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Review

Managing medical and psychiatric multimorbidity in older patients

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Abstract: Aging increases susceptibility both to psychiatric and medical disorders through a variety of processes ranging from biochemical to pharmacologic to societal. Interactions between aging-related brain changes, emotional and psychological symptoms, and social factors contribute to multimorbidity – the presence of two or more chronic conditions in an individual – which requires a more patient-centered, holistic approach than used in traditional single-disease treatment guidelines. Optimal treatment of older adults with psychiatric and medical multimorbidity necessitates an appreciation and understanding of the links between biological, psychological, and social factors – including trauma and racism – that underlie physical and psychiatric multimorbidity in older adults, all of which are the topic of this review.

Keywords: mulitmorbidity, older adults, psychopharmacology, racism, trauma

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Introduction

Multimorbidity, commonly defined as the co-occurrence of two or more chronic medical or psychiatric conditions[1,2] that may or may not directly interact with each other,[3,4] is an issue of increasing importance in primary and specialty care.[5] Sometimes referred to as 'multiple chronic conditions' in the literature,[6] multimorbidity is common,[7–9] and has increased in prevalence in recent decades.[1,6] Prevalence of multimorbidity has been estimated to be approximately 25% of the general adult population in the USA,[10] and at least one in four primary care patients in the UK[11] – the latter group comprising of approximately half of primary care consultations and 75% of prescriptions.[11] Estimates of multimorbidity worldwide are similarly high across low-income, middle-income, and high-income countries,[12] and it has been described as 'now the norm internationally, not the exception',[13] with further increases expected over the coming decade.[14] These increases have been attributed largely to increased population aging as a result of improvements in care and survival from acute and chronic conditions,[6,15,16] and changes in lifestyle factors such as physical activity and obesity.[6]

Multimorbidity is distinct from comorbidity, which considers other conditions within the context of an index disease.[17] The multimorbidity concept reflects the complexity of caring for such patients[18] and acknowledges that these conditions 'collectively have an adverse effect on health status, function, or quality of life [and] require complex healthcare management, decision-making, or coordination'.[19] Multimorbidity itself can be treated as its own entity, as patients with disparate multimorbidity presentations can demonstrate similar health trajectories. A study of community-dwelling adults in Ontario examined progression of three patient groups with disparate chronic illnesses: diabetes, dementia, and stroke. Across all three groups, health service utilization and health service costs increased consistently and substantially with the number of chronic conditions.[7] This finding, despite differences in underlying disease processes, led the authors to address the importance of 'viewing these results with a multimorbidity lens'.[7] This 'multimorbidity lens' can highlight the deep interrelations between psychiatric and medical conditions.

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Patients with multimorbidity face elevated risk of significant adverse health outcomes, beyond what would be expected from their individual conditions.[13,20–25] In addition, compared to those with a single chronic condition, people with multimorbidity are more likely to die prematurely, be admitted to a hospital and have an increased length of stay.[26,27] A variety of mechanisms have been proposed for this,[6,28–30] and much of the elevated risk of adverse outcomes in older adults with multimorbidity is due to interactions between pharmacologic treatments and multimorbidity, resulting from age-related changes in pharmacokinetics and pharmacodynamics that increase the risk of side effects, or from polypharmacy – the taking of several medications by an individual patient – which can increase risk for drug–drug interactions, drug–disease interactions, and a higher risk of adverse drug effects.[31] Multimorbidity is also associated with poorer function and health-related quality of life, and greater risk of depression, frailty, and socioeconomic costs.[18,28,31–37] The consequent poor health and functional decline are associated with earlier exit from work[38] and can increase pressure on social care systems.[14]

Though not solely a feature of aging,[4,39] multimorbidity is most strongly associated with aging.[2,40] For example, a study of adults over age 65 years in Alberta, Canada, found that the prevalence of at least three morbidities was 34%, which rose to 50% over 9 years.[20] However, there are many additional factors that modulate the presence and intensity of multimorbidity. There is clear evidence of a link between multimorbidity and lower socioeconomic status,[41] lower education,[42] adverse childhood experiences,[43] racial discrimination[44] and loneliness.[45–48] 'Stress' and multimorbidity have been associated with increased hospitalizations and mortality through several possible mechanisms.[6,28,29,49,50]

