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Pharmacology applied to geriatric medicine

Older patients, multiple comorbidities, polymedication... should we treat everything?

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ABSTRACT

In this narrative review, options for guiding medical decision-making in the care of elderly patients with multiple coexisting chronic diseases are discussed. Although older adults form a heterogeneous group, many seniors present with moderate to severe functional impairment, complex biomedical or psychosocial conditions and frailty. Multiple comorbidities are a frequent occurrence, leading to polymedication and an increased risk of iatrogenic disease. Recognizing the interactive and dynamic nature of these multiple concomitant conditions introduces complexity into the evaluation of the risk-benefit ratio of available therapies. Therapeutic guidelines for single disease entities do not usually account for possible multimorbidity. Sophisticated modeling of the dynamic nature of multiple comorbidities, drug-disease and drug-drug interactions, and their effect on the response to healthcare, are being published and will be helpful in deciding what should be treated and how. Furthermore, patient values, engagements and concerns should enter the medical decision-making process to ensure that the chosen therapeutic strategy is coherent, appropriate and likely to be followed.

1. Older patients

In developed countries, a growing segment of the population is very elderly (> 85 years). Although a heterogeneous group, some individuals of this age present with moderate to severe functional impairment, complex biomedical or psychosocial conditions and frailty, a state of ill health which compromises the physical ability to respond to stress [1]. Frailty is associated with an increased risk for multiple adverse health-related outcomes. Frailty, like Brownian movements, has been modeled mathematically as a stochastic process. Basically, this implies that it is a complex and dynamic process. For geriatricians, frailty signals "storm ahead"; in such patients, any medical intervention will carry a higher risk. With gradual loss of functional reserve and growing deficits, many older adults present with "geriatric syndromes", such as falls or acute confusion, and present a gradual loss of higher order functions (cognition, upright stature and mobility, continence). Many require palliative or end-of-life care. To ensure that treatment options will be beneficial, a broad view of the problems at hand and a holistic approach to health care is required [2].

2. Geriatric multimorbidity

Geriatricians are trained, when faced with an older individual presenting with multiple different symptoms, to consider several diagnoses rather than a single unifying diagnosis. Most very elderly patients do have several concomitant chronic conditions [3–7]. Hypertension, heart failure, stable angina, atrial fibrillation, hypercholesterolemia, diabetes, osteoarthritis, chronic obstructive lung disease, and osteoporosis, as well as dementia and depression represent the most frequent chronic diseases encountered in the geriatric population [8–10]. Recognizing the interactive and dynamic nature of these multiple concomitant conditions introduces complexity into the evaluation of the risk-benefit ratio of available therapies. It is however an essential step, if one is to avoid iatrogenesis as well as prescription cascades.

Presenting with multiple comorbidities is associated with diminished quality of life, physical disability, psychological disorders, increased use of health care resources, multiple health care providers, polymedication and an overall increased risk of adverse events [11–19]. All of these factors influence the risk-benefit ratio of drug therapy and other treatments. Elderly patients with multiple comorbidities must generally master self-management tasks, a process influenced not only by the disease burden or level of morbidity, but also by specific psychosocial factors [20]. Ten to twenty percent of older adults hospital admissions are due to iatrogenic incidents. Cardiovascular drugs and psychotropic medication are often implicated [21]. Symptoms are often atypical

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and the toxic nature of the event is often poorly recognized. Many iatrogenic events are preventable.

Poor quality of life or disabilities may make certain treatments more attractive, because the potential for improvement is greater than when a patient is only slightly disabled. On the other hand, having several health care providers and consulting with many different specialists may result in loss of overview, uncoordinated prescriptions, dismantled therapeutic objectives and an increased risk of poor health outcomes.

Polymedication is often associated with unexpected side effects, not observed during monotherapy. It may however be necessary and can sometimes provide desirable synergistic effects.

3. Therapeutic guidelines and the very old

The complexity inherent to the presence of multiple concomitant illnesses is mostly ignored in traditional therapeutic guidelines. These are generally conceived with a single disease in mind, and rarely consider the possible effects of comorbidities or comedications [22–23].

Practical advice is available for physicians wishing to extrapolate guideline recommendations to a "non-standard" patient [24].

