Clinical guidelines: what happens when people have multiple conditions?

Elinor Millar, Anthony Dowell, Ross Lawrenson, Dee Mangin, Diana Sarfati

ABSTRACT

More people now live with multimorbidity than with a single long-term condition. Despite this, clinical guidelines remain focused on the management of individual conditions. When the treatment recommendations from multiple different disease-specific guidelines are combined for one individual it frequently leads to interactions between treatments, along with a high burden of treatment for patients. It is also recognised that people with multimorbidity are often excluded from the trials that generate the underlying evidence for these guidelines, and that treatment goals from guidelines often fail to align with patient goals.

This viewpoint discusses the main issues with applying disease-specific guidelines to individuals with multiple long-term conditions, and presents a set of eight recommendations to improve care for people with multimorbidity in New Zealand.

Multimorbidity (the coexistence of more than one long-term condition) is now the norm among those with long-term conditions, with more people living with multiple conditions than with a single one.[1] Multimorbidity is associated with decreased quality of life, high healthcare burden, high healthcare costs, and is contributing to ethnic health inequality in New Zealand.[2–4]

In contrast to this, research and healthcare, particularly that outside of primary care, has become increasingly sub-specialised, with ever more technical treatments for individual conditions.[5] Worldwide there is a focus on quality improvement and evidence-based practice, and in some jurisdictions incentives for care in the form of pay-for-performance.[6] Both clinicians and policy makers look to evidence-based clinical guidelines to improve the quality of care delivered to patients, ensure consistent care across populations and to best utilise limited resources.

But what happens if clinicians apply multiple clinical guidelines to an individual with multiple long-term conditions? Does this result in high-quality care and the optimisation of resources? Clinical guidelines, in line with research, usually focus on the diagnosis and management of a single disease. There is growing concern among GPs that applying the recommendations from multiple clinical guidelines to a single patient with multimorbidity is neither "desirable nor feasible."[7,8]

The scenario

Imagine you are a GP caring for a 72-year-old woman with diabetes, hypertension, osteoporosis, COPD and depression. Her cardiovascular risk is calculated as 10–20%, she has a BMI of 35 and is a current smoker. You diligently review the clinical guidelines to ensure you are providing her with 'optimal' care. If the clinical guidelines were followed for each individual condition, the resulting treatment regime is outlined in Table 1.

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Table 1: Treatment regime for hypothetical patient with diabetes, hypertension, osteoporosis, COPD, depression and moderate cardiovascular risk.

Lifestyle modifications
• Healthy eating
• Weight reduction
• Physical activity
• Other lifestyle modification specifically for depression, eg, sleep hygiene, participating in meaningful work
• Smoking cessation
Medications
• Metformin
• Sulphonylurea
• LAMA/LABA
• Antidepressant
• ACE inhibitor
• Simvastatin
• Vitamin D
• Calcium
• Bisphosphonate
Other health professionals
• Diabetes nurse
• Respiratory nurse
• Dietician
• Respiratory physio/pulmonary rehabilitation programme
• CBT/counselling
Follow up
• Every 3–6 months
• Blood tests
• Annual flu vaccination
• Retinal screening
• Foot screening
• Renal screening
• Other screening programs

The problem

Clinical practice guidelines do not usually address the balance between benefit and harms of treatment recommendations for people with more than one condition. This can lead to four key problems:

Interactions

When treated 'by-the-book', multimorbidity very quickly leads to polypharmacy. One of the most immediate and obvious concerns is the possibility of drug-drug or drug-disease interactions. The treatment regime for our hypothetical patient results in one theoretical drug-drug interaction; however, the interactions will vary depending on the conditions in question.

When researchers reviewed each of the UK National Institute of Health and Care Excellence (NICE) clinical guidelines for type 2 diabetes, heart failure and depression in relation to 11 other common long-term conditions, they found several significant drug-drug interactions if the guidelines were followed, including risk of bleeding, CNS toxicity and renal associated harm. Approximately 20% of the identified interactions involved a drug recommended as first line treatment, with very few of the interactions highlighted in the guideline of the index condition. [9]

The concern around interactions and adverse events has been raised by GPs as a problem in utilising clinical guidelines for people with multimorbidity.[10,11] There is also the added challenge of figuring out the significance of each reported interaction, both in terms of the severity of the interaction, the likelihood of the interaction occurring and the source and validity of the evidence underlying both.