Treatment of multimorbidity requires, by definition, care that crosses organizational or sectional boundaries,[51,52] and multimorbidity has been described as a 'defining challenge' for health systems worldwide.[53] Despite recognition of this increasingly critical priority for health systems and health research globally,[5] and projections that the prevalence will continue to increase,[14] most healthcare is still designed to treat individual conditions rather than providing the optimal comprehensive, person-centered care required for patients with multimorbidity.[1,54,55] Single-condition treatment guidelines lead to fragmented and sometimes-contradictory care, increasing the risk of polypharmacy and burdensome increases in medical treatments and healthcare services that are strongly associated with the number of chronic conditions.[56] Single-condition treatments lead to care that is inefficient and unsatisfactory for patients and providers.[57]

Appropriate management of medical and psychiatric multimorbidity requires a radical shift in conceptualizing and treating medical illness, seeing multimorbidity and its diseases in a greater, more holistic view of health, and appreciating the multifactorial contributors and substantial heterogeneity of people with multiple chronic conditions.[58] This is best facilitated using a bio-psycho-social informed model, examining several factors that contribute to and influence multimorbidity:

- *Biologic factors*: Including 'hallmarks of aging' such as epigenetic changes, telomere shortening, genomic instability and cellular senescence; inflammation; associations between psychiatric and medical illness (e.g. chronic medical conditions and depression, stroke and depression, Parkinson's disease and anxiety/depression); and interactions between pharmacologic treatments and multimorbidity;
- *Psychological factors*: Including the bidirectional links between psychology and disease that encompass individual factors and the effect of trauma; and
- *Social and socioeconomic factors*: Including racism, social structures, and social connection.

This review will summarize each of these factors contributing to multimorbidity in older adults and discuss best practices for management of multimorbidity. We will present a review of appropriate pharmacologic management of patients with multimorbidity, including the implications of multimorbidity for polypharmacy and vice versa, and then review approaches for delivering comprehensive, whole-person care for this complex subset of patients.

Biologic factors underlying multimorbidity

Several biological mechanisms in older adults increase susceptibility to diseases in multiple organ systems, including the brain.[59,60] One set of

mechanisms concerns biochemical changes that are associated with aging, or the so-called 'hallmarks of aging'. In addition, medical conditions can increase the risk of psychiatric conditions through various mechanisms, and vice versa, ultimately leading to multimorbidity.

The hallmarks of aging

A growing body of literature focuses on the mechanisms connecting aging to multimorbidity.[6] The 'geroscience hypothesis',[61] focuses on age-related biochemical changes called 'hallmarks of aging', which include genomic instability, epigenetic effects, telomere attrition, cellular senescence, loss of proteostasis, and mitochondrial dysfunction.[61–64] These mechanisms are thought to underlie age-related increases in disease and multimorbidity, but have also been associated with multimorbidity across age groups.[65]

Genomic instability refers to an accumulation of genetic damage that is associated with impaired health at a cellular and tissue level. It can be affected by internal factors such as generation of reactive oxygen species and spontaneous hydrolytic reactions, or external factors such as ultraviolet radiation and environmental changes.[66,67]

Epigenetic effects are altered gene expression and function influenced by behaviors and the environment.[6] With underlying mechanisms involving histones, DNA methylation, and micro-RNA dysregulation,[68] epigenetic processes have been implicated in the development of chronic inflammatory disease[69] and certain cancers.[70]

Telomere attrition describes the degradation of telomeres – the non-coding 'caps' at the ends of chromosomal DNA strands – which occurs with ongoing cell replication; telomeres are known to shorten with age[71] and oxidative stress.[72] There is much uncertainty surrounding the influence of telomeres,[73] as research has found an inverse association between telomere length and multimorbidity (including mental health conditions) in men, but not women.[74] Telomere shortening has been associated with carcinogenesis,[75] inflammatory conditions,[76] and neurodegenerative diseases such as Alzheimer's.[77,78]

Cellular senescence is the process in which cells stop dividing, leading to substantial limitations in the regeneration potential of cells and tissues. It is associated with depletion or exhaustion of stem cells[63,64] and is affected by genomic instability and proteostasis.[6] Cellular senescence has been found to impact allostasis, 'the adaptive physiological response activated when homeostasis is disrupted during acute stress'.[79]

Loss of proteostasis refers to difficulties in the regulation of cell proteins – such as misfolding of proteins, inaccurate translation fidelity, and impaired autophagy – that contributes to impaired intercellular communication and plays a major role in aging-related diseases.[6] Problems related to proteostasis have been implicated in skeletal muscle aging, vascular problems, and neurodegenerative diseases including Parkinson's and Alzheimer's.[80] These problems have been related to an increase in oxidative stress and inflammation,[80] a process sometimes referred to as 'inflammaging'.[81]

