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EDITORIALS

Guideline recommended treatments in complex patients with multimorbidity

New evidence is reassuring, but every patient is different

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Multimorbidity is an increasing problem for both clinicians and patients. Aging populations, the increased complexity of managing chronic illness, and the tendency of guidelines to focus on a single disease have created a "perfect storm" of treatment burden. Consider the following patient: "Mrs S is a 79 year old woman with osteoporosis, osteoarthritis, type 2 diabetes mellitus, hypertension, and chronic obstructive pulmonary disease who takes 12 separate drugs in 19 doses five times during a typical day. A drug review revealed three drug-disease interactions, nine drug-drug interactions, and eight potential drug-food interactions." With this hypothetical case, a decade ago one study showed that the application of multiple guidelines to a patient with multimorbidity creates three problems[1]: firstly, as comorbidity is a common reason for exclusion in clinical trials it is not known whether treatment effects in patients with multimorbidity are equivalent to those in patients with single diseases.[2 3] Secondly, the application of multiple disease oriented guidelines bears the risks of potentially harmful interactions between diseases and treatments.[4 5] Thirdly, an uncritical application of multiple guidelines adds to the burden of treatment of patients with multimorbidity, which may exceed patients' willingness or capability to cope.[6]

In a linked paper, pioneering work by Tinetti and colleagues (doi:10.1136/bmj.h4984) tackles the first of these three problems.[7] Using three years' follow-up of population data representative of older US citizens who had at least two out of nine common chronic conditions, the authors investigated the effects on survival of nine guideline recommended and frequently prescribed drugs in older patients with multimorbidity taking multiple drugs. In line with the high prevalence of cardiovascular diseases, drugs recommended for these conditions were at the core of their analyses. In comparison with effects shown in randomised trials, the authors found a similar mortality reduction associated with four drugs (β blockers, calcium channel blockers, renin-angiotensin system blockers, and statins), variable effects with respect to comorbidity in one drug (warfarin), and a lack of effects on survival with the remaining three drugs (metformin, clopidogrel, and selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors).[7]

These findings are in line with those from previous studies. For instance, a recent individual patient data meta-analysis of large randomised trials found comparable effects of statins on major coronary and vascular events in patients with or without previous coronary heart disease, type 2 diabetes mellitus, and hypertension.[8] In observational studies, statins reduced mortality also in older and very old patients, with or without diabetes or frailty, irrespective of the presence or absence of coronary heart disease or of glucose lowering drugs.[9-11] Tinetti and colleagues' work adds another important piece of evidence: statins and other guideline recommended cardiovascular drugs seem to be effective in complex patients with multiple conditions taking a mean number of 10 drugs daily.

However, the benefits of statins are attenuated in certain subpopulations: another large meta-analysis found that they had little or no effect in people with end stage kidney disease receiving dialysis.[12] Furthermore, the effectiveness of treatment strategies may vary with age, such as treatment intensification guided by brain natriuretic peptide levels in adults with chronic heart failure. This strategy was beneficial for patients aged 60 to 75 years but not for those aged 75 years or older, which might be due to differing patterns of comorbidity.[13] Patterns may play a role when considering the generalisability of Tinetti and colleagues' results: with more than 10 000 known diseases, there are vast numbers of potential combinations within individual patients, and attempts to identify patterns (or clusters) of diseases have yielded inconsistent results.[14 15] Variability in disease patterns and severity make multimorbidity a highly heterogeneous condition. Many patients have less common diseases, which may also have an effect on treatment benefits.

Most of the medical conditions selected by Tinetti and colleagues have concordant therapeutic pathways and treatment goals. Potentially harmful interactions may occur more often in discordant coexisting conditions such as asthma and chronic heart failure. Although some patients in the study did not receive guideline recommended treatment, this may have been a doctor's

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deliberate choice rather than mere variation in practice, and this introduces the possibility of confounding. The real benefits of β blockers in heart failure could be exaggerated, for example, because some unexposed patients had comorbid asthma. These patients were unable to take β blockers[16] and at the same time had a higher mortality due to their asthma.[17]

As the authors point out, such unmeasured confounding cannot be excluded in observational studies. Since we cannot conduct randomised controlled trials evaluating treatments in all relevant combinations of comorbidities, we have to accept some uncertainty.

As discussed by Tinetti and colleagues, many questions remain about the effects of guideline recommended treatments in different patient groups with other conditions and outcomes of interest. However, the new study reassures us that treatments may be broadly as effective in patients with multimorbidity as they are in patients with single diseases, so guidelines may be safe and effective, as "we have little with which to replace them."[18] But the other two problems of interactions and treatment burden remain. We cannot assess whether a specific treatment is beneficial for a patient without considering potential interactions between diseases and treatments. We must also establish a clear understanding of each patient's circumstances, preferences, and treatment goals, along with close follow-up of goal attainment.[19] Only then will patients avoid being "left confused and even tyrannised when their clinical management is inappropriately driven by algorithmic protocols, top-down directives, and population targets."[20]

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