 8-week course involving a 20-minute intervention each day. Many clinical programs use a similar program design, which has shown to be adequate to elicit desired benefits [17].

However it does not seem to be necessary for pre-operative programs to be as long as eight weeks to elicit desired effects. MM therapy given for the first time 24 hours before an operation has been shown to be beneficial. For example, Manyande *et al.* [39] reported reduced scores for post-operative pain and distress, and ward analgesic consumption for surgical patients given a 15-minute audio recording 1 day before elective abdominal surgery. Other studies have reported similar results [18,34,40]. Thus, although the benefits of MM are generally associated with regular practice (which may discourage some from taking up the practice), these findings imply that MM therapy involving short mental training may produce benefits even when undertaken in the days before surgery.

Limitations to MM therapy in the surgical context

There are potential limitations to MM as a pre- and post-operative therapy for surgical patients. The success of MM programs can be limited by surgery type and patient attributes, such as physical or cognitive impairment [14]. The stress associated with a hospital admission and surgery may impair a patient's ability to learn a new skill such as MM [41].

Implementation of standardised programs across healthcare providers may require additional funding, development of standardised educational material, and targeted training for healthcare professionals. Estimates of the resources needed would also vary according to differences between practices and institutional infrastructure. However, the cost of implementing MM programs may be recovered at least in part by improved recovery, reduced length of stay, reduced complication rates and reduced analgesic consumption [14,24,39,42]. Further cost-benefit analysis of MM programs for surgical patients may be warranted to better understand the organisational fiscal advantages associated with the use of MM therapies.

The effect size of MM intervention on post-operative outcomes has been subject to debate. Some studies investigating the use of pre-operative mind-body therapies in the surgical context failed to establish changes to post-operative outcomes such as pain and duration of hospital stay [14]. For example, Scott and Clum [43] observed no significant effects of treatments on outcome measures such pain, anxiety and analgesic intake after an attentional control regimen initiated 24hr prior to abdominal surgery. Other studies described mixed outcomes of such protocols [14,39]. It has been suggested that heterogeneity in study design and differences in the surgical context in which they are examined restrict generalizations being formed into the effectiveness of individual protocol design [14]. This is additionally hampered by fluid definitions of 'mind-body therapies' and noted methodological flaws consistent throughout much of existing literature, such as reduced sample size, inadequate controls and insufficient study duration [14,17]. Additionally, it is difficult to account for the influence of external factors on broader research outcomes. Factors such as insurance coverage may exert control on measures such as duration of hospital stay which may distort findings [14]. Further research may need to be conducted to reconcile these considerations and establish the clinical scope of MM.

It is unknown how receptive patients would be to learning MM around the time of surgery. Patients may be sceptical of or uninformed about mind-body therapies [17]. It is also unclear if the religious connotations associated with MM would promote or hinder patient participation [17]. Some patients may be discouraged by anything resembling a religious practice or indeed the opposite may be true [17]. Such phenomena may be subject to many individual patient factors and could be difficult to predict in the absence of empirical data. Future enquiry may seek to better understand the influence of individual patient preferences and values on MM adherence. It may be reasoned that patient education and evidence-based practice could also help dispel misconceptions about MM therapy and foster its adoption amongst the wider community, but research would be needed to corroborate this.

Conclusion

Since its adoption by Western society, MM has become increasingly used as a clinical tool. With an ageing population and increased demand for surgical interventions, complementary therapies such as MM should be considered. In the surgical setting, MM may reduce pain, anxiety, and distress, improve contentment, psychological state, and recovery time, and could decrease the need for high levels of medication and the risks associated with polypharmacy. Beyond its physiological effects, MM may also benefit those seeking relief from mental and physical stresses encountered during their hospital admission. Further research and development are needed to establish viable standardised treatment programs. Despite the mixed opinions about MM, it is likely that future medical practitioners will regard MM as a powerful therapeutic option in addition to its pharmacological counterpart.

Conflicts of interest

None declared.

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Management of chronic post-surgical pain: an overview

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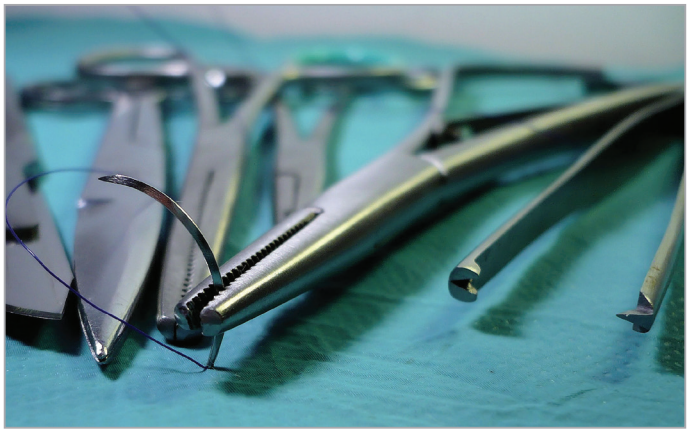
Abstract: Chronic pain is an anticipated complication of any surgery despite comprehensive treatment modalities to combat it. The development of chronic pain is attributable to a larger variety of inherent risks. Due to both the individual and social costs of chronic, unremitting pain, the value in preventing its development is paramount. Considering the complex pathophysiology of pain, chronic post-surgical pain (CPSP) development requires a multimodal understanding that involves understanding the physiological, psychological, and social circumstances of the patient. Prevention and management of CPSP starts preoperatively, addressing the patient's risk factors and expectations to anticipate and create a more personalised plan for pain control. Intraoperative measures include local anaesthesia and pharmacological analgesic therapies. postoperatively, a multidisciplinary approach utilising both pharmacological and non-pharmacological strategies can be used. Pharmacological treatments include individualised opioid-based patient controlled analgesia in conjunction with prostaglandin inhibitors, central nervous system pain receptor modulators, and nerve blocks. Non-pharmacological management includes transcutaneous electrical stimulation and acupuncture. A good understanding of how CPSP develops can aid in managing CPSP that can result in better control of chronic pain.

Pain in the perioperative period is a common and anticipated complication of surgery. Pain can be attributed in part to surgical factors such as nerve injury, inflammation, and infection. In addition, chronic pain development is dependent on a larger variety of putative risks that include past medical history of chronic pain and perioperative anxiety (Table 1) [1]. Chronic post-surgical pain (CPSP) is classified by the International Classification of Disease 11, as persisting pain for at least three months after surgery or tissue trauma, with the exclusion of other or pre-existing causes (such as infection and malignancy) [1,2]. The presentation of CPSP is often variable and may occur in relation to deep tissue or skin trauma at the surgical site, referred from viscero-somatic convergence, or related to nerve injury during surgery [3,4].

While epidemiological accounts vary, the populations at risk of developing CPSP are variable depending on the types of surgery and the likelihood of nerve injury. Current literature indicates that CPSP occur in 10-50% of surgical cases. In orthopaedic surgery related CPSP, up to 5% of all surgical patients report severe disabling pain at one year postoperatively, and a further 10% report lesser pain [1,3,4]. In a UK study of 5000 patients considering frequency and cause of chronic pain in the secondary care setting, 22% of outpatients attributed surgery as the major cause of their chronic pain [3,5]. As chronic pain is difficult and costly to manage and has a major impact on quality of life and productivity, the socioeconomic health burden is potentially enormous considering the volume of surgeries performed annually [1,5].