Mitochondrial dysfunction, or impairment in these important metabolic cell components, is associated both with aging and disease.[82] Mitochondrial dysfunction can be exacerbated by oxidative stress[83] and influences the function of stem cells that underlie cellular senescence.[6] Mitochondrial impairments in T cells have been shown to affect multiple organ systems and cause a multimorbid presentation in a mouse model.[84]

Psychiatric and medical multimorbidity

There is a bidirectional relationship between physical and psychiatric conditions. Medical illness and mental illness frequently co-occur,[85–87] and the presence of a single mental disorder increases the likelihood of another mental disorder.[85] Additionally, mental disorders' phenotypes contribute to declining physical health. Depression and anxiety influence medication adherence,[88,89] and patients have been found to put medical illnesses in a secondary role until mental health concerns have been addressed.[90] Conversely, psychosocial factors including depression, social isolation, and excessive alcohol consumption have all been highlighted as potential modifiable risk factors for dementia by the *Lancet* Commission on dementia prevention, intervention, and care.[91,92]

Multimorbidity is linked to premature mortality among psychiatric patients.[93] In addition, the total burden of medical and psychiatric multimorbidity has been associated with mortality in middle-age and older veterans with type 2

diabetes, with substance use, psychosis, and depression comprising the mental illnesses most associated with mortality in diabetic patients.[94]

Although this review focuses on multimorbidity beyond the lens of individual diseases' comorbidity patterns, and a comprehensive discussion of these comorbidities is beyond the scope of this article, a review of some of the evidence is provided. A recent review article examined the evidence surrounding care for dementia, depression, and delirium in primary care settings.[62] Depression and anxiety have been linked to hypertension and increased risk of death,[95] possibly related to increased levels of circulating catecholamines in these patients.[96] The links between chronic pain and psychiatric disturbances have been extensively explored.[97,98] As another example, asthma is associated with anxiety, mood, substance use disorders, and dissociative and somatoform disorders.[85,99]

There is evidence in multimorbidity research of certain disorders appearing in 'clusters', wherein one disorder increases the likelihood of having another. This topic was examined by a study of community-dwelling adults in Sao Paulo, Brazil.[85] Authors found that that depression, dysthymia, substance use disorders, and obsessive–compulsive disorder (OCD) were the psychiatric conditions most associated with the presence of another psychiatric disorder. Psychiatric conditions associated with medical multimorbidity included cognitive impairment, nicotine dependence, somatoform disorders, and dissociative disorders. Additionally, chronic medical multimorbidity was associated with depressive and anxiety disorders: depression, dysthymia, phobias, and generalized anxiety disorder. Of note, in this study panic disorder, OCD, bipolar disorder, bulimia, alcohol, and substance use disorders showed no association with medical multimorbidity.[85]

Interactions between pharmacologic treatments and multimorbidity

The aging body undergoes significant changes in the pharmacokinetics and pharmacodynamics of medications. Pharmacokinetics examines how drugs are absorbed, distributed, metabolized, and excreted by the body, whereas pharmacodynamics examines the biochemical and physiological effects of drugs and their mechanisms of action. Changes in both pharmacokinetics and pharmacodynamics in aging can produce geriatric conditions, such as delirium, falls, frailty, dizziness, syncope, and urinary incontinence, that interact highly with multimorbid chronic medical conditions, such as diabetes, hypertension, and psychiatric conditions.[100]

Pharmacokinetic changes with aging include:[101,102]

- Slightly decreased absorption of some drugs associated with increased gastric pH and delayed gastric emptying, although enteric coated tablets tend to undergo an increased rate of absorption given the coating breaks down more rapidly in alkaline fluid.[103,104]
- Changes in volume of distribution for both lipophilic and hydrophilic drugs corresponding with increases in body fat, and reductions in lean body mass, total body water, and serum albumin.
- Changes in metabolism related to decreased hepatic mass and blood flow.
- Potentially impaired renal elimination of drugs as renal blood flow and glomerular filtration rate decrease.

