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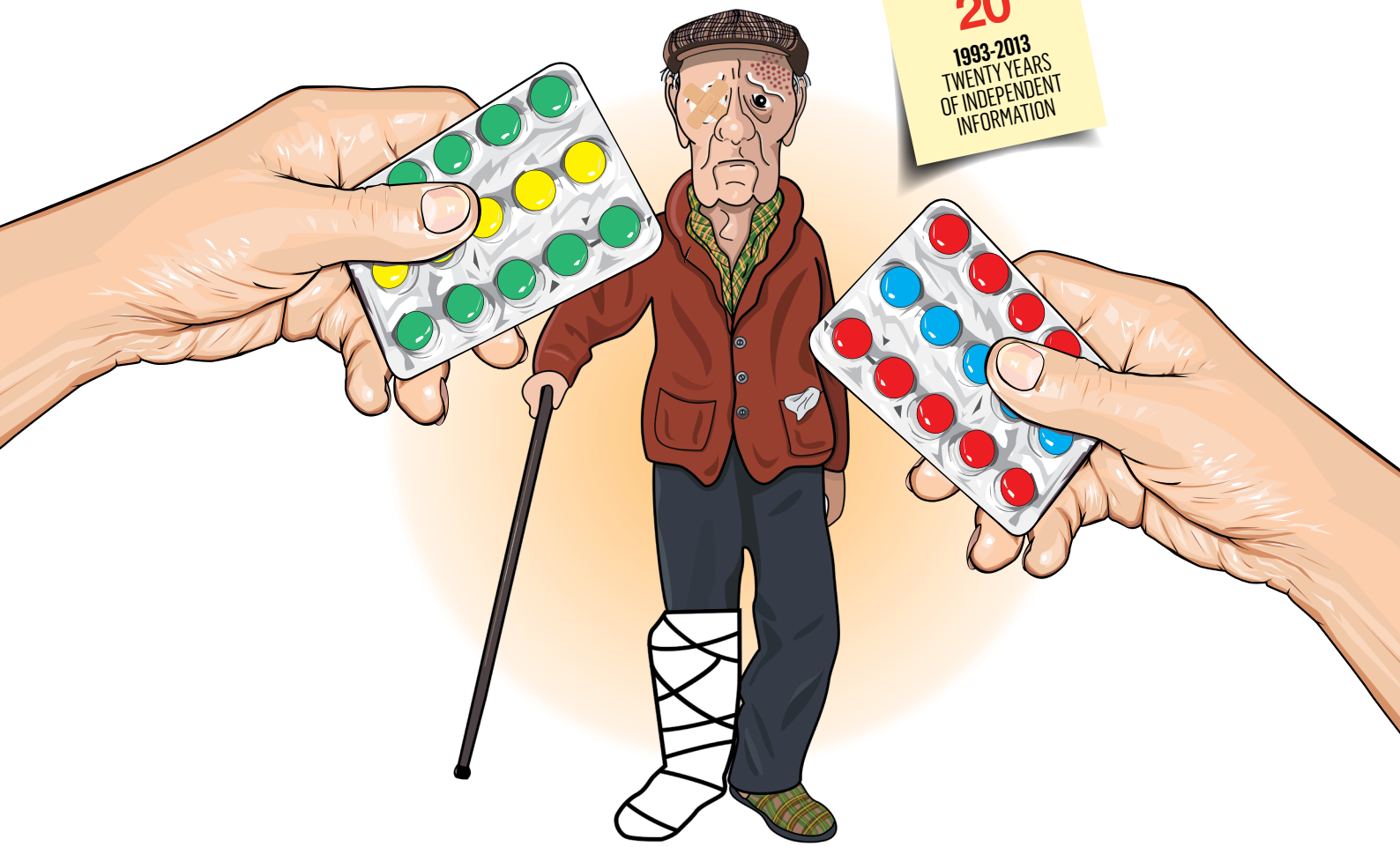

abstract

Objective: to review the concept of multimorbidity and the factors related to polypharmacy. **Material and methods:** a critical review was carried out based on the evidence available on Medline from clinical trials and observational studies on multimorbidity (last update, 31 December 2012). **Results and conclusions:** the current basic knowledge on the interrelation of diseases is very limited, partly because the scientific method maximizes internal validity, but excludes patients with co-morbidity. The elderly patient is usually excluded from studies included in clinical guidelines. The Health Care System should dispose of mechanisms to ensure the correct representation in studies of the population who will ultimately receive pharmacological treatment. We should study profoundly ways to optimize the use of drugs with synergic effects in clusters or in a combination of diseases. **Key words:** multimorbidity, co-morbidity, pluripathology, complexity, polypharmacy, elderly, iatrogenic.