Burden of treatment

"*Advances in diagnosis and treatment have the paradoxical effect of adding incrementally to the work of being sick*."[12]

As well as the obvious interactions between treatments, there is also the issue of the burden of multiple treatments, which can be high for patients with multimorbidity.[13,14] This is clear in our hypothetical patient; along with the complex medication regime, they will also receive—likely repeatedly—advice on lifestyle modifications, have multiple health professionals to see, and several follow-up appointments to schedule.

A US study looked at six of the most prevalent long-term conditions in primary care and found that, depending on the combination of conditions, patients with three long-term conditions (who adhere to all of the most recent US clinical practice guidelines) would have to take between six and 13 medications per day and spend an average of 50–70 hours a month on health-related activities.[15] This burden of treatment, along with the burden of illness itself, is unmanageable for many people and frequently

leads to patients with multimorbidity prioritising their conditions and management.[16,17]

Patients, carers and their health professionals often have differing views about how and what to prioritise.[18,19] Treatment prioritisation is complicated even further when patients have to see multiple specialists, where each specialty operates independently and with each specialty prioritising their own organ system. Patients are often landed with the additional burden of being the default communicator between different clinicians. Healthcare providers need to collectively focus on matching the burden of treatment with patient's capacity to cope, and current clinical guidelines are antithetical to this.[12] Despite the prevailing rhetoric of accounting for patient priorities, there are few tools to assist with this for patients with multimorbidity.[20]

Level of evidence in patients with multimorbidity

Assuming medication interactions are avoided, and that a treatment regime has been agreed upon, what is the evidence that the advice in guidelines will improve outcomes for the multimorbid patient? Unfortunately, the evidence is lacking.

Clinical guidelines generally present the highest quality evidence relating to a particular condition. However, patients with multimorbidity and older adults are often excluded from the clinical trials that provide this evidence.[21–24] One study found that patients with comorbidities were excluded from 81% of randomised controlled trials published in high-impact journals.[25] Clinical trials also frequently recruit from secondary care and are limited to people with severe disease, which means that the reported benefit is likely to be greater than the benefit seen for those with milder disease.[26] This all means that clinical guidelines are often based on evidence of uncertain relevance to real patients in primary care.[27]

In the limited proportion of trials that do include people with multimorbidity, there is generally poor reporting on the prevalence of comorbidities and inadequate power and/or lack of pre-specified subgroup analysis to accurately distinguish how multimorbidity modifies the treatment effect.[21] Having comorbid conditions may significantly reduce the benefit suggested by trial results.[28,29] How best to apply 'average' trial results, made up of different benefits to individuals, especially to multimorbid patients with high competing risk, is an ongoing challenge.[30,31]

A second issue is that even if the individual recommendations in a clinical guideline are rational and evidence-based, that does not mean that the sum of benefits of multiple different recommendations are either linearly additive or effective.[32] Clinical guidelines do not currently take into account the cumulative impact of treatment recommendations, or of the cumulative harms of treatment.[33]

All of this uncertainty leaves the GP prescribing nine medications for our theoretical patient, and they are both left wondering: how much good will these treatments do? How much harm? Without this information, their ability to formulate an effective treatment regime is exceptionally challenging.

Targets/outcomes

The GP of our hypothetical patient also wonders how much risk reduction there will be for the patient by following the treatment recommendations in the guidelines. And importantly a reduction in the risk of *what*? And over what time period? Is the patient's limited life expectancy taken into account? Risk often does not predict negative outcomes in older people in the same way as in younger, yet data are often extrapolated. Unfortunately, the clinical guidelines rarely take this information into account.

This is becoming an increasing concern for GPs, who recognise that guidelines frequently fail to target the outcomes which are of greatest concern to their patients, such as quality of life.[10,34] Clinical guidelines rarely discuss applicability to patients with limited life expectancy and similarly rarely recommend when to stop treatment. Uhlig et al have called this the "Disease-Life Expectancy" interaction, whereby a person's life expectancy limits the effectiveness of an intervention, eg, having end-stage COPD will change the potential benefit of cancer screening.[35]

Effectively applying clinical guidelines to the management of multimorbidity requires an understanding of the balance between short and long-term risks and goals, which is seldom discussed in clinical guidelines. It can be highly challenging to prioritise the benefits and risk for multiple treatment recommendations without knowing explicitly what outcome the treatments are aiming to achieve and what the patient's goals and priorities are. In this sense some GPs feel that guidelines overcomplicate the management of multimorbidity, and do not assist with the adaptation of risk and benefits of treatment to achieve patient's goals.[10]

The possible solutions

Although New Zealand no longer has its own clinical guidelines programme, international guidelines are adapted for use in New Zealand, and clinical management pathways are frequently being developed. Below are recommendations to improve care for people with multimorbidity.