Pharmacodynamic changes related to aging likely result from decreased brain volume and changes in vascular distribution and increased blood–brain barrier permeability,[105] which increase the aging brain's susceptibility to many medication classes. These changes likely account for older adults' differing responses to several pharmacologic agents compared to younger people, such as increased sedation and postural sway observed with benzodiazepines, and the cognitive effects of anticholinergics in older people demonstrated by Bishara *et al.* and others.[106,107] Indeed, anticholinergics have been associated with greater risk of mortality among people living with dementia.[108]

Delirium is a condition that deserves particular attention among this population. Defined as an alteration of attention and awareness with an underlying medical cause,[109] it is often a consequence of interactions between pharmacologic treatments and multimorbidity in older adults. It can often be avoided by tapering or discontinuing medications that contribute to the condition, but these decisions must be weighed against the benefits of treating the underlying condition. For example, although several common analgesics, antibiotics, and antivirals are believed to precipitate or prolong delirium,[110] inadequate control of pain or infection are also known risk factors for delirium.[111] Though all medications should be

considered to potentially cause or prolong delirium, several classes of medications commonly used in psychiatry are believed to be particularly deliriogenic, including antidepressants such as mirtazapine, SSRIs and tricyclics; mood stabilizers including lithium and the anticonvulsant medications valproate and carbamazepine; and medications with strongly anticholinergic properties including various hypnotic agents and antipsychotics.[112]

Psychological and emotional factors in multimorbidity

Beyond distinct psychiatric syndromes, there are bidirectional relationships between multimorbidity and various psychological factors, including personality characteristics, defense mechanisms, and psychological distress. Positive psychological factors, particularly those relevant to aging such as wisdom, can also play a protective role against multimorbidity. Thus, attention to psychology is an important consideration when treating patients with multiple chronic conditions.

'Negative' psychological factors

Dating to the 1960s, researchers have been reporting on negative psychological factors' roles in the development of illnesses such as ALS,[113] breast cancer,[114] amenorrhea,[115] and melanoma.[116] This work continues today, with recent articles examining personality characteristics associated with cluster headaches[117] and the predictive value of emotional suppression on later development of breast cancer through modulation of immune factors,[118] among others. The sense of lacking control over one's life in multimorbidity has also been postulated to exacerbate anxiety and a chronic stress response,[119] possibly contributing to an increased risk of unhealthy behaviors such as smoking.[45] Efforts to examine the psychological aspects of dealing with multimorbidity include a meta-synthesis of qualitative studies[120] that found that multimorbidity is experienced as moments of complexity, not counts of illnesses. A more recent qualitative scoping study examining community assets in multimorbidity[121] identified three central themes of the patient experience: lack of a 'joined up' approach; loss of control *versus* confidence; and mental well-being and hope through reducing isolation. How people conceptualize their multimorbidity influences self-perception and self-management of their conditions[121,122] and level of engagement with treatment.[123]

One instructive example is the role of emotional avoidance in certain types of chronic pain conditions, which often occur within the context of multimorbidity.[97] These chronic pain conditions, called centralized or nociplastic pain, are defined as pain without clear evidence of actual or threatened peripheral tissue or nervous system damage[124] and include musculoskeletal conditions such as nonspecific low back and neck pain, pelvic pain, temporomandibular disorders, tension headaches, fibromyalgia, as well as interstitial cystitis, irritable bowel syndrome, and others – all of which frequently co-occur. There is a strong link between childhood trauma, attachment problems, and these painful conditions.[125–127] Moreover, the presence and severity of centralized pain conditions are highly associated with unhealthy emotional regulation strategies, including defense mechanisms such as suppression,[128,129] and this is especially the case with anger.[130] Conversely, emotional approach coping has been associated with lower pain severity among patients with chronic pain and multimorbidity.[131] Yet clinicians often do not ask enough about people's childhoods, past traumas, and emotion regulation in the course of chronic pain treatment.[132] Consideration of the critical psychological drivers of centralized pain has important treatment implications, as the 'treatment of choice'[133] for centralized pain is emotional awareness and expression therapy (EAET), a psychological approach that encourages approach rather than avoidance of difficult emotional experiences, such as healthy anger, grief, guilt, and love.[134] Clinical trials of EAET in older adults with multimorbidity show complete or nearly complete resolution of chronic pain (i.e., greater than 70% pain reduction) in a substantial minority of patients.[135,136]

Psychological distress

Multimorbidity is associated with 'psychological distress'[137,138] – a term referring to the range of human psychological responses to the environment, including disease states.[138,139] In one study, an association between psychological distress and multimorbidity was found to remain even after controlling for potential confounding factors such

as age, sex, perceived social support, and economic status. External factors such as educational level, marital status, and the number of people in the same dwelling also did not affect this association.[137]

Unlike psychiatric diagnosis, psychological distress is not a distinct clinical entity, but correlates with stress and overall mental health.[137,138] It has been linked to reduced adherence to medical treatments,[88,89] as well as adverse health behaviors and premature mortality.[137,140] Psychological distress and chronic illness have a negative, synergistic effect on vitality and functioning[141] and can intensify the perceived effects of multiple illnesses.[138] While debate continues about the value of simple condition counts versus weighted indexes based on severity/impact,[9,142,143] a cross-sectional study of 238 patients with multimorbidity in primary care found psychological distress to be associated with increasing severity of illness measured by the Cumulative Illness Rating Scale (CIRS),[137] rather than a simple count of diseases.