The challenge of managing multimorbility

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Objective

The objective of this paper is to review and define the concept of multimorbidity and its consequences related to pharmacology. From an overall perspective, we will look at related aspects to the inherent polypharmacy in these patients, present an alternative view to the conventional approach of management and explore the possibilities of an individually-based approach that takes into account the specific situation of each patient.

Introduction

One day an 85 year-old patient comes to his primary care physician for some prescriptions. He has a personal medical history of chronic obstructive pulmonary disease (COPD), type 2 diabetes mellitus, osteoporosis, osteoarthritis and hypertension. The patient is accompanied by his wife convalescent from a recent admission to hospital and incipient cognitive impairment. Both have visual and auditory problems and need some help with regard to daily activities, although for the moment they still live in their own home. Their family physician ponders over what treatment is best for these patients offered from clinical guidelines and whether it would be possible to put it into practice.

Over the last few years the health panorama has changed overwhelmingly, with the advent of more elderly patients characterized by pluripathology, chronicity and complexity. The health system has at the same time shown difficulties in adapting to this new situation. For example, in Navarre, an indirect reflection of pluripathology can be observed from the data available from the Drug Prescribing Services, that shows that 42% of the population above 75 years was under treatment with 6 or more drugs between September and November 2011. Moreover, the concept of multimorbidity gains importance every day and this is due to two fundamental reasons: the aging population (and so the percentage of multimorbidity increases rapidly) and the challenge at clinical level to face the complexity in patients with multimorbidity.[1]

Currently, basic knowledge of the relationship among diseases is very limited, in part because of the existing confidence in the scientific method that maximizes internal validity, but excludes those patients with comorbidity in both epidemiological studies and in clinical trials. Some of the challenges about studying multimorbidity include the absence of both a clear definition and an international consensus on the quantification of this condition.

Think beyond drugs seek nondrug alternatives first

Consider potentially treatable underlying causes of problems rather than just treating the symptoms with a drug

Look for opportunities for prevention rather than focusing on treating symptoms or advanced disease

Use the test of time as a diagnostic and therapeutic trial whenever possible

Practice more strategic prescribing. Use only a few drugs and learn to use them well

Avoid frequent switching to new drugs without clear, compelling evidence-based reasons

Be skeptical about individualizing therapy

In numerous occasions the terms comorbidity, mutimorbidity, frailty or complexity have been used indiscriminately in medical literature. On the other hand, the concurrence of multiple diseases demands the need for numerous drugs and their use is based on the results of clinical trials in patients with a single disease, and extrapolated to populations not represented by these studies. This fact raises doubts for physicians with regard to the advisability of many drugs, especially for elderly patients or those with complex medical conditions.

What is multimorbidity and what does it imply?

Chronic disease refers to those clinical conditions that last for more than a year, require continuous medical care and/or limit daily activities.[2] The majority of the patients with chronic diseases have more than one concomitant pathology.[3] Coronary disease, for example, is found isolated in only 17% of the patients.[4] In Spain, there are little data on multimorbidity[5] despite the fact that up to 98% of patients in some primary care consultancies are older than 65 years.[6,7] The clinical course of these patients is not well known[8] and diagnosis is made difficult because of methodological limitations. In elderly patients, for example, chronic diseases are usually under diagnosed.[9] When a combination of diseases include mental and physical disease, the situation is more complex and the prognosis usually even worse.[10] Moreover, according to the inverse care law of multimorbidity,[11,12] the availability of good medical is inversely related to the need for it in the population.