1. Provide the appropriate information needed to practice person-focused care

Clinical judgement, which integrates research evidence with the patient's priorities and circumstances, will always be essential for making treatment decisions; however, clinical guidelines frequently fail to provide the information needed to support this process. Clinical guidelines that provide clear, summarised and comparable information on the benefits and risks of different treatments alongside the effect of no treatment would help with prioritisation of treatment recommendations for patients with multimorbidity.[10,33] This should include an indication of the magnitude of benefit, over what time period the benefits usually accrue, the numbers needed to treat (and harm) and when to consider stopping or reducing treatment.[36,37] Although this information is occasionally available in the full comprehensive version of guidelines, it is often difficult to interpret and even more difficult to compare across guidelines.

There should also be an honest account of the limits of knowledge and generalisability: what is not known, what is based on intermediate outcomes indicators only and the extent to which the literature suffers publication and other biases.[38] There also needs to be a clear explanation of the outcome that is likely to change with treatment, which will help align treatment with patient goals. Guidelines should avoid making recommendations where there is no evidence, and avoid extrapolating risk where there is no evidence.

2. High-quality evidence

The exclusion of patients with multimorbidity and older adults from every stage of guideline development is a major limiting factor in providing guidance that is appropriate for them.[39] Multimorbidity needs to stop being seen as a 'nuisance variable',[39] and rather, pragmatic trials should be designed and conducted to reflect the needs of the population and include participants with multimorbidity. This would then allow for the stratification of results by comorbidity and polypharmacy level, which would also provide information on treatment modification effect of some conditions.[40,41]

There will be challenges to doing this, including: measuring multimorbidity, difficulties in study design to maximise internal and external validity, and difficulties with heterogeneity of treatment effects and disease expression.[41] A multidisciplinary group created a comprehensive set of recommendations for addressing these challenges, including: identifying, defining, measuring and routinely reporting the within-study prevalence of common comorbid conditions and considering powering to support multimorbidity-related subgroup effects.[41]

There is an added challenge in that drug companies design trials, select the trial populations and report their results to maximise the benefit:harm ratio, and to optimise the internal validity of the study.[42] Trials are designed to extend the market to as wide a range of the population as possible rather than defining, with more precision, the groups who benefit the most. There is current effort in the US to require trials for cancer treatment to include participants that reflect the population (in terms of age and comorbidities).[43] This could be extended

to other clinical trials and could also be supported by research funding bodies, regulators and journal editors requiring trial populations to reflect the intended treatment population.[42]

There are other challenges for guideline developers, including the fact that the actual harm of many interactions (both drug-drug and drug-disease) are poorly quantified.[9] Pharmacovigilance programmes, where much information could be gathered about harms and interactions, are inadequately funded globally. Research that aims to understand and quantify these risks in the general population would be hugely valuable, and would allow patients, families and clinicians to better discuss the pros and cons of multiple different treatments.

3. Make better use of existing evidence

Clearly it will take time to create an evidence base that includes people with multimorbidity. In the meantime it may be possible to make better use of existing evidence to inform guideline development.

Firstly, clinical guidelines aimed at primary care should largely be written by GPs, who have far greater experience applying guidelines in primary care than other clinicians. A Canadian study looked at a range of national and provincial clinical guidelines and found that of the 2,495 contributors to 176 guidelines, only 423 (17%) were primary care physicians.[44] While being primarily led by GPs, having a range of expertise involved in the overall process is vital to ensure that guidelines correctly manage the interface between primary and secondary care. The HealthPathways website has been developed in this way, with pathways largely led by GPs and reviewed by subject matter experts (usually secondary care clinicians).[45] Although there is no published research on the rigour behind the development process and the subsequent recommendations, HealthPathways appears to be valued, accepted and deemed effective by primary and secondary care clinicans.[46]

Another way to better use existing evidence would be to undertake modelling that incorporates diverse patient characteristics to provide better information on benefit and harms, for example: adjusting for decreased life expectancy or taking into account the poorer physical outcomes for those with depression.[37] This concept has been utilised in response to cancer screening, whereby the time to accrue benefit is weighed up against potential harms.[35,37,47] Not all of the data needed to populate these models will be available in the literature, in which case it may require input from experienced clinicians. The usefulness of this kind of model in respect to guideline development requires further investigation.[37]