Formerly, conceptualisation of chronic pain was limited to uni-factorial models of biomedical causality. These models sought to explain pain as corresponding directly to bodily damage with severity being a measurement of extent (for example, using a visual analogue scale or



numeric pain rating scale), rather than patient interpretation of injury [1,6]. However, the lack of a clear relationship between extent of tissue/nerve damage and pain severity indicates there is a psychological and sociological component to pain, with the additional influences of motivation and secondary gains (family, work, and "the sick role") [6]. These aspects were heavily enforced by operant learning factors, which develop into "pain behaviours" of avoidance, and cognitive factors based around beliefs and expectations of pain post-surgery [7]. Patients who have a past medical history including emotional or psychiatric stressors, have increased work-related injuries and claims, negative attitudes to treatments, and previous chronic pain diagnosis are at an increased risk of developing chronic pain syndromes [1,8]. To demonstrate this point, a large 2007 prospective surgical cohort study using preoperative psychological questionaries (Item-36 Short Form Health Survey) with postoperative acute pain scores for 625 patients undergoing minor, intermediate, and major surgeries, found that fear of the long-term consequences of surgery predicted increased pain in the six month postoperative follow-up period, independent of the type of procedure and other somatic factors [7].

Generally, surgical pain can be attributed to three main mechanisms: inflammation, direct nerve injury, and increased sensitisation [1,2]. Inflammatory pain arising from tissue trauma and ischaemia is an unavoidable aspect of most surgeries [4]. Although the release of local inflammatory mediators like tumour necrosis factor alpha and interleukins 1 and 6 are needed to a certain degree for healing, they can result in hyperalgaesia (augmented sensitivity) and allodynia (misperception of non-painful stimuli) long after the expected healing time from surgery [1,4]. These outcomes are attributed to peripheral nerve sensitisation and are often managed with anti-inflammatory medications both intraoperatively and on an outpatient basis [4]. In conjunction, pain developing from direct nerve injury (compression, stretch, or transection) can have a similar presentation in addition to hyperpathia (exaggerated pain), paraesthesia/dysaesthesia (abnormal sensation) and even hypoesthesia (decreased sensation) [1,4]. For example, nerve injury arising from fetal head descent through the birth canal during labour may result in compression or stretch of lumbosacral nerve roots resulting in radiculopathy from 8% elongation, while 15% elongation can result in axon disruption and axonotmesis [7].

Pain sensitisation is also a major precipitating factor for the transition from acute to chronic pain. The pathophysiology of sensitisation is attributed to increased excitability of both central and peripheral nerve fibres (in addition to decreased inhibition from dorsal horn spinal neurons) [1,10]. Centrally, sensitisation is linked to upregulation of N-methyl-D-aspartate (NMDA) receptors in the dorsal horn causing the "wind-up" phenomenon of pain, with peripheral changes from prolonged inflammation or opioid exposure linked to 'hyperalgesic priming' at the afferent sensory nerve level [1,2]. Ectopic activity in transected nerves has also been associated as the underlying cause for the spontaneous pain characteristics of some neuropathic states that involves maladaptive plasticity within the nerve nociceptive system post-injury [1]. It is predominantly owing to this sensitisation (with input from patient psychology) that the major risk factor for developing CPSP is severe acute post-surgical pain, making acute pain management of foremost importance for CPSP prevention [1,2].

Owing to its complexity, pain management warrants a comprehensive and surgery specific multimodal approach [5]. This starts preoperatively with patient risk factors and expectations addressed to anticipate potential complications and acceptable therapies. Furthermore, following procedure specific guidelines produces better clinical outcomes with appropriate discharge and rehabilitation planning incorporating a pain clinic follow-up [2]. For example, open colorectal procedures may benefit from thoracic epidurals to reduce postoperative pain, nausea, and vomiting, while laparoscopic abdominal procedures, with minimal tissue injury, often do not require the same cover [11]. These considerations should be made preoperatively with patient expectations taken into account and the risk of neuropathic/nerve injury considered for procedure appropriate analgesia [2].

Intraoperatively, local and systemic therapies can be used to target the aforementioned biomedical risks and can be further broken into nociceptive and neuropathic targets. Systemic therapies often involve opioid and limited non-opioid options for nociceptive pain, with opioid use being limited by adverse effects (such as respiratory depression and vomiting) [2].

Patient-controlled analgesia (PCA) remains a cornerstone of postoperative pain management, with early postoperative intravenous opioids providing better analgesia than conventional parenteral opioid regimens, with greater patient satisfaction particularly for nociceptive pain [2,11]. There is little evidence that any particular opioid delivered via PCA is superior to another in regard to analgesic or adverse effects in general, but individual patients may tolerate one opioid better than another, and safety of administration can be impacted by hospital staff education [12].

In regards to non-opioid analgesics, there is fair evidence to support their complementary use with opioid analgesics [2]. Medications in this category that target nociceptive pathways include non-steroidal anti-inflammatory drugs (NSAIDs) which are superior to paracetamol (although combining both increases efficacy), and selective COX-2 inhibitors (a subtype of NSAIDs) which offer further advantages over their non-selective counterparts in particular with regard to platelet dysfunction, blood loss, and renal impairment [2,11]. Other multimodal analgesic options that can assist in neuropathic pain management involve intravenous local anaesthetics (such as lignocaine), which has been shown to reduce opioid requirements after abdominal surgery and to decrease the risk of nausea, vomiting, and duration of postoperative ileus, and so decrease the length of hospital stay [12,13]. Locally, lignocaine can also be injected proximally to surgical sites intraoperatively as a preventative somatic analgesia, although a 2005 meta-analysis of 66 randomised controlled trials (comparing preoperative analgesic interventions with similar postoperative analgesic interventions via the same route) and a 2005 randomised controlled trial assessing pain relief in laparoscopic gynaecological surgery suggested the use of pre-emptive local infiltration was associated with a more limited, but still beneficial effect on post-surgical visceral pain [14,15].

The importance of multimodal approaches targeting not only the nociceptive, but also the neuropathic and central neurons can be seen in the prevention of wind-up phenomena and central sensitisation [6,12]. For this, therapies targeting not only opioid, but also substance P, calcitonin gene-related peptide, aspartate, glutamate, gamma-aminobutyric acid (GABA), and NMDA receptors can be used to target pain on multiple levels of the pain pathway [1,2]. Examples of neuropathic treatments include perioperative use of gabapentin and pregabalin, which have both been shown to decrease postoperative opioid requirements [13,16]. Similarly, a meta-analysis of 29 randomised controlled trials indicated a small yet significant decrease in CPSP with intra- and postoperative ketamine use [8]. Furthermore, peri-operative intravenous ketamine also reduces opioid use and postoperative nausea and vomiting compared with placebo, in addition to being cost effective and useful in opioid-tolerant patients [2,17].

Concurrently, the use of regional blocks or neuraxial methods such as femoral nerve blocks may reduce the use and side effects of systemic opioids whilst facilitating early mobilisation and recovery (thereby reducing the psychological impact of illness) [8]. Risk of infection exists, but is predominantly preventable by sterile precautions. Likewise, the risk of neuropathy from this procedure is low and countered generally by the use of ultrasound guidance [11]. Additionally, while

Table 1. *Risk factors for CPSP development.*

Preoperative	Intraoperative	Postoperative
• Pre-existing chronic pain condition • Co-morbidities • Repeat surgery • Psychological distress • Preoperative anxiety • Younger age • Female • Work related • Genetic predisposition	• Surgical risk to nerves • Major surgery • Infection/haemorrhage/complications • Anaesthetic techniques • Surgical procedures involving: major body cavities, large joints, deep tissues, increased risk of ischaemia	• Severe acute pain • Neurotoxic chemotherapy • Radiation therapy to site • Depression • Anxiety • Inadequate care (perceived or real)
Special considerations • Morbidly obese • Previous or current opioid abuse • Concurrent opioid prescription • Older age		

regional blocks present an increased risk of procedural complications depending on the block used (for example, brachial plexus blocks risk pneumothorax), these are far rarer than complications of opioid use and often outweigh them on a clinical outcome basis for controlling neuropathic pain [11,18].

In terms of patient education, better pain relief is achieved by structured preoperative education and written information, rather than routine information with generalised verbal discussion [2]. Although identification of preoperative risk factors may assist in targeted patient education and expectation management (Table 1), other interventions, such as pre-surgical hypnosis and music therapy, have been found to be reliable for decreasing CPSP as an outcome indicated by six month follow-up surveys and postoperative pain surveys [1, 7]. Identification of factors that will make pain management more difficult, such as obesity, history of opioid abuse, and current opioid use may assist in appropriate pre and post-surgical management [1,2].

