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From Bedside to Bench: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Comorbidity and Multiple Morbidity in Older Adults*

Cynthia M. Boyd¹, Christine S. Ritchie², Edmond F. Tipton³, Stephanie A. Studenski⁴, and Darryl Wieland⁵

¹Division of Geriatric Medicine and Gerontology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland ²Center on Aging, University of Alabama - Birmingham School of Medicine, Birmingham ³Reserve Educational Assistance Program, VA Medical Center, Birmingham, Alabama ⁴Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania ⁵Division of Geriatrics, Department of Medicine, University of South Carolina School of Medicine, Columbia, South Carolina, USA

Abstract

Most aging patients have multiple concurrent health problems. However, most current medical practice and research are largely based on a single disease model, failing to account for the simultaneous presence of multiple conditions. Clinical trials, practice guidelines, and pay-for-performance schemes may thus have limited applicability in older patients. We report on the 2005 American Geriatrics Society/National Institute on Aging conference on Comorbid Disease and Multiple Morbidity in an Aging Society. The two-day conference was designed to clarify concepts of multiple concurrent health conditions; explore implications for causation, health, function and systems of care; identify important gaps in knowledge; and propose useful next steps. While the

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Correspondence: Darryl Wieland, PhD, MPH, 3010 Farrow Road, #300A, Columbia, SC 29203, USA.
darryl.wieland@palmettohealth.org.

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conference did not attempt to standardize terminology, we here develop the concepts of comorbidity, multiple morbidity, condition clusters, physiological health, and overall health as they were used. The present report also summarizes sessions addressing the societal burden of comorbidity, and clinical research on particular diseases within the framework of comorbidity concepts. Next steps recommended include continuing clarification of terms and conceptual approaches, consideration of developing and improving measures, as well as developing new research directions.

Keywords

Burden of illness; health status assessment; nosology; pathological conditions; signs and symptoms

INTRODUCTION

Among the shifts in health accompanying population aging is the increasing prevalence of individually cooccurring diseases, disorders, or health conditions (seen as distinct “clinical entities”). Clinicians caring for older patients often need to deal with three or more distinct, usually chronic diseases (present in 43% of all Medicare beneficiaries), and may not be able to focus on only one disease (1)

Despite their ubiquity, multiple co-occurring conditions receive short shrift in medical research and education. Clinical guidelines for particular diseases sometimes deal with single additional health conditions, but rarely with two or more (2). Most research on multiple co-occurring conditions has a “comorbidity” focus, originally defined as a disease or diseases in a patient in addition to a primary or an “index” disease (3). Comorbidity studies - e.g., cancer with specific other conditions - have established a research foothold (4). However, clinical and epidemiological research focused on multiple morbidity (no index disease) is only very recently emerging (5–7).

The importance of multiple co-occurring health conditions was recognized with the convening of a Taskforce on Comorbidity Research Issues in 2003–4 by the National Institutes of Health through the National Institute on Aging [NIA]. The Taskforce focused on conceptual and methodological complexities of multiple co-occurring health conditions (8–11). Soon after, the American Geriatrics Society, with NIA support, convened a two-day conference in March 2005, “Comorbid Disease and Multiple Morbidity in an Aging Society”. Its purposes were to summarize research on the impact of comorbidity and multimorbidity on health and society and current clinical comorbidity research, and to identify new directions for investigation. This was the second of the series of “From Bedside to Bench” convocations, intended to focus research attention on understudied areas of concern in geriatrics.

Here, we begin with a clarification of terms, and discuss the conceptual terrain of the conference. We then focus on the health and societal effects of multiple occurring health conditions. A synopsis table of the clinical research on comorbid conditions presented at the conference is provided. We close with identification of areas which warrant new investigation raised by participants in small groups. Articulating a formal research agenda, providing a comprehensive review, or reviewing existing comorbidity or case-mix indices, were beyond the scope of this conference, and are not attempted here.

MULTIPLE CO-OCCURRING CONDITIONS: TOWARD DEFINITIONS AND CLARIFICATION OF KEY CONCEPTS

“Multiple co-occurring conditions” have been approached using various terms and conceptual frameworks, and a consensus has not been achieved on terminology and what the terms signify. For example, where Feinstein had defined “comorbidity” as diseases in addition to an index disease (then not including impairments, pre- or subclinical conditions that might be counted today) (3), Yancik - summarizing the NIA Comorbidity Taskforce - defines “comorbidity” as “the total burden of biological dysfunction” (11), i.e., what some others now mean by “multimorbidity” or “multiple morbidity” (6, 7). However, “comorbidity” and “multimorbidity” are often used interchangeably to denote a sum of conditions (whether at the level diagnoses, system impairments, risk factors, sub- or pre-clinical conditions; chronic and acute, etc.)