'Positive' psychological factors

In contrast to psychological distress, 'patient empowerment' – a concept reflecting patients' increased understanding, involvement, and agency in managing their own health[144,145] – has been found to result in better self-engagement and more favorable health outcomes in multimorbidity.[146,147] More broadly, the 'positive psychiatry' concept highlights the important protective role of positive psychosocial characteristics such as optimism, resilience, and social engagement on improving outcomes in a variety of conditions, both psychiatric and somatic.[148] This work demonstrates that psychological factors can confer benefits, not just vulnerabilities, and hints at possible opportunities for enhancing the treatment of multimorbidity.

In qualitative reviews, people with multimorbidity find that engaging in behavioral strategies with a social or spiritual component helped them take responsibility for leading a purposeful life beyond the confines of their conditions,[121] with some commentators noting how patients perceive and understand their own multimorbidity can affect interventions and provision of care.[149] For example, those who see multimorbidity as a challenge may be more likely to seek resources and support, whereas those who see it as a burden may be subject to psychological and psychiatric setbacks. Studies highlight the need for greater awareness for the social support available to these patients,[150] as social connectedness across the life course interacts with their psychological resilience.[151]

Social factors and racism in multimorbidity

Though often framed as a health issue, multimorbidity is greatly influenced by social determinants of health and lifestyle factors,[152] as material, psychosocial, and behavioral determinants of health have all been associated with multimorbidity.[5,45] In addition, the patient's social environment – including adverse childhood experiences as well as current social isolation and loneliness – plays an important role in multimorbidity. Finally, an emerging area of research and scholarship points to the important contribution of racism to multimorbidity among minoritized patients.

Social determinants of health

The prevalence of multimorbidity is greater among ethnic minorities and individuals with fewer educational qualifications.[33,56,153,154] It occurs a decade earlier in socioeconomically deprived communities[2,11] and is associated with premature death, poorer function and quality of life, and increased healthcare utilization.[6] One systematic review of social determinants of multimorbidity found low household income to be the strongest associated factor for the prevalence or incidence of multimorbidity, with odds ratios ranging from 2 to 4.5 across studies.[152] Certain combinations of conditions are found more commonly in more deprived groups, including multimorbidity involving mental health conditions.[2,11] When considering multimorbidity with 10 or more functional limitations, prevalence is 90% higher in the most deprived quintile compared to the least deprived quintile.[45] Interestingly, the gap appears to be widest in the older working-age population and those just after retirement age.[11,155,156] Lower educational attainment also has an association with multimorbidity,[119] with one systematic review describing a 64% increased risk of multimorbidity when lower educational level was compared to higher education level.[55] The landscape of multimorbidity is further complicated in low- and middle-income countries by the overlap of compounding factors including adverse environmental and early life stressors linked to poverty, limited social infrastructure, and poorer family coping mechanisms that translate into chronic diseases occurring at earlier ages.[157,158]

Lifestyle factors

Lifestyle factors, including smoking status, alcohol intake, decreased physical activity, and diet have been associated with development of multimorbidity,[26,156,159] with smoking frequently found to be a highly significant factor.[160] The greater prevalence of tobacco smoking among those with mental health conditions[161] is posited to underlie increased medical multimorbidity in patients with psychiatric diagnoses.[162]

Many mental illnesses involve changes in sleep, and associations have been found between sleep duration and multimorbidity in many countries.[163–166] Physical activity could modify the odds of having multimorbidity among poor sleepers.[163] Case reports discuss the effect of physical ailments on mental health problems,[121] and loneliness and social isolation influenced by mental conditions can influence physical health due to health-damaging behaviors including sedentariness and poor nutrition.[18,62,167]

Adverse childhood experiences and allostatic load

Adverse childhood experiences, long known to increase risks of high-risk behaviors, mental illness, and greater prevalence of the leading causes of death in adults,[126] have also been associated with the complexity and severity of multimorbidity in adults.[43] Proposed mechanisms for this include increased hypothalamic–pituitary–adrenal axis activation, cortisol levels, inflammation, DNA methylation, and telomere shortening.[29,30,49,50] This could be accounted for by the concept of 'allostatic load', the 'wear and tear' on the body's efforts to maintain homeostasis during periods of chronic stress.[168] The heightened neural or neuroendocrine response to stress imposes additional burdens on the body and has been implicated in a broad range of health conditions, affecting many organ systems. Psychological stress is correlated with higher allostatic loads,[33] which could underlie many of the factors affecting multimorbidity discussed throughout this review.

