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ANALYSIS

Adapting clinical guidelines to take account of multimorbidity

Care of patients with multimorbidity could be improved if new technology is used to bring together guidelines on individual conditions and tailor advice to each patient's circumstances, say **Bruce Guthrie and colleagues**

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Most people with a chronic condition have multimorbidity, but clinical guidelines almost entirely focus on single conditions. It will never be possible to have good evidence for every possible combination of conditions, but guidelines could be made more useful for people with multimorbidity if they were delivered in a format that brought together relevant recommendations for different chronic conditions and identified synergies, cautions, and outright contradictions. We highlight the problem that multimorbidity poses to clinicians and patients using guidelines for single conditions and propose ways of making them more useful for people with multimorbidity.

Guidelines and multimorbidity

Guidelines have the potential to improve the care of people with chronic disease[1] but seldom explicitly account for people with multiple conditions. This reflects the way in which clinical evidence is created but does not match everyday practice, where multimorbidity is common. The figure⇓ illustrates this using data from UK primary care electronic health records taken from a study of the prevalence of multimorbidity in 1.75 million people.[2] Most people with any chronic condition have multiple conditions, and although the degree of multimorbidity increases with age, this applies to younger patients as well, particularly those living in the most socioeconomically deprived areas, where multimorbidity develops 10-15 years earlier than in more affluent areas.[2]

Clinical decision making is more difficult in people with multimorbidity because clinicians and patients often struggle to balance the benefits and risks of multiple recommended treatments[3] and because patient preference rightly influences the application of clinical and economic evidence.[4] Robust synthesis of clinical and economic evidence produces rational guidance for individual conditions, but combining recommendations for patients with multimorbidity can result in harmful or burdensome overall treatment regimens.[5][6] Take, for an example, an older person with chronic obstructive pulmonary disease, type 2 diabetes, osteoporosis, hypertension, and osteoarthritis. When US guidelines for these conditions were examined, only one of the five explicitly acknowledged potential comorbidity, and the recommendations made were sometimes contradictory and implied a drug and self care regimen that would be unfeasible for many patients.[6] Similar problems apply to National Institute for Health and Clinical Excellence (NICE) guidelines in the UK.[7]

Polypharmacy is an important consequence of following guidelines in people with multimorbidity.[6][7] Polypharmacy can be appropriate, but it is associated with riskier prescribing[8] and is often particularly problematic in people who are physically frail or have cognitive impairment. Additionally, single disease guidelines rarely explicitly consider applicability to individuals with limited life expectancy, who are unlikely to benefit from long term preventive treatment,[4][9] and virtually never make recommendations about when chronic treatments should be stopped.

We therefore need to design new forms of clinical guidelines and evidence summaries that support informed initiation—and cessation—of treatment for chronic disease in people with multiple conditions. The main target audience is generalist clinicians with overall responsibility for a patient rather than a disease focus, but specialists also need to consider the effect of their recommendations on their patients since they will usually be being treated for other conditions.

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How can guidelines better inform treatment of people with multimorbidity?

Although similar problems arise in terms of the cumulative burden of non-pharmacological treatments, we focus on decisions about medicines for chronic conditions, since this is where the accumulation of individual disease recommendations is most problematic. We propose several ways to improve existing guidelines.

Cross reference guidelines using electronic delivery

Reflecting the way that they are created, existing guidelines require clinicians and patients to read separate documents for every condition that a patient has, and there is little cross referencing between guidelines. A notable exception is the NICE guideline on depression in adults with a chronic physical health problem, which provides advice on choice of antidepressant medicine depending on physical comorbidity and coprescribing, as well as guidance on collaborative care approaches when there is evidence that they improve physical or depression outcomes.[10]

Although cross referencing existing guidelines for all possible combinations of conditions would rapidly make them unreadable, this could be overcome by using electronic formats that present different recommendations depending on demographic and clinical information provided through screening questions (if web based) or coded data (if embedded in electronic health records).

Simple versions that only recommend treatments to consider starting, avoiding, or stopping would be potentially useful as a starting point while more complex, fully cross referenced versions are developed and tested. Such development should be informed by the patterns of comorbidity that are most common. For example, dementia is rarely a comorbidity of common physical conditions (fig 1⇓),[2] but many people with dementia have physical conditions. Cross referencing in this situation is likely to be predominantly in terms of the management of physical conditions in people with dementia. In contrast, depression and pain are common comorbidities of many other conditions, implying that most clinical guidelines should explicitly cross reference specific guidance as NICE already does for depression. Developing systematic and appropriate cross referencing is no small task, but it is only what individual clinicians are expected to do every day for individual patients.