Before continuing with this paper, it is fundamental to clarify some concepts. The formal definition of multimorbidity is the presence of two or more diseases in the same patient, with each diagnosis of each disease based on established criteria but not causally related with the primary diagnosis. Feinstein, originally described comorbidity as "any additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study".[13] Later on, Van de Akker, redefined the concept, reserving the term multimorbidity to describe the concurrence of various acute or chronic diseases and medical conditions in the same person without taking into account the index disease.[14,15] This concept would be similar to pluripathology that different authors have quantified in different ways according to the number, type and severity of the diseases. Another concept to take into account is morbidity burden, that is equivalent to the total sum of physiological alterations with impact on the individual´s reserves.[16] This entity is intimately linked to the geriatric concept of frailty.[17] Finally when taking into account the patient holistically by including non-health related factors, the concept of patient complexity arises, which though similar, is more extensive than mere clinical complexity derived by disease.[18]

Whenever possible, start treatment with only one drug at a time

Maintain heightened vigilance regarding adverse effects. Have a high index of suspicion for adverse drug effects

Educate patients about possible adverse effects to ensure that they are recognized as early as possible

Be alert to clues that you may be treating or risking withdrawal symptoms

A graphical representation of these concepts can be seen in figure.[1] With the regard to the patient presented, each of the diseases shown would represent a comorbidity, in the case where we decided that one of them was more important or was the index disease. The patient's multimorbidity or pluripathology would be the whole of the enumerated diseases and this would be complemented with other health related aspects, like the probable situation of frailty that is possibly present. Lastly, non-health related issues (for example, social situation) would complement all the previous information and on the whole, this would bring us close to the complete level of complexity which faces us.

Multimorbidity has multiple consequences. It increases hospital stay and complications,[19] worsens the degree of disability,[20] mortality,[21] functional status and quality of life,[22] re-admissions to hospital,[23] or the adequate

management of other concurrent diseases.[24] From an economical perspective, the costs of patients with at least 5 chronic diseases represent 89% of the annual budget of Medicare, as the costs increase exponentially with the number of medical problems.[25,26]

Quantification of multimorbidity

Numerous indexes and scales have been proposed to quantify multimorbidity.[27-29] There are simple methods such as enumerating the different entities or counting the number of drugs, which offers some clear correlation with prognosis. However, counting assumes for example, that psoriasis bears the same weight as cancer. One more adequate system is to create indexes in relation to the impact and results of disease. Charlson was a pioneer in his analysis of the concept by creating the most widely used index,[30] although in many occasions medical literature uses it as an index of multimorbidity instead of comorbidity. This index was developed from a cohort of patients treated with breast cancer and included only 19 diseases that were not representative of the complexity of elderly patients and moreover, assigned the highest scores to diseases of scarce prevalence among the elderly such as the Acquired Immune Deficiency Syndrome (AIDS).

A review of different comorbidity indexes identified others that possibly could play a more important role in complex populations such as the elderly.[27,28] One of them is the Cummulative Illness Rating Scale,[31] that is summarized in table 1, with some brief instructions on its use. However, an objective evaluation and quantification of the complexity of the patients with pluripathology remains a challenge.[32] A debate is still on with respect to basic methodological aspects such as the number and class of diseases to consider in each study.[33]

Approach new drugs and new indications cautiously and skeptically. Learn about new drugs and new indications from trustworthy, unbiased sources

Do not rush to use newly marketed drugs

Be certain that the drug improves actual patient-centered clinical outcomes rather than

Just treating or masking a surrogate marker

Classification of multimorbidity

The possible combinations of diseases are infinite, so the type of relations between them in a single patient should be structured. Basically these combinations can be concurrent (diseases randomly coexist), grouped or in clusters (statistically significant associations between diseases with no causal explanation), causal (groups of diseases with a physio-pathological relationship, like for example, by sharing a common risk factor) or secondary to other diseases (one disease that cannot be explained without its precursor).[34]

Despite the progressive increase in chronic disease with age, knowledge of how diseases are distributed or coincide in a single patient is very limited.[35] The term multimorbidity helps to displace thinking from a disease-based perspective to an individual-based perspective. While quantification refers to comorbidity indexes, classification by combination employs methods such as conditional counting, proportions of patients with pairs of diseases, relative associations with odd ratios and cluster analysis.

