Debate & Analysis

Why evidence still matters to general practice:

James Mackenzie Lecture 2019

INTRODUCTION

When Sir James Mackenzie moved back from London to St Andrews to establish the Institute of Clinical Research in 1919, he was given an opportunity to reflect on his research and explain why a clinical research institute was needed. In his address delivered at the opening of the Institute and in other publications,[1,2] Mackenzie outlined the simultaneous importance of clinical observation: building an evidence base for diagnosis, prognosis, and therapeutic advances; and establishing a systematic approach to clinical care. In this Mackenzie Lecture, I hope to draw parallels between these observations of Mackenzie with the ongoing importance of evidence to the clinical care of patients in primary care in the 21st century. My aim is to illustrate why evidence still matters to clinical general practice using examples that address the domains of diagnosis and prognosis, as well as a critical examination of the risks and benefits of drug therapy. Though these examples are contemporary, Mackenzie's observations in relation to the clinical and methodological issues are prescient and relevant to 21st-century clinical practice.

INTEGRATION WITH PATIENTS' DECISION MAKING

Mackenzie understood that researchers should be clear in both their research question and the methods they employ to carry out research, saying *'those engaged in medical research should pause and consider what they are doing … and be certain that their methods are suited to their purpose'*. In this observation, Mackenzie showed considerable foresight in relation to the significant methodological and analytical advances in research methods that have occurred since his time.[3] Most particularly there has been the establishment of evidence-based medicine (EBM) in the application of clinical epidemiology to patient care.[4] These methodological considerations by Mackenzie are the forerunner in relation to the array of study designs that address important clinical domains in relation to aetiological, diagnostic, prognostic, and therapeutic research. EBM provides a framework that acknowledges the inherent biases that are a threat to the internal validity of observational research and proposes solutions in terms of analyses that utilise multivariable regression to account for bias and confounding. Furthermore, in terms of experimental study designs, particularly the randomised controlled trial (RCT), proposals that enhance analysis and reporting of RCTs are now a requirement for researchers who hope to publish in high-standard medical journals. Standardised reporting of observational and experimental clinical research has been a vital ingredient in enhancing the validity and transparency of clinical research.[5]

To give a clinical example, incorporating patient preferences in terms of individual choice and cost in the 2019 UK National Institute for Health and Care Excellence clinical practice guidelines for high blood pressure has been the subject of comment, with a *Lancet* editorial stating that lowering the threshold for drug treatment initiation would have shown 'true grit'. Research we conducted in this clinical area has shown that things are not so simple. While a decision aid that formally incorporates patient preferences and combines individualised prognostic cardiovascular risk can enhance knowledge and reduce decisional conflict, the end result was that a similar proportion of patients decided to take blood pressure-lowering drugs. Indeed, we found that patients when faced with this real-life decision were seldom conventionally rational in their decision making, with nearly half of those patients making a treatment choice that was at odds with the quantified treatment choice recommended by the decision aid.[6] In addition, at a health policy level, treatment of 'high-risk' patients is both cost-effective and clinically effective. For patients at lower cardiovascular risk, the health policy decision remains a willingness-to-pay dilemma in terms of marginal cost-effectiveness of blood pressure-lowering drugs.[7] This discordance between recommendations from clinical practice guidelines for lower-risk patients and what these patients may or may not wish to do themselves has been shown in other clinical conditions such as atrial fibrillation.[8] Indeed preferences of patients may well be a significant component in relation to 'therapeutic inertia' where initiation and intensification of preventive therapies involve patients in the consideration of the trade-offs in risks and benefits of drugs.[9] These studies illustrate that a strong methodological approach can be taken in real-life clinical settings but that research outputs may not be what are anticipated by clinical researchers, and may reflect variable preferences among patients who are taking part in research, echoing the realism of clinical practice, an experience that Mackenzie was familiar with.[1]

IMPORTANCE OF CLINICAL OBSERVATION

Mackenzie had a clear perspective on the importance of clinical observation, saying *'opportunity must be had of seeing disease from its onset until its end … out of the mass of symptoms those that are essential only are recorded'*.[1] In this quotation, we can see that Mackenzie had a keen sense of understanding that some symptoms carry greater diagnostic weight than others when considering likely leading target conditions such as cancer, heart disease, or infection. The modern, evidence-based approach that is equivalent to Mackenzie's thinking is in the production and use of clinical prediction rules. These are formal rules that quantify the contribution of history, examination, and diagnostic test findings, stratify a patient's probability of having a target disorder, and may recommend a 'decision' that may encompass a further diagnostic test, treatment, or referral.