Finally, non-pharmacological methods including transcutaneous electrical stimulation and acupuncture have been shown to reduce postoperative pain, particularly in the setting of back surgery and ambulatory knee surgery when compared to placebo, with the aforementioned psychological methods (distraction, music, and video) being of potential use in paediatric populations. However, the evidence for these is limited and variable in the literature [2,11].

In conclusion, CPSP is a common, inherently complex, and costly complication of surgery. Managing chronic post surgical pain from a multimodal multidisciplinary approach may improve pain control.

Conflicts of interest

None declared.

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School refusal: identification and management of a paediatric challenge

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Sarah is currently a fourth year medical student at Griffith University with a keen interest in psychiatry. She was inspired to write this article after being exposed to the prevalence of school refusal during a medical elective in child and adolescent psychiatry.

Abstract: School refusal is not truancy, but both are serious behavioural problems that can have detrimental consequences. Management of school refusal involves ruling out organic causes and assessing contributing factors, such as anxiety and depression. Empirical treatment involves a collaborative approach of cognitive and behavioural therapies involving the child, parents, and school. This article highlights the heterogeneous nature of school refusal, its identification, assessment and management, and the implications for future research.

Introduction

At first glance, school refusal appears to be a relatively straightforward phenomenon that all youth may experience at some point during their school years. However, youth-motivated school absence is a significant public health problem affecting schools and households around Australia. Nationally, the average attendance rate of state secondary school students is approximately 85%, with the Northern Territory experiencing the lowest rate of attendance at 75% [1]. In Queensland, an estimated 30% of state secondary school students had an attendance rate below 90%, or had missed more than 20 days of school over one school-year [2]. Of the reasons given, 'unexplained' absences accounted for more than 25% of the total absences [3]. Due to financial and legal issues associated with chronic absenteeism, health professionals are put under increasing pressure by parents and schools to find a solution to the child's 'problem.' This strain may lead doctors to write generic medical certificates or practice 'defensive medicine' in order to avoid professional and legal risks.

Definition

School refusal is not a psychiatric diagnosis, but rather a symptom that encompasses a range of possible diagnoses or social problems. There are many terms in the literature that are used to describe the different types of absenteeism. Firstly, child-motivated absenteeism differs from 'school withdrawal' in that the latter refers to situations where a family deliberately keeps their child at home for various reasons, such as due to financial reasons or to care for an ill family member [4]. Child-motivated absenteeism is typically categorised into those with school refusal and those displaying truancy (Table 1). 'School refusal' is generally thought to encompass difficulties attending or staying in school, and is associated with extreme emotional distress [4–7]. The child stays home with their parents' knowledge, despite the parents having made a reasonable attempt to encourage the child to attend school. Children exhibiting truancy, in contrast, are more likely to display antisocial tendencies, such as vandalism and theft, rather than emotional distress [4–7]. Truants' motives for absenteeism include a lack of interest in school-work, unwillingness to conform to the school's code of behaviour, and an over-riding desire to engage in externalising behaviour, such as disruptive acts or alternative tangible reinforcers on a school day [4–7]. In addition, parents are often unaware of or disinterested in their child's school absence. The separation of absenteeism into school refusal and truancy has been criticised for the bias shown to children with school refusal who are often perceived sympathetically and judged to be worthy of treatment, while the

term 'truant' raises punitive connotations and the need for discipline [8,9]. Due to this bias, children labelled truants are under-represented in current literature and it is unclear whether interventions differ between this group and children with school refusal, particularly due to a lack of strong supporting evidence with regards to the effectiveness of common psychological treatments in groups with externalising behaviour, such as truancy [10,11]. Groups inclusive of differing causes of absenteeism should be a future research objective. Until then, since management of school absenteeism is critical for all youth, it is therefore important to be aware of this bias and assess each child individually and thoroughly.

Epidemiology

Approximately 1–5% of all school-aged children will demonstrate school refusal behaviour at some point [6,7]. Although it can occur at any age, school refusal is more common between 5–7 years and 12–14 years of age. These age groups correspond to periods of transition to primary and secondary school, respectively [7]. The prevalence of school refusal seems to be unaffected by gender, socio-economics or intelligence [7,12]. One study showed that a high prevalence of adolescents with school refusal and co-morbid depression also experienced learning difficulties, which may have been a causal factor in their school refusal [13]. In a study assessing parental and familial risk factors for school refusal in children, physical punishment by parents, history of organic disease in parents or the child, and positive psychiatric history in a parent or relative were found to be significant [14]. There have been conflicting arguments in the literature regarding the role of family dysfunctions such as conflict, strict parenting or isolation, and school refusal [15,16]. These various aetiological factors emphasise the heterogeneous nature underlying school refusal and the necessity for future studies with larger sample sizes to assist in delineating predisposing risk factors.

Clinical features

The onset of school refusal can occur acutely, such as on the first day of a new school term, or gradually, such as increasing reluctance to attend school until outright school refusal. Non-attendance can occur sporadically, or continually for weeks or months [6]. The emotional distress that often accompanies school refusal can manifest

Table 1. *Differentiating school refusal from truancy.*

School refusal	Truancy
• Likely to stay home, often with parents' knowledge • Likely to include underlying anxiety-related disorders and/or depression • Is not strongly associated with oppositional defiant disorder • Assessment should include ruling out organic causes first • The School Refusal Assessment Scale-Revised tool can assist diagnosis • Requires evaluation of school-related and familial stressors, including child safety • Management includes input from a paediatrician or multi-disciplinary child and adolescent mental health services team • Effective treatment involves cognitive and behavioural therapies with parental and school participation	• Likely to seek external rewards away from home, often without parents' knowledge • Can involve underlying anxiety-related disorders and/or depression • Is more strongly associated with oppositional defiant disorder and conduct disorder • Assessment should include ruling out organic causes and substance misuse • The School Refusal Assessment Scale-Revised tool can assist diagnosis • Requires evaluation of school-related and familial stressors, including child safety • Management may include input from a paediatrician or multi-disciplinary child and adolescent mental health services team • Currently lacking strong evidence-based treatment in literature

behaviourally, physiologically, and cognitively [6,7]. Behaviours include remaining in bed, refusing to leave the car, crying, or having temper tantrums. Physiological symptoms include abdominal pain, nausea, vomiting, headaches, diarrhoea, sore throat, sweating, and frequent urination. On a cognitive level, children often have irrational fears about school attendance [7]. A case example of school refusal outlining the presentation, investigations, and management is included (Table 2).

Chronic school refusal has a strong association with anxiety-related disorders [17,18]. Common diagnoses include separation anxiety disorder, generalised anxiety disorder, social phobia, specific phobia, and adjustment disorder with anxiety [7,18]. There appears to also be age-related trends in regards to the diagnoses, for example younger children are often assessed to have separation anxiety whereas adolescents tend to be diagnosed with phobias [7]. These phobias are often in relation to social situations where there is an irrational fear of being criticised. People with an anxiety-related disorder often have co-morbid depression; and certainly, there is a high prevalence of school refusal in children with diagnosed or sub-clinical depression [18].

Children with school refusal can also display argumentative and aggressive behaviour when pressure is exerted upon them to attend school. This type of externalising behaviour leads to many of these children being diagnosed with oppositional defiant disorder [7]. It is important to note that in school refusal, this externalising behaviour is not displayed in multiple settings, but primarily contained to the home environment. By definition, conduct disorder-type behaviours, such as social disregard and violence, are not characteristic of school refusal, but more often associated with truancy.

Assessment

As with any clinical presentation, a thorough history and medical examination must be taken to rule out organic causes. Only reasonable investigations relevant to the presenting physical symptoms should be conducted [19]. Obviously, if a chronic medical condition were to be uncovered, the primary focus of management would be appropriate referral and education [20].