Some examples of these analysis are the studies that have shown a statistically significant association between osteoarthritis and visual alterations,[20] osteoarthritis and arterial hypertension,[36] or cardio-pulmonary pathology and motor and sensory alterations.[37] Other authors have proposed different types of clusters[38,37,39,36,4,26] but the methodologies are too heterogenous to make any global extrapolations. The heterogeneity of these aspects explains why for example, Schäfer,[40,41] selects three prevalent clusters (1- cardiovascular/metabolic disease 2- anxiety/depression/somatoform pain 3- neuropsychiatric disease) while Van den Bussche proposes triads of 6 most prevalent chronic diseases (hypertension, lipid metabolism alterations, chronic lumbar pain, diabetes, osteoarthritis, and chronic coronary disease).

Through observation of these combinations, we can attempt to guess what consequences will derive from the different interactions and synergies. Given a hypothetical context of infinite disease combinations, a systematic review shows the possibility of classifying patients in models and clusters of multimorbidity[79-99] (figure 2).

Multimorbidity and polypharmacy

Multimorbidity usually implies polypharmacy in chronic patients. To improve the quality of medical care and reduce clinical variability, the management of chronic diseases is based on specific clinical guidelines for each individual disease, usually written by specialists that focus their research on patients with no multimorbidity, making extrapolation difficult and increasing the risk of iatrogenia.[42,43-48] The elderly are commonly excluded from all type of studies, just like patients with complex medical problems (dementia, frail patients, with renal or liver impairment or under treatment with multiple drugs). While clinical research still gives priority to economic benefits, the situation of exclusion of the elderly is perpetuated. There should exist mechanisms by which health care systems safeguard the correct representation of the population which will finally receive pharmacological therapy.

Moreover, interventions derived from these clinical guidelines could be less effective in patients with multimorbidity than those patients included in the trials, and although effective, the benefits could be lower given a shorter life expectancy.[49,50] On repeated occasions it has been shown that the majority of clinical guidelines do not comply with methodological standards.[51,52] In fact, despite the perceived criticism in medical literature with regard to methodology, in the last two decades there has been no improvement in the adoption of quality standards.[52] Moreover, many of the recommendations are contradictory and imply personal care measures that are not easy for many patients. Consequently, these recommendations raise doubts even among physicians themselves.[43, 53, 54]

The recommendations could be more useful for chronic diseases if they provided and identified synergies, warnings and contraindications. This could be done by software programs that incorporate guidelines,[55] or through tools that are under development such as meta-analysis of multiple therapeutic comparisons, that provide estimations of all pairs of possible comparisons.[56]

Meanwhile, the benefits of numerous pharmacological treatments taken simultaneously remain dubious, and the possible worsening of a disease condition due to the other coexisting treatment or the pharmacological impact derived from following clinical guidelines also remain unknown.[43] We should shift our focus from disease-oriented guidelines to those that consider the particular characteristics of each patient. What may prove beneficial for one patient, may not work for another with multimorbidity.[3,50]

Be vigilant about indications creep

Do not be seduced by elegant molecular pharmacology or drug physiology

Beware of selective reporting of studies

Work with patients for a more deliberative shared agenda. Do not hastily or uncritically succumb to patient requests for drugs, especially drugs that they have heard advertised

Leaving aside the considerations on clinical guidelines, the problem of polypharmacy is gaining increasing importance. Depending on the definition employed in each study, polypharmacy ranges between 25 to 80% on elderly patients.[57-59] Linked to this concept is inadequate prescription, and depending on the source, its incidence can oscillate from 14% under the Beers criteria, 40% in hospital geriatric outpatient care according to the STOPP (Screening Tool of Older Persons Prescriptions) criteria or up to 92% in hospital-based studies according to the MAI (Medication Appropriateness Index) criteria. Different groups of criteria have been developed to detect inappropriate medication in elderly patients, including Beers[60] criteria, the PRISCUS list for the elderly, [61] the Good Palliative-Geriatric Practice (GP-GP) algorithm,[62] the IPET (Improved Prescribing in the Elderly Tool),[63] the MAI64 and STOPP,[65] criteria in its Spanish version.[66]