Table 1 provides terms and concepts having salience at the conference, and applicable to multiple co-occurring conditions. “Comorbidity” describes a framework wherein one specific disease or condition is the primary focus, and the other distinct entities are the comorbid conditions modifying the course and the treatment of an individual with the index condition. “Multiple morbidity” or “multimorbidity” can be defined as the total burden of biological dysfunction. A complementary framework to understanding multiple cooccurring conditions is to address specific disease/condition “clusters”; here, the questions may be different than those concerning additive effects of morbidities atop an index disease. The construct of multimorbidity - an extension of the biomedical disease model - is defined against the background of an encompassing construct of total biological health or functioning. Finally, individual health has social, psychological, economic and environmental dimensions. Traditional geriatrics approaches, such as comprehensive geriatric assessment and team management, tend to address multiply morbid conditions to the extent that they affect or are affected by other dimensions of health and functioning. There is growing recognition that the complexity of patients is not captured by lists of diagnoses or biological disease burden alone (12, 13).

While not directly addressed at the conference, it is important to address the classification and development of research on geriatric syndromes (such as falls, delirium, incontinence and frailty). These are “multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render [an older] person vulnerable to situational challenges” (14). The casting of these syndromes as “phenotypes” (observable characteristics of an individual determined by the genotype and environment) lends geriatric syndromes to a “cautious, rigorous, incremental approach to [definition]”. The refinement of these definitions require careful review of the evidence supporting such classification and development of their preliminary criteria in an iterative process (15). Work on geriatrics syndromes can be understood as nosology addressing particular multiple morbidities, manifested as outcomes that are of great significance in older patients. Geriatric syndromes offer the opportunity to elucidate the multiple etiological factors and interacting pathogenetic pathways associated with a particular phenotype or outcome (as in the case of incontinence, falls, or pressure ulcers). At the same time, research in geriatric syndromes addresses health complexities outside of biological processes by emphasizing the effect of social, psychological, and environmental factors on the manifestation of geriatric syndromes (13).

MULTIPLE CO-OCCURRING CONDITIONS: THEIR DIVERSE IMPACTS AND CLINICAL IMPLICATIONS

Prevalence

Among a 5% nationally representative sample of Medicare claims for 1999, multiple conditions are highly prevalent. Conditions were defined at the level of Major Diagnostic Categories (MDC), such that having two MDCs meant having illness in two major organ systems. Sixty-four percent had two or more conditions, 43% three or more, and 24% four or more conditions. On average, study participants had 2.34 chronic conditions, increasing from 1.88 conditions for ages 65 through 69, to 2.71 conditions for individuals 85 and older (1). Among beneficiaries with heart failure, depression, or diabetes, 80%, 71%, and 56% respectively have four or more other chronic conditions, in addition to the index disease. The prevalence of multiple conditions increases with age.

Function and quality of life

Comorbidity profoundly affects function and quality of life. In a study of community-dwelling persons over age 55, physical disability rose exponentially with numbers of conditions, plateauing at six. Social disability showed a similar but less dramatic rise (16).

Specific combinations influence function differentially. In the Women's Health and Aging Study, arthritis with visual impairment caused mobility impairments, while arthritis with stroke affected higher function and self care. The findings suggest that while greater severity of a single disease can cause disability by itself, less severe disease may produce disability in the presence of another condition (17). The synergy between specific conditions can be dramatic. Data from the NHANES Epidemiologic Follow-up Study were used to evaluate the association of the presence of osteoarthritis and heart disease at the original NHANES interview (1971) with difficulty with ambulation and transfers at follow-up (1982). The odds ratio of having mobility disability was 2.3 for heart disease only, 4.3 for arthritis only, and 13.6 for both heart disease and osteoarthritis (18).

The Longitudinal Aging Study in Amsterdam provides evidence of the pathway from multimorbidity to disability. Subjects aged 55 or older at initial interview self-reported their ability to perform six usual daily activities, and were asked about the presence of seven chronic conditions. Three years later, the likelihood of functional decline was correlated with the initial number of chronic illnesses. The odds ratio for decline was 1.6 for one condition increasing to 4.1 for three or more conditions (19). In the Medicare Current Beneficiary Survey, newly reported chronic conditions were also associated with onset of functional dependency (20).