In addition to a detailed history of the presenting physical symptoms, a health practitioner should consider the predisposing, precipitating, and perpetuating issues of the child's school refusal in terms of individual, family, school, and community factors. Attention should be given to the family function, the reactions and responses of those surrounding the child to their school refusal, and peer relationships in school [19]. Liaising with the school for information about the child's attendance records and academic progress would be useful to look for trends in absenteeism and potentially undiagnosed learning difficulties. In addition to days missed, it is also important to enquire about tardiness, early departures from school, missed lessons, and time spent out of class. Discussion about the child's behaviour and social interactions are vital to exclude victimisation from bullying [21].

Table 2. *School refusal case example.*

Presentation
Elle is a 13-year-old girl who presented to the GP with her parents. Since starting high school a few months ago, the school has expressed concern about Elle's frequent skipped lessons and whole-day absences. Elle complained of stomach-aches and headaches, as well as feeling nauseous and dizzy on weekday mornings.
Investigations
Initial workup assessed her physical complaints. Differentials included hyperthyroidism, substance abuse, migraine, cardiac arrhythmias, puberty-related conditions, stress, and anxiety. When physical examination and investigations were negative, attention turned to Elle's psychological symptoms and risk factors at home, school, and within the community. It was discovered that Elle had significant fears, and worries excessively about socialising with peers and performing well on her school-work. She was frequently bullied at school because of her quiet and reserved nature. Her anxiety was perpetuated by a tense family relationship at home. Both of Elle's parents believe in stringent discipline.
Management
Due to the complex issues present, Elle was referred to adolescent mental health services. After another evaluation, including grading Elle's symptoms on the School Refusal Assessment Scale-Revised, it was concluded that Elle's social anxiety could be best managed with CBT within a multimodal treatment plan. This involved regular psychosocial therapies with Elle and her family, as well as coordination and negotiation with the school for her return to class.

Formal assessment

Standardised behavioural checklists and mental health scales can be given to the child, their parents, and the school teachers to assist in delineating problems and comparing the severity of behaviours at school and home [19]. The School Refusal Assessment Scale-Revised (SRAS-R) is one of the widely accepted checklists used internationally to assess the functional model of school refusal behaviour, such as positive and negative reinforcements [22]. Determining the functional profile of school-refusing behaviour can also assist in identifying underlying psychiatric diagnoses [23]. The SRAS-R has been verified as having good validity, reliability, and utility [5,24]. However, a recent study has highlighted the ambiguity of certain items on the SRAS-R and suggests that some questions should be removed for improved validity and reliability [25]. The use of the scale can be extended across more generalised populations of school absenteeism, including truancy [26].

Child safety

Finally, health practitioners should be wary of the possibility of an unsafe home situation that the child may be exposed to, as this can contribute to school refusal. For example, a child may feel anxious and hesitant about leaving home if they feel the need to portray a protective role for a parent under domestic violence [20]. Mandatory reporting laws exist in all Australian states and territories for suspected cases of child abuse and neglect. Given the slight differences amongst states regarding child abuse legislation and protocol, it is advisable to check the details applicable to your jurisdiction [27]. Provisions within legislation protect practitioners from liability for reporting confidential information if the report was made in good faith. If a practitioner is uncertain about reporting, they can contact the local child protection unit or a paediatrician for discussion and advice [28].

Prognosis

A quarter of refusals are estimated to remit spontaneously or are dealt with successfully by the family and school without practitioner intervention [5]. However, school refusal has detrimental consequences for the majority of the remaining cases that go undetected and unmanaged. Short-term consequences include poor academic performance, family conflict, and damaged peer relationships. Long-term outcomes include social isolation, employment issues, and increased risk of ongoing internalising mental health problems and developing a psychiatric illness in adulthood, such as panic disorder and agoraphobia [19,29]. On first presentation, risk factors that indicate a poorer prognosis of returning to school consist of severe or long-standing school refusal, being adolescent or of older age, and having a co-morbid psychiatric illness, particularly depression [7,19].

Although there is a strong emphasis on a timely return to school for refusers, few published studies are available that report the long-term implications of return to school. One study concluded that there was enduring improvement in family relationships after the resolution of the child's school refusal, however, there appeared to be no difference in the long-term social or emotional adjustment [30]. Another retrospective study found long-term improvement in educational and employment outcomes after school refusal treatment, except for those diagnosed with social phobia and learning difficulties; however, the study was limited by small sample size [31]. Further controlled studies investigating the long-term functional impact of managing school refusal need to be conducted.

Treatment

The primary objective of treatment for youth displaying school refusal is timely return to school. Behavioural therapies and cognitive behaviour therapy (CBT) have been widely studied and accepted as first line treatment where school refusal is associated with the primary diagnosis of an anxiety disorder [32–37]. Unfortunately, studies are limited by high treatment drop-out rates and inconsistent results on follow-up [33,37]. There is also a lack of randomised controlled trials investigating interventions other than CBT variants, such as group therapy or hypnotherapy [32,38,39]. These limitations indicate the need for future research with better-controlled studies and reproducible results, as well as considering other intervention types. More recent studies have found that CBT is most likely to be successful when it is incorporated into a multimodal treatment method involving the child, parents, and school [40,41]. Due to its heterogeneous nature, some cases of school refusal can be complex and persistent, therefore it is recommended that the child be referred to a paediatrician or to child and adolescent mental health services, which include inter-disciplinary teams, for holistic long-term management, which might include medication.

The child

Child treatment plans should be individually tailored, depending on the psychological basis of their school refusal as well as their developmental level [42]. This may initially include relaxation training for those with substantial physiological manifestations of anxiety. By reducing feelings of anxiety, children are better engaged to utilise various CBT strategies. Cognitive therapy can be used to scope the relationship between a child's emotions and their behaviour, and ultimately facilitate school attendance by problem-solving and modifying maladaptive cognitions [7,43]. Social skills training is beneficial in addressing any deficits in social skills, which may be contributing to the school refusal, as well as managing the social anxiety associated with talking about their absence to peers or teachers [43]. Improving communication between parent and child is also an important component of CBT. Ultimately, graded exposure and planned return to school should be encouraged, involving the child and their teacher with modification of schoolwork and improved in-class support. Regular positive reinforcement should be used to assist progression, and monitoring for relapse is essential.

The parents

Parental and family support is crucial for successful return to school. It has been observed that improvement can be made only through positive influence and when the child is convinced that their parents are determined to achieve regular school attendance [44]. Parents should be taught to employ contingency plans and behaviour management strategies, such as ignoring inappropriate behaviour and positively reinforcing appropriate behaviours. Heeding signs of parental psychopathology and initiating anxiety management education may also help parents maintain their composure and focus when facilitating their child's school attendance [7,43]. This may include arranging for parents to receive mental health services or marital therapy.

The school

The practitioner and parents should also closely liaise with the child's school in order to enable a smooth return to school. It is important to educate school staff about school refusal behaviour and associated psychological issues, to dispel potential misconceptions about students with school attendance difficulties. School staff are encouraged to accommodate special arrangements, including modifying schoolwork and assessment, and allowing graduated attendance, such as only coming in for favourite lessons or for the first part of the day. Supportive teachers and 'peer buddies' are recommended to ensure the child's experience of school is positive [43]. Complaints of somatic symptoms should be treated tentatively, and unless the child is clearly unwell, they should remain at school.