The Beers criteria have predominated in international geriatric literature. Initially designed to detect inadequate prescription in nursing homes, they were reviewed for adaption to the community. However, despite the wide diffusion of these criteria, they have been criticised in Europe. Up to 50% of the drugs included in the Beers criteria are not available in the majority of the European countries and are irrelevant for the majority of prescribers. Furthermore, many of the drugs included are not absolutely contraindicated and, also there is a growing number of drugs that are potentially inappropriate that are not mentioned in these criteria.

There are numerous studies that compare different strategies of inadequate prescription with different results according to location and context. Nevertheless, the STOPP-START (Screening Tool Alert Right Treatment) is currently gaining importance in geriatric medical literature especially in Europe.[66-68] We can access the current updated version recently reviewed by the Andalusian School of Public Health.[69]

Frequently, we find studies that show evidence of adverse effects of a single drug when treating a single disease and this obliges us to balance the best evidence on benefits with the adverse effects expected of each drug.[70,71] Moreover, certain combinations of diseases modify therapeutic effects and the probability of receiving adequate pharmacological treatment.[24,72] Beyond the pejorative term of polypharmacy, it is necessary to study the pharmacological possibilities available in order to optimize drug treatments with synergic effects when applied to clusters or combination of diseases. Moreover, focus should not be on withdrawing all drugs. As the authors of the STOPP-START criteria affirm, there are some occasions when it takes a long time to incorporate the use of drugs with proven evidence for the elderly into clinical practice. Moreover besides the role of drugs, studies can be carried out on the contribution to health of certain foods or beverages, the role of exercise and the ever present though controversial vitamin D.[73]

With respect to the case we presented at the introduction, when the patient entered in the roulette of evaluation by different specialists and the consensuated guidelines are applied, he was to be treated with at least 19 doses of 12 different drugs, taken at 5 moments throughout the day and with the risk that at least 10 interactions or adverse events could occur.[43] What was supposed to be the best of treatments turns out to be a nightmare. The indicated drugs for hypertension (diuretics) can alter the lipid profile or interact with the oral antidiabetic agents (hydrochlorothiazide can reduce the efficacy of glibenclamide). The intake of aspirin along with glibenclamide can increase the risk of hypoglycaemia, and moreover, aspirin can reduce the efficacy of lisinopril. If an NSAID is added, then more problems can occur affecting the kidney function and there is a greater risk for gastrointestinal bleeding. If a proton pump inhibitor is used to prevent gastrointestinal side effects, then we add to the possibility of more interactions such as those derived from an eventual introduction of biphosphonates. In the case of receiving calcium, this could reduce the efficacy of aspirin. Moreover, if corticoid therapy is required due to COPD, diabetes treatment would require adjustment and the long-term effects of steroid therapy would have to be considered (osteopenia, sodium and water retention, lipid profile, electrolyte imbalance, steroid myopathy, glaucoma, etc.). If they occur, the functional implications of these last two effects are a clear example of how a patient would pass from the limits of frailty to a situation of disability. Moreover, this becomes even more complicated when considering the possible interactions that different foods can produce by modifying efficacy or pharmacological absorption.[43] No current guideline has faced the challenge of managing real patients by taking into account all these factors, which therefore shows the difficulty in external validity and application in daily practice.