Social connection and living alone

Social connections – ranging from dyadic relationships within a community to larger networks – have been found to influence chronic illness self-management, with larger networks and networks with friends in addition to family associated with better outcomes.[169] A recent systematic review[152] examined the association between multimorbidity and living situation. Two high-quality studies found that living alone was associated with increased incidence of multimorbidity versus cohabitating, including one demonstrating an increased risk of up to 20%.[170] Possible explanations could include social isolation associated with living alone, or the potential need to cohabitate when health declines. However, two other studies included in the review did not find an association between incidence of multimorbidity and living situation.

When other living compositions are considered, mixed results have been found when considering living as a couple, living with children, or in care homes.[152,171] Mixed results were also found when comparing homeownership, renting, and living in social housing, indicating social housing residents had a significantly lower odds of multimorbidity.[152] In older adults, objective social isolation was not found to be associated with depressive symptoms or psychological distress, but subjective isolation from family and friends was implicated.[172]

Racism and discrimination

As discussed previously, ethnic minorities face a higher incidence of multimorbidity, with prior work showing increased vulnerability to conditions such as obesity, hypertension, cardiovascular disease, and earlier onset of multimorbidity identified across minoritized ethnic groups.[33,173] Minoritized groups also face increased likelihood of comorbidities contributing to multimorbidity, such as diabetes during the first year of psychotic illness.[173] The reasoning for these inequities has traditionally been framed in terms of differences in socioeconomic factors such as income, education, and occupation, but recent evidence has suggested that these ethnic and racial disparities persist after controlling for socioeconomic factors.[173,174] Some commentators have framed race as a 'socially constructed proxy for structural determinants'[175] affecting health in many domains. This coincides with the rising academic interest in 'syndemics',[176] a public health concept exploring the overlapping influences leading to clustering of diseases in certain populations. First conceptualized by Merrill Singer in relation to the AIDS epidemic in the 1990s,[177] a syndemic was defined as a set of closely intertwined and mutual

enhancing health problems that significantly affect the overall health status of a population within the context of a perpetuating configuration of noxious social conditions.[178] The list of social, structural, and contextual factors influencing ethnic and racial disparities include, but are not limited to: poverty, segregated housing, enslavement, colonialism, neocolonialism, systematic exclusion from opportunities, and unequal interaction with the healthcare system.[176]

Rather than conceptualizing race and ethnicity as a 'risk factor', which runs the risk of classifying the issue as biologic, economic, or cultural and potentially places blame on individuals within a group, commentators have suggested looking at 'racism, not race' at intrapersonal, institutional, and structural levels.[175] Racial and ethnic discrimination exists in many forms, having been studied across many racial groups,[44,179–182] in forms ranging from childhood racial discrimination, everyday discrimination, and major discriminatory events (i.e., infrequent incidents that require a significant shift or adjustment in one's life).[44,182] A 2015 meta-analysis found racism to have a deleterious effect on physical and mental health,[183] and racial discrimination has been associated with a two-fold risk for reporting one 12-month psychiatric disorder, and three-fold risk for reporting two or more psychiatric disorders.[184]

Beyond these individual disease links, there is mounting evidence that the effects of discrimination and minoritization can increase risk of comorbidities leading to multimorbid clinical presentations. Compared to those who face no discrimination, people who experienced everyday discrimination were significantly more likely to report multimorbidity in a dose-response manner across multiple populations.[44,179,181,185] Poorer health-related quality of life and self-rated health, both predictors of mortality, have been found in several minoritized ethnic groups.[173,174] Language barriers could account for some instances of poor care among immigrants, who may have difficulty making their needs known to providers; improving access to professional interpreters has the potential to improve clinical care in these cases.[186]

The effect of racism and discrimination on multimorbidity appears to operate through, or in concert with, the biological and psychological factors discussed earlier. Discrimination is associated with allostatic load: in a review of 11 studies, 9 found a significant positive association between discrimination and allostatic load.[182] Types of discrimination positively associated with allostatic load included lifetime discrimination, childhood racial discrimination, and everyday discrimination.[182] Additionally, social epigenetics studies have reported changes in DNA methylation and epigenetic aging among people who faced discrimination, neighborhood disadvantage, childhood adversity, and low socioeconomic status in childhood and adulthood.[187]