Pharmacotherapy

Pharmacological treatment may be considered adjunct to the cognitive and behavioural therapies, especially when the child has severe underlying anxiety or depressive symptoms, or when they have not responded to the comprehensive psychosocial treatments offered [45]. Based on existing clinical trial studies, there is little satisfactory evidence that supports the effectiveness of commonly prescribed medications. There appears to be some evidence favouring the tricyclic anti-depressant (TCA), imipramine, with concomitant psychosocial therapy as a superior therapy to placebo combined with psychosocial therapy [46–48]. Short-term outcomes consisted of improved school attendance and reduction in anxiety and depressive symptoms [47]. These positive findings were not maintained in a naturalistic one-year follow up study [48]. TCAs can be problematic due to their unpleasant side-effects and toxicity, including cardiovascular complications [49]. Selective serotonin reuptake inhibitors (SSRI), such as fluoxetine, have weaker evidence of efficacy for school-refusing children, showing no significant difference in therapeutic efficacy between combined CBT-and-fluoxetine therapy and CBT alone [50–52]. Despite this, SSRIs tend to be favourable in practice as they are shown to be effective in reducing depressive symptoms in children and adolescents, and are less likely to cause serious adverse effects [52–54]. Children on medication require regular review for response and side-effects.

Conclusions

School refusal is a challenging problem for health practitioners, families, and schools. Early identification and management reduces the risk of detrimental short- and long-term consequences. Management of school refusal can be complicated and arduous, and needs active participation from the child's parents and school, as well as possibly paediatricians and mental health services. The preferred management of school refusal involves a multimodal treatment approach and CBT. There should be more awareness and understanding about this mental health risk and the potential for early intervention to promote the health and wellbeing of the future generations.

School refusal is a growing topic of interest in the literature. However, the current literature is largely limited by selection of the absentee population, lack of intervention types, poor sample sizes and follow-up, conflicting outcomes, and lack of long-term sequelae after return to school. In order to establish the efficacy of school refusal interventions, future research could benefit from further adequately powered randomised controlled studies with independent reproducible results. There should also be a focus on investigating groups with different causes of absenteeism, such as truancy, as well as management modalities other than CBT and their long-term effects.

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Conflicts of interest

None declared.

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Pacific partnerships: exploring the Fijian healthcare and medical education systems

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Madeleine is a third year medical student who is passionate about global health. She is interested in health policy and research.

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We walk with our host between the palm trees and brightly painted bungalows, touring the community care centre for elderly and disabled Fijians. The surrounds belie the grim conditions that must be endured by the patients who live here. There is one patient in particular whom our host wants us to meet — a middle-aged man with an intellectual disability and diabetes who has lived at the home for most of his adult life. He greets us warmly and chats with our host in Hindi whilst we take in his condition. His left foot is extensively bandaged, but the skin left visible is swollen and mottled. Our host, who is the chair of our sister-committee based in Fiji, explains that the patient's foot has been gangrenous and in need of surgical assessment for the past five years, but they have been unable to facilitate this. His gangrenous foot has frequently been infested with maggots, despite the dedicated care of the facility's nurse. There is just one nurse employed in the forty-bed facility. Due to limited resources, she must wash the patient's foot barehanded with soap and water. The nurse shows us her supplies: a scanty collection of antibiotics, antihypertensive medications, metformin, and needles and syringes. Recently, she was grateful when our host provided her with latex gloves to wear whilst caring for the patients. The lack of medical resources and the understaffing of care facilities were just some of the issues we encountered during our brief, but enlightening, stay in Fiji. Through Friends4Fiji, a student-led partnership between Monash University and Umanand Prasad School of Medicine (UPSM), our Fijian counterparts, facilitated a week-long placement and education outreach program. We divided our time between undertaking a placement at the local hospital and assisting in the delivery of an anatomy teaching program for Fijian medical students, led by Dr Michelle Lazarus, a senior anatomy lecturer from our university.

Medical students in Fiji face challenges that we can scarcely imagine in Australia, extending from their academic resources to their expected time commitment. The information provided to students, and, by extension, doctors, is frequently outdated and incomplete, making it difficult to develop evidence-based medical practices [1]. Despite this, the students we worked with through the committee went beyond the required learning in order to develop a solid foundation. With limited resources, they are unable to rely on specialist journals or opinions, hence students are taught to think creatively, a skill they must rely upon in their future practice [1]. In the university we visited, frequent turnover of university administrators and lecturers had led to disruption of the curriculum such that some cohorts missed out on formal teaching of whole body systems in their anatomy course. Students described being reliant on textbooks and plastic models for anatomy teaching. There is no body donor program for dissection classes, and dissections are limited to animal carcasses at the local abattoir. Senior students must meet significant time requirements, with sixth-year students expected to perform weekly 'on call' shifts and night shifts, as well as attending wards on the weekends. These requirements may be explained by the inadequate hospital staffing levels, identified by comparing staff-to-population ratios with the projected numbers needed [2]. Having

medical students performing intern-level tasks assists in alleviating doctors' workloads without costing the national health budget further, as 60% of the budget already directly funds the workforce [2]. This shortage of fully qualified doctors has also been identified as impacting on medical training, causing a lack of post-graduate training opportunities, which contributes to emigration following student graduation [2,3]. With the many challenges these students face, it was deeply satisfying to observe their thirst for knowledge that extended beyond the curriculum, and we feel that we met a genuine need with the teaching program that we implemented.

As mentioned, the challenges faced by these students grow substantially when they become doctors, leading to a crisis of emigration among Fijian doctors and a subsequent growing reliance on foreign doctors [2,3]. 'Push' factors, which drive young professionals out of Fiji, include heavy workload and lack of promotion prospects and are coupled with 'pull' factors, which draw graduates to overseas positions, such as better pay and training opportunities in developed nations [4]. Ultimately, the high numbers of doctors leaving, particularly from the public sector, have been attributed to a complex career decision-making process involving work-related frustrations, with the primary motivation being income [3,5]. This interplay creates diverse problems, from workforce shortages and a lack of specialist training positions for graduates, to a lack of research conducted and published by Fijian authors. Among students we spoke with, intentions for future employment were divided. For those planning to stay in Fiji, students were motivated by a desire to give back to their community, with a student stating, "we study to help people, and Fiji needs A LOT of help," and another explaining, "it will also be a good opportunity to actually help the people of Fiji get the best medical services from doctors." Among students considering leaving Fiji, key motivators were gaining experience and learning advanced medicine, with one student stating, "I do tend to look forward to study and work overseas due to their high standard of education and learning programmes." Whilst many of the students we spoke with had entered medicine with the very intention

of giving back to their community by developing much needed skills, one can appreciate the frustrations they face. Every day, when these graduates go to work, they face shortages of essential medications and supplies, which interfere with patient care. There are also shortages in onshore graduate specialist training programs, which are limited to anaesthesia, medicine, obstetrics and gynaecology, paediatrics, and surgery [6]. These graduate options are a fraction of what is offered internationally, and do not meet the demand for specialists in Fijian hospitals, making it difficult for practitioners to receive adequate guidance for patient care [1,3]. The medical students we met in Fiji had diverse career aspirations. One student had greatly enjoyed her rotation at the psychiatric hospital in Suva, and was keen to pursue a career in this field, noting the dire need for more psychiatrists in Fiji. However, due to a lack of training positions, this student was contemplating leaving Fiji to pursue psychiatry training internationally. Despite the competitive nature of entering the postgraduate training programs, the number of specialists accepted into these programs does not meet public need, with only 48.5% actually working in the public sector following completion of specialist training [3]. Though there were many recognised benefits of working in Fiji, including cultural acceptance and religious responsibility, many doctors in Fiji experience significant frustrations with the facilities, bureaucratic processes, and the salaries they receive, factors that the students we spoke with already identify as concerns [3,5].