Mackenzie wrote about the diagnostic dilemma of appendicitis: *'if we take a common complaint like appendicitis, there are certain signs which are held to indicate the presence of disease … when only a few of the symptoms are present, appendicitis may simulate numerous other conditions'*.[2] Our own work in relation to the Alvarado clinical prediction rule for appendicitis shows that validation of the rule holds for men, but there is a systematic over-prediction in relation to children and women.[10] This finding continues to have important implications in terms of referral threshold and operative decision making, with women more than twice as likely to undergo surgery compared with men, with the removal of a histologically normal appendix being the end result.[11] We have followed on this work by developing a register of clinical prediction rules that are relevant in primary care settings,[12] anticipating that these rules are going to become more commonly used in future clinical practice.

SYSTEMATIC APPROACH TO CLINICAL CARE

Throughout his clinical academic career in both England and Scotland, Mackenzie advocated an organised, systematic approach to the care of patients and the examination of clinical outcomes, emphasising that *'the real purpose of record-taking is to relate the life-*

history of disease … so that the signs which reveal the disease and show its progress … indicate danger can be recognized'.[13] We have now reached a stage where electronic health records, particularly in relation to prescribing and hospital activity, have become an essential component of EBM that seeks to assess appropriateness of care and reduce unwarranted medical practice variation. Championed by Wennberg and other US academics, many developed countries now have health atlases that examine domains of medical practice variation.[14] Scrutiny of underuse of effective care (clinical situations where interventions for which benefits far outweigh the risks) alongside examination of variation and potential overuse in preference-sensitive (more than one accepted treatment available) and supply-sensitive (clinical activities determined by the capacity of the local healthcare system) care shows that the rational use of evidence-based interventions enables safe, cost-effective care.[14]

Our research group has a particular interest in medical practice variation in the context of a prescription drug's appropriateness and safety. The volume and quantity of drugs prescribed to patients is increasing steadily.[15] Though bringing many benefits, polypharmacy can also produce substantial iatrogenic harm.[16] We have been able to examine how metrics of drug safety and appropriateness strongly relate to treatment burden in terms of polypharmacy.[17,18] In addition, systematisation of prescribing has enabled greater recognition of the potential harms of interacting drugs such as alcohol;[19] while coprescribing of other prescription drugs and periods of treatment transition for 'high-risk' drugs such as methadone are strongly associated with adverse outcomes including mortality for patients.[20] This systematisation of prescribing practice is a 21st-century equivalent of documenting clinical care for the purposes of using evidence to examine and critically reflect on patient outcome, a process that Mackenzie pioneered in his time.[13] We have also been able to utilise computer-based clinical decision support for prescribing practice as an intervention that seeks to complement academic detailing with a pharmacist with the aim to reduce potentially inappropriate prescribing. This 21st-century adjunct to systematic prescribing practice did reduce prescribing of some classes of potentially inappropriate drugs such as maximum-dose proton pump inhibitors, but for other drugs such as extended prescription of benzodiazepines it proved insufficient to change prescribing practice.[21] Again, these disappointments in the outputs of research are issues that Mackenzie highlighted and reported in a pragmatic way.[1]

CONCLUSION

In his clinical and research activities, Mackenzie pioneered a systematic approach to clinical care that enabled careful clinical observation and follow-up of patients. Such an approach produces what we now know as clinical evidence that relates to aetiology, diagnosis, prognosis, treatment, and harm for patients. The structures that Mackenzie proposed to support this systematic approach are the forerunners of what is now seen as key ingredients to clinical and research infrastructure: electronic coding of disease and illness alongside diagnostic (laboratory and radiological) and therapeutic (prescribing) practice. The clinical evidence that these systems produce are the cornerstone of rational, patient-centred care. I hope that I have convinced you that these 21st-century approaches to the generation and use of evidence in clinical care would have met with approval from James Mackenzie.

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Provenance
Freely submitted; not externally peer reviewed.

This text is based on the James Mackenzie Lecture, given in London on 22 November 2019. A video of the lecture is available at: https://www.youtube.com/watch?v=nCUQV0BhSfQ

DOI: https://doi.org/10.3399/bjgp20X709241

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