Avoid mistakenly prescribing additional drugs for refractory problems, failing to appreciate the potential for patient nonadherence

Avoid repeating prescriptions for drugs that a patient has previously tried unsuccessfully or that caused an adverse reaction

Discontinue treatment with drugs that are not working or are no longer needed

In an analysis of this hypothetical patient, Dr. Boyd and her team established a series of premises and evaluated the appropriate clinical recommendations with regard to the patient circumstances. They showed that nearly all the guidelines ignored comorbidities of the patient, the quality of the evidence in elderly patients was far from desirable, while the life expectancy, the social situation or necessary support by caregivers and the patient and family´s wishes were not considered. The complexity implied in the management of different drugs is quite difficult to take on, given the patient circumstances and this becomes even more difficult by the inherent limitations of different geriatric syndromes such as visual and auditory impairment, or cognitive deterioration of the spouse. These geriatric syndromes are usually given secondary importance, as if they were not diseases, but in reality they have important clinical repercussions. The interactions that can occur as a result of following clinical guidelines is another aspect which is often ignored or given little value, and non-pharmacological measures convert our patient into a slave of the clinical situation.[43] Moreover, the possibility of interactions among the diseases our patient presents reflect the real complexity we face when making therapeutic decisions (figure 2).

The situation, far from improving, keeps the elderly patient excluded from clinical guidelines with important repercussions at different levels. A recent example is a GesEPOC guideline for the management of patients with COPD. Precisely the elderly represent the population who would most benefit if data on elderly patients was available but not extrapolations of scientific evidence demonstrated in younger populations.[74]

Ultimately different alternatives are coming up with regard to the management of these complex patients, such as medication reconcilliation through interventions aimed at improving the quality of prescription and avoiding any risks or discrepancies during the patients journey through the health care system.[75] An interesting initiative is the development of principles of conservative prescribing. Based on a combination of scientific studies and common sense, Schiff and cols advise on a series of principles that ensure a more conservative or prudent[76] approach to prescription and which we point out as "tags" throughout this article. Some physicians and pharmacists in Spain have published these principles in an excellent blog.[77]

Given this situation, different models of health care for chronic patients are under development. It is evident that precise identification of patients with multimorbidity is necessary as well as the development of cost-effective and specific interventions directed towards improving health results.[32] Yet there remains to establish whether in sectors of the population such as the elderly, the abstract conception of the terms described above is more useful than the mere management of frail patients through either an integral geriatric approach or by the quantification of functional measures.

Work with patients' desires to be conservative with medications

Consider longer-term, broader effects. Think beyond short-term beneficial drug effects to consider longer-term benefits and risks

Look for opportunities to improve prescribing systems, changes that can make prescribing and medication use safer

Acknowledgments

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Table 1. Cumulative illness Rating Scale for Geriatrics.[31,78]

	0	1	2	3	4
Cardiac					
Arterial hypertension					
Vascular, lymphatic, haematopoyetic					
Respiratory (lungs, bronchi, trachea)					
Ear, Nose and throat (ENT)					
Upper digestive tract (oesophagus, stomach and duodenum, pancreas, except diabetes)					
Lower digestive tract (intestines, hernias)					
Hepatic (liver biliar tree)					
Renal (only kidneys)					
Other reproductive and urinary (ureter, bladder, urethra, prostate, genitals)					
Muscular-skeletal – skin (muscule, bone, skin)					
Neurological (brain, medula, nerves, except dementia)					
Endocrine-metabolic (including diabetes, thyroid, breasts, systemic infections, toxicity)					
Psychiatric/behavioural (includes dementia, depression, anxiety, agitation-delirium, psycosis)					

0 No problem **1** Mild **2** Moderate **3** Severe **4** Extremely severe
Each disease should be classified in the appropriate system. If there are different problems in the same system, only the most severe is evaluated (for example a patient with well controlled angina (2) and terminal heart failure (4) would score 4. Some diseases such as cancer can be evaluated in more than one category (for example, lung cancer with bone metastasis treated with anti-inflammatory agents would be scored as "4" in respiratory and "2" in muscular-skeletal sections).

Figure 1. Definitions of multimorbidity or pluripathology.