The table⇓ shows an example of simple cross referencing of recommended chronic drug treatments for a 76 year old woman with hypertension,[11] atrial fibrillation,[12] osteoarthritis,[13] and moderately severe depression.[10] [14] Depending on response to treatment, between three and eight drugs are recommended with several important cautions and relative contraindications that should influence treatment choice. Although not the focus here, guidelines often also make lifestyle and self care recommendations that also overlap in complex ways,[6] [7] notably in this case those relating to exercise for hypertension, osteoarthritis, and depression.[10-14]

People with multimorbidity will also commonly have patterns of illness that do not neatly fit disease categories, in which case syndrome focused guidance or tools will often be relevant. If the patient described in the table was having falls, for example, then a more holistic approach that cuts across disease specific guidance would be appropriate to consider the potential contribution of both her conditions (atrial fibrillation, osteoarthritis) and her treatments (antihypertensives, drugs to control atrial fibrillation, and antidepressants).[15]

Provide guidance about treatments most likely to benefit and least likely to harm

Most clinicians use short or quick reference versions of guidelines that recommend treatments but usually give little indication of the magnitude of likely benefit, or over what period benefit accrues and when to consider stopping treatments. Although the full guidelines do describe the magnitude of expected benefit, it is usually not easy to compare the absolute benefit of different treatments, which is what doctors need to know when deciding on treatment for people taking multiple medicines or with limited life expectancy. This applies particularly to preventive treatments rather than treatments for symptoms (when an individual's response can be assessed).

Existing guidelines do not routinely summarise clinical and economic evidence in a way that makes such differences explicit, which is not helpful in tailoring treatments to an individual patient's circumstances and preferences. Consistently summarising evidence from a variety of sources and different formats is not easy, but the GRADE summaries used by the Cochrane Collaboration are an example of such a format.[16] One problem is that although relative risk reduction may be reasonably stable across populations, absolute benefit varies widely depending on an individual's baseline risk of the outcome. This makes presenting absolute estimates of benefit like number needed to treat (NNT) difficult in paper guidelines because multiple numbers need to be shown, which is likely to be confusing. Electronic guidelines that present the best information available for individual patients would help reduce the potential for information overload and confusion.

The table⇓ shows the NNT for our hypothetical patient for the two preventive drug regimens recommended. Both regimens are highly effective, but the benefits of oral anticoagulation on prevention of stroke and total mortality are greater and accrue more rapidly than treatment of hypertension with up to three drugs. In many circumstances, clinicians would recommend both, but actual treatment will vary depending on the patient's preferences; these are particularly important for treatments such as warfarin that require intensive monitoring and modification of lifestyle.[5]

Decision making therefore has to appropriately balance clinical evidence of benefit and harm, and individual preferences. Critically, both of these may change over time, with the development of ischaemic heart disease making control of hypertension relatively more important, or the development of a life limiting cancer making it less important. Providing meaningful comparative data on likely benefit and harm in an individual is not straightforward, but this is again an argument for systematically embedding what data exist in individualised guidelines to support clinicians and patients in decision making rather than providing virtually no data on comparative effectiveness as currently happens.

Make better use of existing evidence

In practice, there will often not be good evidence of benefit or harm for individual patients, either because trials systematically exclude older people and those with multimorbidity[17] [18] or because findings are not reported or made available for meta-analysis stratified by comorbidity. The underlying evidence could and should be improved by including more older people in trials[17] and by explicitly examining effectiveness in patients with common comorbidities (as trials of interventions in people

with diabetes or coronary heart disease and depression demonstrate[19]).

However, there are several ways in which existing evidence could better inform guideline recommendations. Economic modelling of benefit and harm can be modified to incorporate information about key patient characteristics and pathways of care for people with single conditions and multimorbidity. This may mean, for example, consideration of worse physical outcomes in people with comorbid depression, or accounting for reduced life expectancy in people with multimorbidity where, for example, a patient with type 2 diabetes and severe heart failure has minimal chance of receiving any benefit from very tight glycaemic control but has an immediate risk of harm from hypoglycaemia. The idea of estimating the time at which slowly accruing benefits outweigh immediate or constant rate harms has been applied to cancer screening, but to our knowledge has not been used in guideline development.[9] [20]

Some of the data required to populate these models will not be available in the published literature. In this situation, structured expert elicitation methods can be used that systematically capture expert knowledge and judgment about uncertain quantities.[21] These methods facilitate the population of an economic model when data are sparse, but it is vital that the modelling process includes an explicit measurement of the key uncertainties in the data and, ideally, uses formal methods to quantify the value of further research and inform its direction.[22] The feasibility and usefulness of these kinds of modelling approaches requires careful examination, but current approaches that largely ignore the sickest patients are clearly not optimal.

Conclusion

Clinical decision making requires judgment because evidence is imperfect, and treatment has to consider patient circumstances, preferences, and the available healthcare budget. From this perspective, guidelines will always have limitations, but existing guidelines can and should be improved as we suggest.