The lack of basic supplies and difficulties patients faced when accessing critical healthcare in the Fijian facilities were more significant than either of us anticipated. The Fijian public health system relies on a combination of taxpayer funding and external support through a number of United Nations agencies and nations including New Zealand, Australia, and the USA [2]. During our placement at the local hospital it quickly became apparent how underfunded and under-resourced this system is. Every investigation we considered ordering was carefully scrutinised by our supervising doctor, with a much heavier reliance placed on clinical assessment. This in turn impacts medical education, as students and doctors cannot rely on investigations being available and are hence required to think critically and to have a broad knowledge base. The lack of adequate technology to maintain evidence-based practice has also led to pressure from pharmaceutical companies presenting misleading information to doctors, placing further stress on doctors to avoid influence where possible [3,5]. This was particularly evident with medical imaging, which is limited in Fiji due to a paucity of technicians and facilities. Fiji has just three CT scanners [2] and the one located at our hospital was broken for the duration of our placement, and had been for quite some time. This stems from the fact that much of the machinery is donated second-hand from other nations and there is a reliance on this non-functional equipment, which impacts on delivering care to patients [1,2]. On the wards in the hospital, basic items which Australian doctors would consider essential for patient care were scarce. We particularly noticed the lack of access to products for safe hand hygiene practices and personal protective equipment. The lack of access to this basic equipment, combined with insufficient funds for medicines, were identified as primary concerns among the workforce, further contributing to emigration [2,5]. When it comes to ongoing care, shortages of essential medications make it difficult for the doctors to maintain a regular supply for their patients [6]. All medications are monitored monthly and sourced through the government-funded Fiji Pharmaceutical Services, however "stock-outs" are common [2]. The strategies in place for drug regulation are poor, and the quality of imported drugs is a concern to Fijian doctors due to a potential lack of stringent quality testing [1,2]. It was an incredibly steep learning curve to experience such fundamental differences in resources, and has certainly made us much more aware and grateful for what we have readily available in metropolitan Australian hospitals.

Another major difference identified during our stay was the restricted nature of mental health care in Fiji. As one student we spoke with stated, "mental health is mostly ignored in Fiji." Despite the national emphasis on institutional care for people with ongoing mental illnesses, there is just one dedicated psychiatric hospital in Fiji, located in Suva [7]. This hospital offers generalised psychiatric services, however, like many other areas in Fiji, there are no sub-specialist psychiatric services available [2]. Within the wider community, psychiatric help is limited. At the hospital where we undertook our placement, those suffering acute psychiatric illness or at risk of committing suicide could be cared for in the euphemistically-named 'Stress Ward'; however there was no psychiatrist or specialised staff available. As few students are able to undertake placement at the specialised mental health hospital, the stress ward and community placements comprise much of their practical experience of mental health. When asked their thoughts about mental health care in Fiji, students identified it as an improving area that still needed more work, with one student explaining, "five to seven years ago, no one bothered about mental illnesses and brushed it aside. So many women had never heard of the term 'post-partum depression'. Now they get screened regularly. Mental health was an unaddressed issue in the past but we are getting there." Whilst progress has been made to reduce stigma associated with mental illness through education and awareness by mental health advocacy groups, 42% of Fijians still report that they would be embarrassed to seek medical help for a psychiatric issue [2,8]. This attitude towards mental illness is far better in urban centres than in more remote regions, and level of educational attainment is positively correlated with receptiveness towards people with mental illnesses [7]. However during our visit to a community care facility, we noted residents with schizophrenia who spent most of each day bed-bound. Whilst these patients have access to antipsychotic medication, there is no access to counselling or rehabilitation workers who could help them return to the community. Standardised clinical treatment guidelines and referral protocols are still being developed by the relatively new Mental Health Clinical Services Network, which hopes to make mental health a priority through advocacy and legislation [2]. The Fijian medical students we spoke to were eager to cultivate the positive trend of increased community awareness and knowledge, combating the stigma of mental illness which predominates in Fijian society.

During our stay and discussions with the Fijian students, we learnt that similar to our own university, there was a slight female predominance of students. However, gender roles in Fiji have a clear effect on the academic and medical culture, something we particularly noticed as an all-female teaching team. In Australia, the challenges that women face in medicine are well documented, from sexual harassment to reduced earning potential [9,10]. However, in Fiji, females face even greater social and economic disadvantage, and this perception pervades many aspects of their academic and healthcare systems [2]. The majority of the lecturers and university administrators we met during our time in Fiji were male, and male authors contribute five times more than female authors in research conducted by Fijians [11]. In saying this, the 'Learning Evidence-based Medicine and Research in Unison' program developed by Friends4Fiji has seen an equal number of male and female students from UPSM engage with research, and many students, both male and female, spoke of a desire to develop research skills. Within the wider health workforce, 95% of nurses are female, and despite the medical student ratio observed, two thirds of doctors are male [5]. Community health workers, poorly paid basic healthcare workers in rural village areas, are likewise predominantly female [11]. In the specialty field, however, it seems that change is occurring, with almost 40% of graduate specialists being female, and gender having little impact on decisions to resign [3]. Furthermore, the high number of female medical students may represent an exciting

potential shift towards a more equitable future for Fijian women. The student response to our teaching by the end of the week was particularly rewarding. In a program of didactic teaching delivered by male academics, female students expressed being inspired to think of themselves as future educators and academics.

Fiji is a nation of two major ethnic groups; ethnic Fijians make up 57% of the population, and Indo-Fijians make up 37% of the population [2]. Something neither of us anticipated was the emphasis placed on race within the health system, where one of the key characteristics identified on each patient profile is the ethnicity of the patient: Fijian, Indo-Fijian, or other. One of the reasons cited to explain this is the differing epidemiological profiles of the two groups, with ethnic Fijians more likely to contract infectious diseases, and Indo-Fijians more likely to have ongoing non-communicable diseases, particularly cardiovascular disease [2]. However, a number of other key differentiating features have been identified within not only the wider population but also the health workforce, and it was clear that racial differentiation was a part of their culture. Within the wider community, mental health outcomes are far worse among Indo-Fijians, with a suicide rate of 24 per 100,000 compared to four per 100,000 per annum for ethnic Fijians [2]. Within the health workforce, there has been significant Indo-Fijian emigration, with much of this being attributed to the political coup in 2000 against the first Indo-Fijian Prime Minister, leading to disillusionment and ongoing concerns among Indo-Fijian doctors [3]. Conversely, among Fijian researchers, Indo-Fijians contributed more than ethnic Fijians (58% versus 40%) [11]. We observed this racial differentiation in all hospital relationships - patient to patient, doctor to patient, and doctor to doctor - as well as in the education setting. It was much more pronounced than it would be in Australia, and again it was something we needed to learn to adjust to during our stay.

Despite the brevity of our stay, we gained a profound insight into healthcare delivery in an under-resourced setting. We were extremely fortunate to have our stay facilitated by a dedicated group of medical students through the Friends4Fiji committee, and we made lasting friendships that have helped to solidify and grow our partnership. It was a challenging, but valuable, experience to be thrust into a position of responsibility that we had not yet encountered as clinical students in Australia. While on placement in Fiji, we were actively making medical decisions in consultation with our supervising doctor. We came to admire the Fijian students who, despite the challenges of their medical education, are thrust into a role of critical responsibility much earlier than in our program. To be able to apply the knowledge we have gained in our studies and also make a difference in patient care was extremely rewarding. Gaining insights into the lives of these students and seeing the issues facing their nation through their eyes was a unique experience. Given all we gained through this experience, it was extremely rewarding to also be able to help fulfil a need for further anatomy teaching, guided by our dedicated and supportive lecturer, Dr Michelle Lazarus. We also hope to engage the students in joint research projects, furthering our knowledge and developing our evidence-based medicine skills together. Our hope is to continue to grow this partnership between our two universities by fostering relationships between medical students and creating opportunities for student exchange.

Conflicts of interest

None declared.

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Medscape and iPhone apps: The stethoscope of the 21st-century medical student? App review

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Sam is in his fourth year at James Cook University and somehow enjoying the workload. He is passionate about rural and tropical health, especially finding a way to integrate new technology into clinical practice.

To many medical students, the ability of consultants to recall the pathogenesis of a rare condition or the dosing schedules for a myriad of medications seems unattainable. This feeling is further emphasised when we are confronted with patient questions that can make us feel grossly underqualified. If only there was a way to carry our library of textbooks into the clinic for quick consultation! Enter Medscape: a free app for iPhone, iPad and Android devices. Medscape's comprehensive features may be an invaluable tool, whether it is in the clinic, writing assignments, or as a study aid for exams.