Implications of multimorbidity for polypharmacy and vice versa

Implications of multimorbidity for polypharmacy

Taking a disease-focused approach rather than viewing patients through the lens of multimorbidity increases the risk of adverse drug effects, drug–drug interactions, drug–disease interactions, and potentially problematic polypharmacy,[31,188–190] which is a known contributor to many adverse outcomes and health complications. Treatments optimal for a patient with one disease are not necessarily optimal – and may be inappropriate – for someone with multiple conditions.[191] Part of the reason for this is that medications can inhibit or potentiate each other's effects, or pharmacodynamics,[13,37,191–193] and lead to potentially harmful 'prescribing cascade' where new medications are added to treat the side effects of others (e.g. a proton pump inhibitor is added to address gastrointestinal side effects from a nonsteroidal anti-inflammatory drug). Additionally, a systematic review of medication-related problems in older primary care patients noted that identification of potentially inappropriate medication prescribing can be country-and context-specific, even when using well-recognized guidelines such as Beer's criteria and STOPP/START.[194–196]

Of particular interest when dealing with multimorbidity that involves psychiatric conditions is the fact that many medications identified as being high-risk are commonly prescribed for psychiatric conditions. A retrospective cohort study of adverse drug reactions in the geriatric psychiatry unit of a university hospital in Germany found that 62% of the agents involved in adverse drug reactions were psychotropic agents, and 38% were non-psychiatric medications.[197] Second-generation antipsychotics were the most involved agents, followed by antihypertensives, antidepressants, first-generation antipsychotics, and anticonvulsants.

Implications of polypharmacy for multimorbidity

Polypharmacy has been associated with increased risk for drug–drug interactions, adverse drug effects, and cognitive and functional impairment in patients with multimorbidity. In older patients with multimorbidity, polypharmacy has been linked to increased risk of falls, as well as increases in hospital admissions, length of stay, frailty, and mortality.[198–200] Adverse events due to drug–drug interactions are substantially increased when multiple drugs are taken,[201] and polypharmacy has also been related to potentially inappropriate medication prescribing.[202] While there is no consensus definition for the number of medications constituting polypharmacy, it generally ranges from 5 to 10.[203,204] However, even at lower counts of medication, polypharmacy can be harmful: a 24% increase in mortality has been observed as patients' regimen increases from one medication to four.[205]

Polypharmacy that includes medications prescribed for both chronic medical and chronic psychiatric conditions can lead to substantial increases in adverse events for patients with multimorbidity. For example, medications correlated with fall risk include benzodiazepines, benzodiazepine receptor agonists such as zolpidem, antidepressants, antipsychotics, and medications with strongly anticholinergic properties.[206,207] A study of adverse drug reactions among psychiatric inpatients with multimorbidity found that extrapyramidal events were the most common adverse drug effect, followed by alterations in heart rate or blood pressure, and thirdly electrolyte disturbances including SIADH, hyponatremia or hypokalemia.[197] In linking these agents with the most frequent adverse drug reactions, the authors noted that antipsychotic medications are a known contributor to extrapyramidal side effects and join tricyclic antidepressants as the two main psychotropic agents known to influence blood pressure and heart rate – with an increased risk of the latter effect when they are taken in combination with cardiovascular agents such as antihypertensives and various diuretics.[197] Another example of the increased risk from polypharmacy for medical and psychiatric conditions in the finding that SSRIs and SNRIs can promote electrolyte disturbances such as hyponatremia when used alongside thiazide diuretics.[197]

Conversely, efforts to review and decrease prescriptions can reduce hospitalization and death in nursing home patients[208,209] and reduced mortality in ambulatory settings.[210] Previous studies have indicated the importance of working with an interdisciplinary team including pharmacists, nurses, and other professionals.[211–213] Judicious prescribing of psychiatric medications includes attempting to taper medications to lower doses at regular intervals and avoiding prescribing multiple agents in the same medication class (e.g. multiple antidepressants, multiple antipsychotics). Efforts to reduce psychotropic medications have reduced rate of falls, 'albeit with highly variable results across studies'.[214] Complete discontinuation of benzodiazepines has been shown to improve cognitive function in some adults over age 65 years, particularly in nursing homes.[215]

Toward improved management of multimorbidity

A greater appreciation of the multifactorial underpinnings of multimorbidity helps promote a better management approach for psychiatric and medical multimorbidity. For instance, recognizing that nonmodifiable biological factors related to aging contribute to multimorbidity can guard against providing overly aggressive treatment. Recognizing the impact of psychology and behavior on multimorbidity can help providers identify factors that would be best addressed by psychological and behavioral treatments that confer low risks for older patients. Recognizing the effects of social determinants of health could also help guide providers to inquire about patients' social situations and perhaps consider strategies to increase social connection rather than adding another risky medical treatment.