4. Explicit cross-referencing

A frequent recommendation for improving clinical guidelines for people with multimorbidity is explicit cross-referencing between guidelines for different conditions.[9,33,37,40] This is becoming increasingly common due the use of online guidelines. As well as linking to other guidelines, existing guidelines could also highlight areas of synergism or cautions/contradictions between treatment regimens and common medications.[33,37] Explicitly outlining to patients the co-benefits between treatment regimens may be an effective way of improving self-management.[19]

5. Consider specific multimorbidity guidelines

Another approach is to consider the optimal management of multimorbidity as an entity in and of itself. This approach aligns to models of care for people with long-term conditions in general (eg, Flinders Program,[48] the Stanford Chronic Disease Self-Management Program[49] and the Expert Patients Programme [50]) all of which aim to support people to better self-manage and are potentially useful for people with multimorbidity.

There is important ongoing research into the optimal management of multimorbidity. For example, the 3D study, a randomised-controlled trial based in the UK, which aims to improve the management of people with multimorbidity in the primary care setting. The study intervention is complex, and includes changes to the practice organisation, with improvement to continuity of care and replacing clinical reviews for individual conditions with patient-centred reviews with a holistic focus.[51]

The National Institute for Health and Care Excellence (NICE) has recently published a guideline specifically relating to the

clinical management of multimorbidity, which includes a comprehensive review of the current evidence. In it they emphasise the importance of an integrated and coordinated approach to care that involves an explicit assessment of the preferences and goals of treatment from the patient's perspective and careful evaluation of the potential benefits and harms of combined treatments.[52]

6. Create guidelines that address common clusters

It may be possible to create guidelines that address common combinations of conditions. Obviously having a guideline for every possible combination of conditions isn't possible or practical: 20 common long-term conditions results in 4,845 possible combinations of four long-term conditions.[53] However, it would be possible to use available literature on the clustering of conditions to prioritise guideline development.[54] This could also result in the development of guidelines that target particular risk factors shared across comorbid conditions.

7. Communication between clinicians

Experienced GPs will have their own tools and approaches for managing multimorbidity. This may include practicing patient-centred care that does not align perfectly with clinical guidelines. Unfortunately, this may be compromised when a patient is referred to subspecialist care, where the focus will likely be on 'organ-specific interventions'.[10] Patients with multimorbidity frequently experience gaps in care coordination and receive conflicting advice from clinicians.[55] In order to ensure that treatment burden, patient priorities and treatment goals are taken into account; when recommending treatment, it is vital to have clear communication between clinicians. This could include utilising information technology systems such as the Shared Care Record to document reasons medications are stopped, or noting if there is a reason a patient is not on a guideline recommended treatment, such as: "minimising treatment burden, does not align with patient goals".

8. More awareness during development process

Finally, and arguably most importantly, there needs to be more consideration of those with multimorbidity in the guideline development process. This includes the involvement of people with multimorbidity in the development process. More people have multimorbidity than a single long-term condition; guidelines need to be designed for those who are going to be using them. As well as making it an explicit objective to create a guideline that is as relevant as possible to those with multimorbidity, this may also involve considering how best to identify high-risk interactions.[9,40] Failing this, guidelines need to be more explicit about the applicability of the recommendations to patients with multimorbidity.[56]

Final comments

With all of these recommendations it is possible that the result will be overly complex guidance that is unusable. There must be a compromise between providing clear and concise treatment recommendations, and completely ignoring the complexity of patients in the real world. The heart of the original definition of evidence-based medicine is clinical judgement or phronesis, as there are always limitations to evidence, and in addition, individual decisions have to take account of patient preferences, differing individual circumstances and constraints of healthcare systems. Clinical guidelines have limitations, but the current guidance can, and should, be improved to support this process.

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Author information:
Elinor Millar, Research Fellow, Department of Public Health, University of Otago, Wellington; Tony Dowell, Professor, Department of Primary Health Care and General Practice, University of Otago, Wellington; Ross Lawrenson, Professor, University of Waikato, Hamilton; Dee Mangin, Professor, Department of Family Medicine, McMaster University, Canada; Diana Sarfati, Professor, Department of Public Health, University of Otago, Wellington.

Corresponding author:
Dr Elinor Millar, Department of Public Health, University of Otago, PO Box 7343, Wellington.
elinor.millar@otago.ac.nz

URL:
http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2018/vol-131-no-1472-23-march-2018/7530

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