The Medscape application has a number of features that make it unique compared to other medical apps (Table 1). Primarily, it is a free application. All information is peer-reviewed, and in an easy to read format that is available both on- and offline. Another advantage is that the Medscape app covers a broad range of topics, providing a range of detailed information for almost every clinical scenario (Figure 1). The categories covered include:

Drugs: A comprehensive list of pharmacotherapies, including prescription, over-the-counter, and alternative medications (Figure 2). For every medication listed, the app provides the generic and commercial names, dosage and indications, administration, adverse effects, warnings, pregnancy information, basic pharmacology and pharmacokinetics, images, and formulary.

Conditions: Medscape provides detailed information about a wide range of conditions, from allergic asthma to Zollinger-Ellison syndrome. Each condition is divided into the following sections: overview, clinical presentation, differential diagnosis, work-up, treatment and management, and follow-up (Figure 3). Over 1,000 conditions are included within the application, however it is important to note that this list is not exhaustive, as some rarer conditions are not covered. Overall, however, using this section for any disease is more than sufficient information for a medical student or junior doctor level.

Procedures: A list of many procedures listed by specialty as well as a large atlas of anatomy is included (Figure 4). Articles do however primarily use text to transmit information. Topics such as these may benefit more from greater use of visual adjuncts and illustrations.

Drug Interaction Checker: This tool allows the user to add up to 30 medications concurrently and view the subsequent potential interactions that may occur between these medications. This tool will prove useful when assessing older patients, or those with multiple co-morbidities who are often subject to polypharmacy, to check for interactions.

Pill Identifier: A tool that allows the user to input information about a medication's appearance (shape, colour, etc.), and generate a list of possible medications that match the description. While in theory this

Table 1. *Summary of Medscape features.*

Feature	Pro	Con
Drugs	Detailed monographs on thousands of drugs	Pharmacology section can be too brief for beginning medical students
Conditions	Contains detailed information for over 4,400 conditions Begins with summary page for quick access Details each condition from aetiology to treatment and prevention Offline access	Very detailed; information can be difficult to absorb "on the go" Arranged by specialty, so some background knowledge is needed to find the condition
Procedures	Highly detailed descriptions of thousands of procedures	
Drug Interaction Checker	Can show interactions of 30 different medications at a time	Shows all interactions, including minor interactions that do not require attention
Pill Identifier	Can be used for patients unaware of medication names	Highly U.S. focused Only works online
Calculator	Over 130 calculators Integrated with 600 drugs for dosage calculations	
Formulary	-	Of no real use in Australian medical practice Only available online
Directory	-	Of no real use in Australian medical practice Only available online