Factors that determine a guideline's applicability include the patient's pretest probability of the disease, his or her perception of the value of the intervention, whether the community has the necessary resources to implement the guideline's recommendations and the general acceptability of the proposed health care strategy in the patient's specific context [24]. One should ask: is my patient so different from the patients included in the clinical trials used to make the recommendations, that their results would not be applicable to him? [24] Often enough with polymorbid or elderly patients, the answer to this question is "yes, my patient *is* too different", and the recommended therapeutic strategies must be individually redefined.

4. Embracing complexity

More recent research is embracing the complexity of polymorbid polymedicated patients so that clinical recommendations might account for it and individualized therapeutic options might be more fully substantiated.

Several examples of this surge for a more integrated understanding of the therapeutic needs of older frail adults can be given:

- suggestion of including cognition in vascular risk factor clinical practice guidelines [25];
- plea for inclusion of long-term care residents in osteoporosis treatment trials [26];
- agreement to increase glycemic recommendations for target haemoglobin A(1c) from $< 7\%$ to $<$ or $= 8\%$ in the presence of frailty [27];
- suggestion that prostate cancer guidelines be adapted to health status based on instrumental activities of daily living (IADL) and activities daily living (ADL), comorbidity evaluation by cumulative illness scoring rating-geriatrics and screening for malnutrition [28].

5. Complexity of multiple concomitant drug-disease and drug-drug interactions

Drug-drug interactions are one of the major problems associated with polymedication [29]. Tools to anticipate and prevent adverse drug-drug interactions exist. We frequently use the following:

- cytochrome P450 (CYP) pharmacokinetic (PK) drug interaction card [30] (free);
- Multicheck, Epocrates™ [31] (basic module free);
- Lexi-Interact, Lexi-comp™ [32] (for sale).

Many others exist, of which the Olten-based, CYP450-PGP IA Checker, in German language [33] (free).

Most tools however, do not integrate the dynamic nature of interactions involving more than two drugs, or those associated with both inducers and inhibitors of metabolic enzymes or drug transporter systems. Nor do they account for the clinical characteristics of special populations such as children or very old persons or patients with renal or hepatic disease.

Attempts to tame these complicated issues and to offer convenient tools for research and practice are being made.

Such challenges have been taken up by an interesting and award winning start-up, Simcyp. This innovative enterprise provides software for simulating drug absorption, distribution, metabolism and excretion (ADME) in virtual populations and is presently used mainly prior to clinical trials in humans, although bridging the way to clinical practice is one of the long-term goals. Extensive information on demographics, genetics, environmental factors and disease state is plugged into the platform, so as to make it possible to investigate complex "real-life" scenarios including the likelihood and effects of drug-drug interactions, genetic polymorphisms or altered physiological functions.

Jamei, presenting the Simcyp® population-based ADME simulator [34], states that "The development of a comprehensive and robust platform to simulate and predict PK behaviour in populations is a challenging task demanding close collaboration in an inter-disciplinarily team with collective experience in physiology, epidemiology, pathology, molecular biology, system biology, metabolism and transport, experimental and theoretical PK and PD (pharmacodynamics), pharmacy, pharmacology, medicine, mathematics, statistics, control systems, bioinformatics, paediatrics, geriatrics and software engineering. In turn, maximising the value of the platform with regard to its application requires a concerted effort amongst industrial and academic partners in sharing and pooling non-proprietary information and expertise while preserving key intellectual property."

The group has studied the inter-individual variability of drug exposure (as expressed by the area under the time concentration curve [AUC]) in the presence of multiple drug-disease or drug-drug interactions.

For example, according to the Simcyp® simulator, if a victim substrate is metabolised 50% by CYP 1A2, 30% by CYP2D6 and is excreted renally (20%), then a complete inhibition of CYP 1A2 is expected to produce the following changes in the substrate's PK:

- a typical healthy adult may not increase the AUC more than two fold;
- an elderly patient with renal failure: 2.7 fold;
- an individual who lacks functional CYP2D6 for genetic reasons: 3.5 fold;
- a poor CYP2D6 metaboliser with renal failure (25% function): 11 fold.

Although sophisticated prescription tools may help individualize therapy in the near future, physicians treating elderly vulnerable patients need to come to terms with the fact that many older adults' expectations of doctors and the health care