An increasing number of co-occurring chronic diseases adversely impacts health-related quality of life (HRQoL). The Cumulative Illness Rating Scale (CIRS), the Charlson index, and the Functional Comorbidity Index (FCI) all predict HRQoL. Research comparing the ability of these three indices to predict HRQoL scores (on the SF36), demonstrated that the CIRS was more closely correlated with HRQoL than the FCI or Charlson. Both the CIRS and FCI showed correlations for each of the SF36 Physical and Mental Scale categories ($p < 0.01$ for each) (21).

Healthcare utilization and costs

Multimorbidity affects cost, health care utilization and setting of care. In a national sample of paid Medicare claims in 1999, expenditures per patient were strongly correlated with number of chronic conditions. Patients with no chronic conditions averaged \$ 211 per year, rising to \$ 1154 for one condition, \$ 2394 for two conditions, \$ 4701 for three types of

conditions and \$ 13,973 for four or more (1). Beneficiaries with five or more had an average of 14 physician visits and 49 prescriptions per year.

Comorbidity increases hospitalizations that might be avoided by timely, effective primary care. In addition, the risk of avoidable complications during hospitalization is strongly correlated with number of conditions (1).

The complexity of the relationship between multimorbidity and resource utilization is illustrated by an analysis of the Epidemiological Study of the Elderly. Hypertensive community-dwelling people aged 75 to 85 years were divided into groups with hypertension alone; hypertension and vision or hearing impairment; hypertension and heart disease, stroke or diabetes; and hypertension plus vision or hearing impairment and heart disease, stroke or diabetes. Although the likelihood of being alive and at home steadily declined with the number and severity of these diseases, the likelihood of requiring long-term care was higher for the hypertensives with only vision or hearing impairment, because the vascular disease patients were more likely to die rather than need long-term care. This highlights the importance of considering competing risks in judging the impact of multiple conditions (22, 23).

Implications for health care systems

Most clinical research and health-care delivery have a single disease focus. This focus has led to the development of clinical practice guidelines oriented toward patients with no or perhaps one additional comorbid condition (24). Adherence to these guidelines in a patient with several comorbid conditions could lead to a complex medication and behavior change program of unknown benefit and meaningful burden to the patient and the caregiver (2). Single condition-based research also provides inadequate information to clinicians regarding risks and benefits, in many instances leaving patients and providers to their own judgment regarding appropriateness of certain interventions, such as screening or the adoption of a burdensome medication regimen such as anticoagulation in advanced illness (2, 23, 25).

Single condition-based health-care delivery contributes to fragmented patient care with little attention to or reimbursement for coordination of care among multiple providers or conditions. Use of single condition-based measures of quality for pay-for-performance may lead to overemphasis of some interventions at the expense of other important interventions. Because current quality measures usually focus on easily measured indicators, important but more difficult outcomes such as caregiver burden, symptom burden, goals of care and integration of patient preferences in treatment decisions may be neglected. Excluding multimorbid patients from the denominators of eligible populations for these standards may appropriately reduce the pressure to meet single conditionbased performance standards, but also shifts focus away from complex patients (2). Services oriented towards patients with multimorbidity aimed at preventing or ameliorating geriatric syndromes, supporting caregivers, and minimizing functional decline (such as hearing aids, eye glasses, “prehabilitation”, and oral care) also do not factor into most reimbursement schemes, and thus are not routinely used by patients who could benefit (26).

RESEARCH ON MULTIPLE CO-OCCURRING CONDITIONS

Clinical investigations

Comorbidity has important clinical implications for both diagnosis and treatment. Table 2 highlights work presented at the conference on specific conditions as index diseases with comorbidity, as comorbidities, and within the context of multimorbidity.

Barriers

Clinical work such as represented in Table 2 is vital as the population enrolled in clinical trials often is not representative of those having the disease - patients with significant comorbidities (27). Clinical trial results most accurately represent the average patient in a trial (28). While the number of trials with explicit age exclusions has declined and enrollment of older patients has increased for some conditions, enrollment of older people still under-represents older patients affected by these conditions (29). At the same time, the number of heart failure clinical trials excluding participants with specific comorbidities increased from 1985 to 1999, with more than half excluding participants with major hepatic, renal or hematologic comorbidities (27). Results from uncontrolled observational trials for treatment decisions of commonly excluded subgroups may be proven wrong when controlled trials are undertaken (30, 31).

Patients with multimorbidity are frequently successfully recruited into less disease-specific trials focusing on outcomes of interest to older people with multimorbidity, such as falls, physical function, quality of life, remaining at home, and delirium (26, 32–35). Such work argues for the feasibility of enrolling complex patients into clinical trials and identifies successful strategies to improve their wellbeing. How to best manage specific disease combinations in these complex patients (e.g., in terms of prioritization among therapies, or incorporation of patient preferences) is unknown (2, 36, 37).