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Table

Table 1| Recommended medium to long term drug treatment for a 76 year old woman with hypertension, atrial fibrillation, osteoarthritis, and moderately severe depression

Condition	Recommended treatment	Example cross referencing/important drug interactions	Number needed to treat
Hypertension[11]	Target blood pressure (BP) <140/90 mm Hg:	Medicine choice has to be aligned to treatment for atrial fibrillation	Compared with placebo, 50 people need to be treated with up to three antihypertensive drugs for 4.5 years to prevent one stroke (fatal or non-fatal), and 84 people need to be treated for 4.5 years to prevent one death from any cause[23]
	Calcium channel blocker		
	+ ACE inhibitor (if BP uncontrolled)		
	+ Thiazide-like diuretic (if BP uncontrolled)	Increased risk of digoxin toxicity if diuretic induced hypokalaemia	
	+ Spironolactone or other drugs (if BP uncontrolled)	Spironolactone increases digoxin plasma concentration	
		Consider risk of falls from treatment[15]	No evidence for a tighter BP target[24]
Atrial fibrillation with high untreated ventricular rate[12]	Rate control:	Medicine choice has to be aligned to hypertension treatment	Compared with placebo, 25 people need to be treated with an oral anticoagulant for one year to prevent one stroke (ischaemic stroke is reduced, haemorrhagic increased), and 59 people need to be treated for one year to prevent one death from any cause[25]*
	β blocker or rate limiting calcium channel blocker		
	+ Digoxin if rate remains uncontrolled	Increased bleeding risk of warfarin or aspirin in combination with NSAID or SSRI	
	Prevention of stroke:		
	Oral anticoagulation		
	Aspirin if patient declines oral anticoagulation	Consider risk of falls from condition/rate control treatment[15]	
Osteoarthritis in knees and hands with moderate pain and functional limitation[13]	First line analgesia in conjunction with non-pharmacological treatments:	Increased bleeding risk of oral NSAID in combination with warfarin, aspirin or SSRI	Effectiveness can be judged by an individual's response to treatment
	Paracetamol	Oral NSAID may worsen blood pressure control	
	Topical NSAID		
	Second line analgesia if first line ineffective:	Oral NSAID carries renal risk in combination with ACE inhibitor and diuretic	
	Oral NSAID + PPI	Drug interactions with warfarin (eg, tramadol, PPI)	
	Oral opiate	Increased risk of constipation from combination of opiates and calcium channel blockers	
		Consider risk of falls from condition or opiates[15]	
Persistent moderate depression[10 14]	If unresponsive to psychosocial interventions and supportive care treat with or SSRI or alternative antidepressant if patient has particular comorbidities or is prescribed particular other medicines	Bleeding risk of SSRIs in combination with warfarin (avoid) or aspirin (caution); consider adding gastroprotection with a proton pump inhibitor	Effectiveness can be judged by an individual's response to treatment
		Hyponatraemia risk of SSRI in combination with diuretics	

ACE=angiotensin converting enzyme; NSAID= non-steroidal anti-inflammatory drug; SSRI= selective serotonin reuptake inhibitor; PPI=proton pump inhibitor.

*Assumes annual stroke risk of 4% based on $CHADS_2$ score of 2.

Figure
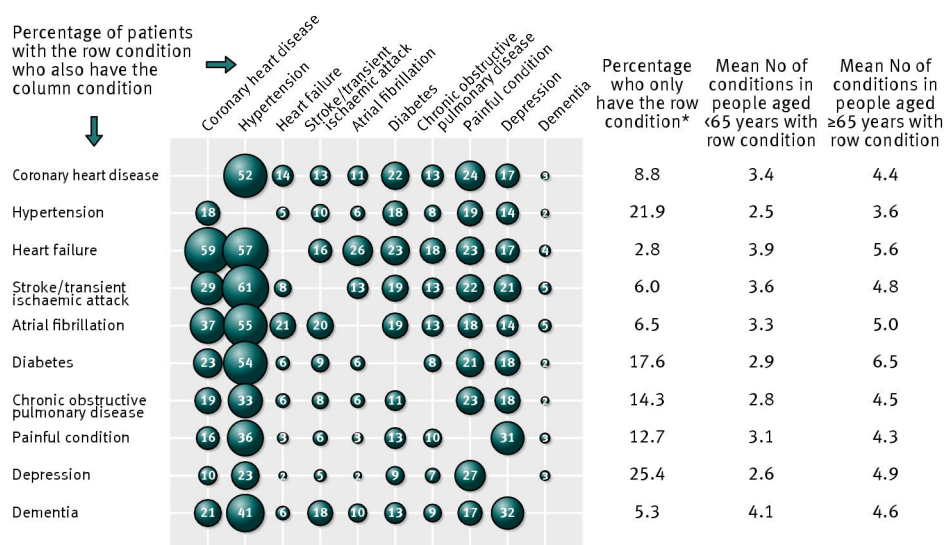
Comorbidity of 10 common conditions among UK primary care patients[2]