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EDITORIALS

Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity

A cascade of failure

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Polypharmacy, defined as the chronic co-prescription of several drugs, is often the consequence of the application of disease specific guidelines, targeting disease specific goals, to patients with multiple chronic diseases. One common consequence of polypharmacy is the high rate of adverse drug reactions, mainly from drug-drug interactions (the ability of a drug to modify the action or effect of another drug administered successively or simultaneously).[1] The risk of a drug-drug interaction in any particular patient increases with the number of co-existing diseases and the number of drugs prescribed.[2]

In a linked paper, Dumbreck and colleagues (doi:10.1136/bmj.h949) selected three clinical guidelines produced by the National Institute for Health and Care Excellence (NICE)—type 2 diabetes, heart failure, and depression—and systematically looked for possible drug-disease and drug-drug interactions in relation to another 11 NICE guidelines for potentially comorbid chronic conditions.[3] Drug-disease interactions were relatively uncommon and mostly occurred between the recommended drug and chronic kidney disease. But the authors identified many potentially serious drug-drug interactions, most of which were overlooked by the index guideline.

In general, few disease specific guidelines consider that target patients can also have other diseases, treated with other drugs. Recent guidelines for chronic illnesses such as chronic obstructive pulmonary disease (COPD), heart failure, and diabetes mellitus have attempted to account for likely comorbidities. Unfortunately, these guidelines consider only one comorbid disease at a time and provide few specific recommendations about how to manage people with multiple comorbidities.[4 5] In June 2007, the American Thoracic Society and the European Respiratory Society convened an international workshop on disease guidelines to discuss the integration of multiple comorbidities, using COPD as an index disease model.[6] Among other recommendations, researchers and guideline developers called for more research on potential interactions between a comorbidity and a drug for the index disease, between a drug for a comorbidity and a drug for the index disease, between the index disease and a drug for a comorbidity, and also between recommendations for non-pharmacological treatments.[7]

One of the biggest challenges in preventing drug-drug interactions is the substantial gap between theory and clinical practice. Despite specific regulatory pathways for drug development and marketing, we have so far failed to consider pharmacological agents in a holistic way. Drugs have a network of effects that go well beyond a single specific drug target,[8] particularly in patients with multimorbidity. Unwanted effects that are severe and unexpected can surface only during post-marketing surveillance, after many patients have potentially been harmed.

Older patients are particularly vulnerable. Prevalence of multimorbidity increases with age, along with the prevalence of polypharmacy. Advancing age is accompanied by physiological changes in the pharmacokinetics and pharmacodynamics of several drugs that might increase the risk of drug-drug interactions. Finally, older people are still under-represented in guidelines and in the studies on which these guidelines are based.

In every stratum of the population, under-reporting of adverse events from drug-drug interactions means we have little idea of their true prevalence and clinical impact. The European Medicines Agency has already suggested that "spontaneous reports of adverse events can be used to identify patterns of drug-disease and drug-drug interactions that were not apparent before authorization of the drug."[9] Better education for both patients and doctors about the importance of reporting these events is urgently required.

Drugs can also interact with genes, and we have barely touched on the potential for an additive effect between drug-drug interactions and genetic factors. Clopidogrel is a good example of a drug with a genetically variable therapeutic effect. If a genetically poor metaboliser (with lower bioavailability of active drug) is co-prescribed a proton pump inhibitor, which further

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reduces the therapeutic effect of clopidogrel, vascular risk increases in an unpredictable way.[10]

How should doctors manage patients with multiple diseases to help to prevent a cascade of problems that starts with inadequate guidelines and moves through polypharmacy to an increased risk of drug-drug interactions? A multifaceted approach is required that views the patient holistically and uses the available tools more effectively and in a more integrated way.

Firstly, each patient needs a comprehensive assessment with a view to developing (together) a personalised therapeutic regimen that balances benefits and harms and takes full account of the patient's priorities and preferences. The same assessment needs to consider the many factors that can influence a drug's effectiveness, beyond the narrow efficacy that underpins disease specific guidelines. In older patients, these factors could include cognitive and functional impairment, and lack of social support.[11]

Secondly, doctors should have the support of properly evaluated and integrated technologies. Potential drug-drug interactions across all possible combinations of chronic disease are too numerous for doctors to remember or for guidelines to mention. We know that good computerised prescription support tools can alert doctors to potential problems efficiently, helping to improve prescribing and reduce interactions.[12]

Guideline developers might also explore the potential of adaptive electronic based guidelines that allow interactive searching for specific conditions. One team is developing on-line tools to create multi-layered interactive guidelines that are updated automatically, integrate with decision support tools, and can be used on tablets and smartphones. The new format would allow doctors to access several guidelines at once and interrogate them using structured questions.[13]

More research is needed to make guidelines effective and safe for patients with multimorbidity. In the meantime, new electronic tools, better use of old ones, and comprehensive assessments of patients will help doctors to optimise drug treatments by processing all the available information about each patient's diseases, drugs, and characteristics. For this group of vulnerable patients, doing the right thing could be better than doing the thing right.

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