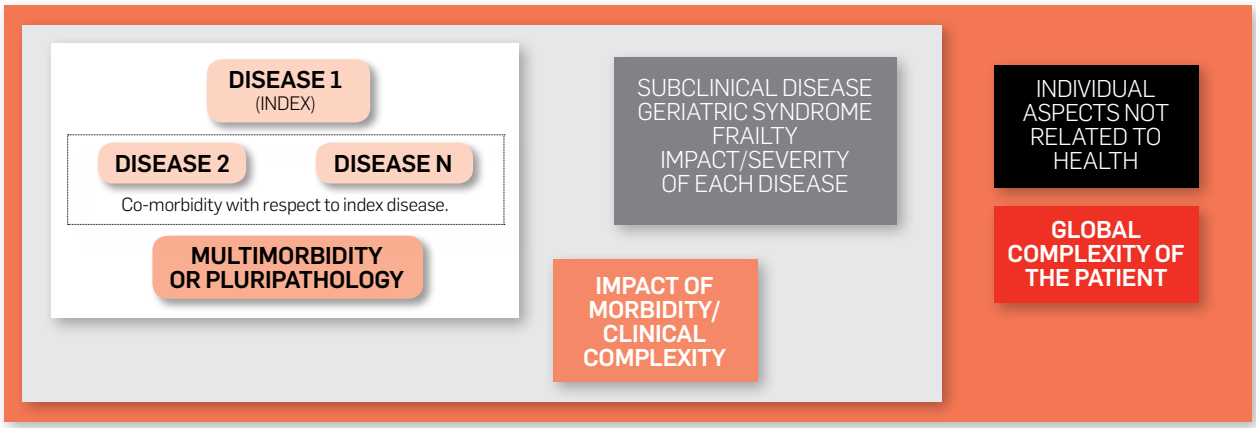
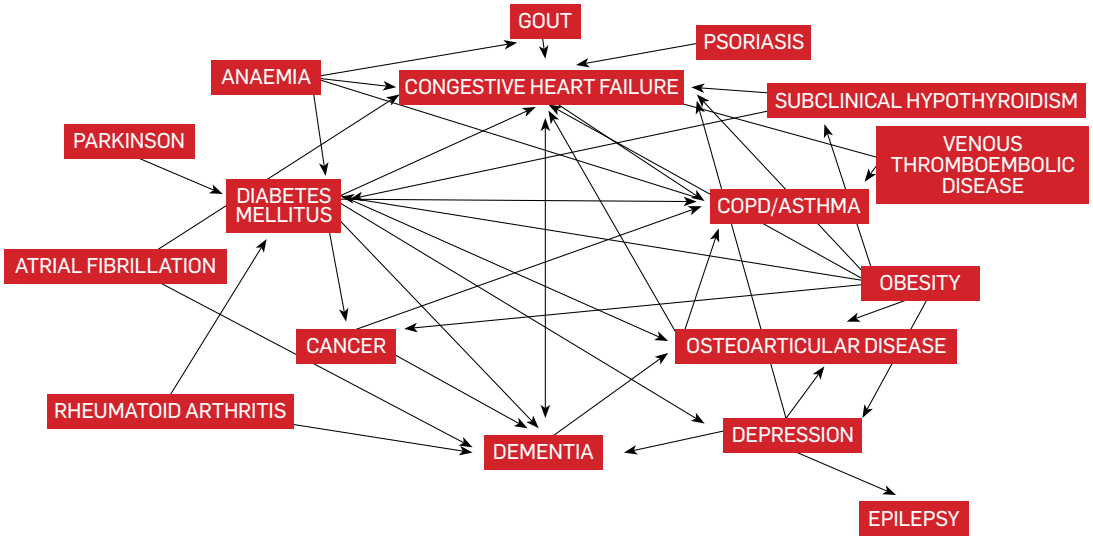


Figure 2. Possible interactions among diseases.



CONCLUSIONS

Over the last few years, the number of elderly patients with chronic and complex pluripathology has increased, and Health Systems need to adjust to the new conditions.

Currently, basic knowledge on the interrelation among diseases is very limited, in part because the scientific method maximises internal validity but excludes patients with comorbidity.

The elderly patient is usually excluded from the studies on which clinical guidelines are based. There should exist mechanisms for the Health Systems to ensure the correct representation of this population where the treatments will ultimately be applied.

When the elderly patient is evaluated independently by different departments or specialties it is highly probable that the patient ends up with a high risk of iatrogenia, especially if no adequate and optimal adjustment of pharmacological treatment is made.

We should keenly search for the optimal use of drugs effects in cases of clusters or combinations of diseases.

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