Toward an agenda

A final task was to identify next steps for research and practice. Working in breakout groups, participants identified different areas of research and general research questions (Table 3). Recognizing the importance of multiple co-occurring conditions, conference participants viewed new observational, interventional, and health services research studies as essential. Regardless of perspective on multiple co-occurring conditions (Table 1), improvement of measures and development of data sources is necessary. With improved measures and data, multiple co-occurring conditions can be investigated as cause (exposure), consequence (outcome), confounder, or effect modifier in clinical, epidemiologic, and health services research (10). While numerous questions arose from comorbidity, condition cluster and multiple morbidity perspectives, there was particular interest in summarizing multiple morbidities in ways that incorporate markers of severity, physiologic function, and/or physical impairment, toward improving clinical prediction (25, 38, 39). Future multimorbidity measures might include basic markers of physiological functions across key systems (see Table 1), e.g., serum albumin, creatinine, etc., comprising a battery analogous to the APACHE tools (40); they might also include physical performance measures, summarize physiologic impairments of both preclinical and clinical conditions, and encompass geriatric syndromes. Such systems could not only be compared to - or extend - diagnosis-based measures of comorbidity, but become frameworks within which to examine interactions and demands between/among physiological systems (9).

CONCLUSION

While there is growing interest in multiple co-occurring conditions, we have yet to achieve consensus on conceptual approaches and terms. As summarized here, the 2005 NIA/AGS Conference on Comorbid Disease addressed this developing field, considered some of the health and societal effects of multiple occurring health conditions, and reviewed research on several conditions prevalent in older people within the comorbidity framework. Next research steps, as developed by conference participants, will help elucidate optimal measures of multimorbidity, better understand biological and behavioral bases of

multimorbidity, and ultimately lead to improved health care delivery and outcomes for those experiencing multimorbidity.

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Table 1

Terms and frameworks for the study of multiple co-occurring health conditions.

Terms/Approach	Definition	Examples	Advantages	Limitations
Comorbidity	Single index condition focus, affected by another specific - or a number of specific - concurrent conditions; or sums (weighted/un-weighted) of defined conditions (no index condition) - used as independent variable in research (some call this multimorbidity - 6)	Cancer, with heart disease, or as part of a composite measure of illness burden (41).	May improve specialist knowledge, practice, or disease management for patients with fewer/ more defined comorbid conditions. Various comorbidity measures are available and have proven important outcome predictors. Data are available in charts or administrative records, but may be prone to error and biases.	Index-focus ignores interactions beyond the specific combinations studied; fails to capture that relationships and implications for treatment are multidirectional (e.g., CHF complicates cancer treatment, but cancer or its therapies alter how CHF is managed). Relevance to older patients with aging-related changes to physiologic reserve is limited. Little understanding of the patho-physiologic links between scale scores and outcomes.
“Clusters”	Group of two or more specific diseases, impairments or health conditions (disease/ condition pairs or triads).	Studies of arthritis and vision impairment.	Includes epidemiological study of conditions that may co-occur at greater-than-chance rates.	May overlook effects of other health conditions as well as non-biological (social, psychological, etc.) factors on cooccurrence or associated outcomes (e.g., disability).
Multiple Morbidity or Multimorbidity	The total burden of biological dysfunction or physiologic dysregulation (8–11).	Approximated by the accumulation of presumably discrete diseases, impairments and health conditions.	A chronic analogue of the APACHE (used for assessing acute physiologic derangement - 40) might better characterize biological health status in older patients with multiple interacting physical problems (9).	Improvement over extant scales depends on recognition, beyond diagnosed diseases, of pre- or sub-clinical conditions or impairments, and dysfunctions against background of age-related biological change. No instruments presently exist.

Table 2

Key points from specific examples of diseases/conditions which co-occur (cancer, diabetes, COPD, HIV, depression, alcohol abuse, cardiovascular disease).