Yet most available clinical guidelines continue to use single-disease guidelines despite the fact that simply counting the number of diseases may be inadequate to correctly address the issue and can contribute to fragmented and poorly coordinated care that is potentially harmful.[7] An example of multimorbidity's additive risk in older adults was found by Whitson *et al.*'s study of 3878 participants. The authors found a three-to-sixfold increase in various forms of disability in patients who had both cognitive and visual impairments compared to only one of these conditions.[25] Beyond recognizing the multiple biopsychosocial risk factors for multimorbidity and the limitations of single-disease guidelines, specific components of care for patients with multimorbidity include the provision of whole-person care and care coordination.

Whole-person care

Optimal multimorbidity management involves placing an emphasis on what matters most to people, and taking into account the needs, values, priorities and perspectives of patients and their families – the essence of whole-person care.[121,138,216,217] People with multimorbidity face the challenge of finding the appropriate balance between managing symptoms and diseases while avoiding having their lives controlled by the demands of their treatment plan.[218] Additionally, both patient and provider can face shifting priorities and demands, as different conditions can alternate in and out of the forefront in terms of their influence on the patient's overall well-being.[218,219] As such, it is important to reassess the patient's goals, values, and priorities frequently when providing care. One common priority for patients is continuity of care within a coordinated, interdisciplinary model.[2,15,16,40]

Care coordination and systemic interventions

In addition to medication management, recognizing the significance of psychosocial factors, and eliciting patients' needs and perspectives,[121,216] providers can place renewed focus on care coordination – particularly as poorly coordinated care leads to the aforementioned issues with single-disease treatment. As previously mentioned, patients will defer management of physical health until mental health needs are addressed. Studies also indicate that people with serious mental illnesses often have particularly severe disparities in healthcare due to fear and stigma.[220] Moreover, there is a role for mental healthcare providers in helping patients address their physical health needs. One-third of patients in a Danish study expressed interest in diabetes support from mental healthcare professionals,[221] highlighting a significant role for mental healthcare practitioners within interdisciplinary care teams. On a system-wide level, it is also important that prevention and community work are prioritized over crisis work and hospitals, while noting that prevention strategies should be equitable in addition to effective, as some individual-level behavioral change interventions require substantial agency to implement effectively and can thus widen socioeconomic inequalities in health.[5] Coordinated care addressing the many aspects of multimorbidity offers the best opportunity for health promotion. For instance, new models of care that provide mental and physical healthcare integration are being developed and include community multidisciplinary teams with geriatrician input, joint medical/psychiatry inpatient units, care home intervention teams, and huddles in which complex patients may be discussed.[222] Initiatives, such as the American Association for Geriatric Psychiatry Scholars Program,[223,224] which encourage more trainees to enter fields such as geriatric medicine and geriatric psychiatry – both of which have experienced problems recruiting – can increase the number of specialists available to join multidisciplinary teams and promote improved care for older patients with multimorbidity.[225]

Conclusions

Multimorbidity, or the co-occurrence of two or more chronic medical or psychiatric conditions, is a complex and increasingly common phenomenon, especially among older adults. It is important for the clinician to recognize that the presence of multimorbidity is influenced by multiple biological (e.g. epigenetic changes, inflammation), pharmacological (e.g. polypharmacy, changes in pharmacokinetics/pharmacodynamics), psychological (e.g. defense mechanisms, psychological distress), and social (e.g. loneliness, social connection) factors. Understanding these contributing factors can guide clinicians to avoid cumulatively implementing a risky single-disease approach, but instead to focus on optimizing medication management, improving care coordination, and treating the whole person, including the patient's goals, values, and priorities to improve overall well-being.

Declarations

Ethics approval and consent to participate

Not applicable (review article). There is no ethical approval number and there were no human subjects to provide consent.

Consent for publication

Not applicable (review article).

Author contributions

David M. Carlson: Conceptualization; Writing – original draft; Writing – review & editing.

Brandon C. Yarns: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

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