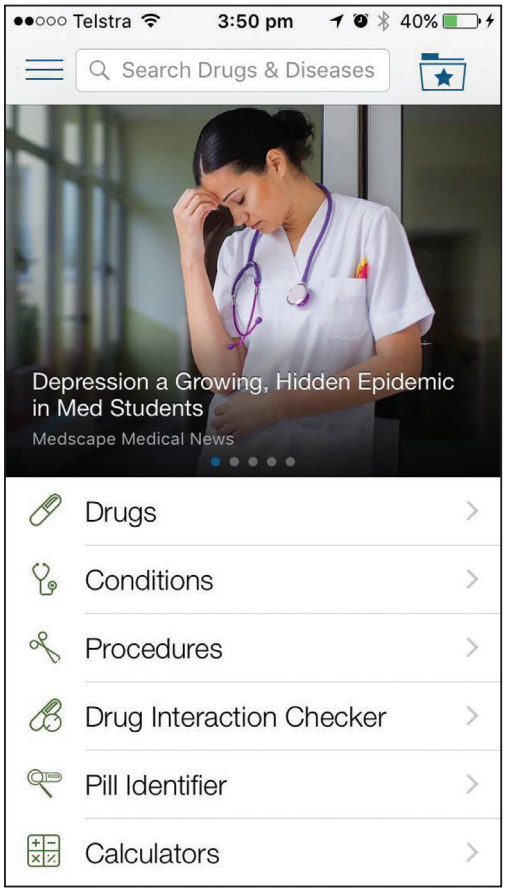

***Figure 1**. Home page of Medscape app, displaying a current news story and available sections.*

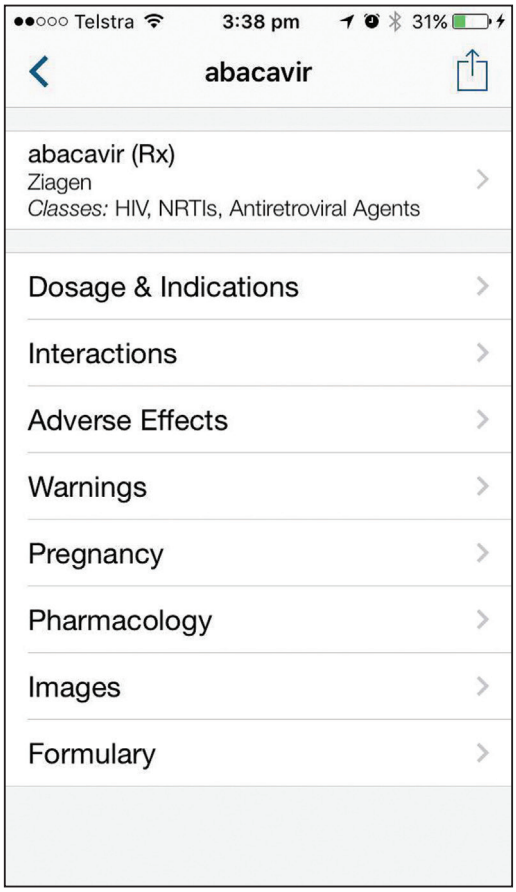

***Figure 2**. Example from "Drugs" section displaying available features.*

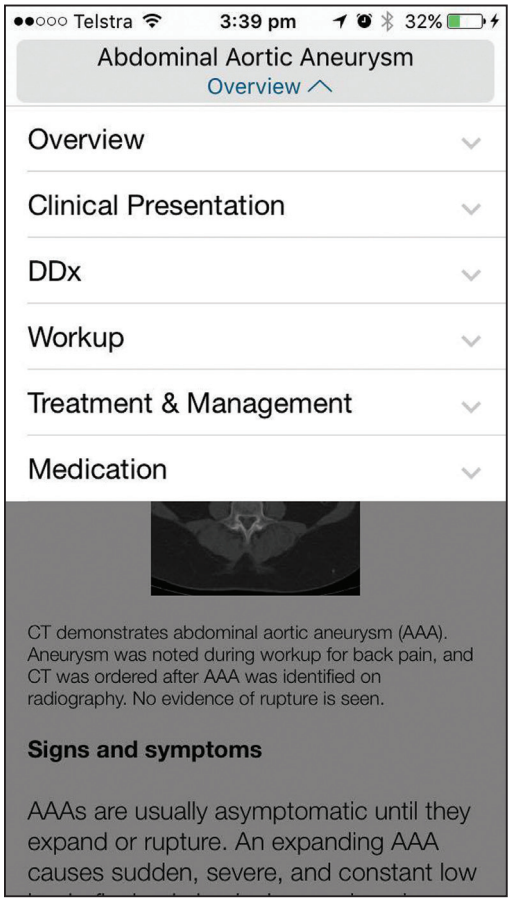

***Figure 3**. Example from "Diseases & Conditions" showing available features.*

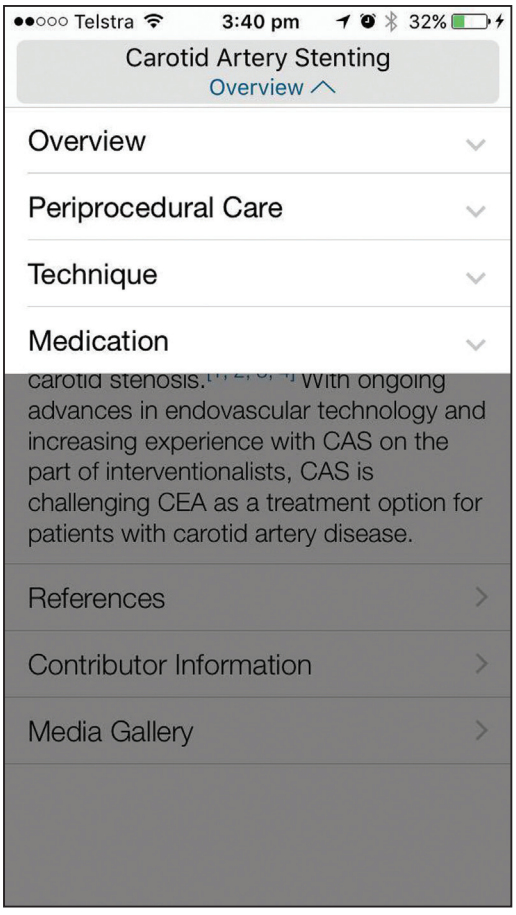

***Figure 4**. Example from "Procedures" section, displaying available features.*

could be a useful tool for patients who cannot remember the name of their medication, in practice it is not particularly accurate, and customised towards medications available in the USA. As such, this tool appears to have limited utility in an Australian setting. For example, searching for features of Panadol capsules leads one to a page of 500 possible medications, none of which are the drug in question.

Calculators: Over 150 medical calculators and clinical decision-making scores (e.g. Glasgow Coma Scale, Warfarin Bleeding Risk, Framingham Risk Score, etc.) are provided, arranged by specialty. This section is ideal for quick calculations when a computer is not available: for example, when calculating a patient's renal function to see if they are contraindicated for a pharmacotherapy.

Formulary: The formulary tab on this app is designed to provide clinicians with a reference of which medications are subsidised at their hospital or state. However, as the app is designed to suit the USA market, this feature is not applicable in Australia.

Directory: This section provides a directory that lists nearby hospitals and specialists according to GPS location of the mobile device. However, this is another feature designed for the American market and thus has serious compatibility issues for Australian users.

Conclusion

The Medscape mobile application is not perfect. As of version 5.5 it remains U.S.-centric, rendering features such as the drug formulary, directory, and pill identifier almost useless for Australian medical students and clinicians, which is a major drawback. I have also found that suggested dosing regimes can differ from Australian standards, as per the Australian Therapeutic Guidelines. Finally, by extension, Australian names of commercial medications are not listed. Aside from this, the drug pharmacology section can be very brief, so it may be more suitable for a refresher rather than learning drugs primarily through the app.

Overall, however, I have found that this app can be a fantastic tool for a medical student to have in a clinical setting, or as a reference tool for studying, and acts as far more than just a medical encyclopaedia. It is especially suited to those who wish to brush up on conditions already learned, or to extend their learning. All features other than images and pill identification are available offline, which may be useful in areas where internet access is limited, such as the clinic. The app works smoothly, and is well laid out and easy to navigate. The app manages the delicate balance between not enough information and too much irrelevant information very well when compared to similar medical applications available on smart devices, making it indispensible to any student anticipating some difficult patient or consultant questions.

In the digital age, our patients expect the medical fraternity, and by extension, medical students, to be more knowledgeable than ever. As such, in the author's opinion, this app is a fantastic way to provide additional information, and may help students and clinicians alike to provide better patient care.

Conflicts of interest

None declared.

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Australasian Students' Surgical Association

Launch and leadership day – event report

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On Saturday, 18 March 2017, the Australasian Students' Surgical Association executive hosted the inaugural launch and leadership day at the Royal Australasian College of Surgeons, Queensland headquarters. The day hosted twenty-two medical student representatives across Australia and New Zealand, including surgical society presidents and committee members.

The program included two keynote presentations from Doctor John Quinn and Doctor Richard Lewandowski, both internationally and domestically renowned surgeons who are based in Brisbane.

Doctor Quinn, the first Vascular Surgeon trained in Australia and the Executive Director of Surgical Affairs for the Royal Australasian College of Surgeons delivered an informative session on the requirements for acceptance into surgical training pathways. His talk was particularly useful as he kindly answered many questions from students about selection criteria and the variety of opportunities medical students and junior doctors can pursue to increase their chance as prospective applicants in future years.

Doctor Lewandowski, an esteemed plastic and reconstructive surgeon and the Co-Founder of Operation Smile, gave an eye opening discussion about the opportunities of philanthropic work outside the constraints of domestic practice. His stories and photographs of patients he's worked with overseas were inspirational, and gave students an insight into the wide possibilities of surgical training.

Following the keynote presentations, a "RACS Specialties" panel session was hosted, with a fantastic range of local surgeons:

- Doctor John Quinn, vascular surgeon;
- Doctor Richard Lewandowski, plastics and reconstructive surgeon;
- Doctor Rosslyn Walker, paediatric surgeon;
- Doctor Carina Chow, colorectal surgeon;
- Doctor Rumal Jayalath, neurosurgeon;
- Doctor Grant Fraser-Kirk, plastics and reconstructive surgeon; and
- Doctor Damian Fry, general surgeon trainee and RACSTA representative

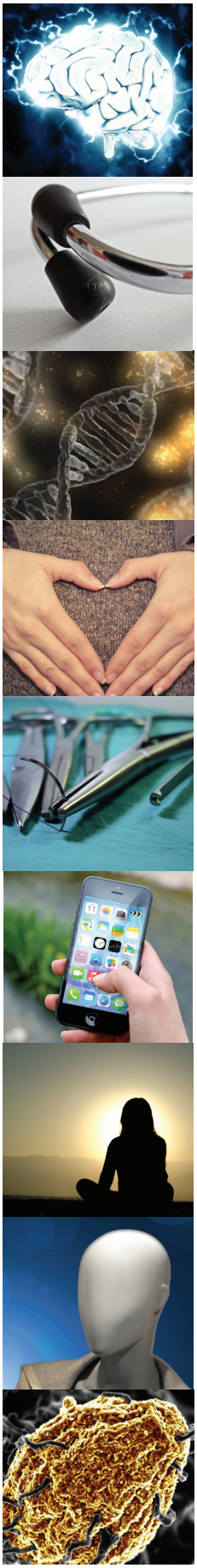
We are so thankful for these wonderful surgeons on so kindly giving up their time to provide such an insightful discussion about topics including choice of specialist training, pathway selection process and the expansion and development of surgical careers. The students found this session particularly beneficial and were grateful for the surgeons kindly answering their questions.

The afternoon comprised of four workshops, aimed at providing the student representatives with skills to assist them in working to improve their university student society to provide education and resources for students to develop a pre-vocational interest in surgery. These workshops included:

- Mr Allan Mason, from Encore Accounting who spoke about budgeting for surgical societies and personal finances through training years;
- Mrs Jane Clark, a Senior Marking Consultant for VIE Marketing, who ran a practical session on skills to improve advertisement of surgical societies to engage students;
- ASSA workshop covering leadership scenarios, an overview of the upcoming Australasian Students' Surgical Conference (ASSC);
- ASSA strategic planning session, allowing students to collectively brainstorm beneficial resources for surgical societies, including the academic portfolio, as run by Cameron Wells on the ASSA executive.

On behalf of the Australasian Students' Surgical Association executive, I would like to thank Thalia Nguyen, the Administrative Officer for the RACS Queensland office for her guidance in facilitating the launch. We are very grateful for ongoing support from the attending surgeons, and thank them for so kindly giving up their time to provide such insight to the medical student representatives and the executive.

Finally, I'd personally like to thank the current executive team for so diligently working to create this launch, and I hope this initiative is continued and expanded in future years.



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