Term/Approach	Key Points
As an index condition	<p>Prevalence:</p> <ul style="list-style-type: none"> - Other comorbidities are prevalent with index condition (e.g. cancer, CVD, COPD) (42–46) - Health disparities in burden of comorbid disease (HIV) (47) <p>Framework for considering co-existing conditions:</p> <ol style="list-style-type: none"> dominant conditions eclipsing the management of other health problems, concordant conditions representing parts of the same overall pathophysiology vs discordant conditions, or symptomatic vs asymptomatic conditions (48) <p>Diagnosis:</p> <ul style="list-style-type: none"> - Underdiagnosis of comorbidities in people with depression or HIV (49, 50) - Comorbidities affect who should be screened for cancer (23) <p>Treatment:</p> <ul style="list-style-type: none"> - Changes treatment options (23, 51) - Changes observed utilization (cancer, diabetes, HIV) (50) - Changes self-management <p>Outcomes:</p> <ul style="list-style-type: none"> - Changes prognosis of index disease (23, 51–56) - Treatment of comorbidity may improve success of treatment for index disease (e.g. HIV) (57)
As a complicating comorbidity of other condition(s)	<p>Outcomes:</p> <ul style="list-style-type: none"> - Negative impact on health outcomes (58) - May have both positive or negative effects, depending on disease (e.g. alcohol use) - Amplifies morbidity from other conditions - Heighten vulnerability to stressors (59, 60) - Decrease adherence (43)
As part of multiple morbidity or multimorbidity	<p>Prevalence:</p> <ul style="list-style-type: none"> - Some diseases are highly prevalent among people with multimorbidity (diabetes, CVD) with disease in isolation rare - A disease may increase the risk of conditions, syndromes and impairments (61) - Shared predisposing factors <p>Treatment:</p> <ul style="list-style-type: none"> - Optimal health system for these complex patients (48, 62) - Interventions may improve outcomes for more than one disease (63–65) <p>Interactive Effects beyond Diseases:</p> <ul style="list-style-type: none"> - Alcohol has unknown effect on multimorbidity

Table 3**Research questions.**

Measurement Issues for Clinical or Research Purposes	
1	Does an index of clinical or functional impairments or physiologic parameters provide better predictive value than measures based solely on diseases? Or should comorbidity (based on diseases), impairments, physical performance, and disabilities be best described as different entities?
2	How are severity, fluctuating acuity, pre- and sub-clinical conditions addressed in measurement?
3	What are the genetic, behavioral and environmental etiologies of preclinical and clinical conditions? What are the interactions among them?
4	Does minimizing specific interactions preserve specific functions?
5	How do multiple conditions cluster in late-life populations? What conditions co-occur at rates greater than chance? What do such clusters tell us? Some may point to previously unrecognized processes which precipitate the multiple abnormalities constituting the observed cluster, e.g., "inflammation" as a cause of atherosclerosis, malnutrition, neurodegeneration and frailty (66). Others might help aggregate the multiple conditions around a known, precipitating condition, e.g., atherosclerosis, neuropathy and depression around diabetes (67).
6	Geriatric syndromes may appear as comorbidities and patients with multimorbidity are at higher risk for geriatric syndromes. How should geriatric syndromes be included in measurement?
Index Condition Perspective: Comorbidity	
1	How do specific comorbidities alter the effectiveness of treatment for an index condition?
2	How do specific comorbidities affect the course of other diseases?
3	Does treatment of an index condition worsen the course or severity of other conditions (e.g., treatment of COPD with ipratropium and risk of urinary retention)?
Multimorbidity Perspective	
1	What are the best methods for clinical decision-making incorporating patient preferences and priorities within the context of existing evidence about the risks, benefits and burdens of treatment for multimorbid conditions?
2	How does multimorbidity influence prognosis?
3	What are the optimal points of transition from disease orientations to functional and palliative approaches? (68)
4	How does multimorbidity impact symptom burden, distress and quality of life?
5	At what point(s) or clinical populations is it most useful to shift from a comorbidity to a multimorbidity framework in clinical management and research?
6	What are the effects of the number of drugs on expected responses to therapies and adverse events? How can polypharmacy with its known problems be distinguished from appropriate use of multiple medications?
7	What are the best methods of evaluating patient experience for people with multimorbidity?
8	What are the inter-relationships between geriatric syndromes and multimorbidity?
9	What are the best methods of addressing multimorbidity to reduce the risk and impact of geriatric syndromes?
Health Care Systems	
1	How is utilization of treatments or screening procedures altered by co- or multimorbidity?
2	What is optimal system of care for multimorbid older patients?
3	What health-care system reforms will prevent the development of co- and multimorbidity and improve health of people with these conditions?
4	What are effects of health system reforms on people with co- and multimorbidity?
5	What reforms will optimally change provider behavior?
6	How can integration and coordination of care be improved?
7	What are optimal roles for specialists and generalists to improve outcomes important for people with multiple co-occurring health conditions?

Measurement Issues for Clinical or Research Purposes

- 8 What are the implications of multiple co-occurring conditions for assessing quality of care and determining suitable reimbursement?
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